Data from more than 20 well-executed case–control or cohort studies have demonstrated that cigarette smoking is a very significant risk factor (two- to sixfold increase in risk among current smokers) for subarachnoid hemorrhage (SAH), and that the risk increases in a dose-dependent manner.\textsuperscript{3,10–12} The association between smoking and SAH is stronger than that between smoking and any other cerebrovascular disease. Furthermore, persons who smoke more than 20 cigarettes per day have an increased risk. In fact, no controlled study has shown a nonsignificant association between smoking and the risk for SAH.

In North America and Europe, the prevalence of smoking in patients who have experienced an SAH ranges from 45 to 75\%, whereas in the general adult population it ranges from 20 to 35\%.\textsuperscript{3,5,10–12} Men and those in younger age groups smoke more than other groups—both in patients with SAH and in the general population. Approximately 40\% of SAHs can be attributed to current smoking.\textsuperscript{5,10} Cigarette smoking seems to increase the risk of rupture of an unruptured aneurysm by increasing its growth rate.\textsuperscript{5,6} In addition, smoking increases the risk of formation of de novo aneurysms.\textsuperscript{6}

Few researchers have focused on the influence of cigarette smoking on either outcome or survival after SAH.\textsuperscript{1,5,8,9} The effect of smoking on the occurrence and severity of delayed symptomatic cerebral ischemia after SAH has been investigated by some researchers.\textsuperscript{1,2,4,7,12} In prospective follow-up studies,\textsuperscript{1,5,8,9} cigarette smoking did not significantly affect outcome after SAH. In a population-based study conducted by Longstreth, et al.,\textsuperscript{8} a current smoking status before SAH had no significant independent effect on 30-day survival (WT Longstreth, personal communication, 2001). Similarly, nonsignificant associations between smoking status and death or poor outcome were demonstrated in two hospital-based studies.\textsuperscript{1,9}

In a Helsinki study,\textsuperscript{1,4} 29\% of 291 patients with a verified aneurysmal SAH died after bleeding; in most cases death was caused by either the initial hemorrhage or early rebleeding during or soon after transportation. It was very unlikely that the smoking statuses of patients who died before admission to an emergency department would have been different from those of the patients who were admitted. Neither a current smoking status nor the number of cigarettes smoked per day before SAH affected patient outcome, mortality, or the occurrence of early rebleeding. On the other hand, the mean cell volume of erythrocytes was directly associated with poor outcome. This mean cell volume is increased by both cigarette smoking and alcohol consumption. It was heavy alcohol consumption, not smoking, that impaired overall outcome after SAH.\textsuperscript{1} Furthermore, our recent prospective follow-up study showed a significant association between the rupture of a previously unruptured aneurysm and cigarette smoking, but smoking did not affect mortality after the aneurysm had ruptured (45\% compared with 43\%).\textsuperscript{5}

On the other hand, in a large metaanalysis, cigarette smoking before SAH was shown to increase somewhat the risk for symptomatic vasospasm.\textsuperscript{12} There was also a trend for smoking (particularly heavy smoking before SAH) to increase the occurrence of delayed ischemia after aneurysmal SAH in our hospital-based study,\textsuperscript{1,4} but in two other studies with smaller patient populations a significant association was demonstrated between current smoking status and symptomatic vasospasm, probably due in part to chance.\textsuperscript{2,7} In addition, smoking a cigarette after SAH during the vasospasm phase can cause extensive, acute brain infarction in patients who previously had good-grade SAH.\textsuperscript{4,7} Although cigarette smoking seems to be associated with delayed symptomatic vasospasm, no clear association could be shown between smoking before SAH and angiographic evidence of vasospasm in large cerebral arteries during the second week after SAH.\textsuperscript{2} Thus, smoking before SAH may depend on mechanisms of action other than large-artery vasospasm to increase risk for infarction and symptomatic vasospasm after SAH.

New studies of the effect of preictal factors on outcome after SAH are needed to improve and understand recovery from this serious disease. Pobereskin publishes a report of
such a study in an exceptionally large patient population (800 patients with SAH, who had 520 verified cases of aneurysm during a 5-year period) in this issue of the Journal of Neurosurgery. In the paper entitled “Influence of premorbid factors on survival following subarachnoid hemorrhage,” he found that patient age older than 60 years, cigarette smoking, and, marginally, female sex were associated with death after SAH. The mean mortality rate among smokers was approximately one half that of nonsmokers, even after adjustment for age and sex. This adjustment was essential because logistic regression tests, which were conducted in a blinded manner, indicated merely an association between variables and not any causal relationship. Without adjustment for confounding factors, one could erroneously conclude that young men recover better after SAH than others because they have smoked. Thus, in the series conducted by Pobereskin, age and sex did not explain this exceptionally strong association between smoking and improved survival after SAH.

