1: Neurology. 2003 Oct 28;61(8):1122-4. Full Text Neurology Links

Comment in:
Neurology. 2003 Oct 28;61(8):1032-4.
Neurology. 2004 Aug 24;63(4):763; author reply 763.

Smoking is a risk factor for multiple sclerosis.

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The authors determined the relationship between tobacco smoking and the risk of developing multiple sclerosis (MS) in a general population of 22,312 individuals living in Hordaland, Norway in 1997. A total of 87 individuals reported having developed MS. The risk of MS was higher among smokers than among never-smokers (rate ratio 1.81, 95% CI 1.1 to 2.9; p = 0.014). Studies on how smoking interacts with disease onset may contribute to determining the causal agents of this disease.

PMID: 14581676 [PubMed - indexed for MEDLINE]

Comment in:

1: Curr Opin Neurol. 2006 Jun;19(3):248-54. Links

Epidemiology and natural history of multiple sclerosis: new insights.

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PURPOSE OF REVIEW: The cause of multiple sclerosis remains elusive. We review recent epidemiological studies of genetic and environmental factors that influence susceptibility to the disease and its clinical course. RECENT FINDINGS: Genetic advances strengthen the association of multiple sclerosis with the human leukocyte antigen (HLA)-DRB1 allele and interferon-gamma polymorphisms and suggest that apolipoprotein E alleles play an important role. In the environmental realm, nested case-control studies show that prior Epstein-Barr virus exposure is overrepresented in multiple sclerosis. Smoking has been associated with both risk of multiple sclerosis and progressive disease. Vitamin D deficiency might tie together environmental clues with higher multiple sclerosis prevalence rates; dietary vitamin supplementation is also associated with reduced multiple sclerosis risk. Natural history studies demonstrated dissociation between relapses and disease progression, facilitated the ability to distinguish neuromyelitis optica and related syndromes from typical multiple sclerosis, and spawned the exploration of large datasets to model long-term disease activity. SUMMARY: Our understanding of the

contributions of specific genetic and environmental factors that contribute to multiple sclerosis has improved. Further refinements will eventually allow powerful longitudinal studies to assess genetic and environmental interactions with implications for prediction of individual disease susceptibility, clinical course, and response to therapy.

PMID: 16702830 [PubMed - indexed for MEDLINE]

1: Lupus. 2006;15(11):737-45. Links

Cigarette smoking and autoimmune disease: what can we learn from epidemiology?

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Cigarette smoking has been causally linked to the development of multiple autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, Graves' hyperthyroidism, and primary biliary cirrhosis, among others. We review the known biologic effects of cigarette smoke, in particular its actions on the immune system, and the epidemiologic evidence associating smoking with increased risk of each of these autoimmune diseases. Interactions between cigarette smoking and genetic and immunologic factors, such as the human leukocyte antigen (HLA)-shared epitope, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and anti-double stranded DNA antibodies, may point to mechanisms in disease pathogenesis.

PMID: 17153844 [PubMed - in process]

1: Neurol Sci. 2005 Dec;26(5):334-9. Links

Multiple sclerosis and lifestyle factors: the Hordaland Health Study.

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This study compared multiple sclerosis (MS) patients (n=87) with the general population and with people reporting angina pectoris (n=109), asthma (n=1,353) and diabetes (n=219) regarding health-related quality of life (SF-12), working status and lifestyle factors including smoking, alcohol consumption, body mass index (BMI) and leisure physical activity. The study was cross-sectional and included the birth cohorts from 1950 to 1957 living in Hordaland County, Norway in 1997. A total of 22,312 people participated, yielding a response rate of 65%. The MS

patients had a high rate of smoking and a low mean BMI, despite lower leisure physical activity compared with the rest of the study population. This suggests that it may be advisable to increase the focus on smoking, physical activity and the balance between energy intake and use.

PMID: 16388368 [PubMed - indexed for MEDLINE]

1: Brain. 2005 Jun;128(Pt 6):1461-5. Epub 2005 Mar 9. FULL FINAL TEXT OXFORD JOURNALS Links

Cigarette smoking and the progression of multiple sclerosis.

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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.

PMID: 15758034 [PubMed - indexed for MEDLINE]

doi:10.1093/brain/awh471 *Brain* (2005), **128,** 1461–1465

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.

Keywords: smoking; multiple sclerosis; progressive clinical course; cohort

Abbreviations: CI = confidence interval; GP = general practitioner; NO = nitric oxide; OR = odds ratio

Received October 30, 2004. Revised January 11, 2005. Accepted February 7, 2005. Advance Access publication March 9, 2005

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

We wish to thank the GPs that make GPRD-based research possible, Drs James Robins and Sonia Hernández-Díaz for their expert assistance, and Rebecca Hoffmann and Dorothy Zaborowski for their technical help. This research was funded by the National Multiple Sclerosis Society (RG 3236A1/1).

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Smoking is a risk factor for multiple sclerosis

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Abstract—The authors determined the relationship between tobacco smoking and the risk of developing multiple sclerosis (MS) in a general population of 22,312 individuals living in Hordaland, Norway in 1997. A total of 87 individuals reported having developed MS. The risk of MS was higher among smokers than among never-smokers (rate ratio 1.81, 95% CI 1.1 to 2.9; p = 0.014). Studies on how smoking interacts with disease onset may contribute to determining the causal agents of this disease.

NEUROLOGY 2003;61:1122–1124

Substantial epidemiologic evidence implicates environmental factors in the etiology of multiple sclerosis (MS).[1] An infectious agent has been considered the most likely exogenous factor, but other environmental factors may also have a role in causing MS. A few case-control studies on the effect of smoking have all shown some association but, for most studies, nonsignificant results.[2] A recent prospective study of two large cohorts of female nurses found an increased frequency of MS among the smokers and demonstrated a dose-response relationship.[2]

We determined the relationship between tobacco smoking and the risk of developing MS in a general population of 22,312 people living in Hordaland, Norway (the Hordaland Health Study 1997–1999).

