A cohort study is one of the most important methods of investigating epidemiologically the etiological significance of possible risk factors on the occurrence of stroke. The Adult Health Study of the Radiation Effects Research Foundation, which began in 1958 under the aegis of the Atomic Bomb Casualty Commission, is one of a series of epidemiologic studies of the late effects of exposure to ionizing radiation on the atomic bomb survivors in Hiroshima and Nagasaki. This cohort study provides a wealth of information on changes in the incidence over time in cardiovascular diseases, including ischemic heart disease and stroke.

When the study began, the population at risk of a stroke was about 16,500 individuals who were free of cerebrovascular disease at the time of their first medical examination. During 26 years of follow-up, 865 cases of definite or probable strokes have been ascertained. When the cases were classified into strokes arising from cerebral hemorrhage, on the one hand, and cerebral infarction, on the other, age-adjusted incidence rates revealed a declining trend for both types, but especially for cerebral hemorrhage. The results of a multivariate analysis of risk factors showed that hypertension was the most significant predictor of stroke. It appears, however, that stroke occurrence in Japan varies with life style changes in accordance with the results from a comparative study of Japanese men living in Japan and in Hawaii.

**INTRODUCTION**

In Japan, as national statistics reveal, stroke has been one of the leading causes of death for a long time\(^1\). Although stroke mortality has declined markedly since the 1970's, its prevention remains one of the nation's major health issues since the total number of deaths due to stroke exceeds 100,000 per year. This decline in stroke deaths has generally been attributed to changes in the Japanese life style that have accompanied economic success, that is, improved dietary
habits, reduced work load, better housing, and so on. Another important contributor, however, has been the success of advances in methods, clinical and public health, of controlling high blood pressure levels in the Japanese population.

It is well-known that there is some difference in the view of clinicians and public health persons as to the trend in occurrence of coronary heart disease. Clinicians claim that heart disease is still rising in frequency whereas epidemiologists believe this is no longer so. This difference in point of view may merely reflect the fact that the population of Japan has been aging dramatically and with this aging has come an increase in the number of patients with coronary heart diseases. But it does not follow from this that age-specific rates are continuing to change. Another possible interpretation is a time-dependent change in case fatality rate for coronary heart disease which is then reflected in a difference between disease occurrence and mortality. Although there is no difference in point of view regarding stroke occurrence, a longitudinal or a cohort study which can provide incidence data is essential to confirm the apparent declining trend in stroke mortality.

Strokes can be clinically categorized into four major types, namely, cerebral infarction (thrombo-embolic attack), cerebral hemorrhage, subarachnoid hemorrhage, and "undetermined". The national statistics of Japan show a decline in age-adjusted mortality for both cerebral infarction and cerebral hemorrhage, but the decline is more rapid for the latter. It is important to know whether a similar trend is seen in the incidence data.

An analysis of the association between stroke and possible risk factors is another interesting issue which can contribute importantly to the assessment of the role of environmental factors in disease occurrence. The Adult Health Study is one of the oldest cohort studies of cardiovascular diseases in Japan\(^{(2)}\). The authors will describe the design of this longitudinal study and briefly review some of the results obtained.

**STUDY DESIGN**

At the Radiation Effects Research Foundation (formerly, the Atomic Bomb Casualty Commission, ABCC), a number of epidemiological studies are being conducted to investigate the late effects of exposure to ionizing radiation on the atomic bomb survivors in Hiroshima and Nagasaki. One of these is a cohort study with approximately 20,000 individuals in which efforts to detect the occurrence of certain diseases have been continued since 1958, mainly by means of biennial clinical examinations. As a part of this study, the presence of cardiovascular or cerebrovascular diseases is routinely recorded. Figure 1 shows the size and design of the cardiovascular disease incidence study. The population at risk of stroke in this incidence study was initially 16,491 individuals who underwent medical examination at least once and who were free of stroke at the first examination. To determine the incidence rate, they have been followed until the time disease occurred, their last examination took place, or death intervened. For the case ascertainment, all medical records were reviewed when there was an indication of stroke from any one or more of the following sources: clinical diagnosis, death certificate, or autopsy findings, regardless of the principal diagnosis. Since participation rates in the Adult Health Study are fairly high (75–85\%) and virtually all death certificates can be obtained, there are few, if any, stroke cases that are missed. In the review of the medical records, fixed, detailed criteria were used which were applicable over the entire study period. Strokes were classified into four clinical categories: cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, and undetermined. The diagnostic criteria for the classification by type have been described elsewhere\(^{(3,4)}\). Briefly, the clinical diagnosis of a stroke
required a history of an abrupt onset of localized neurologic deficit (e.g., hemiparesis or aphasia) with confirming signs on physical examination. A death certificate diagnosis of cerebrovascular disease was not accepted unless there was confirming clinical evidence such as hemiplegia. In reviewing the autopsy records, simple lacunae were not considered evidence of stroke.

