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Smoking is a major preventable risk factor for Rheumatoid arthritis Estimations of risks after various exposures to cigarette smoke

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Abstract

Background—Earlier studies have demonstrated that smoking and genetic risk factors interact in providing an increased risk for Rheumatoid Arthritis (RA). Less is known on how smoking contributes to RA in the context of genetic variability, and what proportion of RA that may be caused by smoking.

Objectives—To determine the association between amount of smoking and risk of RA in the context of different HLA-DRB1 shared epitope (SE) alleles, and to estimate proportions of RA cases attributed to smoking.

Design, Setting, and Participants—Data from the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) case-control study encompassing 1204 cases and 871 controls were analysed.

Main Outcome Measure—Estimated odds ratio to develop RA and excess fraction of cases attributable to smoking according to amount of smoking and genotype.

Results—Smoking was estimated to be responsible for 35 % of the ACPA+ cases. For each HLA-DRB1 SE genotype, smoking was dose-dependently associated with increased risk of ACPA + RA (p-trend<0.001). In individuals carrying two copies of the HLA-DRB1 shared epitope, 55 % of ACPA-positive RA were attributable to smoking.

Conclusions—Smoking is a preventable risk factor for RA. The increased risk due to smoking is dependent on amount of smoking and genotype.

Keywords

Rheumatoid Arthritis; Smoking; HLA-DRB1; Case-control studies; Epidemiology

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Competing Interest: None to declare.

Introduction

Smoking is the most established environmental risk factor for developing rheumatoid arthritis (RA)[1]. One hypothesis on the effect of smoking is that smoking causes citrullination of peptides and in the context of RA susceptibility genes contributes to elicitation of immunity to these citrullinated proteins/peptides, and eventually to the onset of RA [2-5].

It is now of interest not only to decipher the etiology of RA in the light of this gene-environment interaction, but also take a public health perspective in determining the number of cases of RA attributable to smoking in different genetic contexts. We have therefore used our population-based study Epidemiological Investigation of Rheumatoid Arthritis (EIRA), to estimate the relative risk for RA conferred by different amounts of smoking in the context of different HLA-DRB1 genotypes, and to estimate the excess fraction of RA cases attributed to smoking.

Methods

Set up

EIRA is a population based case-control study. Information was collected from incident RA cases and controls matched for age, gender and residential area recruited between May 1996 and December 2003. We enrolled cases aged 18-70 years from 19 clinics located in the south and middle parts of Sweden. Almost all of the rheumatology units in the study area participated in the study. Each case was diagnosed according to the ACR of 1987 criteria for RA [6] by rheumatologists at the corresponding clinic and was invited to participate in the study. Controls were randomly selected from a population register with consideration taken to sex, age and residential area and then sent a questionnaire by post. We managed to collect genetic, anti-body and questionnaire information from 1205 cases (85%) and 872 controls (52%). We asked five questions regarding smoking: present and previous smoking, time point for start and/or stop of smoking and amount of cigarettes smoked per day.

We classified the amount of smoking into three groups (0-9, 10-19 and 20- pack years). One pack year is equivalent to smoking 20 cigarettes per day for one year.

We genotyped SE alleles for participants who contributed blood samples. SE was defined as DRB1*01, DRB1*04 or DRB1*10 in the HLA-DRB1 locus [7].

Antibody levels were measured by using the Immunoscan-RA Mark2 enzyme-linked immunosorbent assay and the cut-off limit for ACPA-positive RA was set to 25 U/ml. Details on study design, data collection, exposure information, genotyping and serological analysis are given elsewhere [2,8-10].

Ethical approvals were obtained from relevant ethical committees and all the participants consented to contribute to the study on voluntary basis.

Statistical analysis

We calculated odds ratios of developing RA associated with different categories of smoking and presence of SE alleles together with 95 percent confidence intervals by using logistic regression models. Interaction between smoking and presence of SE alleles was evaluated as departure from additivity of effects [11-12] and was estimated by calculating the attributable proportion due to interaction (AP) [12].

All analyses were adjusted for the matching variables, age, sex, and residential area.

Trend test for a dose response relationship regarding smoking and risk of developing ACPA-positive RA was performed separately for each SE allele category as suggested by Armitage[13].

We calculated the excess fraction (of cases) attributable to smoking in percent (EF%) [14] as an indicator of the relevance of smoking as a risk factor for RA in the population. EF was calculated in relation to RA overall as well as to ACPA-positive RA and different HLA-DRB1 genotypes.

SAS version 9.1 for windows (SAS Institute, Cary, NC) was used to analyse all data.

Results

A total of 61 percent of RA cases were ACPA positive. We have chosen to focus on ACPA-positive RA since we have not found any association between smoking, SE alleles or their combination regarding increased risks of developing ACPA-negative RA (the OR associated with smoking was 0.6 (95% CI: 0.4 – 1.0) and with SE 0.8 (95 % CI: 0.4 – 1.7), as reported previously [2].

