Although coronary heart disease (CHD) is a major cause of mortality worldwide, Japan is known as the nation with the lowest CHD morbidity and mortality among the developed countries. However, the age-adjusted incidence of acute coronary syndrome in Japan has not decreased over the past 4 decades. More recently, a study has shown that the incidence of CHD among Japanese workers has tripled from the 1960s to the 1990s, presumably because of lifestyle changes (e.g., high-fat diet and sedentary lifestyle). Thus, issues regarding the prevention of CHD have emerged in Japan as well.

Effective prevention of CHD could be achieved by identifying individuals at high-risk for CHD and performing subsequent interventions with regard to their risk factors. To this end, several novel biomarkers beyond the traditional risk factors have been investigated, and above all, C-reactive protein (CRP) has been studied intensely and nearly verified as a predictor of CHD. Consequently, the American Heart Association and the Centers for Disease Control and Prevention have issued a guideline on the application of CRP to clinical practice for CHD risk evaluation. They have defined high CHD risk as CRP >3 mg/L and low risk as <1 mg/L.

However, few prospective or cross-sectional studies have been conducted to assess the relationship between CRP and CHD in Japanese. Although one study has prospectively reported a positive association between CRP and CHD among Japanese-Americans in Hawaii, this population has been demonstrated to have 40% higher age-adjusted CHD mortality than Japanese living in Japan, presumably because of the differences in lifestyle. Meanwhile, several studies have reported that CRP is related to various atherosclerotic risk factors and their clustering, a condition conceptualized as metabolic syndrome (MS). Given that MS is linked to an increased incidence of CHD, it can be speculated that increasing CRP is associated with increasing coronary events even in Japanese. Recently, however, the CHD predictability of MS has been reported to be inconsistent and inferior to that of the Framingham Risk Score (FRS) validated estimation of coronary risk.

Therefore, the aim of this cross-sectional study was to investigate the association of high-sensitivity CRP (hs-CRP) with the Framingham Risk Score among Japanese male workers in Japan in order to infer the association between CRP and CHD in Japanese.

**Methods**

**Study Subjects**

In 2002, we studied a population of 2,784 Japanese men, aged 35–66 years, working at the Aichi Prefectural government.

**Background**

Although numerous studies have demonstrated a positive association of high-sensitivity C-reactive protein (CRP) with the incidence of coronary heart disease (CHD), little information exists regarding this issue in Japanese.

**Methods and Results**

The association between CRP and the Framingham Risk Score (FRS) was investigated in 2,523 middle-aged Japanese men without a medical history of CHD. CRP was significantly associated with this score obtained from all FRS factors. After dividing subjects into 4 categories of relative risk estimate for CHD, the geometric mean of CRP (mg/L) increased gradually with the CHD risk (below average: 0.39 [95% confidence interval, 0.37–0.41], average: 0.58 [0.50–0.67], moderately above average: 0.70 [0.57–0.86], high: 0.79 [0.58–1.09], trend p<0.001). However, it should be noted that the mean CRP concentration of the high-risk group was only 0.79 mg/L and a greater proportion (63.8%) of the high-risk subjects was in the low-risk range of CRP (<1 mg/L).

**Conclusions**

Circulating CRP well reflect the estimated CHD risk, indicating that CRP may be useful for coronary risk stratification in Japanese also. However, the details of the CRP level in Japanese must be investigated further by prospective studies to determine the Japanese-specific cutoff points for CHD risk evaluation.
CRP and Estimated Coronary Risk in Japanese Men

Table 1  Relative Risk Estimate for CHD According to the FRS and Age

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Relative risk estimate for CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Below average</td>
</tr>
<tr>
<td>35–39</td>
<td>≤2</td>
</tr>
<tr>
<td>40–44</td>
<td>≤3</td>
</tr>
<tr>
<td>45–49</td>
<td>≤5</td>
</tr>
<tr>
<td>50–54</td>
<td>≤6</td>
</tr>
<tr>
<td>55–59</td>
<td>≤7</td>
</tr>
<tr>
<td>60–64</td>
<td>≤8</td>
</tr>
<tr>
<td>65–66</td>
<td>≤9</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; FRS, Framingham Risk Score.