Methods. *Study population.* The study was cross-sectional and included questionnaires and a clinical examination.[3] The study population included the cohort of all 29,400 individuals born between 1953 and 1957 and a random sample of those born in 1950 and 1951, who all resided in Hordaland County on December 31, 1997. A total of 22,312 individuals participated, with an age of 40 to 47 years at the time of the study and with a participation rate of 65%. The clinical examination included measurements of blood pressure, height, weight, and waist and hip width. The questionnaire included information on a number of health variables and lifestyle factors.

Measurements. Information on smoking was obtained by asking about current and previous smoking, including the age at which smoking started. Information on education was given in five levels. The participants were asked to report whether they had developed MS or several common diseases, including myocardial infarction, angina pectoris, stroke, asthma, and diabetes. They were also asked to report the year of onset of the disease. The study protocol was approved by the Regional Ethics Committee and by the Norwegian Data Inspectorate.

Statistical analysis. We determined the relationship between smoking and the risk of developing MS using a Cox proportional hazard regression model with smoking (never or ever) as a time-dependent covariate. Age was used as the time scale in the Cox model; individuals were considered nonsmokers up to the reported age of starting smoking and past or current smokers thereafter. The year of onset of MS was defined as the endpoint for the patients with MS and the non-cases were censored at time of the study. The parameter estimated in this model is a rate ratio (RR), which is approximately the ratio of risk of developing MS at any time between an individual who smoked and one who never smoked. Because early unrecognized symptoms of MS may have induced changes in smoking behavior, we also conducted analyses classifying individuals according to their smoking status 4 years before the onset of disease. The RR for the other chronic diseases were calculated using the same model. All analyses were performed stratified by sex.

Results. A total of 87 individuals reported having MS. This gives an age-specific prevalence rate of 390 per 100,000. All patients with MS who were current smokers and most who were former smokers had started smoking before the onset of MS. The only exceptions were two patients, one who began smoking 5 years after the onset of disease and one who started smoking the same year as the onset of disease. The mean duration from start of smoking to onset of disease was 15.2 years (range 1 to 31 years). Age at disease onset was missing for 16 patients with MS and was set to 32.6 years (mean age at onset in the remaining patients with MS) in the analysis. Six of those had never smoked, nine started smoking between 16 and 22 years of age, and one patient started smoking at age 35

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Received December 11, 2002. Accepted in final form May 22, 2003.

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Table *The number of smokers and risk estimate (rate ratio) for six common diseases among 22,312 subjects in the general population of Hordaland County, Norway*

Disease	No. of patients*	Never smoker, n (%)	Current or past smoker, n (%)	Ratio ratio† (95% CI)
Multiple sclerosis	86	21 (24.4)	65 (75.6)	1.81 (1.13–2.92)
Myocardial infarction	76	9 (11.8)	67 (88.2)	4.53 (2.26–9.01)
Angina pectoris	108	17 (15.7)	91 (84.3)	3.30 (1.96–5.55)
Stroke	93	27 (29.0)	66 (71.0)	1.48 (0.94–2.35)
Asthma	1,350	446 (33.0)	904 (67.0)	1.21 (1.05–1.39)
Diabetes	216	85 (39.4)	131 (60.6)	0.86 (0.65–1.13)
Total population	22,240	8,239 (37.0)	7,892 (35.5)	1.00

* Information on smoking was missing for 72 individuals including one patient with multiple sclerosis.

† Rate ratio estimated in a Cox proportional hazard regression model with smoking as a time-dependent covariate. Smoking individuals are being compared with nonsmoking individuals at the same age for the risk of developing the disease. All analyses were performed stratified by sex.

years. Exclusion of these cases from the analyses did not change the results.

The RR estimated by the Cox model comparing ever-smokers with never-smokers was 1.81 ($p = 0.014$) (table). The RR was 2.75 for men and 1.61 for women. An analysis excluding the patients who started to smoke less than 4 years prior to the onset of disease gave an RR of 1.74 ($p = 0.024$). Further, an analysis including educational level gave an RR of 1.75 ($p = 0.023$). The RR was significantly increased also for myocardial infarction, angina, and asthma.

Discussion. This study of a large general population found that the risk of developing MS among individuals who smoked was nearly twice as high as in never-smokers. Taken together with the significantly increased risk of MS among smokers found in the recent prospective study of female nurses in the United States[2] and the similar (albeit nonsignificant) increases found in two prospective studies in the United Kingdom,[4,5] this result strongly suggests that cigarette smoking is a risk factor for MS. The results in the current study showed that the excess risk among men who smoke is at least as high as that among women who smoke. These findings add MS to the list of diseases, including various types of cancer, cardiovascular diseases, and rheumatoid arthritis, for which tobacco smoking represents a risk factor.

The diagnosis of MS for the patients in this study was based on self-report. Nevertheless, patients who have been diagnosed as having MS are well aware of their diagnosis, and individuals who have not been given this diagnosis will probably not report having MS. A large study of female nurses in the United States found that as many as 93% of the respondents who reported having MS were confirmed by hospital files.[2] A similar validity of the disease status is expected in the current study population, which represents a high-risk area that has been extensively studied and where the community is familiar with the disease.[6-8] The age-specific prevalence rate, including patients with neurologist-based diagnosis only, in a study of the same county in 1994 was 338 per 100,000 people 40 to 49 years old.[8] This is slightly lower than the rate found in the current study, assuming the same frequency of nonresponse among patients with MS as the rest of the population (390 per 100,000). This could reflect a small increase in the prevalence rate during these 4 years or that the patients with MS in the current study had a slightly higher response rate than did the total study population. In any case, any misclassification of disease status introduced by self-report is not likely to have resulted in the increased risk of MS found among smokers. Further, there is little reason to believe that patients with MS who smoke would be more likely to participate in the study compared with subjects without MS who smoke.

