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Smoking and non-smoking tobacco as risk factors in subarachnoid haemorrhage

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Objective – Swedish snuff is a particular form of non-smoking tobacco with high nicotine content. It is unknown whether this form of tobacco is a risk factor similar to smoking for suffering subarachnoid haemorrhage (SAH). In the present study we report our finding concerning smoking and snuff as risk factors for the disease. *Method* – We analysed 120 consecutive patients with SAH regarding consumption of tobacco, in order to evaluate if snuff also is associated with an increased risk of SAH. *Results* – The relative risk of SAH was about 2.5 times higher for smokers compared with the background population. Consumption of snuff was not associated with an increased risk. *Conclusions* – It seems unlikely that nicotine is solely responsible for the rupture of cerebral aneurysms. The final cause of the increased risk for suffering SAH has to be sought in other factors associated with tobacco smoking.

L.-O. D. Koskinen, P. C. Blomstedt

Division of Neurosurgery, Department of Pharmacology and Clinical Neuroscience, Umeå University Hospital, Umeå, Sweden

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Lars-Owe D. Koskinen, Department of Neurosurgery, University Hospital, S-901 85 Umeå, Sweden
Tel.: +46 90 7852826
Fax: +46 90 122448
e-mail: lars-owe.koskinen@neuro.umu.se

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Subarachnoid haemorrhage (SAH) is one of the most severe diseases affecting adults and senils. With an incidence of about 10/100,000/year and severe consequences concerning morbidity and mortality, SAH constitute a great challenge to modern health care. Even though some improvements have been made in the care of these patients, the mortality rate is still about 40–50% (1–3), and the major cause of death and disability is the initial bleeding itself. A way to decrease the morbidity and mortality following the initial bleeding is to prevent the patient from re-bleeding. Successful management with tranexamic acid has been shown to prevent the patient from ultra-early and early re-bleedings (4). The necessity to identify risk factors for SAH in order to prevent the disease before it evolves is obvious.

Several risk factors have been identified as playing a role in the rupture of cerebral aneurysm; e.g. hypertension, alcohol abuse, anticonceptives and above all cigarette smoking (5–13). In these studies a clear correlation has been shown between smoking and the risk of developing SAH, with relative risk ranging from 1.9 to 5.2. Several studies have also shown the risk to be dose dependent (5, 7–11). Interestingly, smoking has also been shown to affect cerebral blood flow (14). However, factors that are responsible for the increased risk of suffering an SAH in smoker are unknown. If nicotine itself is a risk factor, then one could assume that consumption of non-smoking tobacco would also lead to an increased risk. This is a question that has, to our knowledge, not been studied earlier. Swedish snuff is a particular form of non-smoking tobacco, used almost exclusively in Sweden and to a minor extent in Finland. It is made by unfermented tobacco and has a water content of about 50%, in contrast to the dry snuff used in other countries. The snuff is placed under the upper lip in order to let nicotine diffuse through the mucosa. Snuff has a higher content of nicotine compared with cigarettes. It is estimated that an average consumer of snuff gets a daily dose of about 120–150 mg nicotine/day, which equals a consumption of about 20–30 strong cigarettes (15).

Nineteen percent of Swedish males and females between the age of 16 and 84 use cigarettes on a daily basis (16). Twenty percent of the male population in the same age uses snuff, while the

number of female consumers is negligible (16). However, there are great differences in cigarette smoking and the use of snuff in relation to age (16).

The main objective of this investigation was to study whether non-smoking tobacco was also a high risk factor, similar to cigarette smoking, in relation to SAH. We also describe the patient cohort in terms of disease severity, age distribution and anatomical localization of aneurysms.

Preliminary results were presented at the annual meeting of the Swedish Society of Medicine (17).

Materials and methods

This study comprises 131 consecutive patients with spontaneous SAH admitted to the Department of Neurosurgery at the Umeå University Hospital during the period 970101–981231. Our neurosurgical department serves the northern part of the country corresponding almost to half the area of Sweden. However, the area holds only about 0.9 million inhabitants.

Information concerning use of tobacco and other factors that might be associated with SAH was obtained by auto-anamnesis, using a standard questionnaire. When auto-anamnesis was not possible, the relatives were interviewed. The interviews were performed by predetermined selected neurosurgeons and a research nurse. Out of 131 patients complete data for 120 were adequately collected. These 120 patients were further evaluated in this study. The patients were classified as tobacco consumers, previous smokers (ex-consumers and non-consumers. Previous and current use of tobacco was documented concerning type of tobacco, amount of tobacco consumption for the different types of tobacco and years of use. Smoking load was calculated by the formula 1 pack-year = 20 cigarettes × 360 days. The patients were also interviewed concerning their state of general health, hypertension, diabetes, medication, anticonceptives and alcohol consumption.

