tion system could therefore be an additional risk factor in the generation of hemorrhagic cerebral lesions.

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Yoshio Komachi, M.D., Chairman; Heizo Tanaka, M.D., Takashi Shimamoto, M.D., Kyoko Handa, M.D., Minoru Iida, M.D., Koji Isomura, M.D., Saburo Kojima, M.D., Toshihisa Matsuzaki, M.D., Hideki Ozawa, M.D., Hiroshi Takahashi, M.D., and Yoshizo Tsunetoshi, M.D.

SUMMARY A Japan Collaborative Study of Stroke covering 20 regional and occupational population groups was conducted with the support of the Ministry of Health and Welfare. In this study 17,423 males and 16,856 females, aged 40 to 69, were followed up prospectively from 1975 to 1979. The average annual incidence of all types of stroke was 3.94 for men and 2.52 for women per 1,000 population. The incidence of cerebral hemorrhage for men and women stood at 1.26 and 0.59 and that of cerebral infarction at 1.87 and 1.10 respectively. The difference in incidence between the sexes was large particularly in the age range of 40–49. The incidence of all types of stroke, cerebral hemorrhage and cerebral infarction increased with age. The incidence of all strokes in Japan during the period 1975–1979 appears to have decreased in comparison with that in 1960–1969, but tended to be still higher than that in Western countries.

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EPIDEMIOLOGICAL STUDIES of stroke in Japan have been implemented in several pilot communities since around 1960, and they are gradually spreading throughout the country. The Japanese Ministry of Health and Welfare selected twenty population groups randomly from these studies and set up a group of investigators for the "Epidemiological Study on the Relationship between Stroke and Nutrition" (hereinafter referred to as the "Japan Collaborative Study of Stroke"). The aim of this study group is to measure accurately the incidence of stroke and to investigate the nutritional factors that govern the regional differences in the incidence by a standardized method.

In this first report of the Japan Collaborative Study of Stroke we deal with the incidence rates of stroke during the second half of the 1970s and compare them with those in other developed countries.
Methods

Population Groups Studied

The location of the population groups studied is shown in figure 1, and their geographical and occupational features in table 1. The proportion accounted for by farming villages is high, because in Japan epidemiological studies are generally easier to make in rural areas than in urban areas. Fuse (Population group ID 12) and Uoshima (15) represent fishing villages. Meguro (07) refers to an occupational group consisting of ward office employees in Tokyo, Osaka I (09) to one consisting of clerical employees of a certain company, and Osaka II (10) to one consisting of blue-collar workers engaged in the machinery production line of another company. In Hokkaido, Tokai and Kinki II, there were no population groups in which the epidemiological study could be made in accordance with the standardized method.

The population from 40 to 69 years old, based on the 1975 national census, was used as the denominator for the incidence rate. The total population of 20 groups came to 17,423 males and 16,856 females, the sex and age distribution being as shown in table 2.

The observation period was set at five years from 1975 through 1979. For groups in which the epidemiological study started after 1976, however, the observation period was set at 2 to 4 years.

Registration of Stroke Patients

A center for stroke registry was established in each population location in order to get a hold of all the patients who had a new stroke, exclusive of recurrence, during the study period. The centers, reflecting the characteristics of the population groups concerned, were set up in public health centers, departments of health in villages, towns and cities, medical schools, major local hospitals, or centers for adult diseases. The methods used for the development of the stroke registry were those outlined by the WHO study.1-2

Sources of Notification

Notification of suspected stroke to each center was made by general practitioners, hospital physicians and public health nurses in charge of the locality. Patients were also referred from old people's homes, tuberculosis sanatoriums and mental hospitals. Local voluntary laymen's associations for control of stroke were organized, and some other organizations such as women's associations, clubs for the aged and societies of village leaders also took part in the registry. The patients were referred by these organizations as well.

Death certificates and medical bills sent to the payment funds of various health insurance plans were reviewed periodically. Records of medico-legal autopsies and records of ambulances dispatched from fire stations were reviewed in several centers.