In the medical community, there is a general misconception that in collecting data in a large patient population, researchers need not take as much care with their study design. This can cause fundamental systematic errors in the design and performance of a study, which may easily lead to unexpected correlations that are not biologically plausible. Systematic errors that lead to biases cannot be corrected with any kind of statistical method that can be used only for the control of errors caused by chance. Therefore, large studies must be performed as carefully as small ones.

Because the results of Pobereskin’s retrospective study are in obvious conflict with those of previous prospective studies, one must use caution when interpreting the kind of protective effect cigarette smoking has on mortality after SAH. This may nullify the beneficial medical health education advanced in several previous epidemiological studies. After findings of this study are disseminated, cigarette companies will likely insist that cigarette smoking may not exacerbate SAH because, although smokers may have an increased risk for SAH, they have, correspondingly, a lower incidence of mortality. Thus, death due to SAH will not be much changed by smoking habits.

There are some sources of serious systematic bias in Pobereskin’s study. The most serious potential bias involved the coding of smoking. The author did not personally interview patients or their relatives, but instead relied on different nurses’ interviews of patients on admission to various hospitals. As part of their workload, tens or likely hundreds of nurses in various busy emergency rooms, neurosurgical clinics, and so forth, coded patients’ smoking statuses by using standard questionnaires or admission checklists (smoking: yes/no), without additional information about duration, amount, or cessation of smoking, and so forth, making coding unreliable. The patients’ statuses for premorbid smoking and hypertension were extracted from these medical records without validation of the data.

Data obtained in primary care centers or emergency departments in patients who are dying or who have poor clinical grades cannot be very reliable due to the nature of the work performed by personnel while trying to save the patient’s life. At the very least, data obtained in emergency departments of separate hospitals in patients with poor-grade SAH cannot be as reliable as those obtained by nurses in the neurosurgical clinic in patients with good-grade SAH who are being prepared for surgery. It was also surprising that the proportion of missing data on cigarette smoking in this retrospective study was exceptionally low (1%), compared with previous retrospective or prospective studies. Possibly, some busy nurses may have guessed the patient’s smoking status while filling out the checklist.

To avoid this kind of fundamental bias, the researcher or his assistants should have interviewed patients and/or relatives to confirm smoking status by using a structured questionnaire. The reliability of the study would have been significantly increased, with a relatively short increase in time spent on the additional work. In my experience, family members willingly provide this information, even after the death of the patient, if they believe they can help future sufferers of SAH. A comparison of the rate of smoking in this study with those in other studies of SAH is not convincing. In fact, it seems quite probable that the effects of cigarette smoking in patients with a poor initial condition or in those who died was underestimated.

In addition, cerebral aneurysms were found in only two thirds (65%) of all cases of SAH, reflecting a relatively conservative diagnostic and therapeutic policy toward ruptured intracranial aneurysms. This is supported by the fact that only three consultant neurosurgeons were responsible for treating ruptured aneurysm cases in a catchment area of 1.5 million inhabitants. During the same time period, in most Western neurosurgical centers, more than half of all patients with SAH underwent surgery a median of 1 to 2 days after bleeding. In more than 200 patients who died of bleeding, the diagnosis was based only on the computerized tomography (CT) scan; there had been no verification of the aneurysm by autopsy or angiographic studies. It is well known that patients harboring an aneurysmal SAH and an expansive intracerebral hematoma (ICH) have a significantly higher risk of death than other patients with an aneurysmal SAH. Several patients with fatal ICH may, in reality, have experienced spontaneous hemorrhage in the basal ganglia or other sites; a large spontaneous ICH is difficult to distinguish from aneurysmal bleeding with an expansive hematoma without using angiography or autopsy, and spontaneous ICH is much more common than SAH. Avoiding this kind of misdiagnosis is important because patients with spontaneous ICH are significantly older and have a significantly lower incidence of smoking than patients with SAH.3 This kind of error may have led in part to the finding of a protective effect of smoking against death from SAH.

Previously, diagnoses obtained from hospital discharge registers or other official registers have been shown to be unreliable because these are filled out by persons with various levels of expertise. Patients with SAH, spontaneous ICH, or other stroke subtypes have quite often been assigned erroneous codes. The CT scans should have been reexamined by an expert on cerebrovascular diseases to reduce the possibility of a misdiagnosis in cases in which there was no aneurysm verification. This was not done in the present series because the films were destroyed before the study. An analysis of mortality risk factors therefore should also have been performed separately for patients with verified aneurysms.

