A 15.5-Year Cohort Study on Risk Factors for Possible Myocardial Infarction and Sudden Death within 24 Hours in a Rural Japanese Community

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Japan is one of the developed countries with the lowest death rate from ischemic heart disease. In addition, secular trends in the rates have been decreasing since 1960. Since the intake of fat has been increasing with lifestyle westernization, however, it is much concerned that both mortality and morbidity of ischemic heart disease may shift to the increasing trends soon or later. An understanding of the natural history of ischemic heart disease specific to Japanese is now needed for development of a preventive scheme in the near future; to date, however, there have been few reports on the natural history among Japanese in Japan. In the present paper, we report the results of a 15.5-year cohort study for occurrence of ischemic heart disease in Akadani-Ijimino district (hereinafter referred to as A-I district), Shibata City, Niigata Prefecture, Japan, although the study may be a so-called “classic” epidemiology. Incidence of possible myocardial infarction and sudden death within 24 hours has been determined among all residents and among subgroups stratified according to possible risk factors present at the baseline examination in 1977.

METHODS

Study District
The city of Shibata is located in the northern part of Niigata Prefecture and includes a commercial residential area in the center and an agricultural area around it. A-I district belongs to the agricultural area. Although the majority of the families used to be farmers who supplemented their income with side-jobs in other occupations, they are now regularly hired employees in factories and offices who are engaged in farming works only in the rice-planting and harvesting seasons.

Baseline Examination
Using all the residents aged over 40 years, that is, 1,182 men
and 1,469 women, as the population eligible, a baseline examination was conducted in July, 1977. The details of the method are as described in previous reports\(^3,4\).

Out of the items examined at entry, epidemiological analysis was made for 11 possible risk factors: systolic (SBP), diastolic (DBP) or mean blood pressure (MBP=1/3 SBP+2/3DBP), electrocardiographic abnormality (ECG abnormality: high R wave)\(^5,6\), and smoking.

For the current analyses, ECG abnormality was defined as the presence of high amplitude of R waves (the Minnesota code: 3-1, 3-3), S-T junction depression (4-1, 2, 3, 4) and/or T wave items (5-1, 2, 3, 4).

As for funduscopic examination, the right eye was photographed with a non-mydriatic fundus camera (Canon, Tokyo). With a 35 x 35 mm film projected on a screen, the Keith-Wagner classifications were made after discussion among three physicians including an ophthalmologist.

Using nonfasting blood, the measurement of serum total cholesterol was made with Auto Analyzer AA-II (Technicon, New York), and the standardization was achieved by participation in the Lipid Standardization Program of the Centers for Disease Control, Atlanta, Georgia through the Osaka Prefectural Center for Adult Diseases (present name: Osaka Medical Center for Cancer and Cardiovascular Diseases), Japan\(^7\).

Urine samples were collected approximately 2 hours after a meal and the level of albumin and glucose was determined by use of Uristix (Ames Miles-Sankyo, Tokyo). Alcohol consumption and smoking habits were assessed on the basis of a standardized questionnaire method by trained interviewers. Alcohol consumption was recorded as 1) non-drinkers, 2) drinkers<2 drinks/day, and 3) drinkers=2 drinks/day (1 drink=12 g of ethanol), since there was no ex-drinker in the cohort. As for smoking, the subjects were classified into four groups: 1) non-smokers, 2) ex-smokers, 3) moderate smokers<20 cigarettes/day and 4) heavy smokers=20 cigarettes/day.

**Follow-up**

Excluding those who were diagnosed as having the past history of myocardial infarction and angina pectoris on efforts on the initial examination, the subjects were designated as the cohort members. They have been on the follow-up observation since July, 1977. The present paper reports results of the observation up to December, 1992.

The occurrence of possible myocardial infarction and sudden death within 24 hours in this cohort was determined using both active surveillance and registry\(^4,8\). Under the surveillance system, all cohort members were reexamined annually using the same procedures as at baseline.

Those who survived and failed to undergo the follow-up examination were contacted by telephone or visited at their home by a staff member to determine whether or not a myocardial infarction occurred.