The validity of the smoking data was supported by a clear relationship with other smoking-related diseases such as myocardial infarction and angina pectoris. Further, because the questions on smoking were included in a large questionnaire with many questions and a possible relationship between smoking and MS is not well known, there is little reason to believe that the patients with MS would report their smoking history differently from the rest of the study population. Interpreting the level of education as an indirect measure of socioeconomic status, the results indicated that smoking was not a confounding factor for social-economic status.

Several biologic models could explain the increased risk of MS among smokers. These include effects of smoking on the immune system, direct effects of smoking on the blood–brain barrier, and toxic effects of smoking on the CNS.[2] The relevance of these mechanisms and the role of specific components of cigarette smoke such as nicotine or cyanide could be explored in experimental animal studies.

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Hashimoto's encephalopathy

Postmortem findings after fatal status epilepticus

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Abstract—The clinical features of Hashimoto's encephalopathy have been attributed to a cerebral vasculitis, but pathologic material is rarely available. The authors describe an individual with Hashimoto's encephalopathy complicated by fatal status epilepticus. Postmortem examination demonstrated mild perivascular lymphocytic infiltration throughout the brain and leptomeninges plus diffuse gliosis of gray matter in the cortex, basal ganglia, thalami, hippocampi, and, to a lesser extent, the parenchymal white matter.

NEUROLOGY 2003;61:1124–1126

In 1966 Brain et al.[1] described an individual already known to have autoimmune thyroid disease who presented with recurrent stroke-like episodes occurring independently of the thyroid status. The term "Hashimoto's encephalopathy" was coined, and gradually it has become apparent that the clinical features of this condition include intermittent confusion and impairment of consciousness, psychosis and hallucinosis, stroke-like episodes, myoclonus, and tremor.[2,3] These features have at times been attributed to a vasculitic process, although the pathologic evidence is extremely limited.[4,5] We report brain pathology in a case of Hashimoto's encephalopathy.

Case report. A 40-year-old man was brought to the accident and emergency department after collapsing at home. A series of generalized tonic–clonic convulsions were witnessed by the paramedical staff with, on one occasion, apparent interruption of respiration and cardiac output for a period of 1 minute. Cardiopulmonary resuscitation was given throughout this period of time. Inquiry revealed no prior history of epilepsy, but 3 months earlier, the patient had presented to his general practitioner with a history of malaise, weight loss, and tremor of several weeks' duration. Hyperthyroidism was suspected, and propanolol was prescribed while the thyroid status was investigated. Hypothyroidism was demonstrated, and thyroxine 100 μg daily was then given. During the next month, the patient's condition deteriorated. According to his family, he became intermittently confused and incapable of running his computing business. Impaired concentration was evident, and recent conversations and events were not well recalled. In addition, the patient developed rapid, brief, jerking movements of the limbs that made writing impossible. The movements persisted in sleep and compelled the patient's wife to sleep separately.

On admission, the patient was apyrexial. The cardiovascular, respiratory, and abdominal systems were normal. There was no response to verbal or painful stimuli. The eyes were open and the pupils dilated but reactive. The fundi were normal. The corneal reflexes and the response to nasal tickle were absent. The limbs were flaccid. The tendon reflexes were present but depressed, and the plantar response was equivocal. Rhythmic twitching of the eyelids and right hand was observed.

Biochemical and hematologic indexes were normal. Toxicology, cryoglobulin, and porphyria screens were negative. Thyroid-stimulating hormone was increased at16.6 mU/L (0.1 to 5.0 mU/L), but free thyroxine was normal at 16.3 pmol/L (10 to 30 pmol/L). Thyroid peroxidase (TPO) antibodies were present in the serum at an initial concentration of 1,271 IU/mL. The remainder of the autoantibody screen was negative. A CT scan of the brain revealed no abnormality. The CSF was proteinaceous (153 mg/dL) but acellular and sterile. TPO antibodies were present in the CSF. EEG revealed bifrontal spike and sharp wave activity occurring at a frequency of approximately 1/s on the left and 1 to 3/s on the right.

A diagnosis of Hashimoto's encephalopathy was made.

The patient was prescribed IV hydrocortisone 200 mg 6-hourly on the day of admission, methylprednisolone 500 mg daily on the following 3 days, and hydrocortisone 200 mg twice daily thereafter. He also received tri-iodothyronine 20 μg 8-hourly and initially acyclovir 10 mg/kg 8-hourly plus ceftriaxone 2 g daily. Seizures were treated using diazepam and a loading dose of phenytoin on admission followed by thiopentone anesthesia when clinical examination and EEG monitoring revealed ongoing epileptic activity. Subsequently, prolonged EEG monitoring revealed continuing independent bifrontal ictal activity with occasional generalization. Propofol was introduced and augmented by a series of anticonvulsants including sodium valproate, phenobarbitone, and chlormethiazole; however, ictal activity was never fully suppressed.

Three days after admission, the TPO titer had fallen to 727 IU/L and by the sixth day to 118 IU/L. On the fourth day, plasma exchange was commenced and was continued for 5 further days. Nine days after admission, the patient became bradycardic and

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Received February 11, 2003. Accepted in final form May 29, 2003.

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Cigarette smoking and multiple sclerosis (MS): Yet another reason to quit

Robin L. Brey, MD

What is MS?

