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Clinical Study

Smoking increases the risk of multiple sclerosis in Queensland, Australia

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ABSTRACT

There is growing evidence for the role of smoking in the aetiology of multiple sclerosis (MS). We have undertaken a large case-control study of smoking in MS and assessed this using a regression model. We have confirmed an association between increased risk of MS and smoking in Queensland, Australia, a region of intermediate risk for MS. The overall adjusted odds ratio was 1.9 (95% confidence interval 1.5–2.5) for ever smokers. There was no statistically significant difference in the risks for males and females. A number of potential mechanisms to explain this association have been postulated including direct and indirect (via vitamin D) effects on the immune system.

1. Introduction

Multiple sclerosis (MS) is an inflammatory condition of the central nervous system [1]. Susceptibility to the disease results from genetic [2] and environmental influences. There is strong evidence for a number of environmental influences, including latitude (likely related to exposure to ultraviolet light and vitamin D levels), Epstein-Barr virus and exposure to cigarette smoke [3–6].

Australia is a nation of intermediate prevalence for MS, with a latitude gradient of increasing prevalence at increasing latitude [7]. Smoking prevalence in Australian adults has declined from 35% in 1980 to 23% in 2001 [8]. A case-control study found smokers to be at higher risk of MS in the relatively high prevalence region of Tasmania [9].

We aimed to establish the effects of smoking on MS susceptibility in the lower prevalence region of Queensland, Australia using a case-control design. The null-hypothesis being tested was that smoking is not associated with an increased risk of MS.

2. Methods

Cases were ascertained by two methods. The first group consisted of attendees to the MS Clinic at the Gold Coast Hospital. Diagnosis of MS was determined using revised McDonald criteria [10]. All patients within the database for whom age, sex and smoking habit were available were included. The second group consisted of members of the MS Society in Queensland, in whom the diagnosis of MS was confirmed by review of the patient's general practitioner and/or neurologist case notes. Controls were identified from the electoral roll. Australia has a mandatory system of electoral enrolment; all adults over the age of 18 years must maintain a current address on the roll. Controls were asked to confirm that they did not have a diagnosis of MS.

Data regarding age, sex, ethnicity, smoking status, clinical history of MS and disease duration were obtained either in person or by postal questionnaire with follow-up by telephone to clarify any ambiguities. For patients seen in the MS Clinic, disease severity was assessed using the Expanded Disability Severity Scale (EDSS) [11] by a neurologist and by questionnaire [12] for those not seen in person. All subjects gave written informed consent for the study. Ethical approval was obtained from the Griffith University Human Research Ethics Committee.

The characteristics of patients and controls were compared by Fisher's exact test and Student's *t*-test. Crude odds ratios (OR) were calculated for patients and controls. A sequential binary logistic regression model was constructed to assess interaction and influence of age, sex (male *versus* female), smoking status (*versus* never as reference category) and ethnicity (Caucasian *versus* other) on MS risk [13].

3. Results

There were 560 patients and 480 controls included in the study (Table 1). There were significant differences between patients and controls for age and sex. Of the patients, 314 (55%) were seen in

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Table 1
Demographics of patients and controls

Characteristic		Patients	Controls	*p* value
Total, n		560	480	
Mean age, years (SD)		50 (12)	57 (15)	<0.0001[a]
Female, n		458	314	
F:M ratio		4.5	1.9	<0.0001[b]
Ethnicity, n (%)	Caucasian	539 (96%)	465 (97%)	
	Other	13 (2%)	12 (3%)	NS
Smoking habit, n (%)	Never	219 (39%)	256 (53%)	
	Ex-smoker	229 (41%)	190 (40%)	NS
	Current	112 (20%)	34 (7%)	

F = female, M = male, NS = no significant difference, SD = standard deviation.
[a] Two sample Student's *t*-test.
[b] Fisher's exact test.

person, and the remainder were contacted by post or telephone. Response rates for the three groups of participants are summarised in Table 2.

Comparison of the demographic and clinical details of the two groups of patients (Table 3) shows that the postal participants were older, with longer disease duration and more likely to have progressive disease with higher EDSS scores. It might be anticipated that patients with progressive disease might be less likely to be attending a clinic. The combined cohort is typical of population-based cross-sectional studies [14].

Ethnicity was unavailable for eight patients and three controls, otherwise data were complete. Smoking habits by age group and sex are displayed in Supplementary Figure 1. Comparison based upon method of recruitment found no significant differences in rates of never smoking or ex-smoking in patients. There were more current smokers in the clinic cohort ($p = 0.0049$) probably reflecting the younger age and lower disease severity of this group.

