An Epidemiological Analysis of Cardiovascular Diseases in Okinawa, Japan

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The purpose of the present study is to determine accurate incidence rates of stroke and acute myocardial infarction among the residents in Okinawa, where the census population was 1,222,398 in 1990 and mortality due to cerebrovascular and heart diseases is lowest in Japan. A co-operative study group including almost all hospitals and clinics in Okinawa was established for the survey. Between April 1, 1988 and March 31, 1991, 4,756 cases of stroke and 1,059 cases of acute myocardial infarction were identified. The average age-adjusted annual incidence per 100,000 population was 137 for stroke and 31 for acute myocardial infarction. In the population aged 40 years and older, the respective values were 315 and 72, indicating the stroke incidence to be 4.4 times higher than that of acute myocardial infarction. The incidence ratio for men to women was 1.7: 1 for stroke and 2.9: 1 for acute myocardial infarction. Among stroke cases, 51.3% were diagnosed as cerebral infarction, 35.7% as cerebral hemorrhage, 7.7% as subarachnoid hemorrhage and 5.3% as others. Computed tomography of the head was performed in 98.4% of all stroke cases. The case ascertainment, evaluated by comparing the registered cases and death certificates in a certain city, was almost complete. The incidence of acute myocardial infarction is still much lower than that of stroke in Japan. (*Hypertens Res* 1992; 15: 111-119)

Key Words: stroke, myocardial infarction, morbidity, epidemiology

Heart disease and cerebrovascular disease are the second and third leading causes of death in Japan, respectively. Mortality due to stroke has decreased in Japan sharply since the 1970's, while the death rate from heart disease has increased, exceeding stroke mortality in 1984 (1, 2). A population-based study in a rural area of northern Japan, however, indicated that in the survey population the 5-year incidence of ischemic heart disease was not increasing and, was much less than that of stroke, which declined by 60% between 1964-1968 and 1979-1983 (3).

Stroke and ischemic heart disease are leading causes of disability. The proportion of elderly people has increased markedly in Japan. It is predicted that about 24% of the total population will be comprised of men and women aged 65 years or older in 2020 (1). Owing to this rapid increase in the aged population, cardiovascular disease will inevitably cause even greater disability and death.

Accurate data on cardiovascular disease including the incidence, outcome and risk factors will greatly contribute to the prevention, treatment and development of appropriate health care facilities.

We conducted this epidemiologic study of stroke and acute myocardial infarction on the subtropical islands of Okinawa where the life expectancy of residents is longest and death rates for cardiovascular diseases are lowest in Japan (1).

Okinawa prefecture is located in the southwest part of Japan (Fig. 1). It is composed of more than 100 islands. People inhabit on the 4 main islands and about 35 smaller islands.

As Okinawa is surrounded by the sea and far from the main islands of Japan, patients with stroke or acute myocardial infarction never move from Okinawa, at least in the acute stage, and they are admitted to a regional central hospital which is equipped with modern apparatus including facilities for computed tomography (CT). Patients suffering stroke or acute myocardial infarction on an isolated, small island are usually transferred by aircraft and admitted to a central hospital on a neighboring island. This "self-enclosed" situation of Okinawa facilitates the procurement of accurate data on the incidence of the cardiovascular disease to an extent not possible in other areas in Japan.

Subjects and Methods

The study population was comprised of all residents in Okinawa. The Census population in 1990 was 1,222,398 (Fig. 2) and 68% of all inhabitants were

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Received and accepted September 4, 1992.

Fig. 1. Okinawa is located in the southwest part of Japan and composed of more than 100 islands. People live on 4 main and about 35 smaller islands.

living in urban areas. Patients who suffered stroke or acute myocardial infarction between April 1, 1988 and March 31, 1991 in Okinawa were registered. Cases with silent myocardial infarction and recurring attacks were included.

Patient registration was achieved through the cooperation of all main hospitals, private hospitals and clinics registered to the Okinawa Medical Association, public health centers and the Environmental and Health Department of the Okinawa Prefectural Government. The study physicians regularly visited these main hospitals where the patients were supposed to be admitted, and investigated medical records, electrocardiograms, laboratory data and CT films. They also visited other medical facilities and carried out similar investigations when informed that the cases had been registered there.

