Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases

P Stolt, C Bengtsson, B Nordmark, S Lindblad, I Lundberg, L Klareskog, L Alfredsson, and the other members of the EIRA study group

Objective: To quantify the influence of cigarette smoking on the risk of developing rheumatoid arthritis (RA).

Methods: 679 cases and 847 controls included during May 1996–June 2000 in a case-control study, using incident cases, comprising the population aged 18–70 years of a defined area of Sweden, were investigated. A case was defined as a person from the study base who received for the first time a diagnosis of RA using the 1987 American College of Rheumatology criteria, and controls were randomly selected from the study base. Self reported smoking habits among cases and controls, and rheumatoid factor status among cases were registered. The incidence of RA in current smokers, ex-smokers, and ever-smokers, respectively, was compared with that of never-smokers.

Results: Current smokers, ex-smokers, and ever-smokers of both sexes had an increased risk for seropositive RA (for ever-smokers the odds ratio was 1.7 (95% confidence interval (95% CI) 1.2 to 2.3) for women, and 1.9 (95% CI 1.0 to 3.5) for men), but not for seronegative RA. The increased risk was only apparent among subjects who had smoked ≥20 years, was evident at an intensity of smoking of 6–9 cigarettes/day, and remained for up to 10–19 years after smoking cessation. The risk increased with increasing cumulative dose of smoking.

Conclusion: Smokers of both sexes have an increased risk of developing seropositive, but not seronegative, RA. The increased risk occurs after a long duration, but merely a moderate intensity, of smoking and may remain for several years after smoking cessation.

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a heterogeneous pattern and a prevalence of about 0.5–0.8% in Scandinavia, more commonly occurring among women than among men. Knowledge of the immunological mechanisms underlying RA has increased and some understanding of the association between genotype and RA has emerged, but still only few conclusive results have been obtained to explain the link between the environment and the risk for RA.

Smoking has so far been shown to be the most plausible environmental risk factor for RA and has been investigated in 12 studies (table 1). The first was an English study published in 1987, analysing data on oral contraceptive use and arthritis, that reported an unexpected association between smoking and referral to hospital for RA. Prevalent cases were used in five of the studies and incident cases in seven of the studies on this issue. In total, seven of the 10 studies examining men separately demonstrated an association between smoking and increased risk for RA, and all four studies examining men separately showed an increased risk among smokers.

A stronger association with smoking has been found for seropositive cases than for seronegative cases, and two studies have observed smoking to be associated only with seropositive RA (RF+ RA), and not with seronegative RA (RF–RA). Three of the five studies investigating the effect of a cumulative dose of smoking on the risk for RA observed a dose-response relationship.

Duration of cigarette smoking has been found to be associated with an increased risk for RA in four of the five studies on this issue, but the effect of intensity of smoking is still controversial. The effect of stopping smoking on the risk for RA has been investigated only to a limited extent.

In summary, previous studies have provided evidence for a link between smoking and the risk for RA but the effect of duration, intensity and cumulative dose of smoking, and smoking cessation, RF status, and sex needs further clarification.

To investigate the influence of environmental factors on the risk of developing RA and the interaction of these factors with genotype we started an extensive case-control study—the Epidemiological Investigation of RA (EIRA) study.

In this report from the EIRA study we investigated aspects of the association between smoking and the risk for RA that have previously only been investigated to a limited extent, and that may have relevance for the creation of biological hypotheses, focusing on the influence of RF status, sex, duration and intensity of smoking, and smoking cessation.

SUBJECTS AND METHODS

As far as we know this study is the first report from an extensive, population based, case-control study, using incident cases, with a study group comprising the population of 18–70 years of age in a geographically defined area in the middle and southern parts of Sweden. The study period for the present report was May 1996–June 2000.

