The influence of current cigarette smoking on the age of onset of rheumatoid arthritis (RA) in individuals with sporadic and familial RA

SIR, We read with interest the paper by Radstake et al. [1] entitled ‘Familial vs sporadic rheumatoid arthritis (RA). A prospective study in an early RA inception cohort’. The main finding of this study was that sibship size is the only relevant risk factor associated with familial RA. No differences in genotypic and phenotypic characteristics, disease severity or radiological damage were observed when comparing familial and sporadic RA in the population studied overall. However, following stratification for gender, males with sporadic RA were older at disease onset than male probands with familial RA [median (range) 57 (24–78) vs 50 (24–61) yr, P = 0.03]. This was not the case regarding female RA cases.

We would suggest that a history of current cigarette smoking could account for the difference in age of onset observed between males with familial and sporadic RA. It is well established that cigarette smoking is a particularly important risk factor for the development of RA, particularly in men [2], and that heavy cigarette smoking, but not smoking per se, is also associated with RA in women [3].

To determine if cigarette smoking at the time of onset of RA influences the age of onset of familial and sporadic RA, we considered RA patients smoking at the time of disease onset and those who had never smoked. Three hundred and sixty unrelated RA patients (age range 28–87 yr) satisfying the above criteria attending rheumatology clinics in two Merseyside hospitals and fulfilling the 1987 American Rheumatism Association (ARA) criteria for RA were studied further [4].

The patients’ age, age of disease onset, family history of disease (first- or second-degree relatives with a history of RA) and smoking history were recorded. Considering those patients with familial (n = 90) and sporadic RA (n = 134) who were smoking at the time of disease onset, there was a striking significant difference in the age at onset when comparing these two groups. The familial RA patients’ median age of onset was earlier than in the sporadic RA patients [40 (18–72) vs 50 (20–75) yr, P < 0.00001]. These differences were observed in both male and female cases (data not shown). On the other hand, comparing patients who had never smoked, the median age of onset of disease was similar in both groups [familial RA (n = 70) 44 (18–75) yr and sporadic RA (n = 66) 46 (19–74) yr, P = 0.6]. These findings are summarized in Table 1.

Considering the smoking sporadic RA cases, there was a trend (P = 0.06) for the age of onset to be later than the never smoked sporadic RA cases [50 (20–75) vs 46 (19–74) yr]. It is possible that for the smoking sporadic RA cases, cigarette smoking is their principal risk factor for the development of their disease and that this risk is only evident following prolonged exposure to cigarette smoke, as is the case with other smoking-related diseases such as lung cancer [5] and pulmonary

<table>
<thead>
<tr>
<th>RA patient type and smoking history at RA onset</th>
<th>Number</th>
<th>Median age at onset (range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic smoker</td>
<td>134</td>
<td>50 (20–75)</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>Familial smoker</td>
<td>90</td>
<td>40 (18–72)</td>
<td></td>
</tr>
<tr>
<td>Sporadic never smoked</td>
<td>66</td>
<td>46 (19–74)</td>
<td>0.6</td>
</tr>
<tr>
<td>Familial never smoked</td>
<td>70</td>
<td>44 (18–75)</td>
<td></td>
</tr>
</tbody>
</table>
emphysema [6]. This process as a risk factor for RA may only become evident after at least 30 yr of smoking and therefore this particular group present later in life.

The opposite trend, however, was observed in familial RA cases. The smoking RA cases’ median age of onset was earlier than in the never smoked cases [40 (18–72) vs 44 (18–75) yr, \( P = 0.16 \)]. It is possible, therefore, that smoking and a particular gene or genes interact to increase the risk of developing RA at an earlier age. In their study, Radstake et al. [1] observed that HLA-DR alleles coding for the shared epitope were similar and not significantly different between patients with familial RA and sporadic RA. However, other possible RA susceptibility genes, such as the alpha 1 proteinase inhibitor Z allele [7], are observed in familial RA [8] as opposed to randomly selected RA [9]. The alpha 1 proteinase inhibitor Z allele interacts significantly with cigarette smoking in diseases such as pulmonary emphysema [10] and this may also be the case in RA. Finally, in view of our findings, we would suggest that the observation of Radstake et al. [1] that disease onset in familial RA cases is earlier than sporadic RA in males, but not females, could be explained by a difference in the prevalence of cigarette smoking between their male and female cases at the time of disease onset.

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Reply

We have the following comments concerning the previous letter [1]. Our study was performed in a well-documented cohort using prospective assessments of disease severity and outcome. We demonstrated that only the sibship size is associated with the risk of familial rheumatoid arthritis (RA) and found that affected males with familial disease were younger at disease onset compared with familial RA females and males with sporadic RA.

In contrast, the above authors [1] performed a cross-sectional study and found that smoking patients with familial RA had an earlier disease onset than those with sporadic RA independent of gender. However, this difference was not present in the non-smoking patients. These authors therefore suggest that a history of smoking could play a role in our population and explain the younger age at disease onset in males with familial RA. Because smoking history was not assessed in our study this cannot be determined.

Nevertheless, it is clear that several environmental and genetic factors, which are still unknown, could play a role in the susceptibility to and/or severity of RA. These potential factors include smoking, pregnancy and hormonal substitution therapy and other socio-economic factors. We do believe that the only way to clarify this question is to perform regression studies and discriminate analysis in well-documented populations considering potential confounders.

The present literature regarding smoking and \(\alpha\)-1-antitrypsin deficiency and their influence on RA are subject to possible bias and confounding. Most [2, 3], but not all [4] studies on the influence of smoking show only a marginal increased risk for RA in smokers and are cross-sectional and retrospective in design. Furthermore, most studies on \(\alpha\)-1-antitrypsin deficiency are biased by the selection of patients with severe arthritis. Moreover, recent genome-wide linkage studies do not point towards potential susceptibility loci on chromosome 14 in the vicinity of the \(\alpha\)-1-antitrypsin gene [5, 6].

Our major criticism of the above-mentioned study is that it is cross-sectional and does not show any inclusion criteria. Another important point is that the definition of familial RA in this study differs substantially from that in ours. The inclusion of both first- and second-degree relatives in the former makes a reliable ascertainment in this circumstance [6]. The way in which this is acquired in the present study is not clearly addressed.

We do not see a good reason why smoking would influence the age at onset of RA only in familial cases. The authors suggest a role of \(\alpha\)-1-antitrypsin deficiency, which seems a very hypothetical statement. We do believe, however, that the proposed relationship
between smoking and age at onset needs further confirmation in larger cohorts.

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