**CHARACTERISTICS OF STROKE**

During the 26-year follow-up period from 1958 to 1984, 865 cases were ascertained as newly occurred stroke cases with high certainly. Based upon the types of stroke, 148 cases were diagnosed as cerebral hemorrhage, 644 as cerebral infarction (either cerebral thrombosis or cerebral embolism), 25 as subarachnoid hemorrhage, and 48 as undetermined type, respectively. When the person-year method was used to calculate age-specific incidence rates, both cerebral hemorrhage and cerebral infarction were observed to increase with age from ages younger than 40 to ages older than 70. The rise in the age-adjusted incidence rate was sharper for cerebral infarction. This finding suggests that the pathogenesis of cerebral infarction is more closely related to the biological changes associated with aging than cerebral hemorrhage. Age-adjusted incidence rates for cerebral hemorrhage and cerebral infarction were both higher in men than women, although the gender difference was more apparent for the latter type of stroke. The trend in gender difference for cerebral infarction is similar to that for myocardial infarction where the incidence in men is more than two time higher than in women. Other epidemiological studies in Japan have shown a similar gender difference for stroke by which we infer that men are more susceptible to arteriosclerotic diseases than women at the same chronological age.

National statistics of Japan show that in the 1950's mortality for cerebral hemorrhage greatly exceeded that for cerebral infarction, and the mortality ratio (cerebral hemorrhage/cerebral infarction) was over ten. The decline in mortality for cerebral hemorrhage was more rapid thereafter than for cerebral infarction, hence the mortality ratio fell to less than...
1.0 in the late 1970's. Since our study population tends to be older than the general Japanese population, the incidence of cerebral infarction was consistently higher than cerebral hemorrhage when age-adjusted incidence rates were calculated by the person-year method (Figure 2). Another interpretation of this finding lies in the difference in case fatality rate between these two types of stroke; the fatality rate for cerebral hemorrhage is known to be higher. However, the age-adjusted incidence rates revealed a clearly declining trend for both types of strokes, but especially so for cerebral hemorrhage. There is, however, the possibility of some underestimation of cases with mild stroke where no unilateral neurological deficit is seen and where the diagnosis can only be made by CT scanning. The results of studies of the occurrence of dementia and of long-term survival after the first event of stroke revealed a significant difference in these outcomes by age at onset.

Figure 2 Temporal change in age-adjusted incidence rate for cerebrovascular disease (Hiroshima/Nagasaki Study)

<table>
<thead>
<tr>
<th>Year</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970</td>
<td></td>
<td></td>
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<tr>
<td>1980</td>
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</tbody>
</table>

Cl: Cerebral Infarction, CH: Cerebral Hemorrhage

RISK FACTORS AND STROKE

Many epidemiological studies have shown hypertension to be a risk factor for stroke. We too have reported a strong association between blood pressure level and stroke incidence in our study group(3). A univariate analysis showed the risk of cerebral hemorrhage to be relatively higher the higher the systolic blood pressure. Although the risk of cerebral infarction also increased with elevation of systolic blood pressure, the association was less striking. As in the case of systolic blood pressure, the incidence of cerebral hemorrhage increased markedly with elevation of diastolic blood pressure. The incidence of cerebral
infarction also increased with increasing diastolic blood pressure, but the relative risk was smaller when compared with cerebral hemorrhage. The results of a multivariate analysis of risk factors, including blood pressure, serum cholesterol, hematocrit, body mass index, smoking habits, alcohol intake, proteinuria, glycosuria, left ventricular hypertrophy as revealed by an electrocardiogram, age, and sex as covariates, revealed diastolic blood pressure to be an independent risk factor for cerebral hemorrhage. In a similar analysis, systolic blood pressure exhibited a stronger association with cerebral infarction than diastolic pressure. However, blood pressure measured at one time is not necessarily sufficient for predicting stroke. It has been reported that the risk of stroke among individuals, whose blood pressures at one point in time were the same but at another point in time were not, was different. Shimizu et al. have examined the relationship of changes in blood pressure with time to stroke incidence in our cohort. The regression coefficient of blood pressure on time (the increase of blood pressure per cycle) was used as an index of the temporal change in blood pressure. Cox’s regression, a technique which is applicable for follow-up studies, was used. The data suggested that a single blood pressure measurement was not sufficient for predicting risk; the individual values accumulated over time or the average over a period of time should be considered for this purpose. In addition to actual blood pressure, the extent of the increase in blood pressure with time was a risk factor, particularly for cerebral hemorrhage.

