EXTENDED REPORT

Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases

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Objective: To quantify the influence of cigarette smoking on the risk of developing rheumatoid arthritis (RA).

Methods: 679 cases and 847 controls included during May 1996–June 2000 in a case-control study, using incident cases, comprising the population aged 18–70 years of a defined area of Sweden, were investigated. A case was defined as a person from the study base who received for the first time a diagnosis of RA using the 1987 American College of Rheumatology criteria, and controls were randomly selected from the study base. Self reported smoking habits among cases and controls, and rheumatoid factor status among cases were registered. The incidence of RA in current smokers, ex-smokers, and ever-smokers, respectively, was compared with that of never-smokers.

Results: Current smokers, ex-smokers, and ever-smokers of both sexes had an increased risk for seropositive RA (for ever-smokers the odds ratio was 1.7 (95% confidence interval (95% CI) 1.2 to 2.3) for women, and 1.9 (95% CI 1.0 to 3.5) for men), but not for seronegative RA. The increased risk was only apparent among subjects who had smoked ⩾20 years, was evident at an intensity of smoking of 6–9 cigarettes/day, and remained for up to 10–19 years after smoking cessation. The risk increased with increasing cumulative dose of smoking.

Conclusion: Smokers of both sexes have an increased risk of developing seropositive, but not seronegative, RA. The increased risk occurs after a long duration, but merely a moderate intensity, of smoking and may remain for several years after smoking cessation.

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a heterogeneous pattern and a prevalence of about 0.5–0.8% in Scandinavia,[1–3] more commonly occurring among women than among men. Knowledge of the immunological mechanisms underlying RA has increased and some understanding of the association between genotype and RA has emerged,[4–8] but still only few conclusive results have been obtained to explain the link between the environment and the risk for RA.[9–18]

Smoking has so far been shown to be the most plausible environmental risk factor for RA and has been investigated in 12 studies (table 1). The first was an English study published in 1987, analysing data on oral contraceptive use and arthritis, that reported an unexpected association between smoking and referral to hospital for RA.[19] Prevalent cases were used in five of the studies[20–24] and incident cases in seven of the studies on this issue.[19 25–30] In total, seven of the 10 studies examining women separately demonstrated an association between smoking and increased risk for RA,[19–22 24 25 27–30] and all four studies examining men separately showed an increased risk among smokers.[20 22 24 28]

A stronger association with smoking has been found for seropositive cases than for seronegative cases,[20 21 24 26 28] and two studies have observed smoking to be associated only with seropositive RA (RF+ RA), and not with seronegative RA (RF– RA).[20 28] Three of the five studies investigating the effect of a cumulative dose of smoking on the risk for RA observed a dose-response relationship.[21 23–25 30]

Duration of cigarette smoking has been found to be associated with an increased risk for RA in four of the five studies on this issue,[21 22 25 28 30] but the effect of intensity of smoking is still controversial.[19 20 25 27–30] The effect of stopping smoking on the risk for RA has been investigated only to a limited extent.[28 30]

In summary, previous studies have provided evidence for a link between smoking and the risk for RA but the effect of duration, intensity and cumulative dose of smoking, and smoking cessation, RF status, and sex needs further clarification.

To investigate the influence of environmental factors on the risk of developing RA and the interaction of these factors with genotype we started an extensive case-control study—the Epidemiological Investigation of RA (EIRA) study.

In this report from the EIRA study we investigated aspects of the association between smoking and the risk for RA that have previously only been investigated to a limited extent, and that may have relevance for the creation of biological hypotheses, focusing on the influence of RF status, sex, duration and intensity of smoking, and smoking cessation.

SUBJECTS AND METHODS

As far as we know this study is the first report from an extensive, population based, case-control study, using incident cases, with a study group comprising the population of 18–70 years of age in a geographically defined area in the middle and southern parts of Sweden. The study period for the present report was May 1996–June 2000.

