Original Contributions

Cigarette Smoking, Hypertension and the Risk of Subarachnoid Hemorrhage: A Population-Based Case-Control Study

RUTH BONITA, M.P.H., Ph.D.

SUMMARY A case-control analysis is used to examine the relation of cigarette smoking, hypertension and the risk of subarachnoid hemorrhage in men and women aged 35-64 years. 45 men and 70 women with subarachnoid hemorrhage were identified as part of a large community based study of stroke, and the controls, 1017 men and 569 women, came from a survey of cardiovascular risk factors conducted in the same community. Cigarette smokers, after adjusting for age, had a significantly increased risk of subarachnoid hemorrhage compared with nonsmokers with relative risks of 3.0 for men and 4.7 for women. The strength of the risk increased with the amount smoked. The association remained significant for each sex after adjusting for hypertension. Those who both smoked and had a history of hypertension had an increased risk of subarachnoid hemorrhage of almost 15 fold compared to those who neither smoked nor had been treated for hypertension. The estimated population attributable risk of subarachnoid hemorrhage associated with cigarette smoking (43%) was greater than that of hypertension (28%) in this population.

THE RELATIONSHIP between cigarette smoking and subarachnoid hemorrhage remains unclear, in part because of the rarity of subarachnoid hemorrhage events in prospective studies and the often inadequate selection of cases in retrospective studies. Subarachnoid hemorrhage, accounting for less than 10% of all stroke episodes, is characterized by a high early case fatality rate and its occurrence in relatively young people, particularly women.

This paper reports the results of an investigation of the relation between cigarette smoking, hypertension and subarachnoid hemorrhage. The cases are compared with a representative group of community controls from the same population using identical questions for both cases and controls. An estimation of the proportion of subarachnoid hemorrhage events that could be attributed to smoking and hypertension is also presented. In addition, a possible interaction between smoking and hypertension is investigated.

Methods

The subarachnoid hemorrhage cases were identified as part of a large community-based study of cerebrovascular disease. All subarachnoid hemorrhage cases occurring in a two year period (1982, 1983) in the Auckland region (total population 829,545) were registered. The study area encompassed one quarter of the total population of New Zealand. Full details of the case-finding methods and diagnostic criteria have been published. Briefly, subarachnoid hemorrhage was defined as a spontaneous rupture of a blood vessel, most often a cerebral aneurysm or arteriovenous malformation leading to bleeding in the subarachnoid space. Diagnosis was based on the abrupt onset of a severe headache and/or impaired consciousness or focal neurological features, associated with at least one of the following clinical signs: lumbar puncture findings of uniform blood-staining and xanthochromia of the cerebrospinal fluid (CSF); computerized axial tomography evidence of blood in the subarachnoid space; cerebral angiographic identification of an aneurysm or arteriovenous malformation; or findings at autopsy.

Information was gathered from patients using a standard questionnaire as soon after the event as possible, and in the case of deaths, the same questionnaire was administered to a close relative after an interval of six weeks. The information collected included, among many other variables, history of treatment of high blood pressure, and cigarette smoking habits. Information about the history of the use (and duration) of oral contraceptives was also obtained, but only for women under the age of 50 years. Hypertension that had been diagnosed and treated was used as a surrogate measure of blood pressure. A current smoker was defined as a person smoking at least one cigarette per day.

The controls for this study came from a separate, but related, community-based survey in Auckland, the sampling methods and results of which have been reported. Briefly, 1017 and 569 men and women 35-64 years were interviewed between January and July 1982.
after being randomly selected from the 1981 general electoral rolls (response rate 82%). The sample size was calculated to enable useful comparisons to be made with risk factor levels measured in future studies. For this reason, 200 persons in each 10 year age/sex group, plus 200 additional males in each of the age groups 45–54 years and 55–64 years, were selected. The questionnaire contained the same questions about blood pressure history, cigarette smoking, and oral contraceptive use as were asked of the subarachnoid hemorrhage cases.

Analyses were restricted to events that occurred in men and women 35–64 years of age. Odds ratios (OR), used as estimates of relative risk, were calculated using the Mantel-Haenszel method controlling for age. Confidence limits (CL) of the relative risks were calculated by the test-based method of Miettinen. The population attributable risks were calculated using the maximum likelihood method of Whittemore as a measure of the public health importance of smoking and hypertension. Multiplicative and additive models were compared using the method of Breslow and Storer.