The diagnosis of SAH was based on typical symptoms with positive findings on CT or lumbar tap. All patients underwent a cerebral angiography except seven moribund patients.

The majority of patients with cerebral aneurysms were treated by early surgery with clip ligature of the aneurysm and pre- and post-operatively treated at the neuro-intensive care unit.

The SAH cohort is considered as the standard population and the background population is the cohort as defined in the official Swedish statistics of 2001 for smokers and 1996–1997 for snuffers (16). This background population is described in detail elsewhere (16). In short, the background population was randomly chosen from all areas of the country in proportion to the inhabitants. A structured interview concerning the use of tobacco smoking (5632 men, 5981 women) and snuffing (5621 men, 5940 women) was performed. The relative risk and the 95% confidence interval in age-stratified groups (direct standardization) were calculated using the present patient cohort. Values are reported as means ± SEM or median and range (discrete variables). Informed consent was obtained from the patient or from relatives in all cases.

Results

Exactly 65.8% of the patients were women (mean age 55.1 years, range 18.7–79.8). The median Hunt & Hess-level was 2 (range 4) and RLS 85 (Reaction Level Scale) (18) was 2 (range 7). Alcohol abuse was reported in 4.2 % and hypertension in 28.8 % of the patients.

Angiography revealed 140 aneurysms in 99 patients (1–4 aneurysms/person). Seven moribund patients were not examined by angiography. In 14 cases no aneurysms were found. This corresponds to a negative angiographic finding of 12.4 %. Of these 99 patients, 94 underwent surgical treatment. Distribution of the aneurysms is shown in Fig. 1.

In this study 55.1% were smokers and 22.0% previous smokers. Taken together, the number of present and previous smokers was 77.1%. Further, 10.8% were consumers of non-smoking tobacco and 1 previous consumer; 4.2% used both smoking and non-smoking tobacco. In 14 cases no aneurysms were found; 50.0% were smokers, 21.4% previous smokers, 7.1% consumers of non-smoking tobacco and 21.4% had never used tobacco. The percentage of smokers, previous smokers and users of non-smoking tobacco were approximately similar in the group with aneurysms and in the group where no aneurysms could be identified. Table 1 presents the age-stratified proportions of smokers and snuffers suffering SAH and the proportion in the control cohort. It is obvious that there is an over-representation of smokers in the SAH group. The relative risk (and confidence interval) of suffering SAH in our patient cohort was 2.63 (1.20–5.72) in men and 2.26 (1.69–3.01) in women in smokers. The 95% confidence limit indicates a statistically significantly increased risk of suffering SAH in smokers. When previous smokers were included in the calculation the risk increased to 4.0. A corresponding increase in relative risk for the snuffers was not detected (Table 1), the relative risk in men was 0.48 (0.17–1.30) and in women 1.30 (0.33–5.18).

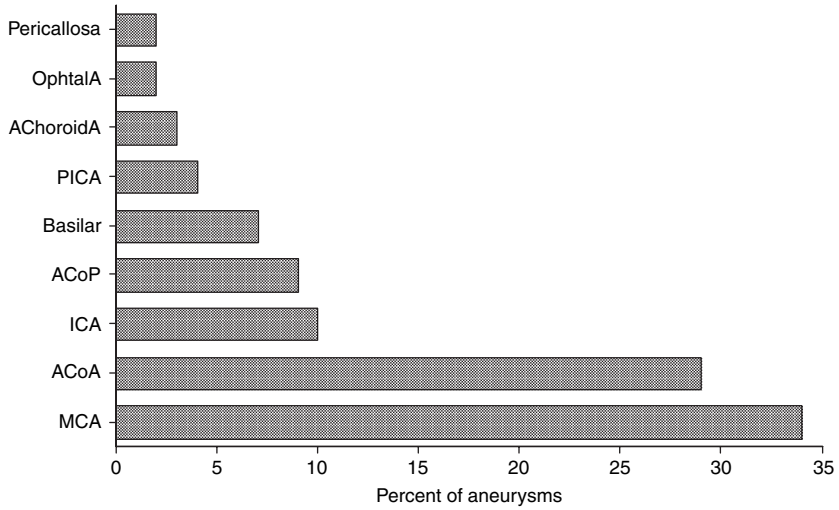

Figure 1. Distribution of the aneurysms found at angiography expressed as percentage of total amount of the aneurysms.

