Effect of Smoking Cessation on Multiple Sclerosis Prognosis

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IMPORTANCE Smoking tobacco is a well-established risk factor for multiple sclerosis (MS), a chronic inflammatory disorder of the central nervous system usually characterized by bouts and remissions and typically followed by a secondary progressive (SP) course. However, it is not clear whether smoking after diagnosis is detrimental.

OBJECTIVE To determine whether smoking after MS diagnosis is associated with a change in time to SP disease.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional study of patients with prevalent MS who smoked at diagnosis (n = 728) taken from the Genes and Environment in Multiple Sclerosis Study, which consists of patients from the Swedish National MS Registry. The study entrance date was at time of first-year smoking. The study was conducted between November 2008 and December 2011, with patient environmental data collected from November 2009 to March 2011 via questionnaire. Study participants were from all counties in Sweden diagnosed as having MS at the time of the Genes and Environment in Multiple Sclerosis Study and registered in the Swedish National MS Registry. Patients with MS with relapsing-remitting disease course or SP were included. These patients' conditions were diagnosed according to the McDonald criteria and the patients responded to recruitment letters with detailed questionnaires.

EXPOSURE Smoking, considered yearly after diagnosis and combined into a time-invariant covariate before diagnosis.

MAIN OUTCOMES AND MEASURES Time to SPMS, measured using an accelerated failure time model, with smoking as a time-varying covariate. Other covariates included sex, age at diagnosis, snuff use, and smoking before diagnosis.

RESULTS The optimized model illustrated that each additional year of smoking after diagnosis accelerated the time to conversion to SPMS by 4.7% (acceleration factor, 1.047; 95% CI, 1.023-1.072; \( P < .001 \)). Kaplan-Meier plots demonstrated that those who continued to smoke continuously each year after diagnosis converted to SPMS faster than those who quit smoking, reaching SP disease at 48 and 56 years of age, respectively.

CONCLUSIONS AND RELEVANCE This study provides evidence that continued smoking is associated with an acceleration in time to SPMS and that those who quit fare better. Therefore, we propose that patients with MS should be advised to stop smoking once a diagnosis has been made, not only to lessen risks for comorbidities, but also to avoid aggravating MS-related disability.

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Multiple sclerosis (MS) is a complex neurological disorder, occurring in approximately 189 of 100,000 individuals in Sweden. A chronic inflammatory disorder of the central nervous system, it manifests in an autoimmune attack against the myelin sheathing axons. Myelin degeneration and subsequent axonal loss result in neurological symptoms such as motor and sensory disturbance, speech and vision impairment, and moderate cognitive decline. After an initial course of irregular and worsening relapses, MS usually changes gradually after approximately 20 years into secondary progressive (SP) disease. The time span from onset to conversion to SPMS is a frequently used measure of disease progression.

Multiple sclerosis disease-modifying treatments are expensive and of long duration, and their effectiveness to delay the SP stage of the disease is debatable. The costs of disease-modifying therapies, such as fingolimod and natalizumab, average approximately $30,000 per year per patient, and additional indirect costs associated with MS treatment push the total costs even higher.

Smoking is a massive global health issue, with large costs to society and an estimated mortality of 6 million people annually. Cigarette smoking is a known risk factor for MS, with the odds ratio for disease development in smokers in the range of 1.2 to 1.5. Furthermore, in the present cohort and a Swedish cohort of incident cases, nearly 60% of patients with MS were smokers, making it a strong avenue for influencing patient outcomes.

Several previous studies have investigated the association of smoking before MS onset with rates or time to conversion; however, to our knowledge, they have not specifically assessed the period after diagnosis or whether continued smoking affects the disease course. The aim of this study was to use the robust data in a Swedish prevalent MS study to clarify the impact of smoking continuation and cessation on time to conversion to SPMS.

Methods

Genes and Environment in Multiple Sclerosis

Study Data Description

The Genes and Environment in Multiple Sclerosis (GEMS) Study is a population-based case-control study including patients with prevalent MS. Individuals were identified from the Swedish National MS Registry and were diagnosed previously as having MS by the McDonald criteria. A total of 6085 patients and 5357 matched control individuals responded between November 2009 and March 2011, and participants provided written informed consent. Ethical approval was obtained from the Regional Ethics Committee in Stockholm and the Research Committee for the Swedish MS Registry, and the study design has been previously described.

