Active and Passive Smoking and the Risk of Subarachnoid Hemorrhage
An International Population-Based Case-Control Study

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Background and Purpose—This study was undertaken to better clarify the risks associated with cigarette smoking and subarachnoid hemorrhage (SAH).

Methods—The study included 432 incident cases of SAH frequency matched to 473 community SAH-free controls to determine dose-dependent associations of active and passive smoking (at home) and smoking cessation with SAH.

Results—Compared with never smokers not exposed to passive smoking, the adjusted odds ratio for SAH among current smokers was 5.0 (95% confidence interval [CI], 3.1 to 8.1); for past smokers, 1.2 (95% CI, 0.8 to 2.0); and for passive smokers, 0.9 (95% CI, 0.6 to 1.5). Current and lifetime exposures showed a clear dose-dependent effect, and risks appeared more prominent in women and for aneurysmal SAH. Approximately 1 in 3 cases of SAH could be attributed to current smoking, but risks decline quickly after smoking cessation, even among heavy smokers.

Conclusions—A strong positive association was found between cigarette smoking and SAH, especially for aneurysmal SAH and women, which is virtually eliminated within a few years of smoking cessation. Large opportunities exist for preventing SAH through smoking avoidance and cessation programs. (Stroke. 2004;35:633-637.)

Key Words: case-control studies • epidemiology • intracranial aneurysm • smoking • subarachnoid hemorrhage

Cigarette smoking is the most important preventable cause of subarachnoid hemorrhage (SAH), with a strong dose-response relationship being shown in many studies,1–3 yet the mechanisms by which smoking leads to the formation and rupture of intracerebral aneurysms and the reversibility of this risk are less well defined. Although passive smoking from exposure to environmental tobacco smoke (ETS) increases the risk of cardiovascular disease,4 including ischemic stroke,5,6 there has been no study of exposure to ETS on the risk of SAH. Here, we report associations between active and passive smoking and smoking cessation and the incidence of SAH in a large epidemiological study.

Methods

Cases
As described in detail elsewhere,7,8 the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS) was a population-based, case-control study of SAH undertaken in 4 cities (Adelaide, Hobart, and Perth, Australia, and Auckland, New Zealand), with a total study population (≥15 years of age) of ~2.8 million during 1995 to 1998. Multiple overlapping sources were used to identify all new hospitalized and nonhospitalized (both fatal and nonfatal) cases of SAH. SAH was defined according to standard criteria7,8 as abrupt onset of severe headache and/or loss of consciousness with or without focal neurological signs and where CT, autopsy, or lumbar puncture revealed focal or generalized blood within the subarachnoid space. We included only patients with proven rupture of an intracerebral aneurysm or those in whom the cause of the SAH could not be identified either by angiography or at necropsy. Institutional ethics committees approved the protocol, and all subjects (or next of kin for cases who were disabled or deceased) provided written informed consent.

