Smoking and Risk of Hemorrhagic Stroke in Women

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Background and Purpose—Several studies established smoking as a risk factor for ischemic stroke and subarachnoid hemorrhage (SAH) in men and women. A recent study added smoking as a risk factor for intracerebral hemorrhage (ICH) in men. In contrast, the impact of smoking on ICH in women is less clear.

Methods—Prospective cohort study among 39 783 US women participating in the Women’s Health Study. Smoking habits and stroke occurrence were self-reported. Stroke cases were confirmed by medical record review. We used Cox proportional hazards model to evaluate the association of smoking with risk of total hemorrhagic stroke, ICH, and SAH. We categorized smoking into never, past, and current smokers of <15 and ≥15 cigarettes per day.

Results—During 9 years of follow up, a total of 70 hemorrhagic strokes occurred, of which 40 were ICH and 29 were SAH. Never smokers and past smokers had equal rates of ICH and SAH. Current smokers of <15 cigarettes per day had a multivariable-adjusted relative risk (RR) of 1.93 (95% CI, 0.75 to 5.02) for total hemorrhagic stroke, 2.15 (95% CI, 0.62 to 7.43) for ICH, and 1.70 (95% CI, 0.38 to 7.60) for SAH. Women who smoked ≥15 cigarettes per day had RR of 3.29 (95% CI, 1.72 to 6.29) for total hemorrhagic stroke, 2.67 (95% CI, 1.04 to 6.90) for ICH, and 4.02 (95% CI, 1.63 to 9.89) for SAH compared with never smokers.

Conclusions—This prospective study indicates an increased risk of total hemorrhagic stroke, ICH, and SAH in women who are current cigarette smokers. The risk increases with the amount of cigarettes smoked. (Stroke. 2003;34:2792-2795.)

Key Words: cigarette smoking • cohort studies • intracerebral hemorrhage • risk factors • subarachnoid hemorrhage

Primary hemorrhagic stroke has a high case fatality, limited treatment options, and a poor, most often disabling outcome.1 Smoking is among the well-established risk factors for ischemic stroke2,3 and subarachnoid hemorrhage (SAH)2–4 for both sexes. Its status as a behavior-dependent risk factor makes it a primary target of prevention campaigns, especially in populations with high prevalences of smokers. However, studies evaluating the association of smoking and intracerebral hemorrhage (ICH) are sparse. A recent study yielded evidence for increased risk of ICH in men who are cigarette smokers,5 but the relation between smoking and ICH in women is less clear. Some studies suggested an increased risk of ICH among women who were current smokers,6,8 whereas other studies had too few ICH cases to evaluate this subtype2,4 or could not find an independent effect of smoking on ICH.7,9

We thus sought to investigate the association between smoking and hemorrhagic stroke, in particular ICH in women. The Women’s Health Study (WHS)10 provided the opportunity of assessing prospectively this association among >39 000 US female health professionals aged ≥45 years at baseline, who have been followed over a period of 9 years.

Subjects and Methods

The WHS is an ongoing randomized, double-blind, placebo-controlled trial designed to evaluate the balance of benefits and risks of low-dose aspirin and vitamin E in the prevention of cardiovascular disease and cancer among 39 876 apparently healthy women. The recruitment process, design, and methods of the WHS have been described in detail previously.10 All study participants gave written informed consent to participate in the WHS. Of the participants, 94.8% were white, 2.3% black, 1.1% Hispanic, and 1.8% of other ethnicity. Baseline information was self-reported and collected by a mailed questionnaire that asked about a large number of cerebrovascular risk factors and lifestyle variables. Each year, participants were sent follow-up questionnaires asking about study end points, including stroke. We included follow-up information from the time of randomization in 1993 through March 31, 2003, for this analysis, with an average follow-up time of 9 years (7.1 to 9.8). Mortality follow-up is 100%, and morbidity follow-up exceeds 95%.

