Cigarette smoking and the progression of multiple sclerosis

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Summary

An increased risk of multiple sclerosis among smokers has been found in several prospective epidemiological studies. The association between smoking and progression of multiple sclerosis has not been examined. We identified patients who had a first multiple sclerosis diagnosis recorded in the General Practice Research Database (GPRD) between January 1993 and December 2000. Their diagnosis and date of first symptoms were confirmed through examination of medical records. Smoking status was obtained from the computer records. To assess the association between smoking and risk of multiple sclerosis, we conducted a case–control study nested in the GPRD. Up to 10 controls per case were randomly selected, matched on age, sex, practice, date of joining the practice and availability of smoking data. To assess the association between smoking and progression of multiple sclerosis, we conducted a cohort study of multiple sclerosis cases with a relapsing–remitting onset. Our nested case–control study included 201 cases of multiple sclerosis and 1913 controls. The odds ratio [95% confidence interval (CI)] of multiple sclerosis was 1.3 (1.0–1.7) for ever smokers compared with never smokers. Our cohort study included 179 cases with a mean (median) length of follow-up of 5.3 (5.3) years. The hazard ratio of secondary progression was 3.6 (95% CI 1.3–9.9) for ever smokers compared with never smokers. These results support the hypothesis that cigarette smoking is associated with an increased risk of multiple sclerosis, and suggest that smoking may be a risk factor for transforming a relapsing–remitting clinical course into a secondary progressive course.

Introduction

The evidence that environmental factors play a prominent role in the development of multiple sclerosis keeps mounting. In addition to the classical migrant studies (Gale and Martyn, 1995), which strongly suggested the existence of environmental factors, recent studies show marked changes in the incidence and geographic distribution of multiple sclerosis that cannot be attributed to genetic factors (Hernán *et al.*, 1999; Wallin *et al.*, 2004).

However, few environmental factors have been consistently associated with multiple sclerosis in epidemiological studies. Cigarette smoking is one of those factors; compared with non-smokers, smokers had a 40–80% increased risk of multiple sclerosis in the four previously conducted prospective studies (all restricted to women) (Villard-Mackintosh and Vessey, 1993; Thorogood and Hannaford, 1998; Hernán *et al.*, 2001).

On the other hand, there are no epidemiological studies on the association between cigarette smoking and the clinical course of multiple sclerosis. Since no modifiable risk factors for multiple sclerosis progression have been identified so far, determining whether cigarette smoking affects the course of multiple sclerosis appears to be a priority. We assessed the

association between cigarette smoking and progression of multiple sclerosis in patients arising from a prospectively followed British population.

Methods
Study population
The General Practice Research Database (GPRD) includes >3 million Britons who are enrolled with selected general practitioners (GPs) (García Rodríguez and Pérez Gutthann, 1998). These physicians have been trained to record their patients' medical and demographic information in a standard manner, and have agreed to supply it anonymously for research purposes. In addition, practices used in this study agree to collaborate in specific research projects by providing photocopies of their patients' paper medical records after personal identifiers have been removed. The information recorded in the GPRD includes drug prescriptions, which are computer generated by the physicians and automatically transcribed into the computer record (according to a coded drug dictionary based on the UK Prescription Pricing Authority), vaccines, medical diagnoses, which are entered using a classification compatible with the International Classification of Diseases, and demographic information. The information on drug exposure, vaccinations and diagnoses recorded in the GPRD has been found to be of satisfactory quality for epidemiological studies (Jick *et al.*, 1991, 2003).

Case ascertainment
Case ascertainment was conducted in two stages. In the first stage, we selected individuals of all ages with a first diagnosis of multiple sclerosis (ICD code 340.0) recorded in the database between January 1, 1993 and December 31, 2000, and who had at least 2 years of active computer-recorded medical history prior to the diagnosis date. We then reviewed each computer record to assign a date of first symptoms to each individual. In the second stage, we contacted the GPs of these potential multiple sclerosis patients and requested photocopies of all multiple sclerosis-related paper records available in the GP's office, including all consultations, specialist referrals, test results and hospital discharges. Paper records cover a longer period, often from birth or childhood, than computer records. Two physician-investigators reviewed the paper medical records independently and blinded to the computerized exposure information, filled out a questionnaire including information on symptoms and diagnostic procedures, and classified the patients into multiple sclerosis, possible multiple sclerosis or no multiple sclerosis diagnosis according to standardized research criteria (Poser *et al.*, 1983). To determine the onset of symptoms of multiple sclerosis, we used the symptoms and criteria proposed by Poser (1994). Cases were also classified by type of clinical course as relapsing-remitting, primary progressive or secondary progressive (Lublin *et al.*, 1996), and an approximate date of onset of progression was determined for secondary progressive forms of the disease. Progression was defined as a continuously worsening disability lasting no less than 6 months and with or without superimposed relapses, minor remissions and plateaus. Discrepancies on case definition and clinical course were discussed until a consensus was reached.

