Factors Related to Stroke Incidence in Hawaii Japanese Men

The Honolulu Heart Study

ABRAHAM KAGAN, M.D., JORDAN S. POPPER, M.D.,
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SUMMARY As part of an ongoing longitudinal study of coronary heart disease and stroke among Japanese men in Hawaii, 8,006 men of Japanese ancestry living on the island of Oahu and aged 45–68 at entry examination have been followed by reexamination and surveillance. One hundred and eleven were found to have evidence of prior stroke at the time of the initial examination. During a six-year follow up period of the remaining 7,895 men, 94 developed definite thromboembolic stroke, 33 definite intracranial hemorrhage, and 6 developed stroke of unknown type. The principal risk factors for thromboembolic stroke were: elevated blood pressure, glucose intolerance, age, and electrocardiographic evidence of left ventricular hypertrophy or strain. Attributes associated with increased risk of intracranial hemorrhage were elevated blood pressure, electrocardiographic evidence of left ventricular hypertrophy or strain, and alcohol intake. Serum cholesterol level was negatively associated with risk of intracranial hemorrhage.

STROKE does not lend itself as readily to epidemiologic study as does coronary heart disease because the age of occurrence is usually greater, while the incidence and mortality rates are lower than in coronary heart disease. Therefore, for equivalent results, cohorts have to be larger or they have to be followed for longer periods of time, or else their entry into a study must come at a later age when response rates are lower or when "risk factors" lose their associative strength due to the overwhelming influence of age itself. Type specific diagnosis is more difficult because there are no pathognomonic laboratory tests corresponding to the electrocardiogram and specific enzyme tests for myocardial infarction, and there are no uniformly accepted indications for the performance of special diagnostic tests such as lumbar puncture, brain scan, angiography, computerized axial tomography (CAT), etc. Moreover, in fatal cases, even at autopsy it may be difficult to distinguish accurately between subarachnoid hemorrhage, due to ruptured aneurysm, primary hypertensive intracerebral hemorrhage and secondary hemorrhage into a thromboembolic cerebral infarction especially if there has been extensive destruction of brain and vascular structures. With ischemic cerebral infarction, it is often hard to be sure whether infarction is due to thrombosis or embolism.

Despite these difficulties, studies have been carried out or are under way, often in conjunction with studies of the epidemiology of coronary heart disease. The present report offers data on stroke incidence during 6 years of follow up of a cohort of Hawaiian Japanese men in a continuing study. The objective is to clarify the epidemiology of stroke and, particularly, to determine the differences, if any, in risk factors for specific types of strokes.

Background

Stroke mortality in Japan has declined since 1960. Investigators at the Atomic Bomb Casualty Commission (ABCC) have found that stroke mortality in Hiroshima and Nagasaki Prefectures, as well as stroke incidence and mortality in the cities of Hiroshima and Nagasaki, has also declined during that time. Men of Japanese ancestry in Hawaii and California have also shown a falling stroke mortality rate since 1960. Their mortality has fallen sharply from the experience in Japan to approximately the experience of Whites in Hawaii, which in turn, is close to that of Whites in the United States. In figure 1, mortality data for the year 1970 are shown for these several populations with rates age-adjusted to that of the age of the Hawaiian population in 1970.

When the ABCC mortality data were compared with those for the Hawaii and California cohorts in the same age groups, it was found that stroke mortality in Japan was 3 times that of the Japanese-American cohorts. Stroke prevalence also was compared in the 3 study sites and the ratios are remarkably similar to the mortality ratios.

A comparison of strokes found at first examination, subdivided into those due to infarction and those due to hemorrhage, shows that the great excess of strokes in Japan is due to infarction and nearly all of these were believed to be due to thrombosis. Caution is necessary in the interpretation of prevalence data for a disease with such a high mortality as stroke, particularly since the mortality from different types of stroke differs.

