〈原　著〉

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Long-term prognosis of stroke and risk factors for death in a general Japanese population: The Hisayama Study

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Background and Purpose: There have been relatively few population-based studies of long-term prognosis and risk factors for death after stroke. We evaluated the 10-year prognosis of stroke, causes of death and risk factors for death (only cerebral infarction group) in a Japanese rural community, Hisayama.

Methods: The study cohort consisted of 333 patients with stroke (cerebral infarction (CI) in 244, intracerebral hemorrhage (ICH) in 60 and subarachnoid hemorrhage (SAH) in 29), who occurred among 1,621 Hisayama residents aged 40 years or older during the 26-year follow-up of a prospective study since 1961. To elucidate the risk factors for death in CI group, we collected the data from the regular health checks within two years of onset. We set up the control group which was consisted of free of stroke in our prospective study and attendance at the health checks in 1973 or 1974.

Results: Calculating age adjusted survival curves by Cox proportional-hazards analysis, CI group's curve declined gradually both men and women. In contrast, ICH and SAH group's curve dropped radically in acute period. Any type of stroke group's mortality was higher than the age-adjusted control group. Evaluating the causes of death by type, CI was most frequent and pneumonia and neoplasm were the next to CI in CI group. While, most ICH and SAH group died of original type of stroke, and neoplasm was most frequent in control group. Multivariate analysis showed that age and low body mass index were significantly ($p<0.05$), and glucose intolerance was marginally ($p<0.1$) independent risk factors for death in CI group.

Conclusion: To improve the long-term prognosis of stroke, the correction of glucose intolerance may be important for CI group in chronic period, in addition to the cure in acute period. Because of the high mortality in acute period, the prevention of the occurrence may need for ICH and SAH group.

Key Words：epidemiology, stroke, prognosis, risk factors, causes of death
疫学調査、脳卒中、予後、危険因子、死因

Introduction

Stroke ranks third as a cause of death in Japan. Furthermore, stroke is a major cause of disability and dementia in the elderly, and related problems in health care have become more important in recent years. Information on survival after stroke and predictors of death help to cope with these problems. Although the literature on survival after stroke is extensive, the majority of studies are based

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on selected series of patients referred to the hospital. Such patients are tend to be more sever cases and often not representative of all stroke cases excluding patients who die rapidly before reaching the hospital or does not attend the hospital. So, prospective study of a defined population can most clearly assessed, but few population-based studies have been able to define accurately the natural history of well-defined pathological subtypes of stroke [1-6].

Since 1961, We have carried out a prospective cohort study in a Japanese subrural community, Hisayama, Japan [7,8]. This study has investigated the epidemiology of cerebrovascular disease in a general Japanese population. We did autopsies on most of the deceased subjects to confirm the cause of death and to examine the brain pathology (total autopsy rate: 82.4%). In addition, less than 2% of the original cohort of the study have been lost to follow-up from 1961 to date. In this article we evaluated the 10-year prognosis of stroke, causes of death and risk factors for death (only cerebral infarction group) in the Hisayama Study.

Subjects and Methods

Follow-up survey

Hisayama is a subrural community adjacent to the metropolitan area of Fukuoka on Kyushu Island in southern Japan. The population of the town is approximately 7,000, and the distributions of age, sex and occupational status is considered almost identical to those for the whole of Japan for 30 years. Since1961, we have carried out a prospective epidemiologic study of cerebrovascular disease focused on subjects aged 40 or over. A detailed description of this survey was published previously [7,8].

1,621 of both sexes aged 40 or over who had never suffered cerebral stroke were recruited from the Hisayama residents (88.1% of the total population of the same age-range) in 1961 as a cohort, and they have prospectively been followed-up for 26-year period between November 1, 1961 and October 30, 1987. We collected information about new cardiovascular events through daily monitoring system established by the study team, local practitioners, and the town government. Members of our study group visited the town at least once a week to maintain contact with physicians and the staff of the local health and welfare office. At least once a week we also surveyed the 3 major hospitals near the town, to which Hisayama residents usually are admitted if need be. Regular health checks were given biennially to obtain information on any new cardiovascular events missed by the monitoring network. Every year we used mail or telephone to contact all the cohort subjects who had not had these regular health checks or who had moved out of town in order to detect new neurological conditions. When we suspected new neurological symptoms, the subject was carefully evaluated by the study physicians, and the effort made to obtain further diagnostic information, including lumbar puncture, cerebral angiography or recently brain CT scans.

