Decreasing Trend in Incidence and Mortality from Stroke in Hisayama Residents, Japan

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SUMMARY The incidence and mortality from stroke during the period 1961 to 1976, among 1,621 subjects aged 40 and over at entry, in Hisayama community, Kyushu Island, Japan, were analyzed. A major age-related decline in the incidence of cerebral hemorrhage and infarction occurred in both sexes. The average annual incidence of cerebral infarction also fell continuously in both sexes throughout the whole observation period. The 5-year annual mortality rate from cerebral hemorrhage also showed a decrease in men, but fluctuated in women. The 5-year mortality from cerebral infarction slightly increased in both sexes.

A LONG-TERM DECLINE in death rates from cerebrovascular diseases has been reported in the United States1 as well as in Japan,2 where a decreasing mortality from cerebral hemorrhage is conspicuous. A declining incidence of stroke has also been reported by a study of Rochester, Minnesota.3 There are no reports of yearly changes of incidence or mortality from stroke in a well-defined population in a community. The recognition of altering morbidity and mortality from stroke in the cohort of this study year by year would indicate whether cardiovascular surveillance (Hisayama study of Cerebrovascular Disease) has a beneficial effect on the prevention of stroke.

A prospective epidemiologic study of the development of cardiovascular diseases including stroke in a general population sample from Hisayama, Japan, has been underway since 1961. This report presents data indicating an alteration of incidence and mortality from stroke in this population during early, middle, and late 5-year periods throughout the sequential follow-up period.

Material and Methods
Hisayama Prospective Study

In Hisayama, a prospective community study was begun in 1961 with emphasis on detecting the incidence of cerebrovascular disease. The 1960 census figures indicated that the number of residents aged 40 and over was 1,841 or 27.6% of the population, identical to the average for Japan (28.0%). The annual variation in the population has remained small (less than 4%). Of a total of 1,841 persons aged 40 and over (90.1%) 1,658 were collected from the town registries and were given an initial screening examination. At that time 25 residents were found to have hemiplegia due to stroke. By October 31, 1961, 12 persons had died or moved out of town. Since November 1, 1961, excluding these 37 cases, 1,621 persons (707 men and 914 women), over 40 years old, have been under observation including biennial recording of blood pressure, ECG, examination of the ocular fundi, as well as other tests.2 Details of the methods of examination and follow up have been described elsewhere.4 Briefly, the study has the following features.

Members of our study group visited the town at least once weekly to maintain contact with physicians and the staff of the central town health office. Whenever a stroke occurred each patient was carefully evaluated as soon as possible and the type of cerebrovascular disease was determined by a member of our cerebral vascular research group. Confronted with a patient with presumed cerebrovascular disease in the field, we made a judgement almost exclusively based on the temporal profile of the onset, evolution, and course of the symptoms. This was usually accomplished with reasonable accuracy by a detailed history and neurovascular examination.5 At times a consultation was indicated and ancillary diagnostic studies were made. Some patients with doubtful diagnosis were brought to the university hospital for further examination and diagnostic evaluation including skull and chest x-ray, ECG, CSF, cerebral angiography, radioisotope brain scanning and, recently, computerized tomography. When a person died, an effort was made to obtain permission for autopsy from the family. Autopsies were performed at the Department of Pathology of Kyushu University. The brain was carefully examined after slicing at one cm intervals. Histological observations were also performed routinely. For subjects who moved away, follow up has been complete and none of the original cohort has been lost. The circumstances surrounding all illness and the death of each study-subject have also been sought by scrutiny of all available medical...
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information including hospital and physician records and postmortem data to determine the diagnosis and the underlying cause of death.

