Risk Factors for Cerebral Hemorrhage and Cerebral Infarction in a Japanese Rural Community

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SUMMARY  A ten-year follow-up study of stroke among residents 40 years and older in a rural community located on Shikoku Island, Japan, was completed in 1977. The response rate for the initial examination was 85% of 920 males and 90% of 1,012 females. Seven hundred and seventy-two males and 901 females who were initially free of stroke were followed from July 1967 through June 1977. The incidence of all strokes was 10.47 per thousand person-years for males and 6.41 per thousand person-years for females. The statistically significant risk factors for stroke were age, male sex, elevated blood pressure, ECG abnormalities, and funduscopic abnormalities. Elevated blood pressure was the strongest risk factor and mean arterial pressure was the best predictive measure. Twice as high a proportion of strokes were subclassified as cerebral hemorrhage (26%) in this study as have been reported in comparable studies in the United States (12–15%). An inverse relationship between serum cholesterol levels and cerebral hemorrhage incidence, but not cerebral infarct, was observed. High alcohol intake was a risk factor for cerebral hemorrhage but not for cerebral infarct. No relationship between stroke and weight was observed despite the relationship of stroke to blood pressure and of weight to blood pressure.

STROKE is one of the most serious health problems occurring in Japan. It has been the leading cause of death since 1951 and is also a major contributor to disability, particularly for those aged 40 years and over.1,2 Treatment of stroke is unlikely to restore the patient to his original condition; therefore, prevention is the most logical approach to resolution of stroke morbidity and mortality. An understanding of the natural history of stroke is essential for development of a prevention scheme; to date, however, there have been few reports on the natural history of stroke among Japanese in Japan. In this paper we report the results of a ten-year cohort study for occurrence of stroke in Taisho. Incidence of cerebral hemorrhage and cerebral infarction has been determined among all residents and among subgroups stratified according to risk factors present at the time of the baseline examination in 1967.

Methods

Study District

Taisho is located along the Shimanto River in the western part of Kochi prefecture and covers an area of 199.5 square kilometers (fig. 1). The town is in the mountain area of the island at elevations of 200 to 500 meters above sea level. The principal industries are forestry and small-scale agriculture. Most of the residents are either farmers or wood-cutters who supplement their income with part-time jobs in other occupations. Their economic status is lower than that of Japanese living in the urban areas.

Initial Examination

All residents of Taisho 40 years or older were invited to undergo an examination in July, 1967. The examination included administration of a questionnaire, physical examination, and collection of specimens for laboratory determination.

The questionnaire solicited information on demographic characteristics, smoking, diet, alcohol consumption, physical activity, personal medical history, family medical history, and symptoms.3-10 The clinical examination included determination of height and weight, casual blood pressure, ocular funduscopy, and administration of a chest X-ray and a resting electrocardiogram (ECG). Blood specimens were collected for determination of serum total cholesterol and urine specimens for determination of albumin and glucose. The physical examination included cardiac auscultation and neurologic examination.

The casual blood pressure was measured using a Riva-Ricci sphygmomanometer. To reduce measurement error and bias, the standard procedure recommended by WHO for indirect determination of blood pressure was used.8,9 The ECG was recorded using twelve leads. Results were coded using the Minnesota code.8 The funduscopic examination was performed by an ophthalmologist after the right pupil was dilated using tropicamide and phenylephrine hydrochloride. Results of the funduscopic examination were coded on the two- or three-level scale on the basis of narrowing
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of arterioles, irregularity in caliber, hemorrhage, hard and soft patch, papilledema, an increase in arteriolar reflex, and arteriovenous crossing. Funduscopic findings were also recorded using the Scheie classification and the Keith-Wagener classification. The serum total cholesterol was determined by the method of Zak-Henly. Venous blood was drawn without regard to the time of the previous meal. Serum was separated by centrifugation and stored at -20°C. Quality control was maintained by using the X-r control charts for pooled and standard sera (Hyland Division, Travenol Laboratories, Inc., California).

The degree of over- or underweight was expressed as the percentage deviation of the actual level (M) from the standard level (S), \( \Delta\% = (M-S)/S \). For this study, the standard weight was based on a table of average weights by height and sex developed by Minowa et al.

Urine samples were collected approximately two hours after a meal and the levels of albumin and glucose determined by use of a Uristix (Ames Company, Ltd.). Smoking was recorded as the average number of cigarettes smoked per day and alcohol consumption was recorded as the equivalent volume of saké.