A mass screening examination (the response rate for the examination averaging 69% for males and 78% for females) was conducted annually for each population group, which helped find missing patients. Non-respondents for the examination were contacted by telephone or visited at their home by a center staff to determine whether or not a stroke had occurred.

In the case of the occupational group (Population group ID 07, 09 and 10), patients were found mainly through the mass screening examination, for which the response rate was more than 95%. Death certificates, bills to the payment funds of health insurance associations, sick leave reports, medical certificates for suspension from employment, compensation payment records for sickness and injuries, and clinical records of in-company clinics were also reviewed periodically. Patients were also referred by the physicians, public health nurses, and others in charge of in-company health management.

Verification of Diagnosis

All patients who were alive at the time of referral to each center were examined by a staff physician from the center, and their clinical histories were confirmed. If possible, ECG, ophthalmoscopy, a cerebrospinal fluid test and various hematological tests were also performed. If a patient was dead at the referral time, a physician from the center collected clinical information from the relatives of the patient and the certifying physician. The patient information on the clinical history, results of various special procedures, particularly findings of computed tomography (CT) and cerebral angiography, and results of autopsy was collected from the clinical records of clinics and hospitals.

Several (usually three) physicians and neurologists...
Table 1  Observation Period, Population, and Geographical and Occupational Features in 20 Population Groups, The Japan Collaborative Study of Stroke, 1975-1979