Controls
Controls with no history of SAH were randomly selected from electoral rolls of the same catchment area from which the cases arose and frequency matched to cases by sex and age (10-year strata) on the basis of projected rates. A postal invitation to participate in the study was followed up with a telephone call. Replacements were sought when potential control subjects could not be reached by telephone or by personal visit after several attempts. On the assumption that proxy interviews would be required for ~40% of cases because of death or disability, matching also included proxy interviews with a nominated relative or other reliable informant. Controls were enrolled in the study during the same time period as cases.
TABLE 1. Characteristics of SAH Cases and Controls by Smoking Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=165)</th>
<th>Controls (n=77)</th>
<th>Past Smoker, n (%)</th>
<th>Controls (n=146)</th>
<th>P*</th>
<th>Never Smoker</th>
<th>Controls (n=246)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>49±13</td>
<td>50±15</td>
<td>58±16</td>
<td>58±15</td>
<td>0.89</td>
<td>62±18</td>
<td>55±18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>95 (58)</td>
<td>42 (55)</td>
<td>47 (52)</td>
<td>74 (51)</td>
<td>0.66</td>
<td>105 (74)</td>
<td>168 (68)</td>
<td>0.16</td>
</tr>
<tr>
<td>White</td>
<td>145 (88)</td>
<td>72 (94)</td>
<td>79 (87)</td>
<td>144 (99)</td>
<td>0.18</td>
<td>121 (86)</td>
<td>239 (96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever married</td>
<td>143 (87)</td>
<td>67 (87)</td>
<td>86 (95)</td>
<td>139 (95)</td>
<td>0.94</td>
<td>128 (91)</td>
<td>215 (87)</td>
<td>0.23</td>
</tr>
<tr>
<td>Education, high school or greater</td>
<td>139 (86)</td>
<td>68 (89)</td>
<td>73 (82)</td>
<td>126 (86)</td>
<td>0.43</td>
<td>89 (66)</td>
<td>214 (87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lives alone</td>
<td>31 (19)</td>
<td>13 (17)</td>
<td>13 (14)</td>
<td>22 (15)</td>
<td>0.72</td>
<td>38 (27)</td>
<td>50 (20)</td>
<td>0.12</td>
</tr>
<tr>
<td>Physically inactive†</td>
<td>111 (70)</td>
<td>59 (77)</td>
<td>63 (76)</td>
<td>97 (66)</td>
<td>0.27</td>
<td>101 (78)</td>
<td>170 (69)</td>
<td>0.08</td>
</tr>
<tr>
<td>Alcohol excess‡</td>
<td>42 (35)</td>
<td>19 (28)</td>
<td>12 (20)</td>
<td>18 (14)</td>
<td>0.34</td>
<td>10 (14)</td>
<td>22 (11)</td>
<td>0.53</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>56 (35)</td>
<td>18 (24)</td>
<td>44 (49)</td>
<td>56 (38)</td>
<td>0.08</td>
<td>79 (57)</td>
<td>87 (35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>4 (2)</td>
<td>2 (3)</td>
<td>3 (3)</td>
<td>15 (10)</td>
<td>0.94</td>
<td>11 (8)</td>
<td>20 (8)</td>
<td>0.92</td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>12 (7)</td>
<td>9 (12)</td>
<td>17 (19)</td>
<td>31 (21)</td>
<td>0.26</td>
<td>23 (16)</td>
<td>28 (11)</td>
<td>0.17</td>
</tr>
<tr>
<td>History of intermittent claudication</td>
<td>10 (6)</td>
<td>5 (6)</td>
<td>10 (11)</td>
<td>8 (5)</td>
<td>0.90</td>
<td>8 (6)</td>
<td>18 (7)</td>
<td>0.09</td>
</tr>
<tr>
<td>First-degree family history of SAH</td>
<td>38 (24)</td>
<td>25 (32)</td>
<td>23 (26)</td>
<td>32 (22)</td>
<td>0.17</td>
<td>37 (27)</td>
<td>51 (21)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Comparing cases with controls in each group.
†Defined according to sedentary lifestyle criteria specified in the text.
‡Defined as >2 standard drinks of alcohol per day in men and >1 drink of alcohol per day in women.

Outcome Measures

Data were collected through structured in-person interviews with cases and controls by trained research nurses using standardized questionnaires and medical records review as soon as possible after the subject was notified or identified. Information obtained included sociodemographic characteristics; weight and height for calculation of body mass index (BMI); highest level of education achieved; smoking status; use of alcohol; history of hypertension, diabetes mellitus, ischemic heart disease, or intermittent claudication; and first-degree family history of SAH. Subjects were categorized as sedentary or active on the basis of whether they undertook activities that lead to “puffing” or “panting” of ≥15 minutes at least once weekly,8 and from their reported usual weekly intake of alcohol (number of standard [10-mg] drinks per week), they were categorized as consuming excess alcohol if men had >14 drinks per week and women had >7 drinks per week.

Smoking status was classified as never, current (smoking at least 1 cigarette, cigar, or pipe per day for the previous year), past (smoked regularly but not in the previous year), and passive to ETS (lived with someone who smoked regularly for at least 1 year). We also recorded the amount and type of tobacco smoked, ages for starting and stopping smoking, number of years exposed to ETS, and current and past (>1 year ago) exposure to ETS. Current and past smokers were categorized into light (=20 cigarettes per day) and heavy (>20 cigarettes per day) smokers. Lifetime exposure to tobacco smoking was measured in pack-years, and levels of exposure to ETS at home were expressed in number of years of exposure.

Statistical Analysis

The sample size of 432 provided 80% power with 2-tailed significance level (α=0.05) for detecting relative risks of 1.6 attendant on exposures in 20% of the population. Multivariable unconditional logistic regression models were developed to calculate odds ratios (ORs) as estimates of relative risks with 95% confidence intervals (CIs) for the incidence of SAH in relation to various levels of exposure to tobacco smoke (active, former, and passive). Never smokers who were never exposed to ETS served as the control group. Models were constructed for each type of exposure to smoking and SAH, with adjustment for matching factors (age, sex, study center, and use of proxy respondent), major confounders, and risk factors on the basis of results of the univariate analysis in which a variable was judged to be significant if it altered the effect estimate by ≥10%.10 To test whether a variable was an effect modifier, we carried out analyses stratified by the exposure in question, with potential interactions examined between hypertension, lean BMI (<25 kg/m²), and alcohol excess with respect to the effect of cigarette smoking on SAH.11 Aneurysmal and nonaneurysmal SAH cases were analyzed separately and combined. Population attributable risk of SAH associated with smoking was calculated according to a method described by Schlesselman,11 which uses the estimate of the relative risk when confounding exists. Values of P<0.05 were considered statistically significant. All analyses were carried out with SAS software.12