Results

The age and sex distributions of the subarachnoid hemorrhage cases and the community controls together with the number of males and females who had a history of hypertension, who were current smokers, or who fell into both categories, are shown in table 1.115 cases (45 men and 70 women) were available for comparison with 1586 controls (1017 men and 569 women).

### Hypertension

Those with a history of treatment for hypertension at the time of the subarachnoid hemorrhage event were compared with those who had never been treated for hypertension. Overall, 16% of the controls (14% of the men and 19% of the women) had a history of treatment for hypertension at the time of the interview compared to 38% (22% of the men and 48% of the women) of the subarachnoid hemorrhage cases (fig. 1). The relationship between hypertension and the risk of subarachnoid hemorrhage controlling for age is presented in table 2. For men and women combined, hypertension was associated with an increased risk of subarachnoid hemorrhage with a relative risk of 3.4 (95% CL: 2.3, 5.7); that is, people who had a history of treatment for hypertension were more than three times as likely to develop subarachnoid hemorrhage than people who had never been diagnosed and treated for hypertension. The relationship was stronger in women than in men but this sex difference was not statistically significant (p > .05).

### Cigarette Smoking

Current smokers were compared with those not smoking (including ex-smokers) at the time of the subarachnoid hemorrhage. Among the controls, 28% and 25% of men and women respectively were current smokers compared to 51% and 59% of men and women respectively, among the cases. Smoking was associated with a significant increase in the risk of subarachnoid hemorrhage in each sex with a relative risk of 3.8 for both sexes combined (table 2). Men who smoked were three times more likely to develop subarachnoid hemorrhage than those who were not current smokers; among women the association was stronger but this sex difference was not statistically significant (p > .05). The risk was twice as high in the age group 35–44 years (OR = 5.8; 95% CL: 4.0, 8.4) as in the age group 45–64 years (OR = 2.8; 95% CL: 1.8, 4.3) but these age differences were not statistically significant (p > .05).

A dose-response relationship between the number of cigarettes smoked and the risk of stroke was observed, although the test for linear trend did not reach statistical significance. The risk for those smoking 1–20 cigarettes per day was 3.3 (95% CL: 2.0, 5.3) compared to non-smokers, while the risk for heavier smokers (more than 20 cigarettes daily) was 5.4 (95% CL: 3.0, 9.7) compared to non-smokers (table 3). The pattern was...
similar when men and women were examined separately. Ex-smokers were not at an increased risk (OR = 1.0; 95% CL: 0.5, 1.9).

Oral Contraceptives

Information on the use of oral contraceptives was available only for women aged 35–49 years. There were 31 cases and 289 controls in this age range for whom oral contraceptive information was available. 68% of cases and 88% of controls had been users of oral contraceptives. There were too few current users to analyze this group separately. No significant association between oral contraceptive use and subsequent subarachnoid hemorrhage was observed (OR = 0.5; 95% CL: 0.2, 1.2). However, 77% of the cases compared with 28% of the controls in this subset were current smokers and the risk associated with smoking was nine-fold (OR = 9.2, 95% CL: 4.3, 19.4).

The relationship between high blood pressure and cigarette smoking and subarachnoid hemorrhage was examined using the maximum likelihood method. In both sexes hypertension and cigarette smoking were each independently associated with an increased risk. Furthermore, a synergistic effect between smoking and hypertension was observed (fig. 2) with the risk associated with smoking and hypertension combined increasing almost fifteen-fold (OR = 14.7, 95% CL: 9, 24) compared to those who neither smoked nor had a history of hypertension. The relative risks presented for smoking are likely to be conservative since the non-smoking category included ex-smokers. These results closely parallel the findings of a similar analysis of all other stroke types (excluding subarachnoid hemorrhage), although in that study, as would be expected, the risk of stroke in association with hypertension was more marked. An advantage of this study is that both cases and controls were selected from a defined population and the response rates were high (over 95% of cases and 82% of controls), thus making it unlikely that a biased selection of either cases or controls could have contributed to the associations found. Bias due to disease misclassification is also unlikely because well defined criteria were used and no subarachnoid hemorrhage events occurred in the controls.

