Risk Factors for Fatal Subarachnoid Hemorrhage
The Japan Collaborative Cohort Study

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Background and Purpose—The present study aimed to identify risk factors for mortality due to subarachnoid hemorrhage (SAH) using a comprehensive questionnaire from the Japan Collaborative Cohort (JACC) Study, a Japan-wide population-based prospective study.

Methods—A total of 109,293 individuals (45,551 men and 63,742 women, aged 40 to 79 years) free of stroke at entry participated in the JACC Study between 1988 and 1990. Participants were followed up annually until they died or moved away from the surveyed community, or until the end of 1999. A diagnosis of death from SAH was based on the International Classification of Diseases, 10th revision (ICD-10). The age-adjusted univariate and multivariate hazard ratios (HR) and 95% confidence intervals (CI) of various factors were calculated in sex-stratified and sex-specific analyses using the Cox proportional hazards regression model.

Results—A total of 244 individuals (88 men and 156 women) died from SAH during the follow-up of 1,086,963 person-years. Our univariate analyses confirmed that preference for salty foods and history of blood transfusion, as well as hypertension, family history of stroke, cigarette smoking, heavy alcohol consumption, and low BMI, had statistically significant associations with mortality due to SAH. Multivariable analyses revealed that history of blood transfusion was an independent significant risk factor (HR=4.2 [95%CI, 2.1 to 8.5]) for men, while preference for salty foods or heavy drinking were not.

Conclusions—History of blood transfusion was found to be an independent risk. The association between SAH and blood transfusion warranted further study.

Key Words: blood transfusion □ cohort studies □ risk factors □ subarachnoid hemorrhage

Among all subtypes of stroke, subarachnoid hemorrhage (SAH) is the most deadly, and mortality associated with SAH remains high at 40% to 60%, despite advances in diagnostic and therapeutic developments during the past decades.1,2 Although no gene responsible for SAH or intracranial aneurysms has been found, a positive family history of SAH is a well-established risk factor.3,4 Several factors, such as hypertension, cigarette smoking, heavy alcohol consumption, low BMI, and estrogen deficiency, have been reported to be associated with SAH.3–12

The JACC Study is a large cohort study, and has followed up for >1 million person-years.13 A baseline, comprehensive questionnaire was administered to all participants. Previously, we found mental stress as a risk factor for death due to SAH in women, based on our prospective study, with comprehensive questionnaires, has enabled us to determine versatile risk factors. Risk factors for SAH have never been evaluated in a large cohort study. In the present study, taking an advantage of the large cohort study, we systematically searched for risk factors for fatal SAH.

Methods

Study Cohort
The Japan Collaborative Cohort Study (JACC Study) was initiated in 1988 and enrollment continued until the end of 1990. Details of our...
research methods have been published elsewhere. A total of 110 792 individuals (46 465 men and 64 327 women, aged 40 to 79 years) living in 45 communities across Japan participated in municipal health screening examinations and completed self-administered questionnaires. We excluded 914 men and 585 women from the analysis because of a previous history of stroke at baseline. Therefore, 45 551 men and 63 742 women were enrolled in our study.

**Questionnaire**

The questionnaire contained questions that elicited the following items: (1) medical history (hypertension, diabetes mellitus, heart disease, renal disease, hepatic disease, gastroduodenal ulcer, blood transfusion, operation, injury); (2) family history (stroke, hypertension, diabetes mellitus, coronary heart disease); (3) smoking status (never, past or current smoking, and the average number of cigarettes smoked per day); (4) alcohol consumption (never, past or current drinking, the average frequency of drinks per week, and the average number of drinks per day); (5) lifestyle (physical activity, sleeping); (6) mental stress; (7) occupation; (8) dietary habits of food and drink (salty or fatty foods, tea, coffee); (9) height and weight; (10) educational level; (11) hormonal factors; and (12) systolic blood pressure (SBP) and diastolic blood pressure (DBP) (self-recorded after measurement at health check-up). Body mass index (BMI) was calculated as weight/(height)^2.

We defined systolic hypertension as SBP ≥140mm Hg and diastolic hypertension as DBP ≥90mm Hg. Hypertension was defined as systolic or diastolic hypertension. The average number per day in cigarettes or cigarette equivalents (cigarettes/day) smoked were classified into 4 categories: nonsmoker (never or ex-smoker), light smoker (1 to 9 cigarettes/day smoker), middle smoker (10 to 19 cigarettes/day smoker), and heavy smoker (≥20 cigarettes/day). The amount of alcohol intake was assessed by use of a traditional Japanese unit of sake (“go”), 1 go (180 mL) containing almost 23 g of absolute alcohol, which corresponds to 1 bottle (663 mL) of beer, 2 single shots (75 mL) of whiskey, or 2 glasses (180 mL) of wine. The average amount drunk per day was classified into 4 categories: nondrinker (never or ex-drinker), light drinker (<1 go/day), middle drinker (1 to 4 go/day), and heavy drinker (>5 go/day). BMI was categorized as low (BMI <18.5), middle (18.5≤BMI<25.0) and high (BMI ≥25.0). Mental stress was reorganized into 3 categories by combining the categories of high and extremely high stress because of the low percentages. We also reorganized the preference for salty or fatty food, from 5 to 3 (preference, medium, distaste) categories.