These findings of differences in stroke prevalence and mortality have been supported by an autopsy study which shows a greater frequency of cerebrovascular disease, both as an incidental finding and as a cause of death, in Hiroshima decedents than in
Honolulu decedents, with cerebral infarction found more frequently in Hiroshima than in Honolulu in a ratio of 2:1. 12

Methods

The Honolulu Heart Study is a prospective investigation of coronary heart disease and stroke in men of Japanese ancestry born in the years 1900–1919 and living on the island of Oahu in 1965. It was organized in conjunction with companion studies in Hiroshima and Nagasaki in Japan (at the ABCC, now renamed the Radiation Effects Research Foundation) and at the School of Public Health in Berkeley, with a common protocol to allow comparison of results. 13

In Honolulu, 8,006 men participated in a baseline examination during the period 1965–1968. The methods of study included self-administered questionnaires, interviews by dietitians, nurses, and doctors, physical examinations, electrocardiograms, and laboratory determinations including serum lipids, uric acid, and glucose, one h after a 50 g glucose load. In addition, there has been careful surveillance of hospital discharges for the occurrence of heart disease and stroke, a careful scrutiny of all death certificates of men belonging to the target population, and careful necropsy examination according to a prescribed protocol of those who have died and whose families permitted the examination.

Ninety-five percent of the survivors returned 2 years later for a second examination; and 90% of the survivors returned for a third examination 6 years following the first. A screening neurologic examination was part of each of the regular examinations. Although the neurologist did not participate in the first examination, he did review the available records of suspect men and judged whether cerebrovascular disease was present in order to delineate a population at risk for long-term follow up. The records reviewed included hospital charts, physicians’ office notes and the screening neurologic examination and nurse’s history. During the second and third examinations all those with histories or physical findings suggesting cerebrovascular disease were referred to the neurologist for timing of specific episodes and for definitive diagnosis according to the criteria outlined below. Most prevalence cases (i.e., those occurring before the first examination), as well as those incidence cases which had occurred between the first and second and between the second and third examinations, were examined by the neurologist at that time.

In addition to the routine examinations, careful and complete mortality surveillance was maintained throughout the period of follow up for the detection of deaths due to cerebrovascular disease. In all cases with definite and suspect diagnoses of cerebrovascular disease, death certificates, hospital and autopsy records were reviewed by the neurologist for his diagnosis. Careful surveillance was also maintained on Oahu hospital discharges and suspect stroke cases among Japanese men in the appropriate birth cohort were reviewed by the neurologist for a specific diagnosis according to the following criteria. Medical practice in Honolulu is such that virtually all patients with suspected stroke are hospitalized.

The diagnosis of definite stroke required the relatively sudden onset of a neurological deficit lasting at least 2 weeks (or until death) with and without the presence of blood in the cerebral spinal fluid. Stroke-like episodes attributable to other disease processes such as blood dyscrasias, neoplastic disease, head injuries, surgical accident, meningocoecephalitis, fat embolism, epilepsy or cardiac arrest were excluded. Definite strokes could usually be classified as thromboembolic or hemorrhagic on the basis of the clinical picture, findings at surgery, or autopsy. Computerized axial tomography was not available in Hawaii during the time period covered in this study. Focal neurologic deficits, usually without prolonged unconsciousness, nuchal rigidity, fever or pronounced leukocytosis, and in the absence of known bloody spinal fluid, were con-
sidered to indicate a thromboembolic event. Patients with intracranial hemorrhage were identified on the basis of focal neurologic deficits, headache, loss of consciousness, and bloody spinal fluid obtained from an atraumatic lumbar puncture or on the basis of surgical findings. Intracerebral hematoma was distinguished from subarachnoid hemorrhage by the presence of lateralizing signs or occasionally by the evidence of an aneurysm or a space occupying lesion from radiologic or ultrasonic studies in patients in deep coma.