After 15 years of follow up 503 subjects of the original 1,621 have died, and 416 were autopsied (82.7%). During 15 years of observation 203 strokes occurred and 171 of these died; autopsy was performed on 150 (87.7%). Morbidity and mortality analyses were separately assessed because stroke death rate can not be used as an indirect measure of the incidence of stroke. Patients who had their first stroke in the study period were included in the determination of incidence. For mortality studies, patients were included who had a stroke within a few months prior to death, and whose neurologic signs and symptoms were considered to be severe enough to be the cause of death. Table 1 provides data on the patients with cerebral hemorrhage and infarction included in the study. Thirty-four patients had cerebral hemorrhage during 15 years and 29 of them died within 2 weeks after onset. Four survived more than 2 months and died from other causes, however, in one an old hematoma in the brain was confirmed by postmortem examination. Six were excluded because the date of onset was obscure. There were 142 cerebral infarctions observed during the 15 years and they were believed to be non-embolic in origin. Clinical signs of more than 24 hours duration were present in all and those patients who were believed to have a TIA were omitted. During the 15 years 112 patients with infarction died. The underlying cause of death was ascribable to cerebral infarction in 61. In addition, 5 who had an initial episode of cerebral infarction died from cerebral hemorrhage. For the analysis of mortality from cerebral hemorrhage, a total of 34 patients were counted. Also excluded from the analysis of both incidence and mortality because of their small number were 14 patients with subarachnoid hemorrhage (13 died) and 7 patients with ill-defined stroke (6 died).

Procedure for Analysis

The entire follow up period of 15 years was divided into three 5-year periods defined as early (November, 1961 to October, 1966), middle (November, 1966 to October, 1971) and late (November, 1971 to October, 1976). The incidence and mortality from stroke were compared among the 5-year periods. As the cohort grew older each individual who belonged to the cohort was yearly moved along a scale of both calender time and age as with the birth cohort pattern of analysis. Thereafter, person-years of experience (PYE) was calculated in order to utilize fully the period of observation for each individual and weigh properly his contribution to the study.

Results

The average annual age-specific incidence of both types of stroke for the 15-year follow up period is shown in table 2. The incidence for cerebral hemorrhage and cerebral infarction rose rapidly in senescence, but it was more conspicuous for cerebral infarction where the incidence increased stepwise with advancing age each decade in both sexes. The cerebral hemorrhage incidence in men was about 3 times higher than that for women and for cerebral infarction about 2 times. When data were evaluated for the entire period of 15 years, cerebral infarction occurred

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Died</th>
<th>Autopsied (%)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH</td>
<td>34</td>
<td>25 (75.8)</td>
<td>29 CH</td>
</tr>
<tr>
<td>CI</td>
<td>142*</td>
<td>103 (92.0)</td>
<td>5 CI</td>
</tr>
<tr>
<td>Total</td>
<td>176</td>
<td>128 (88.3)</td>
<td>34 CH, 61 CI</td>
</tr>
</tbody>
</table>

*Six cases with obscure onset were excluded.

<table>
<thead>
<tr>
<th>Age*</th>
<th>Men</th>
<th>Cerebral Hemorrhage</th>
<th>Women</th>
<th>Cerebral Infarction</th>
<th>Men</th>
<th>Cerebral Hemorrhage</th>
<th>Women</th>
<th>Cerebral Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
<td>Rate</td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td>1.4</td>
<td>0</td>
<td>—</td>
<td>1</td>
<td>0.8</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>50-59</td>
<td>6</td>
<td>1.9</td>
<td>2</td>
<td>0.5</td>
<td>7</td>
<td>2.2</td>
<td>5</td>
<td>1.3</td>
</tr>
<tr>
<td>60-69</td>
<td>11</td>
<td>4.1</td>
<td>3</td>
<td>1.9</td>
<td>34</td>
<td>12.7</td>
<td>16</td>
<td>4.8</td>
</tr>
<tr>
<td>70-79</td>
<td>4</td>
<td>3.1</td>
<td>2</td>
<td>1.0</td>
<td>22</td>
<td>16.7</td>
<td>26</td>
<td>12.7</td>
</tr>
<tr>
<td>80+</td>
<td>2</td>
<td>6.1</td>
<td>1</td>
<td>1.5</td>
<td>15</td>
<td>48.6</td>
<td>17</td>
<td>22.4</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>2.8</td>
<td>8</td>
<td>1.0</td>
<td>79</td>
<td>8.9</td>
<td>64</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*Age at stroke CI/CH: Men 3.2, Women 5.2; PYE = person-years of experience.
TABLE 3  Average Annual Age-Specific Mortality of Strokes per 1,000 PYE Among Hisayama Population Aged 40 and Over (1961-1976)