When a cohort subject died, an effort was made to obtain permission for autopsy from the family. Autopsies were performed at the Department of Pathology of Kyushu University. We reviewed all the available clinical information and interviewed the attending physicians and the families of the deceased subjects. The underlying diseases were chosen as causes of death for each individual. Diseases linked to the underlying cause of death were classified into the following categories, based on the International Classification of Disease (ICD, 9th revision): cerebrovascular diseases (ICD430-438) , ischemic heart disease (ICD 410-414), other heart diseases (ICD 393-398, 402, 416, 420-429), malignant neoplasm's (ICD 140-165, 170-175, 179-208), pneumonias (ICD 480-487), and others. Cerebrovascular diseases were additionally classed into cerebral infarction (CI) (ICD 434), intracerebral hemorrhage (ICH) (ICD 431) and subarachnoid hemorrhage (SAH) (ICD 430). We also included sudden death, occurring within 1 hour of onset of symptoms without other cause of death, to ischemic heart disease.

During the follow-up period, 340 patients with occurrence of stroke were identified and followed-up to establish their long-term prognosis. The determination of diagnosis of stroke and its type was made based on clinical history, neurological exami-

nation, all available clinical data including brain CT and autopsy findings. According to the classification of stroke, 244 (120 men and 124 women) had CI, 60 (40 men and 20 women) had ICH, and 29 (6 men and 23 women) had SAH. We excluded 7 unclassified strokes from our cohort. We set the control group which was consisted of free of stroke in our prospective study and attendance at the health checks in the middle of the follow-up period 1973 or 1974. During the follow-up period, 852 subjects (414 men and 438 women) died, 704 (82.6%) of whom underwent autopsy. 267 stroke subjects died, and we examined the brain at autopsy in 236 (88.4%) of them. We established the control group which was consisted of free of stroke in our prospective study and attendance at the health checks in the middle of the follow-up period, 1973 or 1974.

The starting point of follow-up was the onset of stroke in case group and the attendance date at the health checks on 1973 or 1974 in controls group. And the end point was death in deceased subjects and 10-year follow-up or October 31, 1987 in Survival subjects. No one was lost to follow-up.

Risk factors for death

To elucidate the risk factors for death in CI group, we collected the following data from the regular health checks within two years of onset: age at onset, sex, alcohol consumption (yes or no), smoking (yes or no), history of glucose intolerance (yes or no) [9], antihypertensive therapy (yes or no), average of three systolic and diastolic blood pressures (mmHg), body mass index (kg/m^2), abnormal ECG findings including left ventricular hypertrophy (Minnesota cord 3-1) and ST depression (Minnesota cord 4-1, 2, 3), atrial fibrillation (Minnesota cord 8-3), and serum total cholesterol (mg/dl). The categories used in the definition of glucose intolerance have been described in a previous report.

Statistical analysis

The SAS program package was used for the computer analysis. Mean values were compared by Student's two tailed t-test, and frequencies by the χ^2-test. Survival curve of each stroke type was calculated using Cox's proportional hazard analysis after adjustment for age. We estimated the age-adjusted and multivariate relative risks of each potential risk factor for death by using the β coefficients from Cox's proportional hazard analysis. Age and gender were included in all the multivariate analyses.

Results

Long-term prognosis

Table 1 shows the clinical characteristics of the

Table 1. Characteristics of the subjects at entry, the Hisayama study

Factors	Men		Women	
	Stroke n=166	Control n=166	Stroke n=167	Control n=167
Age at entry (year)	71±10	69±8	75±10	74±9
Alcohol consumption (%)	70	54 **	9	7
Smoking (%)	70	64	12	16
Glucose intolerance (%)	24	22	10	7
Systolic blood pressure (mmHg)	164±31	144±25 **	167±29	150±25 **
Diastolic blood pressure (mmHg)	89±15	78±12 **	87±14	79±11 **
Antihypertensive therapy (%)	21	6 **	16	6 **
Hypertension a) (%)	69	35 **	63	37 **
Body mass index (kg/m^2)	21±3	21±3	22±4	22±3
Abnormal ECG b) (%)	45	20 **	43	29 *
Atrial fibrillation c) (%)	8	2 **	6	2 *
Total cholesterol (mg/dl)	178±43	177±34	202±46	197±37

