Cigarette smoking as a cause of aneurysmal subarachnoid hemorrhage and risk for vasospasm: a report of the Cooperative Aneurysm Study

BRYCE K. A. WEIR, M.D., GAIL L. KONGABLE, M.S.N., NEAL F. KASSELL, M.D., JOHN R. SCHULTZ, PH.D., LAURA L. TRUSKOWSKI, M.S., ASHLEY SIGREST, PH.D., AND THE INVESTIGATORS

Section of Neurosurgery, University of Chicago, Chicago, Illinois; and Neuroclinical Trials Center and Department of Engineering and Statistics, University of Virginia, Charlottesville, Virginia

Object. Cigarette smoking is associated with aneurysmal subarachnoid hemorrhage (SAH) and subsequent vasospasm. The purpose of this study was to quantify this association.

Methods. Nearly 3500 patients with SAH from North America and Europe have been enrolled in five different multicenter, controlled studies coordinated at the Neuroclinical Trials Center of the Virginia Neurological Institute at the University of Virginia. Among the prospective data gathered were whether the patient smoked at the time of their most recent SAH and the evolution of angiographic vasospasm. The rate of smoking in the patients enrolled in the studies was compared with the expected rate by using a chi-square statistic adjusted for age and gender, in the general population in the United States (U.S.) and Europe. In virtually all age and gender subgroups, and for the combined populations in the five clinical trials, patients with SAH reported current smoking rates 2.5 times higher than expected based on U.S. and European national surveys (p < 0.0001). Cigarette smoking was also associated with younger age at onset of SAH (5–10 years, p < 0.0001) and increased incidence of clinically confirmed vasospasm (p < 0.0005).

Conclusions. The findings of a significantly increased representation of current cigarette smokers in the study populations and association with younger age at the time of SAH and increased incidence of vasospasm concur with recent reports of smoking as a significant risk factor for ruptured aneurysms and subsequent vasospasm.

Key Words • aneurysm • subarachnoid hemorrhage • smoking • vasospasm • age

The examination of a possible relationship between cigarette smoking and the rupture of cerebral aneurysms began when Bell and Symon found a highly significant number of cigarette smokers among 208 patients with ruptured cerebral aneurysms compared with the general population in Great Britain, after adjusting for age. Based on their analyses, these authors suggested that continued smoking increases the risk of suffering an aneurysmal subarachnoid hemorrhage (SAH) by a factor of 3.9 for men and 3.7 for women. For patients with ruptured aneurysms, they found that 16% were nonsmokers but that 59% smoked more than 20 cigarettes per day. In contrast, smoking rates for patients with SAH related to arteriovenous malformations or those with no angiographically visualized abnormalities were similar to expected rates in the general population.

In the past decade there has been remarkable consistency of results in both case-controlled and prospective cohort studies of patients with aneurysmal SAH with respect to smoking as a risk factor. However, no clear association with vasospasm has been found. In a recent report an increased risk of vasospasm associated with smoking is described. We considered it of interest to examine these relationships in the comparatively large datasets of patients with ruptured aneurysms that were gathered recently in prospective clinical trials analyzed at the Neuroclinical Trials Center (NTC).

Clinical Material and Methods

Patient Selection

One European and four North American randomized clinical trials of patients with SAH were conducted between 1987 and 1994. A total of 3441 patients were enrolled in these five trials (1023 in the European trial and 906, 365, 245, and 902 patients, respectively, in the four North American trials). Patients who were at least 18 years of age who had an angiographically documented saccular aneurysm as the cause of SAH gave consent and were randomly assigned to groups in each trial. The exclusion criteria are described in detail in the papers reporting the results.

