Sex, Smoking, and Risk for Subarachnoid Hemorrhage

Joni Valdemar Lindbohm, MD; Jaakko Kaprio, MD, PhD; Pekka Jousilahti, MD, PhD; Veikko Salomaa, MD, PhD; Miikka Korja, MD, PhD

Background and Purpose—Women are at higher risk for subarachnoid hemorrhage (SAH) than men for unknown reasons. Also cumulative effects of smoking have been neglected among prospective studies. We studied associations between smoking habits and SAH and interactions between known SAH risk factors in a prospective population-based study.

Methods—The population-based FINRISK study cohort of 65,521 individuals was followed up for 1.38 million person-years. We used the Cox proportional hazards model to calculate hazard ratios and evaluated additive and multiplicative interactions between study variables, with all analyses adjusted for known SAH risk factors.

Results—During follow-up, we identified 492 SAHs (266 women). Smoking had a linear dose-dependent and cumulative association with risk for SAH in both sexes. Women smoking >20 cigarettes per day had a hazard ratio of 8.35 (95% confidence interval, 3.86–18.06) compared with a hazard ratio of 2.76 (95% confidence interval, 1.68–4.52) in men in the same cigarettes per day group. Hazard ratios differed by sex in all cigarettes per day and pack-year categories; this association was stronger in women in all categories (P=0.01). When an adjusted model included interaction terms between sex and cigarettes per day or pack-years, female sex was no longer an independent SAH risk factor. Former smokers had a markedly decreased risk for SAH in both sexes when compared with current smokers.

Conclusions—Smoking has a dose-dependent and cumulative association with SAH risk, and this risk is highest in female heavy smokers. Vulnerability to smoking seems to explain in part the increased SAH risk in women.

Key Words: cohort studies ■ risk factors ■ sex characteristics ■ smoking ■ subarachnoid hemorrhage

According to prospective cohort studies, smoking is the most important lifestyle risk factor for subarachnoid hemorrhage (SAH)1–3 and accounts for at least one third of all cases.4,5 In addition, earlier studies report that women are at higher risk for SAH with adjusted hazard ratios (HRs) from 1.4 to 1.9 compared with men,1–3 but the reason for this sex difference has remained unresolved. Retrospective case–control studies have suggested that an increasing number of cigarettes smoked per day (CPD) elevates the risk gradually.5,6,7

Our aim was to examine associations between smoking habits and SAH in a large, population-based, prospective cohort. We also focused on interaction or effect modification between smoking habits and sex because this approach remains unstudied. In addition, we evaluated whether smoking elevates the risk of sudden deaths from SAH outside hospitals or in emergency rooms more than hospitalizations. Finally, we evaluated the effect of smoking cessation on risk for future SAH.

Methods

Data Collection

The research protocol has been described in detail.2,8,9 In brief, the National FINRISK Surveys have been conducted every 5 years since 1972, with independent, population-based, random samples from various geographical areas of Finland. Alcohol consumption, history of hypertension, medication for hypertension, smoking status, and socioeconomic status were assessed by a standardized self-administered questionnaire. Individuals with a history of hypertension or medication for hypertension received the classification hypertensive. Experienced nurses performed clinical measurements including systolic blood pressure, height, and weight and acquired semifasting blood samples for cholesterol measurement after at least 4-hour fasting.

Follow-Up

Follow-up started at enrollment and ended at first-ever SAH, death, or on December 31, 2011, whichever came first. The nationwide Hospital Discharge Register and Causes of Death Register identifies fatal (including outside of hospital and emergency-room SAH deaths) and nonfatal SAHs with high accuracy.10 Sudden deaths from SAH were defined as deaths away from hospitals and those occurring...
in emergency rooms. Sudden deaths from SAH were confirmed in autopsy, and a nosologist checked and corrected the underlying cause of death when necessary. The follow-up was complete for deaths and hospitalizations, when hospitalized patients continued to live in Finland. Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement guided the reporting.

