Effect of Smoking on Remission Proportions Differs Between Male and Female Patients with Rheumatoid Arthritis: A Study Based on the IORRA Survey

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ABSTRACT. Objective. To analyze sex difference in the effect of smoking on remission proportions in patients with rheumatoid arthritis (RA).

Methods. Subjects were Japanese patients with RA who participated in the IORRA survey conducted in April 2011 and reported smoking status. Clinical characteristics, treatment status, and the percentages achieving remission were compared between subjects stratified by sex and smoking status. To confirm the differential effects of sex and smoking status on remission, we used multivariate logistic regression models with the dependent variable as 28-joint Disease Activity Score (DAS28) remission.

Results. Among 810 men and 4206 women, 162 (20.0%) and 3173 (75.4%), respectively, were never smokers; 208 (25.7%) and 314 (7.5%), respectively, were current smokers. In men, never smokers tended to have higher remission proportions than past and current smokers. In contrast, smoking status seemed not to affect remission in women. Except for lower corticosteroid dose in male never smokers, no significant differences were observed in comparing treatment status. By multivariate analyses, male past and current smokers were negatively associated with DAS28-erythrocyte sedimentation rate remission compared to male never smokers [OR 0.66 and 0.61, 95% CI (0.44–0.98) and (0.39–0.96), respectively]. However, female past and current smokers were not associated with remission compared to female never smokers [OR 1.04 and 1.19, 95% CI (0.86–1.25) and (0.91–1.54), respectively].

Conclusion. We demonstrated that the effect of smoking on remission proportions differed between men and women. Our findings suggest that both sex and smoking status are important considerations when planning a treatment strategy for patients with RA.

Key Indexing Terms:
RHEUMATOID ARTHRITIS   SMOKING   SEX DIFFERENCES   DISEASE ACTIVITY   REMISSION

It is well known that rheumatoid arthritis (RA) has a strong sex bias, which accounts for differences between men and women in important disease aspects such as incidence rates, clinical characteristics and outcomes, and mortality rates. Several studies have shown that male patients with RA respond more favorably to treatment than female patients. In a large observational cohort study of Japanese patients with RA, we also observed that female patients exhibited more progressive functional disability compared to males.

Smoking is the greatest known environmental risk factor for developing RA. The interaction between smoking and genetic factors can potentially trigger the production of citrullinated proteins in the lung prior to clinical synovitis. Smoking has also been associated with the formation of rheumatoid nodules, rheumatoid factor (RF) positivity, and radiographic progression. Further, smokers with RA in several studies have demonstrated poorer therapeutic response.

Although smoking adversely affects treatment response in RA, whether the effect of smoking on RA disease activity differs between men and women has not been fully investigated. Thus, this cross-sectional study aimed to evaluate the effects of smoking on treatment status and remission proportions, and to examine the effect of the interaction between sex and smoking status on remission proportions in Japanese patients with RA.

MATERIALS AND METHODS
IORRA cohort. The IORRA (Institute of Rheumatology, Rheumatoid Arthritis) cohort is a large observational cohort of patients with RA seen in daily practice at the Institute of Rheumatology, Tokyo Women’s Medical

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RESULTS

Data on smoking status, age, disease duration, J-HAQ score, CRP, and each item of the DAS28-ESR were available for 5016 of 5356 (93.6%) patients with RA. Figure 1 shows the numbers and proportions of patients with RA in each category of smoking status stratified by sex and decade of age. As shown in Figure 2, 3335 patients (66.5%) were never smokers, 522 (10.4%) were current smokers, and 1159 patients (23.1%; 440 males and 719 females) were past smokers. More than 95% (3173/3335) of never smokers and nearly 60% (314/522) of current smokers were female (Figure 2A). Of the 5016 patients, 162 of the 810 males (20.0%) and 3173 of the 4206 females (75.4%) were never smokers; 208 males (25.7%) and 314 females (7.5%) were current smokers (Figure 2B).

