

## Short report

# Cigarette smoking and subarachnoid haemorrhage: a population-based case-control study

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**SUMMARY** Smoking habits were analysed in 114 patients with subarachnoid haemorrhage, less than 70 years old, obtained from an epidemiological study. One control, matched for age, sex, and domicile, was selected for each patient. Current cigarette smokers were significantly more prevalent among cases than controls, and the relative risk of subarachnoid haemorrhage compared with non-smokers was 2.7 in men and 3.0 in women. The so called metastatic emphysema theory with increased elastolytic activity in the serum of smokers is proposed as biochemical basis for the increased risk of subarachnoid haemorrhage.

A possible association of cigarette smoking with an increased risk of subarachnoid haemorrhage has been noticed during the last 10 years. The studies published have been based either on stroke patients discharged from hospitals<sup>1,2</sup> or cohorts of women followed-up for adverse effects of oral contraceptives.<sup>3-5</sup> Quite recently, the results of the Framingham Study have been published.<sup>6</sup> In these studies cigarette smoking was considered a risk factor of subarachnoid haemorrhage. The need for population based studies to evaluate the risk factors for subarachnoid haemorrhage has, however, been recently emphasised.<sup>7</sup> In the present study we aim to fulfil this need with respect to cigarette smoking.

### Patients and methods

The patients in the present study are from an epidemiological study performed during 1976-78 in Central-Finland.<sup>8</sup> A follow-up questionnaire including items on smoking habits was sent in 1980 to all 123 patients younger than 70 years, or in case of death, to a near relative. Completed forms were returned by 120 patients. One for age ( $\pm 2$  years), sex, and domicile (Central-Finland) matched control for each patient was in 1984 selected from the "Alphabetical List of the Finnish Population 1979". Starting from the position of the index case the first person in alphabetical order fulfilling the criteria was chosen. Men with the same sur-

Table 1 Age and sex distribution of patients. The number of verified aneurysms is given in brackets

Sex	N	-29	30-49	50-69 years
Males	58 (42)	7 (5)	22 (18)	29 (19)
Females	56 (36)	4 (4)	26 (20)	26 (12)
Total	114 (78)	11 (9)	48 (38)	55 (36)

name as the index case were excluded because of possible consanguinity. Eight of the controls chosen had died between 1979 and 1984, and the next person suitable was taken. The controls were sent an identical questionnaire as the cases, 114 control subjects returned completed forms. The 114 cases control pairs form the basis of the present study. The smoking habits of the controls at the time of subarachnoid haemorrhage of the index case were analysed. Smoking habits were classified as current vs. non-smokers (including ex-smokers). The age and sex distribution, as well as the number of patients with proven arterial aneurysms, are shown in table 1. The diagnosis of subarachnoid haemorrhage was confirmed in 50 (86%) of male and 42 (75%) of female subjects by angiography and/or necropsy; in the others the diagnosis was clinical, including blood stained cerebrospinal fluid.

The relative risks and the 90% confidence intervals were calculated from the number of discordant pairs, and McNemar test was used to calculate the chi-square value.<sup>9</sup>

### Results

Current cigarette smokers were more prevalent among cases than controls, 69% resp. 40% of males ( $\chi^2 = 9.0$   $p < 0.005$ ), and 27% resp. 12% in females ( $\chi^2 = 3.8$   $p = 0.05$ ). Thirty seven out of 58 pairs in

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Received 3 December 1985 and in revised form 11 April 1986.  
Accepted 17 April 1986

Table 2 Number of discordant pairs according to smoking habits by sex

	Case	Control	N		Case	Control	N
Males	+	-	27	Females	+	-	12
	-	+	10		-	+	4
Relative risk 2.7 90% confid. interval 1.3-5.7 $\chi^2 = 6.9$ p < 0.01				Relative risk 3.0 90% confid. interval 0.9-11.5 $\chi^2 = 3.1$ p < 0.1			

+ = current cigarette smoker  
- = ex- and non-smoker

men and 16 out of 56 pairs in women were discordant with respect to smoking habits. The relative risk of subarachnoid haemorrhage of current smokers compared to non-smokers was 2.7 for men and 3.0 for women (table 2). The relative risks for subarachnoid haemorrhage patients with verified aneurysm were of the same magnitude; 3.0 (90% confidence interval 1.3-7.3) for men and 3.3 (0.9-19.0) for women.