Our review of medical records confirmed 438 (61.4%) of the 713 first-stage cases as cases of multiple sclerosis with a first diagnosis on or after January 1, 1993. The remaining 275 subjects were not confirmed because (i) they had a diagnosis of possible (59)

or prevalent (83) multiple sclerosis; (ii) they did not have multiple sclerosis (52); or (iii) medical records could not be obtained because the patient had transferred to another practice (71) or died (10). Ninety-eight percent of the confirmed cases had been seen and diagnosed by a neurologist in the UK, and 85% of the diagnoses were supported by a positive result on MRI. The date of first symptoms retrieved from the computer records was, on average, 24 months later than the date of first symptoms retrieved from the paper records. The earliest date of first symptoms was assigned to each case.

Of the 438 multiple sclerosis cases, 282 had their first symptoms while in the study cohort (i.e. after their first computer-recorded medical information), and 201 (71%) had a known smoking status before first symptoms.

Study design
We used a nested case–control design to evaluate the association between smoking and risk of multiple sclerosis (relapsing–remitting or primary progressive), and a cohort design to evaluate the association between smoking and secondary progression in cases with a relapsing–remitting clinical onset.

The cases in our case–control study were the 201 individuals with a confirmed diagnosis of multiple sclerosis between January 1, 1993 and December 31, 2000, and with smoking information in the GPRD before first symptoms. Up to 10 controls per case were randomly selected, matched on age (± 1 year), sex, practice, date of joining the practice (± 1 year) and availability of information on smoking status. Controls had to be alive, free of a multiple sclerosis diagnosis and present in the database at the date of first symptoms of their corresponding case (the index date).

Our cohort study included the 179 (out of 201) cases who were classified with relapsing–remitting multiple sclerosis at disease onset. Individuals were followed from the date of first multiple sclerosis symptoms until secondary progression, death, date of medical records review or December 2000, whichever came first.

Exposure assessment
The most recently known smoking status at the index date and the status 3 years before the index date were determined from the computerized medical records. Subjects were classified as current, past or never smokers. We present results for ever (current or past) versus never smokers to obtain stable estimates in subgroup analyses with small sample size. No data on duration or intensity of smoking were available.

Statistical methods
In the nested case–control study, we used conditional logistic regression to estimate odds ratios (ORs), and their 95% confidence intervals (CIs), adjusted for the matching factors. Under our design, the OR is a consistent estimator of the incidence rate ratio of multiple sclerosis in smokers versus non-smokers. In the cohort study, we used Cox proportional hazards regression to estimate the incidence rate (hazard) ratio of secondary progression in smokers versus non-smokers, adjusted for age at first symptoms, sex and first symptoms including motor deficit/weakness.

Human subjects
This research was approved by the Human Subjects Committee of the Harvard School of Public Health, and by the Scientific and Ethical Advisory Group of the GPRD.

Table 1 *Characteristics of multiple sclerosis cases and controls*

	Multiple sclerosis cases	Controls
Women (%)	141 (70.1)	1348 (70.5)
Age		
Mean (SD), years	36.0 (9.1)	36.0 (9.1)
<30 years (%)	61 (30.4)	568 (29.7)
30–39 years (%)	73 (36.3)	726 (37.8)
40–49 years (%)	52 (25.9)	476 (24.9)
>50 years (%)	15 (7.5)	143 (7.5)
Mean (median) no. of health encounters before index date	20.7 (13)	21.4 (15)
Mean (median) no. of health encounters after index date	45.3 (38)	24.3 (17)
Course of the disease (%)		
Relapsing–remitting	159 (79.1)	
Primary progressive	20 (9.9)	
Secondary progressive	22 (11.0)	
First symptoms (%)"		
Optic neuritis/diplopia	52 (25.9)	
Sensory symptoms	103 (51.2)	
Motor deficit/weakness	38 (18.9)	
Ataxia/dysarthria/limb incoordination	33 (16.4)	

*The total does not add up to 100% because some subjects had more than one symptom at onset.