Data are presented as the mean ± SD or frequency, a) SBP ≧160 or DBP ≧95 or antihypertensive therapy(+)
b) Minnesota Cord 3-1, 4-1,2,3, c) Minnesota Cord 8-3 **p<0.01, *p<0.05 vs. stroke

subjects on entry. The mean age at entry of stroke patients was significantly older than that of control both men and women. The frequency of alcohol consumption was significantly higher for stroke compared with control in men. The systolic and diastolic blood pressure were significantly higher in stroke both men and women. The frequency of antihypertensive therapy, abnormal ECG, and atrial fibrillation were all significantly higher for stroke compared with control both men and women.

Calculating age adjusted survival curves by Cox proportional-hazards analysis (Figure 1), stroke group's curve dropped radically in acute period and declined gradually after one-year. The 10-year survival rate of stroke group was 30% in men and 41% in women, which were significantly lower than that of control (77%). The survival rate of males was lower than that of females, but the two curves were not significantly difference.

Figure 2 shows the survival curves by each type of stroke in men. CI group's curve declined gradually, whereas ICH and SAH group's curve dropped radically in acute period. SAH patients died all within 6 month. The survival rate of ICH dropped to 32% by 1-year and was stable after that. The 10-year survival rate was 35% in CI, 23% in ICH, and 74% in control. Each type of stroke's survival rate was significantly lower than that of control.

We show the survival curves by each type of stroke in women (Figure 3). They were similar trend to men's one. The mortality of ICH was worst, and the 10-year survival rate was 49% in CI, 25% in ICH, and 35% in SAH.

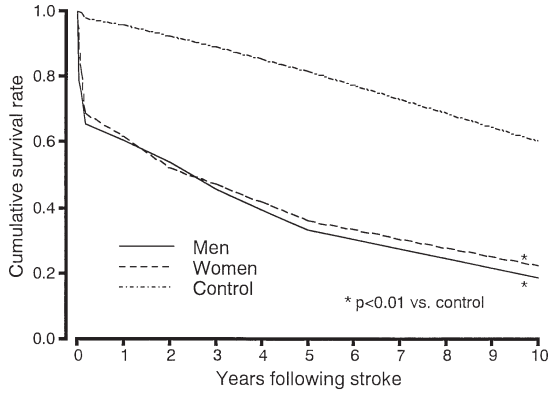

Figure 1. Age-adjusted survival rates after stroke, the Hisayama study, 1961-1987

Cause of death

We evaluated the causes of death by type (Table 2). In CI group, CI (55.3%) was most frequent cause of death, and pneumonia (14.9%) and neoplasm (13.8%) were the next to CI. In this case, CI included initial and recurrence CI death. While, most of ICH and SAH group died by original type of stroke , because of high mortality rate in acute phase. In control group, neoplasm (38.6%) was most and pneumonia (33.1%) was second most frequent. Women's causes of death were similar trend to men's one.

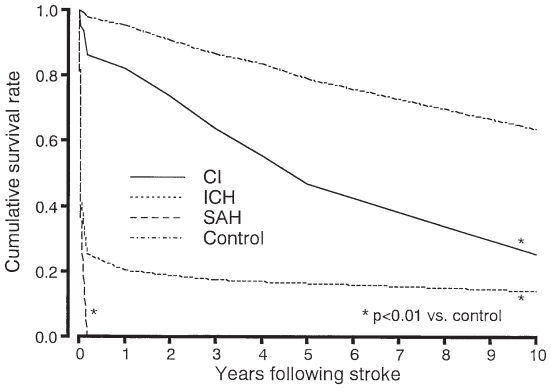

Figure 2. Age-adjusted survival rates by type after stroke for men, the Hisayama study, 1961-1987;
CI: cerebral infarction, ICH: intracerebral hemorrhage, SAH: subarachnoid hemorrhage