Patients in the five studies were treated with hypervolemic therapy if it was clinically indicated. The patients in two of the studies were randomized to receive nica-
TABLE 1
Clinical trials of SAH included in this survey

<table>
<thead>
<tr>
<th>Study</th>
<th>Years of Enrollment</th>
<th>No. of Patients</th>
<th>No. W/ Smoking Data (%)</th>
<th>*</th>
</tr>
</thead>
<tbody>
<tr>
<td>European tirilazad Phase III trial (EASAH)</td>
<td>1991–1993</td>
<td>1023</td>
<td>966 (94)</td>
<td></td>
</tr>
<tr>
<td>Canadian tirilazad Phase II trial (CANADA)</td>
<td>1990–1992</td>
<td>245</td>
<td>228 (93)</td>
<td></td>
</tr>
<tr>
<td>placebo-controlled nicardipine</td>
<td>1987–1989</td>
<td>906</td>
<td>849 (94)</td>
<td></td>
</tr>
<tr>
<td>North American Phase III trial (NCSAH) I</td>
<td>1989–1991</td>
<td>365</td>
<td>332 (91)</td>
<td></td>
</tr>
</tbody>
</table>

* Reported status of patient as current or former smoker in time period immediately prior to most recent SAH. Percentages represent the percentage of patients in the randomized sample in whom smoking data were reported.

dipine HCl, whereas patients in the remaining studies received nimodipine and were randomized to receive some dosage of Tirilazad mesylate for the prevention of vasospasm. Cerebral vasospasm was defined as neurological deterioration that occurred between Days 4 and 14 post-SAH that could not be attributed to another cause, was associated with increased transcranial Doppler flow velocities, and was confirmed on cerebral angiography or by clinical improvement after hypervolemic therapy.

The smoking data, which were collected in a standardized fashion across the five trials, classified patients as current smokers, former smokers, or nonsmokers. The definition of a current smoker was any patient who was smoking, even if intermittently, at the time of the SAH. The definition of a former smoker was any patient who had smoked at least 100 cigarettes and now smoked every day or most days. Overall smoking prevalence in the U.S. (25.6%) and a breakdown of smoking prevalence by age and gender subsets of the population were reported.

Smoking Data for General Population in the United States

To determine the prevalence of smoking in adults in the United States (U.S.) during 1992, the National Health Interview Survey-Cancer Control and Epidemiology Supplements collected self-reported information on cigarette smoking from a random sample of 36,075 civilian, noninstitutionalized adults aged 16 years or older in that year. The survey defined a current smoker as a person who had smoked at least 100 cigarettes and now smoked every day or some days. Overall smoking prevalence in the U.S. (25.6%) and a breakdown of smoking prevalence by age and gender subsets of the population were reported.

Smoking Data for General Population in Europe

To determine the prevalence of smoking in European adults, the national counterparts of the World Health Organization’s Health for All committee collected self-reported information on cigarette smoking from a random sample of 15 million civilian, noninstitutionalized adults aged 16 years or older in the countries of the European region during the period from 1992 to 1994. In this survey of 42 countries, a current smoker was defined as a person who had smoked at least 100 cigarettes and now smoked every day or most days. Overall, smoking prevalence in Europe was 29%, ranging from 28 to 40% among the countries participating in the NTC studies. Smoking prevalence by gender was reported, but age subsets of the European population were not available.

Statistical Methods

For each clinical trial sample, the observed smoking rate was compared with the expected smoking rate by using a chi-square statistic. Smoking prevalence rates in the U.S. were used to project expected smoking rates for U.S. and Canadian study populations. The expected rate of smoking for the overall sample was calculated from age- and gender-specific estimates of smoking prevalence for noninstitutionalized adults in the U.S. for the year 1992. The expected rate was adjusted for the age and gender distribution of the sample. For each North American trial, comparisons of observed and expected smoking rates in all age and gender subsets with a sample size of at least 20 individuals were undertaken. For each tested sample, the observed and the expected prevalence based on general population data is reported, as well as the ratio of observed and expected prevalence.

