Low-Risk Profile for Cardiovascular Disease and Mortality in Japanese

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Background Some studies focusing on low-risk profiles for cardiovascular disease have been reported in Western countries. Yet, few reports have examined, with substantial longevity, the low-risk profile for cardiovascular disease in the Japanese population. This study examines whether having a favorable risk factor profile yields lower all-cause mortality and whether the proportion of those with a low-risk profile is larger in the Japanese population.

Methods and Results A total of 8,339 men and women aged 30–69 years without a history of cardiovascular diseases for 19 years, who had participated in the 1980 National Survey on Circulatory Disorders after being randomly selected from throughout Japan, were followed. Low risk was defined as having all of the following baseline characteristics: blood pressure (BP) <120/80 mmHg; no antihypertensive medication; serum cholesterol 160–240 mg/dl (4.14–6.22 mmol/L); no history of diabetes; and non-smoker. The long-term mortality of the low-risk group was compared with that of others using the Cox proportional hazard model. The prevalence of low risk was 9.4% of all participants. The multivariate-adjusted hazard ratios for low-risk individuals compared with others were as follows: 0.33 (95% confidence intervals (CI), 0.15–0.74) for cardiovascular disease and 0.63 (95% CI, 0.46–0.88) for all-cause mortality. The most attributable risk factor for all-cause mortality was high BP (≥120/80 mmHg).

Conclusion Japanese individuals with favorable cardiovascular disease risk profiles had lower mortality from cardiovascular disease and all-causes than those without. (Circ J 2008; 72: 545–550)

Key Words: Cardiovascular diseases; Mortality; Risk factors

Recently, studies focusing on the low-risk profile for cardiovascular disease (CVD); that is, having all of the optimal CVD risk profiles, such as lower blood pressure (BP), optimal total cholesterol (TC), no diabetes, non-smoker and so on, have been reported in Western countries. These studies usually showed that participants with a low-risk CVD profile had a lower all-cause mortality than others.

Japan has the longest lifespan in the world. Beyond the very low infant mortality rate, some reasons might explain this. Crude mortality due to coronary heart disease in Japan is one-third that of the United States. The age-adjusted stroke mortality rate in Japan has decreased markedly during the past few decades and the it is now approaching that in Western societies. This lower CVD mortality rate might partly explain why the Japanese have such a longer life span compared with the rest of the world. To understand the lower CVD and all-cause mortality rate in the Japanese population, it should be of interest to know whether they have a more prevalent low-risk profile. Yet, to date, few reports have examined the prevalence of a low-risk CVD profile and the relationship between a low-risk profile and mortality in Japan. Therefore, in the present study we analyzed data accumulated over a period of 19 years from a representative cohort of the general Japanese population to clarify: (1) whether having a favorable risk factor profile yields lower all-cause mortality, as well as CVD mortality; (2) whether the prevalence of a low-risk profile is larger among Japanese than among Western populations; and (3) which CVD risk factors are mostly attributable to all-cause death in Japanese.

Methods

Participants
This cohort participated in the 1980 National Survey on Circulatory Disorders. A total of 10,546 individuals (4,640 men and 5,906 women; aged 30 years), who were selected randomly from 300 health districts throughout Japan, participated in the survey, which comprised a medical history, physical examinations, blood tests and a self-administered
**Table 1 Baseline Characteristics of the Study Participants (Comprising 3,658 Men and 4,681 Women Aged 30–69 Years in 1980), Low-Risk Group and Others, NIPPON DATA80**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low-risk group*</th>
<th>Others</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. participants (%)</td>
<td>784 (9.4)</td>
<td>7,555 (90.6)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.0±9.6</td>
<td>48.5±11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male (%)</td>
<td>13.9</td>
<td>47.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.9±2.9</td>
<td>22.9±3.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>109±6.7</td>
<td>137±20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>67.7±6.3</td>
<td>82.7±12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>4.9±0.51</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Serum glucose (mmol/L)</td>
<td>5.1±0.95</td>
<td>5.59±1.71</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>0</td>
<td>37.0</td>
<td></td>
</tr>
</tbody>
</table>

*Low-risk was defined as having all of the following at base line: SBP <120 mmHg and DBP <80 mmHg; receiving no antihypertensive treatment; 4.14 mmol/L <serum total cholesterol concentration <5.22 mmol/L; non-fasting serum glucose concentration <<11.1 mmol/L; or fasting serum glucose concentration <<7.1 mmol/L; no history of diabetes, myocardial infarction, stroke and angina; and current non-smoker.

