

SHORT REPORT

Risk factors for aneurysmal subarachnoid haemorrhage: the Tromsø study

J Isaksen, A Egge, K Waterloo, B Romner, T Ingebrigtsen

J Neurol Neurosurg Psychiatry 2002;**73**:185–187

Objectives: To conduct a population based case-control study with premorbid registration of potential risk factors to address the difficulty in identifying risk factors for aneurysmal subarachnoid haemorrhage (SAH). SAH is rare in prospective studies, and retrospective studies may have a selection bias.

Methods: The Tromsø health study is a population based survey of risk factors for cardiovascular disease in 27 161 subjects. 26 cases of aneurysmal SAH were identified in which risk factors were registered before the bleeding. Four age and sex matched controls were selected for each case. A backward logistic regression analysis was conducted and odds ratios (ORs) for significant risk factors were calculated. Systolic and diastolic blood pressure, cigarette smoking habits, serum concentrations of lipoproteins, body mass index, and coffee consumption were analysed.

Results: The crude annual incidence rate of aneurysmal SAH was 8.84/100 000 population. The proportion of current smokers was significantly ($p = 0.003$) higher in patients with SAH (73.1%) than in controls (41.3%). Drinking more than five cups of coffee per day was more common among patients (85%) than controls (59%) ($p = 0.004$). Mean (SD) systolic blood pressure was higher ($p = 0.017$) in patients (154.0 (32.5)) than in controls (136.3 (23.3)). Regression analysis showed that cigarette smoking ($p = 0.04$), systolic blood pressure ($p < 0.0001$), and coffee consumption ($p = 0.004$) were independent risk factors for SAH. The OR of current smokers versus never smokers was 4.55 (95% confidence interval (CI) 1.08 to 19.30) and the OR of drinking more than five cups of coffee a day was 3.86 (95% CI 1.01 to 14.73). The OR of an increase in systolic blood pressure of 20 mm Hg was 2.46 (95% CI 1.52 to 3.97).

Conclusions: Cigarette smoking and hypertension are significant independent risk factors for aneurysmal SAH. A high coffee consumption may also predispose patients to aneurysmal SAH.

The incidence of subarachnoid haemorrhage (SAH) is about 10/100 000 population yearly. SAH still has a high morbidity and lethality.^{1,2} Reliable prediction of risk factors for aneurysm formation has been difficult because of the rarity of SAH in prospective studies and a possible selection bias in retrospective studies.

The Tromsø health study is a large population based survey that gives an opportunity to study SAH in relation to premorbid recordings of the most common risk factors for cardiovascular disease.³ The aim of this study was to assess the association between SAH and cigarette smoking, hypertension, serum cholesterol concentration, and other possible risk factors.

MATERIALS AND METHODS

Study population and the Tromsø health study

We identified cases of SAH in the population of the municipality of Tromsø in northern Norway during the 12 year period 1986–97. Crude incidence rates were calculated on the basis of demographic data from the Norwegian Social Science Data Services. The mean size of the population during the study period was 52 792, range 48 091–57 485. A steadily growing population caused the wide range. The University Hospital of Tromsø is the only hospital in the municipality, and over 90% of patients with diagnosed SAH in our region are admitted to our department during the first day after bleeding.⁴

The Tromsø Study is a single centre, prospective, cross sectional, population based health survey of inhabitants in the municipality of Tromsø, Norway. The study's objective is to investigate determinants and risk factors for disease, with the main focus on cardiovascular disease. The study design includes repeated population health surveys to which total birth cohorts and randomly chosen sample populations are invited to answer a questionnaire, undergo physical examination, and give blood samples. The examination included standardised measurements of height, weight, blood pressure, and biochemical analyses. Systolic and diastolic blood pressure, serum concentrations of total cholesterol and high density lipoproteins (HDL), and body mass index (BMI) were recorded as continuous variables. Coffee consumption and cigarette smoking habits were recorded as category data. Coffee consumption was classified as ≤ 5 or > 5 cups a day. Smokers were classified as never smokers, previous smokers, or current smokers. The survey was initiated in 1979 and has been repeated three times, most recently in 1994–5. At present, 27 161 inhabitants have been examined at least once.⁵ Seventy eight per cent of the eligible population has participated in the study.