For the North American trial sample, the patient’s age at the time of aneurysm rupture was compared using an unbalanced two-way analysis of variance procedure for current, former, and nonsmokers in each gender group. The difference in mean age between current smokers and nonsmokers and former smokers and nonsmokers is also reported for subgroups of men and women in each study. Because the nonsmoking group was used for multiple comparisons in the combined sample for each study, the tests were not considered to be independent and a Bonferroni-adjusted significance level of 0.01 was adopted for each comparison. This ensured that the overall significance level of the interaction of smoking status and gender on age was maintained at a probability value of 0.05 or less.

Smoking prevalence rates reported for the countries participating in the European clinical trial were used to project expected rates for the European study population. The expected rate of smoking for the general European sample was calculated from gender-specific estimates of smoking prevalence for the years 1992 to 1994. For this sample, the observed prevalence and the expected prevalence based on general population data are reported, as well as the ratio of observed and expected prevalence. The age at the time of SAH was compared using an analysis of variance procedure for current, former, and nonsmokers in each gender group, and the mean age difference was reported (significance at p < 0.05).

The incidence of vasospasm in the smoking and nonsmoking groups was compared across all studies by using the Cochran–Mantel–Haenszel test. Estimates of odds ra-
Cigarette smoking, SAH, and vasospasm

### TABLE 2
Demographic characteristics of SAH in the five study populations

<table>
<thead>
<tr>
<th>Study*</th>
<th>Percentage Male</th>
<th>Mean Age in Years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASAH (865)</td>
<td>32</td>
<td>48.6 (21–81)</td>
</tr>
<tr>
<td>CANADA (228)</td>
<td>37</td>
<td>46.9 (23–74)</td>
</tr>
<tr>
<td>NICSAH I (849)</td>
<td>36</td>
<td>47.2 (18–79)</td>
</tr>
<tr>
<td>NICSAH II (332)</td>
<td>32</td>
<td>50.0 (22–82)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses in this column represent the number of patients in the randomized sample for whom smoking data were reported.

### TABLE 3
Current smoking rates for patients enrolled in the five clinical trials of SAH being reviewed

<table>
<thead>
<tr>
<th>Study*</th>
<th>Observed Rate (95% CI†)</th>
<th>Expected Rate‡</th>
<th>Ratio§</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASAH (865)</td>
<td>59% (56–62)</td>
<td>26</td>
<td>2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EASAH (966)</td>
<td>46% (43–49)</td>
<td>29</td>
<td>1.5</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>CANADA (228)</td>
<td>60% (54–66)</td>
<td>26</td>
<td>2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NICSAH I (849)</td>
<td>50% (57–63)</td>
<td>26</td>
<td>2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NICSAH II (332)</td>
<td>59% (54–64)</td>
<td>25</td>
<td>2.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Numbers in parentheses in this column represent the number of patients in the randomized sample for whom smoking data were reported.
† Calculated using the chi-square statistic.
‡ Expected rate of current smoking was based on age and gender distribution of the study sample and current smoking rates in the U.S. and Europe for 1992.
§ Ratio of observed over expected smoking rate for study sample.

### Results

**Demographic Characteristics**

Four North American studies were conducted between 1987 and 1994 and comprised a total of 2418 patients with aneurysmal SAH. In one European study conducted between 1991 and 1993, 1023 such patients were enrolled. In each study, smoking information was reported for more than 90% of the randomized patients. Table 1 lists the clinical trials of aneurysmal SAH included in this survey. The demographic characteristics of the study populations with reported smoking data are shown in Table 2. Approximately one third of the patients in each study were male. The females who were enrolled in the studies tended to be older than the males.

### Smoking and Age

**Somoking Characteristics at Time of SAH**

Approximately 60% of the patients enrolled in the four North American studies were reported to be current smokers at the time of SAH. In contrast, the rate of current smoking expected in each of the North American studies from U.S. smoking survey data was only 25 to 26%. Thus, the smoking prevalence in the North American clinical studies was almost 2.5 times the expected prevalence (p < 0.0001). The single European trial conducted between 1991 and 1993 had a lower proportion of current smokers (46%) or 1.5 times the expected rate of current smoking in Europe (29%; p < 0.0001), as shown in Table 3.