Smoking

Those participants who reported no smoking at all or <100 cigarettes in their lifetime were considered never-smokers. Occasional smokers had smoked on a nondaily basis during the past 6 months before enrollment. Recent quitters were participants who had quit smoking within 6 months before enrollment; former smokers had quit >6 months before enrollment. Current smokers reported how many cigarettes they smoked per day on average, separately for manufactured and self-rolled cigarettes, and the sum of the two comprised their CPD.

On the basis of previous studies, we estimated that 1 cigarette increased risk for SAH as much as 1 cigarette and 1 pipeful of tobacco as much as 3 cigarettes. For analyses, we divided smoking status into 8 categories: never-smokers, occasional smokers, former smokers, recent quitters, and further to 4 groups of current smokers. Current smokers were categorized on the basis of CPD into 1 to 10, 11 to 20, 21 to 30, and ≥31 CPD. Analyses using pack-years (PYs) included only current smokers. PYs were calculated by multiplying the number of CPD by the number of years the person had smoked before enrollment; this number was then divided by 20 (one pack=20 cigarettes). PYs were categorized as none (for all but current smokers), <5 PYs, 5 to 10 PYs, and then in 10-PY intervals until >50 PYs. Smoking status was available for 99.4% of the participants, CPDs for 99.2%, and PYs for 98.8% of the current smokers.

Statistical Analyses

Because of <2% of missing data per variable, we used complete case analyses. We used the Cox proportional hazard model to calculate HRs and 95% confidence intervals (CIs) in adjusted models. On the basis of previous prospective and population-based studies, our final model included age, smoking, systolic blood pressure, body mass index, cholesterol, sex, and study area and year. The preliminary models examined also the role of alcohol consumption and socioeconomic status. According to Schoenfeld residuals and log-log inspection, our models met the proportional assumption criteria. The likelihood ratio test (LRT) served to evaluate the evidence of multiplicative interactions and departure from linearity in adjusted models; a LRT P value of <0.10 was considered evidence of possible interaction. A method described by Andersson et al served in assessing additive interactions by calculating a relative excess risk because of interaction, attributable proportion, and synergy index (SI) in adjusted models. We defined the evidence for additive interaction as strong when at least 2 of relative excess risk because of interaction, attributable proportion, or SI had P values <0.05. Competing risk incidence estimates were calculated by the method described by Fine and Gray. Population attributable risk was estimated by the following formula: population attributable risk=p_i[(HR-1)/(HR-1)+1], where p_i is population fraction of smokers. All statistical analyses used Stata Corp version 12.1 (Stata Corp, College Station, TX).

Ethics Statement

Ethical approval came from the corresponding ethics committee according to the commonly required research procedures and Finnish legislation for each survey, and the study was conducted according to the World Medical Association’s Declaration of Helsinki on ethical principles for medical research. From 2002 onward, written informed consent has been provided by each participant.

Results

Cohort

The study cohort comprised 65,521 participants (33,805 women) who participated in the baseline surveys between 1972 and 2007. A total of 492 first-ever SAHs (266 women) were recorded during the 1.38 million person-years of follow-up. The mean and median ages of the participants were 45.3 (SD, 12.1) and 45.0 years. Median follow-up time for SAH cases was 14.8 years and for the whole cohort 21.1 years.

