

Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis

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Abstract

Objectives. Smokers have an increased incidence of rheumatoid factor (RF) and rheumatoid arthritis (RA) and one report has also indicated that smoking may also adversely influence the severity of RA.

Methods. Sixty-three women with advanced RA answered a structured questionnaire that included detailed information about their smoking history. The women were also evaluated clinically and radiologically.

Results. Heavy smoking (≥ 20 pack-yr) was associated with rheumatoid nodules ($P = 0.01$), a higher HAQ score ($P = 0.002$) and a lower grip strength ($P = 0.01$). Smoking was also associated with more radiological joint damage ($P = 0.02$). A positive correlation was observed between smoking and RF levels, in particular IgA RF and a combined elevation of IgM and IgA RF.

Conclusions. Smoking has an adverse effect on disease progression in patients with RA. An association was also observed between smoking and those RF types that predispose to RA and have the highest diagnostic specificity for this disease.

KEY WORDS: Smoking, Rheumatoid arthritis, Rheumatoid factor, Prognosis.

The cause of rheumatoid arthritis (RA) is unknown, but several interactive factors are believed to play a role, including genetic constitution and environmental agents. Smoking may be an important environmental factor. It is known that smoking influences the immune system but its overall effect is not fully understood [1]. However, studies have shown that smokers have an increased incidence of raised rheumatoid factor (RF) [2, 3] and of RA [4–8]. A Finnish population study indicated that raised RF was found twice as often in both current and ex-smokers than in non-smokers, and the proportion of smokers increased with increasing RF titre [4]. In monozygotic twins discordant for RA, smoking has been reported to be more common amongst the affected twin [7]. Furthermore, a recent report suggests that smoking may adversely affect the prognosis of RA patients [9]. Studies on the association between smoking, RF and RA have been based on agglutination tests which preferentially detect IgM RF. However, a prospective population study in Iceland has shown that individuals who only have raised IgM RF do not have increased prevalence of RA compared with RF-negative controls [10]. Studies have also shown that IgA RF is more closely associated with RA, especially when found in combina-

tion with IgM RF [11, 12]. Furthermore, IgA RF has been associated with an unfavourable prognosis in RA [13–16].

To our knowledge, the association between smoking and disease severity in RA patients has not been analysed before in the context of the IgA RF isotype, which is characteristically raised in patients with severe RA.

Materials and methods

Patients

Sixty-three women with RA according to the 1987 American College of Rheumatology criteria gave informed consent and were recruited for the study. They were all attending the rheumatology out-patient clinic at the University Hospital in Reykjavík. Their mean age was 57.7 yr (range 24–77) and the mean disease duration was 13.7 yr (range 5–27).

The patients answered a structured questionnaire about their disease, drug treatment for RA, co-morbid conditions and relevant sociodemographic factors, including education and social class. A detailed smoking history was obtained and smoking was quantified in pack-yr for all former and current smokers. The patients were evaluated clinically by a rheumatologist and by a specially trained physician who did not know about their smoking history. The numbers of swollen joints, rheumatoid nodules and joint deformities and grip

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strength were recorded, and functional impairment was evaluated by the Stanford Health Assessment Questionnaire (HAQ) [17].

Radiographic evaluation

Radiographs of hands were available for 61 (97%) of the participants. New radiographs were obtained for those patients who had not been evaluated radiographically for more than 3 yr prior to the study or who had been radiographically evaluated only within 3 yr after the onset of their disease. Three patients who did not fulfil these criteria were included in the analysis as their exclusion did not have any effects on the results.

The films were examined by an experienced radiologist who did not have access to the clinical data or the smoking history of the participants. The joint changes were interpreted quantitatively according to the criteria recommended by Sharp *et al.* [18] as modified by Kaye *et al.* [19], allowing a maximum score of 168 for both hands. A total score below 20 was not considered to represent significant RA-associated joint damage, scores from 20 to 49 indicated mild but definite damage, scores from 50 to 99 moderate damage, and scores of 100 or more severe damage. Scoring was carried out twice and the recorded findings were highly consistent.