The myocardial infarction and sudden death registration system was established in the Shibata City–Toyosaka City–Kita-Kambara County Medical Association in July, 1977. Suspected patients were referred to the registry by all general practitioners in the Shibata area (29 clinics with beds and 23 clinics without beds) and by the Niigata Prefectural Shibata Hospital (the only general hospital in the city) and the nearby Kita-Kambara County Hospital in Suibara. Patients were also referred by public health nurses and by lay personnel in charge of health services. The records of the Division of Emergency Services of the Shibata Fire Department, the national health insurance records, and medical records of the clinics and hospitals were also regularly reviewed by a staff physician. Information about fatal myocardial infarctions and sudden deaths was obtained by review of all death certificates with supplementary clinical data obtained from the certifying physicians. The majority of the patients with myocardial infarction were examined by cardiologists from the Niigata Prefectural Shibata Hospital.

**Verification of Diagnosis**

Clinical histories of the patients were collected from subjects themselves if possible, their relatives and certifying physicians, whether or not the patients were survival.

Information collected included identifying information, personal health status and treatment received prior to myocardial infarction and death, early stages of the present attack, and clinical and laboratory findings at the first medical examination. This information and the review of hospital records were considered jointly by 3 staff physicians to determine if the patient met the criteria as a myocardial infarction or a sudden death case.

**Definition of Myocardial Infarction and Sudden Death**

Acute myocardial infarction was defined as a clinical syndrome resulting from sudden and persistent curtailment of the myocardial blood supply. It was characterized by severe and prolonged (at least half an hour) cardiac pain and other symptoms and signs of cardiac damage, and, if available, by electrocardiographic and laboratory evidence of myocardial necrosis (Q waves and CPK, GOT and LDH)\(^9,10\).

In the present study, only those subjects who had been observed in apparent good health but who expired within 24 hours of such observation were included in the category of...
Statistical Analyses of Risk Factors

Since the free living population was employed as the subject, there were some drop-outs from the cohort due to death, migration and other reasons during the follow-up period. The Cox proportional hazard regression model with a person-year approach (PHGLM Procedure, SAS ver. 5) was used so as to make maximum use of data.

In the univariate proportional hazard analysis, sex and age were stratified, and relative risk or hazard ratio of possible myocardial infarction (PMI) and sudden death within 24 hours (24SD) was estimated for each of 12 possible risk factors, described in the section of “Baseline Examination”, by an increase of 1 standard deviation for a continuous variable and 1 unit change for a discrete or coded variable. In addition, the dose-response relation of risk of PMI or 24SD, to six major risk factors was presented by graphs of the relative risk at quartile or four-category recordings of the factors: SBP, DBP, serum total cholesterol, BMI, alcohol consumption and smoking.

In the multivariate analysis, sex and age were stratified, and 9 of the 11 variables were entered into the model as independent variables. Since SBP was strongly correlated to DBP, only MBP was adopted as a representative marker of blood pressures. Statistically significant variables were selected at the level of p<0.05 by the stepwise procedure.

RESULTS

Response Rate and Person-year Incidence of Myocardial Infarction and Sudden Death

As shown in Table 1, the response rate of the baseline examination was 84.5% (999/1,182) for men and 92.6% (1,360/1,469) for women. Excluding those with a previous history of acute myocardial infarction and angina pectoris on efforts at the initial examination.

Table 1 Population, number of persons examined at the initial examination and number of cohort members in Akadani-Iijimino district (A-I district), Shibata City, Niigata Prefecture, Japan, July, 1977.

| Age at entry | Men | Women |
|--------------|-----|-------|
| 40–49        | 430 | 462   |
| 50–59        | 336 | 432   |
| 60–69        | 262 | 329   |
| 70–          | 154 | 246   |
| Total        | 1,182 | 1,469 |

IHD (Ischemic heart disease) includes those with a previous history of acute myocardial infarction and angina pectoris on efforts at the initial examination.

As for myocardial infarction, only ten of 24 cases were confirmed by severe and prolonged chest pain and by ECG findings and/or rise in serum enzymes. Three cases were detected by the ECG tracings taken during the follow-up examinations, and, afterwards, they were confirmed to have had clinical symptoms. Although the chest pain which lasted for more than 30 minutes was described for all of the rest, the findings of ECG and serum enzymes were not available. In a previous study by the same investigators, the rate of agreement between clinical diagnosis without ECG and enzymatic findings and confirmation by these findings and other procedures was 78% for acute myocardial infarction and the rate for non-myocardial infarction was 63% (date not published). This suggests that the level of accuracy for the current study was relatively high. Thus, about 40% of “myocardial infarctions” in the present study is considered to be “possible”, but not “probable”.

