Smokers and non-smokers with rheumatoid arthritis have similar clinical status: data from the multinational QUEST-RA database


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Abstract

Objectives

To analyse clinical severity/activity of rheumatoid arthritis (RA) according to smoking status.

Methods

The QUEST-RA multinational database reviews patients for Core Data Set measures including 28 swollen and tender joint count, physician global estimate, erythrocyte sedimentation rate (ESR), HAQ-function, pain, and patient global estimate, as well as DAS28, rheumatoid factor (RF), nodules, erosions and number of DMARDs were recorded. Smoking status was assessed by self-report as “never smoked”, “currently smoking” and “former smokers”. Patient groups with different smoking status were compared for demographic and RA measures.

Results

Among the 7,307 patients with smoking data available, status as “never smoked,” “current smoker” and “former smoker” were reported by 65%, 15% and 20%. Ever smokers were more likely to be RF-positive (OR 1.32:1.17-1.48, p<0.001). Rheumatoid nodules were more frequent in ever smokers (OR 1.41:1.24-1.59, p<0.001). The percentage of patients with erosive arthritis and extra-articular disease was similar in all smoking categories. Mean DAS28 was 4.4 (SD 1.6) in non-smokers vs. 4.0 (SD 1.6) in those who had ever smoked. However, when adjusted by age, sex, disease duration, and country gross domestic product, only ESR remained significantly different among Core Data Set measures (mean 31.7mm in non-smokers vs. 26.8mm in ever smoked category).

Conclusion

RA patients who had ever smoked were more likely to have RF and nodules, but values for other clinical status measures were similar in all smoking categories (never smoked, current smokers and former smokers).

Key words

rheumatoid arthritis, smoking, HAQ, DAS


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Introduction
Smoking is associated with an increased risk and a higher prevalence of many diseases, and it has been implicated in the pathogenesis of rheumatoid arthritis (RA), particularly when associated with antibodies, cyclic citrullinated peptides (anti-CCP) and the shared epitope (1-3). In fact, it is postulated that the sequence of events begins with protein citrullination in a subclinical phase before the symptoms start (2). The first study with evidence of an association between smoking and RA risk was an epidemiological investigation of effects of sex hormones on RA (4). Later publications confirmed the association of tobacco and RA, but especially in RF-positive RA (5-8).

The studies relating to smoking with RA clinical characteristics have demonstrated an association of smoking with rheumatoid factor (RF), rheumatoid nodules (9-11), higher clinical disease activity (12), need of more treatment (13), and with a greater erosion score (12). However, other studies could not confirm an association of RA severity with smoking (14, 15). Thus, conflicting data are reported concerning severity of RA as measured by the American College of Rheumatology (ACR) Core Data Set and other clinical measures in relationship to smoking status. The QUEST-RA (Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis) (16) multinational database of RA patients seen in usual clinical care at several clinics in different countries provided us an opportunity to analyse the relationship between smoking and the clinical status of RA patients (clinical severity and disease activity).

Patients and methods
Establishment of database
QUEST-RA was established in 2005 with the objectives to promote quantitative assessment in usual rheumatology care, and to develop a baseline cross-sectional database of consecutive RA patients seen outside of clinical trials in regular care in many countries. Three or more rheumatologists from each participating country were asked to enrol 100 consecutive unselected patients (16).

As of June 2009, the QUEST-RA multinational database included 8,039 patients from 86 sites in 32 countries including Argentina, Brazil, Canada, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, Hungary, India, Ireland, Italy, Japan, Kenya, Kosovo, Latvia, Lithuania, Morocco, the Netherlands, Norway, Poland, Romania, Russia, Serbia, Spain, Sweden, Turkey, the United Arab Emirates, the United Kingdom, and the United States.

Ethics committee approvals
The study was carried out in compliance with the Helsinki Declaration. Ethics Committees or Internal Review Boards of participating institutes approved the study, and a written informed consent was obtained from the patients.