Table 1 displays the characteristics of 370 male and 3487 female patients stratified by smoking status. Among the men, significant differences were observed in age (p < 0.01), DAS28-ESR scores (p < 0.05), SDAI scores (p < 0.05), serum CRP levels (p < 0.05), and ESR levels (p < 0.01). In women, significant differences were observed in age (p < 0.01), disease duration of RA (p < 0.01), ESR levels (p < 0.01), and J-HAQ scores (p < 0.05); however, scores for DAS28-ESR, CDAI, and SDAI showed no significant difference. In both sexes, serum RF levels were the highest in current smokers and the lowest in never smokers. In examining the treatment status, we saw that the proportions of MTX users, corticosteroid users, and biologic users did not differ significantly in either sex (Table 1). The median doses of MTX were also comparable for both men and women. The dose of corticosteroid showed significant difference in male patients (p < 0.05); the median doses of corticosteroid in male never smokers were lower than in past and current smokers.

Figure 3 shows the proportions of patients achieving remission based on the DAS28-ESR, SDAI, CDAI, and Boolean-based remission criteria for clinical trials. Among men, never smokers tended to have higher remission proportions compared to past smokers, and past smokers tended to have higher remission proportions than current smokers. In contrast, smoking status seemed not to affect remission in women regardless of remission criteria. To test differential effects of sex and smoking status on remission, logistic regression analyses were performed. In the initial model analysis, smoking status was associated with DAS28-ESR remission (p < 0.001). We picked up the confounders in this order: J-HAQ, RF positivity, BMI, and biologics use. Deviance analysis showed a significant association of the interaction of sex and smoking status (p = 0.03). Table 2 showed that male never smokers had the highest DAS28-ESR remission proportion, but female never smokers showed no significant difference in DAS28-ESR remission proportion compared to female past and current smokers, after adjusting by confounders. For secondary endpoints,
deviance analyses showed no significant relationships with the interaction term of sex and smoking status (Boolean: 0.51, CDAI remission: 0.07, SDAI remission: 0.16).

**DISCUSSION**

In our study, our examination of smoking status in a large cohort of Japanese patients with RA led to several important clinical observations. As shown in Figure 1, age-specific proportions of never smokers in patients with RA were much higher in women than in men. This difference is not just limited to patients with RA; this is a characteristic feature of Japanese smoking culture. Male patients in each smoking status were more likely to have lower disease activity scores in all the composite measures than female patients (Table 1), and male never smokers tended to show higher remission proportions than past and current male smokers (Figure 3). These results might be affected by the presence of less active disease among men, or the instruments might privilege male patients in terms of disease activity. Except for corticosteroid dose, which showed significant difference according to smoking status in male patients, treatment status did not significantly differ according to smoking status in either sex (Table 1).
1). In multivariate analysis, the effects of smoking on remission proportions differed between men and women (Table 2). Both past and current smoking compared to never smoking were negatively associated with DAS28-ESR remission for male patients, whereas no association was observed for women. Together, these findings suggest that smoking may affect male and female patients with RA differently.

Several studies have cited smoking as a poor predictor of remission in patients with RA. Forslind, et al evaluated 678 patients with early RA mostly treated with nonbiologic disease-modifying antirheumatic drugs and determined that current smoking was an independent negative prognostic factor for DAS28-ESR remission after 5 years². In an analysis of 1612 patients with RA treated with infliximab,

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**Table 1.** Difference of demographic and clinical features or treatment status according to smoking status. Results are percentages or medians (interquartile range) and compared separately for each sex.

