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Smoking–gender interaction and risk for rheumatoid arthritis

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Abstract

The present case–control study was conducted to investigate the relationship between smoking and rheumatoid arthritis, and to investigate formally the interaction between sex, smoking, and risk for developing rheumatoid arthritis. The study was performed in the Central District of Finland. Cases were patients with rheumatoid arthritis and the control group was a random sample of the general population. Logistic regression models were used to evaluate the effect of smoking on risk for rheumatoid arthritis, after adjusting for the effects of age, education, body mass index, and indices of general health and pain. Overall, 1095 patients with rheumatoid arthritis and 1530 control individuals were included. Patients were older, less well educated, more disabled, and had poorer levels of general health as compared with control individuals (all $P<0.01$). Preliminary analyses revealed the presence of substantial statistical interaction between smoking and sex ($P<0.001$). In separate multivariable analyses, past history of smoking was associated with increased risk for rheumatoid arthritis overall in men (odds ratio 2.0, 95% confidence interval 1.2–3.2) but not in women. Among men, this effect was seen only for rheumatoid factor-positive rheumatoid arthritis. There were significant interactions between smoking and age among women but not among men. We conclude that sex is a biologic effect modifier in the association between smoking and rheumatoid arthritis. The role of menopause in the etiology of rheumatoid arthritis merits further research.

Keywords: etiology, interaction, risk, rheumatoid arthritis, sex, smoking

Introduction

The association between smoking and rheumatoid arthritis (RA) has been widely reported [1–21] and was recently reviewed [20]. The specific association between smoking and rheumatoid factor (RF)-positive RA is well known and meets the Bradford Hill criteria for causation [22], namely strength, consistency, plausibility, experimental evidence, coherence, temporality, and biologic gradient of association [1,7,8,16,17,20].

The term 'interaction' refers to a conditional relationship between an independent variable and the dependent variable. An interaction exists when the relationship between an independent variable *x* and an outcome variable *y* varies according to the value of another covariate *z*. The presence of a statistically significant interaction would suggest the presence of an underlying biologic effect modification and provide epidemiologic clues to the etiology and pathogenesis [23].

Among women, hormonal risk factors for RA include age at menarche, progestin use [24], oral contraceptive use [25], termination of pregnancy [26], lactation [27], and short fertile period [28]. Epidemiologic studies do not consistently show that smoking confers an increased risk among women. Indeed, even a protective effect of smoking on risk for developing RA has been described among women [29]. The smoking–RA risk is more consistent across studies on men. Thus, the risk for RA conferred by smoking depends on the sex of the patient. If reports of this interaction effect were confirmed [1], then this would suggest the presence of an underlying sex-specific factor that modifies the association between smoking and RA. Therefore, we conducted a population-based

 RA = rheumatoid arthritis; RF = rheumatoid factor.

case–control study, including 1095 patients with RA identified in the Central Finland RA Database and 1530 control individuals living in the same district.

Patients and method

Cases and controls

Cases were patients drawn from the Central Finland RA Database, located at the Jyväskylä Central Hospital, which is the only rheumatology center in the Central District of Finland (population 263 869 in 2000). All patients were diagnosed to have RA by their physician. The Central Finland RA Database includes demographic measures, treatments, and outcomes of all patients with RA seen in the clinic since January 1993. As of June 2000, the database contained information on 1763 RA patients, 1495 of whom were still alive. The control group was a random sample drawn from the general population. To obtain a population sample, the names and addresses of 2000 people living in the Central District of Finland were obtained from the organization Statistics of Finland (with the permission from the Ministry of Social Affairs and Health, Finland). Statistics of Finland obtains the majority of its data from diverse administrative registers, and produces two-thirds of all Government statistics in Finland (www.stat.fi). The Ethics Committee of Jyväskylä Central Hospital approved the study.