MS is a chronic neurologic disorder of young adults. Inflammation in the nervous system leads to damage to nerves and myelin (covering of the nerves) in the central nervous system (brain and spinal cord). More information about MS can be found on the next page.

What causes MS?

Even after many years of being studied, the cause of MS is still unknown. It is believed that the disease is probably triggered by a combination of factors that are inherited and are present in the environment. The most likely environmental factor seems to be a virus or other source of infection. However, a specific infection has not yet been identified. In this issue of *Neurology,* Riise and colleagues (2003;61:1122–1124) study another common environmental factor that may play a role in triggering MS: cigarette smoking. An editorial by Franklin and Nelson (2003;61:1032–1034) puts these findings into perspective.

Cigarette smoking and the risk for MS

These researchers studied the relationship between cigarette smoking and the risk for developing MS in 22,312 people between the ages of 40 and 47 living in Hordaland, Norway. Information was gathered by using questionnaires and a physical examination. Detailed information about smoking included current and previous smoking history and the age smoking started.

There were 87 people who reported having MS. All patients with MS who were current smokers and most who had smoked in the past had started smoking before they developed MS. Most people started smoking about 15 years before they developed MS. The risk for developing MS was nearly twice as high in people who currently smoked or had ever smoked than in nonsmokers. When men and women were evaluated separately, the risk for developing MS was nearly three times greater for men and one and a half times greater for women who smoked than in nonsmokers. Smoking also increased the risk for heart attacks, angina, and asthma for both men and women.

How could smoking increase the risk for MS?

Smoking causes damage to the cells that form the lining of blood vessels. When these cells, called endothelial cells, are damaged, a number of things can happen. The immune system normally fights off bad agents like bacteria and viruses. When endothelial cells are damaged the immune system can become overactive and turn against the cells of our own bodies. This is called autoimmune disease, and MS is an autoimmune disease. Endothelial cells form a very tight barrier in the brain blood vessels to prevent toxic substances from entering the brain. If endothelial cells are damaged, the brain blood vessels may become leaky. Toxic substances may pass into the brain and cause damage. These are all theories that need to be tested in the future.

What does all this mean to me?

The Surgeon General has been warning everyone for years that smoking cigarettes may be hazardous to our health. Smoking increases the risk for cancer, heart and lung disease, and stroke. MS may be added to that list. How many reasons does a person need to quit smoking? The evidence is obviously mounting.

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About multiple sclerosis

MS is a disabling neurologic disorder of young adults, affecting at least 300,000 Americans. The average age at diagnosis is 30, typically starting between the ages of 15 and 50. Women are affected at least twice as often as men. It is more common in persons of northern European heritage and those living furthest from the equator.

MS involves inflammation within the central nervous system (the brain and spinal cord), followed by the loss of the protective myelin sheaths that surround nerve fibers. When the myelin is damaged, nerve impulses are not quickly and efficiently transmitted. Besides damage to the myelin sheaths, it is now recognized that the nerve fibers, called axons, also are damaged in MS to varying extent. Lesions (called plaques) develop in the brain and spinal cord and can cause the symptoms of MS listed below.

What are the symptoms?

There are several types of MS. Most people with MS begin with relapsing-remitting disease. This means that the symptoms come and go, often leaving the person feeling nearly normal until another relapse, or MS attack, occurs. Symptoms associated with relapses usually develop over a period of days. The problems can last for a matter of days or weeks and then go away, sometimes even without any treatment. New attacks occur at irregular intervals, usually one attack every 1 to 2 years. Common symptoms include:

- Vision loss
- Numbness or tingling
- Weakness or fatigue
- Unsteadiness in walking
- Double vision
- Heat intolerance
- Partial or complete paralysis
- Electric shock sensations when bending the neck

About 50% of patients with relapsing-remitting MS develop a progressive form of MS, called secondary progressive MS, in which there is continual worsening. In this phase of the disease, patients may continue to have relapses or may stop having them altogether. About 15% of patients have progressive worsening from the beginning of their MS and do not experience relapses of MS. This form of MS is called primary progressive MS.

How is MS diagnosed?

The diagnosis of MS is based on a history of multiple attacks over time of neurologic lesions that affect different parts of the central nervous system. Your neurologist will order tests that will help confirm the diagnosis. Usually a magnetic resonance imaging (MRI) scan of the brain (and possibly the spinal cord) is ordered to find evidence of abnormal areas. Lumbar puncture (spinal tap) is also helpful to detect specific problems with the cerebrospinal fluid.

What causes MS?

The cause of MS is unknown. There is strong evidence that MS is immune mediated. This means that the person's own immune system attacks the central nervous system (an autoimmune disease).

What are the treatments?

Currently, there is no prevention or cure for MS. However, this is a promising time for people with MS, as several new medications that affect the underlying disease process have been approved or are awaiting approval by the US Food and Drug Administration (FDA). You should ask your neurologist about the best treatment options for you. Current treatments are divided into three categories:

Medications that treat the symptoms of MS. These include medications to treat depression, decrease muscle stiffness, reduce fatigue, control bladder symptoms, reduce pain, and address sexual dysfunction.

Medications that modify attacks when they occur. These are primarily corticosteroids (a synthesized adrenal hormone) that can shorten an attack.

Medications that modify disease activity. These are taken on a regular basis to help reduce the frequency of attacks and the long-term damage to brain caused by MS. Disease-modifying therapies currently FDA-approved for treating MS include recombinant β-interferons (Avonex, Betaseron, and Rebif), glatiramer acetate (Copaxone), and an immunosuppressant/chemotherapy drug, mitoxantrone (Novantrone).

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Lupus (2006) 15, 737–745
www.lupus-journal.com

ENVIRONMENTAL EXPOSURE

Cigarette smoking and autoimmune disease: what can we learn from epidemiology?

