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# Risk Factors for Aneurysmal Subarachnoid Hemorrhage in Aomori, Japan

Hiroki Ohkuma, MD; Hidefumi Tabata, MD; Shigeharu Suzuki, MD; Md Shafiqul Islam, MD

**Background and Purpose**—Japan is known to have an incidence of aneurysmal subarachnoid hemorrhage (SAH) as high as that in Finland, where SAH is especially common. However, the risk factors for SAH in Japan are unknown. The purpose of this study was to identify the risk factors and then examine their possible roles in cases of SAH in Japan.

**Methods**—Case-control data were collected in the Aomori prefecture between June 2000 and May 2001 and in the Shimokita area between 1989 and 1998. A history of hypertension, cigarette smoking, alcohol consumption, hypercholesterolemia, and diabetes mellitus were examined as possible risk factors for SAH by using stepwise logistic regression analysis.

**Results**—Stepwise logistic regression analysis showed that a history of hypertension and current smoking increased the risk of SAH and that a history of hypercholesterolemia decreased the risk of SAH. Alcohol consumption and a history of diabetes mellitus were excluded from the model, because their log-likelihood ratios were not significant. The adjusted odds ratios, obtained by forcing matching factors, were 2.29 for a history of hypertension (95% CI, 1.66 to 3.16), 3.12 for current smoking (95% CI, 2.05 to 4.77), and 0.41 for a history of hypercholesterolemia (95% CI, 0.24 to 0.71). The prevalence of hypertension in control subjects was 27% in men and 31% in women, whereas the prevalence of cigarette smoking in control subjects was 46% in men and 9% in women.

**Conclusions**—Hypertension and cigarette smoking seem to be independent risk factors for SAH in Japan. The high prevalence of hypertension in both sexes and the high prevalence of cigarette smoking in men in the general population might contribute to the high incidence of SAH in Japan. (*Stroke*. 2003;34:96-100.)

**Key Words:** aneurysm ■ cigarette smoking ■ hemorrhage ■ hypertension ■ risk factors

The incidence of aneurysmal subarachnoid hemorrhage (SAH) ranges widely among reports from different regions of the world and at different points in time.<sup>1-3</sup> The incidence appears to be especially high in Finland.<sup>1,2,4-8</sup> Recent studies,<sup>9-14</sup> including our previous report,<sup>10</sup> suggest that Japan has as high an incidence of SAH as Finland. The reasons for the higher incidence of aneurysmal SAH in Japan and Finland have yet to be determined. One possibility is that a high prevalence of genes linked to aneurysm formation plays a role in the high incidence of SAH in these areas.<sup>15</sup> Other possibilities could include the high prevalence of the risk factors for SAH in the community or a high vulnerability to these risk factors in these countries.<sup>16</sup>

Risk factor identification for aneurysmal SAH has been conducted in many countries,<sup>16-38</sup> including Finland,<sup>18-20</sup> and several factors have been associated with an increased risk for SAH. However, a study of risk factors for aneurysmal SAH has not yet been performed in Japan. The aim of this study was to investigate the risk factors for aneurysmal SAH in Japan and to examine their possible role in the high incidence of aneurysmal SAH in Japan.

## Subjects and Methods

This study was conducted in the Aomori prefecture and a region within this prefecture over different periods of time. The Aomori prefecture is situated in the northernmost part of the main island of Japan, and the region of Shimokita is situated in the northernmost part of the Aomori prefecture (the Figure). According to the census population data of Japan, the Aomori prefecture has a population of 1 475 000, with 88 900 people living in Shimokita.

One part of this study was performed in Shimokita as part of an epidemiological study in this area begun in 1989.<sup>10</sup> The incidence of aneurysmal SAH was investigated between 1989 and 1998 inclusively, and 198 cases of aneurysmal SAH were seen at the Department of Neurosurgery at Mutsu General Hospital, which is the sole institute treating aneurysmal SAH in Shimokita.<sup>10</sup> Another part of this study was performed by 7 neurosurgical institutes located throughout the whole of the Aomori prefecture (the Figure) in the 1 year between June 2000 and May 2001 as part of an epidemiological study of cerebrovascular disease in this prefecture. Institutional ethics committees in each institute approved the protocol.