Physician assessment measures
Patients were evaluated according to a standard protocol to evaluate RA (SPERA), which includes a 3-page clinician assessment and 4-page patient self-report questionnaire (17). The rheumatologists performed a clinical assessment involving a review of clinical features including ACR 1987 RA classification criteria, disease duration, all previous and present disease-modifying anti-rheumatic drugs (DMARDs as well as biologic agents), a joint count which includes swollen and tender joint on a 28-joint count, and doctor global assessment of disease activity, Past or current presence of rheumatoid nodules was recorded as well as erosive/nonerosive disease in the last hands and feet radiographs. Laboratory tests included erythrocyte sedimentation rate (ESR) and positive RF according to the local reference values measured at any time over the disease course. Extra-articular disease was considered in the case of pulmonal fibrosis, pericarditis, vasculitis, Felty’s syndrome or scleritis.

Patient self-report questionnaire measures
Patients completed a 4-page self-report questionnaire, which included demographic data: date of birth, gender, years of formal education and smoking status, reported as “never smoked”, “currently
smoking” and “former smokers”. A standard Health Assessment Questionnaire (HAQ) (18) assessed physical function in activities of daily living with 4 response categories: 0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do. Visual analogue scales (VAS; 0 = best to 10 = worst) were completed for pain and patient estimate of his/her global health. Disease activity score (DAS28) was calculated from physician joint counts, ESR, and patient global estimate of health status (19).

The gross domestic product (GDP) of each country was obtained from a database of the International Monetary Fund and is expressed as 1000 United States dollars (USD) per capita (20). Countries were categorised as “high GDP” when their GDP per capita was >24K USD (16 countries), and “low GDP” countries those with a GDP per capita <11K USD (16 countries).

**Statistical methods**

Descriptive statistics concerning smoking status were calculated for men and women in each country. Analyses for demographic and ACR Core Data Set measures (swollen and tender joint count, pain, patient and doctor global assessment of disease activity, ESR, DAS28 and HAQ) as well as RF, nodules and number of DMARDs were performed according to smoking status. Statistical significance of possible differences was calculated using t-tests and chi-square tests for continuous and categorical variables respectively. Regression models were used to estimate a relationship between categorical variables, adjusted for age, sex, disease duration, and GDP.

The effect of smoking on DAS score index was also analysed by multilevel models, because data consist of clusters (observations on individuals are nested in countries). First, a variance components model with DAS28 and country was conducted to estimate the average value of DAS (constant), the different components of the variance and the intraclass correlation coefficient or percentage of DAS variability due to countries. Then, a full model was used with DAS28 value as a dependent variable and individual variables (smoking, age, sex, disease duration and number of DMARDs used) as independent variables. The constant was modelled by the country GDP plus a random component of the variance (constant). The use of DMARDs was similar in all smoking categories.

**Smoking status and disease activity**

Among the 7,307 patients with self-report information about smoking status, “never smoked,” “current smoker” and “ex-smokers” was reported by 71.5%, 12.4% and 16.0% of women, and 39.0%, 25.1% and 35.8% of men, respectively. The frequency of ever smoked ranged between 68% in Canada to 4% in Egypt (Table I). Apart from male sex, smokers were older, with higher education levels and from high GDP countries (Table II). The percentage of never smoked women was higher in low GDP countries (80.4%) than in high GDP countries (63.7%) (p<0.001).

**Smoking status and disease severity**

RF and nodules were more frequent in ever smokers (OR 1.32;1.17–1.48 and 1.41;1.24–1.59 respectively). The percentage of nodules was 10 in RF-negative patients and independent of smoking status. However, this figure was 28.3% in RF-positive male smokers versus 23.6% in non-smokers (25.6% vs. 19.9% in females). Nodules were also more frequent in current versus former smokers (Table II). The frequency of patients with erosive arthritis and extra-articular disease was similar in all smoking categories.

The use of DMARDs was similar in all smoking categories (Table I; Fig. 1).