Case identification

The study sought to identify incident cases in the study base as soon as possible after the start of the disease. Increasing

Abbreviations: ACR, American College of Rheumatology; BMI, body mass index; CI, confidence interval; EIRA, Epidemiological Investigation of RA (study); OR, odds ratio; RA, rheumatoid arthritis; RF, rheumatoid factor
The evidence of the importance of early treatment of RA has led to the introduction of so-called “early arthritis clinics” as an important component of rheumatology units in Sweden. It has also increased the tendency in primary care to refer cases of suspected RA to rheumatology units for further assessment. All rheumatology units linked to the general welfare system in the study area participated in the study as well as privately run rheumatology units.

In total, 18 study centres reported cases of RA to the study. Initially, two of the centres also reported cases of suspected RA, to enable investigations of undifferentiated arthritis. All cases were assessed and diagnosed by a rheumatologist. Subsequently, cases which did not fulfil the 1987 American College of Rheumatology (ACR) criteria for RA at the time of the report to the study were excluded. In the current report a case is thus defined as a subject from the study base who received a diagnosis of RA according to the ACR criteria for the first time. RF positivity or RF negativity was determined locally by the unit entering the case into the study.

### Selection of controls

For each potential case one control was randomly selected from the study base as a stratified random sample, taking into consideration sex, age, and residential area. If information could not be obtained from the control selected, another control was chosen according to the same principles. Each potential case and control was offered the opportunity to participate in the study, and to answer an extensive questionnaire. Completed questionnaires were obtained from 859 potential cases and 864 controls, the response rate being 96% for the case group and 83% for the controls. Of those 859 potential cases, 163 were excluded as they did not satisfy the 1987 ACR criteria for RA. Seventeen cases and the corresponding 17 controls were excluded because they did not belong to the study base.

### Table 1: Previous studies on the association between smoking and rheumatoid arthritis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Study design, type of cases</th>
<th>Number of cases women/men</th>
<th>Relative risk with 95% confidence interval women/men/both sexes together</th>
<th>Examining separately, the effect of duration, intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessey et al19</td>
<td>1987</td>
<td>Cohort study, incident cases</td>
<td>78/NE*</td>
<td>2.4 [1.8 to 3.2]† / NE / NE</td>
<td>No, yes</td>
</tr>
<tr>
<td>Uhlig et al20</td>
<td>1999</td>
<td>Case-control study, prevalent cases</td>
<td>261/98</td>
<td>1.14 [0.80 to 1.62] / 2.38 [1.45 to 3.92] / 1.46 [1.10 to 1.94]</td>
<td>No, no</td>
</tr>
<tr>
<td>Karlsson et al21</td>
<td>1999</td>
<td>Cohort study, prevalent cases</td>
<td>7697/NE</td>
<td>1.40 [1.28 to 1.53] / NE / NE</td>
<td>Yes, yes</td>
</tr>
<tr>
<td>Silman et al22</td>
<td>1996</td>
<td>Matched twin pairs case-control study, prevalent cases</td>
<td>MZ† 65/14</td>
<td>10.0 [1.42 to 434] / NE / 12.0 [1.78 to 513]</td>
<td>Yes, no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DZ‡ 55/16</td>
<td>2.4 [0.79 to 8.70] / 3.0 [0.24 to 1.58] / 2.5 [0.92 to 7.87]</td>
<td></td>
</tr>
<tr>
<td>Hutchinsonsson et al23</td>
<td>2001</td>
<td>Cases-control study, prevalent cases</td>
<td>160/79</td>
<td>NE / NE / 13.54 [2.89 to 63.28]</td>
<td>No, no</td>
</tr>
<tr>
<td>Reckner-Olsson et al24</td>
<td>2001</td>
<td>Cases-control study, prevalent cases</td>
<td>179/102</td>
<td>2.5 [0.9 to 6.7] / 3.4 [1.5 to 8.4] / NE</td>
<td>No, no</td>
</tr>
<tr>
<td>Voigt et al25</td>
<td>1994</td>
<td>Case-control study, incident cases</td>
<td>349/NE</td>
<td>1.5 [1.0 to 2.0] / NE / NE</td>
<td>Yes, yes</td>
</tr>
<tr>
<td>Symmons et al26</td>
<td>1997</td>
<td>Case-control study, incident cases</td>
<td>115/50</td>
<td>NE / NE / 1.66 [0.95 to 3.06]</td>
<td>No, no</td>
</tr>
<tr>
<td>Hazes et al27</td>
<td>1990</td>
<td>Case-control study, incident cases</td>
<td>135/NE</td>
<td>0.61 [0.42 to 0.89] / NE / NE</td>
<td>No, yes</td>
</tr>
<tr>
<td>Heliövaara et al28</td>
<td>1993</td>
<td>Cohort study, incident cases</td>
<td>229/119</td>
<td>1.1 [0.8 to 1.6] / 4.4 [2.3 to 8.5] / NE</td>
<td>Yes, yes</td>
</tr>
<tr>
<td>Hernandez-Avila et al29</td>
<td>1990</td>
<td>Cohort study, incident cases</td>
<td>217/NE</td>
<td>1.5 [0.9 to 2.3] / NE / NE</td>
<td>No, yes</td>
</tr>
<tr>
<td>Criswell et al30</td>
<td>2002</td>
<td>Cohort study, incident cases</td>
<td>158/NE</td>
<td>2.0 [1.3 to 2.9] / NE / NE</td>
<td>Yes, yes</td>
</tr>
</tbody>
</table>

