Background: Although cigarette smokers are at increased risk of developing multiple sclerosis (MS), the effect of smoking on the progression of MS remains uncertain.

Objective: To establish the relationship between cigarette smoking and progression of MS using clinical and magnetic resonance imaging outcomes

Design: Cross-sectional survey and longitudinal follow-up for a mean of 3.29 years, ending January 15, 2008.

Setting: Partners MS Center (Boston, Massachusetts), a referral center for patients with MS.

Patients: Study participants included 1465 patients with clinically definite MS (25.1% men), with mean (range) age at baseline of 42.0 (16-75) years and disease duration of 9.4 (0-50.4) years. Seven hundred eighty patients (53.2%) were never-smokers, 428 (29.2%) were ex-smokers, and 257 (17.5%) were current smokers.

Main Outcome Measures: Smoking groups were compared for baseline clinical and magnetic resonance imaging characteristics as well as progression and sustained progression on the Expanded Disability Status Scale at 2 and 5 years and time to disease conversion to secondary progressive MS. In addition, the rate of on-study change in the brain parenchymal fraction and T2 hyperintense lesion volume were compared.

Results: Current smokers had significantly worse disease at baseline than never-smokers in terms of Expanded Disability Status Scale score (adjusted P < .001), Multiple Sclerosis Severity Score (adjusted P < .001), and brain parenchymal fraction (adjusted P = .004). In addition, current smokers were significantly more likely to have primary progressive MS (adjusted odds ratio, 2.41; 95% confidence interval, 1.09-5.34). At longitudinal analyses, MS in smokers progressed from relapsing-remitting to secondary progressive disease faster than in never-smokers (hazard ratio for current smokers vs never-smokers, 2.50; 95% confidence interval, 1.42-4.41). In addition, in smokers, the T2-weighted lesion volume increased faster (P = .02), and brain parenchymal fraction decreased faster (P = .02).

Conclusion: Our data suggest that cigarette smoke has an adverse influence on the progression of MS and accelerates conversion from a relapsing-remitting to a progressive course.

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Methods

Patients

The study included 1465 of 1745 patients who completed a self-administered smoking questionnaire during their visit to the Partners Mul-
multiple Sclerosis Center at Brigham and Women’s Hospital between February 13, 2006, and August 29, 2007. To collect smoking history from most patients regularly followed up at the clinic, the questionnaires were distributed systematically to patients. Patients were eligible for the study if they had a diagnosis of clinically definite MS by McDonald criteria at their last visit to the clinic. Excluded patients either never developed definite MS during follow-up (n = 180), were missing a smoking history (n = 74), were exclusively pipe or cigar smokers (n = 8), were missing a disease category or age at baseline (n = 16), or had errors in data entry (n = 2). At baseline, patients were classified into disease groups: relapsing-remitting (n = 1020), secondary progressive (n = 212), primary progressive (n = 63), progressive relapsing (n = 24), clinically isolated syndromes (n = 106), unspecified demyelinating (n = 39), or suspected MS (n = 1). The mean (SD) number of follow-up visits was 6.80 (3.63), with irregular intervals between visits. The duration of clinical follow-up ranged from 0 to 7.63 years (mean [SD]; median: 3.29 [1.81]; 3.63 years). Eighty-five patients only had a baseline clinical visit.

SMOKING HISTORY

Information on smoking history included current smoking status, age at starting and quitting smoking, and mean number of cigarettes smoked per day. Smoking status at the start of clinical observation and MRI was determined using age at the time of the visit and at smoking initiation and smoking cessation. Because for some patients there was a substantial interval between the baseline clinical measurements and MRI, smoking status at baseline for the analysis of clinical and MRI characteristics was determined separately.

CLINICAL OUTCOMES

The 3 clinical outcomes of interest in our study were the EDSS score; the Multiple Sclerosis Severity Score (MSSS), which is a combination of the EDSS and disease duration; and the disease category as classified by the physician. The MSSS was calculated using the global MSSS table provided in the original article. The MSSS was used only for cross-sectional analyses in our study; however, changes in the EDSS score and in disease category were used to define progression (see the “Statistical Analysis” subsection).