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Cigarette smoking has been causally linked to the development of multiple autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, Graves' hyperthyroidism, and primary biliary cirrhosis, among others. We review the known biologic effects of cigarette smoke, in particular its actions on the immune system, and the epidemiologic evidence associating smoking with increased risk of each of these autoimmune diseases. Interactions between cigarette smoking and genetic and immunologic factors, such as the human leukocyte antigen (HLA)-shared epitope, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and anti-double stranded DNA antibodies, may point to mechanisms in disease pathogenesis. *Lupus* (2006) **15,** 737–745.

Key words: cigarette; smoking; autoimmune disease; rheumatoid arthritis; systemic lupus erythematosus; multiple sclerosis; Graves'; hyperthyroidism; primary biliary cirrhosis; epidemiology; risk factor; gene-environment; interaction

Introduction

There is ample evidence that environmental exposures are important in the development of autoimmune diseases. The concordance rates for autoimmune diseases in monozygotic twins are well below 100%, pointing to the influence of environmental factors interacting with genetics in determining disease susceptibility. Among the environmental exposures that have been the best studied, crystalline silica from agricultural and other occupational sources,[1–4] Epstein–Barr virus[5–8] and cigarette smoking have been associated with the development of multiple autoimmune diseases. Cigarette smoking has been causally linked to the development of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), Graves' hyperthyroidism, and primary biliary cirrhosis (PBC)[9–16], among others.

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Cigarette smoke components and systemic effects

Cigarette smoke contains hundreds of potentially toxic components, including tars, nicotine, carbon monoxide and polycyclic aromatic hydrocarbons among others. As an impure mixture, cigarette smoke has multiple known and unknown actions in the human body (Table 1). Two phases of cigarette smoke exist: a tar or particulate phase and a gaseous phase, both of which contain extremely high concentrations of free radicals and cigarette smoke activates endogenous sources of free radicals as well.[17] These toxins and free radicals can interact with DNA,[18] and could cause genetic mutations and gene activation responsible for the development of autoimmune disease. In addition, cigarette smoke has been shown to increase the expression of Fas (CD95) on B and CD4 T lymphocyte cell surfaces.[19] Increasing the sensitivity of these cells to apoptotic signals could add to the burden of apoptotic material to be cleared by an inefficient clearance mechanism in patients at risk for autoimmunity.

The pro-inflammatory effects of cigarette smoke have been well studied in relation to the risk of

10.1177/0961203306069344

Table 1 Biologic effects of cigarette smoke

Mechanism		*Reference*
Tissue damage and increased apoptosis	• Contains free radicals	17, 18, 27
	• Generates endogenous free radicals and lipid peroxidation	129
	• Increases expression of Fas on lymphocytes causing increased sensitivity to apoptotic signals	19
	• Leads to release of matrix metalloproteinases	21, 23
Inflammatory	• Elevates serum fibrinogen	24, 25
	• Increases peripheral leukocyte counts	26, 27
	• Increases neutrophil chemotaxis and recruitment of PMNs, monocytes and macrophages	21–23
	• Increases levels of CRP, IL-6, serum ICAM-1, and E-selectin	28, 29, 130
Immunosuppressant	• Induces abnormalities in T cells and suppresses T cell activation	30–32, 34
	• Reduces NK cell activity	32, 34, 130, 131
	• Decreases serum levels of IgG and IgM	32–34
Anti-estrogenic	• Enhances formation of inactive 2-hydroxy estrogens	35–38

cardiovascular disease and emphysema.[20] Cigarette smoke affects the influx and activation of neutrophils, macrophages and monocytes and increases the release of tissue-damaging matrix metalloproteinases.[21–23] Both current and past smokers have higher fibrinogen levels than non-smokers, and the increase correlates with the number of cigarettes smoked per day.[24,25] Cigarette smoke elevates peripheral blood leukocyte counts[26,27] and is associated with increases in C-reactive protein and IL-6,[28,29] important markers of inflammation in autoimmune diseases. Abnormalities in T-cell function,[30,31] reduction in NK cells[32] and impairment of both humoral and cell-mediated immunity[32–34] have been observed in smokers.

Additionally, cigarette smoking has anti-estrogenic effects through the formation of inactive 2-hydroxy catechol estrogens.[35–38] Women who are smokers undergo menopause earlier than do non-smokers.[39] Estrogens can affect the Th1/Th2 immune balance and estrogens have either pro- or anti-inflammatory actions depending on their concentration and the estrogen/androgen balance.[40,41] Exogenous estrogens can suppress collagen-induced arthritis in mice,[42] as well as decrease susceptibility to its development.[43]

Autoimmune diseases associated with cigarette smoking: the epidemiologic evidence

The association with cigarette smoke has been best established for five important autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus, Graves' disease, multiple sclerosis and primary biliary cirrhosis. This list is by no means exhaustive and other autoimmune diseases such as ulcerative colitis do not have similar associations with smoking. Our goal in reviewing this group of autoimmune diseases together is to draw insights and parallels between the related diseases and their relationships to smoking that may point to cigarette smoke-induced mechanisms of autoimmunity.