Results

Overall, there were 432 cases of first-ever SAH (62% women; mean±SD age, 56.5±17 years), including 330 (76%) caused by definite rupture of an intracerebral aneurysm, and 473 controls (60% women; 55.0±17 years). Information on smoking was available in 391 cases (90.5%) and 469 controls (97.5%). For controls, reasons for nonparticipation (n=325) were no contact (49%), refusal (36%), death (3%), and other (12%). Because the use of tobacco other than from manufactured cigarettes (including hand-rolled cigarette, cigars, and pipe tobacco) among current and former smokers was small (10% in cases, 12% in controls), we did not analyze these groups separately.

Table 1 presents the characteristics of cases and controls by smoking status. Controls were more likely than cases to have gone beyond secondary school level of education, to have a higher socioeconomic status, and to be white, the differences being most significant in past smokers and life-long non-smokers. Variables other than smoking that were related to the risk of SAH were alcohol excess, history of hypertension, and lower BMI. Despite efforts to match by source of information, proxies were used in 173 case subjects (65%) compared with 91 control subjects (32%) (P<0.0001). The mean age of never-smoker cases was ~7 years higher than that of never-smoker controls.
Table 2 shows that the crude risk of SAH in subjects who currently smoked was 3 times greater than in never smokers, but the risk in heavy smokers was almost twice that of light smokers. A dose-response relationship between smoking and SAH was also evident for cumulative exposure as defined by either pack-years or age of starting to smoke, but no risk was evident for ex-smokers and never smokers exposed to ETS at home, even in those with the highest recent or cumulative exposures. Exposure to ETS had no additive effect in either current or ex-smokers.

Table 3 presents the multivariable analyses and confirms that cigarette smoking is a prominent independent risk factor for SAH, with increased ORs after adjustment for matching factors, together with major confounders and risk factors of atherosclerotic vascular diseases, including SAH, obesity, diabetes mellitus, and lean BMI. The ORs were unchanged when the interaction terms of active smoking with hypertension, lean (<25 kg/m²) or very lean (<20 kg/m²) BMI, or alcohol access were introduced and were higher in women than in men and for cases of aneurysmal SAH alone. Although an obvious dose-response relationship for active smoking and SAH was evident, no significant increased risk in ex-smokers compared with controls was seen even in those former smokers with the highest aggregate levels of exposure (Figure). The population attributable risk for SAH associated with current smoking was estimated at 34% (95% CI, 29 to 37); 20% (95% CI, 17 to 22) in women and 13% (95% CI, 8 to 16) in men.

Discussion

This population-based case-control study shows that cigarette smokers have 5 times the risk of SAH compared with nonsmokers and that about one third of all cases of SAH could be attributed to current smoking. In addition, cigarette smoking was found to be both a short- and long-term risk factor for SAH in both men and women, with potentially greater risks for aneurysmal SAH in women. Despite the strong, direct dose-response relationship between smoking and SAH, however, the risks appear to diminish rapidly and largely disappear within a few years of quitting, even in those with the heaviest exposure defined by either dose or duration of smoking. In contrast, there was no significant effect of passive smoking at home, either alone or on top of active smoking, on the risk of SAH.

Cigarette smoking is recognized as a major risk factor for atherosclerotic vascular diseases, including SAH, but less consensus prevails on the nature of the underlying pathophysiological mechanisms. Most studies have aimed to quantify the risk associated with the period of active smoking not just for SAH but also in relation to the number, formation, and growth of intracerebral aneurysms. Few studies have addressed the effect of smoking cessation on the risk of SAH. One case-control study showed that the risk of SAH among smokers was greatest 3 hours after smoking a cigarette but was virtually eliminated 10 years after the last cigarette was smoked.
smoked. An inverse relationship between time since the last cigarette and risk of SAH in past smokers was also observed in Nurses Health Study, although in that investigation, the risk of SAH persisted even after 15 years had elapsed since cessation of smoking. A persistent risk of SAH in past smokers was also demonstrated in a retrospective analysis of risk factors in 323 hospitalized patients with SAH compared with historical controls, but there was no examination of time-dependent associations of risk since smoking cessation. Potential explanations for these conflicting results include confounding, selection bias, information bias, and chance.