Stroke cases were identified according to the criteria of the Ministry of Health and Welfare (4). Criteria for identification of acute myocardial infarction were similar to those used in the MONICA project (5), and both definite and possible myocardial infarction were included. Death within 30 days after onset was defined as acute death.

Evaluation of Case Ascertainment

To evaluate the completeness of the case ascertainment, we reviewed death certificates which had been issued during the study period and related to stroke or acute myocardial infarction in a certain city with a population of 41,245. The death certificate data were compared with the data for the corresponding cases registered in this study.

Fig. 2. Age and sex distribution of the residents in Okinawa. Census population of Okinawa was 1,222,398 (598,669 men and 623,729 women) in 1990.

Statistical Analysis

Crude annual incidence rates were calculated using the census population of Okinawa in 1990 (6). Age-adjusted annual incidence rates were determined by the direct method using the standard population which was derived from the census population of Japan in 1985 (7). Mean ages were expressed as

mean values $\pm$ 1SD. The differences of mean age and case-fatality rates between subgroups were examined using normal distribution. The difference of mean age among the subtype of stroke was tested with one-way analysis of variance. Seasonal variations in the occurrence of stroke and acute myocardial infarction were also examined. The distribution of the number of cases was first tested for differences among 3-month intervals of the year with chi-square test for the goodness of fit. If this test showed significant differences, the period with the highest or lowest frequency was tested to evaluate its difference from the average of the other three periods. A *p* value of less than 0.05 was considered significant.

Results

Incidence of Stroke and Acute Myocardial Infarction

The annual numbers of cases registered were generally constant for both stroke and acute myocardial

infarction (Fig. 3).

During the study period, 4,756 cases (2,573 men and 2,183 women) of stroke were identified. The age was unknown in three cases, consisting of one male and two females with cerebral infarction. Nine-hundred fifty-nine cases (20.2%) were confirmed to be recurrent at the first registration. The average crude annual incidence rate of stroke was 130 per 100,000 population for both sexes (143 for males and 117 for females), and the male:female ratio was 1.2: 1 (Table 1). The average age-adjusted annual incidence rate of stroke was 137 for both sexes (180 for males and 105 for females), and the male: female ratio was 1.7: 1.

In total, 1,059 cases of acute myocardial infarction were registered, of which 695 were male and 364 were female. One-hundred fifty-nine cases (15.0%) were recurrent at the first registration. The average crude annual incidence rate of acute myocardial infarction was 29 per 100,000 population for both sexes (39 for males and 20 for females), and

Fig. 3. Cumulative number of cases by age in each year. The numbers of cases with stroke and acute myocardial infarction were 1,584 and 327 in the first year, 1,618 and 381 in the second year and 1,554 and 351 in the third year, respectively. AMI: Acute myocardial infarction.

Table 1. Average Annual Incidence Rate of Stroke and Acute Myocardial Infarction per 100,000 Population

	Crude				Age-adjusted			
	Total	Male	Female	M/F	Total	Male	Female	M/F
Stroke	130	143	117	1.2	137	180	105	1.7
cerebral infarction	66	77	56	1.4	73	99	48	2.1
cerebral hemorrhage	46	52	41	1.3	49	63	38	1.7
subarachnoid hemorrhage	10	6	13	0.5	11	8	14	0.6
others	7	8	6	1.3	7	10	5	2.0
Acute myocardial infarction	29	39	20	2.0	31	49	16	3.1

M, Male; F, Female. Census population of Okinawa in 1990: 1, 222, 398 (Male: 598, 669, Female: 623, 729). Standard population: 120, 287, 000. Stroke/Acute myocardial infarction (Age-adjusted): 4.4 (Male: 3.7, Female: 6.6).