Table 2 *Association between cigarette smoking and risk of multiple sclerosis*

Smoking status before index date	Multiple sclerosis cases (%)	Controls (%)	OR (95% CI)"
All clinical courses			
Never smoker	109 (54.2)	1160 (60.6)	1.0 (reference)
Ever smoker	92 (45.8)	753 (39.4)	1.3 (1.0–1.7)
Primary progressive			
Never smoker	11 (50.0)	118 (57.6)	1.0 (reference)
Ever smoker	11 (50.0)	87 (42.4)	1.3 (0.5–3.1)
Relapsing–remitting at onset			
Never smoker	98 (54.8)	1042 (61.0)	1.0 (reference)
Ever smoker	81 (45.3)	666 (39.0)	1.3 (0.9–1.8)

*OR = odds ratio; CI = confidence interval.

Table 3 *Association between cigarette smoking and risk of secondary progressive disease among individuals with relapsing–remitting multiple sclerosis*

Smoking status at index date	Individuals	Person-months	Progressive disease	HR (95% CI)"
Never smoker	98	6393	5	1.0 (reference)
Ever smoker	81	4997	15	3.6 (1.3–9.9)

*HR = hazard ratio; CI = confidence interval. Adjusted for age, sex and motor clinical onset (yes, no).

Results

Our analyses on cigarette smoking and risk of multiple sclerosis included 201 multiple sclerosis cases and 1913 matched controls (Table 1). Overall, the proportion of ever smokers before the index date was 45.8% among cases and 39.4% among controls. Compared with never smoking before the index date, the OR (95% CI) of multiple sclerosis was 1.3 (1.0–1.7) for ever smoking, 1.4 (1.0–1.9) for current smoking and 1.0 (0.6–1.8) for past smoking. When the analysis included possible multiple sclerosis cases (228 cases and 2174 controls), the OR (95% CI) of multiple sclerosis for ever versus never smoking was 1.4 (1.1–1.8).

The association between smoking and multiple sclerosis was similar for both relapsing–remitting and primary progressive clinical presentations (Table 2), and it did not vary significantly by sex, although the CIs were wide. Among cases who ever smoked, the proportion of women was 66.3% and the mean (SD) age of first symptoms was 36.3 (9.3) years. When only the 38 cases with a motor onset (and their 368 matched controls) were included in the analysis, the OR was 2.0 (1.0–3.9) for ever versus never smoking.

Our cohort study included the 179 cases who had a relapsing–remitting clinical onset. Of these, 20 individuals (11%) converted to a progressive course during the follow-up (mean and median: 5.3 years). The incidence rate ratio of secondary progression was 3.6 (95% CI 1.3–9.9) for ever smokers compared with never smokers (Table 3). Eighty percent of the progressions occurred by 4.6 years of

follow-up in smokers and by 5.3 years in non-smokers. When the analysis included possible multiple sclerosis cases, the incidence rate ratio (95% CI) of progression for ever versus never smoking was 3.4 (1.2–9.4).

In all analyses, estimates did not change materially when we used smoking status 3 years before the index date.

Discussion

We estimated that the risk of developing secondary progressive multiple sclerosis was more than three times higher in smokers than in non-smokers who had a relapsing–remitting clinical onset of multiple sclerosis. This finding suggests that cigarette smoking may transform, or hasten the transformation of, relapsing–remitting forms of the disease into progressive forms. We also confirmed previous findings indicating that smokers have a moderately increased risk of developing multiple sclerosis compared with non-smokers.

Our results cannot be explained by recall bias because the smoking information was collected prospectively before first symptoms of disease. In fact, we found that multiple sclerosis cases had more health encounters than the controls after the index date, as expected, but they had a similar number before the index date.