<table>
<thead>
<tr>
<th>Population group ID</th>
<th>Population group</th>
<th>Observation period</th>
<th>Geographical and occupational features</th>
<th>Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Ikawa</td>
<td>1975-1979</td>
<td>1,090 1,254</td>
<td>flatland, farmers (rice cultivation), day laborers</td>
<td>Komachi Y, Kojima S, Iida M, Shimamoto T, Konishi M et al</td>
</tr>
<tr>
<td>02 Ishizawa</td>
<td>1975-1979</td>
<td>467 548</td>
<td>mountain + flatland, farmers (rice cultivation), day laborers</td>
<td>Komachi Y, Kojima S, Iida M, Shimamoto T, Konishi M et al</td>
</tr>
<tr>
<td>03 Haguro</td>
<td>1974-1978</td>
<td>1,617 2,012</td>
<td>flatland, farmers (rice cultivation), day laborers</td>
<td>Arai H et al</td>
</tr>
<tr>
<td>04 Akadanilimino</td>
<td>1976-1979</td>
<td>1,022 1,223</td>
<td>mountain + flatland, farmers (rice cultivation, orchard), salaried employees</td>
<td>Tanaka H, Date C, Baba T, Hayashi M, Tanaka Y et al</td>
</tr>
<tr>
<td>05 Tsumagoi</td>
<td>1975-1979</td>
<td>1,176 1,451</td>
<td>tableland, farmers (vegetable cultivation)</td>
<td>Matsuzaki T et al</td>
</tr>
<tr>
<td>06 Yachiho</td>
<td>1975-1979</td>
<td>847 1,026</td>
<td>mountain, farmers (rice cultivation), factory workers</td>
<td>Isomura K et al</td>
</tr>
<tr>
<td>07 Meguro</td>
<td>1975-1979</td>
<td>486 429</td>
<td>ward office staffs in Tokyo</td>
<td>Matsuzaki T et al</td>
</tr>
<tr>
<td>08 Uozu</td>
<td>1975-1979</td>
<td>472 613</td>
<td>mountain + flatland, farmers (rice and mushroom cultivation), day laborers</td>
<td>Handa K et al</td>
</tr>
<tr>
<td>09 Osaka I</td>
<td>1975-1979</td>
<td>2,061</td>
<td>— white-collar workers in a company</td>
<td>Komachi Y, Iida M, Shimamoto T, Konishi M et al</td>
</tr>
<tr>
<td>10 Osaka II</td>
<td>1975-1979</td>
<td>1,336</td>
<td>— blue-collar workers in the production line of machines in a factory</td>
<td>Komachi Y, Iida M, Shimamoto T, Konishi M et al</td>
</tr>
<tr>
<td>11 Yao</td>
<td>1975-1979</td>
<td>2,074 2,302</td>
<td>flatland, a residential and farming district in the suburbs of Osaka City, salaried employees, gardeners, farmers (rice cultivation on small scale)</td>
<td>Komachi Y, Iida M, Shimamoto T, Konishi M et al</td>
</tr>
<tr>
<td>12 Fuse</td>
<td>1978-1980</td>
<td>131 153</td>
<td>a village on the Okinoshima Island in Japan Sea, dry field farmers, woodcutters, inshore fishermen</td>
<td>Seki R, Tada M et al</td>
</tr>
<tr>
<td>13 Yakumo</td>
<td>1975-1979</td>
<td>290 460</td>
<td>flatland, farmers (rice cultivation), day laborers</td>
<td>Seki R, Tada M et al</td>
</tr>
<tr>
<td>14 Daiwa</td>
<td>1978-1980</td>
<td>595 694</td>
<td>mountain, farmers (rice cultivation), woodcutters</td>
<td>Seki R, Tada M et al</td>
</tr>
<tr>
<td>15 Uoshima</td>
<td>1975-1979</td>
<td>113 130</td>
<td>an island in the Seto Inland Sea, inshore fishermen</td>
<td>Takahashi H, Kimura K et al</td>
</tr>
<tr>
<td>16 Ootoyo</td>
<td>1978-1979</td>
<td>997 1,384</td>
<td>mountain, farmers (rice cultivation, sericulture), day laborers</td>
<td>Ozawa H, Komachi Y, Iida M et al</td>
</tr>
<tr>
<td>17 Noichih</td>
<td>1975-1979</td>
<td>1,629 1,970</td>
<td>flatland, farmers (hothouse and outdoor vegetable cultivation, orchard)</td>
<td>Komachi Y, Iida M, Shimamoto T, Konishi M, Ishikawa Y, Tangaki M et al</td>
</tr>
<tr>
<td>18 Tanushimaru</td>
<td>1978-1979</td>
<td>523 640</td>
<td>flatland, farmers (sapling and rice cultivation)</td>
<td>Tashiro H et al</td>
</tr>
<tr>
<td>19 Shibata</td>
<td>1977-1979</td>
<td>214 225</td>
<td>mountain, farmers (rice cultivation), woodcutters</td>
<td>Tsunetoshi Y, Yano A et al</td>
</tr>
<tr>
<td>20 Nishimera</td>
<td>1977-1979</td>
<td>283 342</td>
<td>mountain, farmers (rice cultivation), woodcutters</td>
<td>Tsunetoshi Y, Yano A et al</td>
</tr>
</tbody>
</table>

definition and Classification of Stroke

Stroke was defined as the occurrence of rapidly developing clinical signs of focal disturbance (or global disturbance in the case of deep coma and subarachnoid hemorrhage) which lasted more than 24 hours or resulted in death, and for which there was no apparent cause other than a vascular accident. Signs and symptoms clinically suspected of subarachnoid hemorrhage, cerebral hemorrhage or cerebral infarction were included in this definition, but transient cerebral ischemia entered all patient information obtained on a standardized record form which was adopted from the standard WHO form, and then jointly determined whether or not the case met the criteria for a stroke sufferer. An attempt was made to diagnose the anatomical subtype of stroke: cerebral hemorrhage, cerebral infarction, or other strokes (subarachnoid hemorrhage and undetermined types). In Haguro (Population group ID 03), however, a differential diagnosis of subtypes was not made.