Data collection

A questionnaire was mailed to 1495 candidate patients with RA and to 2000 candidate control individuals in June 2000. A reminder letter was sent 8 weeks later to nonresponders. The response rate for questionnaires among candidate patients was 73% ($n=1095$) and that among candidate control individuals was 77% (1530). Functional status in activities of daily living was measured using the Finnish version of the Health Assessment Questionnaire (score range 0–3) [30]. Pain and global status were assessed on a 100-mm visual–analog scale (range 0–100 from best to worst). Data on date of birth, height and weight, sex, years of education, and current and previous smoking habits (never/ever) were collected. In addition, clinical features of patients were obtained from the database. Seropositivity for RF (Ig-M) was defined according to laboratory references (>30 kU/l). One of us (TS) assessed radiographs of hands and feet according to the Larsen method, and the presence or absence of radiologic erosions was recorded as a dichotomous variable.

Statistical analysis

Data were analyzed in two stages. The initial stage was to test the hypothesis that there is a primary interaction between sex and smoking. This was performed by including a pair-wise product term (i.e. smoking × sex) in addition to the individual variables in a logistic regression model in which the dependent variable was case versus control status. The P value calculated for the interaction term in the logistic regression model was used to determine statistical significance. If this showed the presence of a statistically significant interaction, then a second stage of analyses was performed. In the second stage, parallel case–control analyses were performed for men and women using multivariable logistic regression. The independent variables in these models were age, education, body mass index, Health Assessment Questionnaire disability index, self-reports of pain and overall health assessments, as well as a smoking variable. The last five covariates were included in the model because these can potentially confound the smoking–RA relationship. Separate regression analyses were performed to assess the effect of both the smoking variables (current smoking and past smoking) on the risk for RA. Forward or backward stepwise selections were not used, and all clinically important covariates were included in the multivariable models. We performed Student's t-test to compare differences in mean values and Pearson's χ^2 test to compare differences in proportions. Analyses were performed using STATA® Version 7.0 software (Stata Corporation, College Station, TX, USA).

Results

The mean age of the patients was 62 years (range 19–96 years) and 71% were female; the mean age of control individuals was 55 years (range 30–91 years) and 72% were female. Among RA patients, the mean disease duration was 11.3 years (range 0.2–47 years), 68.6% were RF-positive, and 60% had erosions in their hand or feet radiographs. There were no statistically significant differences in the proportion of seropositivity for RF (67% versus 71%; $P=0.29$), frequency of erosive disease (59% versus 60.3%; $P=0.84$), or disease duration (11.7 years versus 10.5 years; $P=0.06$) between men and women with RA.

In preliminary logistic regression analyses in which any RA was the dependent variable of interest, sex exhibited a statistically significant interaction with current/past smoking (all $P<0.001$). Among women there was significant interaction between age and past smoking ($P=0.01$) but not with current smoking ($P=0.13$). Among men there were no statistically significant interactions between age and current smoking ($P=0.12$) and age and past smoking ($P=0.97$). Subsequent analyses were performed separately for men and women.

Table 1 shows comparisons between patients and control individuals by sex. Among both sexes, patients were older, less well educated, more disabled, and reported poorer general health and increased functional disability and pain in comparison with control individuals. Female patients were less likely to report past or current smoking than were female control individuals. Among men, there was no statistically significant difference in the proportion of current smokers between patients and control individuals,

Table 1

Comparison between patients with rheumatoid arthritis and control individuals according to sex

Parameter	Women			Men		
	RA cases ($n = 777$)	Controls ($n = 1104$)	*P*	RA cases ($n = 318$)	Controls ($n = 426$)	*P*
Age in years (mean ± SD)	62 ± 13	56 ± 15	<0.001	63 ± 12	53 ± 14	<0.001
Education in years (mean ± SD)	9.7 ± 3.8	10.9 ± 4.0	<0.001	8.6 ± 3.3	10.8 ± 4.2	<0.001
BMI (kg/m^2; mean ± SD)	26 ± 4.6	25 ± 4.6	0.54	26 ± 3.8	27 ± 3.7	0.62
Proportion currently smoking (%)	7	14	<0.001	18	21	0.83
Proportion past smokers (%)	16	22	0.02	66	50	<0.001
HAQ disability index (mean ± SD)*	0.89 ± 0.8	0.30 ± 0.6	<0.001	0.68 ± 0.8	0.21 ± 0.5	<0.001
General health VAS (mean ± SD)†	35.1 ± 22	22.4 ± 22	<0.001	31.8 ± 21	20.8 ± 22	<0.001
Pain VAS (mean ± SD)†	34 ± 25	21 ± 25	<0.001	29 ± 23	19 ± 23	<0.001

*Health Assessment Questionnaire (HAQ) disability index (range 0–3); †visual analog scale (VAS; range 0–100, best to worst). BMI, body mass index; RA, rheumatoid arthritis.

but patients were more likely to have smoked in the past than were control individuals (Table 1).