<table>
<thead>
<tr>
<th>Age*</th>
<th>Men Cerebral Hemorrhage</th>
<th>Women Cerebral Hemorrhage</th>
<th>Men Cerebral Infarction</th>
<th>Women Cerebral Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Rate</td>
<td>No. Rate</td>
<td>No. Rate</td>
<td>No. Rate</td>
</tr>
<tr>
<td>40-49</td>
<td>2  0.8</td>
<td>0 —</td>
<td>0 —</td>
<td>0 —</td>
</tr>
<tr>
<td>50-59</td>
<td>7  2.1</td>
<td>1  0.3</td>
<td>0 —</td>
<td>1  0.2</td>
</tr>
<tr>
<td>60-69</td>
<td>7  2.5</td>
<td>3  2.3</td>
<td>5  2.4</td>
<td>3  0.9</td>
</tr>
<tr>
<td>70-79</td>
<td>9  6.9</td>
<td>2  1.0</td>
<td>21 18.7</td>
<td>10 4.2</td>
</tr>
<tr>
<td>80+</td>
<td>1  2.8</td>
<td>2  2.4</td>
<td>10 25.9</td>
<td>11 15.6</td>
</tr>
<tr>
<td>Total</td>
<td>26  2.8</td>
<td>8  1.1</td>
<td>36 4.3</td>
<td>25 2.2</td>
</tr>
</tbody>
</table>

*Age at stroke CH Men: 1.6, Women: 2.0; PYE = person-years of experience.

more frequently than cerebral hemorrhage with a ratio of infarction to hemorrhage of 3.2 in men and 5.2 in women.

Average annual age-specific mortality from cerebral hemorrhage and cerebral infarction is presented in table 3 and shows a pattern similar to the incidence. A strikingly higher death rate from cerebral hemorrhage and infarction among men when compared to women was also found. The ratio of infarction to hemorrhage was 1.5 in men and 2.0 in women, namely, cerebral infarction was more frequently observed.

In table 4 the 5-year incidence of cerebral hemorrhage for each period is presented. There was a decreasing trend in absolute figures of the 5-year incidence for men and for both sexes throughout the whole observation period. When the yearly incidence was recalculated per 1000 of the PYE in the age brackets covered — thus correcting for the aging of the cohort population — the rates were not significantly different for the 3 periods (table 4, fig. 1).

In contrast a marked drop in the number of cerebral infarctions, especially for women, was noted in the middle and late 5-year period when compared to the early 5-year period (table 5). The annual incidence for cerebral infarction calculated per 1000 of the PYE for men and women after age-adjustment gradually fell in chronological order (table 5, fig. 1). There was a statistically significant difference found between the early and late 5-year periods ($p < 0.06$) by Mantel-Haenszel).

The mortality from cerebral hemorrhage is shown in table 6. The age-adjusted mortality in men fell sequentially over the 3 consecutive periods. In women it first fell and then increased. The annual rate per 1000 of PYE in men did not begin to fall until the middle 5-year period and then decreased further through the late 5-year period (table 6, fig. 2). The annual rate in
women also fluctuated. The gradual downward trend for both sexes continued during the three 5-year periods, although there were no statistically significant differences.

The adjusted number and the annual rate per 1000 PYE of death from cerebral infarction are shown in table 7. From 15.6 during the period 1961–1966 the adjusted number of both sexes combined fell slightly to 14.8 for the period 1967–1971 and to 14.2 for 1972–1976. The number of deaths in men or women fluctuated throughout the 3 periods. The annual rate in both sexes rose from the early to the late period of observation but there were no significant differences (table 7, fig. 2).

**Discussion**

Many observations suggest that there is a variation in the relative incidence of cerebral infarction and cerebral hemorrhage. In most of the reports the discussion has been focused on the problems of the ac-

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**TABLE 6** Mortality of CH According to 3 Consecutive Periods Among Hisayama Population Aged 40 and Over (1961–1976)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>PYE</td>
<td>3386</td>
<td>2912</td>
<td>2506</td>
</tr>
<tr>
<td>No.</td>
<td>3415</td>
<td>2851</td>
<td>2434</td>
</tr>
<tr>
<td>Adjusted No.*</td>
<td>10.3</td>
<td>3.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Annual Rate/1,000 PYE</td>
<td>3.0</td>
<td>0.9</td>
<td>1.8</td>
</tr>
</tbody>
</table>

PYE = person-years of experience; CH = cerebral hemorrhage.

