Title

Smoking increases the risk of multiple sclerosis in Queensland, Australia

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Abstract and keywords

There is growing evidence for the role of smoking in the aetiology of multiple sclerosis. We have undertaken a large case-control study of smoking in MS and assessed this through a regression model. We have confirmed an association between risk of MS and smoking in the intermediate risk region of Queensland. The overall adjusted OR was 1.9 (95% CI 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.

[41] multiple sclerosis, [53] case-control studies, [59] risk factors in epidemiology

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 factors 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 multiple sclerosis, with a latitude gradient of increasing prevalence at increasing latitude.[7] Smoking prevalence in Australian adults has declined from 35% in 1980 to 23% by 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.

Methods

Cases were ascertained by two methods. The first group consisted of attendees to the MS clinic at the Gold Coast Hospital. Diagnosis of multiple sclerosis was determined using revised McDonald criteria.[10] All patients within the database for whom age, sex and smoking habit was 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 cases and controls were compared by Fisher's exact test and student's t-test. Crude odds ratios (OR) were calculated for cases and controls. A sequential binary logistic regression model was constructed to assess interaction and influence of age, gender (*male vs. female*), smoking status (*vs. never as reference category*) and ethnicity (*Caucasian vs other*) on MS risk.[13]

Results

There were 560 cases and 480 controls (table 1). There were significant differences between cases and controls for age and gender. Of the cases, 314 (55%) were seen in person, 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 cases (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]

Table 1 – Demographics of cases and controls

Characteristic		Cases	Controls	P-value
N		560	480	
Age (Year) - mean (SD)		50 (12)	57 (15)	p<0.0001[a]
Female – n (%)		458	314	p<0.0001[b]
F:M ratio		4.5	1.9	
Ethnicity – n (%)	Caucasian	539 (96%)	465 (97%)	ns
	Non-white	13 (2%)	12 (3%)	
Smoking habit – n (%)	Never	219 (39%)	256 (53%)	
	Ex	229 (41%)	190 (40%)	ns
	Current	112 (20%)	34 (7%)	

[a] two sample student's t-test
[b] Fisher exact test
ns = no significant difference

Table 2 - Response Rates

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%

Table 3 - Demographics of cases by method of recruitment

Characteristic		Clinic	Postal	
N		305	255	
Age (Years) - mean (SD)		48 (12.5)	53 (12.3)	p<0.0001[a]
Female - n (%)		242 (79%)	216 (85%)	p=0.12[b]
F:M ratio		3.8	5.5	
Ethnicity - n (%)	Caucasian	292 (96%)	247 (97%)	p=0.28[b]
	Non-caucasian	5 (2%)	8 (3%)	
Age at onset (Years) - mean (SD)		33 (10.1)	34 (10.5)	p=0.25[a]
Disease duration (Years) - mean (SD)		15.3 (12.4)	20.2 (13.6)	p<0.0001[a]
EDSS - mean (SD)		3.3 (2.6)	4.6 (2.5)	p<0.0001[a]
Smoking habit – n (%)	Never	110 (36.1%)	109 (42.7%)	p=0.12[b]

	Ex	120 (39.3%)	109 (42.7%)	p=0.71[b]
	Current	75 (24.6%)	37 (14.5%)	p=0.0049[b]
Clinical Course - n (%)	Clinically isolated syndrome	13 (4%)	8 (3%)	
	Relapse remitting	200 (66%)	94 (37%)	p<0.0001[b]
	Secondary progressive	65 (21%)	102 (40%)	
	Primary progressive	27 (9%)	51 (20%)	

[a] student's paired t-test
[b] Fisher's exact test

Ethnicity was unavailable for 8 cases and 3 controls, otherwise data was complete. Smoking habits by age group and gender are displayed in e-figure 1. Comparison based upon method of recruitment found no significant differences in rates of never smoking or ex-smoking in cases. 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 cases, mean EDSS 3.9 (SD 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% 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 confidence intervals overlap.