**Outcomes**

A follow-up survey was conducted annually and end points for each participant were the date of death, the date the subject moved away from the surveyed community, or December 31, 1999. The person-years followed were calculated from the date of completion of the baseline questionnaire to the end point. Eventual cases were defined as those who had died from SAH, while others who had died from other causes or were living at the end of 1999 or had moved away from the surveyed community were censored cases.

For mortality surveillance in each community, investigators conducted systematic reviews of death certificates, which had all been forwarded to the public health center in the area of residency. Mortality data were sent to the Ministry of Health, Welfare and Labor of Japan. The underlying causes of death were defined as the primary causes only and coded according to the International Classification of Diseases, 10th Revision (ICD-10), for National Vital Statistics.

Registration of death is required under the Family Registration Law in Japan and is implemented throughout the country. All deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case. Follow-ups were conducted until the end of 1999; the mean follow-up period was 9.9 years, and the total available data for the statistical analyses were 1 099 662 person-years. Cause-specific mortality was determined by SAH (codes I60.0 to I60.9 or I69.0 of ICD-10). The present study was approved by the Ethics Committees of the Nagoya University Graduate School of Medicine and the University of Tsukuba.

**Data Analysis**

The age-adjusted and sex-stratified or sex-specific hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using the Cox proportional hazards regression model. P<0.05 was considered statistically significant in each analysis. Some questionnaires had nonmarked or missing data; all were treated as deficit data not changing other variables.

We comprehensively analyzed all of the contents in our questionnaire after adjustment for baseline age to seek potential risk factors for SAH. After, we evaluated these potential risk factors in multivariable analyses. For the selection of variables for the multivariate analyses, we used stepwise regression models. Furthermore, we estimated the population attributable risk proportion (PARP) for statistically significant risk factors in multivariable analysis. Each PARP (%) was calculated by the proportion of the participants with the risk factor×(HR−1.0)/HR. The data were managed and analyzed using SAS software (Version 8.2, SAS Institute Inc).

**Results**

**Clinical Characteristics**

A total of 244 individuals (88 men and 156 women) died from SAH among the 109 293 individuals (45 551 men and 63 742 women, aged 40 to 79 years of age) during the follow-up periods. The total annual mortality rate (AMR) for SAH was 22.5 (per 100 000 persons): Female AMR was 24.6 and male 19.5 (Figure 1). AMR increased age-dependently, especially in women. Female AMR doubled the male AMR for every decade after the 1960s.

The demographic characteristics and proportions of several risk factors for SAH among the total baseline participants are shown in Table 1. The mean blood pressure among baseline participants with history of hypertension (mean blood pressure =147/85 mm Hg, n = 15 350) was obviously higher than without any history of hypertension (128/77 mm Hg, n = 50 752) (data not shown).

Mean age and blood pressure, and prevalence of hypertension, family history of stroke, and current smokers were significantly higher for persons who died from SAH than
other participants in both sexes, while there were no differences in the prevalence of drinkers. Mean BMI was lower in SAH cases than in other participants for men (Table 1).

Detection of Potential Risk Factors for Fatal SAH in Univariate Analyses

Significant risk factors for mortality from SAH in age-adjusted univariate analyses are shown in Table 2. Hypertension, systolic hypertension, and history of hypertension had excess risks of mortality from SAH for both sexes. Diastolic hypertension was a significant risk factor for women but not for men. Family history of stroke had a significant excess risk for women, but was marginal for men.

Current cigarette smoking was the most significant risk factor for fatal SAH for both sexes; age-adjusted HR (95% CI) of current smokers compared with those who never smoked was 2.96 (1.82 to 4.81) for women and 3.40 (1.55 to 7.45) for men. Ex-smokers did not have any significantly higher risk compared with never-smokers in both sexes. In terms of a dose-response relationship for smoking, risks started to increase in light smokers for women and in middle smokers for men. The risks, however, were saturated in heavy smokers for both sexes.

Heavy drinkers had a significant excess risk in men (HR=2.08 [95% CI, 1.15 to 3.76]), but a marginal one in women (HR=3.92 [0.96 to 15.91]). Daily drinkers also had a significantly excessive risk than nondrinkers or occasional drinkers in men (HR=1.94 [1.03 to 3.67]).