*Age-adjusted to Hisayama population aged 40 and over in 1961.

**TABLE 7** Mortality of CI According to 3 Consecutive Periods Among Hisayama Population Aged 40 and Over (1961–1976)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PYE</td>
<td>3386</td>
<td>2912</td>
<td>2506</td>
</tr>
<tr>
<td>No.</td>
<td>4415</td>
<td>4021</td>
<td>3547</td>
</tr>
<tr>
<td>Adjusted No.*</td>
<td>10.3</td>
<td>4.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Annual Rate/1,000 PYE</td>
<td>2.1</td>
<td>0.9</td>
<td>1.9</td>
</tr>
</tbody>
</table>
curacy of the stroke diagnosis, the quality and reliability of death certificate information, and the difficulties in finding all strokes in a community. It has also been suggested that the high mortality from cerebral hemorrhage among Japanese, based on death certificates, could be due to substantial misclassification of types of stroke. The procedure in the present study—a meticulous history and careful neurological examination by only one study team—could help remove such a bias. Johnson and his colleagues reported a study on the Japanese population of Hiroshima between 1958 and 1964. They concluded that cerebral thrombosis was under-reported in Japan since they found it occurred twice as frequently as cerebral hemorrhage. Assuming that Hisayama represents all of Japan, our results also confirmed that there is no support for the view of high mortality from cerebral hemorrhage among Japanese compared to that from cerebral infarction.

The stroke death rate could be used as an indirect measure of the incidence of stroke when dealing with the nationwide population, but the effect of distribution of a type of stroke on mortality data, even if accurate, might not be a good measure of the incidence of a type of stroke in a community. Several studies have shown that only about 60% of all strokes noted on any clinical record appear on death certificates. In our cohort population, 5 (3.5%) of 142 persons who had had an initial episode of cerebral infarction died from a subsequent attack of cerebral hemorrhage. Cerebral infarction was not the underlying cause of death in 51 (46%) of 112 persons with cerebral infarction. Even considering death from stroke as a single entity after the verification by autopsy, there is a possibility that the cause of stroke death could have been affected by other diseases, i.e., acute bronchopneumonia in varying degrees was commonly observed at the time of autopsy in patients with an old infarction.

Pathologic findings in the brains in many of the non-fatal cases with cerebral infarction in our community were of multiple, small infarcts in basal ganglia or pons. Clinically, they showed relatively minor neurological disturbances such as a pure motor hemiplegia, a syndrome combining cerebellar ataxia with weakness of the corresponding leg, and dysarthria, compatible with lacunar stroke. Therefore, in this group of patients it is necessary to consider not only long-term survival but the ultimate morbidity shown by the survivors. Why population frequency of cerebral infarction among Japanese determined from death data seems to be underestimated might be explained by the hypothesis that lacunar stroke is common among Japanese. A detailed analysis has not been done, and it is difficult to determine whether the topographic distributions of cerebral infarcts and the etiologic variables are different between Japanese and Caucasian, although some indirect evidence had been found. It has recently been pointed out that the differentiation of lacunar infarction from a small cerebral hemorrhage is frequently difficult.

Recent vital statistics from Japan have revealed that the long-term downward trend in mortality from cerebral hemorrhage appears to have accelerated but deaths attributed to cerebral infarction have increased. This may be due in part to a changing pattern in death certification with fewer deaths attributed to “cerebral hemorrhage” and more to “cerebral infarction.” Our results indicate 2 important possibilities 1) a declining trend in incidence of both types of stroke and mortality from cerebral hemorrhage among Hisayama population could be attributed to special features in Hisayama or 2) could represent true figures for Japan. Whisnant et al. in an initial study of the incidence of stroke in Rochester, Minnesota, for the years 1945 to 1954 and a second study of the same population for the years 1955 to 1969, found that the incidence of cerebral infarction for the 5 years 1965 to 1969 inclusive, had fallen when compared to that of the 15-year period. The authors could not detect any diminishing incidence in cerebral hemorrhage. Yates also suggested that there may be a decrease in the number of people dying from cerebral hemorrhage. But in recent years cerebral thrombosis had been noted as being a more common cause of death. However, Kurtzke re-examined these data and concluded that an increase in the incidence of cerebral infarction may be only apparent, and the evidence for the falling rate of incidence of cerebral hemorrhage was not proven with certainty. In the present study, the small numbers of instances of cerebral hemorrhage may well render the present observation less reliable.