Table 4 – Risk of MS by smoking status

Smoking status	Cases (%)	Controls (%)	Crude OR	(95% CI)	Adjusted OR*	(95% CI)
Never smoker	219 (39.1%)	256 (53.3%)	Ref		Ref	
Ex-smoker	229 (40.9%)	190 (39.6%)	1.4	(1.1 - 1.8)	1.6	(1.2 - 2.1)
Current smoker	112 (20.0%)	34 (7.1%)	3.9	(2.5 - 5.9)	3.6	(2.3 - 5.6)
Ever smoker	341 (60.9%)	224 (46.7%)	1.8	(1.4 - 2.3)	1.9	(1.5 - 2.5)

*Adjusted for age, ethnicity and gender.

Gender 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 gender 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 1.8 (95% CI 1.4-2.5). Exclusion of CIS cases did not change the observed associations with smoking habit.

Table 5 – Risk of MS segregated by gender

	Females	Males

Smoking Status	Crude OR	(95% CI)	Adjusted OR*	(95% CI)	Crude OR	(95% CI)	Adjusted OR*	(95% CI)
Never smoker	Ref		Ref		Ref		Ref	
Ex-smoker	1.5	(1.1 - 2.0)	1.5	(1.1 - 2.1)	1.7	(1.0 - 3.0)	1.9	(1.1 - 3.5)
Current smoker	4.1	(2.4 - 6.9)	3.5	(2.1 - 6.0)	5.0	(2.3 - 11.0)	4.0	(1.8 - 8.8)
Ever smoker	1.9	(1.4 - 2.5)	1.8	(1.4 - 2.5)	2.2	(1.3 - 3.8)	2.3	(1.3 - 4.1)

*Adjusted for age and ethnicity.

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 cases in gender 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 cases) 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.

Smoking has become a less socially acceptable habit, and current or ex-smokers may be more likely to self-report as non-smokers. Alternatively, smokers may be less likely to respond to the initial survey. This trend may affect cases and controls to an equal extent, for different reasons. Cases may have a greater desire to appear to be pursuing healthy habits to their treating clinicians, and non-smoking controls may be more likely to volunteer for health research. In either case, this would lessen any association with smoking. In addition our response rates for cases and controls were similar.

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. The response rates, diagnostic failure rates and risk with smoking were similar. The demographics of the combined cohort were comparable to other population-based cohorts.

The underlying mechanism for the association between smoking and MS is unclear. Cigarette smoke exposure induces a number of changes in immune function, including increased markers of inflammation,[16-20] relative susceptibility to respiratory viruses[21] and changes to post-translational processing of immunogenic proteins that could plausibly increase MS

susceptibility.[22-23] Other components of smoke are particularly toxic to oligodendrocytes and neurons.[24-26]

Smoking habit may be confounded with other risk factors, less easily measurable but responsible for increasing MS susceptibility. It seems unlikely that genetic risk (underlying MS susceptibility) does not influence the choice to take up cigarette smoking. There is little evidence that known genetic susceptibility alleles are associated with a risk taking phenotype. Patients with MS, however, may have a higher intake of alcohol than the general population.[27]

Smokers tend to have lower levels of serum vitamin D than non-smokers.[28-29] The magnitude of risk in Tasmania (where the majority of the population have functional vitamin D deficiency for much of the year) (OR 1.5, 95% CI 1.0 – 2.4) [9,30] is comparable to the risk estimate for the Queensland population presented here. Nevertheless, cigarette smoke induced vitamin D deficiency could be sufficient to increase susceptibility of an individual sufficiently for the development of clinical disease. If a latitude gradient could be demonstrated, where smoking habit has a greater effect at lower latitudes, this could provide support for this hypothesis.

The present study adds to existing data confirming a very clear association between smoking and risk of developing MS. Whilst association does not prove causation, there are clear pathophysiological mechanisms by which smoking can affect both the central nervous system and immune function, and further research on these potential mechanisms is warranted.

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