Persons with low BMI had a significant excess risk for both sexes combined (HR=1.63 [1.06 to 2.50]) in sex-stratified analyses. Sex-specific analyses, however, failed to show a significant association for either sex. We confirmed persons with high mental stress had a significant excess risk for women (HR=1.96 [1.03 to 3.72]). We also found that persons with preference for salty foods had a significant excess risk for both sexes (HR=2.34 [1.30 to 4.20] for women and HR=3.01 [1.07 to 8.47] for men). Finally, we found that men with a history of blood transfusion had an increased risk of mortality from SAH (HR=2.80 [1.61 to 4.85]). Other factors including medication history of hypertension, passive smoking, physical activity, menopausal state, hormone replacement therapy, coffee consumption, or education level did not have any statistically significant associations with mortality from SAH (data not shown).

Evaluation of Possible Risk Factors for Fatal SAH in Multivariate Analyses

In the sex-stratified analyses, hypertension, family history of stroke, current smoking and history of blood transfusion were independent and statistically significant risk factors, and heavy drinking and preference for salty foods were confounded by hypertension, family history of stroke and current smoking (Table 3). Hypertension was the most important risk factor for both sexes (HR=2.70 [1.80 to 4.07], PARP=25.9).

There were several sex-specific risk factors. For women, high mental stress was a discernible risk factor, which had a large PARP (13.1). Although female current smokers had a significant risk, female PARP was low (3.1) because of the few numbers of current female smokers (5.6%). On the other hand, for men, cigarette smoking (HR=3.10 [1.21 to 7.92], PARP=36.2), low BMI (HR=2.72 [1.03 to 7.23], PARP=3.5), and history of blood transfusion (HR=4.20 [2.09 to 8.46], PARP=7.7) were independent risk factors.

We found history of blood transfusion as an independent risk factor for fatal SAH, for which a Kaplan-Meier curve is shown in Figure 2. There might be a possibility that the linkage between blood transfusion and SAH was mediated by other potential confounding factors associated with transfusion. Therefore, we checked confounding effects in the multivariable analysis. We analyzed the effects of blood...
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AMR indicates annual mortality rate; HR (95% Cl), hazard ratio (95% confidence interval).

*All variables are adjusted for baseline age.

†Non-smoker—never smoker or ex-smoker; light smoker=1–9 cigarettes/day (c/d) smoker; middle smoker=10–19 c/d smoker; heavy smoker=20 or more c/d smoker.

‡Never drinker or ex-drinker; light drinker=less than 1 go/day drinker; middle drinker=1 <.2 go/day drinker; heavy drinker=≥2 go/day drinker.

§Low BMI = BMI <18.5; medium BMI = 18.5 ≤BMI <25.0; high BMI = BMI ≥25.0.
transfusion together with the history of heart disease, renal disease, hepatic disease, gastroduodenal ulcer, operation, or injury in multivariable analyses (Table 3). These factors, however, were found not to confound the risk attributable to history of blood transfusion.

Preference for salty foods was confounded in the sex-specific or stratified multivariable analyses. We thus tested differences of mean blood pressure between persons with preference for salty foods and those with distaste for them. Persons with preference for salty foods had significantly ($P<0.001$) higher mean blood pressure (132.5/79.3 mm Hg, $n=21322$) than those with distaste for them (131.5/78.1 mm Hg, $n=10724$).

### Discussion

We confirmed that hypertension, family history of stroke, and cigarette smoking raised a significantly higher risk, 2- to 3-fold, of fatal SAH, in agreement with previous cohort studies$^{4-11}$ and a systematic review$^{12}$ of risk factors for SAH. PARP suggest that hypertension is most important and a common factor for prevention against SAH in both sexes. The present data suggest that smoking cessation might reduce the risk to the levels for nonsmokers.

Our univariate analyses document a hockey stick–shaped relation between alcohol and risk. Heavy drinking is, however, not an independent risk factor for both sexes. These results conflict with previous cohort studies.$^{10,11}$

The present study showed that low BMI was a significant and independent risk factor, especially for men. The present study is congruent with previous reports,$^{4,15}$ but the mechanisms remain unelucidated.

We first document the association with preference for salty foods, although this factor affected SAH through hypertension. This finding is compatible with recent reports.$^{15}$

We found that blood transfusion was a risk factor for fatal SAH, a factor that has not been reported previously. In terms of mechanisms, there are at least 2 possibilities.

