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Chapter 14

Smoking as a risk factor for the radiological severity of Rheumatoid Arthritis: a study on six cohorts


_Under review_
ABSTRACT

Background
Smoking is a risk factor for the development of ACPA-positive Rheumatoid Arthritis (RA). Whether smoking predisposes to severe joint damage progression is not known, since deleterious, protective and neutral observations have been made. We aimed to determine the effect of smoking on joint damage progression.

Patients and methods
Smoking status was assessed in 3,158 RA-patients included in 6 cohorts (Leiden-EAC, BARFOT, Lund, Iceland, NDB and Wichita). In total 9,412 radiographs were assessed. Multivariate normal regression and linear regression analyses were performed. Data were summarized in a random effects inverse variance meta-analysis.

Results
When comparing radiological progression for RA-patients that were never, past and current smokers, smoking was significantly associated with more severe joint damage in Leiden-EAC (p=0.042) and BARFOT (p=0.015) RA-patients. No significant associations were found in the other cohorts, though a meta-analysis on the six cohorts showed significantly more severe joint damage progression in smokers (p=0.01). Since smoking predisposes to ACPA, analyses were repeated with ACPA as additional adjustment factor. Then the association was lost (meta-analysis p=0.29).

Conclusion
This multi-cohort study indicated that the effect of smoking on joint damage is mediated via ACPA and that smoking is not an independent risk factor for radiological progression in RA.
INTRODUCTION

The severity of joint damage in Rheumatoid Arthritis (RA) is highly variable between patients. Genetic factors are estimated to explain half of this variance; environmental factors likely play a role as well. No clear environmental risk factors for joint damage progression have been identified.

Smoking has been implicated as one of the most important environmental risk factors for the onset of Rheumatoid Arthritis (RA), especially for the ACPA-positive subgroup. It has been hypothesized that smoking contributes to the development of RA-related auto-antibodies. Whether smoking influences the severity of RA as well, is less clear. Smoking was associated with more severe radiographic progression in a Swedish study, but this relationship has not been established in other cohorts. Intriguingly, in a North-American cohort, smoking was shown to protect against joint replacement surgery, and a Swiss study showed a trend towards less progression of radiographic joint damage in heavy smokers. The presence of ACPA is associated with more joint damage. It is unclear whether smoking as such affects progression of joint damage or whether smoking induces ACPA-production and thereby affects joint damage progression.

This study therefore aimed to determine the association between smoking and joint damage in RA and whether this association is mediated through ACPA. In total 9,412 radiographs of 3,158 RA-patients, from six cohorts, were studied and the results were summarized in meta-analyses.

PATIENTS AND METHODS

Patients

Cohort 1 consisted of 703 Dutch RA-patients included between 1993-2006 in the Leiden Early Arthritis Clinic (Leiden-EAC), a population-based inception cohort that is described more extensively elsewhere. Hands and feet radiographs were taken at baseline and yearly over 7-years (total number 3,656, mean follow-up 4.9 years) and chronologically scored by one reader unaware of clinical data using the Sharp-van der Heijde score (SHS). The within-reader ICC was 0.91. Treatment strategies differed for different inclusion periods, as described in. Smoking status (present/past/current) was assessed by questionnaires.

Cohort 2 contained 839 RA-patients included between 1992-1999 from the BARFOT-study, a Swedish multicentre observational study of patients with early (disease duration
Clinical, laboratory and radiological assessments were performed at inclusion and after 1, 2 and 5-years. Hands and feet radiographs (total number 2,870, mean follow-up 4.3 years) were SHS-scored by 2 readers. The between-reader ICCs at baseline and 2-years were 0.93 and 0.94 respectively. At inclusion, no patient had got prior treatment with DMARDs or glucocorticoids. During follow-up, 213 patients participated in a 2-year randomized study on low dose prednisolone as an addition to DMARD-therapy. Smoking status (present/past/current) was assessed by the rheumatologist at inclusion.

Cohort 3 consisted of 339 RA-patients that were recruited from a practice in Wichita, Kansas. Serial hands radiographs (total 1,062) were made during 15 years of follow-up. Cohort 4 consists of 885 RA-patients included in the National Databank of Rheumatic Diseases (NDB). Hands radiographs were made at a single time-point. The radiographs of cohorts 3 and 4 were SHS-scored by one experienced reader (ICC=0.98). All patients in these two cohorts developed RA between 1963-1999, thus in eras when early treatment and use of biologics were uncommon. Smoking status was assessed by questionnaires as a binary variable indicating ever or never smoking.