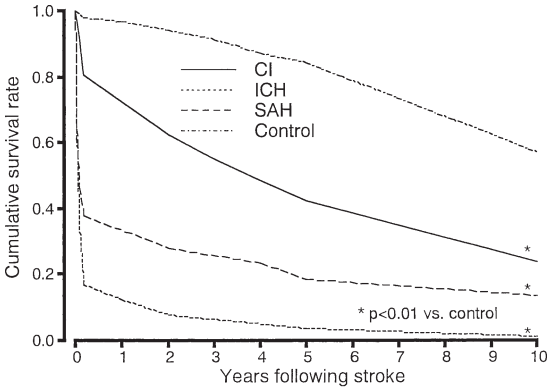

Figure 3. Age-adjusted survival rates by type after stroke for women, the Hisayama study, 1961-1987;
CI: cerebral infarction, ICH: intracerebral hemorrhage, SAH: subarachnoid hemorrhage

Table 2. Causes of death among Hisayama residents during the follow-up period, 1961~87

Cause of death	CI group		ICH group		SAH group		Control group	
CI	104	(55.9)			2	(7.7)		
ICH	8	(3.9)	45	(81.8)				
SAH					22	(84.6)		
Malignant neoplasms	25	(13.7)	2	(3.6)	1	(3.9)	59	(30.3)
Pneumonias	35	(15.7)	1	(1.8)	1	(3.9)	37	(19.0)
Ischemic heart diseases	7	(2.0)	1	(1.8)			10	(5.1)
Other heart diseases	7	(2.0)	1	(1.8)			21	(10.8)
Others	15	(6.9)	5	(9.1)			68	(34.9)
Total	102	(100.0)	55	(100.0)	26	(100.0)	195	(100.0)

CI: cerebral infarction, ICH: intracerebral hemorrhage, SAH: subarachnoid hemorrhage, ( ) %

Risk factors for death

The age-adjusted relative risk of each risk factor for predictor of death in CI group and the 95% confidence intervals on entry into the study are given in Table 3. Low body mass index was significant ($P<0.05$), and glucose intolerance was marginally significant ($P<0.1$) risk factors for death.

To exclude risk factors being significant by chance after age-adjustment and determine the independent risk factors for death, we made a multivariate analysis using the marginally risk factors available in Table 3, age, and sex (Table 4). Age and low body mass index were significantly ($P<0.05$), and glucose intolerance was marginally significantly ($P<0.1$) independent risk factors for death in CI group.

Table 3. Age-adjusted relative risk of predictor for death 10-year follow-up in 244 cerebral infarction group, the Hisayama study (1961~1987)

Factors	RR	95%CI
Body mass index (kg/m^2)	0.80*	0.67-0.96
Glucose intolerance	1.42$^+$	0.96-2.10
Alcohol consumption	1.13	0.81-1.57
Smoking	1.22	0.89-1.68
Systolic blood pressure	1.08	0.93-1.26
Diastolic blood pressure	1.04	0.89-1.22
Antihypertensive therapy	1.13	0.76-1.70
Abnormal ECG [a)]	1.08	0.79-1.47
Atrial fibrillation [b)]	1.01	0.61-1.67
Total cholesterol	1.04	0.89-1.22
Sex (Men vs Women)	1.16	0.85-1.59

RR: relative risk, CI: confidence interval, continuous variables for an increase in risk of 1SD, *p<0.05, $^+$p<0.1, a) b) same as Table 1

Table 4. Multivariate analysis of relative risk of predictor for death 10-year follow-up in 244 cerebral infarction group, the Hisayama study (1961~1987)

Factors	RR	95%CI
Age at entry	1.80**	1.50-2.17
Body mass index (kg/m^2)	0.80*	0.67-0.96
Glucose intolerance	1.42$^+$	0.96-2.10
Sex (Men vs. Women)	1.16	0.85-1.59

RR: relative risk, CI: confidence interval, continuous variables for an increase in risk of 1SD, **p<0.01, *p<0.05, $^+$p<0.1

Discussion

Long-term prognosis

When we compared survival curves by types of stroke, almost of studies showed that CI's curve declined gradually, whereas ICH's and SAH's curve dropped radically in acute period and steady in chronic period. This tendency was also found in our study.