Table 2. Average Annual Incidence Rate of Stroke and Acute Myocardial Infarction per 100,000 Population Aged 40 Years and Older

	Crude				Age-adjusted			
	Total	Male	Female	M/F	Total	Male	Female	M/F
Stroke	337	394	289	1.4	315	417	241	1.7
cerebral infarction	176	217	142	1.5	173	233	112	2.1
cerebral hemorrhage	119	139	101	1.4	113	144	87	1.7
subarachnoid hemorrhage	24	15	32	0.5	24	16	30	0.5
others	18	22	14	1.6	17	24	12	2.0
Acute myocardial infarction	76	107	50	2.1	72	113	39	2.9

Census population aged 40 years and older: 452, 347 (Male: 209, 149 Female: 243, 198). Standard population aged 40 years and older: 50, 412, 000. Stroke/Acute myocardial infarction (Age-adjusted): 4.4 (Male: 3.7, Female: 6.2).

Table 3. Average Annual Age-Specific Incidence Rate per 100,000 Population

Age group	Stroke		AMI	
	Male	Female	Male	Female
0-29	4	2	0	0
30-39	24	18	6	1
40-49	97	65	36	2
50-59	322	173	95	15
60-69	553	273	160	50
70-79	1027	632	261	135
80-	1319	922	221	185

AMI: Acute myocardial infarction

the male: female ratio was 2.0: 1 (Table 1). The average age-adjusted annual incidence rate was 31 for both sexes (49 for males and 16 for females), and the male: female ratio was 3.1: 1.

As the number of patients with stroke or acute myocardial infarction under the age of 40 years was very small, we calculated the incidence per 100,000 population aged 40 years and older. The average crude annual incidence rate for both sexes was 337 for stroke and 76 for acute myocardial infarction and the ratio of stroke to acute myocardial infarction was 4.4: 1 (Table 2). The average age-adjusted annual incidence rate for both sexes was 315 for stroke and 72 for acute myocardial infarction and the ratio of stroke to acute myocardial infarction was 4.4: 1 (Table 2).

Stroke

Overall, the occurrence of stroke became prominent from the fifth decade of age, increased steeply with age, and peaked in the eighth decade (Fig. 3). In males, peak occurrence was in the sixth and seventh decades, while it was in the eighth decade in females (Fig. 4). The average annual age-specific incidence rate per 100,000 population increased with age and peaked in the ninth decade and older in both sexes (Table 3). Among the patients with

stroke, 51.3% were diagnosed as cerebral infarction, 35.7% as cerebral hemorrhage, 7.7% as subarachnoid hemorrhage and 5.3% as others, which included undefined types of stroke and transient ischemic attacks. CT was performed in 98.4% of stroke cases. The average age-adjusted annual incidence rate of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage and others were 173, 113, 24 and 17 per 100,000 population of age 40 years and older, respectively. The male: female ratios for each subtype of stroke were 2.1 for cerebral infarction, 1.7 for cerebral hemorrhage, 0.5 for subarachnoid hemorrhage and 2.0 for others (Table 2).

The mean age of stroke patients was 66.6 ± 14.3 years; it was 64.3 ± 13.7 years for males and 69.3 ± 15.5 years for females and the difference was significant ($p < 0.0001$). The mean ages of the patients with cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage and others were 69.9 ± 12.8 , 63.4 ± 15.0 , 59.1 ± 15.2 and 67.6 ± 13.6 years, respectively. The difference among these values was significant ($p < 0.001$). Mean age was lowest in the patients with subarachnoid hemorrhage and highest in those with cerebral infarction. The mean age of females was significantly higher than that of males in all stroke ($p < 0.0001$) as well as in every subtype of stroke, *i.e.*, 72.3 ± 12.4 vs. 67.6 ± 12.6 in cerebral infarction ($p < 0.0001$), 66.9 ± 15.5 vs. 60.6 ± 13.9 in cerebral hemorrhage ($p < 0.0001$), and 60.9 ± 15.0 vs. 55.2 ± 14.9 in subarachnoid hemorrhage ($p < 0.01$). The ratio of cerebral infarction to cerebral hemorrhage was 1.4: 1 (1.5: 1 for males and 1.4: 1 for females). Under the age of 60 years, cerebral hemorrhage was more common than cerebral infarction. However, cerebral infarction predominated in the seventh decade and older (Table 4).