Cohort 5 consisted of 265 patients from Iceland, referred to Landspítali- The National University Hospital of Iceland or the private clinic of Reykjavik between 1970-2008. Radiographs were made at a single time-point. Joint damage was determined using SHS by two trained readers. The ICCs between and within readers were all >0.95. Smoking status (present/past/current) was assessed by questionnaires.

Cohort 6 consisted of 127 early RA-patients from Lund, Sweden that were prospectively followed during 5-years.[17, 18] Patients were recruited during 1985-1989. Radiographs of hands and feet were taken at baseline and annually for 5-years. Radiographs were scored chronologically according to the Larsen score by one of two readers (ICC between readers 0.94).[19] Smoking status (present/past/current) was assessed by the rheumatologist.

All cohorts had been approved by the local medical ethical committee and all patients had given informed consent. RA was defined according to the 1987-ACR-criteria except for the Lund-cohort, where the 1958-criteria were used.

Statistical methods
Radiographic scores were log10-transformed to approximate a normal distribution. In the Leiden-EAC, BARFOT, Wichita and Lund cohorts, repeated radiographs were available. For these cohorts multivariate normal regression analyses were used with the log10-transformed radiographic score as response variable, as described previously.[20] In the NDB and Icelandic patients, one radiograph per patient had been made. Here
the estimated yearly progression rate was calculated (total SHS divided by disease years since diagnosis at time of radiograph) and linear regression analyses performed. The statistical methods used is extensively described in reference 20. In all cohorts the radiological progression scores were compared between smoking groups, resulting in a relative difference in radiological progression. This effect estimate had no units and could be compared between data-sets. All analyses were adjusted for age and gender. In the Leiden-EAC adjustments were made for the inclusion period (1993-1995, 1996-1999, 1999-2006) as a proxy for treatment strategy as described previously.11 Also in the Iceland data, adjustments were made for inclusion before or after 2000, to correct for different treatment regimes. In the BARFOT-cohort, adjustments were made for participating in a corticosteroid study. No treatment adjustments were made in the cohorts where all patients were included ≤1999 and treatment effects were not observed. Subsequently, all analyses were repeated with ACPA as additional adjustment factor in the regression analyses.

When possible the effect of smoking was first assessed by comparing three categories (present/past/never smokers); for the two North-American data-sets only binary variables were available. The results of the individual cohorts were summarized in an inverse variance meta-analysis testing for random effects. In these meta-analyses, for all cohorts, present and past smokers (combined as smokers) were compared with never smokers. Regression analyses were done using SPSS versions 20.0 (SPSS Inc., Chicago, IL, USA), meta-analyses were performed using STATA. Two-sided p-values <0.05 were considered significant.

RESULTS

Table 1 presents characteristics of the patients from the different cohorts. Overall 52-69% of the RA-patients smoked or had smoked.