RF isotypes

Blood samples were collected for RA measurement by an enzyme-linked immunosorbent assay (ELISA) system described in detail elsewhere [20]. Briefly, microtitre plates were coated with rabbit IgG (40 µg/ml) at 4°C for 24 h. The test samples were diluted 1/20 and an in-house standard that had been calibrated against an International Reference Preparation (Statens Serum Institute, Copenhagen, Denmark) and given a value of 100 arbitrary units (AU) for each RF isotype, was included in each test run. This standard was diluted 4-fold from 1/40 to 1/2560. Aggregated rabbit IgG was used in order to block any free IgG binding sites on RF bound to the solid phase. Monoclonal antibodies (anti-human IgM, IgG and IgA) labelled with alkaline phosphatase were used to detect the RF bound to the solid phase, and the colour reaction was developed using a *p*-nitrophenylphosphate substrate solution. Absorbance was read when the 1/40 dilution of the standard had reached about 1.5 at 405 nm. The mean absorbance for each triplicate was calculated in AU from the linear part of the curve derived from the dilutions of the in-house standard. Values above the upper 95% cut-off level (≥ 25 AU/ml) for 200 normal adults were considered elevated for each RF isotype.

Analysis of the findings

The clinical findings were evaluated and the radiographs assessed without knowledge of the patients' smoking history and RF results. The results are expressed as medians with 25th and 75th percentiles. Differences between groups were evaluated by the χ^2 test with Yates' correction for expected frequencies less than five. The Spearman rank correlation and the Mann-Whitney rank

sum test were used when appropriate. The level of significance was set at $P < 0.05$.

Results

As shown in Table 1, there were no marked differences in age, disease duration or treatment of the patients in relation to the different smoking categories that were analysed. The patients who had never smoked were younger than the current or ex-smokers but the difference was not significant. The groups were also comparable with respect to other relevant sociodemographic factors.

Smoking and clinical findings

A non-significant trend of increasing disease severity was observed when non-smokers, moderate and heavy smokers (≥ 20 pack-yr) were compared. Current smokers tended to have less grip strength ($P = 0.04$) and a higher HAQ score ($P = 0.11$) than patients who had never smoked (data not shown). However, heavy smokers (≥ 20 pack-yr) had rheumatoid nodules significantly more often and more functional impairment, as measured by grip strength and HAQ, than those who had smoked less or not at all, and the heavy smokers also had significantly more radiological joint damage (Table 2). Patients who smoked at the onset of their RA also tended to be more severely affected than those who did not smoke when their disease began, and this was significant for rheumatoid nodules (Table 3).

Smoking and RF isotypes

Only 51% of this cohort had a raised level of one or more RF isotypes. It should be noted in this context that most of the patients had been treated with disease-modifying drugs, including methotrexate, which had been used by about two-thirds of the patients (Table 1). Thirty patients had elevated IgM RF, 26 elevated IgA RF and six elevated IgG RF, and a combined elevation of IgM and IgA RF was detected in 24 of the patients. There was a significant positive correlation between the number of pack-yr and the levels of IgM RF and IgA RF, but not of IgG RF or the total amounts of each immunoglobulin class (Table 4). Those who smoked when their RA began also had higher levels of IgM RF ($P = 0.03$) and IgA RF ($P = 0.01$), and they also more often had a combined elevation of IgM and IgA RF ($P = 0.005$) (data not shown).

Discussion

Our findings indicate that females who are heavy smokers (≥ 20 pack-yr) develop more severe RA than women who smoke less or not at all. Heavy smoking also appears to stimulate the production of IgM and IgA RF, which characterize severe RA [11, 12]. Active smoking at the onset of RA also seemed to have an adverse effect on the progression of the disease and to promote the production of IgM and IgA RF regardless of whether smoking was discontinued after RA was

TABLE 1. Age, disease duration and treatment of the patients in relation to their smoking history

Smoking history	Age ^a (yr)	Disease duration ^b (yr)	Treatment			
			MTX	Corticosteroids	Other DMARDs	NSAIDs only
Never smoked (<i>n</i> = 22)	56 (42–63)	10 (7–17)	15 (68%)	4 (18%)	11 (50%)	4 (18%)
Ex-smokers (<i>n</i> = 21)	64 (48–72)	16 (8–21)	14 (67%)	7 (33%)	9 (43%)	2 (10%)
Current smokers (<i>n</i> = 20)	63 (52–70)	10 (5–16)	12 (60%)	4 (20%)	8 (40%)	3 (15%)
Smoking < 20 pack-yr (<i>n</i> = 43)	59 (44–68)	10 (7–19)	28 (65%)	9 (21%)	20 (47%)	8 (18%)
Smoking ≥ 20 pack-yr (<i>n</i> = 20)	63 (52–70)	13 (8–19)	13 (65%)	6 (30%)	8 (40%)	1 (5%)
Not smoking at RA onset (<i>n</i> = 35)	59 (47–69)	15 (7–20)	23 (66%)	7 (20%)	17 (49%)	6 (17%)
Smoking at RA onset (<i>n</i> = 28)	62 (50–69)	10 (6–16)	18 (65%)	8 (29%)	11 (39%)	3 (11%)

All differences between groups were statistically non-significant ($P > 0.05$).