This study included individuals from the case population of the GEMS Study, specifically those who smoked at MS diagnosis. Data on smoking habits were collected via questionnaire in the form of year interval began, year interval ended, and cigarettes per day or week. Further clinical parameters and patient characteristics were also recorded.

Only patients with relapsing-remitting and SP disease were considered in the study (n = 3107). Patients without a reliable date of diagnosis in the Swedish National MS Registry were removed, leaving 2584 individuals. Patients lacking smoking data or with ambiguous information were removed. After these measures, 226 patients were removed, resulting in 2358 patients remaining, of whom 633 had converted to SPMS. A flow diagram of selection procedures is found in Figure 1.

Definition of Smoking

Smokers for a given year were defined as having averaged at least 1 cigarette per day, and ever smokers were defined as having had 1 such year before diagnosis or more than 20 packs lifetime consumption, using guidelines from the European Community Respiratory Health Survey III.

Because this information was self-reported retrospectively, finer resolution and estimation of smoking habits during the year of diagnosis was not possible, and the diagnosis year was split.

Patients were characterized as never/ever smokers on the basis previously stated. Smokers at diagnosis were classified as those patients who were current smokers per the stated definition during the year before or year of diagnosis because with yearly granularity, a patient may quit the year of diagnosis and still report smoking for that year. Each year prior to diagnosis was considered a year at risk, or smoking-year, if the patient smoked 1 or more cigarettes per day. Among smokers at diagnosis, 2 subsets of individuals were created based on those who had consistent, and therefore comparable, smoking habits from diagnosis to censoring. Continued smokers (continuers) were those individuals who met smoking definitions every year from the year after diagnosis until censoring, while quitters were defined as those who did not smoke per the definitions every year after diagnosis until censoring (ie, stopped smoking completely). Intermittent smokers were those with at least 1 year of smoking and 1 year of nonsmoking after diagnosis until censoring.

Pack-years were calculated as the daily number of cigarettes divided by 20 and summed to provide an aggregate measure of total pack-years both before and after diagnosis.

Primary Analysis

The main analysis included the 728 individuals identified as smokers at diagnosis, of whom 216 converted to SP. The survival model used in analysis was an accelerated failure time (AFT) model, using the main outcome age at SP disease. The year of MS diagnosis was used as the study entry point as opposed to the year of onset owing to inaccuracy and potential bias in the latter. An average lag of approximately 4 years from onset to diagnosis exists in the material because onset date was determined from patient recollection of neurological symptoms that were interpreted to constitute the first bout. Thus, it is possible that a longer period of time from onset to diagnosis is a marker of less-aggressive disease, which may have a milder course that erroneously affects covariate risk estimates. Using the date of diagnosis removes...
any such bias and, more importantly, gives a realistic view of actions that can reasonably be taken; for example, smoking cessation before diagnosis is not a viable recommendation to future patients with MS.

Data were considered in yearly intervals, using the date of diagnosis as study entry and, therefore, the diagnosis year contained 2 partial years, the first of which was included in cumulative smoking before diagnosis as a time-invariant covariate. The partial year after diagnosis and subsequent full years contained smoking after diagnosis as a time-varying covariate. Conversion to SP disease was available as a calendar year only and was considered to occur at the midpoint of the recorded year. Covariates considered included body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) at age 20 years, BMI at the date of survey, sex (male as reference), age at MS diagnosis, and years taking treatment. Body mass index used standard categories (ie, BMI < 18.5 being underweight, 18.5–<25 (normal) as the reference, 25–<30 being overweight, and ≥30 being obese). Censoring occurred when each participant’s survey was collected (2009-2011), if SP disease had not occurred previously.

Model selection was conducted investigating several potential parametric distributions for the AFT model. The Akaike Information Criterion was used to determine model fit. Models were created using smoking amount as one of the alternatives of years smoking before diagnosis and cumulative years smoking after diagnosis, as well as pack-years before diagnosis and pack-years after diagnosis. The log-logistic distribution was determined to most accurately model the existing conditions in all cases, irrespective of whether years smoking or pack-years were used.