Values are presented as the means ± SD or frequencies. P values were tested by t-test or chi-squared test.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
SI conversion factors: to convert glucose to millimoles per liter, multiply by 0.0551; cholesterol to millimoles per liter, multiply by 0.0259.

**Endpoint Determination**

National Vital Statistics was used to clarify the cause of death. In accordance with Japan’s Family Registration Law, all death certificates issued by physicians are forwarded to the Ministry of Health and Welfare via public health centers in the district of residence. The underlying causes of death were coded according to the 9th and 10th revisions of the International Classification of Diseases for the National Vital Statistics. We confirmed death in each health district of the district, gender, and dates of birth and death as key covariates. The significance of an interaction between gender and low-risk status for all-cause and cause-specific mortality was tested using an interaction term for the covariates. The age-adjusted and multivariate-adjusted hazard ratios (HR) for all-cause and cause-specific mortality were calculated using a Cox proportional hazard model. For multivariate analyses, age, gender, BMI and frequency of alcohol consumption (ie, occasional, daily or none) were entered as covariates. The significance of an interaction between gender and low-risk status for all-cause and cause-specific mortality was tested using an interaction term for the continuous and categorical variables in a multivariate-adjusted model. All p-values were 2-tailed and p<0.05 was considered significant. Data are presented as the means ± SD unless otherwise stated.

**Baseline and Biochemical Examinations**

The baseline surveys were conducted by public health centers. Baseline BP was measured by trained observers using a standard mercury sphygmomanometer affixed to the right arm of seated participants who had rested for 5 min. Height in stockinged feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m). Results of a self-administered questionnaire that included questions about participants’ smoking habits, alcohol consumption, current health status and medical history were obtained. Non-fasting or fasting (at least 5 h after the last meal) blood samples were centrifuged at room temperature for 15 min at 1,500 g and within 60 min of collection, and then stored at −70°C. Serum TC concentration was analyzed at a single laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan), using a sequential auto analyzer (SMA12; Technicon, Tarrytown, NY, USA) and the Lieberman–Burchard direct method. This laboratory is a member of the Cholesterol Reference Method Laboratory Network, and the precision and accuracy of serum cholesterol measurements have been certified in the Lipid Standardization Program, administered by the Centers for Disease Control and Prevention, Atlanta. Serum glucose concentrations measured by the cupric neocuproline method were converted into the values used in the hexokinase model. The cohort was divided into the categories ‘low risk’ and ‘other’. Low risk was defined as having the following characteristics at the time of the baseline survey: BP <120/80 mmHg, a level categorized as normal by the JNC 7;19 no antihypertension medication; TC 160–240 mg/dl (4.14–6.22 mmol/L); non-fasting serum glucose <126 mg/dl (7.0 mmol/L); no history of diabetes; and not currently smoking. Although other papers define TC <200 mg/dl (5.18 mmol/L) or fasting serum glucose <126 mg/dl (7.0 mmol/L); no history of diabetes; and not currently smoking. Although other papers define TC <200 mg/dl (5.18 mmol/L) as low risk for CVD,2-5 7 we defined TC as low risk because low TC (ie, <160 mg/dl (4.14 mmol/L)) is associated with increased risk of cerebral hemorrhage13,20,21 and risk for CVD is not increased significantly at TC levels between 200 and 240 mg/dl (5.18–6.22 mmol/L) in Japan13.
We also calculated the population-attributable fraction for all-cause death among the risk factors by the formula:\[ \text{Population-attributable risk} = \frac{\text{Proportion of cases exposed to risk factor} \times (\text{Adjusted HR} - 1)}{\text{Adjusted HR}} \]