Rheumatoid arthritis

An unexpected 2.4 times increased risk of RA among women smokers was first reported by Vessey and colleagues in 1987, in their investigations of oral contraceptive use and the risk of RA in the Oxford Family Planning Association Contraceptive Study.[44] Since then, 11 case-control and four cohort studies have confirmed the increased risk of RA with cigarette smoking (Table 2).[9–11,44–56] Cigarette smoking is now the most conclusively established environmental risk factor for seropositive RA. Epidemiologic studies have revealed that the risk is higher in men (OR range 1.9–4.4 in six case-control studies[45,48,49,52,53,55]) compared to women (OR range 0.6–2.5 in eight case-control studies[44,46–51,53] and three cohort studies[9,11,56]). Among RA patients with first degree relatives with RA, the age at onset is younger in smokers than non-smokers.[57] Both smoking intensity (number of cigarettes smoked per day) and duration are powerful predictors of RA risk, but, as shown in an analysis in the Women's Health Study, smoking duration may be the more important of the two.[9] The risk of developing RA is elevated in both current and former smokers and, in fact, remains elevated for up to 20 years after smoking cessation.[11,56]

Cigarette smoking may be associated with increased RA severity as well, including rheumatoid nodule formation,[58,59] increased joint destruction,[58–60] increased pulmonary disease,[58,61] and decreased functional abilities.[60] A gene–environment interaction may be responsible for the increased severity of RA in smokers. Glutathione-S-transferase (GST) enzymes

are involved in hepatic detoxification of cigarette smoke. Mattey and colleagues have shown that women with RA who had a null polymorphism in the GSTM1 gene (associated with absence of GST enzyme activity) and smoked had much higher levels of radiographic damage, decreased functional outcomes, and higher RF levels than women with RA with either but not both of these factors.[62] Another potential explanation for the increased severity of RA among smokers is a change in the ratio of tumor necrosis factor (TNF)-α to soluble TNF-receptor that may cause increased TNF-α activity.[63]

Cigarette smoking is most closely associated with seropositive RA: both rheumatoid factor (RF) and anti-cyclic citrullinated protein (anti-CCP) antibody seropositivity. This may be in part because seronegative RA is a more challenging diagnosis, and more likely to include misclassified reactive, psoriatic, viral and crystalline arthritides. Work from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) cohort study in Sweden has helped to elucidate an interesting gene–environment interaction that exists between cigarette smoking and the *HLA-DRRB1* 'shared epitope' (SE). A group of *HLA-DRB1* alleles strongly associated with susceptibility to RA share a region of sequence similarity or 'shared epitope' at amino acid positions 70–74 in the third hypervariable region of the *HLA-DRB1* molecule.[49,54,64] They have found that current smokers carrying two copies of the SE are at a 16-fold increased risk of developing RF+ RA (95%CI 7.2, 34.2)[49] and at a 21-fold increased risk of developing anti-CCP + RA (95%CI 11.0, 40.2).[54] Although cigarette smoke is known to induce RF in healthy subjects,[65,66] in analyses of RF+/anti-CCP− and RF−/anti-CCP+ subjects with RA, the EIRA group has shown that the major association of cigarette smoking is with anti-CCP+ RA, and they have proposed a new and elegant model for the pathogenesis of anti-CCP + RA.[54] Employing immunocytochemical staining of citrullinated peptides in bronchoalveolar lavage cells from smokers, non-smokers, and subjects with other types of pulmonary inflammatory diseases, they demonstrated that smoking and pulmonary inflammation both lead to increased numbers of citrullinated peptides in the lungs.[54] They have proposed that cigarette smoking promotes citrullination (the conversion of an arginine to a citrulline residue in certain peptides) and that the subsequent generation of antibodies to citrullinated proteins (anti-CCP antibodies) occurs preferentially in individuals carrying the SE genotypes.[54] As anti-CCP antibodies occur years before the onset of RA[67–69] and citrullination of peptides appears to render them more prone to bind to HLA class II molecules with the SE,[70] the described interactions between smoking and the SE may give rise to RA in at least some individuals.

Systemic lupus erythematosus

To date, three case-control studies have reported significantly increased odds ratios for the development of SLE in smokers,[71–73] while six other studies have not found a clear association (Table 2).[74–78] In several of these studies, which were performed in a

Table 2 Epidemiologic studies of the association between cigarette smoking and selected autoimmune diseases

Autoimmune disease	*No. of studies revealing significantly elevated risk/no. of case-control studies*	*No. of studies revealing significantly elevated risk/no. of cohort studies*	*Range of observed OR (RR) of developing disease*
Rheumatoid arthritis	11/12[2,10,44–47,49,51–55]	4/4[9,11,50,56]	0.6–3.4 * higher risk in men * higher risk for RF+ and anti-CCP+ RA * risk related to smoking duration, intensity, and declines slowly after cessation * smoking associated with more severe disease course
Systemic lupus erythematosus	3/8[71–78]	0/2[79,80]	0.5–6.7 * risk mainly related to current smoking * anti-dsDNA antibodies related to current smoking * cohort studies may be underpowered to detect elevated risk
Multiple sclerosis	1/3[93–95]	2/2[96,97]	1.6–1.9 * risk increases with increasing smoking intensity * smoking associated with worsening course of MS
Graves' disease	8/8[12,107,110,132–136]	1/1[109]	1.3–8.2 * higher risk among current than past smokers * risk related to smoking intensity * smoking also risk for Graves' ophthalmopathy * risk may be higher in women than men
Primary biliary cirrhosis	2/2[16,118]	0	1.6–3.5

wide variety of geographic locations and employed a range of hospital and community-based controls, current smoking was more strongly related to the development of SLE than was past smoking. Only one of these studies showed a dose–response relationship between number of pack years of smoking and the risk of SLE.[72] Three other studies were unable to find a dose effect,[71,73,75] and the remainder did not investigate a dose effect.

The existing case-control studies are a heterogeneous group of studies. Definitions of smoking status (never, past and current), questionnaire response rates in cases and controls, the inclusion of potential confounders, and the timing of the study questionnaire in relation to the onset of SLE, varied widely among the studies. Most strikingly, the results of the Ghaussy study,[71] which was performed in New Mexico and used general medical outpatients as controls, are remarkably higher than those of the rest of the studies: an odds ratio (OR) of 6.69 (95%CI 2.59, 17.30) for current smoking and 3.62 (95%CI 1.22, 10.70) for former smoking, whereas the remainder of the studies reported ORs ranging from 0.9 to 2.3 for current smoking and 0.6–1.2 for former smoking.