Smoking and risk of ACPA-positive RA

Different amounts of pack years smoked without considering SE allele status were associated with ACPA-positive RA in a dose response manner (p -trend<.0001), with the highest OR for ever smokers who had smoked ≥ 20 pack years (table 1).

For ex-smokers the increased risk of ACPA-positive RA was observed to decrease with the duration of time since smoking cessation (p -trend<0.0001).

For intermediate ever-smokers (pack-years 10-19), the increased risk of ACPA-positive RA diminished almost to the level of never-smokers 20 years after smoking cessation. Among heavy smokers, a relatively high OR was still observed even 20 years after cessation of smoking (table 1).

Public health impact of smoking in terms of excess fraction of cases attributable to smoking

We calculated the excess fraction of cases attributable to smoking as an indicator of the relevance of smoking as a public health risk factor. For ACPA-positive RA, the excess fraction attributable to smoking was 35 % (95 % CI 25 – 45) (31 % for women and 42 % for men). The excess fraction attributable to smoking for RA overall (ACPA-positive and ACPA-negative RA combined) was 20 (95 % CI 7 – 26) percent, which indicates that smoking plays an important role in the occurrence of RA overall because ACPA-positive RA is the most common form of RA.

Since smoking interacts with SE alleles (table 2, Figure 1) we also calculated the excess fraction of cases attributable to smoking by HLA-DRB1 SE genotype (table 3). Among ACPA-positive RA cases with double SE alleles 55 % (95% CI 39-67) could be attributed to smoking.

Discussion

This report describe smoking and risk of RA in a novel way regarding the impact of smoking both concerning its contribution to RA and concerning the dose-dependent addition of risk conferred by smoking in individuals with different numbers of HLA-DRB1 risk

alleles. We also provide novel data on effects of cessation of smoking concerning future risk for RA.

The demonstration that approximately one third of cases of ACPA-positive RA, the most severe variant of RA, appear to be attributed to smoking illustrates the impact of smoking as a major cause of RA on the population level. Notable is that this attribution appears to be higher in men than in women. The smoking attribution to RA is however smaller than the smoking attribution to lung cancer which is estimated to be as high as 90 % [15], but similar to that seen for ischaemic heart disease [16].

The data on interactions between smoking and HLA-DR alleles in providing risk for RA in the present report are in accordance with those published from studies in several different countries [4,5,17], including studies from the Nurses Health (NHS) cohort study [5]. In one other US-based case-only study the effects of smoking was more limited but still statistically significant [18].

Other environmental and genetic factors may modify the effects of smoking on the development of RA. There are indications that airborne exposures such as silica and other air pollutants may enhance or possibly dilute the effects of smoking [19]. There are also other life style factors such as alcohol consumption or hormonal factors influencing risk for RA that may interact with smoking [20-21]. Thus, the precise effects of smoking on RA development may vary considerably in various populations, but so far smoking has been shown to be an essential risk factor for RA in a majority of published studies.

We used case-control methodology to generate data regarding risk for RA as a whole as well for ACPA-positive and ACPA-negative RA in the context of various HLA-DR genes and smoking. The fact that more than 50% of RA cases can be attributed to smoking in individuals carrying two copies of the HLA-DRB1 SE genes, illustrates drastically how smoking may affect disease risk differently in different individuals. Although this type of data should not be taken as an argument of genotyping of healthy individuals, they may provide a rationale for specific counselling against smoking for individuals with a family history of RA.

The problem of selection bias always encountered in case-control studies was in the current study minimised by the population-based design and by the observation that smoking habits did not differ between controls with and without blood samples. This, and the fact that identification of controls was made by matching for age, sex and residential area in the same population that generated the cases, makes us confident that the results are reliable from a methodological standpoint.

In conclusion, the data presented in this paper on the impact of smoking on development of RA, warrants more active information on the association between smoking and RA to the general public as well as to relatives of patients with RA.

To which extent cessation of smoking will be able to alleviate an already ongoing RA is yet incompletely known, although it has been demonstrated that smoking contributes to cardiovascular disease, which is the major reason for premature death in RA [22]. There are many reasons for the medical community to communicate the known facts on smoking and RA, with the aim to diminish smoking and prevent RA and its consequences.

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Figure 1.

Odds ratios for different amounts of smoking (pack-years) in combination with none (No SE), one (Single SE) or two (Double SE) copies of SE alleles. The reference group being none smokers without SE alleles.

Table 1

Characteristics of ACPA positive RA cases and controls.