*NE, not examined; †relative risk with 95% confidence interval, calculated by us, based on results in this article; ‡MZ, monozygotic twin pairs discordant for rheumatoid arthritis; §DZ, dizygotic twin pairs discordant for rheumatoid arthritis.
The present study thus comprises 679 cases (489 women, 190 men) and 847 controls (602 women, 245 men) (table 2).

### Exposure

Information about environmental exposures was collected using an identical questionnaire given directly to the cases shortly after they had received information about the diagnosis and was sent by mail to the controls. All questionnaires were supposed to be answered at home.

The questionnaire contained a wide spectrum of questions about demographic and reproductive data, heredity, previous health and measures by the health service, body weight and height, lifestyle factors, occupational exposures, psychosocial and socioeconomic circumstances. The following questions about smoking were used: (1) Do you smoke? (2) If you do not smoke, have you previously smoked? (3) If you have previously smoked, which year did you stop smoking? (4) If you smoke or previously have smoked, when did you start to smoke regularly? (5) How much do you smoke, or did you smoke before you stopped, on average per day? Information was also obtained about the type of tobacco smoked.

Unanswered or incompletely answered questionnaires were completed by telephone with the assistance of people trained for this purpose who were not connected to the individual clinics. This was done for most of the questionnaires and in an identical way for case and control groups. For each case the questionnaire was given directly to the cases using an identical questionnaire given directly to the cases shortly after they had received information about the diagnosis and was sent by mail to the controls. All questionnaires were supposed to be answered at home.

### Table 2: Smoking habits of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Current cigarette smokers</th>
<th>Ex-cigarette smokers</th>
<th>Non-regular cigarette smokers</th>
<th>Other tobacco smokers</th>
<th>Never-smokers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>146</td>
<td>128</td>
<td>22</td>
<td>29</td>
<td>164</td>
<td>489</td>
</tr>
<tr>
<td>Controls</td>
<td>151</td>
<td>150</td>
<td>36</td>
<td>41</td>
<td>224</td>
<td>602</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>46</td>
<td>66</td>
<td>3</td>
<td>32</td>
<td>43</td>
<td>190</td>
</tr>
<tr>
<td>Controls</td>
<td>53</td>
<td>81</td>
<td>14</td>
<td>30</td>
<td>67</td>
<td>245</td>
</tr>
</tbody>
</table>

### Statistical analysis

The incidence of RF+ RA, RF− RA, and RA overall in current smokers, ex-smokers, and ever-smokers was compared with that in never-smokers by calculating the odds ratio (OR) with 95% confidence interval (95% CI). We performed matched as well as unmatched analyses of the data. Odds ratios were adjusted for potential confounding by the Mantel-Haenszel method in the unmatched analyses and by conditional regression analysis in the matched analyses.