Acute Myocardial Infarction

Among 1,059 patients registered, 916 patients were diagnosed as "definite" acute myocardial infarction and 143 patients as "possible" acute myocardial infarction. Electrocardiograms taken at the acute phase could be reevaluated by the study physicians

Table 4. The Ratio of Cerebral Infarction to Cerebral Hemorrhage

Age group	Both sexes	Male	Female
0-29	0.3	0.2	0.4
30-39	0.6	0.6	0.6
40-49	0.6	0.7	0.5
50-59	0.8	1.0	0.6
60-69	1.6	1.6	1.4
70-79	2.3	2.6	2.1
80-	2.1	2.7	1.8
Total	1.4	1.5	1.4

in 938 cases. Six-hundred thirty of these cases (67.2%) were Q wave infarction and 308 (32.8%) were non-Q wave infarction. The infarction site could be determined in 895 cases. Among them, 51.6% were anterior wall, 41.2% were lateral wall, and 7.2% were inferior and/or posterior wall.

The occurrence of acute myocardial infarction became prominent from the fifth decade of age, increased steeply with age and peaked in the sixth and seventh decades in males. In females, it became remarkable from the sixth decade and peaked in the eighth decade (Fig. 4). The mean age of the patients was 66.4 ± 14.3 years for both sexes. It was 62.5 ± 12.7 years for males and 73.9 ± 10.9 years for females, and the difference was significant ($p < 0.0001$). The mean age of all patients with acute myocardial infarction did not differ from that of patients with stroke ($p > 0.33$). The average annual age-specific incidence rate per 100,000 population increased with age and peaked in the eighth decade in males and in the ninth decade and older in females (Table 3).

Acute Death

Five-hundred eighty-five of 4,756 patients with stroke (12.3%) and 242 of 1,059 patients with acute myocardial infarction (22.9%) died within 30 days after onset. The mean ages of cases suffering acute

death were 67.3 ± 16.4 years old (64.0 ± 16.1 in males, 70.8 ± 16.1 in females) in stroke and 73.2 ± 11.9 years old (69.2 ± 12.0 in males, 77.9 ± 10.0 in females) in acute myocardial infarction. Mean age differed significantly between the cases with stroke and acute myocardial infarction ($p < 0.0001$) and between males and females for both diseases ($p < 0.0001$) and among the subtypes of stroke, i.e., 74.5 ± 11.7 vs. 78.3 ± 12.2 in cerebral infarction ($p < 0.05$), 69.3 ± 16.8 vs. 59.9 ± 15.9 in cerebral hemorrhage ($p < 0.0001$), and 65.4 ± 15.4 vs. 58.2 ± 14.7 in subarachnoid hemorrhage ($p < 0.01$).

The case-fatality rates were significantly different between stroke and acute myocardial infarction ($p < 0.0001$, Table 5). The case-fatality rate was significantly higher in females than in males in acute myocardial infarction ($p < 0.0001$). On the contrary, it was higher in males than in females in cerebral hemorrhage ($p < 0.05$). There were no significant sex-related differences in case-fatality rates in all stroke cases, cerebral infarction and subarachnoid hemorrhage ($p > 0.1$). Among the subtypes of stroke, the case-fatality rate was highest in subarachnoid hemorrhage.

Seasonal Variations

The occurrence of cerebral hemorrhage showed seasonal variations ($p < 0.001$): a peak in winter and a trough in summer. However, no significant seasonal differences were found in the other types of stroke and in total stroke cases ($p > 0.05$, Fig. 5). Seasonal variations were likewise not found in the occurrence of acute myocardial infarction ($p > 0.05$).

Case Ascertainment

Eighty-seven death certificates relating to stroke or acute myocardial infarction were identified in the designated city and 85 of them had also been registered in the present study (97.7%, Table 6). There were 31 death certificates in which the cause of death had been diagnosed as so-called "acute heart failure" or "acute cardiopulmonary insufficiency."

Fig. 4. Cumulative number of the cases for 3 years by sex. In males, the numbers of the cases with stroke and acute myocardial infarction were 2,573 and 695, respectively. They were 2,183 and 364 in females. AMI: Acute myocardial infarction.