Table 2  Population by Sex and Age, The Japan Collaborative Study of Stroke (1975 Japan National Census)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Sex</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>8,586</td>
<td>5,415</td>
<td>3,422</td>
<td>17,423</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6,518</td>
<td>6,153</td>
<td>4,185</td>
<td>16,856</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>15,104</td>
<td>11,568</td>
<td>7,607</td>
<td>34,279</td>
</tr>
</tbody>
</table>
Table 3  Average Annual Number of Cases and Incidence Rates of Stroke Subtypes per 1,000 Population, The Japan Collaborative Study of Stroke, 1975-1979

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Sex</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>Total (40-69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
</tr>
<tr>
<td>All strokes</td>
<td>Male</td>
<td>13.87</td>
<td>21.12</td>
<td>33.68</td>
<td>68.67</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>4.90</td>
<td>12.45</td>
<td>25.15</td>
<td>42.50</td>
</tr>
<tr>
<td></td>
<td>Rate</td>
<td>1.62</td>
<td>3.90</td>
<td>9.84</td>
<td>3.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.16)</td>
<td>(1.93)</td>
<td>(1.64)</td>
<td>(1.56)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>Male</td>
<td>4.48</td>
<td>8.27</td>
<td>16.88</td>
<td>29.63</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.85</td>
<td>3.95</td>
<td>11.48</td>
<td>16.28</td>
</tr>
<tr>
<td></td>
<td>Rate</td>
<td>0.57</td>
<td>1.75</td>
<td>5.20</td>
<td>1.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.80)</td>
<td>(2.30)</td>
<td>(1.80)</td>
<td>(1.70)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>Male</td>
<td>6.85</td>
<td>5.23</td>
<td>7.82</td>
<td>19.90</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.35</td>
<td>3.22</td>
<td>4.17</td>
<td>8.73</td>
</tr>
<tr>
<td></td>
<td>Rate</td>
<td>0.24</td>
<td>0.62</td>
<td>1.05</td>
<td>0.59</td>
</tr>
</tbody>
</table>

No.: Average annual number of cases
Rate: Average annual incidence rate per 1,000 population
( ): Ratio of incidence rate for males to that for females
All strokes includes cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, and undetermined type of stroke.

Results
Among the 20 population groups a total of 477 patients (291 men and 186 women) were identified as having had a new stroke during the observation period. As shown in table 3, the average annual incidence of all strokes combined per 1,000 population aged 40-69 years was 3.94 for men and 2.52 for women, for cerebral infarction it was 1.87 for men and 1.10 for women, and for cerebral hemorrhage it was 1.26 for men and 0.59 for women. The age-specific incidence of all strokes, cerebral infarction and cerebral hemorrhage increased with age, being higher in men than in women. The sex differential was greatest for the age group of 40-49 years.

The sex-, age-standardized incidence ratio, SIR, was calculated in order to study the difference in the occurrence of stroke between the population groups. The expected number of cases was the sum of the products of the sex-, age-specific incidences in table 3 and the population by sex and age in each study group. As shown in figure 2, statistically high SIR for all strokes was observed in farming or mountain villages (Ishizawa:Population group ID 02, Haguro:03, Yakumo:13, Otoyo:16 and Nishimera:20) with the exception of Noichi (17), and low SIR in the occupational groups (Meguro:07, Osaka I:09 and Osaka II:10), suburban district (Yao:11), and fishing village (Uoshima:15).

In the present study, about 60-70% of stroke were hospitalized. Information on the special procedures, including CT and angiography, was available for these patients. However, the autopsy rate for all deceased patients fell short of 10%. Thirty to forty percent of the patients depended on clinical diagnoses consisting of the clinical histories and physical examinations. Therefore, the validity of these clinical diagnoses was studied. As for Ikawa (01), Ishizawa (02), Osaka I (09), Osaka II (10), Yao (11), Uoshima (15), Otoyo (16) and Noichi (17) in which the clinical diagnosis was done by the same investigators, a comparison of the antemortem clinical diagnosis with autopsy findings was made on 138 stroke patients and 127 non-stroke patients at a hospital in Akita, Japan. Ninety-