Case identification

The study sought to identify incident cases in the study base as soon as possible after the start of the disease. Increasing

Abbreviations: ACR, American College of Rheumatology; BMI, body mass index; CI, confidence interval; EIRA, Epidemiological Investigation of RA (study); OR, odds ratio; RA, rheumatoid arthritis; RF, rheumatoid factor

Table 1 Previous studies on the association between smoking and rheumatoid arthritis

Author	Year of publication	Study design, type of cases	Number of cases women/men	Relative risk with 95% confidence interval women/men/both sexes together	Examining separately the effect of duration, intensity
Vessey *et al*[19]	1987	Cohort study, incident cases	78/NE*	2.4 (1.8 to 3.2)† / NE / NE	No, yes
Uhlig *et al*[20]	1999	Case-control study, prevalent cases	261/98	1.14 (0.80 to 1.62) / 2.38 (1.45 to 3.92) / 1.46 (1.10 to 1.94)	No, no
Karlsson *et al*[21]	1999	Cohort study, prevalent cases	7697/NE	1.40 (1.28 to 1.53) / NE / NE	Yes, yes
Silman *et al*[22]	1996	Matched twin pairs case-control study, prevalent cases	MZ‡ 65/14	10.0 (1.42 to 434) / NE / 12.0 (1.78 to 513)	Yes, no
			DZ§ 55/16	2.4 (0.79 to 8.70) / 3.0 (0.24 to 158) / 2.5 (0.92 to 7.87)	
Hutchinsson *et al*[23]	2001	Cases-control study, prevalent cases	160/79	NE / NE / 13.54 (2.89 to 63.28)	No, no
Reckner-Olsson *et al*[24]	2001	Cases-control study, prevalent cases	179/102	2.5 (0.9 to 6.7) / 3.4 (1.5 to 8.4) / NE	No, no
Voigt *et al*[25]	1994	Case-control study, incident cases	349/NE	1.5 (1.0 to 2.0) / NE / NE	Yes, yes
Symmons *et al*[26]	1997	Case-control study, incident cases	115/50	NE / NE / 1.66 (0.95 to 3.06)	No, no
Hazes *et al*[27]	1990	Case-control study, incident cases	135/NE	0.61 (0.42 to 0.89) / NE / NE	No, yes
Heliövaara *et al*[28]	1993	Cohort study, incident cases	229/119	1.1 (0.8 to 1.6) / 4.4 (2.3 to 8.5) / NE	Yes, yes
Hernandez-Avila *et al*[29]	1990	Cohort study, incident cases	217/NE	1.5 (0.9 to 2.3) / NE / NE	No, yes
Criswell *et al*[30]	2002	Cohort study, incident cases	158/NE	2.0 (1.3 to 2.9) / NE / NE	Yes, yes

*NE, not examined; †relative risk with 95% confidence interval, calculated by us, based on results in this article; ‡MZ, monozygotic twin pairs discordant for rheumatoid arthritis; §DZ, dizygotic twin pairs discordant for rheumatoid arthritis.

evidence of the importance of early treatment of RA has led to the introduction of so-called "early arthritis clinics" as an important component of rheumatology units in Sweden. It has also increased the tendency in primary care to refer cases of suspected RA to rheumatology units for further assessment. All rheumatology units linked to the general welfare system in the study area participated in the study as well as privately run rheumatology units.

In total, 18 study centres reported cases of RA to the study. Initially, two of the centres also reported cases of suspected RA, to enable investigations of undifferentiated arthritis. All cases were assessed and diagnosed by a rheumatologist. Subsequently, cases which did not fulfil the 1987 American College of Rheumatology (ACR) criteria for RA at the time of the report to the study were excluded. In the current report a case is thus defined as a subject from the study base who received a diagnosis of RA according to the ACR criteria for the first time. RF positivity or RF negativity was determined locally by the unit entering the case into the study.

Selection of controls

For each potential case one control was randomly selected from the study base as a stratified random sample, taking into consideration sex, age, and residential area. If information could not be obtained from the control selected, another control was chosen according to the same principles. Each potential case and control was offered the opportunity to participate in the study, and to answer an extensive questionnaire. Completed questionnaires were obtained from 859 potential cases and 864 controls, the response rate being 96% for the case group and 83% for the controls. Of those 859 potential cases, 163 were excluded as they did not satisfy the 1987 ACR criteria for RA. Seventeen cases and the corresponding 17 controls were excluded because they did not belong to the study base.