Assessment of Smoking Status

We used information on smoking habits as indicated by participants on the baseline questionnaire. We categorized women into never, past, and current smokers. Furthermore, current smokers were categorized into <15 and ≥15 cigarettes per day. After the exclusion of 90 participants with missing information on smoking status and 3

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proportional hazards model to evaluate the association of smoking status and incident stroke. We calculated age-and multivariable-adjusted hazard ratios as a measure for the relative risk (RR) for total hemorrhagic strokes, ICH, and SAH.

**Evaluation of Stroke Cases**

We included first nonfatal or fatal primary hemorrhagic stroke in this analysis. When participants or next of kin reported a stroke event on a follow-up questionnaire, written consent for review of the medical record was obtained. A diagnosis of stroke was confirmed after review of the medical record by an end points committee. A stroke was defined as a focal neurological deficit of sudden onset and vascular mechanism obtained from all available sources, including death certificates and hospital records. The diagnostic evidence for our 70 hemorrhagic stroke cases was obtained from brain imaging in 68 cases (97%) and from autopsy reports in the other 2 cases. The interobserver agreement of the classification of stroke and its subtypes in the WHS has been found to be excellent for the diagnosis of the 3 major subtypes.

**Statistical Methods**

We used direct standardization to adjust categorical baseline variables for age in 5-year age groups. We used the general linear models procedure (SAS version 8.2, SAS Institute) to compare continuous baseline measurements with respect to smoking status, adjusting for age. We used Cox’s proportional hazards model to evaluate the association of smoking status and incident stroke. We calculated age-and multivariable-adjusted hazard ratios as a measure for the relative risk (RR) for total hemorrhagic strokes, ICH, and SAH.

Because of the low numbers of ICH and SAH cases in smoking categories and therefore limited total number of variables that could be included into the multivariable regression models, we sought to build parsimonious models with only important confounding and risk factors for hemorrhagic stroke. We built 2 multivariable regression models. The first model (model 1) controlled for factors that were considered potential confounders of the association between smoking and hemorrhagic stroke. This model included age (continuous), alcohol consumption (<1 drink per week, 1 to 6 drinks per week, ≥1 drink per day), and exercise (<4/wk, ≥4/wk). The second model (model 2) controlled for all factors in model 1 and additionally for factors that were considered potential biological mediators of the association between smoking and hemorrhagic stroke, ie, variables that are affected by smoking and risk factors for hemorrhagic stroke themselves. These factors were body mass index (continuous), hypertension (defined as self-reported systolic blood pressure of ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or current treatment of hypertension regardless of blood pressure) ≥90 mm Hg, or current treatment of hypertension regardless of blood pressure), and history of diabetes.

**Results**

During a mean of 9 years of follow-up (354,899 person-years), a total of 70 hemorrhagic strokes occurred, of which 40 were ICH, 29 SAH, and 1 intraventricular hemorrhage. At baseline, 20,339 participants (51.1%) self-reported to have never smoked, 14,265 (35.9%) reported past smoking, and 5,179 (13.0%) were current smokers, of whom 1,914 (37.0%) smoked <15 cigarettes per day and 3,265 (63.0%) smoked ≥15 cigarettes per day. The age-adjusted baseline characteristics of participants according to their smoking status are shown in Table 1. Participants who were current smokers tended to be younger, exercised less, had lower body mass index, were more likely to be postmenopausal, and were less likely to use hormone replacement therapy.