In the multivariable models, we adjusted for age, body mass index, level of education and indices of functional disability, pain, and general health. Parallel analyses looking at the effect of smoking on the risk of RA were performed in subgroups of patients defined by presence or absence of RF as well as all patients with RA (Tables 2 and 3).

Multivariable analyses for women (Table 2) showed that there was no significant association between current or past smoking and RF-positive or RF-negative RA. Although not statistically significant, the magnitude of risk was consistently less than 1.0 in both RF-positive and RF-negative patients with RA.

For men (Table 3), past smoking was consistently associated with RF-positive RA (odds ratio 2.3, 95% confidence interval 1.3–3.9). Neither current nor past smoking was associated with RF-negative RA. Overall, past smoking (odds ratio 2.0, 95% confidence interval 1.2–3.2) but not current smoking (odds ratio 1.2, 95% confidence interval 0.7–2.0) was associated with increased risk for RA.

Table 2

Adjusted odds ratios for developing rheumatoid arthritis according to smoking and rheumatoid factor status in women

Parameter	Number of observations entering the multivariable model		Odds ratio* (95% CI)
	RA cases	Controls	
All RA			
Current smoking	751	1083	0.7 (0.4–1.0)
Past smoking	504	851	0.9 (0.6–1.3)
RF-positive RA			
Current smoking	452	1083	0.6 (0.3–1.0)
Past smoking	365	851	0.8 (0.6–1.3)
RF-negative RA			
Current smoking	299	1083	0.84 (0.5–1.5)
Past smoking	238	851	0.94 (0.6–1.5)

*Odds ratios are expressed as the expected probability of having rheumatoid arthritis (RA) as compared with those who did not smoke. The confounders adjusted for in the multivariable logistic regression models included age, body mass index, number of years of education, Health Assessment Questionnaire disability index, general health assessment, and pain. CI, confidence interval.

Discussion

In the present study we confirmed the earlier observation that smoking is a risk factor for RA in men but not in women [1,17]. In addition, we statistically tested and confirmed the interaction between smoking and sex, thereby providing evidence in support of a biologic interaction between smoking and RA.

Smoking is known to be associated with production of RF [6,16,20]; RF production, in turn, often precedes the development of clinical disease [12,16]. Furthermore, it appears to be independent of HLA-DR restricted immune response [13]. In our study, we found that this paradigm held well for men but not women. Why could it be? One of the explanations for this could be that the immunologic cascade triggered by smoking and leading to RF production and subsequently to clinical RA is modulated differently in men and in women. The most obvious biologic difference between men and women is the hormonal

Table 3

Adjusted odds ratios for developing rheumatoid arthritis according to smoking and rheumatoid factor status in men

Parameter	Number of observations entering the multivariable model		Odds ratio* (95% CI)
	RA cases	Controls	
All RA			
Current smoking	306	418	1.2 (0.7–2.0)
Past smoking	234	306	2.0 (1.2–3.2)
RF-positive RA			
Current smoking	181	418	1.5 (0.8–2.6)
Past smoking	140	306	2.3 (1.3–3.9)
RF-negative RA			
Current smoking	125	418	0.8 (0.3–1.8)
Past smoking	94	306	1.5 (0.7–3.0)

*Odds ratios are expressed as the expected probability of having rheumatoid arthritis (RA) as compared with those who did not smoke. The confounders adjusted for in the multivariable logistic regression models included age, body mass index, number of years of education, Health Assessment Questionnaire disability index, general health assessment, and pain. CI, confidence interval.

milieu, although other sex-specific factors cannot be ruled out. In our analyses we found a significant age–smoking interaction among women – an observation that is not inconsistent with this hypothesis.