Table 2 Smoking habits of cases and controls

	Current cigarette smokers	Ex-cigarette smokers	Non-regular cigarette smokers	Other tobacco smokers	Never-smokers	Total
Women						
Cases	146	128	22	29	164	489
Controls	151	150	36	41	224	602
Men						
Cases	46	66	3	32	43	190
Controls	53	81	14	30	67	245

The present study thus comprises 679 cases (489 women, 190 men) and 847 controls (602 women, 245 men) (table 2).

Exposure

Information about environmental exposures was collected using an identical questionnaire given directly to the cases shortly after they had received information about the diagnosis and was sent by mail to the controls. All questionnaires were supposed to be answered at home.

The questionnaire contained a wide spectrum of questions about demographic and reproductive data, heredity, previous health and measures by the health service, body weight and height, lifestyle factors, occupational exposures, psychosocial and socioeconomic circumstances. The following questions about smoking were used: (1) Do you smoke? (2) If you do not smoke, have you previously smoked? (3) If you have previously smoked, which year did you stop smoking? (4) If you smoke or previously have smoked, when did you start to smoke regularly? (5) How much do you smoke, or did you smoke before you stopped, on average per day? Information was also obtained about the type of tobacco smoked.

Unanswered or incompletely answered questionnaires were completed by telephone with the assistance of people trained for this purpose who were not connected to the individual clinics. This was done for most of the questionnaires and in an identical way for case and control groups. For each case the point at which symptoms occurred giving rise to a suspicion of RA was used as an estimate of the time of disease onset. The year in which this occurred was defined as the index year. The same index year was used for the corresponding control. Only data on smoking habits from cases and controls up to the index year, and only data on cigarette smoking, but not other types of tobacco smoking, were analysed in the present study.

Subjects who reported that they were regularly smoking during the index year were defined as current smokers, those who reported that they had stopped regular smoking the year before the index year or before were defined as ex-smokers, and people who reported that they never had smoked before or during the index year were defined as never-smokers. Ever-smokers were defined as subjects who fitted the definition for current smokers or ex-smokers. The intensity of smoking, duration of smoking, and the cumulative dose of smoking were estimated. The intensity of smoking was categorised using the following intervals: 1–5, 6–9, 10–19, and ⩾20 cigarettes smoked a day. The duration of smoking was categorised using the following intervals: <10, 10–19, and ⩾20 years of smoking. The cumulative dose of cigarette smoking was expressed as pack-years. One pack-year was regarded as the equivalent of 20 cigarettes smoked per day for one year. The results for pack-years were presented using the intervals: <10, 10–19, and ⩾20 pack-years. The duration from the year of the cessation of smoking to the index year was calculated and categorised into the intervals: 1–9, 10–19, and ⩾20 years.

Potential confounding factors

Age, residential area, socioeconomic class, body mass index (BMI), marital status, parity, and oral contraceptive use were considered as potential confounding factors.

Age was categorised into the following 10 strata: 18–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, and 65–70 years of age. Socioeconomic class was determined by the last occupation during the year before the index year as a marker. Occupations were categorised as follows: (*a*) workers involved in the production of goods; (*b*) workers in the service sector; (*c*) salaried employees at lower and intermediate levels; (*d*) salaried employees at higher levels, executives, university graduates; (*e*) others (for example, pensioners, students, people working from home, and unemployed).

The calculations of BMI were based on self reported current weight in kilograms and height in metres using the formula "weight divided by height squared". Results for BMI were categorised into three strata: <25, 25–29.9, ⩾30. Assessment of marital status was based on the answer "yes" or "no" to the question "Do you live together with another adult person?". The assessment of parity was based on the answer "yes" or "no" to the question "Do you have children of your own?". Assessment of oral contraceptive use was based on the answer "yes" or "no" to the question "Have you ever used oral contraceptives regularly?".