Several hypotheses may explain the effects of smoking on SAH, including enhanced systematic coagulability, inflammation within arterial walls, increased blood pressure, endothelial dysfunction, and the promotion of the degradation of elastin within vessel walls by interfering with α1-antitrypsin. Our finding of a rapid reversal in risk on smoking cessation supports short-term physiological rather than long-term structural effects on the vessel walls of cerebral arteries as being relevant to formation and possibly rupture of intracerebral aneurysms. However, a hazardous synergistic effect of the combination of smoking and hypertension and lean BMI that could potentially increase the likelihood of rupture of intracerebral aneurysms was not supported by our findings.

The present study has several strengths, including the prospective population-based design with inclusion of both hospitalized and nonhospitalized, fatal and nonfatal, well-documented first-ever cases of SAH, thus minimizing possible selection and misclassification biases. We were able to obtain information on exposure in a high proportion of cases and controls using standardized methods, and because controls were representative of the population that gave rise to the cases, the potential for information bias was small. Other advantages include the collection of information on a large number of potential confounding and risk factors such as BMI and alcohol consumption in a large sample of an ethnically and demographically diverse population, thus increasing both the reliability and generalizability of the results. There are some limitations to study, however, many of which are inherent to a case-control design in which differential errors are hard to avoid because information on exposures in cases is obtained under different circumstances from those for controls. In common with other epidemiological studies of SAH, we used proxy respondents to obtain information on exposures in a large proportion of the cases. However, high reliability of proxy-derived data on personal habits and medical history such as those considered in these analyses has been demonstrated elsewhere. Demographic and lifestyle factors in the cases and controls were internally consistent; the controls were better educated, drank less alcohol, had less hypertension, and were more obese than the cases. This finding provides indirect evidence that any errors in the estimates of risk are likely to have been nondifferential, in which case any bias in the associated ORs would most likely be toward the null.

Another weakness is that the study lacked statistical power to detect small risks of SAH in past smokers and subjects exposed to ETS. Given that we used a crude measure of exposure to ETS limited to the home, with no information

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>All Cases of SAH Combined</th>
<th>Aneurysmal SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Current smoker, cigarettes/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>(3.2–12.3)</td>
<td>(1.7–7.5)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>(2.5–10.3)</td>
<td>(1.3–7.6)</td>
</tr>
<tr>
<td>Past smoker, y quit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>(0.8–2.8)</td>
<td>(0.4–1.8)</td>
</tr>
<tr>
<td>5–15</td>
<td>(0.6–7.0)</td>
<td>(0.3–4.5)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>(0.6–4.0)</td>
<td>(0.4–2.9)</td>
</tr>
<tr>
<td>Non-smoker exposed to ETS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–20</td>
<td>(0.8–4.9)</td>
<td>(0.3–1.5)</td>
</tr>
<tr>
<td>20–50</td>
<td>(0.7–2.3)</td>
<td>(0.2–1.3)</td>
</tr>
</tbody>
</table>

*Never smoked with no exposure to ETS as the reference group; all types of tobacco combined.
†Adjusted for matching variables (age, sex, study center, and use of proxy respondent), confounders, and risk factors (history of hypertension, diabetes mellitus, alcohol use, BMI, and ethnicity).
collected on exposure to ETS at the workplace or other areas, it is likely that we underestimated the true association of ETS with SAH. Although the risk associations for SAH in past smokers were not significant, the greater ORs in female ex-smokers that persisted even after 15 years since quitting smoking and the 50% increase among women exposed to ETS suggest that women are more susceptible to this hazardous exposure than men. Because there is mounting evidence that passive smoking is a risk factor for vascular events, we cannot exclude a modest residual hazardous effect of smoking in past and passive smokers, especially in women.

There is overwhelming evidence to support the cardiovascular benefits of smoking cessation, with the provision of advice alone from medical practitioners significantly increasing the rate of quitting and more elaborate counseling and use of nicotine replacement therapy yielding further benefits. Unfortunately, the literature continues to show gaps in the provision of antismoking advice in high-risk groups such as stroke survivors. Our data on smoking and SAH should add support for vigorous public and professional efforts to prevent smoking, especially in women, and to encourage smokers of all ages to stop smoking quickly and completely. The universal application of antismoking activities is imperative to avoid the looming epidemic of subsequent cardiovascular and other adverse health outcomes worldwide.

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References
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