All of the cases of suspected aneurysmal SAH underwent CT scans. The diagnoses of aneurysmal SAH were divided into 3 groups based on these CT findings: (1) patients with SAH on CT scan determined to be due to a ruptured cerebral aneurysm, diagnosed by cerebral angiography and/or aneurysm surgery; (2) patients with CT findings identical to SAH due to ruptured cerebral aneurysms but without either cerebral angiography or aneurysm surgery because of

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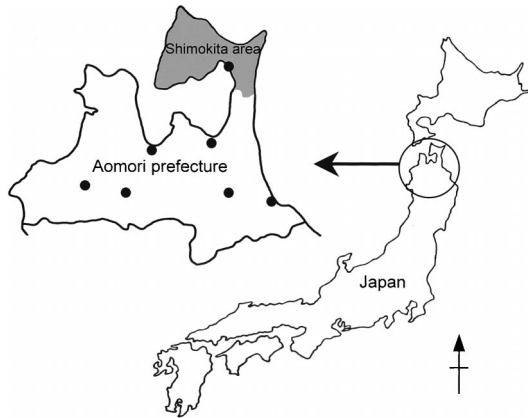
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The geographical location of the Aomori prefecture and the region of Shimokita. Closed circles indicate the location of the institutes participating in the study throughout the whole of the Aomori prefecture. Shimokita (shaded area) is located in the northernmost part of Aomori prefecture.

the patient's poor clinical condition; and (3) patients with SAH determined by lumbar puncture because of ambiguous findings for SAH on the CT scan, followed by diagnosis of a ruptured aneurysm by cerebral angiography and aneurysm surgery. In all cases, the diagnosis of aneurysmal SAH was made by board-certified neurosurgeons.

The control subjects consisted of cases of head trauma seen at the same institute over the same period of time. Control subjects who suffered head trauma due to inebriation were excluded to avoid the potential bias of alcohol abuse. Of the registered control subjects, they were randomly selected to be frequency matched to cases for age (10-year strata) by sex.

Board-certified neurosurgeons at each institute initiated face-to-face interviews with case subjects or control subjects within 24 hours after hospitalization. For patients who were confused, unconscious, dysphasic, or deceased soon after admission, family members with full knowledge of the medical and general history of the patient were interviewed. A structured questionnaire was used to obtain information regarding age, ethnicity (Asian or other), highest level of education, and socioeconomic status. Socioeconomic class was coded according to the Registrar General's Classification<sup>39</sup> and was defined as either nonmanual (class I, II, III nonmanual) or manual (class III manual, IV, and V). The possible aneurysmal SAH risk factors evaluated were a history of hypertension, cigarette smoking, and alcohol consumption; a history of hypercholesterolemia; and a history of diabetes mellitus. The histories of hypertension, hypercholesterolemia, and diabetes mellitus were considered positive if a physician had ever told the patient that they had hypertension, hypercholesterolemia, or diabetes mellitus. To clarify cigarette smoking status, the patients were classified as either nonsmokers, including former smokers who had not smoked for at least 1 year, or current smokers. Alcohol consumption was evaluated on the basis of the usual weekly intake of alcoholic beverages over the previous year. Each alcoholic beverage was calculated as grams of absolute ethanol, and alcohol consumption was divided into nondrinkers, light drinkers consuming <250 g per week, and heavy drinkers consuming 250 g or more per week. The subjects with missing data for any of the variables were excluded from the evaluation.

We tested for differences between case subjects and control subjects by using univariate methods. Categorical variables were compared by the Pearson  $\chi^2$  test, and continuous variables were compared by the Mann-Whitney  $U$  test and Student's  $t$  test. Statistical significance was established at the  $P < 0.05$  level. Variables were included for a stepwise backward logistic regression, and variables with a log-likelihood ratio of  $P > 0.05$  were excluded in a stepwise fashion until each remaining variable was statistically significant. The effect of every significant model parameter was

TABLE 1. Characteristics of Cases and Controls

Variable	Cases (n=390)	Controls (n=390)	P Value
Age, mean	58±13	59±14	NS
Sex			NS
Female, n (%)	271 (69)	271 (69)	
Male, n (%)	119 (31)	119 (31)	
Study area			
Shimokita, n (%)	177 (45)	177 (45)	
Aomori, n (%)	213 (55)	213 (55)	
Ethnicity, Asian, n (%)	390 (100)	390 (100)	NS
Ever married, n (%)	350 (90)	344 (88)	NS
Education>high school, n (%)	118 (30)	127 (33)	NS
Social class, manual, n (%)	236 (61)	188 (48)	0.0007
Use of proxy respondents, n (%)	159 (41)	91 (23)	<0.0001
History of hypertension, n (%)	181 (46)	117 (30)	<0.0001
Current cigarette smoking, n (%)	137 (35)	77 (20)	<0.0001
Alcohol consumption			
<250 g/week, n (%)	65 (17)	82 (21)	NS
≥250 g/week, n (%)	56 (14)	47 (12)	NS
History of hypercholesterolemia, n (%)	25 (6)	49 (13)	0.0047
History of diabetes mellitus, n (%)	23 (6)	31 (8)	NS

