Sex Differences of Risk Factors for Acute Myocardial Infarction in Japanese Patients

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Background Acute myocardial infarction (AMI) is prevalent and has serious consequences including reinfarction and death. Although the risk factors for AMI have been extensively studied in Western countries, they are less well documented in Japan. To determine the risk factors for AMI, we performed a case-control study in unselected patients with AMI.

Methods and Results Risk factors were assessed in 1,925 consecutive patients with a first AMI (age, 28–103 years old; men, 1,353; women, 572), who were admitted to one of the major institutes in Japan, and in 2,279 age- and sex-matched population-based controls. Hypertension (odds ratio (OR), 4.80; 95% confidence interval (CI), 3.80 to 5.95; p<0.01), diabetes (OR, 3.44; 95% CI, 2.50 to 4.75; p<0.01), current smoking (OR, 3.39; 95% CI, 2.78 to 4.18; p<0.01), family history (OR, 1.84; 95% CI, 1.30 to 2.62; p<0.01), and hypercholesterolemia (OR, 1.28; 95% CI, 1.00 to 1.62; p<0.05) were all independent risk factors for AMI. However, obesity (OR, 1.13; 95% CI, 0.92 to 1.50; NS) was not. Hypertension (OR, 4.80; 95% CI, 3.80 to 6.02; p<0.01), current smoking (OR, 4.00; 95% CI, 3.02 to 5.00; p<0.01), and diabetes (OR, 2.9; 95% CI, 2.00 to 4.04; p<0.01) were all independent risk factors for AMI in men. In contrast, only current smoking (OR, 8.22; 95% CI, 3.98 to 18.88; p<0.01), diabetes (OR, 6.12; 95% CI, 3.78 to 12.02; p<0.01), and hypertension (OR, 5.04; 95% CI, 2.92 to 7.52; p<0.01) were independent risk factors for AMI in women. Hypercholesterolemia was an independent risk factor for AMI in men (OR, 1.52; 95% CI, 1.00 to 1.98; p<0.05), but not in women.

Conclusions Hypertension, diabetes, current smoking, family history and hypercholesterolemia are associated with AMI in Japanese patients, and the importance of the risk factors for AMI differs between men and women. Hypertension, current smoking, diabetes and family history are the most important risk factors in men, whereas current smoking, diabetes, hypertension and family history are the most important risk factors in women. Hypercholesterolemia is an independent risk factor for AMI in men, but not in women. To the best of our knowledge, this is the first clinical study to define the relative importance of risk factors for AMI in Japanese patients.

Key Words: Acute myocardial infarction; Japanese patient; Risk factors

Cardiovascular disease is estimated to be the leading cause of death and loss of disability-adjusted life years! Effective prevention requires a global strategy based on the knowledge of importance of risk factors for cardiovascular disease. Current knowledge about the prevention of coronary heart disease and cardiovascular disease is mainly derived from studies in European populations? However, the extent to which these findings apply worldwide is unknown. Some studies reported that risk factors for coronary artery disease vary in different geographic regions, especially Asian countries. For example, dyslipidemia is not a risk factor for coronary artery disease in India! and hypertension is more important in China. In addition, the incidence of ischemic heart disease in Japan has been reported to be the lowest among the Western countries. The differences between Japan and other Western countries may stem, in part, from genetic factors, but it is more likely from the eating habit is the cause; for example, the average plant-based low-fat diet. In the present study, we aimed to clarify the risk factors for acute myocardial infarction (AMI) in the Japanese population. The present study was a large, standardized case-control study, designed as an initial step to assess the importance of risk factors for AMI in Japan.

Methods

The study population was recruited from 20 major institutes in Japan. To identify first cases of AMI, all patients who presented within 24h of symptom onset and were admitted to the coronary care unit or equivalent cardiology ward were screened. Cases were eligible if they had characteristic symptoms plus electrocardiographic changes and elevation of creatin-kinase levels to at least twice the upper limit of the normal range. At least 1 age-matched (up to 5 years older or younger) and sex-matched control was recruited per case in the Health Care Center. Exclusion criteria for controls were identical to those for cases, with the additional criterion that controls had no previous diagnosis of heart disease or a history of exertional chest pain.
Structured questionnaires were administered and physical examinations were undertaken in the same manner in cases and controls. Information about smoking status, personal and family history of cardiovascular disease and risk factors was obtained. Although blood pressure at the time of examination was recorded in both cases and controls, the levels in cases would be systematically affected by AMI and treatment with vasoactive agents such as Î² blockers, angiotensin-converting enzyme inhibitors, nitrates or calcium channel antagonists that could lower blood pressure. Therefore, a self-reported history of hypertension was used in the analysis in addition to the World Health Organization criteria (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg).