Table 1. Baseline characteristics of the study-population

<table>
<thead>
<tr>
<th></th>
<th>Leiden EAC</th>
<th>BARFOT</th>
<th>NDB</th>
<th>Wichita</th>
<th>Iceland</th>
<th>Lund</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>703</td>
<td>839</td>
<td>885</td>
<td>339</td>
<td>265</td>
<td>127</td>
</tr>
<tr>
<td>No of radiographs</td>
<td>3,656</td>
<td>2,870</td>
<td>885</td>
<td>1,062</td>
<td>265</td>
<td>674</td>
</tr>
<tr>
<td>No female (%)</td>
<td>475 (67.6)</td>
<td>538 (69.1)</td>
<td>703 (79.4)</td>
<td>256 (75.5)</td>
<td>214 (80.8)</td>
<td>87 (68.5)</td>
</tr>
<tr>
<td>Age at baseline (mean, SD)</td>
<td>56.5 (15.7)</td>
<td>56.7 (15.4)</td>
<td>49.5 (12.8)</td>
<td>47.8 (14.2)</td>
<td>47.6 (13.7)</td>
<td>50.2 (10.9)</td>
</tr>
<tr>
<td>No. past or present smoker at baseline (%)</td>
<td>317 (50.5)</td>
<td>475 (56.7)</td>
<td>529 (60.3)</td>
<td>193 (56.9)</td>
<td>197 (69.4)</td>
<td>66 (52.0)</td>
</tr>
<tr>
<td>No ACPA+ (%)</td>
<td>368 (52.3)</td>
<td>418 (49.8)</td>
<td>539 (60.9)</td>
<td>275 (81.1)</td>
<td>130 (49.1)</td>
<td>100 (78.7)</td>
</tr>
</tbody>
</table>
In the Leiden-EAC, smoking was significantly associated with the progression of radio-
graphic joint damage (p-value=0.042, Figure 1). When smoking was categorized in two
groups, smokers had a 1.02 (1.00-1.04) times higher progression rate per year (p=0.07).
In the BARFOT-patients, when comparing present, past and never smokers, smoking was
associated with more severe joint damage, an effect that was constantly present over time
(p-value=0.015). When ‘ever smokers’ were compared with ‘never smokers’, significance
disappeared (p=0.12).
When the progression rates were compared between present, past and never smokers in
the Icelandic and Lund cohorts, no significant results were obtained (p=0.75 and p=0.53
respectively). When smokers were compared with non-smokers also no significant results
were obtained (p=0.45 for and p=0.38 respectively).
For the North-American cohorts only binary data were available. In both cohorts smok-
ers had no significant difference in joint damage progression compared to non-smokers
(p=0.16 for the Wichita cohort, p=0.77 for NDB).
However importantly, in all mentioned cohorts, except for the Icelandic data-set, the
directionality of the effect was similar with smokers having more severe joint damage
progression. Subsequently the results on the analyses comparing past and present smok-
ers with never smokers were summarized in a meta-analysis, showing that smoking was
significantly associated with more radiologic progression (p=0.01, Figure 2A).

As smoking predisposes to ACPA-formation and that ACPA is associated with more severe
joint destruction, we repeated all analyses with ACPA-status as additional covariate. No
significant results were obtained in any of the cohorts. The directionality of the effects was
diverse. Also in the meta-analysis, smoking was no longer associated with joint damage
progression (p=0.29, Figure 2B), indicating that the observed effect of smoking was medi-
ated through ACPA-formation.

Figure 1. Joint destruction over 7 years of disease in 703 Leiden-EAC RA-patients according to their smoking
status (being present, past or never smoker). In this analyses, three groups of patients were defined: active smokers, former smokers and never smokers. Active smokers had a 1.01 (1.00-1.02) times higher radiological progression rate per year compared to former
smokers, who had a 1.01 (1.00-1.02) times higher progression rate per year follow-up compared to never
smokers.
In this study we aimed to determine whether smoking is associated with the severity of the course of RA, reflected by the severity of joint damage. In a meta-analysis combining the data of six cohorts, it was observed that smokers had more severe joint damage. However since smoking predisposes to ACPA-development, the analyses were repeated with adjust-
ments for ACPA. Then the association was lost, indicating that the effect of smoking on joint destruction is mediated via the development of ACPA.

Advantages of this study are the large number of radiographs and patients, predominantly recruited in eras when early and aggressive treatment was less common. Hence the disease course of many of these patients may be more reflective of the natural disease course compared to many currently treated RA-patients. Treatment differences occurred in part of the cohorts studied, adjustment were made where appropriate. Some cohorts had serial radiographs and others single radiographs per patient. The former results in more precise estimations of the radiological progression rate, which is reflected by smaller confidence intervals of the effect estimates (see Figure 2).

Part of the patients in the BARFOT, Iceland and Wichita cohorts were also assessed in earlier studies on smoking and joint damage.[6, 8, 10] Given that some previous studies had contradictory results, an advantage of the present study is that we could combine data from these and other cohorts.

Our study has some limitations. Smoking was mainly assessed by questionnaires at disease onset. It is possible that patients may have failed to recall their former smoking habits. We had no information on the number of pack-years or on smoking habits during the disease course. Finally we could not differentiate between past and present smokers in some cohorts, hence in the meta-analysis on all cohorts smokers were compared with non-smokers.

Studies on environmental risk factors for joint damage are relevant as such factors are potentially modifiable. Given that the effect of smoking was mediated via ACPA and that ACPA-development occurs in the preclinical phase of RA, the current data may imply that preclinical environmental factors influence the long-term disease outcome.

ACKNOWLEDGEMENTS

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