MRI PROTOCOL

With few exceptions MRIs were obtained with a T2-weighted, axial dual-echo protocol that included the entire brain (repetition time, 3000 ms; echo time, 30/80 ms; 192 phase-encoding steps; 256 × 256 × 54 voxels with 0.93 × 0.93 × 3-mm nominal voxel size and no intersection gaps). All baseline and follow-up images were obtained using similar 1.5-T machines. Magnetic resonance images were available for 1045 patients; the mean (SD) number of images per patient was 3.76 (2.60), and the follow-up period between the first and last imaging was 2.82 (2.42; range, 0-13.3) years. Spinal cord imaging was unavailable in all patients; thus, no analysis of spinal cord data is included in this article.

TISSUE CLASS SEGMENTATION

An iterative combination of nearest neighbor multichannel clustering (expectation-maximization concept) and template-driven segmentation was used to segment white matter, gray matter, cerebrospinal fluid, and hyperintense white matter signal abnormalities. The addition of a template-driven strategy to the expectation-maximization criterion showed excellent accuracy and robustness. The segmentation-derived, whole-brain, T2-weighted hyperintense lesion volume and brain parenchymal fraction (BPF), a marker of whole-brain atrophy, were measured.

STUDY DESIGN

The relationship between smoking behavior and progression of MS was independently examined in cross-sectional and longitudinal analyses. In the cross-sectional analyses, we examined whether smoking history up to the baseline visit or MRI (ie, the first recorded clinical or imaging examination at the Partners Multiple Sclerosis Center) was related to MS severity at baseline. In longitudinal analyses, we examined whether the smoking history up to baseline contributed to predict the future progression of MS over the follow-up period.

STATISTICAL ANALYSIS

The baseline demographic, clinical, and MRI characteristics were compared using Kruskal-Wallis, Wilcoxon, and χ² tests when appropriate. To adjust for potential confounders, rank analysis of covariance was used for comparisons involving EDSS or MSSS, and linear regression on appropriately transformed variables was used for the MRI characteristics. Potential confounders were age, sex, and disease duration from first symptom. In addition, ever-smokers were categorized into 3 groups on the basis of smoking severity at study entry: 3 or less, 3 to 20, and more than 20 pack-years. Baseline comparisons of these groups were conducted controlling for age, sex, and disease duration. The percentage of patients with primary progressive MS was compared across smoking groups.

The association between smoking and time to conversion from RRMS to SPMS was examined using a Cox proportional hazards model controlling for baseline age, sex, disease duration, and treatment status. Treatment status at baseline was defined as the presence or absence of primary therapy (interferon-beta or glatiramer acetate) and presence or absence of secondary therapy (all other MS treatments). Patients were censored at their last available clinical visit if the disease had not yet progressed. Further, we compared the percentage of patients across the smoking groups with disease progression on the EDSS after 2 and 5 years. Progression on the EDSS was defined as an increase of at least 1 point when baseline EDSS score was lower than 6.0 or an increase of at least 0.5 point when baseline EDSS score was 6.0 or higher. Sustained progression, defined as progression on the EDSS maintained for 2 observations spaced at least 6 months apart, was also investigated. The comparisons of EDSS progression were conducted using logistic regression controlling for baseline age, sex, disease duration, and treatment status.

For longitudinal MRI measurements, mixed-effects models controlling for baseline age, sex, disease duration, and disease course (relapsing-remitting onset or progressive onset) were fit to the BPF and the log-transformed T2-weighted lesion volume. Extreme changes in the BPF (>5% change at consecutive measurements) were excluded from the analyses because these were likely the result of technical error. This reduced the sample size from 3932 magnetic resonance images in 1045 patients to 3887 magnetic resonance images in 1040 patients for the BPF analysis. All images were used for the T2-weighted lesion volume analysis. In all group comparisons, smoking status was defined at baseline even though a subset of patients changed groups; given the few patients who switched groups, any bias introduced by this assumption is likely small. Analysis was completed in the statistical package R version 4 and SAS version 9 for Windows (SAS Institute Inc, Cary, North Carolina).
BASELINE CHARACTERISTICS

At baseline, the patient population consisted of 257 current smokers (17.5%), 428 ex-smokers (29.2%), and 780 never-smokers (53.2%). Only 7 never-smokers began smoking during follow-up, and 57 current smokers stopped smoking during follow-up. The baseline characteristics of the 3 groups are given in Table 1. Compared with never-smokers, the EDSS score was significantly higher in current smokers ($P < .001$, adjusted for age, sex, and disease duration) but not significantly different in ex-smokers (adjusted $P = .47$ for ex-smokers vs never-smokers; $P = .47$ for ex-smokers vs never-smokers). These results were unchanged after controlling for disease course at first visit.