The reported 5-year survival rate after stroke in community based studies ranges from 38% to 55% [2-6]. It was 34.3% (33.3% in men and 36.3% in women) in our study. Although we did not include

recurrent stroke in our inception cohort, in a comparison of 5-year survival rate after stroke among the reported studies, ours showed a rate relatively lower than the others. Dennis et al. [4] reported that 5-year survival rates were 48% in CI, 30% in ICH, and 48% in SAH. In our study, they were 44%, 14%, and 16%, respectively. In a comparison of survival rate by stroke type, hemorrhagic disease's patients of Hisayama showed a rate relatively lower than the others. Particularly in men, all SAH patients died within 6 month. The lower survival rate of stroke may have been for the high mortality of ICH and SAH.

According to the evaluation of sudden unexpected death in the Hisayama study by 17-year follow up, 54% were due to intracranial hemorrhage (ICH and SAH) and 23% were due to coronary heart disease [10]. Also, according to the investigation of the incidence of SAH in the Hisayama study by 22-year follow up, 54% of SAH patients were diagnosed by only autopsy [11]. The higher mortality of ICH and SAH in our study can partly be explained by the fact that 82% of deceased's were verified by autopsy, so we found almost of instantaneous or sudden death by hemorrhagic type of stroke without a correct diagnosis being made before death.

In our study, the age-adjusted survival rate of male patients was lower than that of female patients, but the difference was not significant. The lower survival rate of men may have been for the high frequency of ICH, which is the lowest survival rate of the type of stroke. Sacco et al. [2] reported that the survival rate of females was better than that of males because of better control of hypertension in females. But a few observed better survival in men in community based studies [1, 4, 5].

Cause of death

During the 15-year follow-up period, Matsumoto et al. [6] reported that 80% of ICH and 88% of SAH died of stroke, whereas 36% of cerebral thrombosis died of stroke, 23% died of heart disease, 12% died of pulmonary disease, and 6% died of cancer. In Western, stroke itself is the most common underlying cause of death in the acute phase, however, coronary heart disease is the leading cause of death among long-term survivors [2]. In our study, CI (56%) was most frequent cause of death, pneumonia (16%) and neoplasm (14%) were the next to CI, and 4%died of heart disease in CI group. Stroke deaths were due to the direct effects of the brain lesion or due to complications of immobility resulting from the first stroke. This discrepancy may be due to ethnic differences in the atherosclerotic process. Atherosclerosis in Japanese advances more progressively on intracranial than on coronary arteries, so Japanese have a higher incidence of cerebrovascular disease than cardiovascular disease.

According to the evaluation of accuracy of death certification by the Hisayama study [12], malignant neoplasmas were underdiagnosed, and detection rates for stroke and malignant neoplasmas declined with developing age. The higher frequency of neoplasm death in our study can partly be explained by the fact that we found almost of neoplasmas even in the aged by autopsy.

Risk factors for death

In our study, multivariate analysis showed that age and low body mass index were significantly, and glucose intolerance was marginally significantly in dependent risk factors for death in CI group. Although a number of risk factors for death have been proposed, there has not been universal agreement of risk factors except age, consciousness level and severity of paresis. In addition, heart disease, hypertension, smoking, atrial fibrillation, diabetes mellitus, peripheral vascular disease were reported as significant risk factors for death [1-3, 5, 13, 23-26].

The adverse effect of increasing age on survival after stroke have been several reported. Howard et al. [13] suggested that age may be related to complicating factors that cause death in older patients, for example, pneumonia. Bamford et al. [14] also found a same association due to immobility rather than direct neurological damage.

Hypertension is one of the major risk factors for initial stroke, but its impact on mortality after ischemic stroke is less clear. Some have found hypertension to be a determinant of survival after stroke [2,25], While others have not reported a significant effect [1, 13, 24, 26]. No significant effect of it in

our study may partly be explained by the fact that stroke patients are treated hypertension strictly, or the high prevalence of hypertension of stroke patients prevents the statistical detection.