**Results**

**Baseline Characteristics**

Table 1 shows the baseline characteristics of the 2 categories of participants. Those with a low risk accounted for 9.4% of the total and contained a higher proportion of middle age were much lower than those of individuals having at least one of the risk factors. They defined low risk as serum cholesterol level <200 mg/dl (<5.17 mmol/L), BP (systolic BP (SBP), diastolic BP (DBP)) and glucose concentrations differed significantly between the 2 groups.

**Mortality by Cause, Low Risk vs Other**

Among 109 low-risk men and 675 low-risk women, 9 (all-cause mortality rate, 4.6/1,000 person-years) and 30 (all-cause mortality rate, 2.4/1,000 person-years) died, respectively. These all-cause mortality rates in low-risk participants were lower than those in others (10.4/1,000 person-years in others men and 6.1/1,000 person-years in others women). For both men and women, the multivariate-adjusted HRs (95% confidence intervals (CI)) for all-cause death in low-risk individuals were significantly lower than those in the other group; HR =0.47 (0.24–0.90) in men and HR=0.73 (0.50–1.06) in women. As we did not find any significant relationship between gender and low-risk profile for mortality (p=0.17 for all-cause and p=0.58 for CVD death), we combined the data from men and women in the analyses that followed.

Table 2 shows the number of deaths, age-adjusted rates per 1,000 person-years and the HR of low-risk individuals for all-cause and cause-specific mortality. Crude mortality rates per 1,000 person-years for CVD were 0.4 and 2.5 among the low risk and the other group, respectively. Similarly, all-cause mortality per 1,000 person-years was 2.6 for low risk and 8.0 for the other group. The multivariate-adjusted HRs for CVD death and all-cause death in low-risk individuals were significantly lower than for those in the other group; HR =0.33 (95% CI, 0.15–0.74) for CVD mortality and 0.63 (0.46–0.88) for all-cause mortality. The frequency of deaths due to stroke was only 1 in 784 low-risk individuals (0.1 per 1,000 person-years), but was 154 in 7,555 of the other group (1.1 per 1,000 person-years). Although the risk of cancer mortality was also slightly lower in low-risk individuals (HR=0.90; 0.57–1.40), the difference was not statistically significant.

**Population-Attributable Risk of CVD Risk Factors for All-Cause Mortality**

Table 3 shows multivariate-adjusted HRs for all-cause death according to major CVD risk factors and their population-attributable risk fractions (%). The proportion of cases exposed to non-normal BP, currently smoking were 91.8%, 46.6%, 30.1% and 9.4% of all deaths, respectively. The HRs for high BP, smoking, diabetes, serum cholesterol and all-cause mortality were 1.40 (1.13–1.74), 1.51 (95% CI, 1.31–1.74), 1.20 (1.06–1.37) and 1.81 (1.48–2.22), respectively. Accordingly, the population-attributable risk ratios for all-cause mortality were 26.2%, 15.7%, 5.1% and 4.2% for high BP, smoking, non-optimal serum cholesterol and diabetes, respectively. When we calculated the population-attributable risk fraction for each gender, the population-attributable risk ratios for all-cause death in men were 20.8%, 20.5%, 5.0% and 4.5% for high BP, smoking, non-optimal serum cholesterol and diabetes, respectively, and were 31.8%, 6.0%, 5.6% and 3.2% in women, respectively.

**Discussion**

We found that only a few middle-aged adults had a low-risk profile for CVD. We also found that participants with a low-risk profile had a lower risk not only for CVD mortality but also for all-cause mortality. Moreover, among the major CVD risk factors, we discovered that the population-attributable risk for all-cause death was highest for high BP, followed by smoking.