Given the relationship between smoking and clinical status, the effect of severity of smoking was investigated by comparing patients based on pack-years smoked at study enrollment. Ever-smokers were classified into 3 groups (3–5, 6–20, or >20 pack-years) (Table 2). The EDSS score was significantly lower in the light-smoking group compared with the moderate-smoking group (adjusted $P = .04$) and the heavy-smoking group (adjusted $P = .03$). The MSSS was also significantly higher in the heavy-smoking group compared with the light-smoking group (adjusted $P = .04$) and the moderate-smoking group (adjusted $P = .048$).

The probability of a primary progressive course of MS, as determined at the time of the baseline visit, compared with an initially relapsing course of MS (RRMS or SPMS at the baseline visit) was higher in current smokers (odds ratio, adjusted for age, sex, and disease duration, 2.42; 95% confidence interval [CI], 1.09–5.35) or ex-smokers (adjusted odds ratio, 1.91; 95% CI, 1.02–3.58) than in never-smokers.

The higher degree of MS severity in smokers was also found in analyses of MRI factors. Current smokers had a significantly lower BPF compared with never-smokers (adjusted $P = .004$), although no significant difference was observed between ex-smokers and never-smokers (adjusted $P = .06$). The T2-weighted lesion volume was significantly higher in ex-smokers compared with never-smokers (adjusted $P = .002$), and no significant difference was noted between current and never-smokers (adjusted $P = .22$). There was no significant association between pack-years of smoking and MRI measures after adjusting for age, sex, and disease duration.

LONGITUDINAL ANALYSIS

The survival analysis for conversion from RRMS to SPMS included 891 patients, of whom 154 were current smokers, 237 were ex-smokers, and 500 were never-smokers at baseline. During a mean (SD); median follow-up of 3.34 (1.70; 3.56) years, conversion to SPMS occurred in 72 patients (20 smokers, 20 ex-smokers, and 32 never-smokers) (Figure 1). The conversion from RRMS to SPMS occurred faster in current smokers compared with never-smokers (adjusted hazard ratio, 2.50; 95% CI, 1.42–4.41) but was similar in ex-smokers and never-smokers (1.05; 0.39–1.84). Similar results were obtained in analyses controlling for baseline EDSS score (adjusted haz-
ard ratio, 2.08; 95% CI, 1.15-3.77 for current smokers vs never-smokers; adjusted hazard ratio, 0.95; 95% CI, 0.54-1.68 for ex-smokers vs never-smokers). In contrast, we found no association between smoking status and EDSS progression at the end of 2 years; the percentage in whom disease progressed was 23.3% in smokers, 30.8% in ex-smokers, and 26.0% in never-smokers ($P = .57$, adjusted for baseline age, sex, disease duration, and treatment). The probability of sustained progression also was not significantly different across the groups (adjusted $P = .53$). Similar results were found for progression at 5 years. Results were similar in analyses restricted to patients with RRMS at baseline.

Progression in terms of BPF and T2-weighted lesion volume was investigated (Figure 2). Current smokers compared with never-smokers had a significantly greater increase in T2-weighted lesion volume ($P = .02$, adjusted for baseline age, sex, disease duration, and disease course) and a significantly greater decrease in the BPF (adjusted $P = .02$); however, ex-smokers and never-smokers demonstrated no significant difference on either measure.