Possible stroke was diagnosed when a neurological deficit of relatively sudden onset lasted at least 24 h but the exact duration was shorter than 2 weeks or of unknown duration, and there were no permanent residuals. Some patients with headache and meningeismus consistent with subarachnoid hemorrhage but with possibly traumatic or absent lumbar puncture were also included in this group. A number of these patients had inadequate or conflicting documentation in their hospital records. A few fatal cases without autopsy also fell into this group. Allocation of patients according to stroke type was made using the same criteria as for definite cases, but in a larger proportion of this group it was not possible to decide and these were considered to be possible stroke of unknown type.

Of the 8,006 men originally examined in the Honolulu cohort, 111 were believed to have had a stroke prior to their initial examination, and they were eliminated from the population at risk of stroke incidence. The remaining 7,895 men, aged 45-68 years at the time of entry examination, have been followed by the described re-examination and surveillance procedures.

In presenting the results we have used age-adjusted means calculated by the direct method. In figure 1, the population of Hawaii in 1970 was used as the standard, while in table 1 and in figures 3-7, the age distributions (at first examination) of the men sustaining a definite first stroke during the 6-year follow up period was used.

Results
Based on the neurologist's evaluation, in 6 years 133 new patients have been diagnosed as having a definite stroke, and an additional 49 are believed to have a possible stroke, for an overall average annual incidence for definite and possible cases combined of 3.8 per 1,000, and for definite cases only 2.8/1,000/year.

A division of the definite cases into subtypes (fig. 2) shows 94 (71%) due to thromboembolism, 14% due to intracerebral hemorrhage, and 11% due to subarachnoid hemorrhage. Four percent of the strokes were of unknown type. The incidence of definite cases was 2.0/1,000/year for cerebral infarction and 0.7/1,000/year for intracranial hemorrhage.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>No stroke Mean</th>
<th>Thromboembolic Mean</th>
<th>Hemorrhage Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity index</td>
<td>32.8</td>
<td>32.5</td>
<td>33.0</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>9.5</td>
<td>12.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>139.0</td>
<td>154.0</td>
<td>155.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>82.0</td>
<td>89.0</td>
<td>93.7</td>
</tr>
<tr>
<td>Back skinfold (mm)</td>
<td>16.0</td>
<td>17.0</td>
<td>16.1</td>
</tr>
<tr>
<td>Relative weight (%)</td>
<td>112.0</td>
<td>114.4</td>
<td>114.0</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44.5</td>
<td>45.3</td>
<td>44.2</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>217.0</td>
<td>221.0</td>
<td>199.3</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>6.0</td>
<td>6.01</td>
<td>7.0</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>166.1</td>
<td>192.8</td>
<td>157.0</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>222.3</td>
<td>204.0</td>
<td>201.0</td>
</tr>
</tbody>
</table>

*Age-adjustment constants: 45-49, .1203; 50-54, .2331; 55-59, .2105; 60-64, .2556; 65-69, .1805.
Stroke incidence increased with age. After age adjustment, the variables found to be related to the incidence of thromboembolic stroke were levels of blood pressure (fig. 3), of number of cigarettes smoked daily, of hematocrit (table 1) and of serum glucose after a 50 g glucose load (fig. 4). In addition, prevalence of coronary heart disease and the electrocardiographic (ECG) findings of left ventricular hypertrophy or strain (LVH/LVS), or nonspecific ST-T wave abnormalities were also related to thromboembolic stroke incidence in univariate analysis.

When these factors were combined in multivariate analyses, using the Walker-Duncan method, the risk factors retaining a significant association with the development of definite thromboembolic stroke were systolic blood pressure, age, serum glucose level, and the ECG findings of LVH/LVS. The other risk factors found in the univariate analysis no longer contributed significantly to risk in the multivariate analysis.

Standardized coefficients and t values are shown in table 1 for those variables tested in multivariate analysis, in which significant risk remained for at least one of the types of stroke. As in the case of coronary disease the presence of multiple factors magnified the risk (fig. 5). It is clear, however that the presence of hypertension was the preponderant risk factor (fig. 5b, table 2).