Table 2  Characteristics of the Study Subjects

| Age (years) | 48±7          |
| BMI (kg/m²) | 23±3          |
| Current smoker [n (%)] | 903 (35.8) |
| LDL-C (mg/dl) | 125±90       |
| HDL-C (mg/dl) | 59±14         |
| Glucose (mg/dl) | 95±22         |
| SBP (mmHg) | 129±15        |
| DBP (mmHg) | 80±11         |
| CRP (mg/L) | 0.42 (0.40–0.44) |
| Hypertension [n (%)] | 166 (6.6)  |
| DM [n (%)] | 45 (1.8)       |

n=2,523.
Values are mean±SD, number (%), or geometric mean (95% confidence interval), as appropriate.
BMI, body mass index; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; DM, diabetes mellitus.

Framingham CHD Risk Score

Following the authorized algorithm,2 we calculated the FRS for each subject according to age, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), BP, diabetes mellitus (DM), and smoking behavior (Fig 1). As indicated in the statement on FRS by the American Heart Association and the American College of Cardiology,23 DM was defined as fasting glucose ≥126 mg/dl or self-reported medication for DM, and the scoring of BP was conducted regardless of whether or not the subjects were taking medication for hypertension. Current smokers were classified as having smoking behavior.

Although the validity of FRS in estimating absolute CHD risk has been confirmed only in whites and blacks,23,24 it is considered that the FRS can be used for relative risk estimates in other ethnic groups, including Japanese,23 based on the common assumption that the relative contributions of each FRS factor to CHD risk might be similar in varied populations.23 Therefore, in the present study we particularly focused on the relative risk for CHD estimated by the FRS.23,24 Following the aforementioned statement,3 each subject was allocated 1 of the 4 categories of CHD relative risk estimate (ie, below average, average, moderately above-average, or high), according to their total FRS and age range (Table 1). In this categorization, the average risk refers to that observed in each 5-year range of age from 30 to 74 in the Framingham cohort. The moderately above-average risk and the high risk categories designated an approximately 3-fold and a 4-fold or more higher risk, respectively, compared with the lowest risk in each age category, where the lowest risk is defined as the risk of those with all of the following conditions: LDL-C between 100 and 129 mg/dl, HDL-C ≥45 mg/dl, systolic BP <120 mmHg and diastolic BP <80 mmHg, no DM and nonsmoker.23

Biochemical Analysis

Venous blood samples were drawn from each subject after an 8-h or overnight fast. The samples were stored at −80°C until biochemical assay. LDL-C was determined enzymatically and HDL-C was measured by the phosphotungstic state method. Glucose was enzymatically determined by the hexokinase method. hs-CRP was measured by latex nephelometry (BNII, Dade Behring Co, Ltd), which was sensitive enough to detect 0.02 mg/L. The coefficient of variation for repeated measurements of hs-CRP was 3.1–4.0%.

Statistical Analysis

All statistical analyses were conducted with SPSS version 12.0 (SPSS Inc, Chicago, IL, USA). All continuous variables are shown as mean±SD, except for hs-CRP, which was natural-log-transformed to approximate normal distribution for the analyses, transformed back for data pre-
sentation, and shown as the geometric mean and 95% confidence interval (CI). First, Spearman’s correlation analysis was performed for the hs-CRP and individual FRS factor scores. Subsequently, comparisons of geometric means of hs-CRP among groups were conducted by analysis of variance or analysis of covariance. The test for trend was performed with a polynomial contrast procedure. All reported p-values were 2-sided, and a p-value <0.05 was considered statistically significant.

Results

Characteristics of the study subjects are shown in Table 2. As demonstrated by the mean values of LDL-C, HDL-C, glucose, and BP, the present population was quite healthy. There were only a few persons who were taking medication for hypertension or DM (6.6% or 1.8%, respectively).

hs-CRP significantly correlated with each of all the scores corresponding to the individual FRS factors (Table 3). Among them, the score according to HDL-C concentration was most strongly associated with hs-CRP ($r=0.227$), whereas LDL-C score was least correlated ($r=0.073$). When the geometric means of hs-CRP were compared among the groups classified by the scores corresponding to each FRS factor, the hs-CRP level exhibited an increasing trend along with the elevation of scores for all factors (all trend p<0.05, Fig 1). Because there were only 4 subjects aged ≥65 years, they were included in the group aged 60–64 years in this analysis. The significant associations between hs-CRP and the scores for LDL-C, HDL-C, BP, DM, or smoking were unaltered, even after adjusting for age (all trend p<0.05).

