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## Smoking May Transform Relapsing-Remitting MS Into Secondary Progressive MS CME

**News Author:** Laurie Barclay, MD

**CME Author:** Désirée Lie, MD, MEd

Complete author affiliations and disclosures, and other CME information, are available at the end of this activity.

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April 27, 2005 — Smoking increases the risk of progression of multiple sclerosis (MS), according to the results of a study published in the March 9 Advanced Access issue of *Brain*.

"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)," write Miguel A. Hernán, MD, from the Harvard School of Public Health, in Boston, Massachusetts, and colleagues. "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."

The investigators identified patients with a first diagnosis of MS recorded in the British General Practice Research Database (GPRD) between January 1993 and December 2000. They confirmed the diagnosis and date of first symptoms by medical record review and obtained smoking status from the computer database.

To evaluate the association between smoking and MS risk, they conducted a case-control study nested in the GPRD, randomly selecting up to 10 control subjects per case. Matching was on the basis of age, sex, practice, date of joining the practice, and availability of smoking data. A cohort study of MS cases with a relapsing-remitting onset helped determine the association between smoking and progression of MS.

In the nested case-control study, which included 201 cases of MS and 1,913 controls subjects, the odds ratio (OR) of MS was 1.3 (95% confidence interval [CI], 1.0 - 1.7) for "ever smokers" compared with "never smokers." In the cohort

study, with 179 cases and mean duration of follow-up of 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," the authors write. "We also confirmed previous findings indicating that smokers have a moderately increased risk of developing multiple sclerosis compared with non-smokers."

Study limitations may include possible confounding by other lifestyle factors or differential adherence to treatment by smoking status.

"The growing body of epidemiological evidence on the association between smoking and multiple sclerosis warrants further investigation," the authors conclude. "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."

The National Multiple Sclerosis Society funded this research.

*Brain*. Posted online March 9, 2005.

## Learning Objectives for This Educational Activity

Upon completion of this activity, participants will be able to:

- Describe the association between smoking and MS.
- Examine the risk of secondary progression of MS associated with smoking.

## Clinical Context

Environmental as well as genetic factors are believed to play a role in the development of MS. Recent studies suggest marked changes in the incidence and geographic distribution of MS that cannot be attributed to genetic factors alone. For example, four previous trials with women have shown a 40% to 80% increased risk of MS, with greater risk associated with cumulative exposure to smoking, according to the authors of the current study. They postulate that the free radical nitric oxide (NO), which is increased in plasma by cigarette smoking, may increase axonal degeneration or block axonal conduction, especially in physiologically active axons, thus increasing the risk of MS or MS progression. This is a prospective case-control study examining the relationship between smoking and onset and progression of MS in men and women using the GPRD of the British population.

## Study Highlights

- The GPRD consists of more than 3 million Britons enrolled with general practitioners who provide anonymous information on their patients' profiles and photocopies of their patients' records for research purposes.
- Stage 1 (case finding) of the study involved finding all individuals with a diagnosis of MS (code 340.0 in the *International Classification of Diseases, 9th Revision, Clinical Modification*) in a fixed period between 1993 and 2000. Only patients with at least 2 years of active computer records and specific date of first symptoms assigned were included.
- Stage 2 consisted of classification of patients into MS, possible MS, and no MS groups, and by type of clinical course as relapsing-remitting, primary progressive, or secondary progressive. MS progression was defined as a continuously worsening disability lasting no less than 6 months, with or without superimposed relapses or remissions.
- 269 (61.4%) of 438 patients identified in the first stage had confirmed MS, with 98% having been seen and diagnosed by a U.K. neurologist and 85% having received confirmatory positive magnetic resonance imaging findings. 71% had known smoking status before first symptoms.
- Age, sex, and practice-matched control subjects who were free of MS were found in the ratio of 10:1.
- A nested case-control design was used to evaluate the association between smoking and onset of MS.
- A cohort study of 179 patients classified with relapsing-remitting MS at disease onset was conducted to determine the relationship between MS disease progression and smoking.
- Patients were classified as current, past, or never smokers, using smoking status obtained from medical records.

- Mean age was 36 years, 70% were women, and mean number of health care encounters before the index date was 21 visits annually. Mean yearly number of health care visits after the index date was 45 for those with MS and 24 for the case control subjects.
- Of those with MS, 79% had a relapsing-remitting disease course. 51% first presented with sensory symptoms, 25% first presented with optic neuritis or diplopia, and 19% first presented with motor deficits or weakness.
- The analysis of smoking and MS onset included 201 patients with MS and 1,913 matched control subjects.
- Overall, 45.8% of ever smokers were in the MS group and 39.4% of ever smokers were in the matched control group before the index date.
- Compared with never smoking before the index date, the OR of MS was 1.3 for ever smoking, 1.4 for current smoking, and 1.0 for past smoking.
- The association between smoking and MS was similar for both relapsing-remitting and primary progressive clinical presentations and did not vary by sex.
- Among those who ever smoked, the proportion of women was 66.3% and mean age at appearance of first symptoms was 36.3 years.
- For patients with motor onset only (compared with 368 case control subjects), the OR for developing MS was 2.0 for ever vs never smoking.
- In the cohort with relapsing-remitting disease, 11% (n = 20) converted to a progressive course during a median of 5.3 years of follow-up. The incidence rate ratio of secondary progression was 3.6 for ever smokers compared with never smokers.
- 80% of progressions occurred by 4.6 years of follow-up in smokers and by 5.6 years in nonsmokers.
- When patients with possible MS were included, the incidence ratio of progression for ever vs never smokers was 3.4.

### Pearls for Practice

- Smokers have a moderately increased risk of developing MS compared with nonsmokers.
- In patients with MS whose disease has a relapsing-remitting clinical course, the risk of developing secondary progression is more than three times higher in smokers than in nonsmokers.

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### Target Audience

This article is intended for primary care physicians, neurologists, and other specialists who care for patients at risk of or with MS.