A trend of higher smoking rates among men and lower smoking prevalence among patients older than 64 years of age was observed in the study populations. A breakdown of smoking prevalence by age and gender in the U.S. population survey showed a similar pattern, but these rates were substantially lower than those for all age and gender subsets of the North American SAH study populations. Thus, smoking prevalence ratios varied from 1.7 to 3.5 among the age- and gender-matched subgroups, with no consistent pattern or trend of a higher smoking prevalence ratio in specific age and gender subsets across the North American study populations (Table 4). Almost all comparisons of observed smoking prevalence and U.S. smoking rates were highly significant in the examined subsets for the study populations (p < 0.0001).

J. Neurosurg. / Volume 89 / September, 1998
TABLE 5
Mean age of patients with SAH grouped according to gender and smoking status*

| Smoking Status | Male | | | | | | Female | | | |
|----------------|------|---|---|---|---|---|---|---|---|---|---|---|---|
| Data Source    | Never | Former | Current | p Value | Never | Former | Current | p Value |
| NASAH          | mean  | 51.6 | 52.7 | 46.4 | 0.0005 | 57.7 | 55.8 | 48.7 | 0.0001 |
|                | SD    | 14.3 | 13.8 | 10.6 | 11.9 | 13.0 | 12.0 |      |      |
|                | diff  | 0.0  | -1.1 | 5.2† | 0.0  | 1.9  | 9.0† |      |      |
|                | no.   | 53   | 56   | 169 | 191   | 53 | 344 |      |      |
| EASAH          | mean  | 49.7 | 49.3 | 48.4 | 0.6793 | 55.3 | 50.2 | 48.0 | 0.0001 |
|                | SD    | 15.2 | 13.0 | 11.6 | 13.7 | 15.2 | 12.2 |      |      |
|                | diff  | 0.0  | -1.1 | 5.2† | 0.0  | 1.9  | 9.0† |      |      |
|                | no.   | 81   | 52   | 182 | 326   | 58 | 266 |      |      |
| CANADA         | mean  | 48.0 | 55.7 | 44.6 | 0.0176 | 59.4 | 57.1 | 48.8 | 0.0005 |
|                | SD    | 13.4 | 7.9  | 6.1  | 18.2 | 13.2 | 12.6 |      |      |
|                | diff  | 0.0  | -1.1 | 5.2† | 0.0  | 1.9  | 9.0† |      |      |
|                | no.   | 22   | 11   | 52  | 38    | 20 | 85  |      |      |
| NICS AH I      | mean  | 48.1 | 52.7 | 45.9 | 0.0841 | 55.3 | 52.6 | 47.5 | 0.0001 |
|                | SD    | 16.2 | 10.6 | 11.5 | 15.1 | 12.5 | 12.9 |      |      |
|                | diff  | 0.0  | -4.6§ | 3.5§ | 0.0  | 7.7§ |      |      |
|                | no.   | 68   | 37   | 205 | 172   | 64 | 303 |      |      |
| NICS AH II     | mean  | 52.7 | 56.6 | 46.7 | 0.0366 | 57.0 | 52.8 | 47.9 | 0.0001 |
|                | SD    | 18.4 | 13.4 | 13.7 | 15.7 | 12.8 | 12.4 |      |      |
|                | diff  | 0.0  | -3.9§ | 6.1§ | 0.0  | 4.2§ | 9.1§ |      |      |
|                | no.   | 23   | 21   | 61  | 57    | 35 | 135 |      |      |

* Diff = difference between mean age for subset and that for nonsmokers according to the chi-square statistic; SD = standard deviation.
† p < 0.01.
‡ p < 0.0001.
§ p < 0.05.