Discussion

This community-based case-control analysis of subarachnoid hemorrhage cases and a sample randomly selected from the same population has demonstrated a strong association between cigarette smoking and subarachnoid hemorrhage in men as well as women aged 35–64 years. The strength of the association increased with the amount smoked. Further, there was an interaction between the combined effect of smoking and hypertension and the risk of subarachnoid hemorrhage. The relative risks presented for smoking are likely to be conservative since the non-smoking category included ex-smokers. These results closely parallel the findings of a similar analysis of all other stroke types (excluding subarachnoid hemorrhage), although in that study, as would be expected, the risk of stroke in association with hypertension was more marked. An advantage of this study is that both cases and controls were selected from a defined population and the response rates were high (over 95% of cases and 82% of controls), thus making it unlikely that a biased selection of either cases or controls could have contributed to the associations found. Bias due to disease misclassification is also unlikely because well defined criteria were used and no subarachnoid hemorrhage events occurred in the controls.

### Table 2

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Men</th>
<th>Women</th>
<th>Both sexes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.5(1.2,5.3)‡</td>
<td>3.8(2.3,7.0)</td>
<td>3.4(2.3,5.7)</td>
</tr>
<tr>
<td>Smoking</td>
<td>3.0(2.0,5.2)</td>
<td>4.7(2.9,7.6)</td>
<td>3.8(2.6,5.6)</td>
</tr>
</tbody>
</table>

*Also controlling for sex.

‡95% confidence limits in parentheses; p < 0.05, but all other categories significant at the < 0.001 level.

### Table 3

<table>
<thead>
<tr>
<th>Smoking category</th>
<th>Odds ratio (95% CL)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.0 (0.5,1.9)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-20/day</td>
<td>3.3 (2.0,5.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>20+/day</td>
<td>5.4 (3.0,9.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Men</th>
<th>Women</th>
<th>Both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking*</td>
<td>37 (17,58)‡</td>
<td>47 (32,62)</td>
<td>43 (30,55)</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>15 (1,30)</td>
<td>33 (19,49)</td>
<td>28 (18,39)</td>
</tr>
<tr>
<td>Smoking and/or hypertension</td>
<td>46 (24,69)</td>
<td>59 (42,76)</td>
<td>55 (42,68)</td>
</tr>
</tbody>
</table>

*Controlling for hypertension.

†Controlling for smoking.

§95% confidence limits in parentheses.
A potential source of bias in this study concerns ascertainment of the risk factor status of the subarachnoid hemorrhage cases. Both the patients (and the relatives of deceased cases) and the interviewers knew the disease status at the time of the data collection. It is thus possible that the respondents or the interviewers may have been more likely to identify the presence of one of the risk factors at the time of interview than were the healthy community controls. There is little direct evidence in this study concerning the effect of this source of bias, although it is likely to be minimal since there is no reason to believe that either patients or interviewers suspected either smoking or hypertension to be risk factors for subarachnoid hemorrhage. The suggestion of a dose-response relationship of cigarette smoking and the interaction between smoking and hypertension provide confidence in the validity of the results. Reliance on a surviving spouse or close relative for information about exposure to the studied risk factors was unavoidable for the large proportion of cases (44%) who died within one month of the event. It is impossible to estimate the effects of differential sources of information, although a recently reported study of the validity of questionnaire responses provided by surviving spouses provides some confidence, at least in terms of smoking history. In that study, 100% agreement on smoking history was achieved even after a three year period.17

In the small subset of women for whom information was available on the use of oral contraceptives, there appeared to be no significant association with the risk of subarachnoid hemorrhage. Cigarette smoking on the other hand was associated with a significant increased risk in this same subset.

Three major prospective studies investigating the risks of oral contraceptives2-4 have demonstrated a positive association between cigarette smoking and the risk of subarachnoid hemorrhage. All three studies reported a small number of cases. Only 11 women were identified between 1969-1976 in the Walnut Creek study,2 which involved a 6 year follow-up of 16,759 women less than 55 years; the risk of cigarette smokers was 5.7 (90% CL: 1.8, 17.8) that of non-smokers.

In the Oxford Family Planning Association study,3 13 women with a subarachnoid hemorrhage were identified between 1968-1974. While it was suggested that both hypertension and smoking were associated with the risk of subarachnoid hemorrhage, it is not apparent from this report whether these findings reached statistical significance, or indeed, whether these variables were independently associated with the risk of subarachnoid hemorrhage.