EDSS and disease course were available for all patients, with a mean EDSS of 3.9 (standard deviation 2.6). Disease course was clinically isolated syndrome in 21 (4%), relapsing remitting in 294 (53%), secondary progressive in 167 (30%) and primary progressive in 78 (14%). Risks are given in Table 4 and were highest for current smokers (OR 3.9, 95% confidence interval [CI] 2.5–5.9). Risk of smoking was higher in the clinic cohort (OR 2.0, 95% CI 1.5–2.7) than the postal cohort (OR 1.5, 95% CI 1.1–2.1) but the CI overlap.

Sex was an independent risk factor for MS, OR (females) 2.4 (95% CI 1.8–3.2). Age and ethnicity were not associated. Segregation by sex is shown in Table 5 and gave an adjusted OR for male ever smokers of 2.3 (95% CI 1.3–4.1) and for female ever smokers of 1.8 (95% CI 1.4–2.5). Exclusion of clinically isolated syndrome patients did not change the observed associations with smoking habit.

4. Discussion

We have presented results from a case-control study based in South East Queensland, Australia showing increased risk of MS for current and ex-smokers with an overall adjusted OR of 1.9. These results are consistent with those previously reported. Controls were not well-matched, and differed significantly from patients in sex and age profiles, but these factors were included within the regression model for calculation of adjusted OR. Controls were matched for geographical location (same post codes as patients) but we did not collect socioeconomic demographic data.

Smoking habits were established at recruitment to study, not prior to diagnosis of MS. This could have introduced bias in a number of ways. The diagnosis of MS may provoke a re-examination of smoking habit and smoking cessation, but equally the presence of a disabling illness may promote the habit. Analysis of the Nurses' Health Study cohorts found that a new diagnosis of MS did not significantly alter smoking habits [9]. Smoking habits of adults are usually established before the age of onset of MS [15]. Current smokers demonstrated the strongest association with MS, but there was also a statistically significant association when only ex-smokers were considered.

In research based upon postal survey, those who did not respond may be a source of non-responder bias. Although response rates were similar in patients and controls, the lower response in controls may reflect a higher response rate in patients with a vested interest in this research [16]. It is also recognized that smokers are generally less likely to respond to surveys [17]. As smoking has become less socially acceptable, current or ex-smokers may chose not to respond, or self-report as non-smokers. This trend may affect patients, who wish to appear to be caring for their health when reporting to their treating clinician, and controls, who might under-report smoking or fail to respond to the survey. In either case, this would lessen any association with smoking. The possibility of non-response bias having other effects cannot be completely excluded.

Differences between the clinic and postal cohorts were predominantly due to older age and longer disease duration in the postal cohort; these patients may be less likely to attend a clinic regularly.

Table 3
Patient demographics by method of recruitment

Characteristic		Clinic	Postal	*p* value
Total, n		305	255	
Age, years		48 (12.5)	53 (12.3)	<0.0001[a]
Female, n (%)		242 (79%)	216 (85%)	
F:M ratio		3.8	5.5	0.12[b]
Ethnicity, n (%)	Caucasian	292 (96%)	247 (97%)	
	Other	5 (2%)	8 (3%)	0.28[b]
Age at onset, years		33 (10.1)	34 (10.5)	0.25[a]
Disease duration, years		15.3 (12.4)	20.2 (13.6)	<0.0001[a]
EDSS		3.3 (2.6)	4.6 (2.5)	<0.0001[a]
Smoking habit, n (%)	Never	110 (36.1%)	109 (42.7%)	0.12[b]
	Ex-smoker	120 (39.3%)	109 (42.7%)	0.71[b]
	Current	75 (24.6%)	37 (14.5%)	0.0049[b]
Clinical course, n (%)	Clinically isolated syndrome	13 (4%)	8 (3%)	0.0001[b]
	Relapse remitting	200 (66%)	94 (37%)	
	Secondary progressive	65 (21%)	102 (40%)	
	Primary progressive	27 (9%)	51 (20%)	

Data are presented as mean (standard deviation) unless otherwise stated.
EDSS = Expanded Disability Severity Scale, F = female, M = male, SD = standard deviation.
[a] Student's paired *t*-test.
[b] Fisher's exact test.

Table 2
Response rates among patients and controls

Group	Suspected MS	Not MS/deceased	Eligible, contacted	Replied/enrolled	Response rate
MS clinic	457	44	413	306	74%
MS postal	472	58	414	254	61%
MS total	929	102	827	560	68%
Controls			991	480	48%

MS = multiple sclerosis.