Identification of cases and controls

We used three search strategies to identify all cases of aneurysmal SAH in our study population: firstly, a computerised search of the university hospital's patient administrative database identifying all patients discharged with the disease specific *International classification of diseases*, ninth revision code 430; secondly, a computerised search of the Sympathy Database at the Department of Pathology identifying all cases of SAH diagnosed by necropsy among both hospitalised and non-hospitalised patients; and thirdly, a manual search of the files at the Department of Neurosurgery, identifying all patients treated for ruptured intracranial aneurysms. A total

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high density lipoprotein; OR, odds ratio; SAH, subarachnoid haemorrhage

Table 1 Cardiovascular risk factors in 26 patients with subarachnoid haemorrhage and 104 matched controls

	Cases (n=26)	Controls (n=104)	p Value
Mean (SD) age (years)	53.1 (13.7)	53.2 (13.9)	Matching factor
Male sex (%)	52.4	52.4	Matching factor
Proportion of smokers			0.003*
Current smokers (%)	73.1	41.3	
Previous smokers (%)	15.4	23.1	
Never smokers (%)	11.5	35.6	
Coffee consumption (cups/day)			0.004
≤5 (%)	15.4	40.4	
>5 (%)	84.6	59.7	
Mean (SD) blood pressure (mm Hg)			
Systolic	154.0 (32.5)	136.3 (23.3)	0.017
Diastolic	86.6 (16.1)	78.8 (12.4)	0.03
Mean (SD) serum lipids (mmol/l)			
Total cholesterol	6.4 (1.2)	6.6 (1.2)	NS
HDL cholesterol	1.5 (0.5)	1.6 (0.4)	NS
Mean (SD) body mass index (kg/m ²)	25.1 (3.6)	25.1 (3.9)	NS

*Overall p values. HDL, high density lipoprotein.

of 233 cases were identified (patient administrative database search n = 62, Sympathy search n = 121, and manual search n = 50).

We reviewed the hospital charts of the 233 patients for verification of the diagnosis. Only patients with aneurysmal SAH confirmed by digital subtraction angiography or necropsy were included and were entered into a clinical database (n = 56). These 56 patients constituted the basis for calculation of incidence rates.

The clinical database was then cross linked with the database of the Tromsø health survey. Thirty eight (68%) patients had participated in the survey, but only 26 had done so before the bleeding. These 26 patients were included in our case-control study of risk factors for SAH. The median interval between participating in the survey and time of bleeding was 24 (0–186) months.

We selected four age and sex matched controls from the Tromsø health survey for each of the 26 patients.

Statistical analyses

Results are presented as mean (SD) or as proportions. Data analysis included independent *t* test to test differences between group means. We used χ^2 test for trends to compare differences between two or more groups of category data. Data analysis also included conditional backward logistic regression to analyse quantitative factors associated with SAH. Odds ratios (ORs) were calculated for significant risk factors. Non-parametric and non-dichotomic data were centralised before testing for interactions. All p values are two tailed and $p < 0.05$ was considered significant. SPSS (release 10.0; SPSS, Chicago, Illinois, USA) software was used.

RESULTS

The crude annual incidence rate of aneurysmal SAH was 8.84/100 000 population. Sex specific annual incidence rates were 9.77 for women and 7.88 for men. Mean (SD) age at ictus was 54.5 (14.1), range 41–86 for women and 55.3 (15.8), range 34–87 for men.

Table 1 shows the characteristics of the 26 patients and their matched controls. The proportion of current smokers was significantly ($p = 0.003$) higher in patients (73.1%) than in controls (41.3%). Drinking more than five cups of coffee a day was more common among patients (85%) than among controls (59%) ($p = 0.004$). Mean (SD) systolic blood pressure was higher ($p = 0.017$) in patients (154.0 (32.5)) than in controls (136.3 (23.3)). Serum cholesterol concentration, serum HDL concentration, and BMI had no significant impact.

Table 2 presents the effects of the various risk factors. We analysed systolic and diastolic blood pressure, serum cholesterol concentration, serum HDL concentration, BMI, coffee consumption, and smoking habits simultaneously in the logistic regression model. Only cigarette smoking, coffee consumption, and increased systolic blood pressure were significant independent risk factors for SAH. Cigarette smoking was identified as the most important risk factor, with an OR of 4.55 (95% confidence interval (CI) 1.08 to 19.30) for current smokers and 2.13 (95% CI 1.08 to 19.30) for previous smokers compared with never smokers. The OR for drinking more than five cups of coffee a day was 3.86 (95% CI 1.01 to 14.73) compared with drinking fewer than five cups a day. Hypertension also increased the risk of SAH. The OR for an increase of 20 mm Hg was 2.46 (95% CI 1.52 to 3.97). Analyses of interactions between hypertension and smoking, and hypertension and BMI showed no significant effect.