Although we were not able to test this hypothesis directly in our data (because the relevant reproductive variables were not available), a review of the literature gives some clues. In studies conducted in women-only cohorts, the presence of association between smoking and RA appeared to be dependent on menopausal status of study participants. In a population-based study conducted in Iowa, USA, which examined postmenopausal women only, a dose-dependent effect of smoking was evident (relative risk for RA for current smokers versus never smokers 2.0) [11]. On the other hand, data from the prospective Nurses Health Study [2], which examined all (primarily menstruating) women aged 30–55 years, did not show a statistically significant relationship between current or past smoking and RA. Furthermore, in the Women's Health Cohort Study [7], the effect size of smoking was relatively modest (relative risk 1.39 and 1.49 for all RA and RF-positive RA, respectively) as compared with that in the Iowa study. Interpreting our findings of an interaction between smoking and sex in the light of published data, we propose that being a menstruating woman acts as a biologic effect modifier that blocks the smoking–RF–RA pathway. We did not have the information on menopausal status to test this hypothesis directly. Instead, we conducted multiple pair-wise interaction tests between age and smoking for men and women separately. Interestingly, we found that there was a significant age–smoking interaction among women but not among men. This smoking–sex effect modification paradigm we propose not only might explain a lack of increased risk for RA among women smokers, but also provides a theoretical basis for the observation that smoking reduces the risk for RA in women [29].

There are several areas of substantial strength in the present study. First, the study participants were drawn from a population-based register of RA patients (i.e. a rheumatology clinic in which all patients with RA living in the particular referral area are followed) and the control individuals were drawn from the same, geographically well-defined general population. Second, the participation rates for patients and control individuals were good. Validated diagnoses and exposures were used. The smoking histories were also validated using hospital medical records, by comparing the questionnaire response with the information from the standard clinical history and physical examination. Finally, the numerical strength of this study provided sufficient statistical power to quantitate the risk of smoking on RF-positive and RF-negative RA separately.

The potential limitations of the study also must be addressed. By design, the study was an unmatched case–control study. The control individuals were younger than the cases. Many control individuals were younger than 50 years. This may lead to arguments that control individuals were not old enough to have developed RA and that an age-matched design would have been more appropriate. However, such a bias does not explain our observations as the age differential was found in both men and women. In addition to performing tests of interaction between age and smoking, we adjusted for the effect of age in multivariable models. To address the concern that successive birth cohorts are associated with lower prevalence rates of smoking and leading to bias in our findings, analyses were repeated, adjusting for the effect of calendar year of birth. We found that the results were essentially the same. We believe that matching by age would have been, overall, disadvantageous to the study because such an approach would not allow us to study important interactions between age and other covariates. Unfortunately, data on the temporal sequence of smoking and RA, as well as on any dose–response association, were not available and could not be analyzed.

The differences in the risk estimates for current smoking and past smoking may appear counter-intuitive. The explanation lies in the case–control design of the study. Both smoking and RA can independently increase the risk for mortality; the potential patients who are also continuing smokers are more likely to have died than are smokers in

the general population, thus never entering the study [31]. This differential mortality could have resulted in an underestimation of the association between current smoking and RA. However, it is unlikely that there is a difference in smoking-related mortality between men and women of such a magnitude as to cause the observed sex differential. Another equally plausible explanation would be that the diagnosis of RA might have led to lifestyle changes, leading to cessation of smoking. However, there is little evidence to suggest that onset of RA would affect smoking behavior in men and women in a different manner (i.e. there is no published literature or rationale for supposing that men and women tend to take up or quit smoking differently when they develop RA).

Conclusion

Data presented in this report suggest that factors related to the sex of an individual modify the effect of smoking on the risk of RA. Epidemiologic studies that do not explore and account for the significant smoking–sex interaction are likely to show inaccurate and even biased estimates of the association between smoking and RA. Our study also highlights the need for further research on smoking, RA, and, in addition, their effect modification by sex-related factors like menopause.

Competing interests

None declared.

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