Attributes associated with increased risk of intracranial hemorrhage, using univariate analysis, were age, elevated blood pressure (fig. 3), alcohol consumption (fig. 6) and ECG evidence of LVH/LVS.

Elevated serum cholesterol level was associated with decreased risk of intracranial hemorrhage (fig. 7).

In multivariate analysis, significant risk factors for intracranial hemorrhage were systolic blood pressure, alcohol consumption, LVH/LVS on the ECG, and, inversely, serum cholesterol level. Relevant statistics are shown in table 1.

Discussion
From the carefully controlled previous collaborative studies, we can say with some confidence that the Japanese migrants to the United States, and their offspring, have a substantially lower prevalence and mortality from stroke than ethnically similar residents of Japan. Comparable incidence data are not yet available. The findings suggest some effect in the environment or in the lifestyle of Japanese-Americans acting protectively against stroke. There is, for example, a significant difference in fat and protein intakes as well as in serum cholesterol levels between indigenous and migrant Japanese populations while no substantial difference is found in blood pressure between the 2 populations. Our findings are consistent with the position of Kimura that “... protein and fat malnutrition is one of the risk factors of cerebrovascular disease.” Experimentally, the feeding of spontaneously hypertensive rats — stroke prone (SHRSP) with either high protein or high fat-high cholesterol diets has been shown to be associated with decreased stroke occurrence. Our findings do not support Ueda’s suggestion of a hereditary component in the Japanese propensity to stroke, manifested by the frequency of microaneurysms in cerebral arteries to which he attributes the frequency of cerebral hemorrhage. The lower prevalence of stroke in the migrants is the converse of the coronary heart disease findings in these cohorts.
The preponderance of cerebral infarction due to thromboembolism found in this study and in the previously reported prevalence studies\(^{21,22}\) is consistent with findings reported from other large-scale studies of Caucasians. Kurtzke\(^{1}\) combined stroke incidence data from community studies in Rochester, Minnesota\(^{2,22}\), Middlesex, Connecticut\(^{3}\), Goulburn, Australia\(^{2,23}\), Fargo, North Dakota\(^{2,24}\), Moorhead, Minnesota\(^{2,24}\), and Framingham, Massachusetts.\(^{4}\) He calculated the proportions of various types of stroke and these figures are compared in table 3. Our findings are also consistent with those from the Hisayama study in Japan.\(^{25}\)

Akinkugbe\(^{26}\) reported that stroke caused 12.1% of all deaths in Europe, North America and Oceania and 8% of all deaths in Africa, Asia and Latin America.

He reported that cerebral infarction is the commonest type of stroke in Africa and that intracranial hemorrhage seems to be more important in U.S. Blacks than in African Blacks.

**TABLE 2 Stroke Incidence Multivariate Logistic Function**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Thromboembolic Standardized Coefficient</th>
<th>Thromboembolic Standard Error</th>
<th>Hemorrhagic Standardized Coefficient</th>
<th>Hemorrhagic Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>0.445</td>
<td>5.04</td>
<td>0.537</td>
<td>3.70</td>
</tr>
<tr>
<td>Age</td>
<td>0.324</td>
<td>3.08</td>
<td>0.144</td>
<td>0.81</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.283</td>
<td>3.71</td>
<td>-0.355</td>
<td>-1.66</td>
</tr>
<tr>
<td>LVH/LVS</td>
<td>0.149</td>
<td>2.85</td>
<td>0.218</td>
<td>2.80</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-0.030</td>
<td>-0.28</td>
<td>0.203</td>
<td>2.63</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-0.032</td>
<td>-0.30</td>
<td>-0.380</td>
<td>-2.03</td>
</tr>
</tbody>
</table>