DISCUSSION

The main findings of this population based case-control study are that cigarette smoking, coffee consumption, and hypertension are significant independent risk factors for aneurysmal SAH. We observed no association between SAH and other potential risk factors, such as serum lipid concentrations or overweight.

Previous studies have shown that the annual incidence rates of SAH remain remarkably constant over decades.^{5,6} The observed annual incidence rate of 8.84 in our study is in the lower range of those observed in other Scandinavian studies.¹ Epidemiological studies from Finland and northern Norway found higher incidence rates.^{7–9} Comparison of these incidence rates is, however, difficult since adjustments were not made for different age distributions in the populations. The reason for the low mean age is probably the young constituent of the study population, which is a result of heavy immigration of young people, mostly students.

Retrospective clinical studies of potential risk factors for SAH have conflicting results concerning hypertension, smoking, and other risk factors.^{10,11} Selection bias is probably causing distorted results in such studies. Therefore, premorbid data from prospective population based surveys are desirable. Furthermore, a case ascertainment procedure including computed tomography and digital subtraction angiography is necessary to distinguish aneurysmal SAH from other types of stroke. Studies meeting both these criteria have not been performed, although some, including the Framingham study, reported premorbid registration of risk factors.^{8,11,12} In

Table 2 Risk factors in 26 patients compared with 104 matched controls using multivariate logistic regression analysis

	B (SE)	Multivariate OR (95% CI)	p Value	Univariate OR (95% CI)
Cigarette smoking	0.76 (0.36)	2.13 (1.04 to 4.39)	0.037*	2.39 (1.27 to 4.49)
Never	0.0	1.00 (reference)		1.00 (reference)
Previous	0.76 (0.36)	2.13 (1.04 to 4.39)		2.39 (1.27 to 4.49)
Current	1.52 (0.72)	4.55 (1.08 to 19.30)		5.71 (1.62 to 20.13)
Coffee consumption (cups/day)	1.35 (0.67)	3.86 (1.01 to 14.73)	0.042	4.72 (1.48 to 14.98)
≤5	0.0	1.00 (reference)		1.00 (reference)
>5	1.35 (0.67)	3.86 (1.01 to 14.73)		4.72 (1.48 to 14.98)
Systolic blood pressure	0.05 (0.01)	1.04 (1.03 to 1.06)	<0.0001	1.02 (1.00 to 1.04)
20 mm Hg increase	0.90 (0.24)	2.46 (1.52 to 3.97)		1.62 (1.17 to 2.22)
Total serum cholesterol (mmol/l)	-0.24 (0.25)	0.79 (0.48 to 1.29)	NS	0.89 (0.62 to 1.29)
Body mass index (kg/m ²)	0.02 (0.07)	1.02 (0.89 to 1.18)	NS	1.00 (0.89 to 1.12)

*Overall p value for the effect of smoking based on the dosage dependent categories current smokers, previous smokers, and never smokers.

addition, population based case-control studies contribute useful information despite the lack of premorbid data.¹⁰⁻¹³

The major strength of the present study is that both patients and controls were identified from the same strictly defined cohort of subjects enrolled in a population based health survey. The premorbid registration of risk factors was highly reliable.³ The case ascertainment procedures consisted of reliable neuroradiological methods to avoid inclusion of patients with other types of stroke. Probably the only aneurysmal SAH cases missed were in patients who bled outside the hospital and were not referred or necropsied. The relatively small sample size is a weakness of this study.

We identified current cigarette smoking as the most important independent risk factor for SAH. This is in agreement with previous studies.⁸⁻¹⁰⁻¹⁴ Previous smokers were also found to be at greater risk than never smokers. Their risk was, however, substantially lower than that of current smokers, emphasising the importance of early abstinence from smoking.¹⁵ Hence, there is a dose-response relation between cigarette smoking and the risk of aneurysmal SAH, indicating a causal relation.