The incidence of RA overall and of RA of different RF status was analysed separately for women and men. Because the results for women and men were similar, both sexes were analysed together in the calculations for duration, intensity, cumulative dose, and the effect of stopping smoking.

All analyses were performed using the statistical analysis system (SAS) version 4.0. We only present results from the unmatched analyses as these were in close agreement with those from the matched analyses, but had higher precision.

All results were adjusted for potential confounding by age and residential area. When women and men were analysed together, the results were also adjusted for potential confounding by sex. Adjustments were also made for potential confounding by socioeconomic class, BMI, marital status, parity, and oral contraceptive use, but affected the results only marginally and were not retained in the final analyses.

### RESULTS

Of a total of 679 cases in this study, 489 were women and 190 were men. The mean age at the index year was 50 years among the female cases and 53 years among the male cases. Three hundred and twenty (65%) of the female cases and 124 (65%) of the male cases were RF+. RF status was unknown for two female cases. The mean duration from the estimated disease onset to the time at which the cases were reported to the study
increased risk for RF+ RA but not RF compared with never-smokers (table 3). but not in the younger age group of cigarette smokers when increased risk of developing RF+ RA was evident in the older (18–49 years) and an older (50–70 years) age group. An never-smokers. Separate analyses were made for a younger RF smokers of both sexes (table 3). W e found no increased risk of smoking cessation was restricted to RF+ RA, and was made among ever-smokers compared with never-smokers, and among women and men together.

Of the 279 cases with RF+ RA that had ever smoked, 217 (78%) had smoked for ≥20 years. No increased risk for RA was seen among subjects who had smoked for <20 years (table 4). Among subjects who had smoked for ≥20 years, similar results were found among those with an intensity of smoking of 6–9 cigarettes/day, and those with an intensity of smoking of ≥20 cigarettes/day (table 5). The cumulative dose of smoking was expressed as pack-years. The risk of developing RF+ RA increased as the number of pack-years increased, in a dose dependent manner (table 6). The increased risk for RA remained for about 10–19 years after smoking cessation (table 7).

Demographic and reproductive characteristics such as low socioeconomic class, low level of formal education, being unmarried, nulliparity as well as obesity have previously been discussed as possible risk indicators for RA, while oral contraceptive use has been proposed as a possible protective factor. There is also a possibility that these factors may correlate with smoking characteristics. To adjust for potential confounding,
Influence of cigarette smoking on rheumatoid arthritis

Table 6  Relative risk (RR) with 95% confidence interval (95% CI) of developing seropositive rheumatoid arthritis for 18–70 years old female and male ever-smokers compared with never-smokers by number of years since smoking cessation

<table>
<thead>
<tr>
<th>Number of pack-years</th>
<th>Number of exposed cases</th>
<th>RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>65</td>
<td>1.0</td>
<td>0.7 to 1.5</td>
</tr>
<tr>
<td>10–19</td>
<td>78</td>
<td>1.8</td>
<td>1.2 to 2.6</td>
</tr>
<tr>
<td>≥20</td>
<td>136</td>
<td>2.7</td>
<td>1.8 to 3.9</td>
</tr>
</tbody>
</table>

*Relative risk adjusted for age, residential area, and sex.