Our findings also suggest that low body mass index was a significant risk factor for death. Recently, several studies have reported excess cardiovascular disease mortality among lean hypertensive subjects [15-17]. There were some hypotheses that lean hypertensive subjects have suffered end-organ damage [15], may suffer from higher peripheral vascular resistance than those who are obese [16], and may well carry stronger genetic determinants of cardiovascular disease than obese hypertensive subjects [17]. As the prevalence of stroke patients with hypertension is more than 60% in our study, same process may cause poor prognosis of lean stroke patients. In addition, according to the evaluation of mortality from major causes of death and its risk factors in the elderly in the Hisayama study, low body mass index was a risk factor for death from pneumonia, so to be lean was reflected insufficient nourishment and little resistance to bacterial infectious disease [27].

In our study, glucose intolerance was marginally significantly independent risk factors for death in CI. A few prospective epidemiological studies have reported diabetes mellitus as an independent risk factor for death in stroke patients [23, 24]. In a ten-year prospective study of stroke patients with and without diabetes mellitus, Olsson et al. [18] examined the effect of diabetes mellitus to risk for death after stroke. The risk of death after stroke as calculated with log-rank tests was significantly higher for diabetic patients, and it was increased mainly during the first six months. This has partly been attributed to the development of excessive lactic acidosis [19] and cerebral edema in the brain after an ischemic insult in a hyperglycemia states [20]. While, some studies reported that diabetes mellitus was a determinant of the stroke recurrence [18, 24, 28]. In a 18-year prospective study in Hisayama town, recurrent attacks occurred somewhat frequently among those with diabetes mellitus in males [29]. Its factors might also contribute to the development of brain lesions in diabetic patients, such as an impaired autoregluation of cerebral flood flow, a decreased deformability of erythro- and leucocytes, hypercoagulability, hyperviscosity, a decreased synthesis of prostacyclin with an increased adhesivity of thrombocytes, and an increased adhesion of erythrocytes to endothelial cells [21]. In addition, diabetes is associated with an increased risk for myocardial infarction and a higher mortarity rate [22].

Conclusion: To improve the long-term prognosis of stroke, the correction of glucose intolerance may be important for CI group in chronic period, in addition to the cure in acute period. And early detection of other systemic disease may be important. Because of the high mortality in acute period, the prevention of the occurrence may especially need for ICH and SAH group.

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一般住民における脳卒中の長期予後と死亡の危険因子に関する検討：久山町研究

吉　武　毅　人

背景と目的：地域住民を対象とした脳卒中の長期予後と死亡の危険因子に関する研究は、ほとんど行われていない。このため本研究では、久山町の地域住民を対象に、脳卒中の10年間の生命予後と死因、死亡の危険因子（脳梗塞群のみ）を検討した。

方法：対象集団は、1961年に40歳以上であった1,621人の久山町住民の中で、26年間の前向き調査の追跡期間中に脳卒中を発症した333人（脳梗塞（CI）244人、脳出血（ICH）60人、くも膜下出血（SAH）29人）とした。CI群の死亡に関する危険因子を解析するため、CI発症直前の2年以内の検診データを用いた。前向き調査の追跡集団の中で、脳卒中を発症せず、1973年か1974年の検診を受診した者を対照集団とした。

結果：Cox比例ハザードモデルによる年齢調整後の生存曲線は、CI群では男女ともに緩やかに低下した。一方ICHとSAH群の生存曲線は、急性期に急激に低下した。脳卒中の全ての群の死亡率は、年齢調整した対照集団より高かった。各群で死因の検討では、CI群はCIが最も多く、次いで肺炎と悪性新生物であった。一方、ICHとSAH群ではほとんどが原疾患で死亡しており、対照群では悪性新生物が最も多かった。多変量解析による、CI群の死亡に関連する独立した危険因子の検討では、「年齢」と「低BMI」が有意な（$p<0.05$）、「耐糖能異常」が有意な傾向（$p<0.1$）がある因子であることが示めされた。

結論：脳卒中の長期予後を改善するには、CI群では急性期の治療に加え、慢性期における耐糖能異常の改善が重要であることが示唆された。ICHとSAH群では、急性期での高い死亡率を認めるため、発症予防が重要であることが示唆された。