younger than the nonsmokers on average (47–48 years compared with 55–60 years). Intermediate results were obtained for former smokers in the female subset for each study. In men, the nonsmokers also tended to be older than the current smokers. In the North American trials, the men who were current smokers at the time of rupture were 2 to 6 years younger on average than the nonsmoking men. Mixed results were obtained for the male former smokers. In the male subsets in the North American trials, the probability values for the age comparisons ranged from a highly significant finding for the North American tirilazad Phase III trial (p < 0.0005) to a marginal finding for placebo-controlled nicardipine North American Phase III trials (p < 0.0841). In the European trial, the average age of the men in the different smoking status groups was similar at the time of aneurysm rupture.

**Smoking and Vasospasm**

A higher incidence of vasospasm was found in the groups of smokers in all five studies, independent of their randomized treatment (Table 6). Within all the trials the estimates of relative risk for vasospasm were 1.1 to 1.5 times higher in the smoker subsets, compared with nonsmokers. Although the European study alone showed statistical significance regarding smoking and vasospasm, the four North American studies demonstrated strong trends to support the association between smoking and vasospasm. In all studies combined, an overall significant association was found between smoking and vasospasm (1.2; 95% confidence interval [CI] 1.1–1.4; p = 0.005).

**Discussion**

**Smoking and Risk of Aneurysmal SAH**

Current rates of smoking in patients with aneurysmal SAH in the NTC trials were between two and three times those in the general U.S. and European populations. In our study, 60% of the patients enrolled in the four North American trials and 46% of the patients in the European trial were current smokers at the time of SAH. Although selection bias for a randomized trial may have influenced certain characteristics of our populations, these findings are consistent with previous studies in which an association between SAH and smoking in both prospective cohort and case-controlled studies is reported.2-6,12,13,17,19 In a British study of 217 patients with SAH matched to controls by age, sex, and occupation, the relative risk of SAH for smokers was twice that for nonsmokers (2.12 for men, 95% CI 1.27–3.54; 1.93 for women, 95% CI 1.43–2.61).19 In the Framingham study, 5.184 men and women were studied prospectively for 26 years. Thirty-six cases of aneurysmal SAH were observed. Cigarette smoking was more frequent among patients with SAH than among retrospectively selected control patients without matching for age and sex (51% compared with 6%, p = 0.06).5

In all of the NTC studies, the relative risk was greatest in the current smoker groups, and the relative risk for former smokers was greater than that for nonsmokers. Although the data on the extent of exposure (cigarettes/day) was not examined in our studies, increased smoking exposure associated with increased risk of SAH has been reported. In the Framingham study, the rate of heavy smoking (>20 cigarettes/day) was 50% in the patients with SAH compared with 29% in the age- and
Cigarette smoking, SAH, and vasospasm
gender-matched controls (p = 0.03). In another population-based study, 118,539 women ranging in age from 30 to 55 years and free from all types of stroke when they entered the study in 1976 were followed for 8 years. Two hundred seventy-four patients (0.2%) developed strokes, of which 71 were from SAH. The number of cigarettes that the patients smoked per day was positively associated with the risk of SAH; those women who smoked 25 or more cigarettes per day had a relative risk of 9.8 for SAH (95% CI 5.3–17.9) when compared with those who had never smoked. In a population-based case-controlled study conducted by Longstreth et al., in which 69 patients with SAH were compared with 149 control volunteers matched for age and gender, current smokers had an odds ratio of 4.2 (95% CI 2.7–6.7) when compared with nonsmokers and former smokers combined. Current heavy smokers (> 20 cigarettes/day) had an SAH risk of 11.1 (95% CI 5–24.9), whereas current light smokers (≤ 20 cigarettes/day) had an increased risk of 4.1 (95% CI 2.3–7.3), and former smokers had an increased risk of 1.8 (95% CI 1–3.2) compared with those who had never smoked.