Pobereskin indicates that increased vasospasm in smokers may reduce the severity of the initial hemorrhage. No
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such data showed that smokers would have had an increased acute or prolonged (symptomatic or angiographically verified) vasospasm in cerebral arteries after SAH. Smoking seems to have mechanisms of action other than chronic vasospasm of large cerebral arteries, which may cause cerebral infarction or symptomatic ischemia after SAH. These mechanisms may also impair cerebral circulation during the initial hemorrhage, favoring impaired—not improved—recovery after the initial attack. It is also well known that patients who suffer rebleeding during vasospasm have a greater risk of death than that associated with the initial hemorrhage, suggesting that vasospasm of arteries does not improve recovery after a bleeding event. So, is it really possible that cigarette smoking can improve survival after SAH? On the basis of results obtained in retrospective studies, I would not recommend that patients start smoking after SAH while awaiting surgery, in an attempt to lessen the severity of their next bleeding episode.

References


RESPONSE: Dr. Juvela’s editorial raises two important issues. First, does what we already know about this subject aid in considering the plausibility of these results? I addressed what is already in the literature with regard to cigarette smoking and mortality in the discussion section of the paper. The only article I did not discuss was the recent study by Juvela, et al. Of that patient cohort, he states that “smoking did not affect outcome after aneurysm rupture.” I have read this paper carefully twice and can find nothing about mortality. In any event, there were only 33 cases of SAH in the cohort, which is hardly enough to make any comment on factors affecting outcome. The only comparable population-based study is the one from King County, Washington, in which outcome in 171 patients is described. The number of pack-years of cigarette smoking was compared in patients with good and poor outcomes; however, differences in mortality rates between smokers and nonsmokers were not described. It appears that Dr. Juvela has received a personal communication from Dr. Longstreth with regard to the 30-day survival rate in the King County population. It would be very interesting to know what the mortality rates actually were.

Juvela states that previous research has failed to demonstrate an association between cigarette smoking and mortality and, as far as it goes, this statement is true. It is misleading, however, and he goes beyond the data to suggest that there is no association. Appropriately, Juvela cautions against uncritical acceptance of findings of large studies, but if one seeks differences in mortality rates, the size of the cohort matters. If the sample size is too small, it is possible to obtain a clinically significant result that is not statistically significant. It must be remembered that to show a difference in mortality rates as great as 30% between two groups in which the anticipated rate is 40%, the patient population must total 480 to provide results with 95% confidence. Quite frankly, there are no other studies in the literature that adequately address the issue of cigarette smoking and death from SAH.

That cigarette smoking increases the risk of SAH and the subsequent risk of vasospasm is well founded but irrelevant. The majority of deaths occur before vasospasm becomes an issue and, if smoking somehow does reduce the severity of the initial hemorrhage, this may outweigh its deleterious effects with regard to vasospasm.

The second important issue raised is that of bias. It is suggested that in some of these patients spontaneous ICH and not SAH occurred. I can only repeat that I reviewed all hospital records, and the majority of CT scans were reviewed and interpreted by experienced neuroradiologists who, I think, would dispute the assertion that it is difficult to distinguish between a clot due to hypertension and one from a middle cerebral or anterior communicating artery aneurysm. Twenty-eight patients with either primary head injury or spontaneous ICH were excluded. I am confident that there were no false-positives in this study.

Finally, there is the issue of bias with regard to patient smoking status. This is a very serious concern. If smokers were misclassified as nonsmokers, it seems logical to assume that this would be most likely to happen in the sickest patients. This is exactly the scenario that would bias the results toward a smoking benefit. Every attempt was made to ensure accurate recording of this factor. Smoking status was documented not only in nursing notes but also in the patient history provided by the admitting physician and in the anesthesiologist’s notes. If nothing was recorded, then the smoking status was assumed to be indeterminate. In all other cases there was a definitive yes or no found in the notes. For patients who died before reach-
ing the hospital, readers should ask themselves whether their own primary care physician has noted in their records whether they smoke.

As discussed in my article, the fact that the smoking rates are reasonably similar to those found in other studies does provide a modicum of reassurance on the issue. In addition, it might be sensible to assume that smoking status would be most accurately recorded in the 65% of the cohort who were admitted to the neurosurgical center and the 44% who underwent surgery. A repeated analysis of the data, controlling for age and sex, demonstrated that smoking was still protective at 1 month post-SAH in both groups and also at 1 week post-SAH in patients admitted to the neurosurgical center.

In conclusion, I agree that this study needs replication or repudiation. I freely admit that the results are counterintuitive and that, clearly, further studies are required. It would be very interesting, for instance, to see a description of patients’ Fisher grades and to contrast those of smokers with those of nonsmokers. It would also be intriguing to learn whether prehemorrhage use of aspirin negates the apparent protection afforded by smoking.

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