If a subject was suspected of having had a stroke prior to the initial examination, additional historical information was taken about health status prior, during, and following stroke.

A physician visited the homes of all non-respondents for the initial examination and examined them neurologically for evidence of a prior stroke.

Ascertainment of New Cases of Stroke
Because many stroke patients in Taisho are cared for at home, the occurrence of stroke in this population was determined using both active surveillance and referral. All cohort members were reexamined annually using the same examination procedures as at baseline. Nonrespondents for the follow-up examination were contacted by telephone or visited at their home by a staff member to determine whether or not a stroke had occurred.

New cases of stroke were referred to the investigators by physicians and nurses, records, and institutions in the area.

All patients identified through one of the above techniques who were still alive were examined by a staff neurologist within three weeks after onset. If the patient had died, the staff collected clinical information from the relatives of the patient and from the certifying physician. Results of the physical examination or review were considered jointly by the staff of three neurologists to determine if the patient met the criteria for stroke. Transient cerebral ischemic attacks were not included. An attempt was made to diagnose the anatomical subtype of the stroke: subarachnoid hemorrhage, cerebral hemorrhage, cerebral infarction, or undetermined type.

Subarachnoid hemorrhage was diagnosed if there was a sudden onset of severe headache with only a relatively momentary disturbance of consciousness, signs of meningeal irritation, the absence of focal neurologic signs, subhyaloid hemorrhage, and the presence of blood in the cerebrospinal fluid; cerebral hemorrhage if there was rapid evolution of focal neurological signs, rapid progression to coma, signs of meningeal irritation, elevated blood pressure, headache, and frequently blood-stained cerebrospinal fluid; cerebral infarction if there was a slow gradual development of focal neurologic signs which lasted more than 24 hours, relative preservation of consciousness, and the absence of blood in the cerebrospinal fluid (cerebral infarction included cerebral embolus); and "undetermined" if the history of onset and residual deficit was sufficiently well documented to ensure a high probability that a stroke had occurred but there were incomplete clinical data to subcategorize the type of stroke further.

Results
Response Rates and Prevalence of Stroke
There were 920 males and 1,012 females aged 40 years or older in Taisho in July, 1967. Of these, 780 (84.8%) of the males and 908 (89.7%) of the females responded to the invitation to be examined (table 1). Eight of the males and 7 of the females were found to have clinical evidence of a previous stroke. An inten-
Table 1  Population, Number of Persons Examined at Initial Examination, and Number of Cohort Members in Taisho, Japan, 1967

<table>
<thead>
<tr>
<th>Sex/study factor</th>
<th>Age at entry</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40-49</td>
<td>50-59</td>
<td>60-69</td>
<td>70+</td>
<td>Total</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population eligible</td>
<td>309</td>
<td>242</td>
<td>210</td>
<td>159</td>
<td>920</td>
</tr>
<tr>
<td>Number responding</td>
<td>244</td>
<td>198</td>
<td>191</td>
<td>147</td>
<td>780</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>79.0</td>
<td>81.8</td>
<td>91.0</td>
<td>92.5</td>
<td>84.8</td>
</tr>
<tr>
<td>Number of strokes</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Nonrespondents examined at home</td>
<td>45</td>
<td>31</td>
<td>16</td>
<td>10</td>
<td>102</td>
</tr>
<tr>
<td>Number of strokes</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Prevalence of residents with diagnosis of stroke (per 1,000)</td>
<td>3.5</td>
<td>8.7</td>
<td>29.0</td>
<td>51.0</td>
<td>19.3</td>
</tr>
<tr>
<td>Members of cohort</td>
<td>244</td>
<td>197</td>
<td>188</td>
<td>143</td>
<td>772</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population eligible</td>
<td>353</td>
<td>258</td>
<td>220</td>
<td>181</td>
<td>1,012</td>
</tr>
<tr>
<td>Number responding</td>
<td>307</td>
<td>230</td>
<td>204</td>
<td>167</td>
<td>908</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>87.0</td>
<td>89.1</td>
<td>92.7</td>
<td>92.3</td>
<td>89.7</td>
</tr>
<tr>
<td>Number of strokes</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Nonrespondents examined at home</td>
<td>35</td>
<td>22</td>
<td>13</td>
<td>13</td>
<td>83</td>
</tr>
<tr>
<td>Number of strokes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Prevalence of residents with diagnosis of stroke (per 1,000)</td>
<td>—</td>
<td>7.9</td>
<td>23.0</td>
<td>38.9</td>
<td>14.1</td>
</tr>
<tr>
<td>Members of cohort</td>
<td>307</td>
<td>229</td>
<td>201</td>
<td>164</td>
<td>901</td>
</tr>
</tbody>
</table>

