Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA

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Abstract

Objectives—To investigate the potential relation between cumulative exposure to cigarette smoking in patients with or without rheumatoid arthritis (RA) and a positive family history of the disease.

Methods—239 outpatient based patients with RA were compared with 239 controls matched for age, sex, and social class. A detailed smoking history was recorded and expressed as pack years smoked. Conditional logistic regression was used to calculate the association between RA and pack years smoked. The patients with RA were also interviewed about a family history of disease and recorded as positive if a first or second degree relative had RA. The smoking history at the time of the study of the patients with RA with or without a family history of the disease was compared directly with that of their respective controls. Patients with RA with or without a family history of the disease were also compared retrospectively for current smoking at the time of disease onset.

Results—An increasing association between increased pack years smoked and RA was found. There was a striking association between heavy cigarette smoking and RA. A history for 41–50 pack years smoked was associated with RA (odds ratio (OR) 13.54, 95% confidence interval (95% CI) 2.89 to 63.38; p<0.001). The association between ever having smoked and RA was modest (OR 1.81, CI 1.22 to 2.19; p=0.002). Furthermore, cigarette smoking in the patients with RA without a positive family history of RA was more prevalent than in the patients with a positive family history of RA for ever having smoked (72% *v* 54%; p=0.006), the number of pack years smoked (median 25.0 *v* 4.0; p<0.001), and for smoking at the time of disease onset (58% *v* 39%; p=0.003).

Conclusions—Heavy cigarette smoking, but not smoking itself, is strongly associated with RA requiring hospital follow up and is markedly more prevalent in patients with RA without a family history of RA.

(*Ann Rheum Dis* 2001;**60**:223–227)

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Although both genetic and environmental factors are thought to contribute to the development of rheumatoid arthritis (RA),[1] the cause of this disease remains unclear. The genetics of RA are complex.[2] At the simplest level, there is an increased risk of hospital based RA if a family member also has the disease (odds ratio (OR) 6).[3] The natural history of RA, however, suggests that the disease may be initiated by relatively contemporary environmental factors. Rheumatoid arthritis was first described as recently as 1800 and examination of the visual arts before this time has failed to show any evidence of RA.[4] The low concordance for RA in monozygotic twins[5] highlights the importance played by environmental factors.

One potential environmental agent is cigarette smoking. A Norwegian study reported that men who were current smokers had an increased risk of developing seropositive RA (OR 4.77, 95% CI 2.09 to 10.9).[6] However, this study, did not quantify the number of cigarettes smoked and therefore could not address the potential effects of cumulative exposure to cigarette smoke. In other smoking related diseases, such as emphysema,[7] lung cancer,[8] and ischaemic heart disease,[9] the risk of disease with increasing cumulative exposure to cigarette smoke is increased. In a North American study of female health workers an increased risk of 49% for developing seropositive RA was found in those smoking 25 cigarettes a day for more than 20 years.[10]

Both the above studies investigated community based RA, where there is a lower prevalence of disability than in hospital based patients with RA.[11] This is relevant as current cigarette smokers of 25 pack years or more are 2.4 times more likely to have erosive rather than the milder non-erosive RA than subjects who have never smoked.[12] We therefore undertook a study to test the hypothesis that a high cumulative exposure to cigarettes is associated with RA requiring hospital outpatient treatment, and to examine the potential role of a positive family history of RA underlying this.

Methods

Two hundred and thirty nine unrelated patients with RA (age range 28–87) attending rheumatology clinics in two Merseyside hospitals and fulfilling the 1987 American Rheumatism Association criteria for RA[13] were studied. The patients' age and age of disease onset were recorded. Social class was defined by the Office of National Statistics Classification of Occupations[14] based on the highest employment history of the subject before the age of onset of

Table 1 Characteristics of the patients with rheumatoid arthritis and controls studied

	Patients	Controls
Number	239	239
Sex (No (%))		
Male	79 (33)	79 (33)
Female	160 (67)	160 (67)
Age (years)		
Mean (SD)	60.5 (11.8)	60.5 (11.8)
Age at onset (years)		
Mean (SD)	46.9 (13.2)	NA
Disease duration (years)		
Mean (SD)	13.6 (9.9)	NA
Social class (No (%))		
Classes I–II	29 (12)	29 (12)
Classes IIIN–IIIM	86 (36)	86 (36)
Classes IV–V	124 (52)	124 (52)

disease or in the case of a woman who had never worked, based on her partner's occupation. This classification allocates subjects in one of six social classes according to occupation as follows: I = professional, II = managerial, IIIN = non-manual skilled, or IIIM = manual skilled, IV = partly skilled, and V = unskilled. A positive family history of RA was defined according to strict criteria: (*a*) a first or second degree relative with a history of RA; (*b*) this relative must have been receiving regular follow up in a rheumatology department, received a disease modifying antirheumatic drug, or have the deformities or nodules typical of RA; (*c*) as the population in this region is relatively static, case notes of the relative were checked to verify the history of RA, where possible.