As for sudden death, the number of deaths within an hour was 6. Thirteen persons died within 12 hours. Five persons were found out to be dead at the bed early in the morning and the other two persons seemed to have died out of doors. Therefore, precise information on the time sequence of death was not obtained for these 7 persons, although it was confirmed that they were seen by somebody within 24 hours.
Table 2. Incidence of possible myocardial infarction (PMI) and sudden death within 24 hours (24SD) per 1,000 person-years. 15.5-year follow-up during the period from July 1977 through December 1992. Akadani-Ijimino district (A-I district), Shibata City, Niigata Prefecture, Japan.

| Sex         | Age at entry | Members of cohort | Possible myocardial infarction (PMI) | Sudden death within 24 hours (24SD) |
|-------------|--------------|-------------------|--------------------------------------|-------------------------------------|
|             |              |                   | Number of cases | Incidence rate | Number of cases | Incidence rate |
| Men         | 40–49        | 325               | 2                  | 0.42           | 1                | 0.21           |
|             | 50–59        | 285               | 2                  | 0.51           | 0                | 0.00           |
|             | 60–69        | 238               | 7                  | 2.39           | 7                | 2.39           |
|             | 70–          | 137               | 2                  | 2.02           | 6                | 6.07           |
|             | Total        | 985               | 13                 | 1.01           | 14               | 1.08           |
| Women       | 40–49        | 413               | 1                  | 0.16           | 0                | 0.00           |
|             | 50–59        | 395               | 3                  | 0.53           | 2                | 0.35           |
|             | 60–69        | 311               | 3                  | 0.72           | 4                | 0.96           |
|             | 70–          | 225               | 4                  | 1.99           | 6                | 2.98           |
|             | Total        | 1344              | 11                 | 0.59           | 12               | 0.64           |
| Grand total |              | 2329              | 24                 | 0.76           | 26               | 0.82           |

CI denotes confidence interval; ECG electrocardiographic.
Mean blood pressure = 1/3 systolic blood pressure + 2/3 diastolic blood pressure.
ECG abnormality is defined as high R and/or ST-T change, and optic fundus abnormality is defined as Keith-Wegener class 2-4.
Each multivariate model includes age, mean blood pressure, serum total cholesterol, BMI, ECG abnormality, urinary albumin, urinary glucose. 1 drink = 12g of ethanol.
Relative risks and 95% CI were estimated on basis of Cox regression coefficients. For continuous variables, risks are given for an increase in the variable of 1 standard deviation.

Table 3. Relative risk for possible myocardial infarction (PMI) and sudden death within 24 hours (24SD). Cox proportional hazard model. 15.5-year follow-up during the period from July 1977 through December 1992. Akadani-Ijimino district (A-I district), Shibata City, Niigata Prefecture, Japan.

| Variable                          | Possible myocardial infarction (PMI) | Sudden death within 24 hours (24SD) |
|-----------------------------------|--------------------------------------|-------------------------------------|
|                                   | Sex, age-stratified univariate        | Multivariate                        | Sex, age-stratified univariate        | Multivariate                        |
|                                   | Relative risk 95% CI (p value)        | Relative risk 95% CI (p value)      | Relative risk 95% CI (p value)        | Relative risk 95% CI (p value)      |
| Systolic blood pressure (+21mmHg) | 1.55                                 | 1.20                                | 0.85-1.69 (0.30)                      | 1.46                                |
| Diastolic blood pressure (+12mmHg)| 1.49                                 | 1.05-2.04 (0.025)                   | 1.05-2.04 (0.025)                    |                                    |
| Mean blood pressure (+14mmHg)     | 1.63                                 | 1.39                                | 0.97-1.98 (0.072)                     |                                    |
| Serum total cholesterol (+47mg/dl [1.21mmol/l]) | 0.84-1.86 (0.27)                   | 0.88                                | 0.57-1.37 (0.56)                      |                                    |
| Body mass index (+3kg/m²)         | 1.42                                 | 0.97                                | 0.68-1.41 (0.89)                      |                                    |
| ECG abnormality (definite/none)   | 1.96                                 | 1.45                                | 0.88-3.24 (0.37)                      |                                    |
| Urinary albumin (+++,+++/,±)      | 2.01                                 | 2.87                                | 0.65-3.24 (0.37)                      |                                    |
| Urinary glucose (+,++,++,++,/+)   | 2.96                                 | 1.50                                | 0.57-1.37 (0.56)                      |                                    |
| Optic fundus abnormality (definite/none) | 0.66-13.23 (0.16) | 0.20-11.27 (0.70) | 0.66-13.23 (0.16) | 0.20-11.27 (0.70) |
| Daily cigarettes (≥20g<20)        | 1.08                                 | 0.95                                | 0.33-2.70 (0.92)                      |                                    |
| Daily alcohol drinking (≥2drinks/2drinks) | 0.36-3.26 (0.88) | 0.36-3.26 (0.88) | 0.36-3.26 (0.88) | 0.36-3.26 (0.88) |