Variables	Cases, ACPA positive (n = 736)	Controls (n = 872)	OR (95 % CI) [‡]	P-value
No SE alleles (%)	111 (15.08)	414 (47.5)	Reference.	< 0.0001
SE alleles, heterozygote (%)	383 (52.04)	373 (42.8)	4.0 (3.1 - 5.1)	< 0.0001
SE alleles, homozygote (%)	242 (32.88)	85 (9.75)	11.5 (8.1 - 16.1)	< 0.0001
Never smokers (%)	207 (28.12)	347 (39.79)	Reference	< 0.0001
Ever smokers (%)	529 (71.88)	525 (60.21)	1.8 (1.4 - 2.2)	< 0.0001
Ever smokers, pack years *				
Never smokers (%)	207 (28.2)	347 (39.8)	Reference	< 0.0001
0- 9 (%)	159 (21.6)	219 (25.14)	1.2 (1.0 - 1.6)	0.084 [‡]
10 - 19 (%)	144 (19.6)	134 (15.43)	2.0 (1.6 - 2.6)	< 0.0001 [‡]
20- (%)	225 (30.6)	171 (19.63)	2.6 (2.0 - 3.3)	< 0.0001 [‡]
- P for trend regarding OR for pack years				< 0.0001 [‡]
Years since quitting smoking				
Never smokers	207	347	Reference	< 0.0001
0 - 9	143	177	2.4 (1.8-3.1)	< 0.0001
10 - 19	71	127	1.7 (1.2-2.3)	0.004
20 -	60	133	1.4 (1.0-2.0)	0.08
- P for trend regarding OR for years since quitting				< 0.0001

[‡]Odds ratio (OR) and corresponding 95 percent confidence interval (95% CI) adjusted for sex, age and residential area.[‡]p-value for differences in proportions regarding pack years of smoking between cases and controls.

* Information regarding Pack years missing for one case and one control.

Odds ratios and attributable proportions due to interaction for different doses of smoking and SE alleles, regarding the risk to develop ACPA positive RA.

Table 2

Smoking dose	No SE		Heterozygotic SE (SSE)		Homozygotic SE (DSE)	
	No. ca/co *	OR (95 % CI) ‡	No. ca/co *	OR (95 % CI) ‡	No. ca/co *	OR (95 % CI) ‡
No Smoke	38/154	1.0 (REF) §	107/150	3.2 (2.0 - 4.9)	62/43	6.3 (3.7 - 10.9)
0 - 9 pack years	25/104	1.0 (0.6 - 1.8)	80/96	3.4 (2.1 - 5.6)	54/19	12.0 (6.2 - 23.0)
AP**				0.09 (-0.32-0.49)		0.47 (0.12 - 0.83)
10 - 19 pack-years	18/68	1.2 (0.6 - 2.2)	83/56	7.3 (4.3 - 12.4)	43/10	24.6 (10.9 - 55.8)
AP**				0.53 (0.30 - 0.76)		0.73 (0.50 - 0.95)
20- pack years	30/87	1.9 (1.1 - 3.5)	112/71	8.7 (5.3 - 14.4)	83/13	37.6 (18.3 - 77.4)
AP**				0.51 (0.31 - 0.72)		0.80 (0.67 - 0.94)
p-value for trend		p = 0.11		p < 0.0001		p < 0.0001

* Number of exposed (exp) cases (ca) and controls (co),

** Attributable proportion due to interaction (AP),

‡ Odds ratio (OR) and corresponding 95 percent confidence interval (95% CI) adjusted for sex, age and residential area,

§ Reference category.

Proportion of cases attributable to smoking (Excess Fraction (EF)) by SE alleles, regarding ACPA positive RA, ACPA negative RA and total RA.

Table 3

ACPA positive RA					
No SE		Heterozygotic SE (SSE)		Homozygotic SE (DSE)	
Smoking dose	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)
No Smoke	38/154 Ref [§]	107/150 Ref [§]	62/43 Ref [§]	180/42 55 (39 - 67)	Ref [§]
Ever smoke	73/259 11 (-19 - 33)	275/223 29 (14 - 43)			
ACPA negative RA					
No SE		Heterozygotic SE (SSE)		Homozygotic SE (DSE)	
Smoking dose	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)
No Smoke	90/154 Ref [§]	87/150 Ref [§]	25/43 Ref [§]	28/42 7 (-25 - 38)	Ref [§]
Ever smoke	115/259 -14 (-39 -7)	124/223 0 (-22 - 19)			
Total RA					
No SE		Heterozygotic SE (SSE)		Homozygotic SE (DSE)	
Smoking dose	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)	No. ca/co * EF% † (95% CI)
No Smoke	128/154 Ref [§]	194/150 Ref [§]	87/43 Ref [§]	208/42 47 (30 - 60)	Ref [§]
Ever smoke	188/259 -7 (-28 - 11)	399/223 19 (1 - 34)			

* Number of exposed cases (ca) and controls (co),
† Excess fraction in percent (EF%) with corresponding 95 percent confidence interval (95% CI),
§ Reference category. The EF% attributable to smoking and risk of ACPA+ RA without consideration to SE status is 35 (95% CI: 25 - 45), ACPA- RA EF%= -5 (95% CI: - 21 - 10) and RA total EF%= 20 (95% CI: 11 - 29)