A comprehensive past and current smoking history was taken from the time of inclusion to the study. Cigarette consumption was quantified in pack years. One pack year is equivalent to 20 cigarettes smoked a day for one year. A current smoker was taken to be a smoker of at least one cigarette a day for one year. An ex-smoker was defined as a person who had stopped smoking for at least three months. Control subjects were seen in a north Staffordshire dermatology outpatients clinic. Specifically, the controls all had benign non-inflammatory skin lesions. They were investigated in an identical manner to the

Table 2 Comparison of smoking history between patients with rheumatoid arthritis and dermatology controls

	Current smokers (No (%))	Ex-smokers (No (%))	Never smoked (No (%))	Pack years (median (semi-IQR)) *
Patients (n=239)	100 (42)	55 (23)	84 (35)	18.0 (18.5)
Controls (n=239)	52 (22)	72 (30)	115 (48)	1.0 (8.5)
Significance (p value)	<0.001[2]	0.09†	0.005†	<0.001‡

*Semi-IQR = semi-interquartile range.
†Resulting from a sign test.
‡Resulting from a Wilcoxon signed rank test.

Table 3 Odds ratio for having rheumatoid arthritis with pack years of cigarettes smoked

Pack years	Patients (%)	Controls (%)	Odds ratio* (95% CI)†	Significance (p value)
1–10	112 (47)	161 (67)	0.80 (0.44 to 1.50)	0.496
11–20	15 (6)	35 (15)	0.55 (0.26 to 1.16)	0.111
21–30	34 (14)	26 (11)	1.76 (0.95 to 3.29)	0.068
31–40	30 (13)	7 (3)	5.72 (2.28 to 14.36)	<0.001
41–50	27 (11)	4 (2)	13.54 (2.89 to 63.38)	<0.001
>50	21 (9)	6 (3)	8.41 (2.45 to 28.84)	<0.001
Ever smoked	155 (65)	124 (52)	1.81 (1.22 to 2.19)	0.002

*Calculated using conditional logistic regression.
†95% CI = 95% confidence interval.

patients with RA (by JTL). The patients with RA and controls were then matched for age, sex, and social class.

STATISTICAL ANALYSIS

Conditional logistic regression was used to calculate the odds ratio for having RA. Between patients with RA and matched controls, frequencies were compared using the sign test for categorical data and the Wilcoxon signed rank test for continuous data. Between groups within patients with RA, frequencies were compared with the χ^2 test and continuous data using the two sample t test, where a Gaussian distribution could be assumed, or the Wilcoxon two sample test otherwise (indicated by the quoting of medians rather than means). Statistical significance was set at the 5% level.

Results

Two hundred and thirty nine patients with RA, with a mean (SD) age of 60.5 (11.8) years were studied. Table 1 summarises their demographic details.

CASE-CONTROL STUDY: SMOKING STATUS AT TIME OF STUDY

Patients with RA were significantly more likely to be current smokers than controls matched for age, sex, and social class (table 2). Of the patients with RA, 100 (42%) were current smokers v 52 (22%) of the controls (p<0.001). There was no significant difference in the proportion of subjects who were ex-smokers: 55 (23%) of the patients with RA v 72 (30%) of the controls (p=0.09). Of the patients with RA, significantly fewer had never smoked: 84 (35%) v 115 (48%) of the controls (p=0.005). The difference between pack years smoked in the patients with RA and controls was highly significant (a median value of 18.0 v 1.0; p<0.001.).

There was a dose dependent association between pack years smoked and RA (summarised in table 3). The association between RA and ever having smoked and RA was modest (matched OR 1.81, 95% CI 1.22 to 2.19; p=0.002), but there was a strong association between heavy cigarette smoking and RA with 41–50 pack years (matched OR 13.54, 95% CI 2.89 to 63.38; p<0.001).