To confirm that the magnitudes of the main model were not associated with disease severity, a submodel using smokers at diagnosis with known baseline Expanded Disability Status Scale (EDSS) score was also created. This included all patients with an EDSS score available taken either the year of or year after diagnosis owing to low numbers of the former. This model (n = 221) included a variable to indicate whether this EDSS measurement was offset from diagnosis (score during year of diagnosis, 0; score a year after, 1).

Secondary Analysis
To visually ascertain the practical impact of continued smoking after diagnosis, an uncorrected Kaplan-Meier plot with entrance at diagnosis was created comparing continuers (n = 332) and quitters (n = 118).

All statistical analyses and survival models were created in R version 3.1.1.14 The packages eha and ggplot2 were used for AFT modeling and plotting, respectively. Stata version 14 (StataCorp)15 was used to calculate Kaplan-Meier log-rank test P values.

Results
Basic Statistics
The data are described in Table 1. After removing individuals with incomplete or clearly erroneous information, the number of smokers at diagnosis was 728. Those who were categorized as continuers (n = 332) smoked continuously from the year after diagnosis to censoring, and quitters (n = 118) were defined as those who ceased smoking the year after diagnosis to censoring. Data on never smokers (n = 1012) are included for comparison.

Survival Models
In all models, BMI was not significant and therefore was not included in the final models. The final AFT model using the log-logistic parameterization is presented in Table 2. Each covariate was included with coefficient of regression according to the true time acceleration, which has opposite sign and interpretation to the commonly used AFT parameterization. Therefore, a positive sign corresponds to acceleration greater than 1; that is, time to the event is reduced, while negative coefficients correspond to increased time to the event.

The acceleration factor for years smoking after diagnosis corresponded to 4.7% acceleration in time to SP disease for each successive year of smoking (P < .001). Age at diagnosis was also significantly associated with time to conversion (P < .001), with years taking treatment being borderline significant (P = .048).

The subsequent model using individuals with a baseline EDSS score within 1 year of diagnosis had similar direction effects, with years smoking after diagnosis having a time accel-
Progression in most such studies. However, these previous studies primarily considered ever/never smokers and did not address the effect of continued smoking after diagnosis on the time to conversion, a factor that could possibly influence patient guidance. To our knowledge, this study is the first that establishes that smoking after disease diagnosis is associated with a decreased time to SP disease, by approximately 4.7% per year of additional smoking. Additionally, uncorrected median conversion time among quitters, who ceased smoking after diagnosis, was approximately 8 years after those who continued smoking yearly.

The previously mentioned studies may be discussed in some detail. The 4 reporting the association of smoking with progression time were incident, case-control, or cross-sectional, with a 1.5-year patient visit period. The report by Koch and colleagues was prospective but contained retrospective questionnaires on smoking data for only 54% of the patients and reported no smoking effect on conversion time. The present study most resembles that of Koch et al owing to the retrospective nature of the GEMS Study. Following Koch et al, the present study found similar age at conversion in an uncorrected Kaplan-Meier plot with age at diagnosis at entry for ever and never smokers (Figure 3; n = 1346, 53 years for ever smokers and n = 1012, 52 years for never smokers). However, there is a likely bias in this design owing to left truncation of patients in retrospective data collection as this inherently removes some proportion of the study because of death or nonparticipation. These similar observations indicated that truncation may occur more in smoking patients with worse disease or earlier death, the latter clearly known to be affected by smoking. Therefore, this phenomenon will likely reduce risk estimates of smoking and are not able to be easily corrected without strong assumptions.

Of the previous studies reporting an association of smoking status with progression time, 3 limited smoking status to ever/never. The report by Healy et al was a cross-sectional study that also included ex-smokers. It determined that although ever smokers had faster rates of conversion, ex-smokers did not, causing speculation that some of the smoking effect might be reversible with cessation.