![Figure 2](https://stroke.ahajournals.org/)

**Figure 2.** Sex-, age-standardized Incidence Ratios (SIR) for Stroke Subtypes in 20 Population Groups, The Japan Collaborative Study of Stroke, 1975-1979
eight percent of the cases confirmed as having stroke by autopsy (135/138) and 97% of those confirmed as not having stroke (123/127) had been so designated by clinical diagnosis. Of the 47 cerebral infarctions, 83% had been diagnosed correctly using clinical judgment alone, as had been 71% of the 73 cerebral infarctions and 80% of the 15 subarachnoid hemorrhages.9 As for Akadani-Ijimino (04), a special case-control study was carried out on 143 strokes and 48 non-strokes admitted to a special hospital for stroke in Osaka. The subjects were assigned a diagnosis on the basis of clinical information only. This diagnosis was then compared to the diagnosis of the same individual following completion of CT, angiography and other special procedures. Ninety-seven percent of the patients confirmed as having stroke by CT plus diagnosis (139/143) and 98% of those confirmed as not having stroke (47/48) had been correctly diagnosed by clinical judgment. The rate of agreement between clinical diagnosis and confirmation by CT and others was 82% (61/74) for cerebral infarction, 86% (43/50) for cerebral hemorrhage and 90% (62/69) for subarachnoid hemorrhage.10 Similarly in Yachiho (06), a comparative study of clinical diagnosis with CT plus diagnosis indicated a correct diagnosis in 82% of 260 cerebral infarctions, 66% of 119 cerebral hemorrhages and 79% of 67 subarachnoid hemorrhages.11 The clinical diagnoses for other population groups were checked by means of stroke and
non-stroke reports of the patients admitted to a special hospital for stroke. These case reports were distributed to all stroke registry centers, which were asked to diagnose them in the same manner as they were doing for their own registers. These diagnoses were then compared with autopsy findings and considered to be adequate to identify stroke cases and subtypes. These results suggest that the level of accuracy for the current study is high and comparable with that seen in other countries.

Discussion

Japan has ranked first in international comparisons of the death rate from cerebrovascular disease for both men and women. However, several American investigators raised questions as to the diagnostic accuracy of stroke in Japan and suggested that the high mortality of stroke in Japan was nothing more than an artificial result of the diagnostic fashion.\(^\text{12, 13}\) Consequently, many Japanese epidemiologists have attempted to prove the validity of the clinical diagnosis of stroke. If deaths from cerebrovascular diseases are considered as a single entity, the clinical diagnosis in Japan has been shown to be highly adequate, while the accuracy for differentiating the subtypes of stroke is somewhat open to question.\(^\text{3, 11, 14-18}\) Accordingly, it has come to be taken as a fact that the mortality from stroke in Japan is higher than that in Europe and America.\(^\text{17}\) Death is a reasonable surrogate for incidence, however, only when the interval between occurrence and death is short and the disease has a high case fatality rate. Since stroke does not meet the major criteria for substitution of death rate for incidence,\(^\text{18}\) we have attempted, through an international comparison of the incidence rate, to study whether or not the frequency of stroke in Japan is high.

Although now more data on the incidence of stroke are available from many sources, there still are some difficulties in comparing the incidence between Japan and other countries. The methods of ascertainment, definition and classification of stroke differ from one study to another, and not many reports carry the sex-, age-specific incidences which are required to calculate the adjusted rate. Even if the age-specific incidence is mentioned, it is shown for age decades such as 45–54 and 55–64 in some studies and 40–49 and 50–59 in others. Some are of the community-based survey and others concern the hospital-based survey, although the latter can be used for comparisons if there are only one or two hospitals in the population group concerned and all the inhabitants receive medical consultation or treatment in these hospitals. In addition, some studies
include not only new patients but also patients with recurrent attacks in the numerator of the incidence rate. Accordingly, we have compared the results of the Japan Collaborative Study of Stroke with those of studies which used a comparable methodology.