Smoking Exposure as an Independent Risk for SAH

Age and hypertension are also well-known risk factors for SAH, and it has been speculated that an interaction between these risks and smoking may contribute to the increased incidence of SAH for these patients. In the NTC study populations, cigarette smoking was associated with a younger age at onset of SAH. The average age at SAH was 47 to 48 years for women who currently smoked compared with 55 to 60 years for women who did not. Men in the current smoker group were 2 to 6 years younger at SAH when compared with male nonsmokers. This trend also existed in former smokers when they were compared with current and nonsmokers. In all five of the NTC trials, former smokers were 2 to 3 years younger on average than nonsmokers and 2 to 3 years older at SAH than current smokers. This finding has not been examined in other studies, and there are few other data available to support this; in fact, in most reports increasing age is associated with increased risk of SAH. In one case-controlled study of 181 patients 15 to 45 years of age smoking was reported as a risk factor for cerebrovascular disease when compared with 307 age- and gender-matched controls. Although we may infer from these findings that cigarette smoking increases the risk of SAH, this group was not examined independently of all types of cerebrovascular disease including ischemic stroke and intracerebral hemorrhage.

Adjustments for the effects of age, weight, blood pressure, diabetes, hypercholesterolemia, oral contraceptive use, postmenopausal estrogen therapy, and alcohol intake did not alter the association between cigarette use and the incidence of SAH in other populations. In a British study in 21 patients with stroke and 208 with SAH were compared with 573 control subjects by using case-control methods. The relative risk of SAH for cigarette smokers was 4.5 for men (95% CI 2.4–8.4) and 2.5 for women (95% CI 1.4–4.5) after adjusting for age, race, social class, alcohol consumption, and treatment of hypertension. The estimated increase in relative risk for smokers of either gender was 1.5 for every additional 10 cigarettes smoked daily. In an early population-based case-controlled study published in 1986, Bonita found 45 men and 70 women with SAH to 1017 men and 569 women aged 35 to 64 years who participated in a large community-based survey of cardiovascular risk factors. Cigarette smokers had a significantly increased risk of SAH (3, 95% CI 2–5.2; 4.7, 95% CI 2.9–7.6) for men and women, respectively, after adjusting for age compared in each gender group. The association remained significant for each sex even after adjusting for hypertension. In a cohort study of 121,700 nurses, women who smoked one to 14 cigarettes daily had an age-adjusted relative risk of 2.2 (95% CI 1.5–3.3), whereas those who smoked more than 25 cigarettes daily had an increased risk of SAH (relative risk 9.8, 95% CI 5.3–17.9), after adjustment for the effects of weight, hypertension, diabetes, hypercholesterolemia, oral contraceptive use, estrogen replacement therapy, and alcohol intake. The estimated population-attributable risk of SAH associated with cigarette smoking (43%) was greater than that of hypertension (28%). In a Finnish study, the smoking and drinking habits of 278 patients aged 50 to 60 years with aneurysmal SAH were compared with 314 hospitalized controls. After adjusting for age, alcohol intake, and hypertension, smoking more than 20 cigarettes per day carried a relative risk of 7.3 for men (95% CI 3.8–14.3) and 2.1 for women (95% CI 1.2–3.6) when compared with those in the gender groups who were not current smokers. These data indicate that smoking is likely to be an independent risk factor for SAH and not necessarily associated with other factors known to contribute to this disease.

In several reports it has been concluded that patients who smoked and suffered from hypertension were actually at much higher risk for SAH. Bonita found that hypertensive smokers had a 15-fold higher risk of SAH than normotensive nonsmokers, after controlling for age and gender. Knekt et al. studied the risk factors for SAH among 42,862 men and women aged 20 to 69 years who had participated in a large health survey. During the mean follow-up period of 12 years, 187 cases of SAH were observed. Smoking and hypertension were positively associated with SAH, and the effects were especially elevated among lean, hypertensive smokers, whose risks were 18.3 (95% CI 7.8–42.7) among women and 6.7 (95% CI 2.3–19.7) among men.