COMPARISON OF SMOKING BETWEEN PATIENTS WITH RA WITH OR WITHOUT A FAMILY HISTORY OF RA

One hundred and forty three (60%) patients with RA had no family history of RA (FH −ve RA). When these patients were compared with the patients with RA with a positive family history of RA (FH +ve RA) there were no apparent differences in age, sex or social class (table 4). A comparison of the smoking history was made between these two groups. The RA FH −ve patients smoked significantly more than RA FH +ve patients. More RA FH −ve patients had ever smoked (72% v 54%; p=0.006), were smoking at the time of disease onset (58% v

Table 4 Comparison of demographic and smoking history between patients with rheumatoid arthritis with or without a family history of the disease

	Family history +ve (n=96)	*Family history −ve (n=143)*	*Significance (p value)*
Sex (No (%))			
Male	23 (24)	29 (20)	
Female	73 (76)	114 (80)	0.499*
Age at onset (years)			
Mean (SD)	44 (12.5)	49 (13.5)	0.003†
Smoking at diagnosis (No (%))			
Yes	37 (39)	83 (58)	
No	59 (61)	60 (42)	0.003*
Social class (No (%))			
Classes I–II	11 (11)	19 (13)	
Classes IIIN–IIIM	37 (39)	47 (33)	
Classes IV–V	48 (50)	77 (54)	0.656*
Number of pack years			
Median (semi-IQR)¶	4.0 (13.5)	25.0 (21.5)	<0.001‡

*Resulting from a χ^2 test.
†Resulting from a two sample *t* test.
‡Resulting from a two sample Wilcoxon test.
¶Semi-IQR = semi-interquartile range.

39%; p=0.003), and had smoked a greater number of pack years (median of 25.0 *v* 4.0, p<0.001). The median RA FH −ve patients' cumulative exposure to cigarettes was 25.0 pack years more than the controls with dermatology disease (25.0 RA *v* 0.0 controls; p<0.001), whereas there was no difference for RA FH +ve cases (4.0 pack years *v* 5.0 controls; p=0.980). Furthermore, the mean age at onset of RA FH +ve cases was significantly lower (44 (12.5) years, median age 43, range 18–73) than the FH −ve group (mean age 49 (13.5) years, median age 50, range 19–78; p=0.007) and disease duration was longer in RA FH +ve patients (mean 17.6 years (9.5)) than in RA FH −ve cases (mean 10.8 (9.9) years; p<0.0001).

COMPARISON OF PATIENTS WITH RA NEVER HAVING SMOKED AND PATIENTS WITH RA SMOKING AT THE TIME OF DISEASE ONSET

One hundred and twenty (50%) patients with RA were currently smoking at the time of disease onset. Eighty four (35%) of the patients with RA had never smoked. The mean age of onset differed significantly between these two groups: 43.2 years (13.8) in the patients with RA never having smoked (median age 42, range 18–70) in comparison with a mean age of 47.6 (12.3) (median age 47, range 18–72) in the patients with RA smoking at the time of disease onset (p=0.001). Significantly more of the patients with RA who had never smoked (46 (54%)) had a positive family history of RA than the patients with RA smoking at disease onset (39 (33%); p=0.004).

Discussion

In this study we examined the relation between cigarette smoking in patients with RA attending rheumatology outpatient clinics in Merseyside, an industrial region of the north of England. We found a dose dependent association between pack years smoked and RA. A high cumulative exposure to cigarette smoke was strongly associated with RA. Additionally, the patients with RA with a family history of RA were significantly less likely to be current cigarette smokers at the time of disease onset

and smoked significantly fewer pack years than the RA group without a family history of RA.

The inclusion of controls from a different region of the north of England is unlikely to have introduced a bias as the control subjects were matched for age, sex, and social class, which are the principal determinants of the prevalence of cigarette smoking.[15] It may be that dermatology patients smoke in a different fashion than the general population, but we feel that this is unlikely as we excluded patients with inflammatory skin lesions such as psoriasis, a condition associated with excess tobacco consumption,[16] and atopic eczema, which is associated with asthma and therefore disassociated from heavy cigarette smoking.

Control subjects with malignant skin lesions were also excluded, as such lesions are significantly more common in outside manual workers, such as agricultural workers[17] and welders.[18] Also, the smoking history of people with these particular occupations may not be similar to those of manual indoor workers, who may have smoking constraints imposed upon them. Furthermore, the control subjects matched the RA FH +ve group for pack years smoked. This is important as the smoking history of the RA FH +ve group is typical of that of the adult population aged 18–60 years for our region of the north west of England, with 39% of the RA FH +ve group smoking at the time of diagnosis compared with 39% of adults (18–60) who are current smokers in our region of Merseyside (St Helens).[15]