Smoking

At baseline, 19% of women and 38% of men were current smokers. Men had smoked longer, smoked more daily, and their total exposure (as PYs) was greater than in women (Table 1). Because only 3 occasional smokers had SAH, calculation of HRs for this group was omitted. Current smokers had an HR of 2.77 (95% CI, 2.22–3.46) in comparison with never-smokers. In analysis by sex, HR was 2.20 (95% CI, 1.56–3.10) for male smokers and 3.43 (95% CI, 2.58–4.55) for female smokers. This translates to a population attributable risk estimate of 31% in both men and women. Recent quitters were at higher risk (HR, 1.93 [95% CI, 0.98–3.79]) for SAH than were former smokers (HR, 1.34 [95% CI, 0.98–1.82]). Light smokers (1–10 CPD) were at elevated risk, and this risk increased gradually, reaching an HR of 3.91 (95% CI, 1.97–7.75) among very heavy smokers with >30 CPD (Table 2). A linear dose-dependent relationship also existed between CPD and risk for SAH in all models (Table 2). The association of smoking status with SAH risk was stronger in women in all groups (LRT P=0.01), indicating multiplicative interaction between sex and CPD (Table 2). In the CPD group, 21 to 30 women had an HR of 8.35 (95% CI, 3.86–18.06) compared with an HR of 2.76 (95% CI, 1.68–4.52) in men (Table 2). The cumulative incidence by smoking status and CPD category with a competing risk model in Figure 1 shows the higher lifetime risk in women than in men.

Pack-Years

When compared with never-smokers, current smokers with <5 PYs had an elevated risk, with an HR of 2.13 (95% CI, 1.44–3.16); this risk gradually increased, reaching an HR of 5.62 (95% CI, 2.88–10.97) among those with >50 PYs. PYs had a linear dose-dependent relationship with SAH risk and a stronger association with the risk in women than in men (LRT P=0.08; Table 3). When we compared PY categories of current smokers with nonsmokers (by combining both quitter groups with never-smokers), we found even stronger evidence supporting the sex difference (LRT P=0.02).

Interactions

Because our analysis revealed multiplicative interactions between CPD and sex, and between PYs and sex, we included these interaction terms in a fully adjusted models. In these models, female sex was no longer an independent risk factor for SAH (CPD-model: HR, 1.18 [95% CI, 0.86–1.62] and PY-model: HR, 1.05 [95% CI, 0.82–1.34]). Moreover, an adjusted model (with all categorical variables) including only never-smokers (effects of smoking excluded) showed that female sex was not an independent risk factor (HR, 1.19 [95% CI, 0.85–1.67]). In addition, we found some evidence of an additive interaction between sex and smoking; in the 11 to 20 and 21 to 30 CPD categories, the relative excess risk because of interactions were 2.11 and 6.90 (Figure 2). To conduct analyses similar to those in
previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous prospective studies, previous 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Sudden Deaths From SAH
An adjusted model including only sudden deaths from SAH showed an increased risk in each CPD category when compared with those for hospitalized SAH patients (Table I in the online-only Data Supplement). This model suggested that all CPD categories elevated the risk of sudden death from SAH more in women than in men (Table II in the online-only Data Supplement).

Discussion
Our results suggest that female sex may not be an independent risk factor for SAH, challenging the current understanding of SAH epidemiology. We found that multiplicative and additive effect modification19 between sex and CPD may explain why previous prospective studies2,3,20,21 find female sex to be an independent risk factor for SAH. In other words, if cumulative doses of smoking are not taken into account by sex, categorical analyses may suggest that female sex is a strong risk factor for SAH. We found no other strong multiplicative or additive effect modifications or interactions between any risk factor mentioned in this study. Furthermore, our results confirm retrospective case–control study findings4,6,7 that suggest that smoking is a dose-dependent risk factor for SAH. Even though smoking seems to affect the risk particularly in women, it is important to recognize that the dose-dependent association exists in both sexes and in former and current smokers. Even light smoking (1–10 CPD) elevated the risk for SAH, and this risk increased rapidly after only 0.05 to 5 PYs in both men and women. The risk was lower among former smokers in both sexes, suggesting that smoking cessation reduces risk. Because of difference in smoking prevalence by sex, however, population attributable risk estimate was the same for both sexes. The results were same in all age groups with reasonable number of participants.