CI denotes confidence interval; ECG electrocardiographic.
Mean blood pressure = 1/3 systolic blood pressure + 2/3 diastolic blood pressure.
ECG abnormality is defined as high R and/or ST-T change, and optic fundus abnormality is defined as Keith-Wegener class 2-4.
Each multivariate model includes age, mean blood pressure, serum total cholesterol, BMI, ECG abnormality, urinary albumin, urinary glucose. 1 drink = 12g of ethanol.
Relative risks and 95% CI were estimated on basis of Cox regression coefficients. For continuous variables, risks are given for an increase in the variable of 1 standard deviation.

- not entered into model. •••: entered into model but not selected in the final model.
As systolic and diastolic blood pressures were strongly inter-correlated, mean blood pressure was adopted as an independent variable in the multivariate analysis.
Figure 1. Sex-, and age-stratified relative risk for possible myocardial infarction (PMI) and sudden death within 24 hours (24SD) by the level of systolic blood pressure, diastolic blood pressure, serum total cholesterol, body mass index, smoking and drinking at the initial examination. Cox proportional hazard model. 15.5-year follow-up during the period from July 1977 through December 1992. Akadani-Ijimino district (A-I district), Shibata City, Niigata Prefecture, Japan.
Thus, presumably, all of the sudden deaths in the present study where the 24-hour definition was used would not be attributed to coronary artery disease, but a higher percentage of deaths between 1 and 24 hours after the onset could be attributed to stroke or other diseases.

**Baseline Characteristics and Relative Risk of Myocardial Infarction and Sudden Death**

Results of the sex- and age-stratified univariate analysis are shown in Table 3. Statistically significant relative risk, hazard ratio, of PMI was observed for SBP, DBP, MBP, BMI, and cigarette smoking. For 24SD, DBP and albuminuria were selected as significant risk factors and MBP as a suggestive factor (0.05 ≤ p < 0.1).

**Level of Six Major Risk Factors at Baseline and Risk of Myocardial Infarction and Sudden Death**

The dose-response curves between the risk of PMI or 24SD and SBP, DBP, serum total cholesterol, BMI, smoking or drinking are illustrated in Figure 1. There was a consistent increase in risk of PMI or 24SD with either SBP or DBP, although the risk decreased a little at the third quartile level (Q3), except SBP and PMI.

Although the highest risk for PMI was seen at the third quartile level (Q3) of serum total cholesterol, there was no relationship between serum cholesterol and PMI or 24SD.

The same analyses were carried out for BMI, drinking and smoking. BMI was significantly related to development of PMI, while there was no relation of BMI to subsequent incidence of 24SD. Smoking habits were positively associated with risk of PMI, and the highest risk was observed among the ex-smokers. No relationship was seen between smoking and 24SD, and between drinking and PMI or 24SD.

**Multivariate Analysis**

When sex and age were stratified, the MBP and smoking were selected as independent risk factors for PMI from among the 9 factors, as shown in Table 3. The statistically significant association for 24SD was not observed with any factor. The coefficient of determination, $R^2$, a measure of success of predicting the dependent variable, risk of PMI or 24SD, from the independent variables, which was generalized and extended to the Cox proportional hazard regression model, was 0.10 for PMI and 0.14 for 24SD. Therefore, the fitness of the model to the present study appeared to be good.

**DISCUSSION**

At the time the present study was planned, it was predicted that the incidence of ischemic heart disease would increase during the observation period, because the intake of fat and, therefore, the level of serum cholesterol had increased markedly during the period of rapid economic growth before 1975. As sufficient cases of probable and definite myocardial infarction or of sudden death within an hour were not obtained, the statistical analyses were performed for possible myocardial infarction (PMI) and sudden death within 24 hours (24SD). Thus, this may bias results of this study.