One of the previous studies based on 5 large cohorts studies, involving a 16-year follow-up study of Multiple Risk Factor Intervention Trial (MRFIT) and a 22-year follow-up study of Chicago Heart Association Detection Project in Industry showed that long-term mortality rates for individuals with favorable CVD risk factor profiles in youth and middle age were much lower than those of individuals having at least one of the risk factors. They defined low risk as serum cholesterol level <200 mg/dl (<5.17 mmol/L), BP ≤120/80 mmHg and currently non-smoking. In that study, low-risk individuals comprised only 4.8–9.9% and the age-
adjusted relative risks ranged from 0.42 to 0.60 for all-cause mortality and from 0.15 to 0.28 for CVD mortality, respectively. Another previous study that also investigated low-risk profiles is that by Daviglus and colleagues, who studied 7,302 women (aged 18–39 years) without prior CHD or major electrocardiographic abnormalities, screened between 1967 and 1973, for the Chicago Heart Association Detection Project in Industry. They found that only 20% met all the criteria for low-risk profile, which they defined as: TC <200 mg/dl; BP ≤120/80 mmHg; BMI <25 kg/m2; no anti-hypertensive or cholesterol-lowering medication; no diabetes; and no smoking. They also showed the multivariate-adjusted all-cause relative risk for low-risk women was 0.19 compared with women with 2 or more high-risk factors. Giampaoli and colleagues conducted a 10-year follow-up study of Italian participants aged 35–69 years from 12 population samples. They defined low risk as having all the following applied at baseline: SBP <120 mmHg; DBP <80 mmHg; no anti-hypertensive or cholesterol-lowering medication; serum TC <5.17 mmol/L (<200 mg/dl); BMI, <25.0 kg/m2; non-smoker; and no diabetes. They found that all the factors could be applied to only 3.5% of women and 1.6% of men. Lloyd-Jones et al studied all Framingham Heart Study participants who were free of CVD at 50 years of age. They found that only 3.2% of men and 4.5% of women had all the optimal factors; that is, TC <4.65 mmol/L (<180 mg/dl), BP <120/<80 mmHg, non-smoker and non-diabetic.

When our results for relative risk of low-risk profile for all-cause mortality are compared with those of Stamler et al, whose study used similar criteria and compared the risk of low-risk profile with all others as we did, our results are somewhat modest. Various reasons could explain these discrepancies, which will now be considered. Since we used the low-risk profile for CVD mortality in these studies, the proportion of CVD deaths in all deaths can explain the discrepancy. The World Health Organization’s Health Statistics and Health Information Systems displays a table regarding numbers and rates of registered deaths. In 2000 in Japan, death due to diseases of the circulatory system (ICD10: I00-I99) accounted for 27.5% of all deaths in men.

### Table 3 Population-Attributable Risk of Major Cardiovascular Disease Risk Factors for All-Cause Death, NIPPONDATA80, 1980–1999

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Men and women</th>
<th></th>
<th></th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High BP**</td>
<td>Non-normotensive</td>
<td>High BP**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal BP</td>
<td>Non-normotensive</td>
<td>Normal BP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smoking</td>
<td>Current smoker</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum cholesterol</td>
<td>Optimal***</td>
<td>Serum cholesterol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-optimal</td>
<td>Non-optimal</td>
<td>Non-optimal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Diabetes**</td>
<td>Non-diabetic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,046 (91.8%)</td>
<td>609 (53.4%)</td>
<td>531 (46.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.40 (1.13–1.74)</td>
<td>1.51 (1.31–1.74)</td>
<td>1.20 (1.06–1.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26.2%</td>
<td>15.7%</td>
<td>5.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5%</td>
<td>6.0%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

*High BP (ie, non-normotensive) was defined as SBP ≥120 mmHg, DBP ≥80 mmHg or receiving antihypertensive treatment.

**Diabetes was defined as non-fasting serum glucose ≥11.1 mmol/L or fasting serum glucose ≥7.0 mmol/L or history of diabetes.

***Optimal was defined as serum cholesterol 4.14–6.22 mmol/L.

†Adjusted for age, gender, smoking, hypertension, diabetes, serum cholesterol, BMI and alcohol consumption status.