The main related finding of Koch et al was a lack of association of smoking with age at progression in 117 patients with MS using coarse categories ever/never and cigarettes per day (none, <10, and >10). They reported that pack-years before onset were not associated with baseline EDSS score, while pack-years after onset were significantly associated with Multiple Sclerosis Severity Score. Taken together with the lack of dif-

### Table 1. Basic Statistics From the GEMS Study on Numbers of Never Smokers and Smokers at Diagnosis, Including Those Defined as Quitters and Continuers

<table>
<thead>
<tr>
<th>GEMS Data</th>
<th>Never Smokers</th>
<th>Smokers at Diagnosis</th>
<th>Quitters</th>
<th>Continuers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>1012</td>
<td>728</td>
<td>118</td>
<td>332</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>250 (24.7)</td>
<td>175 (24.0)</td>
<td>31 (26.3)</td>
<td>81 (24.4)</td>
</tr>
<tr>
<td>Female</td>
<td>762 (75.3)</td>
<td>553 (76.0)</td>
<td>87 (73.7)</td>
<td>251 (75.6)</td>
</tr>
<tr>
<td>Mean age at diagnosis, y</td>
<td>35.27</td>
<td>36.63</td>
<td>36.23</td>
<td>38.08</td>
</tr>
<tr>
<td>Mean time from diagnosis to treatment, y</td>
<td>3.15</td>
<td>4.43</td>
<td>2.92</td>
<td>3.73</td>
</tr>
<tr>
<td>Convert to SP disease, No. (%)</td>
<td>234 (23.1)</td>
<td>216 (29.7)</td>
<td>26 (22.0)</td>
<td>123 (37.0)</td>
</tr>
<tr>
<td>Mean time from diagnosis to conversion, y</td>
<td>8.21</td>
<td>8.78</td>
<td>8.88</td>
<td>7.15</td>
</tr>
<tr>
<td>Mean pack-years smoking before diagnosis, y</td>
<td>NA</td>
<td>12.12</td>
<td>11.65</td>
<td>12.97</td>
</tr>
</tbody>
</table>

### Table 2. AFT-Optimized Model Using All Current Smokers at MS Diagnosis

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Weighted Means of Covariates</th>
<th>Acceleration Factor (95% CI)*</th>
<th>P Value for Wald</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, y</td>
<td>34.749</td>
<td>1.048 (1.028-1.069)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>2.694</td>
<td>1.032 (1.001-1.065)</td>
<td>.048</td>
</tr>
<tr>
<td>Smoking after diagnosis</td>
<td>4.965</td>
<td>1.047 (1.023-1.072)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking before diagnosis</td>
<td>17.237</td>
<td>1.004 (0.987-1.022)</td>
<td>.67</td>
</tr>
<tr>
<td>Female</td>
<td>0.781</td>
<td>0.870 (0.679-1.113)</td>
<td>.27</td>
</tr>
<tr>
<td>Snuff use</td>
<td>0.103</td>
<td>0.959 (0.733-1.254)</td>
<td>.76</td>
</tr>
</tbody>
</table>

Abbreviations: AFT, accelerated failure time; MS, multiple sclerosis. *The acceleration factor is given by the true time acceleration. This is such that covariates with values greater than 1 indicate a reduction of time to the event, that is, an effect contributing to reaching secondary progressive MS more quickly.

Discussion

The risk of smoking on MS development has been well established when compared with never and past smokers. Smoking has also been reported to be a risk factor in disease progression in most such studies. However, these previous studies primarily considered ever/never smokers and did not address the effect of continued smoking after diagnosis on the time to conversion, a factor that could possibly influence patient guidance. To our knowledge, this study is the first that establishes that smoking after disease diagnosis is associated with a decreased time to SP disease, by approximately 4.7% per year of additional smoking. Additionally, uncorrected median conversion time among quitters, who ceased smoking after diagnosis, was approximately 8 years after those who continued smoking yearly.

A Kaplan-Meier plot of age at SP conversion among quitters (n = 118) and continuers (n = 332) is shown in Figure 2. Median age at conversion was 56 years for quitters and 48 years for continuers.