Sive effort was made to examine nonrespondents and 102 of the 140 male nonrespondents and 83 of the 104 female nonrespondents were subsequently examined in the home. Nine of the 102 male nonrespondents examined in their home, and seven of the 83 female nonrespondents were found to have clinical evidence of stroke. The total prevalence of stroke among males (respondents plus nonrespondents) was 19.3 per 1,000 and among females was 14.1 per 1,000 (table 1). The prevalence of stroke was higher among those individuals who refused the invitation than among the individuals who responded to the invitation.

The final numbers used for the cohort followed for ten years was 772 males and 901 females. Individuals with evidence of stroke at the baseline examination and nonrespondents to the initial invitation were not included in the cohort followed up. A separate follow-up was made of 93 of the 102 male nonrespondents and 76 of the 83 female nonrespondents.

For the ten years of follow-up, 90% of the males and 94% of the females from the original cohort were successfully followed. One hundred ninety-one males and 128 females of the cohort died from all causes. Sixty-seven males and 69 females migrated. To make maximum use of the data, the person-year method of incidence determination was employed; the results of that analysis are shown in table 2. There were 115 new cases of stroke between July 1967 and June 1977. Thirty of these were subclassified as cerebral hemorrhage, eighty-one as cerebral infarction, two as subarachnoid hemorrhage, and two as undetermined type. The annual incidence determined according to person-year calculations was 10.47 strokes per 1,000 population for males 40 years or older and 6.41 per 1,000 for females 40 years or older (p < 0.01). The difference between the rates of cerebral hemorrhage for males (2.87 per 1,000) and females (1.53 per 1,000) and of cerebral infarction for males (7.47 per 1,000) and females (4.57 per 1,000) was also significantly different (p < 0.05). The increasing incidence with age was statistically significant for cerebral hemorrhage (p < 0.05) and for both cerebral infarction and all strokes (p < 0.01).

In a previous study by the same investigators, the rate of agreement between clinical diagnosis and confirmation by computerized axial tomography and other procedures was 86.0% for cerebral hemorrhage, 82.4% for cerebral infarction, and 68.4% for subarachnoid hemorrhage. This suggests that the level of accuracy for the current study by the same investigators was also high and comparable with that seen in other countries.

Baseline Characteristics Associated with Increased Incidence of Stroke

The standardized morbidity ratio and the risk ratio for stroke according to the presence or absence of factors ascertained at baseline are shown in table 3. The
TABLE 2  Annual Person-Year Incidence of Stroke per 1,000 Population (10-Year Follow-Up During the Period 1967 Through 1977, Taisho, Japan)

<table>
<thead>
<tr>
<th>Sex/age at entry</th>
<th>Cerebral hemorrhage</th>
<th>Cerebral infarction</th>
<th>All strokes*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>Person-years</td>
<td>Incidence per 1,000 person-years</td>
</tr>
<tr>
<td>Males 40-49</td>
<td>3</td>
<td>2,176.0</td>
<td>1.38</td>
</tr>
<tr>
<td>50-59</td>
<td>4</td>
<td>1,759.5</td>
<td>2.27</td>
</tr>
<tr>
<td>60-69</td>
<td>6</td>
<td>1,549.5</td>
<td>3.87</td>
</tr>
<tr>
<td>70+</td>
<td>5</td>
<td>785.5</td>
<td>6.37</td>
</tr>
<tr>
<td>Total males</td>
<td>18</td>
<td>6,270.5</td>
<td>2.87</td>
</tr>
<tr>
<td>Females 40-49</td>
<td>3</td>
<td>2,868.5</td>
<td>1.05</td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
<td>2,090.0</td>
<td>0.96</td>
</tr>
<tr>
<td>60-69</td>
<td>3</td>
<td>1,818.0</td>
<td>1.65</td>
</tr>
<tr>
<td>70+</td>
<td>4</td>
<td>1,090.0</td>
<td>3.67</td>
</tr>
<tr>
<td>Total females</td>
<td>12</td>
<td>7,866.5</td>
<td>1.53</td>
</tr>
</tbody>
</table>

*All strokes includes cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, and undetermined type.