The effect of coffee consumption has rarely been examined before. We found that drinking more than five cups of coffee a day was significantly more common among patients than among controls. This is a new and interesting observation, which needs further investigation.

We observed that premorbid mean systolic blood pressure was significantly higher in patients with SAH than in controls. This observation confirms the findings of previous studies.⁸⁻¹² Bonita¹³ observed an interaction between the combined effect of smoking and hypertension and the risk of SAH, while Longstreth *et al*¹⁰ found no such interaction in their study with an almost identical population based case-control study design. We observed no interaction between smoking and other risk factors in our study.

Hypercholesterolaemia is associated with cardiovascular disease, but the influence of serum cholesterol concentrations on the occurrence of SAH has been little studied. In accordance with the study by Knekt *et al*,⁵ there was no association between risk and serum cholesterol concentration in our study.

In summary, current or previous cigarette smoking, coffee drinking, and hypertension are the strongest risk factors for aneurysmal SAH.

ACKNOWLEDGEMENTS

We are indebted to Professor Egil Arnesen at the Institute of Community Medicine, University of Tromsø, for access to the database of the Tromsø Health Study and for useful help with designing the study and analysing the data.

Authors' affiliations

J Isaksen, A Egge, K Waterloo, B Romner, T Ingebrigtsen, Department of Neurosurgery, Tromsø University Hospital, Tromsø, Norway

Competing interests: none declared

Correspondence to: Dr T Ingebrigtsen, Department of Neurosurgery, Tromsø University Hospital, N-9038 Tromsø, Norway; tor.ingebrigtsen@rito.no

Received 17 October 2001

In revised form 4 April 2002

Accepted 22 April 2002

REFERENCES

- 1 Nilsson OG, Lindgren A, Stahl N, *et al*. Incidence of intracerebral and subarachnoid haemorrhage in southern Sweden. *J Neural Neurosurg Psychiatry* 2000;**69**:601-7.
- 2 Egge A, Waterloo K, Sjøholm H, *et al*. Prophylactic triple-H therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study. *Neurosurgery* 2001;**49**:593-606.
- 3 Thelle DS, Førde OH, Try K, *et al*. The Tromsø heart study: methods and main results of the cross-sectional study. *Acta Med Scand* 1976;**200**:7-18.
- 4 Egge A, Romner B, Waterloo K, *et al*. Results of surgery for aneurysmal subarachnoid haemorrhage in northern Norway. A retrospective study with special focus on timing of surgery in a rural area. *Acta Neurol Scand*. [in press]
- 5 Joakimsen O, Bønnaa KH, Stensland-Bugge E. Reproducibility of ultrasound assessment of carotid plaque occurrence, thickness, and morphology: the Tromsø study. *Stroke* 1997;**28**:2201-7.
- 6 Phillips LH, Whisnant JP, O'Fallon M, *et al*. The unchanging pattern of subarachnoid hemorrhage in a community. *Neurology* 1980;**30**:1034-40.
- 7 Linn FHH, Rinkel GJE, Algra A, *et al*. Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis. *Stroke* 1996;**27**:625-9.
- 8 Knekt P, Reunanen A, Aho K, *et al*. Risk factors for subarachnoid hemorrhage in a longitudinal population study. *J Clin Epidemiol* 1991;**9**:933-9.
- 9 Njølstad I, Arnesen E, Lund-Larsen PG. Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women. *Circulation* 1996;**94**:2877-82.
- 10 Longstreth WT, Nelson LM, Koepsell TD, *et al*. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. *Stroke* 1992;**23**:1242-9.
- 11 Teunissen LL, Rinkel GJE, Algra A, *et al*. Risk factors for subarachnoid hemorrhage. *Stroke* 1996;**27**:544-9.
- 12 Sacco RL, Wolf PA, Bharucha NE, *et al*. Subarachnoid and intracerebral hemorrhage: natural history, prognosis, and precursive factors in the Framingham Study. *Neurology* 1984;**34**:847-54.
- 13 Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. *Stroke* 1986;**17**:831-5.
- 14 Juvela S, Hillbom M, Numminen H, *et al*. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. *Stroke* 1993;**24**:639-46.
- 15 Qureshi AI, Suri MFK, Yahia AM, *et al*. Risk factors for subarachnoid hemorrhage. *Neurosurgery* 2001;**49**:607-13.