It may be possible that a decline in the number of high risk individuals among the population could account for the fall in the incidence of stroke. In order to evaluate this possibility, we have analyzed the frequency of several risk factors measured at entry for stroke patients that were separately assessed during each different period. Among risk factors, aging can be considered negligible, as the rate would show an upward trend if aging influenced the occurrence of the stroke because the cohort grew older year by year. Figure 3, presents the frequency of hypertension, vascular changes in the ocular fundi, ECG, obesity or a high cholesterol and combinations of them found in a percentage of the total number of stroke patients. Although t2 test after age-adjustment (by Mantel-Haenszel) revealed no significant correlations, a high proportion of patients with risk factors was found in the early 5-year period.

It is difficult to explain how the changing pattern in cardiovascular risk factors correlates with the decrease in stroke, since the present study is based on a cohort analysis. To our knowledge there is no available procedure for the estimation of the periodical changes in cardiovascular risk factors with simultaneous consideration for drop-outs by death or major cardiovascular events. However, indirect evidence of the possible waning impact of risk factors for stroke might be shown. For example, it could be expected that treatment and control of hypertension among Hisayama population would be successful, but the initial study was not designed to evaluate the efficacy of...
hypertensive therapy. It was considered important to know the prevalence of hypertension among Hisayama residents at the initial screening and the examination ten years later. Table 8 gives the prevalence of hypertension at the mass-screening in 1961 and in 1973, covering 90% and 80% of all residents. It is evident that the proportion of hypertensive subjects above 60 years of age decreased in 1973 as compared to 1961. As the subjects who belonged to the original cohort must have been over 52 years at the screening

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** Frequency of various risk factors among stroke patients according to 3 consecutive periods (1961-1967). HT = hypertension (SBP 160 and/or DBP 95 mm Hg), ECG = high R and/or ST-T changes, OF = ocular fundus greater than Ila classified by K-W modification, OW = over-weight determined by 10% more than relative weight, HC = cholesterol value more than 200 mg/dl.

<table>
<thead>
<tr>
<th>Age*</th>
<th>1961</th>
<th>1973-74</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of Subjects</td>
<td>HT</td>
</tr>
<tr>
<td></td>
<td>1961</td>
<td>1973-74</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>246</td>
<td>18</td>
</tr>
<tr>
<td>50-60</td>
<td>216</td>
<td>19</td>
</tr>
<tr>
<td>60-69</td>
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<td>34</td>
</tr>
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<td>70-</td>
<td>77</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>707</td>
<td>87</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
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<td>10</td>
</tr>
<tr>
<td>50-60</td>
<td>263</td>
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<td>60-69</td>
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</tr>
<tr>
<td>70-</td>
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<td>24</td>
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<tr>
<td>Total</td>
<td>914</td>
<td>83</td>
</tr>
<tr>
<td>All Total</td>
<td>1621</td>
<td>170</td>
</tr>
</tbody>
</table>

Significance was judged by *x*-test between 1961 and 1973-74.
*Age at the examination.
*Adjusted to sex- and age-distribution in 1961.
in 1973, this finding could be linked to the successful control of hypertension. Garraway et al.\(^{11}\) also considered the possibility that a decreased frequency of hypertension might be related to the reduction in stroke in the Rochester, Minnesota, population, but only the blood pressure data from subjects who had cerebral infarction were considered, and a direct relationship between antihypertensive treatment and prevention of stroke is uncertain.

Precise information on the declining incidence of stroke and its relationship to preventive health measures is not easy to obtain but many studies have found that hypertension is a key risk factor for both intracerebral hemorrhage and occlusive cerebral vascular disease. No other risk factors have been clearly related to all types of stroke. The explanation for the decreasing incidence for cerebral infarction among Hisayama residents may be partially related to the potential effectiveness of hypertension control.

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