Summing these scores corresponding to the individual FRS factors, we computed the total FRS for each subject. Next, all subjects were allocated to 1 of the 4 categories of relative risk estimate for CHD: 2,140 subjects (84.8%) were below-average risk, 219 subjects (8.7%) were average risk, 117 subjects (4.6%) were moderately above-average risk, and 47 subjects (1.9%) were high risk. As shown in
Corresponded to the 75th percentile in Japanese-Americans,11 hs-CRP level of 1 mg/L, the cutoff point for low CHD risk, lower range than Western populations. Specifically, the because their levels of hs-CRP are distributed over a much range (<1 mg/L). This concern also seems to apply to “high risk” subjects had a hs-CRP level in the “low risk” in the present study the greater proportion (63.8%) of the actually at high risk for CHD as having a low risk. Indeed, lead medical practitioners to mistake Japanese who are risk according to the guideline proposed by the Centers for Japanese men was only 0.79 mg/L, a value considered a low risk evaluation. The most important finding of the present study is obviously that the geometric mean of hs-CRP in the high-risk Japanese men was only 0.79 mg/L, a value considered a low risk according to the guideline proposed by the Centers for Disease Control and Prevention and the American Heart Association10 Thus, the application of this guideline might lead medical practitioners to mistake Japanese who are actually at high risk for CHD as having a low risk. Indeed, in the present study the greater proportion (63.8%) of the “high risk” subjects had a hs-CRP level in the “low risk” range (<1 mg/L). This concern also seems to apply to Japanese descendants (eg, Japanese-Americans in Hawaii) because their levels of hs-CRP are distributed over a much lower range than Western populations. Specifically, the hs-CRP level of 1 mg/L, the cutoff point for low CHD risk, corresponded to the 75th percentile in Japanese-Americans11 but to the 33rd percentile in the general American population10

Despite this low CRP level, however, Japanese-Americans in the top quartile of hs-CRP (>1.00 mg/L) have demonstrated an approximately 2-fold higher incidence of myocardial infarction over a 20-year follow-up compared with those below the lowest quartile (<0.32 mg/L).11 Meanwhile, it has been reported that the median hs-CRP among Japanese patients with acute myocardial infarction was 1.3 mg/L.27 Moreover, Wakugawa et al have demonstrated that among the Hisayama Study cohort men in the highest quintile of hs-CRP (>1.56 mg/L) have an approximately 7-fold higher incidence of ischemic stroke than men in the lowest quintile (<0.21 mg/L).28 Thus, when all these findings and our results are taken into account, Japanese with a hs-CRP concentration of 0.8–1.6 mg/L should not be uniformly regarded as having a low or average risk for cardiovascular disease.

Discussion

The significant association of hs-CRP with the 6 risk factors incorporated into the FRS among Japanese has been already demonstrated13–19 and in the present study we have extended these findings to a more clinically applicable form using the FRS, which permitted us to assess the relationship between hs-CRP and a comprehensively estimated coronary risk. In keeping with a previous report from the Pravastatin Inflammation/CRP Evaluation (PRINCE) Study, which mainly dealt with Caucasians25 the circulating level of hs-CRP was also significantly associated with the CHD risk estimated by the FRS in Japanese. Further, we strengthened this finding by showing a significant association between hs-CRP and the calculated CHD risk, independent of obesity, which is known as a major predictor of hs-CRP elevation.26 Thus, the present findings raise the possibility that hs-CRP parallels, to some extent, the CHD risk in Japanese and hence may be useful for their coronary risk evaluation.

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Based on a cross-sectional study to diagnose MS, Oda et al25 have proposed a hs-CRP cutoff point of 0.65 mg/L for Japanese, a value somewhat lower than the mean CRP level of high estimated coronary risk in the present study (0.79 mg/L). Considering the respective characteristics of the FRS and MS, this difference would be appropriate. Namely, the cutoff values of most components of MS are shifted to the value taken as normal in identifying respective risk factors26 so the MS population could include individuals at less CHD risk than those classified as high risk by the FRS. In addition, the important predictors of hs-CRP level, age and smoking,22 are not included in the MS criteria.