**Smoking status and disease activity**

In univariate models, never smokers had higher disease activity compared to those who ever smoked according to all

<table>
<thead>
<tr>
<th>Country</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
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<td>42</td>
</tr>
<tr>
<td>Brazil</td>
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<td>14</td>
</tr>
<tr>
<td>Canada</td>
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<tr>
<td>Denmark</td>
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<td>Egypt</td>
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<td>Finland</td>
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<tr>
<td>France</td>
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<td>11</td>
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<td>Hungary</td>
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<td>35</td>
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<tr>
<td>India</td>
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<tr>
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<td>9</td>
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<td>20</td>
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<td>20</td>
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<td>14</td>
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<td>UAE</td>
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<td>UK</td>
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</tr>
<tr>
<td>USA</td>
<td>42</td>
<td>24</td>
</tr>
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</table>

**Table I.** Smoking status per country and sex (%) in patients with rheumatoid arthritis in the multinational QUEST-RA database.
Smoking and QUEST-RA database / A. Naranjo et al.

7 Core Data Set measures: 28 swollen and tender joint count, physician global estimate, ESR, HAQ-function, pain, and patient global estimate, as well as DAS28 (Fig. 2). A higher DAS28 in never smokers was found both in RF positive RA and RF negative RA (p<0.001).

Multivariate models concerning disease activity and smoking status
In a regression model that included smoking status, age, sex, and disease duration as independent variables and DAS28 as the dependent variable, DAS28 was statistically significantly higher in never smokers (p<0.001). However, when GDP was included in the model, the effect of smoking on DAS28 disappeared. In regression models with each of the Core Data Set variables as a dependent variable, only ESR remained statistically significantly lower in ever smokers (Table II). The variance components model showed that country GDP was responsible for 26% of the variability of disease activity. The full model (random-intercept model) showed that the inclusion of the country economy causes the loss of effect of smoking on DAS28 (p=0.927) (Table III).

Discussion
Since 1987 we have known that cigarette smoking is a risk factor for RA, especially in men with RF-positive RA who are heavy smokers (4, 8, 21, 22). Later it was verified that the relation of smoking was more intense with the CCP, interacting with the shared epitope (2, 3, 23-26). Recently, an interaction between the polymorphisms in glutathione S-transferases and smoking in highly active RA has been observed (27). It is also known that smokers in the general population have an increased frequency of elevated RF (28).

In the present study we also found, as other authors (9-11, 29, 30), an association between smoking and nodules but exclusively in RF-positive smokers.

Table II. Smoking and disease characteristics in patients with rheumatoid arthritis in the multinational QUEST-RA database.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Never smoked</th>
<th>Ever smokers</th>
<th>Current smokers</th>
<th>Former smokers</th>
<th>p never vs. ever</th>
<th>p current vs. former</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>7307</td>
<td>4749</td>
<td>2558</td>
<td>1091</td>
<td>1467</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of patients</td>
<td></td>
<td>65</td>
<td>35</td>
<td>15</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), mean</td>
<td>55.17</td>
<td>54.6</td>
<td>56.2</td>
<td>53.0</td>
<td>58.5</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Women %</td>
<td>5773</td>
<td>71.5</td>
<td>28.5</td>
<td>12.4</td>
<td>16.0</td>
<td>&lt;0.001*</td>
<td>0.25*</td>
</tr>
<tr>
<td>Men %</td>
<td>1468</td>
<td>39.0</td>
<td>61.0</td>
<td>25.1</td>
<td>35.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients from countries with “High” Gross domestic product, %</td>
<td>4097</td>
<td>56.8</td>
<td>43.2</td>
<td>18.0</td>
<td>25.1</td>
<td>&lt;0.001*</td>
<td>0.19*</td>
</tr>
<tr>
<td>Patients from countries with “Low” Gross domestic product, %</td>
<td>3210</td>
<td>75.4</td>
<td>24.6</td>
<td>10.9</td>
<td>13.6</td>
<td>&lt;0.001*</td>
<td>0.24*</td>
</tr>
<tr>
<td>Education (years), mean</td>
<td>11.1</td>
<td>11.0</td>
<td>11.2</td>
<td>11.3</td>
<td>11.2</td>
<td>0.02**</td>
<td>0.24**</td>
</tr>
<tr>
<td>Disease duration (years), mean</td>
<td>10.9</td>
<td>11.9</td>
<td>10.3</td>
<td>9.0</td>
<td>11.3</td>
<td>0.002*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Positive rheumatoid factor %</td>
<td>74.3</td>
<td>72.5</td>
<td>77.7</td>
<td>78.6</td>
<td>77.1</td>
<td>&lt;0.001*</td>
<td>0.38*</td>
</tr>
<tr>
<td>Nodules %</td>
<td>19.4</td>
<td>17.5</td>
<td>23.0</td>
<td>25.5</td>
<td>21.2</td>
<td>&lt;0.001*</td>
<td>0.01**</td>
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<tr>
<td>Severe extraarticular disease %</td>
<td>6.5</td>
<td>6.6</td>
<td>6.7</td>
<td>5.7</td>
<td>7.4</td>
<td>0.88**</td>
<td>0.10**</td>
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<tr>
<td>Radiographic erosions %</td>
<td>61.4</td>
<td>62.1</td>
<td>60.2</td>
<td>58.6</td>
<td>61.5</td>
<td>0.14**</td>
<td>0.15**</td>
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<tr>
<td>Number of DMARDs, mean</td>
<td>2.6</td>
<td>2.5</td>
<td>2.6</td>
<td>2.5</td>
<td>2.7</td>
<td>0.05***</td>
<td>0.04***</td>
</tr>
<tr>
<td>TNF antagonists %</td>
<td>21.2</td>
<td>19.1</td>
<td>25.2</td>
<td>25.3</td>
<td>25.1</td>
<td>0.10***</td>
<td>0.84***</td>
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RA Core Data Set measures