The Royal College of General Practitioners' prospective study of the health associations of oral contraception4 involving a 10 year follow-up of 46,000 women, identified 20 subarachnoid hemorrhage deaths, 17 among oral contraceptive users, and 3 among the controls (non-oral contraceptive users). The relative risk of subarachnoid hemorrhage for ever users of oral contraceptives was 4.0 (95% CL: 1.3, 12.9). It was noted that cigarette smoking was more common in women who died of subarachnoid hemorrhage (71%) than in the other women in the study (48%) but estimates of relative risk were not calculated.

Thirty-six people (14 men and 22 women) who experienced a subarachnoid hemorrhage were identified during a 26 year period in the Framingham study6; of these, only 15 (42%) occurred in people less than 65 years of age. Cigarette smoking was more prevalent in subarachnoid hemorrhage cases than in controls (p = .06) and more subarachnoid hemorrhage cases had a prior history of heavy smoking (20 cigarettes or more per day) than controls (p = .03). Differences were greater in women.

Two retrospective studies using case-control analyses5,1 have shown an association between smoking and subarachnoid hemorrhage in men and women. Both studies are, however, limited by the unrepresentative selection of the cases and the selection of controls from general population surveys which were not designed to ensure that exposure data were collected in a standardized manner. Furthermore, the apparent association between subarachnoid hemorrhage and smoking indicated in these two studies has been questioned since neither study investigated hypertension as a confounder.18

Estimates of the proportion of the cases in the community attributable to cigarette smoking (43%) and hypertension (28%) indicates the public health impact of smoking, in particular. No previous study has suggested a synergistic effect between cigarette smoking, hypertension and the risk of subarachnoid hemorrhage. Extrapolation from the results of this study to the population of New Zealand suggests that up to one half, or approximately 125 (95% CL: 95, 155) subarachnoid hemorrhage events each year, may be explained by exposure to smoking and/or hypertension among people 35-64 years of age. The preventive implications are clear.

Acknowledgments
The author wishes to thank the nurse-interviewers, clerical staff, and the many other professional and lay people who made this study possible, in particular Dr. R. T. Jackson.

References
Early Changes of Experimentally Induced Cerebral Aneurysms in Rats: Scanning Electron Microscopic Study

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SUMMARY To obtain information about the early changes of experimentally induced cerebral aneurysms in rats, the luminal surface of branching areas of their cerebral arteries was examined with a scanning electron microscope. At the branching sites of major cerebral arteries in the control animals, the intima just distal to the apex markedly protruded into the lumen forming a linear bank-like intimal pad. Along and distal to this pad, there was a shallow long groove (juxta-apical groove). Such grooves were much deeper and wider in experimental animals than those in the control rats. By studying various stages of early aneurysmal changes, cerebral aneurysms were proven to develop from such grooves. In deep juxta-apical grooves and small aneurysms, round regenerated endothelial cells with a large number of microvilli were diffusely present. Degenerated cells with balloons and craters were observed intermingled with such regenerated cells. Interoendothelial gaps were also seen.

The present study showed the complex structure of the apex of arterial bifurcation in rats, including bank-like intimal pads. Such complex structures of the branching sites were considered to be responsible for the initiation of cerebral aneurysms due to endothelial injury possibly caused by turbulent flow there.

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We have successfully induced cerebral aneurysms in rats by ligating one common carotid artery, inducing hypertension and/or administering β-aminopropionitrile (BAPN). We showed that hemodynamic stress, hypertension and abnormal metabolism of connective tissue play important etiological roles in the development of cerebral aneurysms. Using this animal model, it is now possible to study the developmental sequence of cerebral aneurysms.

Endothelial injury is known to play an important role in the development of atherosclerosis. We have shown that endothelial injuries induced by hypertension cause further vascular degenerative changes. It is also likely that endothelial injury plays a significant role in the development of cerebral aneurysms.

The purpose of the present study was to examine the intimal changes involved in the development of cerebral aneurysms. Using a scanning electron microscope (SEM), the luminal surfaces of branching areas of cerebral arteries were studied in rats in various stages of early aneurysmal formation. In some cases, plastic...
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