Statistical analysis

The incidence of RF+ RA, RF− RA, and RA overall in current smokers, ex-smokers, and ever-smokers was compared with that in never-smokers by calculating the odds ratio (OR) with 95% confidence interval (95% CI). We performed matched as well as unmatched analyses of the data. Odds ratios were adjusted for potential confounding by the Mantel-Haenszel method in the unmatched analyses and by conditional regression analysis in the matched analyses.

The incidence of RA overall and of RA of different RF status was analysed separately for women and men. Because the results for women and men were similar, both sexes were analysed together in the calculations for duration, intensity, cumulative dose, and the effect of stopping smoking.

All analyses were performed using the statistical analysis system (SAS) version 4.0.[31] We only present results from the unmatched analyses as these were in close agreement with those from the matched analyses, but had higher precision.

All results were adjusted for potential confounding by age and residential area. When women and men were analysed together, the results were also adjusted for potential confounding by sex. Adjustments were also made for potential confounding by socioeconomic class, BMI, marital status, parity, and oral contraceptive use, but affected the results only marginally and were not retained in the final analyses.

RESULTS

Of a total of 679 cases in this study, 489 were women and 190 were men. The mean age at the index year was 50 years among the female cases and 53 years among the male cases. Three hundred and twenty (65%) of the female cases and 124 (65%) of the male cases were RF+. RF status was unknown for two female cases. The mean duration from the estimated disease onset to the time at which the cases were reported to the study

Table 3 Relative risk (RR) with 95% confidence interval (95% CI) of developing seropositive rheumatoid arthritis (RF+ RA), seronegative rheumatoid arthritis (RF– RA), and rheumatoid arthritis overall (total RA) for different categories of cigarette smokers compared with never-smokers by sex and age

	Current smokers compared with never-smokers			Ex-smokers compared with never-smokers			Ever-smokers compared with never-smokers		
	O*	RR†	95% CI	O*	RR†	95% CI	O*	RR †	95% CI
Women 18–70 years									
RF+ RA	105	1.8	1.3 to 2.6	93	1.6	1.1 to 2.3	198	1.7	1.2 to 2.3
RF– RA	39	0.9	0.5 to 1.4	35	0.8	0.5 to 1.3	76	0.8	0.6 to 1.2
Total RA	146	1.4	1.0 to 2.0	128	1.2	0.9 to 1.7	274	1.3	1.0 to 1.7
Women 18–49 years									
RF+ RA	33	1.1	0.6 to 2.0	27	0.9	0.5 to 1.6	60	1.0	0.6 to 1.6
RF– RA	21	0.8	0.4 to 1.6	11	0.5	0.2 to 1.1	32	0.6	0.4 to 1.1
Total RA	54	1.0	0.6 to 1.6	38	0.7	0.4 to 1.2	92	0.8	0.5 to 1.3
Women 50–70 years									
RF+ RA	72	2.5	1.6 to 4.0	66	2.2	1.4 to 3.6	138	2.4	1.6 to 3.6
RF– RA	18	1.0	0.5 to 1.9	24	1.1	0.6 to 2.1	44	1.1	0.6 to 1.8
Total RA‡	92	1.9	1.3 to 2.9	90	1.8	1.2 to 2.7	182	1.8	1.3 to 2.6
Men 18–70 years									
RF+ RA	34	1.8	0.8 to 4.1	47	1.9	0.9 to 3.8	81	1.9	1.0 to 3.5
RF– RA	12	0.7	0.3 to 1.6	19	0.9	0.4 to 1.9	31	0.8	0.4 to 1.6
Total RA	46	1.3	0.7 to 2.4	66	1.4	0.8 to 2.5	112	1.4	0.8 to 2.3
Men 18–49 years									
RF+ RA	6	0.9	0.2 to 4.0	13	1.1	0.3 to 3.4	19	1.2	0.5 to 3.4
RF– RA	3	0.5	0.1 to 2.9	6	1.3	0.3 to 5.0	9	1.0	0.3 to 3.4
Total RA	9	0.8	0.2 to 2.8	19	1.3	0.5 to 3.4	28	1.3	0.6 to 2.9
Men 50–70 years									
RF+ RA	28	2.5	0.9 to 7.0	34	2.6	1.0 to 6.3	62	2.4	1.0 to 5.5
RF– RA	9	0.8	0.3 to 2.1	13	0.7	0.3 to 1.9	22	0.7	0.3 to 1.7
Total RA	37	1.5	0.7 to 3.3	47	1.5	0.7 to 3.1	84	1.4	0.8 to 2.7