<table>
<thead>
<tr>
<th></th>
<th>Never Smokers, n = 162</th>
<th>Male, n = 810</th>
<th>Past Smokers, n = 440</th>
<th>Current Smokers, n = 208</th>
<th>Never Smokers, n = 3173</th>
<th>Female, n = 4206</th>
<th>Past Smokers, n = 719</th>
<th>Current Smokers, n = 314</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>63.2 (48.6, 72.8)</td>
<td>65.6 (58.8, 72.1)</td>
<td>61.6 (54.4, 68.1) †</td>
<td>62.3 (51.7, 69.6)</td>
<td>59.2 (50.0, 66.5)</td>
<td>56.7 (47.5, 64.0) †</td>
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<tr>
<td>Disease duration, yrs</td>
<td>10 (5, 17)</td>
<td>11 (6, 18)</td>
<td>10 (5, 16.8)</td>
<td>13 (6, 20)</td>
<td>10 (6, 16)</td>
<td>10.5 (5, 16)</td>
<td></td>
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<tr>
<td>BMI, kg/m²</td>
<td>22.9 (21.0, 25.1)</td>
<td>22.9 (20.9, 24.5)</td>
<td>22.6 (20.6, 24.6)</td>
<td>20.7 (19.1, 22.6)</td>
<td>20.8 (19.1, 23.1)</td>
<td>20.5 (18.8, 22.6)</td>
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<tr>
<td>DAS28-ESR</td>
<td>2.33 (1.67, 3.10)</td>
<td>2.62 (1.89, 3.48)</td>
<td>2.61 (1.62, 3.49) *</td>
<td>3.03 (2.33, 3.77)</td>
<td>3.03 (2.27, 3.83)</td>
<td>2.85 (2.17, 3.62)</td>
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<tr>
<td>CDAI</td>
<td>3.6 (1.6, 9)</td>
<td>3.8 (1.3, 7.4)</td>
<td>5.1 (1.9, 8.2)</td>
<td>5.3 (2.03, 9.3)</td>
<td>5.5 (2.2, 9.8)</td>
<td>5.1 (2, 8.8)</td>
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<tr>
<td>SDAI</td>
<td>3.9 (1.1, 7.2)</td>
<td>4.3 (1.6, 8.6)</td>
<td>5.3 (2.1, 9.4) *</td>
<td>5.6 (2.3, 9.9)</td>
<td>5.8 (2.4, 10.3)</td>
<td>5.4 (2.1, 9.5)</td>
<td></td>
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<tr>
<td>TJC28</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
<td>0 (0, 2)</td>
<td>0 (0, 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SJ28</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
<td>0 (0, 2)</td>
<td>0 (0, 2)</td>
<td>1 (0, 2)</td>
<td></td>
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<tr>
<td>PtGA, VAS, mm</td>
<td>15 (4, 42)</td>
<td>17 (6, 40)</td>
<td>21 (6, 46)</td>
<td>23 (8, 50)</td>
<td>24 (8, 52)</td>
<td>22 (8, 43)</td>
<td></td>
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<tr>
<td>CRP, mg/dl</td>
<td>0.14 (0.05, 0.65)</td>
<td>0.26 (0.07, 0.85)</td>
<td>0.26 (0.08, 0.9) *</td>
<td>0.13 (0.04, 0.51)</td>
<td>0.12 (0.04, 0.5)</td>
<td>0.11 (0.04, 0.45)</td>
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<tr>
<td>ESR, mm/h</td>
<td>12.5 (6, 26)</td>
<td>19 (9.0, 38)</td>
<td>16 (6, 43) †</td>
<td>24 (14, 40)</td>
<td>22 (12, 39)</td>
<td>20 (11, 33)</td>
<td></td>
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<tr>
<td>RF, IU/ml</td>
<td>22.5 (4, 76)</td>
<td>51.5 (15.8, 165.5)</td>
<td>93 (21.5, 362.5) †</td>
<td>44 (16, 104)</td>
<td>63 (21.5, 186.5)</td>
<td>77 (22, 217)</td>
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<tr>
<td>J-HAQ</td>
<td>0 (0, 0.63)</td>
<td>0.13 (0, 0.63)</td>
<td>0.13 (0, 0.5)</td>
<td>0.5 (0, 1.25)</td>
<td>0.5 (0, 1.13)</td>
<td>0.38 (0, 1)</td>
<td></td>
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</tr>
<tr>
<td>MTX use (%)</td>
<td>69.8</td>
<td>65.9</td>
<td>73.1</td>
<td>72.1</td>
<td>72.5</td>
<td>76.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid use (%)</td>
<td>34.6</td>
<td>43.6</td>
<td>37.5</td>
<td>38.0</td>
<td>39.9</td>
<td>38.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologics use (%)</td>
<td>9.9</td>
<td>12.3</td>
<td>9.1</td>
<td>15.4</td>
<td>16.7</td>
<td>12.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX dose, mg/week</td>
<td>7.85</td>
<td>8 (6, 10)</td>
<td>8 (6, 10)</td>
<td>8 (6, 10)</td>
<td>8 (6, 10)</td>
<td>8 (6, 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid dose, PSL equivalent, mg/day</td>
<td>2.75 (2, 5)</td>
<td>4 (2,225, 5)</td>
<td>4 (2, 5) *</td>
<td>3.1 (2, 5)</td>
<td>3 (2, 5)</td>
<td>3.9 (2,15, 5)</td>
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</tr>
</tbody>
</table>