Table 5. Death within 30 Days after the Onset and the Case-Fatality Rate

	Total (%)	Male (%)	Female (%)
Stroke	585 (12.3)	314 (12.2)	271 (12.4)
cerebral infarction	159 (6.5)	89 (6.4)	70 (6.7)
cerebral hemorrhage	294 (17.3)	177 (19.0) *	117 (15.2)
subarachnoid hemorrhage	120 (32.7)	43 (37.1)	77 (30.7)
others	12 (4.8)	5 (3.5)	7 (6.4)
Acute myocardial infarction	242 (22.9) **	129 (18.6) **	113 (31.0)**#

* $p < 0.05$ vs. female. ** $p < 0.0001$ vs. stroke. # $p < 0.0001$ vs. male.

Fig. 5. Seasonal variations of stroke and acute myocardial infarction from April 1, 1988 to March 31, 1991 in Okinawa. There were no significant seasonal variations in occurrence for total stroke and acute myocardial infarction. However, the occurrence of cerebral hemorrhage decreased in summer and increased in winter significantly ($p < 0.05$). AMI: Acute myocardial infarction. CI: Cerebral infarction. CH: Cerebral hemorrhage. SAH: Subarachnoid hemorrhage.

Table 6. Evaluation of the Completeness of Case Ascertainment by Death Certificates in a Certain city. The Numbers of Death Certificates Issued during the Study Period and the Corresponding Numbers of Registered and Unregistered Cases in the Present Study Are Shown

	Death certificates	Registered cases	Unregistered cases
Stroke	63	61	2
cerebral infarction	28	26	2
cerebral hemorrhage	26	26	0
subarachnoid hemorrhage	8	8	0
others	1	1	0
Acute myocardial infarction	24	24	0

Such cases either died within a few hours after onset or were found dead. As they lacked records such as accurate case histories, electrocardiograms and laboratory data, they were not included in the present study.

Discussion

To be meaningful, the incidence of cardiovascular disease should be established through an epidemiologic study based on complete case ascertainment and high diagnostic accuracy in a sufficiently large population which includes all age-groups, both

genders, various occupations and both urban and rural areas. We perceived that patients in Okinawa with acute cardiovascular diseases such as acute myocardial infarction or stroke were never referred to a hospital outside of Okinawa. In addition, this study was performed with the cooperation of all main hospitals and other smaller hospitals and clinics through the Okinawa Medical Association. To identify patients with acute episodes of cardiovascular disease who had been treated at home without visiting a clinic or hospital, we also enlisted the cooperation of public health centers. Since virtually all medical facilities in Okinawa participated in the

present study, almost all cases of stroke and acute myocardial infarction occurring during the study period were assumed to be identified. The evaluation of case ascertainment supports this supposition.

Diagnosis was made according to the criteria used in the MONICA Project for acute myocardial infarction and the criteria of the Ministry of Health and Welfare for stroke (4, 5). All diagnoses were reviewed by several doctors who were fully familiar with the criteria. CT had been performed in 98.4% of the stroke cases and was utilized to classify stroke into subtypes. Therefore, despite the large population, almost complete case ascertainment and diagnostic accuracy were considered to be achieved in the present study.

Although there may be some differences in the age distribution of the study population, methods of case ascertainment and diagnostic criteria for stroke and acute myocardial infarction, it would be of epidemiologic interest to compare the annual incidence of stroke and acute myocardial infarction and the ratio of these diseases in Okinawa with the respective values in Hisayama, Akita in the northern part of Japan, Honolulu and Framingham (8-13). The Hisayama, Honolulu, and Framingham studies were cohort studies and did not include recurrent cases. In the Honolulu study, mortality from coronary heart disease was included along with acute myocardial infarction, and only Japanese male cases were investigated. The age of the population at the beginning of the study was 40-64 years old in the Hisayama study, 45-68 years old in the Honolulu study and 30-59 years old in the Framingham study and the follow-up periods were 20 years, 6 years and 24 years, respectively. The study performed in Akita was a cross-sectional study and included recurrent cases, but investigated only stroke cases which underwent CT.

If confirmed recurrent cases are excluded, the average crude annual incidence rate of stroke in males in Okinawa becomes 3.1 per 1,000 population aged 40 years and older, compared with 8.1 person-years per 1,000 in Hisayama, 3.2 per 1,000 population aged between 40 to 79 years in Akita, 2.8 person-years in Honolulu and 2.6 person-years in Framingham, respectively. Similarly, the average crude annual incidence rates of acute myocardial infarction in men were 0.9 in Okinawa, 2.1 in Hisayama, 3.0 in Honolulu and 5.5 in Framingham.