*O, number of exposed cases; †relative risk adjusted for age, and residential area; ‡RF status was unknown for two current smoking women aged 50–70.

Table 4 Relative risk (RR) with 95% confidence interval (95% CI) of developing seropositive rheumatoid arthritis for 18–70 years old female and male ever-smokers compared with never-smokers by duration of smoking

Number of years of smoking	Number of exposed cases	RR*	95% CI
<10	26	0.8	0.4 to 1.4
10–19	36	0.8	0.5 to 1.3
≥20	217	2.6	1.8 to 3.6

*Relative risk adjusted for age, residential area, and sex.

Table 5 Relative risk (RR) with 95% confidence interval (95% CI) of developing seropositive rheumatoid arthritis for 18–70 years old female and male subjects who have smoked cigarettes for ≥20 years compared with never-smokers by intensity of smoking

Number of cigarettes smoked a day	Number of exposed cases	RR*	95% CI
1–5	15	1.6	0.7 to 3.7
6–9	24	2.5	1.3 to 4.7
10–19	103	3.0	2.0 to 4.6
≥20	75	2.4	1.5 to 3.7

*Relative risk adjusted for age, residential area, and sex.

was estimated as 10 months, and this duration was ≤12 months among 413 (84%) of the female cases and among 159 (84%) of the male cases.

Among ever-smokers of cigarettes the overall OR for RA was 1.3 (95% CI 1.0 to 1.7) among women and 1.4 (95% CI 0.8 to 2.3) among men, compared with never-smokers (table 3). Among cases of different RF status, female ever-smokers had a relative risk of RF+ RA of 1.7 (95% CI 1.2 to 2.3) compared with never-smokers. The corresponding result for men was 1.9 (95% CI 1.0 to 3.5) (table 3). Results similar to those for ever-smokers were recorded among current smokers and ex-smokers of both sexes (table 3). We found no increased risk of RF– RA among smokers of any category when compared with never-smokers. Separate analyses were made for a younger (18–49 years) and an older (50–70 years) age group. An increased risk of developing RF+ RA was evident in the older but not in the younger age group of cigarette smokers when compared with never-smokers (table 3).

In summary, we found that smoking was associated with increased risk for RF+ RA but not RF– RA, with similar results among current smokers and ex-smokers of both sexes. Hence, the analysis of duration, intensity, cumulative dose, and smoking cessation was restricted to RF+ RA, and was made among ever-smokers compared with never-smokers, and among women and men together.

Of the 279 cases with RF+ RA that had ever smoked, 217 (78%) had smoked for ≥20 years. No increased risk for RA was seen among subjects who had smoked for <20 years (table 4). Among subjects who had smoked for ≥20 years, similar results were found among those with an intensity of smoking of 6–9 cigarettes/day, and those with an intensity of smoking of ≥20 cigarettes/day (table 5). The cumulative dose of smoking was expressed as pack-years. The risk of developing RF+ RA increased as the number of pack-years increased, in a dose dependent manner (table 6). The increased risk for RA remained for about 10–19 years after smoking cessation (table 7).

Demographic and reproductive characteristics such as low socioeconomic class, low level of formal education, being unmarried, nulliparity as well as obesity have previously been discussed as possible risk indicators for RA, while oral contraceptive use has been proposed as a possible protective factor. There is also a possibility that these factors may correlate with smoking characteristics. To adjust for potential confounding,

Table 6 Relative risk (RR) with 95% confidence interval (95% CI) of developing seropositive rheumatoid arthritis for 18–70 years old female and male ever-smokers compared with never-smokers by cumulative dose of smoking

Number of pack-years	Number of exposed cases	RR*	95% CI
<10	65	1.0	0.7 to 1.5
10–19	78	1.8	1.2 to 2.6
⩾20	136	2.7	1.8 to 3.9

*Relative risk adjusted for age, residential area, and sex.