HR, hazard ratio; BP, blood pressure. Other abbreviations see in Tables 1,2.
and 35.3% of all deaths in women. Corresponding values for the same year in the USA was 37.2% for all-cause mortality in men and 41.1% in women. Moreover, mortality rates in Japan due to stroke, which occurs in relatively older individuals, are still higher than those due to CHD, which results in death among younger individuals. Another reason could be that most Japanese men are likely to have been smokers in the past, whereas men who have never smoked might have had a health condition in their youth, such as tuberculosis or asthma. Thus, relatively weaker men might be included in the ‘low risk’ group. However, as we did not obtain information about participants’ histories of non-CVDs, we can’t confirm this speculation.

Although the definition we used was different, the proportion of individuals with a low-risk profile in the present study was mostly similar to that of other studies (3–10%).2,6–7 except for the report by Daviglus et al,5 which studied younger women. Since the prevalence of a low-risk profile was similar to that of other studies and the relative risk of a low-risk profile for all-cause and CVD mortality is rather modest in Japan, Japanese longevity might not be fully explained by a low-risk profile; that is, additional factors might affect the lower CVD risk in Japan. A recent study by Sekikawa et al has found that middle-aged Japanese men have a lower prevalence of coronary artery calcification than middle-aged men in the USA despite having similar levels of BP and low-density lipoprotein-cholesterol, and a higher incidence of diabetes and smoking.28 They also suggested that factors other than the classical major factors are involved in risk for CVD. Thus, an investigation of factors that affect a lower CVD risk in Japan, such as green tea consumption, fish consumption or others, should be encouraged.14,24,25

We assessed the magnitude of the CVD risk factors for all-cause mortality. The criteria for each risk factor were the same as those used to define low-risk status. Among those participants with a low-risk profile in the present study, a few with diabetes had the highest HRs for all-cause death, whereas many with high BP, as defined by JNC 7, had a modest HR for all-cause death. As a result, high BP had the highest population-attributable risk fraction for all-cause death, followed by smoking, serum cholesterol, and diabetes for both men and women. Although the population-attributable fraction was not very high, the prevalence of diabetes is increasing steadily, where the prevalence in 2003 (6.9%) was almost double that in 1980 (3.8%). Taking this into consideration, diabetes should have more impact in the future. A distinct difference between men and women was observed regarding the impact of smoking on all-cause mortality. In men, smoking caused a high population risk, being at the same level as high BP, whereas in women smoking contributed much less to population risk compared with high BP. Apparently, this is because the prevalence of smoking is quite different between men and women (men, 64.8%; women, 8.8%) at the baseline survey.

The present study has some methodological limitations. First, we measured risk factors only once at baseline, so we did not have any information about the status of the participants or changes in lifestyle. Second, we used the original definition of a low-risk profile for serum cholesterol. Thus, direct comparisons between the present study and other Western studies are quite difficult. However, as shown in our previous studies, participants whose serum cholesterol level was between 160 and 240 mg/dl (4.14–6.22 mmol/L) had the lowest CVD mortality risk, which might be because Japanese have not been exposed to a high lipid diet for as long as populations in Western countries, especially at the baseline examination of the study. Hence, our approach should be appropriate for the Japanese population.

In conclusion, the benefit of having a low-risk status is apparent in Japan. Individuals with low CVD risk have lower mortality rates due to all-causes and CVD. The most attributable risk factor for all-cause mortality was high BP. Thus, we reconfirmed the importance of maintaining lower BP as a public health strategy, as well as to stop or never start smoking, and maintain modest levels of TC, as well as lower serum glucose levels.

References


Appendix

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Author Contributions: Dr Yamamoto had full access to all of the study’s data and takes responsibility for the integrity of the data and the accuracy of the data analysis.


Acquisition of Data: Ueshima, Okamura, Kita, Hayakawa, Kadowaki.


Administrative, Technical or Material Support: Ueshima.

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