## Discussion

Cigarette smoking seems, according to earlier studies, to be associated with increased risk of subarachnoid haemorrhage. In some of the studies the prevalence of current smokers has been higher among cases than controls,<sup>4,6</sup> in one study the incidence of subarachnoid haemorrhage was four times higher in current smokers than non-smokers,<sup>5</sup> while in others the results have been expressed as relative risk varying between 2.0 and 5.7, and with confidence limits higher than unity.<sup>1-3</sup> Our study which includes all patients younger than 70 years from a defined population showed relative risks of 2.7 and 3.0 for males resp. females and is in agreement with earlier data.

These relative risks were calculated using controls alive in 1984. If the eight deceased controls replaced by living ones had been current cigarette smokers the relative risks had decreased to 2.2 for men and to 2.4 for women. This situation seems, according to population figures, to be most improbable because only 38% of men and 7% of women of corresponding age in the 1979 population were current smokers. The figures obtained seem thus not to be overestimates. The question of differing recall of smoking habits in cases and controls remains unanswered but seems to us improbable. According to our experience, people in Finland are well aware of their smoking habits and we do not believe that an illness such as subarachnoid haemorrhage in any way distorts this awareness.

In spite of the accumulating evidence that cigarette smoking is associated with an increased risk of subarachnoid haemorrhage, the basic mechanisms behind this association are obscure. That cigarette smoking is not the sole cause of aneurysm formation

is quite evident because several subarachnoid haemorrhage patients have never smoked, namely 22% of the male and 69% of the female patients in our study. Cigarette smoking must in some way be related to an increased tendency of the aneurysm sac to rupture. Enhanced atherosclerosis with ensuing weakening of the aneurysm wall might be one explanation.<sup>2</sup> High blood pressure has been considered an important risk factor of subarachnoid haemorrhage,<sup>1,5,6</sup> and in a recent review smoking-induced hypertension is mentioned as a possible mechanism by which smoking promotes subarachnoid haemorrhage.<sup>7</sup> Temporary increases in blood pressure after cigarette smoking have been observed both in normo- and hypertensive persons.<sup>10</sup> The temporal association between smoking a cigarette and the occurrence of subarachnoid haemorrhage has neither been analysed earlier nor did we do it now. The so called metastatic emphysema effect<sup>11</sup> as an explanation of the increased risk of subarachnoid haemorrhage of cigarette smokers has, to our knowledge, not been mentioned before as a possible biochemical basis for this association. According to this theory the polymorphonuclear neutrophilic leucocytes and macrophages containing proteolytic enzymes, such as elastase, release their enzymes in the lungs after phagocytosis and exposure to smoke. In addition, cigarette smoke reduces by means of its oxidants, possibly also non-oxidatively, the protease inhibitory efficacy of alpha-1-antitrypsin.<sup>12</sup> As a result, increased amounts of active proteolytic enzymes are released into the systemic circulation. These enzymes may cleave elastin and collagen in different parts of the body, and may play a role, for example in the evolution of inguinal hernias<sup>11</sup> and aortic aneurysms.<sup>13</sup> The wall of an intracranial aneurysm sac is composed principally of collagenous connective tissue, with a few islands of elastic tissue, and it is very tempting to incriminate the increased serum proteolytic activity in the sera of smokers as a cause for the increased risk of subarachnoid haemorrhage.

This study was supported by grants from the Yrjö Jahnsson Foundation and the Paulo Foundation.

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