### Table 2. Baseline Characteristics of Patients Based on Smoking Duration (Smokers Only)

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\leq 3$ (n=163)</th>
<th>3-20 (n=327)</th>
<th>$&gt; 20$ (n=164)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>38.9 (11.2)</td>
<td>42.6 (10.7)</td>
<td>50.5 (9.0)</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>Disease duration from first symptom, mean (SD), y</td>
<td>8.60 (8.68)</td>
<td>10.03 (9.73)</td>
<td>12.90 (10.73)</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>Sex. No. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>124</td>
<td>255</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>72</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>BPF, mean (SD)</td>
<td>0.87 (0.05)</td>
<td>0.86 (0.05)</td>
<td>0.85 (0.05)</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>T2 lesion volume, mean (SD), cm$^3$</td>
<td>4.64 (3.75)</td>
<td>5.02 (4.65)</td>
<td>5.10 (4.55)</td>
<td>$.72$</td>
</tr>
<tr>
<td>EDSS score, median (IQR)</td>
<td>1.5 (1.0-3.0)</td>
<td>2 (1.0-3.5)</td>
<td>2 (3.0-6.0)</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>MSSS, mean (SD)</td>
<td>3.31 (2.76)</td>
<td>3.77 (2.76)</td>
<td>4.57 (2.76)</td>
<td>$.002$</td>
</tr>
<tr>
<td>Type of MS, No. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing-remitting</td>
<td>119</td>
<td>211</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>16</td>
<td>59</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Primary progressive</td>
<td>8</td>
<td>17</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>40</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BPF, brain parenchymal fraction; EDSS, Expanded Disability Status Scale score; ellipses, no data available; IQR, interquartile range; MS, multiple sclerosis; MSSS, Multiple Sclerosis Severity Score.

$^a$ $P$ values are for 2 df comparisons of 3 groups.

$^b$ $P$ values are for 2 df comparisons of 3 groups adjusting for age, sex, and disease duration as appropriate. Twenty-five patients had missing number of cigarettes smoked per day, and an additional 6 patients stopped smoking before the study but were missing age at smoking initiation; data for these patients are not included in this table.

**COMMENT**

Aggravation of MS symptoms soon after smoking has been reported in several early studies,$^1^2-$18; however, only 2 previous investigations have examined whether smoking adversely affects MS progression. Hernán et al.,$^3$ in a case-control investigation nested within the United Kingdom General Practice Research Database, reported a 3-fold higher rate of conversion in ever-smokers compared with never-smokers. Those results, however, were based on a small sample of 179 patients with RRMS, of whom only 20 demonstrated disease conversion to SPMS during follow-up. Further, no MRI results were available. Koch et al.$^4$ examined the relationship between smoking and MS progression within a database comprising clinical information collected prospectively since 1985 for 672 patients attending the MS clinic of the University Medical Center Groningen, Groningen, the Netherlands. Smoking information was collected by mailed questionnaires or telephone interviews in 2006 and was available for 364 patients. In this population, smoking was not associated with the rate of conversion from RRMS to SPMS or with time from disease onset to EDSS scores of 4.0 or 6.0.

The reasons for the conflicting results between the 2 studies are not entirely clear; however, a potential source of bias in the Groningen study is that it was conducted more
than 20 years after recruitment of the first patients with MS into the database, and a substantial percentage had died or could not be contacted to complete the smoking questionnaire.

The present investigation, because of its substantially larger sample size, had more statistical power to assess the relationship between smoking and MS progression than the previous studies combined. Further strengths include a detailed smoking history in almost all patients and the availability of multiple clinical examinations and standardized MRI assessments during follow-up. Although the smoking history was collected retrospectively, smoking behavior is usually well recalled; thus, bias from misclassification of smoking status is likely small. The potential bias associated with patients who are more severely ill starting to smoke also seems likely to be small. The potential bias associated with patients who are more severely ill starting to smoke also seems likely to be small. Another possible source of bias that could affect the present and previous studies is preferential selection or retention in the study of smokers with more severe or more rapidly progressive MS or never-smokers with less severe or less rapidly progressive MS. This occurrence cannot be excluded but seems unlikely. As in all observational studies, we cannot exclude the possibility that the results were confounded by unknown factors. These may include genetic mutations that predispose to both addictive behavior and MS severity and other behavioral or environmental exposures, including alcohol consumption, that were not collected on our patients. Our study was conducted in patients seen at a specialized MS clinic, and, therefore, the results may not be generalized to all patients with MS. However, that similar results on smoking and rates of conversion to SPMS were found in the study by Hernán et al,3 which was conducted in a population-based cohort of patients with MS, adds to the generalizability of this finding.