The characteristics determined at baseline are listed in the far left-hand column. For cerebral hemorrhage, the highest risk ratios were observed for elevated systolic and diastolic blood pressures. Electrocardiographic changes, funduscopic changes, and alcohol consumption habits were also significant risk factors for cerebral hemorrhage. Risk ratios for cerebral hemorrhage were less than one among those who had elevated serum cholesterol and those who were overweight, but did not reach statistical significance.

The highest risk ratios for cerebral infarction were for the presence of sclerotic funduscopic findings and for elevated systolic blood pressure. Elevated diastolic blood pressure, hypertensive funduscopic findings, and albuminuria were also significant risk factors for cerebral infarction. ECG findings (high R wave, T wave inversions, and albuminuria) were also significant risk factors for cerebral infarction.

TABLE 3  Standardized Morbidity Ratio (SMR) and Risk Ratio for Stroke According to the Presence (+) or Absence (−) of Each Factor at Entry (Both Sexes, ≥ 40 Years of Age at Entry, 10-Year Follow-Up, Taisho, Japan)

<table>
<thead>
<tr>
<th>Entry factor</th>
<th>Cerebral hemorrhage</th>
<th>Cerebral infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMR (+)</td>
<td>SMR (−)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>≥ 160 mm Hg</td>
<td>3.44</td>
</tr>
<tr>
<td></td>
<td>≥ 95 mm Hg</td>
<td>2.43</td>
</tr>
<tr>
<td>ECG: High R wave</td>
<td>3-1 or 3-3*</td>
<td>2.13</td>
</tr>
<tr>
<td>ECG: ST-T wave</td>
<td>4-1, 4-2, 4-3, 4-4 and/or 5-1, 5-2, 5-3, 5-4*</td>
<td>2.00</td>
</tr>
<tr>
<td>Hypertensive funduscopic findings</td>
<td>≥ Scheie II</td>
<td>1.68</td>
</tr>
<tr>
<td>Sclerotic funduscopic findings</td>
<td>≥ Scheie II</td>
<td>1.61</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>≥ 210 mg/100 ml</td>
<td>0.54</td>
</tr>
<tr>
<td>Relative weight</td>
<td>≥ +10%</td>
<td>0.72</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>≥ + (Uristix)</td>
<td>1.30</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>≥ + (Uristix)</td>
<td>1.38</td>
</tr>
<tr>
<td>Smoking habits</td>
<td>Smoked ≥ 20 cigarettes/day</td>
<td>1.33</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Drank ≥ 180 ml sake/day</td>
<td>1.42</td>
</tr>
</tbody>
</table>

*Minnesota Code*
ST-T wave), elevated blood pressure levels, and abnormal funduscopic findings were significant risk factors for both types of stroke.

**Level of Blood Pressure, Serum Cholesterol and Relative Weight at Baseline, and Risk of Stroke**

The relationship between the risk of cerebral hemorrhage or cerebral infarct and systolic or diastolic blood pressure levels recorded at the baseline examination is shown in figure 2. There was a consistent increase in risk of cerebral hemorrhage or cerebral infarction with increase in either systolic or diastolic blood pressure except for the highest level of diastolic pressure (≥ 100 mm Hg) for cerebral infarction.

The significance of this relationship was determined by looking at the deviation from the average systolic or diastolic blood pressure and the rate of stroke. The relationship between systolic blood pressure and cerebral hemorrhage was significant at the p < 0.01 level, and that between cerebral infarction and systolic blood pressure was significant at the p < 0.05 level. The relationship between diastolic blood pressure and both types of stroke was significant at the p < 0.05 level.

The same analysis was carried out for serum choles-

![Graphs showing the relationship between blood pressure and stroke risk](image)

**Figure 2.** Standardized morbidity ratio for stroke by the level of blood pressure at entry (both sexes, ≥ 40 years of age at entry, 10-year follow-up, Taisho, Japan).
Serum cholesterol levels were negatively associated with risk of cerebral hemorrhage at the p < 0.05 level. No relationship was seen between serum cholesterol levels and risk of cerebral infarction.