Comparisons of our rates of PMI and 24SD with those reported in Japan and other countries are difficult because of differences in ascertainment and diagnosis of myocardial infarction and sudden death. In addition, our study has used the person-year incidence determination for PMI and 24SD. To facilitate comparisons with other studies in Japan and other countries, we have recalculated the incidence of PMI and 24SD in the A-I district using age-specific and sex-specific rates which included all cohort members in the denominator. The resulting incidence of PMI was 0.84 per 1,000 population aged 40-69 years for men and 0.40 per 1,000 for women, and that of 24SD was 0.61 for men and 0.35 for women. The rates of PMI ranged from 0.27 to 2.56 per 1,000 (median=0.88) for men and from 0.15 to 0.8 per 1,000 (median=0.37) for women according to a multicenter study, in which we participated, sponsored by the Japanese Ministry of Health and Welfare for the period of 1975-1990. The rates of 24SD were between 0.04 and 1.13 (median=0.27) for men and between 0.08 and 0.75 (median=0.26) for women. Thus, A-I district appears to have the same incidence of PMI as a higher incidence of 24SD than the average for whole Japan.

The incidence of probable myocardial infarction and sudden death mostly within 2 hours from some different studies in the US and European countries for the comparable period appeared to take a figure up one place in comparison with ours: incidence of probable myocardial infarction of 3.7 to 13.1 per 1,000 for American and European middle-aged men, and incidence of sudden death within 2 hours of 1.0 to 3.6 per 1,000 for the men.

Blood pressure at baseline, whether recorded as SBP, DBP, or MBP, was correlated with the risk of PMI, but only DBP with the risk of 24SD. Particularly, a clear dose-response relationship was seen between SBP and PMI. This relationship of acute myocardial infarction with BP is consistent with studies in Japan, the United States and European countries. According to some cohort studies conducted in rural Japanese populations, no relationship or a slight and inverse relationship was observed between the level of serum cholesterol and occurrence of myocardial infarction, as seen in our study. In an urban population in Japan and many populations in the US and European countries, however, hypercholesterolemia is regarded as one of the strongest risk factors for ischemic heart disease. The heterogeneity of patients with myocardial infarction is presumably one of the reasons for the discrepant findings on the pathogenic effect of serum cholesterol. According to some autopsy studies in Japan, the massive type of myocardial infarction was closely related to hypercholesterolemia, smoking and other atherogenic factors measured before death, but the scattered type was related only
to hypertension. An inverse relationship was clearly observed between the scattered type and serum cholesterol levels prior to death. In addition, there was no relationship between myocardial infarction as a single entity and serum cholesterol in a rural Japanese population, as A-I district, where the scattered type (ca.70% of MI) was more frequent than the massive type, but a clear and positive relationship between overall myocardial infarction and serum cholesterol was observed in a large city population where the westernization of lifestyle, particularly dietary intake, advanced much more than in rural areas and the massive type (ca.80% of MI) was predominant, probably as in the US and European countries. If the ratio of the massive to scattered type increase with increasing in the level of serum cholesterol in Japanese rural populations, a significantly positive association of serum cholesterol with overall myocardial infarction would be seen.

We identified cigarette smoking as a risk factor for PMI. This is in agreement with other studies in Japan and western countries. However, the highest risk of PMI and 24SD was observed among the ex-smokers. They had stopped smoking because they had already had hypertension and other risk factors as well as smoking (data not shown).

Because alcohol consumption was positively associated with both blood pressure and serum HDL-cholesterol levels (Serum HDL-C was not measured at baseline, but 10 years later[33]), a clear relationship was not seen between drinking and PMI in A-I district.

A significant association of BMI, an obesity index, with PMI was seen in the univariate analysis. In this population, BMI was correlated to blood pressure levels more strongly than to serum lipid.

Albuminuria was found in 155 persons during the initial examination, and they showed a statistically significant relative risk for 24SD in the univariate analysis. Albuminuria may be due to hypertension or arteriosclerotic renal dysfunction, because only 19 of those with albuminuria had chronic nephritis or nephrosis.

In the current study, we entered the considerable number of patients only with clinical observation into the category of myocardial infarction and used 24-hour since apparent good health for a definition of sudden death. Therefore, it is difficult to summarize the results. However, hypertension and cigarette smoking appear to be risk factors for possible myocardial infarction in A-I district. The influence of abnormality in lipid metabolism on the development of possible myocardial infarction and sudden death within 24 hours was modest. Thus, it may be said that the risk factors for myocardial infarction in rural Japanese are simpler than those in western countries.

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