The mechanism by which smoking contributes to aneurysm formation and SAH is not clearly understood. Atheroma formation and the acute rise in blood pressure associated with smoking have been implicated, as well as other mechanisms of accelerated vascular atherogenesis. In a report of a systematic review of papers in which SAH was recognized as a distinct entity and which included comparable case and control subjects with confirmed diagnoses of SAH, it was concluded that smoking, hypertension, and alcohol abuse are important risk factors for SAH. Within that review of nine longitudinal studies and 11 case-control studies, smoking emerged as a significant risk factor in every analysis.

Smoking and Vasospasm

Although various clinical and demographic characteristics have been assessed to determine predictors of cerebral vasospasm post-SAH, smoking has not been as carefully

J. Neurosurg. / Volume 89 / September, 1998
examined in this regard. In a recent report of 70 patients with SAH a significant association was demonstrated using multivariate analysis between symptomatic vasospasm and cigarette smoking (p = 0.03; odds ratio 4.7, 95% CI 2.4–8.9). An increased relative risk of vasospasm was associated with smoking in each of the NTC studies. The risk was greatest in the European study and more moderate in the North American studies. In the five studies combined, an increased relative risk of 1.22, 95% CI 1.07–1.4 was found (p = 0.005). The thesis that cigarette smoking causes arteriopathy and influences aneurysm formation and rupture also supports the impact of smoking on vasoactivity. It is suggested that smoking might act on cerebral endothelial function in a manner similar to its induction of coronary arterial vasospasm.

This is a significant finding regarding the predictability of cerebral vasospasm after SAH and has implications in the monitoring and use of prophylactic hypervolemic therapies in patients with a history of smoking.

Conclusions

Our material represents by far the largest population of patients with aneurysmal SAH in whom specific information on smoking has been obtained. It is clear that there is a highly significant association between a history of cigarette smoking and the development of aneurysmal SAH. We believe it to be highly likely that there is a causal relationship between smoking and the development of aneurysms and their subsequent rupture that is independent of other known risk factors. We suggest that some component(s) of cigarette smoke damage the cerebral artery wall, most likely the single layer elastica, in a cumulative fashion. Aneurysmal dilation is therefore more likely to occur than if the sole pathogenetic mechanism is hemodynamic damage.

Aneurysm rupture appears to be dose dependent in persons who smoke, because it increases with increased exposure, lessens after smoking cessation, and occurs at an accelerated pace in younger patients. This finding should be carefully investigated because it signifies an increased impact of the economic loss caused by SAH in a much younger portion of the expanding aging population. In many reports a strong dose–response relationship has been found between the number of cigarettes smoked daily and the risk of SAH. However, it is encouraging that this excessive risk diminishes among former smokers and may largely disappear in 2 to 4 years after smoking cessation.

Because the case/mortality rate of SAH remains at 40 to 50% despite continuing improvements in the recognition and treatment of patients who experience this disease, the predominant cause of death after SAH is the direct effect of the initial hemorrhage, and the second greatest cause of mortality and morbidity is vasospasm. The greatest impact on SAH is clearly achieved by prevention of aneurysm formation and rupture. This study supports smoking cessation as a method of lowering the risk of SAH and subsequent vasospasm. Because smoking is a modifiable risk factor, this is yet another reason for those in the medical profession to actively encourage their patients to stop smoking and to work against those interests that seek to increase the number of cigarette smokers in our population.

Acknowledgments

The authors express their gratitude to the Investigators and Coordinators of the NTC trials as listed in the respective papers, and to Teresa Germanson, Ph.D., and Ms. Lori Elder for their help in preparing this manuscript.

References


Manuscript received March 6, 1998.
Address reprint requests to: Bryce K. A. Weir, M.D., Department of Neurosurgery, University of Chicago, 5841 South Maryland Avenue, Chicago, Illinois 60637.