The same type of analysis was done for the relationship of relative weight to risk of cerebral hemorrhage or cerebral infarction. Although the highest risk for cerebral hemorrhage was observed in the lowest level of relative weight, there was no overall relationship between relative weight and either cerebral hemorrhage or cerebral infarction.

This analysis was also done for a combination of elevated blood pressure, ECG abnormality, and funduscopic abnormality (fig. 4). The risk of cerebral hemorrhage or cerebral infarction was highest in individuals with all three risk factors present. The second highest risk for cerebral hemorrhage was seen among residents with both elevated blood pressure and ECG abnormality. The second highest risk for cerebral infarction was seen among individuals with both elevated blood pressure and funduscopic abnormalities. SMR’s among individuals without an elevated blood pressure were considerably lower than for any group with elevated blood pressure, except for those with both funduscopic and ECG abnormalities.

**Figure 3.** Standardized morbidity ratio for stroke by the level of serum cholesterol at entry (both sexes, ≥ 40 years of age at entry, 10-year follow-up, Taisho, Japan).

* The decreasing trend (slope) is significantly different from zero at the p < 0.05 level.
Elevated Blood Pressure
(≥ 160mmHg and/or ≥ 95mmHg)
ECG Abnormality
(High R and/or ST-T Changes)
Funduscopic Abnormality
(≥ K-W II)

Cerebral Hemorrhage

Cerebral Infarction

* statistically significant from subgroup of (−, −, −) at the p < 0.01 level

Finally, this analysis was done for a combination of elevated blood pressure, serum cholesterol, and relative weight, as shown in figure 5. Elevated blood pressure alone conferred the highest risk of these three variables for cerebral hemorrhage and approximately the same risk as all three risk factors combined for cerebral infarction. The elevated blood pressure in combination with either an elevated serum cholesterol or overweight reduced the risk. The effect of elevated serum cholesterol and overweight in reducing the risk among individuals with elevated blood pressure was less for cerebral infarction than for cerebral hemorrhage.

Multivariate Analysis

The net and joint effect of each factor listed in the left-hand column of table 4 was determined by multiple logistic function using the formula below:

\[ P = \frac{1}{1 + \exp(-A \cdot \Sigma B_i X_i)} \]

where P is the probability of developing cerebral hemorrhage or cerebral infarction and \( X_i \) are the independent variables. The parameters of the equation, A and B, were estimated by using the Duncan-Walker maximum likelihood method. To isolate relevant risk factors, all of the coefficients, B, were put on the same scale; i.e., standardized coefficients were used. Thus, the standardized coefficient was considered a measure of the association between the independent variable (\( X_i \)) and the risk of stroke, taking into account the effect of all other factors.

In table 4 a negative sign preceding the value for the standardized coefficient indicates that the factor had a
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FIGURE 5. Standardized morbidity ratio for stroke according to combination of blood pressure, serum cholesterol and relative weight at entry (both sexes, ≥ 40 years of age at entry, 10-year follow-up, Taisho, Japan).

Discussion

Sources of error

Many studies have stressed the importance of a high response rate for epidemiologic studies.6, 25, 27 In this study as well, we found the characteristics of respondents to our initial examination to be different from those of nonrespondents. Nonrespondents had a higher prevalence and incidence of stroke and a higher total death rate than respondents. The extent of bias due to nonresponse was greater for the baseline examination than for follow-up, in which the response rate was 90% for males and 94% for females.

Case ascertainment of stroke in the majority of studies in the United States and elsewhere has relied on reports of the attending physician of the patient, death certificates, and examination of cases identified by a study physician.27 We included these methods in the current study, but in addition, examined all members of the cohort annually. Thus, only strokes which left no residuals and were not noted by the medical community would have been missed.

A third source of error in studies of stroke is the diagnosis. A study done by us in Osaka comparing clinical diagnosis with diagnosis by computerized ax-
The average annual age-, sex-adjusted incidence of stroke was compared to comparable rates derived for the United States. These age-specific rates were compared to comparable rates derived for Taisho. Incidence of stroke in Taisho was higher in each age group than for the comparable populations in the United States.

Comparison between stroke in Japan and the U.S.