^aMean (range).

^bMedian (interquartile range).

MTX, methotrexate; DMARDs, disease-modifying anti-rheumatic drugs, including gold, hydroxychloroquine, salazopyrin and CPH-82 (Reumacon™); NSAIDs, non-steroidal anti-inflammatory drugs.

TABLE 2. Relationship between the amount of smoking and disease severity measures

	Smoking (pack-yr)		Significance
	< 20 (<i>n</i> = 43)	≥ 20 (<i>n</i> = 20)	
Rheumatoid nodules	16%	45%	$P = 0.01$
Joint damage (X-rays) ^{a,b}	24 (6–88)	62 (16–103)	$P = 0.02$
Swollen joints (areas) ^a	2 (0–4)	3 (1–4)	NS
Loss of functional ability (HAQ) ^a	0.5 (0.1–1.0)	1.1 (0.8–1.6)	$P = 0.002$
Grip strength ^a	98 (60–147)	70 (39–96)	$P = 0.01$

^aMedian (interquartile range).

^bRadiographic score.

NS, not significant.

TABLE 3. Disease severity measures in relation to smoking at disease onset

	Smoking at disease onset		Significance
	Yes (<i>n</i> = 28)	No (<i>n</i> = 35)	
Rheumatoid nodules	39%	14%	$P = 0.02$
Joint damage (X-rays) ^{a,b}	50 (16–100)	27 (5–88)	NS
Swollen joints (areas) ^a	3 (0–4)	2 (1–4)	NS
Loss of functional ability (HAQ) ^a	0.9 (0.4–1.3)	0.5 (0.2–1.1)	$P = 0.11$
Grip strength ^a	86 (58–124)	91 (55–149)	NS

^aMedian (interquartile range).

^bRadiographic score.

NS, not significant.

diagnosed. Our study cohort was not sufficiently large to allow analysis of certain confounding variables or the timing of smoking in relation to disease onset and prognosis. The smokers could therefore be analysed only in terms of the total number of pack-yr and whether the participants smoked when their RA was diagnosed. The association between smoking, disease severity and RF cannot be explained by differences in age, disease duration or treatment.

Several studies have indicated that smokers have increased prevalence of RA [4–8]. Furthermore, one recent study has indicated that smoking may also increase disease severity in RA patients [9]. Our study confirms and extends this observation, as heavy smoking

TABLE 4. Correlations between RF isotypes, age, disease duration and smoking

	Spearman's rank correlation	Significance
IgM RF vs pack-yr	$r = 0.32$	$P = 0.04$
IgG RF vs pack-yr	$r = 0.21$	NS
IgA RF vs pack-yr	$r = 0.35$	$P = 0.03$
Total IgM vs pack-yr	$r = 0.09$	NS
Total IgG vs pack-yr	$r = -0.03$	NS
Total IgA vs pack-yr	$r = -0.21$	NS
Age vs pack-yr	$r = 0.17$	NS
Disease duration vs pack-yr	$r = 0.009$	NS

NS, not significant.

in our cohort was associated not only with rheumatoid nodules and radiological joint damage but also with significantly more functional impairment (HAQ score) and less grip strength. Moreover, a correlation was observed between smoking and increases in the levels of those RF isotypes that are characteristic of severe RA [13, 15]. Although inaccurate recall of smoking history is a potential source of misclassification in cross-sectional studies [21], it is difficult to see how this could cause a bias towards a positive association between smoking and RA severity as well as raised levels of those RF isotypes that are preferentially found in RA patients with an unfavourable prognosis [11–16]. However, the association between smoking and IgM and IgA RF was significant but not very strong ($P = 0.04$ and 0.03 respectively).

It is now well established that smokers have an increased prevalence of raised RF [2, 3], in particular those isotypes that are associated with RA [12], and various other effects of smoking on the immune system have been reported. Thus, production of interleukin 4 has been reported to be increased in smokers [22], and smokers have also been found to have a decreased $CD4^+/CD8^+$ T-cell ratio [23]. However, further studies are required to elucidate the mechanisms whereby smoking triggers and aggravates RA, and the potential confounding variables.

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