The results of numerous studies including 4 rigorous prospective investigations and a population survey19 provide strong support for smoking as a risk factor for development of MS.1 That this association reflects a causal effect is suggested, albeit not proved, by the fact that the risk of MS increases with the duration and intensity of smoking and declines with time since quitting smoking.20 Further, preliminary results suggest that exposure to passive smoking may also increase the risk of

Figure 2. Change in the brain parenchymal fraction (BPF) and log-transformed T2-weighted lesion volume over time. The unadjusted trend over time is provided. The change over time in the BPF was significantly greater in current smokers compared with never-smokers (adjusted P=.02). The change over time in T2-weighted lesion volume was significantly greater in current smokers compared with never-smokers (adjusted P=.02). Red circles indicate current smokers; green circles, ex-smokers; and black circles, never-smokers.
The present findings provide additional evidence that smoking may adversely affect the underlying disease process in MS and suggest that these adverse effects of smoking may extend from the period preceding the clinical onset of MS to at least conversion to a progressive phase. Further, the observation that the rate of conversion from RRMS to SPMS was significantly higher in current smokers than in ex-smokers provides evidence that the adverse effects of smoking may be at least in part reversed by quitting.

An adverse effect of smoking on MS progression would be consistent with the results of experimental studies and of epidemiologic investigations of other neurodegenerative or autoimmune diseases. Components of cigarette smoke may have neurotoxic effects, and tobacco smoke components such as cyanides have been associated with demyelination in animals. Other chemicals in smoke (eg, nicotine) can compromise the blood-brain barrier or have immunomodulatory effects. Further, cigarette smoking contains nitric oxide, and nicotine may induce the release of nitric oxide in the central nervous system; nitric oxide metabolites in the cerebrospinal fluid may contribute to axonal degeneration and are associated with MS progression. In some previous studies in healthy individuals, smokers were found to have smaller gray matter volume and a higher brain lesion load. Similar effects in patients with MS may explain the baseline difference in the BPF between smokers and never-smokers in our study and may possibly contribute to accelerated conversion to a progressive phase. In epidemiologic studies, a neurotoxic effect of tobacco smoke is supported by its association with optic neuritis. In contrast, the association between smoking and increased risk of several autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, Graves hyperthyroidism, and primary biliary cirrhosis suggests that the effects of smoking may be at least in part related to its effects on the immune system. Cigarette smoke increases the frequency and duration of respiratory infections, which have been linked to risk of MS and to the occurrence of MS relapses.

Three additional limitations should be considered when interpreting our results. First, because our study population did not include healthy control subjects, we could not determine the specific effect of smoking on MRI measures in patients with MS; some general consequences of smoking could have been mistakenly attributed to MS progression. Second, spinal cord imaging was unavailable in all of our patients, and, therefore, we cannot determine whether smoking has adverse effects on the spinal cord. Third, although smokers had greater disease severity than nonsmokers insofar as both clinical and imaging measures, a dose-response effect was evident only for clinical progression; this result should be validated in an outside sample.

In conclusion, the results of this large and in part prospective investigation support the hypothesis that cigarette smoking has an adverse effect on progression of MS as measured by clinical and MRI outcomes. Although causality remains to be proved, these findings suggest that patients with MS who quit smoking may not only reduce their risk of smoking-related diseases but also delay the progression of MS.

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Author Contributions: Dr Ascherio had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ali and Ascherio. Acquisition of data: Ali, Guttmann, Chitnis, Glanz, Buckle, Houghtens, Stazzone, Moodie, Berger, Duan, Khoury, and Weiner. Analysis and interpretation of data: Healy, Guttmann, Chitnis, Berger, Bakshi, and Ascherio. Drafting of the manuscript: Healy, Ali, Chitnis, Duan, and Ascherio. Critical revision of the manuscript for important intellectual content: Healy, Guttmann, Glanz, Buckle, Houghtens, Stazzone, Moodie, Berger, Bakshi, Khoury, Weiner, and Ascherio. Statistical analysis: Healy and Ascherio. Obtained funding: Weiner and Ascherio. Administrative, technical, and material support: Houghtens, Berger, and Duan.

Study supervision: Guttmann, Chitnis, Houghtens, Bakshi, and Weiner.

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REFERENCES