The death rate from cerebrovascular disease has recently decreased in developed countries. 17-19 This declining trend accelerated around 1970. This was due to the downward trend in the incidence of stroke through the control of hypertension. Therefore, comparison has to be made as to strokes during the same periods. In this report, data are divided between those for 1960-1969 and those after 1970, although part of the data for the second half of the 1950s is included in the data for the 1960s.

Japan can be divided into 12 geographic regions (fig. 1). According to the standardized mortality ratio (SMR) for cerebrovascular disease by region, SMR is generally high in Tohoku, Kanto II and Hokuriku, low in Kinki I, and average in other regions. 17 As illustrated on the left side of figures 3-a (males) and 3-b (females), there was a large difference in stroke incidence during the period 1960-1969 between the population groups (Aomori, Ikawa and Yachiho) in Tohoku and Kanto II and those in Western countries, except for blacks in Evans County, U.S. 18-23 However, the incidence for clerical employees, blue-collar workers and physicians in Osaka (Kinki I) was on the same level as that for population groups in the U.S.

In addition to the data for Japan as a whole obtained from the Japan Collaborative Study of Stroke, those from the groups which not only reported the incidence of stroke in the 1960s but also participated in the Study are shown on the right side of figures 3-a and 3-b. In the 1970s, the incidence of stroke in Japan decreased to reach the level of that in countries from Europe and America in 1960-1969. In general, however, there still is a difference between Japan and Western countries even in the 1970s, 18-34 because the incidence in the latter appears to have fallen off from the 1960s to the 1970s, although the difference has become smaller. The rates in some Japanese population groups (males in Yachiho and Yao) where community intervention trials for stroke have been carried out since around 1960 are similar to or a little lower than those for European and American populations.

The incidence of not only cerebral infarction but also cerebral hemorrhage is generally higher in Japan.
than in Western countries (figs. 4 and 5). However, further studies are required to determine whether there exist any differences in the incidences of stroke subtypes between Japan and other countries. Data available are too few to make an international comparison of subtype incidences if the observation period is taken into account.

As shown in figure 2, many of the population groups (Population group ID 02, 03, 04, 05 and 08) in Tohoku, Kanto II and Hokuriku have an SIR for all strokes higher than 1. Although Iwao(01) and Yachino(06) belong to Tohoku and Hokuriku, the SIR is low, because the community intervention trial for stroke there has been actively implemented. On the other hand, Yakumo(13), Otoyo(16), Shiiba(19) and Nishimera(20) show the highest SIR for all strokes or cerebral hemorrhage despite their belonging to geographical regions where the mortality from cerebrovascular disease is average. In these population groups, people are adhering to the traditional Japanese dietary habits characterized by unbalanced diets (high in salt and carbohydrates, and low in animal fat and protein) which are considered to be associated with the risk of angionecrotic stroke occurring frequently in Japan. Furthermore, was it not until the second half of the 1970s that the stroke control program was introduced there.

**Epidemiological Study Group on the Relationship Between Stroke and Nutrition**

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NALOXONE is a well known and commonly used morphine antagonist. Recently several reports of other possible clinical uses for naloxone have been proposed. These include treatment for septic shock, hypovolemic shock, hypothermia, hypoxia, and spinal cord trauma. Our attention was caught by the dramatic report of reversal of cerebral ischemia in gerbils and in two humans. These workers report rapid (within 5 minutes) but temporary (less than 20 minutes) reversal of hemiplegia in two patients with subarachnoid hemorrhage. They noted a similar reversal of hemiplegia in experimentally induced stroke in gerbils. A subsequent report of naloxone reversal of hemiplegia has also emerged. However, Faden has noted a similar reversal of cerebral ischemia in gerbils and in two humans. These reports suggest that naloxone may offer promise as a treatment for cerebral ischemia. The present report describes the effects of naloxone on the neurologic status of 13 patients with acute stroke.

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