<table>
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<th></th>
<th>All</th>
<th>Never smoked</th>
<th>Ever smokers</th>
<th>Current smokers</th>
<th>Former smokers</th>
<th>p never vs. ever</th>
<th>p current vs. former</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28-ESR, mean</td>
<td>4.2</td>
<td>4.4</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>0.28***</td>
<td>0.43***</td>
</tr>
<tr>
<td>Swollen joints, mean</td>
<td>4.2</td>
<td>4.3</td>
<td>4.0</td>
<td>4.1</td>
<td>3.9</td>
<td>0.09***</td>
<td>0.38***</td>
</tr>
<tr>
<td>Tender joints, mean</td>
<td>6.7</td>
<td>7.3</td>
<td>5.7</td>
<td>5.9</td>
<td>6.6</td>
<td>0.09***</td>
<td>0.64***</td>
</tr>
<tr>
<td>MD global, mean</td>
<td>2.9</td>
<td>3.0</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>0.24***</td>
<td>0.98***</td>
</tr>
<tr>
<td>ESR, mean</td>
<td>30.0</td>
<td>31.7</td>
<td>26.8</td>
<td>25.6</td>
<td>27.7</td>
<td>&lt;0.001*</td>
<td>0.19***</td>
</tr>
<tr>
<td>HAQ Function, mean</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.23***</td>
<td>0.42***</td>
</tr>
<tr>
<td>Pain, mean</td>
<td>4.1</td>
<td>4.1</td>
<td>3.9</td>
<td>4.0</td>
<td>3.8</td>
<td>0.09***</td>
<td>0.06***</td>
</tr>
<tr>
<td>Pt Global, mean</td>
<td>4.0</td>
<td>4.1</td>
<td>3.9</td>
<td>3.9</td>
<td>3.8</td>
<td>0.13***</td>
<td>0.06***</td>
</tr>
</tbody>
</table>

*aIncludes pulmonal fibrosis, pericarditis, vasculitis, Felty syndrome, and scleritis.
*T-test, **Chi square test, ***Adjusted by age, sex, disease duration and country gross domestic product

Fig. 1. Disease-modifying anti-rheumatic drugs (DMARD) use according to smoking status, sex, and gross domestic product (GDP). Countries were categorised as “high GDP”: GDP per capita >24K USD; and “low GDP”: GDP per capita <11K USD.
**Smoking and disease severity**

If it is clear that smoking intervenes somehow in the pathogenesis of the disease, controversy exists on the effect of tobacco use on disease activity and severity. In fact, several prospective studies have obtained conflicting results in this aspect. The effect of smoking on joint damage in Wolfe’s study (31) was only detected in patients with very long smoking exposure history, and in Saag’s cohort the association was driven by the association between RF and joint damage (9). Moreover, regarding radiological severity the results are conflicting, both in cross-sectional (9, 11, 28) and in prospective studies (12-14, 29). Two large prospective studies with arthritis of different disease duration suggested that cigarette smoking does not accelerate RA disease progression (13, 14).