Table 7  Relative risk (RR) with 95% confidence interval (95% CI) of developing seropositive rheumatoid arthritis for 18–70 years old female and male ex-smokers compared with never-smokers by number of years since smoking cessation

<table>
<thead>
<tr>
<th>Number of years*</th>
<th>Number of exposed cases</th>
<th>RR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–9</td>
<td>74</td>
<td>2.2</td>
<td>1.4 to 3.3</td>
</tr>
<tr>
<td>10–19</td>
<td>41</td>
<td>1.5</td>
<td>0.9 to 2.5</td>
</tr>
<tr>
<td>≥20</td>
<td>25</td>
<td>1.0</td>
<td>0.5 to 1.9</td>
</tr>
</tbody>
</table>

*Number of years between smoking cessation and index year.  †Relative risk adjusted for age, residential area, and sex.

Besides the variables age, sex, and residential area, stratification was performed according to socioeconomic class, BMI, marital status, parity, and oral contraceptive use. However, these had a minor influence on the results and were not retained in the final analysis.

**DISCUSSION**

According to the results in this study, cigarette smokers of both sexes have an increased risk of developing RF+ RA, but not RF− RA, compared with never-smokers. The increased risk of developing RA occurred after a long duration but merely a moderate intensity of smoking, and remained for several years after smoking cessation. We also found that the risk of developing RA increased in a dose dependent manner as the cumulative dose of smoking increased.

This study was designed as a case-control study with incident cases. Besides being more cost efficient, a case-control study using incident cases may provide better opportunities than a cohort study for obtaining accurate information about smoking habits before disease onset. The use of exposure information from baseline in a cohort study, with a long follow up period, is sensitive to substantial bias from exposures that tend to vary with time, cigarette smoking being one example. Because smoking habits have declined during recent decades, a prospective cohort study using only baseline data for smoking would tend to underestimate the effect of smoking on the incidence of RA. A disadvantage of a case-control study with retrospective collection of exposure data compared with a cohort study using prospectively collected exposure data is the higher risk for differential misclassification of exposure due to recall bias that differs between cases and controls. As the use of prevalent cases increases the risk for recall bias we only included subjects from the study base who for the first time had received a diagnosis of RA. The duration between the estimated disease onset and inclusion in the study was 12 months or less for 84% of the cases—that is, the cases were “incident”. All rheumatology units linked to the general welfare system in the study area reported cases to the study, as did privately run rheumatology units. The introduction of so called “early arthritis clinics” in many parts of Sweden has increased the possibilities of identifying a high proportion of incident cases in our study base. A set of adequate diagnostic criteria is an important precondition for an epidemiological study of RA. In the present study we defined cases according to the ACR criteria, which are fairly clear and easy to use in clinical practice but have the limitation of sometimes being inadequate in early cases of RA.

Some cases might have been unidentified in our study, for instance cases diagnosed in primary healthcare facilities that were never referred to a rheumatology unit. It is not likely that the exposure to smoking of these unidentified cases would substantially differ from the exposure of identified cases. Hence, this potential error would probably not seriously bias the relative risk estimates. The response rate in the study was high—96% for cases and 83% for controls. If the smoking habits of participating controls differed from those controls who did not participate, this might have biased the estimated relative risk. However, even if it is assumed that all non-responding controls were smokers (which is highly unlikely), an increased relative risk for RF+ RA associated with smoking would still be observed. Furthermore, the observed discrepancy between RF+ RA and RF− RA would be unaffected. Cases and controls may possibly recall their previous smoking habits differently. However, we only observed an association between smoking and RF+ RA. It is most unlikely that RF+ cases and RF− cases recall their smoking habits differently. Matched as well as unmatched analyses of the data were performed, with similar results. The unmatched analyses used more controls than cases and these additional controls received index years from cases that had previously been excluded from the study. The duration between the estimated disease onset and the report to the study was ≤12 months among 83% of these excluded cases compared with 84% among the rest of the cases, which indicates that the distribution of index years among the additional controls was similar to that of the rest of the controls. We hence assess that the use of these additional controls did not bias the results, but increased the precision.