A meta-analysis statistically combining the effect estimates from the seven case-control studies and two cohort studies[79,80] that have examined cigarette smoking as a risk factor for SLE,[81] revealed a modestly increased risk posed by current smoking (RR 1.5 [95%CI 1.09, 2.08]), but no increased risk associated with past smoking (RR 0.98 [95%CI 0.75, 1.27]). A sensitivity analysis in which the outlying study by Ghaussy *et al.*[71] was excluded, showed that it did have a large influence on the summary effect estimate, and was responsible for much of the statistical heterogeneity observed between studies. Without this study, the OR for current smoking was still elevated at 1.31 (95%CI 1.02, 1.70). These results suggest that current smoking may be an instantaneous hazard for the development of SLE, much as it is for the development of coronary artery disease, and that, with time after the cessation of smoking, the risk of SLE returns to that observed in those who have never smoked.

One biologic mechanism potentially involved in the link between smoking and SLE was provided by a recent case-control study by Freemer and colleagues that reported an association between current smoking and the presence of anti-dsDNA antibodies among 140 smokers and 270 non-smokers with SLE.[82] In current smokers compared to non-smokers, an OR of 4.0 (95%CI 1.6, 10.4) for anti-dsDNA antibody seropositivity was found. There was no increased risk of these antibodies in former smokers compared to non-smokers. It is hypothesized that smoking causes DNA damage and the formation of DNA adducts, thereby producing anti-dsDNA antibodies.[82] The estimated half-life of these adducts is nine to 13 weeks,[83] possibly explaining the transient nature of smoking's effect on anti-dsDNA production.

This mechanism would also explain the epidemiologic association of active cigarette smoking with increased severity of SLE. Ward and colleagues reported the more rapid development to end stage renal disease in smokers[84] and Ghaussy and colleagues found increased SLE disease severity (higher SLE Disease Activity Index scores) over a six-month period in smokers compared to non-smokers.[85] Smoking is also associated with discoid lupus[86] and, more predictably, with avascular necrosis[87] and thrombotic complications in lupus.[88]

Multiple sclerosis

The etiology of multiple sclerosis is unknown, but it is thought that MS is mediated by autoreactive T-cells directed against components of myelin.[89] MS affects approximately two times more women than men[90] and is associated with HLA class II alleles. MS has been observed to have increased prevalence in Northern latitudes world wide, although there are many exceptions[91] and this may be in part due to vitamin D deficiency.[92] The relationship between cigarette smoking and MS has been investigated in five epidemiologic studies (Table 2). Two studies of cohorts of women followed for contraceptive practices in the 1990s found suggestive but not significantly elevated rates of MS among female smokers of >15 cigarettes a day.[93,94] A case-control study in Canada reported an elevated risk of MS (RR 1.6, 95%CI 1.0, 2.4) among ever smokers compared to never smokers, and even higher risk among those who smoked 20–40 cigarettes a day (RR 1.9, 95%CI 1.2, 3.2).[95] The prospective Nurses' Health Study cohorts confirmed an elevated risk of developing MS among both current smokers (RR 1.6, 95%CI 1.1, 2.1) and past smokers (RR 1.2, 95%CI 0.9, 1.6), compared to never smokers.[96] A cross-sectional study of 22 312 individuals living in one city in Norway in 1997 found 87 cases of MS with an elevated risk of 1.8 (95%CI 1.1, 2.9) in ever smokers compared to never smokers.[97]

Cigarette smoking seems to exacerbate MS, both chronically and acutely. Cigarette smoking also causes a transient worsening of motor functioning on a battery of tests in MS patients, compared to healthy controls.[98] In a retrospective study using data from the General Practice Research Database in Britain, Hernan and colleagues have shown that cigarette smoking increases the risk of transforming a relapsing-remitting clinical course into a secondary progressive course.[99] Nicotine, free radicals, or other substance contained in cigarette

smoke, may cause axonal degeneration or block axonal conduction, especially in axons that are already damaged or demyelinated.

Graves' hyperthyroidism

Graves' disease is one of the most common autoimmune diseases among women, with a prevalence of over 1%.[100] It often occurs in conjunction with autoimmune rheumatic diseases and has increased incidence in the post-partum period. Characterized by hyperthyroidism, goiter, ophthalmopathy and pretibial myxedema, Graves' is mediated by autoantibodies to the thyrotropin (TSH) receptor that stimulate thyroid hormone synthesis and secretion and thyroid growth. Genetics, as for most autoimmune diseases, are clearly important with a concordance rate of 17–35% in monozygotic twins.[101,102] Environmental risk factors for Graves' have been studied in mainly small case-control studies. The onset of Graves' has been associated with stressful life events,[103–105] high iodine intake,[106] and cigarette smoking.[107–109]