Table 3. Risk for SAH by PY Exposure Among Current Smokers Relative to Never-Smokers for All Cases, and Separately by Sex

<table>
<thead>
<tr>
<th>PY category</th>
<th>Overall, HRs and 95% CI</th>
<th>No. of SAHs</th>
<th>Men, HRs and 95% CI</th>
<th>No. of SAHs</th>
<th>Women, HRs and 95% CI</th>
<th>No. of SAHs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smokers (reference category)</td>
<td>1</td>
<td>214</td>
<td>1</td>
<td>47</td>
<td>1</td>
<td>161</td>
</tr>
<tr>
<td>0.05–5</td>
<td>2.11 (1.42–3.12)</td>
<td>31</td>
<td>1.88 (0.97–3.66)</td>
<td>11</td>
<td>2.16 (1.32–3.53)</td>
<td>20</td>
</tr>
<tr>
<td>5–10</td>
<td>2.54 (1.71–3.76)</td>
<td>32</td>
<td>1.59 (0.84–3.03)</td>
<td>12</td>
<td>3.40 (2.09–5.54)</td>
<td>20</td>
</tr>
<tr>
<td>10–20</td>
<td>2.99 (2.17–4.13)</td>
<td>55</td>
<td>2.01 (1.27–3.18)</td>
<td>30</td>
<td>4.37 (2.81–6.78)</td>
<td>25</td>
</tr>
<tr>
<td>20–30</td>
<td>2.94 (1.95–4.43)</td>
<td>33</td>
<td>1.97 (1.17–3.32)</td>
<td>23</td>
<td>4.99 (2.59–9.60)</td>
<td>10</td>
</tr>
<tr>
<td>30–40</td>
<td>3.64 (2.27–5.84)</td>
<td>22</td>
<td>2.60 (1.50–4.50)</td>
<td>18</td>
<td>5.12 (1.86–14.10)</td>
<td>4</td>
</tr>
<tr>
<td>40–50</td>
<td>4.67 (2.47–8.81)</td>
<td>11</td>
<td>3.30 (1.60–6.79)</td>
<td>9</td>
<td>7.39 (1.78–30.70)</td>
<td>2</td>
</tr>
<tr>
<td>&gt;50</td>
<td>5.62 (2.88–11.00)</td>
<td>10</td>
<td>4.75 (2.36–9.56)</td>
<td>10</td>
<td>...</td>
<td>0</td>
</tr>
<tr>
<td>Linearity departure P</td>
<td>0.10</td>
<td>...</td>
<td>0.80</td>
<td>...</td>
<td>0.07</td>
<td>...</td>
</tr>
<tr>
<td>Increase per PY</td>
<td>1.02 (1.01–1.03)</td>
<td>...</td>
<td>1.02 (1.01–1.03)</td>
<td>...</td>
<td>1.03 (1.02–1.05)</td>
<td>...</td>
</tr>
</tbody>
</table>

The HR for never-smokers is the reference category (HR=1). Model is adjusted for age, sex, SBP, BMI, cholesterol, study year, and area. BMI indicates body mass index; CI, confidence interval; HR, hazard ratio; PY, pack-year; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

Figure 1. Incidence rates of subarachnoid hemorrhage (SAH) shown by a competing risks model; the y axis describes competing risk rate, and the x axis, age in years. Competing risk rate described by sex and by smoking status; never-smokers (dash-dot black), former smokers (dash-dot gray), 1–10 CPD (dash black), 11–20 CPD (dash gray), 21–30 CPD (solid black), and 30< CPD (solid gray). No SAH cases was observed in women smoking >30 CPD. The model is adjusted for age, body mass index, CPD, cholesterol, systolic blood pressure, sex, study year, and study area.
The strengths of our study include, to our knowledge, the following: the longest follow-up—40 years—among cardiovascular risk factor studies, the highest number of first-ever SAHs among prospective SAH risk factor studies, a prospective set-up reducing risk for information bias and reverse causality, a population-based cohort including sudden deaths from SAH, detailed data on smoking that allow reliable subgroup analyses, and accurate SAH diagnosis. These factors enabled us to calculate the additive interactions preferred in describing biological interactions, and thereafter, our results indicated that smoking is more hazardous to women.