Blood samples were drawn and centrifuged from every individual after admission. We assessed glucose tolerance in all subjects with fasting blood glucose levels according to the American Diabetes Association criteria. We defined current smokers as individuals who smoked any tobacco in the previous 12 months and included those who had quit within the past year. Hypercholesterolemia was defined as treatment with anti-hypercholesterol agents such as statin etc, or when patients had serum blood cholesterol levels 220 mg/dl or higher. Obesity was defined as a body mass index of >25 kg/m².

All data from patients with AMI were transferred by...
FAX to Kumamoto University, where quality-control checks and statistical analyses were performed. The appropriate regulatory and ethics committees in every institute approved the present study. All participants provided informed consent before taking part in the study.

Estimated odds ratios (ORs) and confidence intervals (CIs) were calculated by using different methods and were within 5% of each other, with a slight attenuation of effect estimates in the unconditional vs conditional models.9 Statistical analyses were performed by using SAS version 8.2 (SAS, Cray, NC, USA). All statistical tests of hypotheses were 2-sided and a p value of less than 0.05 was considered significant.

**Results**

Between January and December 2002, 1,925 consecutive patients were enrolled with a first AMI (age, 28–103 years old; mean age, 67.7±12.3 years old; men, 1,353; women, 572), who were admitted to one of the major institutes in Japan. In addition, 2,279 age- and sex-matched population-based controls were enrolled. The overall median age of cases with AMI was approximately 9 years lower in men (65.0±12.2 years old) than in women (74.0±9.9 years old). Fig 1 provides the overall ORs for individual risk factors adjusted for age and sex. Hypertension (OR, 4.80; 95% CI, 3.80 to 5.95; p<0.01), diabetes (OR, 3.44; 95% CI 2.50 to 4.75; p<0.01), current smoking (OR, 3.39; 95% CI, 2.78 to 4.18; p<0.01), family history (OR, 1.84; 95% CI, 1.30 to 2.62; p<0.01), and hypercholesterolemia (OR, 1.28; 95% CI, 1.00 to 1.62; p<0.05) were all independent risk factors for AMI. However, obesity (OR, 1.13; 95% CI, 0.92 to 1.50; NS) was not.

Fig 2 shows the sex differences in the ORs for individual risk factors. Hypertension (OR, 4.80; 95% CI, 3.80 to 5.95; p<0.01), current smoking (OR, 4.00; 95% CI, 3.02 to 5.00; p<0.01), and diabetes (OR, 2.9; 95% CI, 2.00 to 4.04; p<0.01) were all independent risk factors for AMI in men. In contrast, current smoking (OR, 8.22; 95% CI, 3.98 to 18.88; p<0.01), diabetes (OR, 6.12; 95% CI, 3.78 to 12.02; p<0.01), and hypertension (OR, 5.04; 95% CI, 2.92 to 7.52; p<0.01) were all independent risk factors for AMI in women. Hypercholesterolemia was an independent risk factor for AMI in men (OR, 1.52; 95% CI, 1.00 to 1.98; p<0.05), but not in women.

Fig 3 shows the risk factors for the younger AMI patients who were under 65 years of age. Hypertension (OR, 6.50; 95% CI, 4.40 to 9.05; p<0.01), current smoking (OR, 4.10; 95% CI, 2.98 to 5.42; p<0.01), diabetes (OR, 3.86; 95% CI, 2.22 to 5.86; p<0.01), family history (OR, 2.62; 95% CI, 1.42 to 4.04; p<0.01), and hypercholesterolemia (OR, 2.48; 95% CI, 1.66 to 3.26; p<0.01) were all independent risk factors for AMI. However, obesity (OR, 1.22; 95% CI, 0.90 to 1.82; NS) was not.

**Discussion**

The present study defines the risk factors for AMI in Japanese patients. The effects of these risk factors were consistent in men and women across different geographic regions of Japan, suggesting that the results are applicable to the entire Japanese population. The effects of these risk factors are particularly striking in young men and women indicating that most premature myocardial infarctions are preventable. In Western countries, the 2 most important risk factors are smoking and abnormal lipids.10 Together, they account for approximately two-thirds of the population-attributable risk of AMI. Hypertension has long been established as a strong, independent, etiologically significant risk factor for cardiovascular disease.11 Obesity, and diabetes are the next most important risk factors in men and women, but their relative effect varies in different regions of the world. In fact, the present study shows that the 3 most important risk factors in Japan are hypertension, smoking and diabetes. We also showed that hypertension is the most important risk factor for AMI in Japan.