Bias in the selection of the controls is unlikely because we used study designs that minimize or eliminate this bias: a case–control study nested within a well-defined dynamic

population and a prospective cohort. Restriction of the analysis to individuals with smoking information in the database is not expected to cause bias because the recording of information took place before first symptoms of multiple sclerosis and therefore it was not influenced by the presence of disease. The presence of confounding by other lifestyle factors (e.g. diet and physical activity) or differential adherence to treatment by smoking status is possible, but unlikely to explain fully the strong association between smoking and progression.

The increased risk of multiple sclerosis among smokers in our study agrees with the findings from all previous prospective studies. In the Oxford Family Planning Association Study (Vessey et al., 1976), the incidence of multiple sclerosis in women who smoked >15 cigarettes per day was 1.8 (95% CI 0.8–3.6) times greater than in never smokers (Villard-Mackintosh and Vessey, 1993). In the Royal College of General Practitioners' Oral Contraception Study, the incidence of multiple sclerosis in women who smoked >15 cigarettes per day was 1.4 (95% CI 0.9–2.2) times greater than in never smokers (Thorogood and Hannaford, 1998). In the Nurses' Health Study and the Nurses' Health Study II, the pooled incidence rate of multiple sclerosis in women who were current smokers was 1.6 (95% CI 1.2–2.1) times greater than in never smokers, and the incidence of multiple sclerosis increased with the cumulative exposure to smoking (Hernán et al., 2001). None of these studies evaluated the association between cigarette smoking and risk of clinical progression of multiple sclerosis.

Although we can only speculate about the mechanisms that link cigarette smoking and progression of multiple sclerosis, some experimental evidence, briefly reviewed below, points to a potential role of the free radical nitric oxide (NO). The permanent neurological deficit that characterizes progressive disease is arguably a result of axonal loss (Scolding and Franklin, 1998: Coles et al., 1999: Trapp et al., 1999), and exposure to NO has been shown to cause axonal degeneration or block axonal conduction, especially in axons that are physiologically active (Smith et al., 2001: Kapoor et al., 2003) or demyelinated (Redford et al., 1997). Elevated levels of NO metabolites in the CSF are associated with clinical progression of multiple sclerosis (Rejdak et al., 2004). These findings suggest that exposure to NO may be an 'upstream' or relatively early event within the axonal degenerative cascade (Waxman, 2003). Because cigarette smoke contains NO, smoking increases NO plasma levels according to most (Miller et al., 1997: Sarkar et al., 1999: Zhou et al., 2000), but not all (Node et al., 1997), studies, and nicotine induces the production of NO in the CNS (Suemaru et al., 1997: Smith et al., 1998: Lee et al., 2000: Tonnessen et al., 2000), it is conceivable that cigarette smoking may increase the NO concentration at the sites of multiple sclerosis inflammatory lesions. These elevated NO levels would contribute to axonal degeneration and thus to the permanent deficits observed in the secondary progressive forms of the disease.

The more modest association between smoking and risk of multiple sclerosis could be explained by the preferential vulnerability of oligodendroglia, compared with astrocytes and microglia, to NO (Mitrovic et al., 1995, 1996: Smith et al., 1999) and N-nitroso compounds (Ledoux et al., 1998). These chemicals are present in, derived from or induced by components of cigarette smoke. N-nitroso compounds may generate NO (Tanno et al., 1997) and, conversely, nitrosating agents [which readily combine with locally available nitrosatable compounds to form N-nitroso compounds (Challis and Kyrtopoulos, 1977: Miwa et al., 1987)] can be synthesized endogenously via the NO synthase (Bartsch and Frank, 1996).

Other hypothesized mechanisms (Hernán et al., 2001) relating smoking and multiple sclerosis include chronic cyanide intoxication leading to widespread demyelination along with selective loss of oligodendroglia [interestingly, thiocyanate is an effective catalyst of nitrosation (Fan and Tannenbaum, 1973: Oshima et al., 1982: Licht et al., 1988)], immunomodulatory effects of cigarette smoke components and predisposition to autoimmune responses in smokers, the direct effect of cigarette smoke components on the blood–brain barrier, and smoking-mediated increased frequency and persistence of infections.

The relevance of these potential mechanisms is unclear, but the growing body of epidemiological evidence on the association between smoking and multiple sclerosis warrants further investigation. This line of research may provide some clues into the pathogenesis of multiple sclerosis and perhaps new insights into the prevention of the disease and its progressive forms.

Acknowledgements

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