Table 1 Prevalence and standardized proportions of smokers and snuff users in subarachnoid haemorrhage (SAH) cases and controls

		Prevalence of smoking				Prevalence of snuff			
		Men		Women		Men		Women	
Age (years)	SAH cases (men/women)	Control	SAH	Control	SAH	Control	SAH	Control	SAH
16–24	2/0	12.0	50.0	18.6	–	22.3	0.0	0.6	–
25–34	1/4	14.0	100.0	16.6	50.0	30.6	0.0	2.1	0.0
35–44	3/10	17.6	0.0	23.7	54.5	25.8	20.0	1.9	0.0
45–54	20/26	22.4	63.2	24.2	70.4	19.0	15.8	0.8	7.4
55–64	10/17	23.6	63.6	24.5	66.7	10.0	9.1	0.3	0.0
65–74	4/17	16.2	20.0	14.4	31.6	8.7	20.0	0.0	0.0
75–84	1/5	7.2	0.0	7.9	20.0	9.0	0.0	0.0	0.0
Standard estimate		16	42	19	42	18	9	1	1
Relative risk		1.0	2.63 (1.20–5.72)	1.0	2.26 (1.69–3.01)	1.0	0.48 (0.17–1.30)	1.0	1.30 (0.33–5.18)

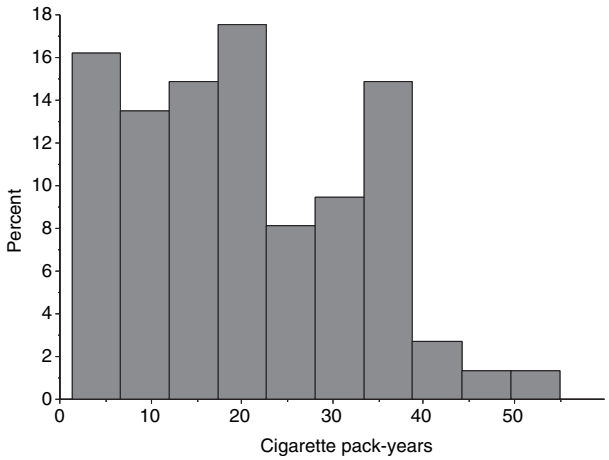

Figure 2. Smoking load expressed as cigarette pack-year (1 pack-year = 20 cigarettes × years of smoking).

The patients' smoking load was 20.4 pack-years (range 1.25–55) with a mean consumption of 14.6 cigarettes a day (range 1–40). The mean duration of smoking was 27.6 years (range 2–55). As depicted in Fig. 2 the distribution of smoking load reveals no cluster pointing to a dose-dependent relationship for suffering SAH. The mean duration of consumption of non-smoking tobacco was 20.4 years (range 4–55) with a mean consumption of 3 days/packet (range 1–14). Consumption of non-smoking tobacco was not correlated with age at onset of SAH.

Discussion

As shown in previous studies (5–13) the risk of SAH is significantly increased in cigarette smokers. This increase is visible even in previous smokers, although diminished. In our study the relative risk of suffering an SAH is about 2.5 times higher in smokers than in non-smokers, with an increasing prevalence in youngsters and middle-aged. When including the previous smokers this risk is increased to 4 times. This is

in good accordance with other studies (5–13). The cause of this increased risk is unknown. If one judges from this study the increased risk seems unlikely to be caused by nicotine alone. Had this been the case, then one would also expect to find an increased risk for SAH in the consumers of non-smoking tobacco. This was not the case. It thus seems evident that other mechanisms are responsible for the increased risk of suffering an SAH in smokers. It has been suggested that the basic mechanism behind rupture of saccular aneurysms in smokers is a qualitative deficiency of α_1-antitrypsin (19–21). This view has however been challenged recently (22). We found no clear evidence of a relationship between the tobacco consuming duration and the onset of SAH.

Considering the background population it is known that the smoking rate is slightly lower in our region compared with the whole country (16). Thus, our results might underestimate the relative risk of suffering an SAH in the smoking group. It is also known that snuffing is slightly more common in the northern part of Sweden (16). If snuffing would be a risk factor for SAH one would expect a higher incidence in our patients and thus an overestimation of the relative risk. However, we found no evidence of an increased relative risk of suffering SAH in snuffers.

Localization of aneurysm, negative findings on angiography, age and sex distribution were all in accordance with previous studies (1–3, 11, 13). We confirm that there is an increased risk for women to suffer from SAH than men.

In conclusion, the use of non-smoking tobacco is not correlated with an increased risk for rupture of cerebral aneurysms. Cigarette smoking, on the other hand, is clearly correlated with the development of SAH. As the amount of available nicotine is higher in snuff than in tobacco, it is unlikely that nicotine itself is responsible for the increased risk of suffering SAH. Another cause to the development of SAH must be sought in tobacco smoke. It is more likely that a combination of several harmful chemicals existing in tobacco smoke is the cause of the increased risk for SAH.

The only rational way of reducing the risk of suffering an SAH is to inform the population about the harmful effects of cigarette smoking. We advice all our patients stop smoking.

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