Appreciation of the crucial role of risk factors in the development of coronary heart disease has been a major advance in understanding and treating this important disease. Extensive epidemiological research has established...
cigarette smoking, diabetes, dyslipidemia and hypertension as independent risk factors for coronary heart disease. In addition, treatment of these risk factors has been convincingly shown to reduce the risk of future cardiovascular events. These 4 risk factors have often been labeled as ‘conventional’ risk factors because of the strength of evidence supporting their role in the pathogenesis of coronary heart disease. In the present study, we showed that cigarette smoking, diabetes, and hypertension are also strong independent risk factors for AMI in Japan, but that hypercholesterolemia is less important. One of the possible reasons is a different lifestyle, especially in elderly Japanese individuals, because they often consume a low-calorie, low-fat diet that is high in vegetables and avoid a sedentary lifestyle. In fact, we found that hypercholesterolemia was an important risk factor for AMI in patients less than 65 years old. As is true for so many countries, Japanese dietary habits are undergoing substantial changes. Younger Japanese individuals often prefer a Western lifestyle, and so the incidence of dyslipidemia, hypertension, glucose intolerance and obesity is increasing in the younger generation. Therefore, the incidence of coronary heart disease is increasing, and dyslipidemia will become a more important independent risk factor for coronary heart disease in the near future.

Despite major advances in diagnosis and treatment, coronary heart disease remains the leading cause of morbidity and mortality in both men and women in Western countries. At any given age, the prevalence of coronary heart disease is greater in men than in women. Nonetheless, several recent reports have concluded that women with coronary heart disease have a worse prognosis than men. Thus, we examined whether there are sex differences in the risk factors for AMI. Our results showed that smoking is the most important risk factor for AMI in Japanese women. The reason for a sex difference in the effects of smoking on the cardiovascular system is still unclear. Smoking is also one of the major risk factors for respiratory diseases such as lung cancer and chronic obstructive pulmonary disease (COPD), and it is well known that women may be more susceptible to severe COPD than men. A similar phenomenon may occur in the cardiovascular system in women. In contrast, some investigators reported that quitting smoking is less important for reducing the risk of AMI in women. Smoking showed a graded relationship with the odds of a myocardial infarction without either a threshold or a plateau in the dose-response relationship. In particular, smoking even 5 cigarettes per day has been reported to increase the risk. Thus, there is no safe level of smoking, and non-smoking and smoking cessation is very important in Japanese individuals, especially women. Our results indicated that AMI is more common in men as compared with women in Japan. Furthermore, the mean age of men with AMI is higher that of women. These results are in agreement with previous reports from Western countries. In the present study, hypertension and diabetes are also associated with a greater OR in women as compared with men. Usually, women with these factors were approximately a decade older than men. It is possible that atherosclerosis may have already developed in women with hypertension or diabetes at a later age than in men. The protective effects of women gender itself might have gone in the women with hypertension or diabetes.

The OR for AMI in individuals with a family history was approximately 1.8. In addition, the OR for each risk factor increased in patients with AMI who were younger than 65 years-old compared with the overall study population. This finding suggests that the effect of family history on the risk of AMI might be mediated through known risk factors that result from a shared lifestyle, in addition to genetic factors.

The importance of modifying risk factors is supported by data from randomized trials or persuasive evidence of causality from observational studies. We and other investigators showed that a pill that combines a statin, antihypertensive therapy, and aspirin together with avoidance of smoking, could potentially reduce the patient risk of developing AMI in Japan. Lifestyle modification has been shown to be important in other countries for reducing the risk of AMI, and the present study suggests that lifestyle modification is also important in Japanese men and women of all ages.

Study Limitations
The present study had several limitations. First, a case-control design was potentially confounded if there was a differential ascertainment of risk factors between cases and controls. We minimized this factor by using standardized methods of data collection for both cases and controls. Second, the inclusion of only cases with a first AMI reduces the possibility that individuals with previous cardiovascular disease might have substantially altered their lifestyle or risk factors before the event. Third, we attempted to minimize bias in the selection of controls by excluding individuals in whom the risk factors that we were interested in studying were implicated as being protective or harmful. Our results were quantitatively similar for men and regions of Japan. Furthermore, the measurement of serum cholesterol levels was conducted within a few days after occurrence of AMI. In addition, some patients, even in the control group, had anti-dyslipidemia agents such as statin before AMI occurred. And finally, although renal failure is also one of the important risk factors for AMI, we unfortunately did not assess the effects of renal failure on AMI in the present study. Further studies are required to clarify the role of hypercholesterolemia and renal failure in Japanese patients with AMI.

Conclusion
In conclusion, hypertension, diabetes, current smoking, family history and hypercholesterolemia are associated with AMI in Japanese patients. In addition, there are sex differences in an order of importance related to risk factors for AMI. Hypertension, current smoking, diabetes and family history are the most important risk factors in men, whereas current smoking, diabetes, hypertension and family history are the important risk factors in women. Hypercholesterolemia is an independent risk factor for AMI in men, but not in women. To the best of our knowledge, this is the first clinical study that defines the relative importance of risk factors for AMI in Japanese patients.

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Risk Factors for Acute Myocardial Infarction