*\( T^{*} = \) Standardized Coefficient
A value of 2 or greater indicates statistical significance at \( p < 0.05 \).
It appears to be a universal finding among all stroke epidemiology studies that the single most important risk factor for stroke, whether of cerebral infarction or of intracranial hemorrhage, is hypertension. In addition, Paffenbarger, et al.,²⁷ in a study of California longshoremen, found heart disease and abnormal glucose metabolism as factors increasing stroke mortality. Heyman et al.,²⁸ in their report on the study of stroke in Evans County, Georgia, found risk factors for stroke, in addition to hypertension, were obesity, increased hematocrit and electrocardiographic abnormalities. In the Framingham study, Gordon and his colleagues²⁹ found, after blood pressure elevation, impaired cardiac function, electrocardiographic evidence of left ventricular hypertrophy, increased serum cholesterol level, impaired glucose tolerance and cigarette smoking as factors in the incidence of cerebral infarction.

The Framingham study reported a rising risk of stroke associated with decreasing blood pressure, the "hockey stick curve" for blood pressure relationships to stroke.³⁰ Our data do not show this curve for the relation between systolic blood pressure and incidence of brain infarction in men. We find rather, no significant deviation from a linear relationship between systolic blood pressure and the risk of stroke.

In a discussion of stroke risk factors, the epidemiologic study group headed by Stallones³⁹ also found age, cardiovascular disease and diabetes to be risk factors, in addition to elevated blood pressure.

Akinakuge³⁰ showed higher triglyceride levels in Nigerians with cerebral infaracts than among normal Nigerians. He also found diabetes to be a risk factor, in addition to high blood pressure. Kannel, et al.,³¹ found both beta and pre-beta lipoprotein levels related to brain infarction, with pre-beta not related when account was taken of the associated cholesterol levels; and, in any case, they indicated that "lipid influence(s) in the absence of other contributors is "feeble."

Gertler and his colleagues,³² in a case-control study, along with blood pressure, also found triglycerides to be an important risk factor in those with normal glucose tolerance tests, and in those with abnormal glucose tolerance tests, uric acid level seemed to be a risk factor, in addition. Bonsal, et al.,³³ in addition to high blood pressure, showed as risk factors for ischemic infarction the levels of serum triglycerides and pre-beta lipoproteins, and of uric acid in cases less than 40 years of age.

Among a few representative recent studies in Japan, in a survey of 2 villages in Akita Prefecture, one a fishing village, the other a farming village, Kamiyama, et al. found no appreciable difference in blood pressure.³⁴ The farm villagers had higher stature, lower weight, lower levels of serum cholesterol and a higher death rate from cerebrovascular disease than did the fishing villagers. No distinction was made in this study as between ischemic and hemorrhagic cerebrovascular disease. Konishi, et al.³⁵ found that 58% of patients with cerebral hemorrhage had serum cholesterol levels lower than 180 mg %, while only 39% of patients with cerebral infarction had serum cholesterol at that low level. Hirota et al. in an analysis of cerebrovascular disease from the Hisayama study³⁶ found age, hypertension, proteinuria, and electrocardiographic evidence of high amplitude R and depressed ST segments, as risk factors for stroke. They found no association with serum lipid levels. Komachi et al.,³⁷ comparing 10 population groups in Japan, found a positive correlation between prevalence of hypertension and mean intake of NaCl and the incidence of stroke. They also found a negative correlation between mean total serum cholesterol levels and the incidence of strokes, both cerebral hemorrhage and cerebral infarction.

Brust,³⁸ in an angiographic study of cerebrovascular disease in different ethnic groups in Hawaii, found more extracranial disease, defined as 50% or greater stenosis or occlusion of the neck arteries, among Caucasians than among Japanese. The Japanese ratios of extracranial to intracranial arterial disease differed from the Caucasian ratio significantly at p < .05. He reported a decreasing ratio of intracranial to extracranial disease going from Issei (first genera-
tion Japanese) to Nisei (second generation Japanese) to Caucasians. This is suggestive evidence supporting the finding in Ni-Hon-San study autopsy material of less small vessel disease in Hawaii Japanese compared to Hiroshima Japanese.