However, in one of these studies more need of treatments in current smokers was observed (13). Moreover, RA patients with a history of heavy smoking seem to be more likely to show a poor response to TNF antagonists (32). However, another study shows that patients who continue taking their initial biologic medication have a similar smoking status to those requiring switching or discontinuation (33).

Regarding the association of smoking and extra-articular disease, conflicting results have been observed in a few studies (13, 15, 28, 34, 35). Finally, one paper showed association of cigarette smoking with interstitial lung disease (36).

**Smoking and disease activity**

The effect of smoking on DAS28 has been analysed in few research articles; in some it is concluded that smoking does not have an influence on DAS (13, 14), whereas in another an increase of DAS in current and former smokers was found (29). In the study by Westhoff et al. (13) those who stopped smoking after disease onset had the highest DAS28 when compared to never, former and current smokers. In our study patients who have never smoked appeared to have poorer clinical status than patients who smoked or discontinued smoking, but in a regression model the influence of smoking status on DAS28 was lost when GDP was included. In the multilevel analysis, the effect of country GDP on DAS28 was as high as 26%, and 11% in the adjusted model.

Female patients from low GDP countries have a more active arthritis. In fact, in two reported articles of QUEST-RA multinational database, women have poorer scores than men in all Core Data Set measures (37) and disease activity levels were higher in “low GDP” than in “high GDP” countries at much greater levels than according to whether patients were taking or not taking methotrexate, prednisone and/or biological agents (38). In our study the only activity measure that persisted significant after adjusting for GDP was the ESR, which was higher in never smoked, findings opposite to those reported in a few studies (13, 29).

**Smoking and pain**

Some authors postulate that smoking may simultaneously have two conflicting influences on disease outcome: a detrimental influence mediated by RF, and also a yet unexplained protective effect (14, 39). In fact, we did not find any association between the activity and severity of RA and smoking status. However, we cannot prove or disprove these two theories. When analysing a larger number of RA patients we could not find the association proven in small studies. On the other hand, several population studies have found a statistically significant association between current and former smoking and the prevalence, intensity and range of pain (40-43). However, results on pain tolerance of smokers and non-smokers are conflicting; in one study it was...
observed that nicotine had an effect on increase in pain threshold in men but not in women (44). In a mouse model of collagen-induced arthritis, neither smoking nor nicotine exposure aggravates development of arthritis; both were associated with a lower level of anti-collagen II antibodies and a delay of arthritis onset (45).

Regardless of the outcome of RA activity status in non-smokers, smokers, and former smokers, RA patients should still be strongly encouraged to stop smoking because of the known substantial effects of smoking on cardiovascular disease, additional to the known effects of longstanding disease activity on the cardiovascular system (46, 47).

**Limitations of our study**

A potential limitation of a cross-sectional analysis includes: first, left censoring (a probable higher mortality rate among smokers prior to acquisition of these data in a rheumatology clinic), and lack of ascertainment of data on pack-years. Second, a cross-sectional database does not allow us to establish a causal relationship between exposure and outcome. Third, we do not have a detailed radiographic damage score given that we only gathered information for the presence or absence of erosions in last available x-rays. Fourth, anti-CCP status was not available in all the participating centres.

**Conclusion**

RA patients who had ever smoked were more likely to have positive RF and nodules, but values for other clinical status measures were similar in all smoking categories (never smokers, current smokers and former smokers). Though we have not found differences in disease activity and severity of RA and our data cannot confirm this assertion, it must be remembered that cigarette smoking is harmful to the health, not only increasing the risk of RA but also increasing the risk of cardiovascular disease (already raised in RA), bronchitis and cancer.

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References


13. Westhoff G, Rai R and Zink A: Rheumatoid arthritis patients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers of the same serological group. Rheumatology 2008; 47: 849-54.


25. Morgan AW, Thomson W, Martin SG et al.: Reevaluation of the interaction between HLA-DRB1 shared epitope alleles, PTNP22, and smoking in determining susceptibility to autoantibody-positive and autoantibody-negative rheumatoid arthritis in a large UK population.
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