NS indicates not statistically significant.

qualified by its odds ratio (OR) and a 95% CI. Adjusted ORs were also reported by forcing matching factors, such as age, sex, and use of proxy respondent. In addition to identifying the factors that increased the risk of SAH, the contribution of each risk factor to the overall occurrence of SAH in the general population was calculated as a population-attributable risk according to the following formula: population attributable risk=population fraction (OR-1)/[population fraction (OR-1)+1].<sup>40</sup>

## Results

In Shimokita, 198 cases with aneurysmal SAH were seen during the 10 years from 1989 to 1998. However, 21 cases were excluded from the evaluation of risk factors, because they lacked sufficient information about risk factors. During the same period, 428 control subjects with head trauma were seen at the same institute. Of these control subjects, 43 were excluded because of missing data. From the remaining control cases, 177 subjects were randomly selected to be frequency matched to cases for age (10-year strata) by sex. In Aomori, 213 cases with aneurysmal SAH were registered from 7 institutes during the year from June 2000 to May 2001 after 32 cases with missing data for any of the variables were excluded. During the same period, 483 control subjects were seen at the same institutes; 48 subjects were excluded because of missing data, and 213 control subjects with head trauma were randomly selected to be frequency matched to cases for age (10-year strata) by sex. Therefore, there were 390 case subjects and 390 frequency-matched control subjects.

Table 1 shows the distribution of cases and controls by variables that might affect the risk of SAH. Controls were significantly more likely than cases to have a higher socioeconomic status. Significantly more proxy respondents were used in case subjects. No significant differences in marital

**TABLE 2. Risk Factors for Aneurysmal SAH**

	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
History of hypertension				
No	209 (54)	273 (70)	1.0	1.0
Yes	181 (46)	117 (30)	2.38 (1.75–3.24)	2.29 (1.66–3.16)
Cigarette smoking				
Never or former smoker	253 (65)	313 (80)	1.0	1.0
Current smoker	137 (35)	77 (20)	2.47 (1.76–3.46)	3.12 (2.05–4.77)
History of hypercholesterolemia				
No	365 (94)	341 (87)	1.0	1.0
Yes	25 (6)	49 (13)	0.45 (0.26–0.77)	0.41 (0.24–0.71)

SAH indicates subarachnoid hemorrhage; OR, odds ratio; CI, confidence interval.

\*From a multiple logistic regression analysis adjusted for age, sex, and use of proxy respondent.

status and educational status were seen. Variables significantly related to the risk of SAH were a history of hypertension, current cigarette smoking, and a history of hypercholesterolemia. The prevalence of hypertension in the control subjects was 27% in men and 31% in women, whereas the prevalence of cigarette smoking in the control subjects was 46% in men and 9% in women.

Logistic regression analysis initially included all risk factors: a history of hypertension; cigarette smoking; alcohol drinking; a history of hypercholesterolemia; and a history of diabetes mellitus. Alcohol drinking and a history of diabetes mellitus were excluded from the model, because their likelihood ratios were not significant. The final model parameters are given in Table 2. Crude ORs showed that a history of hypertension and current smoking increased the risk of SAH and that a history of hypercholesterolemia decreased the risk of SAH. When only nonsmokers who had never smoked were considered the referent group for current smokers, the crude OR of current cigarette smoking was 2.71 (95% CI, 1.92 to 3.84;  $P < 0.0001$ ). The adjusted ORs, obtained by forcing matching factors, such as age, sex, and use of proxy respondent, were 2.29 for a history of hypertension (95% CI, 1.66 to 3.16), 3.12 for current smokers (95% CI, 2.05 to 4.77), and 0.41 for a history of hypercholesterolemia (95% CI, 0.24 to 0.71). The population-attributable risk of a history of hypertension was 28% and of current cigarette smoking was 30%.