### Table 1. Age-Adjusted Baseline Characteristics of Study Participants (n=39,783) According to Smoking Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Never Smokers (n=20,339)</th>
<th>Past Smokers (&lt;15 cigarettes/day) (n=14,265)</th>
<th>Current Smokers (&lt;15 cigarettes/day) (n=1,914)</th>
<th>Current Smokers (&gt;15 cigarettes/day) (n=3,265)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD), y</td>
<td>54.5 (7.2)</td>
<td>55.0 (7.0)</td>
<td>54.1 (6.5)</td>
<td>55.3 (6.3)</td>
</tr>
<tr>
<td>Body mass index (SE), kg/m²</td>
<td>26.1 (0.04)</td>
<td>26.2 (0.04)</td>
<td>25.3 (0.12)</td>
<td>25.5 (0.09)</td>
</tr>
<tr>
<td>Hypertension†, %</td>
<td>26.4</td>
<td>25.5</td>
<td>23.2</td>
<td>25.4</td>
</tr>
<tr>
<td>Exercise ≥4/week, %</td>
<td>10.8</td>
<td>12.6</td>
<td>6.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Alcohol consumption, %</td>
<td>≤1/week</td>
<td>66.3</td>
<td>47.6</td>
<td>52.7</td>
</tr>
<tr>
<td></td>
<td>2–6/week</td>
<td>27.7</td>
<td>38.0</td>
<td>32.9</td>
</tr>
<tr>
<td></td>
<td>≥1/day</td>
<td>6.0</td>
<td>14.4</td>
<td>14.4</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>2.6</td>
<td>2.5</td>
<td>2.1</td>
<td>3.0</td>
</tr>
<tr>
<td>History of high cholesterol‡, %</td>
<td>29.2</td>
<td>29.4</td>
<td>28.5</td>
<td>31.1</td>
</tr>
<tr>
<td>Oral contraceptives§, %</td>
<td>67.4</td>
<td>71.2</td>
<td>71.8</td>
<td>70.9</td>
</tr>
<tr>
<td>Postmenopausal, %</td>
<td>53.2</td>
<td>54.9</td>
<td>59.4</td>
<td>59.9</td>
</tr>
<tr>
<td>Hormone replacement therapy, %</td>
<td>41.8</td>
<td>43.2</td>
<td>36.5</td>
<td>37.9</td>
</tr>
<tr>
<td>Randomized aspirin assignment, %</td>
<td>50.0</td>
<td>50.2</td>
<td>49.2</td>
<td>49.1</td>
</tr>
</tbody>
</table>

Continuous values are means and all other values are frequencies unless stated otherwise.

SD indicates standard deviation; SE, standard error.

*Adjusted for age (40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and ≥70)

†Hypertension was defined as self-reported systolic blood pressure of ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or current treatment of hypertension regardless of blood pressure

‡History of elevated total cholesterol level ≥240 mg/dL

§Ever taken oral contraceptives.
The age-adjusted and multivariable-adjusted RRs of total hemorrhagic stroke, ICH, and SAH according to smoking status are summarized in Table 2. Compared with never smokers, past smokers had no increase in the risk of total hemorrhagic stroke, ICH, or SAH. Overall, current smokers had multivariable-adjusted (model 1) RR of 2.78 (95% CI, 1.54 to 5.00) for total hemorrhagic stroke, RR of 2.47 (95% CI, 1.08 to 5.65) for ICH, and RR of 3.15 (95% CI, 1.35 to 7.32) for SAH compared with never smokers. With regard to the amount of cigarettes smoked, current smokers of <15 cigarettes per day had multivariable-adjusted (model 1) RR of 1.93 (95% CI, 0.75 to 5.02) for developing a hemorrhagic stroke, RR of 2.15 (95% CI, 0.62 to 7.43) for ICH, and RR of 1.70 (95% CI, 0.38 to 7.60) for SAH compared with never smokers. Current smokers of ≥15 cigarettes per day had multivariable-adjusted RR of 3.29 (95% CI, 1.72 to 6.29) for developing a hemorrhagic stroke, RR of 2.67 (95% CI, 1.04 to 6.90) for ICH, and RR of 4.02 (95% CI, 1.63 to 9.89) for SAH compared with never smokers.

Additional adjustments for potential biological mediators (model 2) and adjustment for use of oral contraceptives or hormone replacement therapy, postmenopausal status, history of elevated cholesterol (≥240 mg/dL), educational status, or ethnicity did not substantially change the effect estimates of the association between smoking and any of the hemorrhagic stroke types.