Table 7 Relative risk (RR) with 95% confidence interval (95% CI) of developing seropositive rheumatoid arthritis for 18–70 years old female and male ex-smokers compared with never-smokers by number of years since smoking cessation

Number of years*	Number of exposed cases	RR†	95% CI
1–9	74	2.2	1.4 to 3.3
10–19	41	1.5	0.9 to 2.5
⩾20	25	1.0	0.5 to 1.9

*Number of years between smoking cessation and index year.
†Relative risk adjusted for age, residential area, and sex.

besides the variables age, sex, and residential area, stratification was performed according to socioeconomic class, BMI, marital status, parity, and oral contraceptive use. However, these had a minor influence on the results and were not retained in the final analysis.

DISCUSSION

According to the results in this study, cigarette smokers of both sexes have an increased risk of developing RF+ RA, but not RF– RA, compared with never-smokers. The increased risk of developing RA occurred after a long duration but merely a moderate intensity of smoking, and remained for several years after smoking cessation. We also found that the risk of developing RA increased in a dose dependent manner as the cumulative dose of smoking increased.

This study was designed as a case-control study with incident cases. Besides being more cost efficient, a case-control study using incident cases may provide better opportunities than a cohort study for obtaining accurate information about smoking habits before disease onset. The use of exposure information from baseline in a cohort study, with a long follow up period, is sensitive to substantial bias from exposures that tend to vary with time, cigarette smoking being one example. Because smoking habits have declined during recent decades, a prospective cohort study using only baseline data for smoking would tend to underestimate the effect of smoking on the incidence of RA. A disadvantage of a case-control study with retrospective collection of exposure data compared with a cohort study using prospectively collected exposure data is the higher risk for differential misclassification of exposure due to recall bias that differs between cases and controls. As the use of prevalent cases increases the risk for recall bias we only included subjects from the study base who for the first time had received a diagnosis of RA. The duration between the estimated disease onset and inclusion in the study was 12 months or less for 84% of the cases—that is, the cases were "incident". All rheumatology units linked to the general welfare system in the study area reported cases to the study, as did privately run rheumatology units. The introduction of so called "early arthritis clinics" in many parts of Sweden has increased the possibilities of identifying a high proportion of incident cases in our study base.[32] A set of adequate diagnostic criteria is an important precondition for an epidemiological study of RA. In the present study we defined cases according to the ACR criteria, which are fairly clear and easy to use in clinical practice but have the limitation of sometimes being inadequate in early cases of RA.

Some cases might have been unidentified in our study, for instance cases diagnosed in primary healthcare facilities that were never referred to a rheumatology unit. It is not likely that the exposure to smoking of these unidentified cases would substantially differ from the exposure of identified cases. Hence, this potential error would probably not seriously bias relative risk estimates. The response rate in the study was high—96% for cases and 83% for controls. If the smoking habits of participating controls differed from those controls who did not participate, this might have biased the estimated relative risk. However, even if it is assumed that all non-responding controls were smokers (which is highly unlikely), an increased relative risk for RF+ RA associated with smoking would still be observed. Furthermore, the observed discrepancy between RF+ RA and RF– RA would be unaffected. Cases and controls may possibly recall their previous smoking habits differently. However, we only observed an association between smoking and RF+ RA. It is most unlikely that RF+ cases and RF– cases recall their smoking habits differently. Matched as well as unmatched analyses of the data were performed, with similar results. The unmatched analyses used more controls than cases and these additional controls received index years from cases that had previously been excluded from the study. The duration between the estimated disease onset and the report to the study was ⩽12 months among 83% of these excluded cases compared with 84% among the rest of the cases, which indicates that the distribution of index years among the additional controls was similar to that of the rest of the controls. We hence assess that the use of these additional controls did not bias the results, but increased the precision.