Adjustment for socioeconomic class, BMI, marital status, parity, and oral contraceptive use had minor influence on the results of the study and was not retained in the final analyses. A relationship between these factors and RA is theoretically possible, but so far insufficiently studied, and will be investigated in forthcoming studies. It has been suggested previously that dietary habits are an important factor for the risk of developing RA. It is also likely that there is some correlation between dietary habits and smoking habits. However, we did not control for dietary habits in this study because we had insufficient information.

In this study smokers of both sexes had an increased risk of developing RF+ RA, but not RF− RA. These results are in agreement with the results of two previous studies, which determined an increased risk for RF+, but not RF− RA among male smokers. However, those studies did not find an association between smoking and RA of either RF status among women. The result in the present study extends a finding by Symmons et al, who observed that smokers have a higher risk of developing seropositive arthritis than seronegative arthritis when both sexes are analysed together. Our study is the first to demonstrate that the association between smoking and RA among men, as well as among women, is clearly dependent on RF status.

The results in previous articles for the association between smoking and RA among women have been somewhat inconsistent. Our study, however, is the only population based case-control study using incident cases that has investigated the association between smoking and RA among women and men separately, and adds evidence to the notion that smokers of both sexes have an increased risk of developing RA compared with never-smokers.

We found that the risk of developing RA associated with smoking required a long duration, but merely a moderate...
intensity, of smoking. These results agree with a suggestion in a cohort study using prevalent cases by Karlsson et al. that duration, but not intensity, of smoking is associated with an increased risk of RA in women.21 Similar results have been presented in another cohort study, but only for men, using incident cases by Heliovaara et al.22 The evidence for an association between duration of smoking and the risk for RA is increasing as it now has been observed in five of the six studies on this issue. The evidence for the effect of the intensity of smoking, however, is still conflicting as two previous studies have suggested an association between increased intensity of smoking and increased risk for RA.23 24 The discrepancy in the results for the effect of the intensity of smoking on the incidence of RA may be due to a considerable degree of recall bias about the number of cigarettes smoked a day, especially because the intensity has probably varied with time. The data on the effect of duration of smoking may be more accurate, as the number of years of smoking may be more easily recalled.

In this study the risk of developing RA was observed to increase as the cumulative dose of smoking increased, an observation that is in concordance with some previous results25 26 and may be regarded as support for the view that smoking is a causal factor for the development of RA.

We also observed that the increased risk for RF+ RA remained for up to somewhere between 10 and 19 years after smoking had stopped. This finding extends a result by Heliovaara et al, who also observed an increased risk for RA among ex-smokers after more than 14 years of follow-up.27 The observed differential effect of smoking on the incidence of RF+ RA and RF− RA in this study may be because RF is an epiphenomenon or acts as an inflammatory mediator, or may be due to an interaction between smoking and genotype. The second possibility finds support in previous findings of a higher prevalence of RF in smokers than in non-smokers in some healthy populations,37 38 and previous observations that RA is sometimes preceded by RF positivity.39 40 The possibility that RF or some associated factor is the link between smoking and the risk of RA increases the interest in investigating the role of B lymphocytes in the pathogenesis of RA.41 Further evidence of a major role for B cells in this respect comes from observations that selective B cell blockade has the potential to modify the course of RA.42 The third possibility is supported by results pointing towards an association between RF status and genotype among subjects with RA or inflammatory polyarthritis43 and by a study observing that smoking is associated with more severe disease outcome among women with a certain genotype.44

The finding that the increased risk for RA associated with smoking requires a long duration, but merely a moderate intensity, of smoking, and may remain for several years after smoking has stopped, indicates that the mechanism behind the effect of smoking is complex, slow, or delayed. The molecular pathways behind the increased risk of RA associated with smoking are still to be investigated. Our principal hypothesis is that an interaction between smoking and genotype is of fundamental importance for the increased risk of RA associated with smoking. This issue will be investigated in a future work within the EIRA study.

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