Nevertheless, the present and the other cross-sectional studies were not ideal for determining the Japanese-specific cutoff point of hs-CRP. Furthermore, it has been clearly demonstrated that the associations of atherosclerotic risk factors with coronary events are continuous29 so their cutoff points have been determined to some extent arbitrarily from the numerous evidence31 This could be also the case for hs-CRP, as most studies have shown a dose–response relationship between circulating hs-CRP level and the cardiovascular disease risk.32 The gradient association between hs-CRP and the CHD risk shown in Fig 2 agrees with these observations. Further prospective studies, therefore, are needed to determine the appropriate cutoff point of hs-CRP for detecting Japanese at high CHD risk.

The mechanisms to explain why the hs-CRP concentration is low in Japanese are not clear, but could be explained in part by their lower adiposity. However, some investigators have reported that differences among races in the hs-CRP level cannot be fully explained by differences in the metabolic risk factors33 suggesting the possibility of genetic reasons. The present study supports the material ethnic difference in hs-CRP level, because the individuals in the high estimated coronary risk group should have had abnormal metabolic factors. Nevertheless, from a pathophysiologic perspective, it seems worthwhile to investigate the link between the low hs-CRP level even in the high risk state and the low CHD incidence in Japanese, because the conditions of most traditional risk factors (eg, total cholesterol level and BP) in Japan are not so different nowadays than in the United States and cannot fully explain the much lower CHD incidence in Japan.34–36 Moreover, the prevalence of smoking, a strong predictor of CHD, is higher in
Japan.

We observed a few interesting findings through the analyses of relationships between hs-CRP and each FRS factor. First, those aged 60 years or more showed far higher hs-CRP than the other age groups (Fig 1), implying the existence of a threshold in the association between age and hs-CRP. Although the exact reasons for this finding are unclear, it may reflect the deterioration of risk factors other than age in older subjects (mean FRS without age of those aged ≥60 and that of those aged <60 years were 1.75 and 0.96, respectively, p<0.001). Besides, decreased testosterone, a condition usually observed in elderly men, may be a link, because testosterone has been shown to have an anti-inflammatory function.

Second, those in the lowest category of HDL-C (<35 mg/dL) demonstrated a lower hs-CRP level than those with HDL-C between 35 and 44 mg/dL, suggesting an “inverse U-shaped” association between hs-CRP and categorized HDL-C (quadratic trend p=0.007). This might not be conclusive, because fewer subjects were allocated to the group with the lowest HDL-C, and its CI was wide. However, some individuals with low HDL-C reportedly have a particular type of apolipoprotein A-I, demonstrating lower development of atherosclerosis than expected from their HDL-C concentrations. In addition, it has been recently suggested that the serum HDL-C concentration does not always properly represent its anti-inflammatory function. Thus, it seems worthwhile to investigate the association of HDL function with inflammation among Japanese.

Study Limitations

First, only a few subjects were allocated to the high-CHD risk category; however, we considered that the distribution of hs-CRP levels in our high-risk group was not largely biased toward a low concentration, because the mean hs-CRP value in this group (0.79 mg/L) approximated the value of 1.00 mg/L, which distinguished the highest CHD risk population among Japanese-Americans in Hawaii.

Additionally, the ratio of mean hs-CRP concentration between the high and the low risk groups (ie, 2.0) was almost similar to that observed in the PRINCE Study. A second limitation is that all subjects in the present study were men. The issue of gender difference in hs-CRP level remains controversial; so further studies are needed to estimate the association between hs-CRP and the CHD risk in Japanese women. Finally, we studied the association of hs-CRP with the CHD risk using the scoring algorithm of traditional risk factors. Therefore, whether hs-CRP predicts CHD independently of those risk factors remains to be elucidated.

Conclusion

This cross-sectional study showed that hs-CRP reflected well the CHD risk estimated from FRS in Japanese men, raising the possibility that hs-CRP could be useful for their coronary risk stratification. More importantly, the mean hs-CRP concentration of the “high” CHD risk category was as low as 0.79 mg/L, and 63.8% of the “high” risk subjects were in the range of “low” coronary risk according to the hs-CRP level of the existing guideline. Therefore, application of this guideline is likely to overlook Japanese at high coronary risk. The present data are important because they have clinical implications, not only for Japanese in Japan but also for the estimated 2.6 million Japanese descendants living overseas. Thus, further prospective studies should be conducted to confirm hs-CRP as a CHD predictor for Japanese, particularly whether it is independent of traditional risk factors, and to determine the specific cutoff point.

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