## Discussion

Risk factors for aneurysmal SAH have been investigated by many studies.<sup>16–38</sup> In the present study, hypertension, cigarette smoking, alcohol consumption, hypercholesterolemia, and diabetes mellitus were evaluated. In Japan, the use of oral contraceptives and hormone replacement therapy is not popular, and thus they were not evaluated in this study.

Hypertension has been the most frequently investigated risk factor,<sup>19,20,24–26,28,32,34,36,37</sup> because hypertension is believed to induce aneurysm formation by increasing hemodynamic stress. Among previous reports, only 1 was unable to find a positive association between hypertension and an increased risk of SAH.<sup>20</sup> Teunissen et al<sup>16</sup> reported in their systematic review of risk factors for SAH that combined estimates of the previous studies had shown that the risk of

SAH for hypertension was significantly increased in both longitudinal studies (relative risk [RR], 2.8; 95% CI, 2.1 to 3.6) and case-control studies (OR, 2.9; 95% CI, 2.4 to 3.7). Ruigrok et al<sup>17</sup> reported in their literature review that the population-attributable risk of hypertension for SAH was 17%. Stronger associations of hypertension with an increased risk of SAH have been seen in women than men.<sup>19,24,25,36,37</sup> The results of the present study are compatible with those of previous studies.

Cigarette smoking has also been frequently investigated as a risk factor for SAH.<sup>18–21,23–26,28,36</sup> Combined estimates of these studies show that current smoking increases the risk of SAH in both longitudinal studies (RR, 1.9; 95% CI, 1.5 to 2.3) and case-control studies (OR, 3.5; 95% CI, 2.4 to 3.7).<sup>16</sup> The population-attributable risk of cigarette smoking was estimated to be 20%.<sup>17</sup> Although the mechanism by which smoking increases the risk of SAH has not been clarified, 2 possible mechanisms have been proposed. Smoking-induced hypertension might promote aneurysm formation, or a temporary increase in blood pressure after cigarette smoking may promote aneurysm rupture.<sup>18,41</sup> Long-term smoking can weaken the vessel walls of cerebral arteries by releasing proteolytic enzymes into the systemic circulation, which could result in the formation of an aneurysm.<sup>18,41</sup> Previous reports investigating both hypertension and smoking as risk factors for SAH revealed that cigarette smoking can increase the risk for SAH independent of hypertension.<sup>19,20,24–26,28,36</sup> This suggests that aneurysm formation induced by cigarette smoking is mainly attributable to the harmful influence of smoking on the vessel walls. The results of the present study with multiple logistic regression analysis showed that cigarette smoking is an independent risk factor for SAH, which is consistent with this hypothesis and previous reports.

Evaluation of the role of alcohol consumption in SAH reveals that combined estimates of longitudinal studies show that drinkers have a greater risk than nondrinkers. In fact, drinking  $<150$  g/week (RR, 2.8; 95% CI, 1.3 to 6.3) and drinking  $>150$  g/week (RR, 4.7; 95% CI, 2.1 to 10.5) increased the risk of SAH.<sup>16</sup> Combined estimates of case-control studies showed that heavy drinking ( $>150$  g/week) increases the risk of SAH (OR, 1.5; 95% CI, 1.1 to 1.9).<sup>16</sup> The population-attributable risk of drinking alcohol (300 g/week

or more) has been shown to account for 21% of the risk.<sup>17</sup> However, the present study was unable to show a correlation between alcohol drinking and an increased risk for SAH. The mechanism by which alcohol consumption increases the risk of SAH is unknown. One possibility is that long-term heavy drinking might contribute to the formation of an aneurysm through hypertension, because regular alcohol consumption is an independent cause of hypertension.<sup>42</sup> However, 1 study<sup>20</sup> that investigated both recent alcohol consumption and hypertension as risk factors showed alcohol consumption within 24 hours preceding the onset of an SAH was an independent factor associated with an increased risk of SAH. This suggests that aneurysm rupture might be induced by recent heavy drinking. However, no studies have investigated the effect of long-term drinking and hypertension as risk factors for SAH. Therefore, whether long-term drinking is, in fact, really associated with an increased risk for SAH independent of hypertension remains unclear. However, according to the results of the present study, which used multiple logistic regression analysis to avoid the possibility of habitual drinking induced hypertension affecting the occurrence of SAH, long-term alcohol consumption was not found to be an independent risk factor for SAH.