These comparisons indicate that the incidence rate of acute myocardial infarction is lowest in Okinawa and highest in Framingham among the four regions studied. The incidence rate of stroke in Okinawa seemed to be lower than that in Hisayama and Akita, but still higher than that in Honolulu and Framingham.

The reasons behind the relatively low incidence of cardiovascular disease in Okinawa remain unknown. Some people may attribute it to the relatively low salt intake of residents in Okinawa compared with those who live in other areas in Japan. According to recent nutrition surveys performed in Japan, the Japanese average salt intake is about 12 g per day, but it is only about 10 g per day

for residents of Okinawa (14). However, in the population aged 15 years and older, the proportion of the people with hypertension or borderline hypertension is 41% in Okinawa and 37% in Japan as a whole (1, 14), and the difference is not statistically significant ($p > 0.1$). Mild climate may possibly contribute to the low incidence of cardiovascular disease in Okinawa. Some studies have shown a significant relationship between low temperature and the occurrence of stroke (10, 15).

The proportion of cerebral hemorrhage in men with stroke was about 36.0% in Okinawa, 24.7% in Hisayama, 31.2% in Akita, 14.3% in Honolulu and 7.7% in Framingham, respectively. The reasons for the highest relative frequency of cerebral hemorrhage in Okinawa among the five regions are also not known. This may be partly due to a high rate of performing CT in the present study. CT can reveal small hematomas that might be misdiagnosed as cerebral infarction by clinical judgement. According to previous studies which compared clinical diagnosis with autopsy or findings of computed tomography of the head, a correct clinical diagnosis was made in 65-86% of cerebral hemorrhage, 64-85% of cerebral infarction and 68-90% of subarachnoid hemorrhage cases (10, 16, 17). Some people may suggest that the high proportion of cerebral hemorrhage and high rate of performing CT in the present study reflects the poor identification of cerebral infarction with mild symptoms. However, this suspicion is off the point because the case-fatality rate within 30 days after onset was not high but rather low in comparison with previous studies (18-20) and case ascertainment was estimated to be almost complete. Poor management of hypertension may be one of the reasons for the high proportion of cerebral hemorrhage in Okinawa.

Subarachnoid hemorrhage occurred predominantly in women as in other studies (9, 20, 21). However, the proportion of subarachnoid hemorrhage in the present study was lower than in other previous studies in Japan (10, 16, 17, 22) and almost similar to those in the United States and in France (19, 23). Some previous studies showed that more than 75% of subarachnoid hemorrhage cases occurred in the age group under 60 years old (24, 25). However, similar to the study in Akita prefecture (53.9%) in Japan (10), it was only 52.9% in the present study.

Although no seasonal variations in the occurrence of total stroke cases and acute myocardial infarction cases were found, the present study showed that even in subtropical areas, cerebral hemorrhage was associated with significant seasonal variations. Previous reports in Australia and Akita prefecture showed similar trends, *i.e.*, a high incidence of cerebral hemorrhage in winter and a low incidence in summer (10, 15). This phenomenon may suggest that even mildly low temperatures have a greater influence than previously suspected on the occurrence of cerebral hemorrhage.

A significantly higher case-fatality rate in women than in men within 30 days after onset was found for acute myocardial infarction. This may partly be

attributed to the significantly higher mean age of women than men, differing by about 11 years. However, the case-fatality rate in the acute phase in Okinawa is still lower than in previous reports (26, 27).

The present study showed that the incidence of acute myocardial infarction is still much lower than that of stroke in Japan and suggests that the low incidence of cardiovascular disease may be one of major reasons for the longevity of the residents in Okinawa. Further investigations are needed for in-depth analyses of risk factors and factors influencing patient prognosis. Such studies should greatly contribute to understanding of the mechanism, prevention and treatment of cardiovascular disease.

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APPENDIX

Co-operative Study Group of Morbidity and Mortality of Cardiovascular Diseases in Okinawa (COSMO Group)

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