We confirmed previous findings that cigarette smoking itself is modestly associated with RA. For ever having smoked, the association with RA is modest (matched OR 1.81, 95% CI 1.22 to 2.19). This is a similar association to that observed by Symmons *et al* in a community based study[19] (OR 1.66, 95% CI 0.95 to 3.06). However, the number of cigarettes smoked was not quantified in Symmons's study, or in other studies[6 20] investigating the association between cigarette smoking and RA. Therefore no direct comparison can be made between these studies and our own observations about the risk for heavy cigarette smoking. Our study shows the need to quantify the number of cigarettes smoked when studying the relation between cigarette smoking and its association with RA. The strong association with a high cumulative exposure to cigarettes may partly underlie the observation that the incidence of RA increases with age. In keeping with this hypothesis, a Finnish study observed a 20-fold increased incidence of RA in men currently smoking as opposed to men who had never smoked after individual follow up of 14 or more years.[20]

We found a modest non-significant association between smoking and RA in subjects who had smoked less than 30 pack years. However, we found that prolonged exposure to cigarette smoke resulted in a strikingly increased risk of developing RA for patients with a 41–50 pack year cigarette habit. This has implications for studies in countries in which heavy cigarette smoking is extremely uncommon. An example of this is a large prospective study over 20 years

in Finland designed to examine the relation between cigarette smoking and the development of RA.[20] The study found no relation between cigarette smoking and RA in Finnish women. However, only 2.5% of the women studied were current cigarette smokers of more than 15 cigarettes a day and few would be exposed to more than 30 pack years of cigarettes. In contrast, a recent large North American community based study did observe a significantly increased risk of RA in women smoking more than 25 cigarettes a day for more than 20 years.[10] The increased risk observed in the North American study is modest, but this study had a low response rate (22%). Non-responders in RA studies tend to be older,[6] have greater comorbidity, and are poorer than responders.[21] It is likely that smokers are over-represented in those particular non-responder groups and therefore the association with RA might have been underestimated. It is noteworthy that our findings apply to the patients with more severe RA seen in patients attending out-patients clinics, and are not necessarily true for milder, community based RA. Most studies investigating the association between cigarette smoking and RA have been community based studies.[6 10 19 20 22 23]

Genetic factors are of clear importance in the development of RA. Family history of RA was chosen as a simple surrogate marker for genetic predisposition. The criteria for "RA" in relatives were made as stringent as possible, to avoid the common mistake of calling a degenerative disease "rheumatism" or "RA". Forty per cent of our RA group had a family history of RA. This is higher than previously reported in the literature. However, these studies included first degree relatives only.[5]

We found that RA FH +ve patients had an almost identical pack year history to that of their respective controls and smoked significantly less than the RA FH −ve patients. On average, the patients who were RA FH +ve had had the disease for longer (6.8 years) than patients who were RA FH −ve. In keeping with this finding, patients with RA with disease associated major histocompatibility complex genes appear to develop RA before those who do not.[24] These data also suggest that RA does not predispose patients to smoke more heavily, as has been previously suggested,[25] because the FH +ve group had had RA the longest but smoked the least. Our observation that patients with RA who have never smoked have a significantly increased prevalence of a family history of RA than those who smoke at the time of diagnosis would affect the interpretation of the many studies that have investigated the genetics of RA without recording the smoking history.

The reasons why prolonged cigarette smoking should be strongly associated with the development of RA are not clear. A recent study by Wolfe found that rheumatoid factor concentration in a group of patients with RA was related to the number of pack years smoked, irrespective of the smoking status of the patient at the time of the study.[26] A longitudinal community study of healthy subjects found that the persistence of rheumatoid factor significantly increases the risk, 7.5-fold for the development of RA,[27] and there is certainly a strong association between cigarette smoking and rheumatoid factor production in healthy subjects.[28] We propose the hypothesis that prolonged heavy cigarette smoking, but not smoking itself, results in increased rheumatoid factor production, and that in part this explains the relation of increasing pack years smoked and the association with RA. Surprisingly, no studies of other possible mechanisms to explain the association between cigarette smoking and RA have been carried out.

This study may, in part, explain the increased mortality found in RA,[29] as current data show that continued cigarette smoking throughout adult life doubles age-specific mortality rates, nearly trebling them in late middle age.[30]

This study was not designed to consider whether an association between cigarette smoking and RA is causal. As possible evidence, we would cite the reduced incidence of RA in the UK over recent years,[31] coinciding with an overall reduction in smoking evident over the past 30 years. In 1971 45% of the adult population were current smokers,[32] as compared with 28% in 1996.[15] An unfortunate corollary is that this trend may be reversed in the years to come as the proportion of young girls smoking is increasing.[15] If the recent trend for increased cigarette consumption in young woman continues, a new epidemic of RA may occur, not immediately, but in the time it takes to smoke the equivalent of 30 or more pack years of cigarettes.

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