The results of this study showed that a history of hypercholesterolemia decreased the risk of SAH. On the other hand, previous studies have reported equivocal results. For example, Adamson et al<sup>26</sup> showed that total cholesterol concentration increased the risk of SAH and suggested that an atherosclerotic profile might contribute to SAH. However, they did not investigate the effect of hypertension as a risk factor for SAH. Other previous studies investigating both serum cholesterol and hypertension as risk factors showed that cases with low serum cholesterol were more frequently found among SAH cases, although this trend did not reach statistical significance in these studies.<sup>19,32,34</sup> However, a recent study has found that a low serum cholesterol level is significantly related to the risk of SAH.<sup>30</sup> Thus, more studies using multiple logistic regression analysis are needed, including possible variables to further confirm the role of the serum cholesterol level as a risk factor for SAH.

The incidence of SAH is known to be high in Finland.<sup>1,2,4-8</sup> The pooled incidence of 3 Finnish studies estimated 21.4 cases per 100 000 person-years,<sup>1</sup> whereas the pooled incidence of studies performed in other countries was 7.4 cases per 100 000 person-years.<sup>1</sup> Recent Japanese studies, including our previous report, have suggested that the incidence in Japan is as high as that in Finland.<sup>9-14</sup> Investigating the reasons for the high incidence in Finland and Japan may lead to a clarification of the etiology of the aneurysm and its rupture.

The high proportion of the elderly in Finland and Japan may partially contribute to the high incidence of aneurysmal SAH, because it has recently been established that the incidence of aneurysmal SAH increases with age. Our previous study<sup>10</sup> revealed that the annual incidence of aneurysmal SAH of 21.0 per 100 000 population in Shimokita did not change when adjusted to the Finnish population, but it was reduced to 12.1 per 100 000 population when adjusted to an age distribution similar to the world population. Although the

**TABLE 3. Prevalence of Risk Factors in Controls in Previous Case-Control Studies and the Present Study**

Country (Year Published)	Hypertension, %		Current Smoking, %	
	Men	Women	Men	Women
Finland (1993) <sup>20</sup>	16	19	45	29
Finland (1987) <sup>18</sup>			40	12
United States (1994) <sup>36</sup>		31.8		
United States (1978) <sup>25</sup>		10.7		33.0
England (1979) <sup>37</sup>		4.4		
New Zealand (1986) <sup>24</sup>	14.0	19.0	27.9	24.6
Japan-Aomori (the present study)	27	31	46	9

incidence of SAH in Japan and Finland decreases after adjusting for age, it remains nearly twice as high as the incidence in other countries.

In terms of risk factors for SAH, the vulnerability to the risk factor or the prevalence of the risk factors for SAH in the communities of Finland and Japan may differ from other countries and may contribute to the high incidence of SAH.<sup>16</sup> The present study and Finnish studies<sup>18-20</sup> have revealed that, compared with other countries, the risk factors and their degree of association with an increased risk for SAH are not different. This suggests that the vulnerability to the risk factor does not differ among countries.

To evaluate the prevalence of a risk factor in a community, the rates of the risk factor in the control subjects in case-control studies or in the community population in longitudinal studies were compared by using previous studies of risk factors for SAH and the present study. The prevalence of hypertension in control subjects in the present study was 27% in men and 31% in women. These percentages were higher than most of the other countries, which had prevalence rates of 14% to 16% in men and 4.4% to 31.8% in women (Table 3). In the present study, the prevalence of cigarette smoking in control subjects was 46% in men. This is the same as the Finnish rate of 40% to 45% and is higher than the rate in New Zealand of 27.9%. According to the annual survey of national health reported by the Ministry of Health and Welfare in Japan, the prevalence of cigarette smoking during the recent 5-year period from 1995 to 1999 was 49.2% to 52.7% in men and 9.8% to 11.6% in women, which was quite similar to the results of this study (Table 3). Therefore, the high prevalence of hypertension and cigarette smoking in men and the high prevalence of hypertension in women might contribute to the high incidence of SAH in Japan. However, differences in the prevalence of these factors between Japan, Finland, and other countries were not marked. Because the risk of SAH is in part genetically determined,<sup>15</sup> a high prevalence in Japan and Finland of genes linked to aneurysm formation may also play a role in the high incidence of SAH in these areas. This possibility should be clarified by further studies.

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