Adjustment for socioeconomic class, BMI, marital status, parity, and oral contraceptive use had minor influence on the results of the study and was not retained in the final analyses. A relationship between these factors and RA is theoretically possible, but so far insufficiently studied, and will be investigated in forthcoming studies. It has been suggested previously that dietary habits are an important factor for the risk of developing RA.[14] It is also likely that there is some correlation between dietary habits and smoking habits. However, we did not control for dietary habits in this study because we had insufficient information.

In this study smokers of both sexes had an increased risk of developing RF+ RA, but not RF– RA. These results are in agreement with the results of two previous studies,[20 28] which determined an increased risk for RF+, but not RF– , RA among male smokers. However, those studies did not find an association between smoking and RA of either RF status among women. The result in the present study extends a finding by Symmons *et al*, who observed that smokers have a higher risk of developing seropositive arthritis than seronegative arthritis when both sexes are analysed together.[26] Our study is the first to demonstrate that the association between smoking and RA among men, as well as among women, is clearly dependent on RF status.

The results in previous articles for the association between smoking and RA among women[19–22 24 25 27–30] have been somewhat inconsistent. Our study, however, is the only population based case-control study using incident cases that has investigated the association between smoking and RA among women and men separately, and adds evidence to the notion that smokers of both sexes have an increased risk of developing RA compared with never-smokers.

We found that the risk of developing RA associated with smoking required a long duration, but merely a moderate

intensity, of smoking. These results agree with a suggestion in a cohort study using prevalent cases by Karlsson *et al* that duration, but not intensity, of smoking is associated with an increased risk of RA in women.[21] Similar results have been presented in another cohort study, but only for men, using incident cases by Heliövaara *et al*.[28] The evidence for an association between duration of smoking and the risk for RA is increasing as it now has been observed in five of the six studies on this issue. The evidence for the effect of the intensity of smoking, however, is still conflicting as two previous studies have suggested an association between increased intensity of smoking and increased risk for RA.[25 30] The discrepancy in the results for the effect of the intensity of smoking on the incidence of RA may be due to a considerable degree of recall bias about the number of cigarettes smoked a day, especially because the intensity has probably varied with time. The data on the effect of duration of smoking may be more accurate, as the number of years of smoking may be more easily recalled.

In this study the risk of developing RA was observed to increase as the cumulative dose of smoking increased, an observation that is in concordance with some previous results[21 23 24] and may be regarded as support for the view that smoking is a causal factor for the development of RA.

We also observed that the increased risk for RF+ RA remained for up to somewhere between 10 and 19 years after smoking had stopped. This finding extends a result by Heliövaara *et al*, who also observed an increased risk for RA among ex-smokers after more than 14 years of follow up.[28]

The observed differential effect of smoking on the incidence of RF+ RA and RF– RA in this study may be because RF is an epiphenomenon or acts as an inflammatory mediator, or may be due to an interaction between smoking and genotype. The second possibility finds support in previous findings of a higher prevalence of RF in smokers than in non-smokers in some healthy populations,[33 34] and previous observations that RA is sometimes preceded by RF positivity.[35 36] The possibility that RF or some associated factor is the link between smoking and the risk of RA increases the interest in investigating the role of B lymphocytes in the pathogenesis of RA.[37–39] Further evidence of a major role for B cells in this respect comes from observations that selective B cell blockade has the potential to modify the course of RA.[40] The third possibility is supported by results pointing towards an association between RF status and genotype among subjects with RA or inflammatory polyarthritis[7–9] and by a study observing that smoking is associated with more severe disease outcome among women with a certain genotype.[41]

The finding that the increased risk for RA associated with smoking requires a long duration, but merely a moderate intensity, of smoking, and may remain for several years after smoking has stopped, indicates that the mechanism behind the effect of smoking is complex, slow, or delayed. The molecular pathways behind the increased risk of RA associated with smoking are still to be investigated. Our principal hypothesis is that an interaction between smoking and genotype is of fundamental importance for the increased risk of RA associated with smoking. This issue will be investigated in a future work within the EIRA study.

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