Comparisons of our stroke rates with those reported in other countries is difficult because of differences in ascertainment and diagnosis of stroke. In addition, ours is the only study which has used the person-year incidence determination for stroke. To facilitate comparisons with other studies of stroke in Japan and the United States, we have recalculated the incidence of stroke in the population of Taisho using age-specific and sex-specific rates which included all cohort members in the denominator. The resulting incidence was 4.8 per 1,000 population aged 40–69 years for males and 2.9 per 1,000 for females in Taisho. This compares with an estimated rate of 5.5 per 1,000 for males and 3.1 per 1,000 for females according to studies by the Japanese Ministry of Education for the period 1958–1972. Thus, Taisho appears to have a lower incidence of strokes than the average for Japan.

The average annual age-, sex-adjusted incidence of cerebral infarction for 18 years of follow-up in the Framingham study (U.S.A.) was estimated to be 1.9 per 1,000 population aged 45–74 years, using the 1970 census population of the U.S., compared to 3.3 per 1,000 for residents aged 45–74 years in Taisho.

The Epidemiology Study Group of the American Joint Committee for Stroke Facilities estimated the midpoint incidence rates from a number of different studies in the United States. These age-specific rates were compared to comparable rates derived for Taisho. Incidence of stroke in Taisho was higher in each age group than for the comparable populations in the United States.

Twenty-six percent of all strokes were subclassified as cerebral hemorrhage in Taisho, compared to a range of 23–36% from studies in other Japanese communities. This compares to figures from the United States of 12% and 15% of all strokes.

Thus, a higher proportion of cerebral hemorrhage appears to be characteristic of stroke occurrence in Japan. These proportions are affected, however, by differences in the age and sex distributions of the population.

Risk factors for Stroke

Blood pressure. In this study, as in other studies, the incidence of stroke increased with age and was consistently higher in males than in females. Blood pressure at baseline, whether recorded as systolic blood pressure, diastolic blood pressure, or mean arterial pressure, was highly correlated with the risk of stroke. This was clearly a dose-response relationship with risk of cerebral hemorrhage and cerebral infarction. This relationship of stroke incidence with blood pressure is consistent with studies in Japan and the United States.

It was possible from our study, from the Framingham study, and from the report of...
Komachi to compare the relative strength of the various measures of blood pressure as indicators of risk. Contrary to the view in clinical practice, we found systolic pressure to be a better predictor than diastolic pressure.

**Serum Cholesterol.** Komachi, Ueshima et al., Omae et al., Okada et al., and Kagan et al. have all reported an inverse relationship to serum cholesterol levels and occurrence of cerebral hemorrhage. Our findings are in agreement with these investigators. In addition, Okada et al. compared the incidence of cerebral hemorrhage in groups with various combinations of levels of cholesterol and blood pressure. We found, as did Okada and colleagues, that the risk was lower among groups with an elevated blood pressure and elevated cholesterol than among groups with an elevated blood pressure only.

We found no relationship, however, between levels of serum cholesterol and incidence of cerebral infarction. This is in agreement with the 12-year and 22-year follow-up in the Framingham study, the results of the Evans County study, the Los Angeles Heart study, the Seal Beach study, and the Birmingham study. Case-control studies have also reported an inconsistent relationship between serum cholesterol and cerebral hemorrhage. Despite the fact that none of the major epidemiological studies in the United States has found a clear association between level of serum cholesterol and risk of cerebral infarction, hypercholesterolemia is still regarded as a major factor in the development of stroke. This is due to the evidence derived from animal experimental studies and autopsy studies that link serum cholesterol levels to development of atherogenesis.

The difference in the rate of stroke in Japan and the United States may result from different factors. It is well known that the fat intake in the American diet is very high compared to that in the Japanese diet, and that the salt intake is low in American diets compared to that in Japanese diets. The dietary intake of salt in Taisho was estimated by the 24-h recall method to be 21 g of salt per day. Dahl estimated the average salt intake in Brookhaven, New York, to be 14 g per day, in Hiroshima to be 14 g per day and in Akita to be 26 g per day.

**Weight.** Although a high risk of stroke might be expected among persons who were overweight, obesity was not found to be a risk factor in the Taisho population. In fact, the results implied that the level of relative weight might be associated with a decreasing risk of stroke, particularly of cerebral hemorrhage (table 4, fig. 5). Ueshima et al. found the same inverse relationship to weight in Akita, but Okada et al. found no clear relationship between relative weight and the risk of stroke in residents of Akabane and Asahi. The investigators noted that a higher proportion of thinner individuals in Taisho were engaged in heavy physical labor and had a tendency to take a larger amount of salt and a lower amount of fat than heavier residents. Thus, in order to determine the effect of relative weight on the risk of stroke in Japan, it will be necessary to carry out further analyses separating the confounding effects of salt intake and fat intake on relative weight.