However, our study also has limitations. First, because of the study design, we do not know how the participants’ smoking patterns evolved during the period after the baseline survey. Although smoking habits are quite stable, during a long follow-up, about half of all smokers will quit, as based on a birth-cohort analysis. This, however, only should weaken the associations between SAH and CPD and between SAH and PYs. The same applies to associations between sex and CPD and between sex and PYs. Second, we could not include alcohol consumption in our final adjusted model because of the small number of never-smokers with high alcohol consumption, as we have reported earlier. Nevertheless, the associations of CPD and PYs with SAH remained essentially the same whether or not alcohol consumption was included in the adjusted model. Moreover, because socioeconomic status relates to smoking habits, alcohol consumption, and other cardiovascular disease risk factors, as well as SAHs, we also included in our analysis socioeconomic status as years of education. This adjustment, however, did not change the associations or effect modifications significantly, so we excluded it from the final model. Third, we could not take into account medication for hypertension and hypercholesterolemia. This could theoretically affect interactions between other risk factors but would be unlikely to change the effect modification observed between sex and smoking. Finally, the external validity of Finnish studies is sometimes questioned, as the incidence of SAH is believed to be exceptionally high in Finland. The first study on the nationwide incidence of SAH in Finland, which, as in Finland, also include sudden deaths in their incidence estimates. In fact, the first study on the nationwide (not only population-based) incidence of SAH in Finland, which identified 6885 incident SAHs during 79,083,579 cumulative person-years, confirmed recently that the Finnish incidence rate of SAH is not exceptional, when compared with incidences that include sudden SAH deaths outside hospitals. This indicates that our results are perhaps generalizable.
Conclusions
Our results suggest that smoking is an important dose-dependent risk factor for SAH and has a stronger association with this risk in women. This effect modification seems to explain why previous studies report female sex as an independent risk factor for SAH. The results emphasize the importance of worldwide smoking cessation agendas and active treatment of nicotine dependence.

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Disclosures
J. Kaprio has consulted for Pfizer on nicotine dependence from 2012 to 2014. The other authors report no conflicts.

References
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**SUPPLEMENTAL MATERIAL**

**Supplemental Table I.** HRs and 95% CIs for different SAHs types by CPD group. The HR for never-smokers is the reference category (HR = 1).

<table>
<thead>
<tr>
<th>Different SAH types</th>
<th>All SAHs cases</th>
<th>Non-fatal SAHs cases</th>
<th>Sudden death SAHs cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR and 95% CI</td>
<td>HR and 95% CI</td>
<td>HR and 95% CI</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>1</td>
<td>292</td>
<td>118</td>
</tr>
<tr>
<td>1-10</td>
<td>2.33 (1.76-3.08)</td>
<td>63</td>
<td>2.36 (1.67-3.33)</td>
</tr>
<tr>
<td>11-20</td>
<td>2.52 (1.95-3.24)</td>
<td>96</td>
<td>2.21 (1.59-3.07)</td>
</tr>
<tr>
<td>20&lt;</td>
<td>3.36 (2.35-4.81)</td>
<td>39</td>
<td>2.46 (1.50-4.04)</td>
</tr>
</tbody>
</table>

Model adjusted for age, sex, SBP, BMI, cholesterol, and study year, and area.

**Supplemental Table II.** HRs and 95% CIs for fatal SAHs by CPD group. The HR for never-smokers is the reference category (HR = 1).

<table>
<thead>
<tr>
<th>Sudden death SAHs</th>
<th>Men HR and 95% CI</th>
<th>Women HR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cases</td>
<td>cases</td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1-10</td>
<td>1.57 (0.53-4.69)</td>
<td>4</td>
</tr>
<tr>
<td>11-20</td>
<td>1.68 (0.76-3.69)</td>
<td>10</td>
</tr>
<tr>
<td>20&lt;</td>
<td>3.91 (1.74-8.80)</td>
<td>9</td>
</tr>
</tbody>
</table>

Model adjusted for age, sex, systolic blood pressure, BMI, cholesterol, study year and area.