It has been reported, with regard to serum cholesterol level and development of cerebral hemorrhage, that the increase of cerebral hemorrhage was high in the group with the lowest serum cholesterol values. In our population, Lin et al. have reported that the risk was high in males in the high and low cholesterol groups. In a multivariate analysis, however, serum cholesterol was negatively correlated with the occurrence of cerebral hemorrhage and the effect of cholesterol on the development of cerebral hemorrhage was greater the lower the cholesterol level. A similar inverse relation between serum cholesterol level and the risk of death from hemorrhagic stroke has been seen in middle-aged American men. No significant correlation was found for any serum cholesterol level in males or females insofar as the occurrence of cerebral infarction is concerned.

Many studies of stroke in Japan have failed to find a significant relationship between serum cholesterol and cerebral infarction, whereas studies of American populations have frequently described a positive relationship. This difference might reflect a difference in pathogenesis in cerebral thrombosis attributable to dietary variation which will be described in more detail in the following paragraph. Marked changes in life style, including dietary habits, have occurred in Japan during the last few decades, and these changes may be reflected in biological measurements such as blood pressure and serum cholesterol. In our cohort, average serum cholesterol level has increased more than 20 mg/dl in almost all age groups. This could contribute to the temporal change in the risk factor and stroke association. An analysis of the temporal changes in the association derived by risk factor modification is underway in our population, and preliminary results show a slight variation in cholesterol and stroke association. The role of variables other than blood pressure and serum cholesterol have also been examined and the results from a multivariate analysis indicate that stroke incidence is related to the level of the following variables: age, proteinuria, left ventricular hypertrophy in the electrocardiogram, diabetes and so on.
It has been well-established that mortality from ischemic heart disease in Japan is low when compared with that in the United States and, conversely, that mortality from stroke is higher in Japan. When this difference was first recognized, it was uncertain whether it was attributable to genetic or environmental factors. In order to examine the relationship of ischemic heart disease and stroke to environmental factors, a large-scale epidemiologic cohort study (known as the Ni-Hon-San Study) was initiated in 1965 on males in Japan (some of the Hiroshima/Nagasaki cohort) and Japanese-American males residing in Hawaii and in the San Francisco Bay Area of California. It was assumed that, on average, the genetic differences between these groups would be small; whereas it was known that the variation in environmental and life style factors was large\(^{(13,14)}\). The life style of the Japanese have become progressively more similar to those in "western" countries, and hence the results obtained in this comparative study might provide important insights into the occurrence of cardiovascular diseases among the Japanese in the future.

Figure 3 summarizes the findings of this study. The incidence of coronary heart disease was lower in Japan where it was half that observed in Hawaii\(^{(14)}\). The incidence of strokes, classified into two types, cerebral hemorrhage and cerebral infarction (thrombo-embolic stroke), was also compared \(^{(13)}\). For each type the incidence in Japan was about three times as great as that in Hawaii. Blood pressure was the most important single risk factor, followed by age for strokes regardless of type in both Japan and Hawaii. Since blood pressure levels did not differ between Japan and Hawaii, one possible explanation for the large difference in stroke incidence between the two cohorts may lie in the fact that the intake of animal protein and saturated fat, which is inversely associated with stroke incidence, is much greater in Hawaii than in Japan. This explanation finds support in epidemiologic and experimental studies in Japan which suggest that dietary animal protein and fat exert an inhibitory effect on the incidence of stroke. Pathological studies of cerebrovascular lesions have revealed small vessel sclerosis and atherosclerosis of the circle of Willis to be the two major causes of cerebral infarction, but the frequency of small vessel sclerosis was higher in Japan while atherosclerosis of the circle of Willis was more severe in Hawaii\(^{(15)}\). Small vessel sclerosis appeared to be more closely related to cerebral infarction than atherosclerosis. And this may be the explanation for why the incidence of cerebral infarction is higher in Japan than in Hawaii.

Finally, we believe epidemiologic and clinico-pathological studies of stroke in the Japanese population should be continued in the light of the association of the occurrence of stroke with life style. We further note that during the period of observation in Hiroshima and Nagasaki marked time-dependent changes have occurred which make this cohort uniquely applicable to the situation in other developed countries.
FOLLOW-UP STUDY OF STROKE

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