The main related finding of Koch et al was a lack of association of smoking with age at progression in 117 patients with MS using coarse categories ever/never and cigarettes per day (none, <10, and >10). They reported that pack-years before onset were not associated with baseline EDSS score, while pack-years after onset were significantly associated with Multiple Sclerosis Severity Score. Taken together with the lack of dif-

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A Kaplan-Meier plot with the age at conversion to secondary progressive (SP) disease for smokers at diagnosis who quit smoking completely (n = 118) and smokers at diagnosis who smoked continuously (n = 332).

A surprising feature of this study was that no increased risk has been reported for never smokers (n = 1012) compared with ever smokers (n = 1346).

It is impossible to rule out the presence of confounders in any association study. Potential confounders might include unobserved variables associated with smoking, which were not captured by the GEMS Study questionnaire or clinical data. However, the inclusion of smoking habits before diagnosis could act as a marker of smoking-related lifestyle factors, thereby correcting for potential unobserved effects. Both years taking treatment and baseline EDSS score were included in a subsequent model to insure that disease severity at onset was adequately considered.

Smoking measured by pack-years had similar associations with time to conversion as years of active smoking, suggesting that these may be approximate proxies of each other. A surprising feature of this study was that no increased risk was present based on the number of years of smoking or pack-years smoked previous to diagnosis. Healy and colleagues reported faster conversion rates among current smokers, but not ex-smokers, indicating that previous smoking may predispose to the disease but not necessarily drive progression. This may imply that the risk for MS development associated with smoking involves separate mechanisms than the effect of continued smoking on driving disease course. More likely is that smoking creates a milieu that increases the chance of MS development, events that once initiated continue to progress, albeit more rapidly in continued smokers. Indeed, a previous study reported reduced indoleamine 2,3-dioxygenase activity in smokers with MS, as well as altered cytokine and chemokine levels, contributing to reduced numbers of CD4+, CD25+, and FoxP3+ regulatory T cells. This indicates pathways that may contribute to autoimmune development also contribute to disease progression because indoleamine 2,3-dioxygenase has been shown to reduce inflammation in experimental autoimmune encephalomyelitis. Cigarette smoking is already known to be associated with susceptibility to various forms of autoimmunity including rheumatoid arthritis and systemic lupus erythematosus. There are several additional suggested avenues by which cigarette smoking might affect MS disease development, which have been covered in detail elsewhere, and smoking may also be associated with the effectiveness of treatment.

These findings are also striking in a wider perspective. Smoking is the only risk factor for MS to date shown to be associated with disease outcome—none of the more than 150 genetic risk factors have so far been shown to be markers of severity. Approximately 60% of Swedish patients with MS are smokers, reflecting a potentially large overall health benefit. The widespread use of disease-modifying drugs for MS, at high cost for society, is still controversial regarding its long-term effectiveness. A 20-year estimate of treatment effectiveness reported only 0.60 and 0.94 quality-adjusted life-years gained with standard (Avonex [interferon β-1a], Betaferon [interferon β-1b], Rebif [interferon β-1a], or Copaxone [glatiramer acetate]) and natalizumab treatment, respectively. In contrast, smoking cessation constitutes a possible effective intervention to implement in MS management at modest costs with important benefits. The mean societal cost per patient yearly after conversion (moderate EDSS score, ≥25 000 [US $38 769]) has been estimated to be more than double that before conversion (mild EDSS score, 12 000 [US $18 609]).
Despite some limitations of the prevalent study design, which should reduce smoking risk estimates, the findings presented are reasonable because smoking is a well-established risk factor for MS and measures to control for disease severity and other potential confounders have been taken. The alternative, to conduct a prospective study with more than a 10-year follow-up, would be impractical and raises ethical questions on how to advise patients with MS in the meantime. Thus, we suggest that these results should be regarded as sufficient to recommend smoking cessation to patients.

Conclusions

This study demonstrates that smoking after MS diagnosis has a negative impact on the progression of the disease, whereas reduced smoking may improve patient quality of life, with more years before the development of SP disease. Accordingly, evidence clearly supports advising patients with MS who smoke to quit. Health care services for patients with MS should be organized to support such a lifestyle change.

REFERENCES