* p value < 0.05. † p < 0.01 by Kruskal-Wallis test or chi-squared test. BMI: body mass index; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; TJC: tender joint count; SJC: swollen joint count; PtGA: patient’s global assessment; VAS: visual analog scale; CRP: C-reactive protein; RF: rheumatoid factor; J-HAQ: Japanese Health Assessment Questionnaire; MTX: methotrexate; PSL: prednisolone.

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**Figure 3.** Sex difference in remission proportions according to smoking status. N: never smokers; C: current smokers; P: past smokers; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; Boolean trial: Boolean-based remission criteria for clinical trials.
were shown, but no significant relationships were found for
and DAS28-ESR remission proportion (primary outcome)
strated statistically significant differences in multivariate
analysis.
was considered small. Moreover, our study also demon-
data were minimal, and thus patient selection bias, if any,
in our study, 5016 (93.6%) had complete datasets. Missing
reported in Saevarsdottir,
sectional design, our sample size was larger than that
males compared to females. Although we used a cross-
months. Female non-current smokers also experienced
were predictive of a good response to MTX after 3 to 4
found that male, non-current smokers and low HAQ score
compared to males. Variations in smoking intensity may be
pack-year history, they may be affected less by smoking
subjects (5.3 vs 2.96, respectively), current smokers showed
significantly higher values of ESR, TJC, and SJC than never
smokers after MTX treatment, although sex difference was
not considered19. As management of RA has improved over
the last 10 years, disease activity of patients has gradually
decreased in clinical practice32,33. It is important information,
therefore, that the interaction of sex and smoking status was
significantly associated with whether clinical remission is
achieved, even in patients with lower disease activity.
RF production has been reported to be associated with smoking34,35. Serum levels of RF were significantly associ-
ated with smoking status in both males and females in our
study. These findings were consistent with previous reports10,11,14,18,36,37. Therapies including the use of
anti-tumor necrosis factor (TNF) drugs have been reported to
influence the remission proportions of patients with RA38.
In our study, patients were treated based on individual disease
activity, comorbidities, and to some extent, the physician’s
own protocol. However, in comparing treatment in each
smoking status by sex, no significant differences were
observed except for lower corticosteroid dose in male never
smokers. This finding suggests that treatment status did not
account for the sex differences observed regarding the effect
of smoking.
In our present study, we identified sex differences regarding the effect of smoking on RA remission. The impor-
tance of these differences and the underlying mechanisms
contributing to these differences remain unclear because we
could not fully address these issues in this cross-sectional
observational study. However, because RA seems to be a
highly heterogeneous disease,9,39,40 it is reasonable that male
and female smokers displayed different phenotypes, and that
this difference could contribute to apparent differences in
remission proportions, particularly in patients who exhibit
relatively mild disease activity.
There are some limitations to our study. First, we did not
consider pack-year smoking history or the time since quitting
smoking. If female current and past smokers have a lower
pack-year history, they may be affected less by smoking
compared to males. Variations in smoking intensity may be
an important factor to consider when evaluating the effect of
smoking on disease activity. Mattey, et al reported that the
intensity of previous smoking was associated with poor
response to TNF antagonists for patients with RA15.
Westhoff, et al showed that nonsmokers and those with < 20
pack-years had a better treatment response than heavy

Table 2. OR for DAS28 remission according to sex and smoking status, adjusted by the confounders. OR were described by using the references of male never smokers and female never smokers, which were calculated from the same logistic regression model.