The findings based on multivariate analysis of our data of significant risk factors for thromboembolic stroke, of elevated blood pressure, increasing age, serum glucose level, and ECG evidence of LVH/LVS, are consistent with findings from the cited epidemiologic studies. With regard to the risk factors for intracranial hemorrhage, the findings of a relation to systolic blood pressure level, and to ECG evidence of LVH/LVS are consistent with previous studies in Caucasian populations. However, the finding of an inverse relationship of risk of hemorrhage to the level of serum cholesterol has not been reported in Caucasian populations, although, as noted above, it has been reported in studies of other Japanese cohorts.

It has been suggested by Kuller and his colleagues that populations with a high prevalence of hypertension and low lipid levels (for example, Japan) would tend to have a higher ratio of intracranial, both thromboembolic and hemorrhagic, to extracranial cerebrovascular disease. This hypothesis is supported by the findings of Heyman, et al. in Evans County. It is further supported by findings in Honolulu and Hiroshima, if instead of contrasting extracranial and intracranial arterial disease we make the distinction between large vessel disease (neck arteries and circle of Willis) and small vessel disease (penetrating intraparenchymal arteries).

The principal risk factors about which there seems to be general agreement in all these epidemiologic studies have been elevated blood pressure and cardiac abnormalities, especially left ventricular hypertrophy. It is not clear whether the increased risk associated with left ventricular hypertrophy is simply due to the fact that this finding represents hypertension of greater severity or of longer duration, or both, or whether the finding is associated with other manifestations of cardiac dysfunction such as congestive heart failure. Factors which have been inconsistent in their relation to risk of cerebral infarction include glucose intolerance, elevated lipids, elevated hematocrit, and cigarette smoking.

There is also consistency in the finding of elevated blood pressure and ECG abnormality as risk factors for cerebral hemorrhage. Needing further confirmation is the suggestion that alcohol intake and lower levels of serum cholesterol may be associated with increased risk of cerebral hemorrhage. Alcohol intake could, presumably, act through its relation to blood pressure elevation, or possibly through a hypocholesterolemic effect of malnutrition in heavy drinkers, or by an independent effect of alcohol per se due to some unknown mechanism.

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Incidence of Transient Cerebral Ischemic Attack in Hawaii Japanese Men

The Honolulu Heart Study

GEORGE G. RHOADS, M.D., JORDAN S. POPPER, M.D., ABRAHAM KAGAN, M.D., AND KATSUHIKO YANO, M.D.

SUMMARY At the Honolulu Heart Study 7,895 men of Japanese ancestry, 45-68 year-old, who were free of previous stroke at the baseline examination (1965-1968) were followed 6 years for the development of transient cerebral ischemic attacks (TIA). Fifty-one men developed probable or possible episodes. In multivariate analysis TIA was associated with preceding hypertension, cigarette smoking and coronary heart disease. It was less common in men who were facile with written Japanese language, in those who consumed alcohol, and in those who were physically active. During an average follow up of 3 years after these TIA events 2 strokes occurred, vs 0.7 expected. This prognosis is more favorable than that reported by other studies.

Stroke, Vol 11, No 1, 1980

THE EPIDEMIOLOGY of transient cerebral ischemic attack (TIA) has been examined in different settings and recently reviewed.1 Studies in which patients are interviewed after cerebral thrombosis suggest that 35–50% have premonitory transient symptoms, usually occurring within a few months of their stroke.2,3 At face value these reports imply that the incidence of TIA in the community is nearly as large as the stroke incidence, considering that some transient episodes are not followed by stroke. Such reports are difficult to interpret, however, since both the patient and the interviewer are acutely aware of the stroke. How many ostensibly healthy older people would recall suggestive neurologic symptoms if questioned in detail under similar circumstances is not known.

A second approach is to identify patients with TIA who come to selected medical facilities for care. Only more definite episodes are identified in these studies since the symptoms must be severe enough to cause...
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Stroke. 1980;11:14-21
doi: 10.1161/01.STR.11.1.14

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

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