Discussion

In this large prospective cohort of apparently healthy women, current smoking increased the risk of total hemorrhagic stroke, ICH, and SAH. The risk increased with the amount of cigarettes smoked per day. Women who smoked ≥15 cigarettes per day at baseline had a >2-fold increase in the risk of ICH (RR, 2.67; 95% CI, 1.04 to 6.90) and a 4-fold increase in the risk of SAH (RR, 4.02; 95% CI, 1.63 to 9.89). The association between smoking and total hemorrhagic stroke, SAH, and ICH is similar to that in men. The result that past smokers did not have increased risk of total hemorrhagic stroke, ICH, or SAH may indicate that smoking cessation leads to a decreased risk of hemorrhagic stroke and its subtypes in women, an effect that was previously documented for ischemic stroke and for SAH.

Several studies from different populations found a strong association between cigarette smoking and SAH in women. In contrast, the association between smoking and ICH is less clear. Results from the Nurses Health Study showed an increased risk of SAH among women who currently smoked, with a strong dose-response relationship. Overall, women who currently smoked had approximately a 5-fold increase in the risk of SAH (RR, 4.96; 95% CI, 3.13 to 7.87). Although there was a suggestion for increased risk of ICH among current smokers (RR, 1.46; 95% CI, 0.77 to 2.78), this result did not reach statistical significance. Results from the multivariable regression models of another study that evaluated the association between cholesterol and ICH also indicated that women who were current smokers had a 1.6-fold (RR, 1.64; 95% CI, 1.13 to 2.37) increase in risk of ICH. Other studies had too few ICH cases to evaluate the
association between smoking and ICH, or there was a suggestion of increased risk in univariate analyses but not after multiple adjustments.7 Other studies did not find a positive association between smoking and ICH in women.8,9

The biological association between smoking and ischemic stroke, as well as SAH, is well established.17,18 Potential links between smoking and ischemic stroke are structural arterial wall damage and atherosclerosis19 leading to ischemic stroke. Smoking has also been linked to the presence,15 formation,18 and rupture17 of aneurysms, the main cause of spontaneous, nontraumatic SAH. The increased risk of ICH among current smokers might also be explained by structural damage to the arterial wall,19 by affecting small intraparenchymal arteries and leading to their rupture.

The strengths of this study are its large size, long follow-up with high mortality and morbidity follow-up rates, and the prospective method of data collection. All stroke cases were confirmed by detailed medical record review. All hemorrhagic stroke cases were confirmed on the basis of neuroimaging or autopsy reports, and interrater agreement in the classification of stroke categories was excellent.12 Participants of the WHS were all health professionals, making this cohort very homogeneous, which reduces confounding by several variables, including access to medical care, educational attainment, and socioeconomic status.

There are several limitations to this study. We had few cases of ICH and SAH in some of the smoking status categories. As a result, the precision of the effect estimates is limited, as reflected by the wide CIs that, however, did not overlap a RR of 1.0. Information on smoking and all other covariates was collected by self-administered questionnaires, raising the potential issue of inaccurate reporting. However, health professionals have been shown to provide reliable health-related information on smoking20 and other cardiovascular risk factors.21 We had 90 women with missing information on smoking habits and excluded them from the analysis. None of these participants, however, developed a hemorrhagic stroke during follow-up.

In addition, our study is observational, and despite adjustment for several variables, residual confounding remains a possible alternative explanation of our findings. Women who are participating in the WHS are all health professionals, most of whom are white. Thus, while these factors are unlikely to be confounders, our results may not necessarily generalize to other populations. However, although the incidence of hemorrhagic stroke is different in different ethnic groups,22 we suspect that the impact of smoking on the incidence of hemorrhagic stroke and its subtypes is similar in white and other populations. This is supported by a similar prevalence of current smoking in different ethnic groups of patients with hemorrhagic stroke.23,24

In summary, this large, prospective study in women, with 9 years of follow-up, confirmed the role of smoking as a risk factor for total hemorrhagic stroke and SAH and identified smoking as a risk factor for ICH. The risk increased with the amount of cigarettes smoked. The association observed is similar to that documented in men. These data add further support to the many health benefits of abstaining from smoking.

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