<table>
<thead>
<tr>
<th>Reference: Male Never</th>
<th>Reference: Female Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male past 0.66 (0.44–0.98)</td>
<td>Male never 2.13 (1.48–3.07)</td>
</tr>
<tr>
<td>Male current 0.61 (0.39–0.96)</td>
<td>Male past 1.40 (1.12–1.75)</td>
</tr>
<tr>
<td>Female never 0.47 (0.33–0.67)</td>
<td>Female current 1.19 (0.91–1.54)</td>
</tr>
<tr>
<td>Female past 0.49 (0.33–0.72)</td>
<td>Female past 1.04 (0.86–1.25)</td>
</tr>
<tr>
<td>Female current 0.56 (0.36–0.86)</td>
<td>Female current 1.19 (0.91–1.54)</td>
</tr>
</tbody>
</table>

The confounders adjusted for in the analysis included the Japanese Health Assessment Questionnaire scores, rheumatoid factor positivity, body mass index, and biologics use.

Hyrich, et al noted that current smoking was an independent negative predictor for higher European League Against Rheumatism (EULAR) response at 6 months12. Despite the cross-sectional design of our present study, our results were consistent with those of previous longitudinal studies showing that male patients who never smoked had better remission proportions than current smokers.

Ours is the largest study to date, to our knowledge, examining the influence of sex on the effect of smoking on remission proportions among patients with RA, and it is the first study showing the sex differences of the smoking effect by multivariate analysis. Sex differences in the effect of smoking were investigated previously by Saevarsdottir, et al, who analyzed a smaller population of 487 patients with early RA treated with MTX monotherapy30. The study found that male, non-current smokers and low HAQ score were predictive of a good response to MTX after 3 to 4 months. Female non-current smokers also experienced higher remission proportions than female current smokers, although statistical significance was not reported. Our results were similar to these longitudinal findings regarding the larger effect of smoking on disease activity observed in males compared to females. Although we used a cross-sectional design, our sample size was larger than that reported in Saevarsdottir, et al. Of the 5356 RA participants in our study, 5016 (93.6%) had complete datasets. Missing data were minimal, and thus patient selection bias, if any, was considered small. Moreover, our study also demonstrated statistically significant differences in multivariate analysis.

In men, significant associations between smoking status and DAS28-ESR remission proportion (primary outcome) were shown, but no significant relationships were found for secondary endpoints (SDAI, CDAI, and Boolean trial). This is presumably due to the larger weight on ESR in DAS28 than in the other instruments31, and the relatively low disease activity in our subjects. With regard to measures of remission in our male subjects, significant differences according to smoking status were observed in CRP and ESR levels but not in TJC28, SJC28, and PtGA score. In the previous study to determine smoking influences on treatment response in RA patients with higher median DAS28-ESR score than our subjects (5.3 vs 2.96, respectively), current smokers showed significantly higher values of ESR, TJC, and SJC than never smokers after MTX treatment, although sex difference was not considered19. As management of RA has improved over the last 10 years, disease activity of patients has gradually decreased in clinical practice32,33.
smokers. However, in another study, high smoking intensity did not predict poor EULAR response at 6 or 12 months in patients with RA treated with their first anti-TNF drug, although heavy smokers had the poorest drug survival. Therefore, if smoking intensity in male subjects in our present study was higher than that in female subjects, this difference may not necessarily account for sex differences of remission proportions. A second limitation is that we did not evaluate HLA-shared epitopes (SE) and anticitrullinated protein antibodies (ACPA), representative factors associated with both smoking and RA risk. Although genetic factors cannot be examined in daily practice, Mollenar, et al and Saevarsdottir, et al reported that HLA SE were not associated with persistent remission or treatment response. The relationship between ACPA and the effect of smoking on disease activity should be evaluated longitudinally in future studies. A third limitation is that we did not consider sociological differences between the sexes. Sociological status should be included in future studies because it is an important factor associated with smoking status and intensity and has implications for etiology and the natural history of autoimmune diseases.

This is the first study, to our knowledge, to demonstrate a significant sex difference in the effect of smoking on remission proportions by multivariate analysis. In men, past and current smoking compared to never smoking were negatively associated with DAS28-ESR remission, whereas no association between smoking status and remission was observed in women. A careful assessment is still needed because smoking or sex are not the only risk factors for remission, and the problem remains unresolved whether male never smokers have better response to RA treatment or are simply underestimated by disease activity assessment instruments used in our study. However, our findings suggest that both sex and smoking status should be considered when developing a treatment strategy for patients with RA. Further longitudinal research is warranted to determine the influence of sex differences on the effect of smoking on RA treatment response.

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