No consistent relationship has been observed between degree of overweight and risk of atherosclerotic brain infarction in the Framingham study and the Evans County study, but the results of the Los Angeles Heart Study suggested that there was an increased risk of cerebral thrombosis with increasing relative weight which was not seen for cerebral hemorrhage. Despite the inconsistent findings in the American studies and our finding of no relationship, the clinical literature advocates maintaining normal body weight because obesity is related to hypertension, hyperlipidemia, diabetes mellitus and cardiac malfunction.

**ECG abnormalities.** The risk of either cerebral hemorrhage or cerebral infarct was over three times as great among individuals with ECG "R" wave abnormalities as in those without. The risk of cerebral hemorrhage or cerebral infarction was over twice as high for those with "ST-T" wave abnormalities as without. These findings are in agreement with those of Okada et al. in Japan and with the results of the Framingham and Evans County studies in the United States. Individuals with both abnormalities of ECG and elevated blood pressure had an even greater risk of stroke than persons with either of these abnormalities alone. These findings are in accordance with those of investigators in Japan and the United States.

**Funduscopic findings.** Among the residents of Taisho with funduscopic abnormalities greater than or equal to grade 2 according to Scheie's scoring, risk for cerebral infarct was greater than for cerebral hemorrhage. Using the Keith-Wagener classification, the risk of stroke increased with advancing grade of funduscopic findings. These results are in agreement with those of other investigators in Japan. The presence of funduscopic abnormalities in addition to elevated blood pressure increased the risk of stroke in Taisho. In the Hisayama study this relationship was found for cerebral infarct but not for cerebral hemorrhage. Okada et al., however, reported findings similar to ours. The preponderance of the evidence suggests that fundus examination is a useful tool in predicting the risk of stroke. Unfortunately, examination of the fundus has not been used often in epidemiologic studies in the United States, because serious observer differences are noted in grading vessel caliber and retinal lesions on funduscopy. Fortunately, a new type of fundus camera has been developed which does not require dilation of the pupil. This camera has been used widely in mass screening in Japan and it could be adopted in the United States as well.

**Alcohol and Smoking Habits.** Alcohol intake was associated with an increased risk for cerebral hemorrhage but not for cerebral infarction. Kagan et al. observed a dose-response relationship between alcohol
intake and the incidence of cerebral hemorrhage among Japanese men living in Hawaii. It is not clear what the mechanism is for the effect of alcohol on stroke, but it is possible that it is related to the intake of salty foods often consumed with alcoholic drinks in Japan.

A significant relationship was not seen between smoking habits and incidence of either cerebral hemorrhage or cerebral infarction. This is consistent with the findings of other investigators and is the reverse of the relationship found with coronary heart disease.38, 40, 82, 83

Summary and Conclusions

The overall rate of stroke has been found consistently to be higher in Japan than in the U.S. The proportion of strokes classified as cerebral hemorrhage is also twice as high in Japan as in the U.S. ECG changes, funduscopic changes, alcohol intake, elevated serum cholesterol and elevated blood pressure — particularly systolic pressure — have been consistently reported in U.S. and Japanese studies to be risk factors for cerebral hemorrhage. For cerebral infarct, reports are consistent for ECG changes, funduscopic changes, and elevated blood pressure as risk factors. Since funduscopic changes are risk factors for both cerebral hemorrhage and cerebral infarct, more careful routine examination of ocular fundus is warranted.

Acknowledgments

The authors express their appreciation to the physicians in the Second Department of Internal Medicine (Head: Prof. Masahisa Wada, M.D.) and the Department of Ophthalmology (Head: the late Prof. Ichizo Ikeda) of Osaka City University Medical School, and to the physicians, public health nurses, and other staff members in the Department of Public Health of Taisho Town, Kochi Prefectural Kubokawa Public Health Center, the Department of Public Health and Labor of Kochi Prefecture, and the Hata-Gun Medical Association. Appreciation is also extended to Virginia Hansen, Epidemiology Division Editor, School of Public Health, University of California, Los Angeles.

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doi: 10.1161/01.STR.13.1.62

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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