It is well known that viral agents, such as human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV), and hepatitis B and C virus (HBV, HCV) are transmitted by transfusion.$^{16}$ There are many case reports concerning SAH associated with HIV infection in children.$^{17,18}$ However, the prevalence of HIV infection through transfusions may be extremely rare in the present cohort.$^{19}$ A recent case-control study has reported that recent infection was an independent risk factor for SAH.$^{20}$ HCV infection is reported to be associated with dissection of the cerebral artery and a cause of SAH.$^{21}$ These lines of evidence appear to suggest that known or unknown infectious agents might be involved in the pathogenesis of SAH through transfusions.

There are case reports concerning SAH associated with autoimmune diseases.$^{22}$ Their association is mediated by vasculitis. A recent case-control study has reported that transfusion was associated with the development of systemic lupus erythematosus.$^{23}$ In Japan before 1990, when this study began, transfusion did not involve the removal of donor’s leukocytes by filtration from the transfused red cells.$^{24}$ There is epidemiological evidence that immunomodulation induced by transfusion facilitates the recurrence of malignancy or the postoperative infections.$^{25,26}$ In terms of mechanisms, microchimerism is postulated.$^{27}$ Thus, immunomodulation might be directly or indirectly associated with fatal SAH. The male-specific risk of transfusion also remains unknown.

The present study has several limitations. First, we used mortality data not incidence data as end points. However, the widespread use of CT scans in Japanese local hospitals since the 1980s has probably made a death certificate detailing SAH as the cause of death sufficiently accurate.$^{28}$ However,
SAH might be difficult to distinguish from intracerebral hemorrhage without using angiography or autopsy.

Second, we used simple questions relating to histories, lifestyles, habits, and other pieces of information at baseline. The validity and reliability of these questions could not be evaluated. It is well known that there are large variations in questionnaire results for factors such as lifestyles. However, information on simple history of transfusion or surgery can be relatively robust. Furthermore, because the present study design is a prospective cohort, it is less likely that any systematic bias might deviate the results.

Third, bleeding diathesis due to anticoagulant use or hemodialysis or other disease conditions could not be explicitly analyzed in this study due to lack of information. Bleeding diathesis, which is often treated with blood transfusion, is known to increase risks of fatal SAH, which was the target outcome in this study. Thus the lack of information may illustrate a deceptive association between SAH and transfusion. To evaluate this possibility, the histories of various diseases and conditions that are known to be associated with bleeding diathesis or transfusion were included in the multivariable analysis (Table 3). The analysis revealed...
blood transfusion as an independent risk factor, suggesting that the association might not be deceptive. Due to the lack of critical information and/or type 1 errors in multiple testing, the present association, however, awaits further confirmation.

In conclusion, we found that blood transfusion is an independent risk factor for SAH. Confirmation of association between blood transfusion and fatal SAH in other populations, and investigations for its mechanisms warrant further research.

Appendix

Present Members of JACC Study and Affiliations

The present members of the JACC Study and their affiliations are as follows: Dr Mitsuru Mori (Sapporo Medical University School of Medicine), Dr Yutaka Motohashi (Akita University School of Medicine), Dr Ichiro Tsuji (Tohoku University Graduate School of Medicine), Dr Yoshikazu Nakamura (Jichi Medical School), Dr Haruo Mikami (Chiba Cancer Center), Dr Yoshiharu Hoshiyama (Showa University School of Medicine), Dr Hiroshi Suzuki (Niigata University School of Medicine), Dr Hiroyuki Shimizu (Gifu University School of Medicine), Dr Takesumi Yoshimura (Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health), Dr Haruo Mikami (Chiba Cancer Center), Dr Yoshiro Matsuo (Tokyo University School of Medicine), Dr Toshio Kuroki (Gifu University), Dr Yo-ichi Kato (Showa University School of Medicine), Dr Hiroshi Suzuki (Niigata University School of Medicine), Dr Ichiro Tsuji (Tohoku University Graduate School of Medicine), Dr Shuji Hashimoto and Dr Yoshinori Kanda (Kyoto University Center for Student Health), Dr Taokun Heli (Nagoya Medical University), Dr Takeshi Kiyama (Nagoya University Graduate School of Medicine), Dr Norihiko Hayakawa (Research Institute for Radiation Biology and Medicine, Hiroshima University), Dr Takesumi Yoshimura (Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health), Dr Katsuhiko Fukuoka (Kurume University School of Medicine), Dr Tomonori Kitagawa (Cancer Institute of the Japanese Foundation for Cancer Research), Dr Toshio Kuroki (Gifu University), Dr Yoshiyuki Ohno (Asahi Rosai Hospital), Dr Naoyuki Okamoto (Kanazawa Cancer Center), Dr Hideo Shio (Moriyama Municipal Hospital), Dr Kazuo Tajima (Aichi Cancer Center Research Institute), and Kyoko Okuyama (Nagoya University Graduate School of Medicine).

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Yamada et al Risk Factors for Fatal SAH 2787
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