In a 2002 meta-analysis of 25 studies of the association between thyroid disease and smoking (only eight of which were limited to Graves' alone), the summary odds ratio for current smoking was 3.30 (95%CI 2.09, 5.22) and it was 1.41 among past smokers (95%CI 0.77, 2.58) (Table 2).[108] In a 2005 study in the Nurses' Health Study II, a prospective cohort of 115 109 women aged 25–42 at entry, 543 incident cases of Graves' were identified between 1989 and 2001. Cigarette smoking was confirmed to be a strong and time-dependent risk factor for the development of Graves'.[109] The relative risk among current smokers was 1.93 (95%CI 1.54, 2.43) and among past smokers it was 1.27 (95%CI 1.03, 1.56). As in RA, the risk was related to smoking intensity and was highest in women who smoked >25 cigarettes a day (RR 2.63, 95%CI 1.71, 4.04). Smoking appears to be an especially strong risk factor for Graves' ophthalmopathy[110–113] and the risk of Graves' declines with smoking cessation.[108] Again, the mechanisms of smoking's effect on Graves' and its ophthalmopathy are unknown. Several effects have been posited, including enhanced generation of reactive oxygen species,[112,114] increased concentrations of soluble adhesion molecules such as s-ICAM-1[111] and increased production of autoantibodies in this autoantibody mediated disease.[115]

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC), characterized by the progressive destruction of intrahepatic biliary ducts, is another autoimmune disease of unclear etiology, associated within individuals and families with other autoimmune diseases, such as scleroderma, lupus, and autoimmune thyroid disease. Autoantibodies, including antinuclear antibodies and anti-mitochondrial antibodies, are often present at high titer, and the latter react specifically with the components of 2-oxodehydrogenase enzymes in the liver.[116] The concordance rate in first degree family members is high, pointing to an important genetic component of susceptibility.[117] Cigarette smoking has recently been associated with increased risk of incident PBC in two case-control studies (Table 2). In NorthEast England, Howel and colleagues found an elevated risk of developing PBC among smokers (among smokers of 20 or more years, OR 3.5, 95%CI 1.9, 6.3).[16] In a larger, USA-wide case-control study, Gershwin and colleagues assessed risk factors for PBC among over 1000 PBC pts from 23 centers compared to healthy age-, race-, sex- and geography-matched controls. They also reported an increased risk of PBC associated with cigarette smoking (OR for ever smokers of >100 cigarettes 1.6, 95%CI 1.3, 1.9).[118]

Conclusions

Cigarette smoking is not associated with increased risk of all autoimmune diseases. While RA, SLE, MS, Graves'; and PBC all appear to be associated with cigarette smoking, other autoimmune diseases may not be so. The relationship between smoking and inflammatory bowel disease, for example, is complex. While Crohn's disease is associated with smoking[119–122] and smoking exacerbates the clinical course of the disease,[123–125] smoking is protective against ulcerative colitis.[119,126–128] The pathophysiologic basis for these associations is not known.

There are epidemiologic challenges to studying risk factors for rare diseases. Retrospective case-control studies are prone to recall bias, in which participants who have developed autoimmune disease recall past exposures differently than non-affected control individuals. Case-control studies must also deal with bias that could be introduced by the choice of control subjects that are not representative of the source population. Prospective studies, on the other hand, have the advantage of more accurately measuring cigarette smoke exposure before the onset of disease, but are time-consuming and expensive to perform as many healthy subjects must be followed for many years to collect a sample size of affected individuals suitable for analysis. For example, two large prospective cohort studies, the Nurses' Health Study and the Black Women's Health Study,[79,80] did not observe an association between cigarette smoking and the development of SLE. Thus, the possibility that these cohort studies,

which had 67 and 85 cases of SLE respectively, lacked the power to detect a small effect must be considered. Whether cigarette smoking elevates the risks of diseases such as scleroderma, Sjogren's, and inflammatory myositis is unknown given the difficulty in studying these rare conditions.

Additional methodological challenges to epidemiologic studies are posed by the conglomerate nature of cigarette smoke and the heterogeneous nature of these diseases. The composition of cigarettes over the years has changed and the effects of low-tar and filtered cigarettes on the quantities of inhaled toxins are unknown. Passive exposure to cigarette smoke (second hand smoke) has been linked to a variety of chronic diseases, including asthma, coronary heart disease and cancer, but has not been well studied in relation to autoimmune diseases. Moreover, exposure to second hand smoke may vary considerably by geographic location.

The immunologic and genetic subphenotype of individual autoimmune diseases appears to be important in determining smoking-related risk; smoking elevates the risk of seropositive RA, but not seronegative RA, and even more dramatically the risk of seropositive RA among subjects with the *HLA-DRB1* shared epitope.[49] Similarly, cigarette smoking appears to be related to the risk of anti-dsDNA antibodies within SLE, a very heterogeneous disease. The racial and genetic compositions of the populations examined in the different epidemiologic studies also contribute to imprecise and differing estimates.

The picture of how environmental exposures lead to autoimmune diseases in genetically predisposed individuals is starting to come into focus. Closer scrutiny of the similarities and differences between these autoimmune diseases, in terms of their epidemiology and basic immunology, may help to elucidate some of the mechanisms underlying the pathogenesis of autoimmune conditions. Continued exploration of how cigarette smoking acts as a trigger of autoimmunity is necessary. Animal models and basic research into the biologic effects of the constituents of cigarette smoke, as well as ongoing large cohort studies will advance our understanding of disease mechanisms. Evidence from epidemiologic studies should be put to use on two fronts: 1) the prevention of autoimmune disease: understanding the relationship between smoking and autoimmune disease provides the possibility of preventing it in high risk individuals, if we can prevent or reduce smoking; 2) understanding of the mechanisms of disease pathogenesis. The citrullinated peptide/anti-CCP antibody story coming to light in RA is fascinating, and probably not the only one of its kind. Similar mechanisms may be at work in related autoimmune diseases. Understanding of these mechanisms opens the door to new treatments. The search for new genes, in particular non-HLA genes, which predispose to autoimmune conditions is ongoing, and the search for gene–environment interactions involving smoking and other environmental exposures should proceed in parallel.

Acknowledgements

This study was supported by grants NIH P60 AR47782, R01 AR49880, K24 AR052401, and an Arthritis Foundation/American College of Rheumatology Arthritis Investigator Award.

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