Fruit and Vegetable Intake and Mortality from Cardiovascular Disease Are Inversely Associated in Japanese Women but Not in Men¹,²

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Abstract

Some epidemiological studies undertaken in Western countries have demonstrated that high intake of fruit and vegetables results in decreased risk of cardiovascular disease (CVD). The objective of this study was to examine the hypothesis that high intake of fruit and vegetables lowers CVD mortality in a population-based cohort of Japanese subjects. In 1992, fruit and vegetable intake was assessed in 13,355 men and 15,724 women in Takayama, Gifu, Japan using a validated FFQ. During the follow-up (1992–99), 200 men and 184 women died from CVD. For women, the highest quartile of vegetable intake compared with the lowest was marginally significant and inversely associated with CVD mortality after adjusting for total energy, age, and nondietary and dietary covariates [hazard ratio (HR) = 0.62; 95% CI, 0.36–1.08; P-trend = 0.007]. An inverse trend with borderline significance was also observed in fruit intake, excluding CVD deaths in the first 2 y of this study, after adjusting for the above-mentioned covariates (HR = 0.83; 95% CI, 0.51–1.34; P-trend = 0.10). In men, CVD death was not associated with fruit (HR = 1.16; 95% CI, 0.77–1.74; P-trend = 0.61) and vegetable (HR = 0.81, 95% CI: 0.49–1.34; P-trend = 0.47) intake. These data suggest that higher intake of vegetables is associated with reduced risk of death from CVD for women. J. Nutr. 138: 1129–1134, 2008.

Introduction

Cardiovascular disease (CVD)⁶ is the main cause of death in Western countries and in the Asia-Pacific region, including Japan (1). In many epidemiological and clinical studies, it has been suggested that the risk factors for CVD, including hypertension, obesity, insulin-resistance diabetes, and hypercholesterolemia, are essentially influenced by diet (2–10). Because dietary habits are correctable, it is possible for individuals to adopt healthy eating habits that have a protective effect against CVD. Several laboratory studies have shown that compounds in fruit and vegetables, which have an antioxidant effect, provide beneficial effects on atherosclerosis and CVD (11–16). On the other hand, a diet high in fruit and vegetables has another advantage, namely, that of lowering the dietary glycemic load and energy density (17).

In some epidemiological studies, the direct association between fruit and vegetable intake and the risk of CVD has been studied extensively and the results have shown a relationship between high fruit and vegetable intake and reduced risk of stroke and ischemic heart disease (18–25). However, most of these studies have been conducted in Western countries. To our knowledge, there have been only 2 prospective cohort studies that examined the relationship between the estimates of fruit and vegetable intake and CVD in Asian countries, both conducted in Japan (24,25). One study demonstrated that the risk of CVD was inversely associated with fruit, but not vegetable, intake. In the other study, CVD mortality was inversely associated with leafy vegetable intake. A prospective study that was conducted using dietary patterns in China examined the association between vegetable intake pattern and CVD mortality (26). However, vegetable intake was not assessed in the study. Studies on the relationship between fruit and vegetable intake and CVD in Asian countries are too few to compare the findings with those of studies conducted in Western countries. We examined the association between fruit and vegetable consumption and mortality from CVD in a cohort of men and women in a community in Japan (Takayama Study).

Materials and Methods

Study population. Subjects were cohort members from the Takayama Study, which was a population-based cohort study conducted in Takayama, Gifu, Japan in September of 1992. A detailed description has been reported elsewhere (27). Eligible participants were nonhospitalized residents of...
Takayama aged ≥35 y. At baseline, a self-administered questionnaire designed to obtain information on demographic characteristics, smoking and drinking habits, diet, exercise, and reproductive and medical histories was distributed to 36,990 residents. Subjects who left pages blank and/or inappropriately completed the questionnaire were excluded from the cohort [criteria shown in (27)]. The final number of subjects in the Takayama Study was 31,152 (14,427 men and 17,125 women). The participation rate was 85.3%.

Assessment of diet and exercise. Dietary history was assessed using a semiquantitative FFQ that included 169 food items. Participants reported average consumption frequency and usual serving size for each food in the previous year. The individual intake of food and nutrients was estimated from the frequency of intake and portion size using the Standard Tables of Food Composition in Japan (28). Fourteen items for vegetables [cucumber, tomato, lettuce, celery, broccoli, cauliflower, cabbage, green vegetables (including spinach and pepper), carrot, pumpkin, mountain plant, Japanese radish, legumes, and other vegetables (including eggplant and onion)], 12 items for fruits (orange, grapefruit, melon, banana, kiwi, mandarin orange, peach, watermelon, apple, pear, Japanese persimmon, and strawberry), and other foods including fruits and vegetables as ingredients were taken into account to estimate the individual intake. Soy products were not included as vegetables. The validity and reproducibility of the FFQ were demonstrated by comparing it with other dietary assessment methods, including 3-d food records, 4 24-h diet recalls, and 12 1-d diet records over 1 y (29). The Spearman correlation coefficients between the questionnaire and the 12 1-d diet records over 1 y for the intake of fruit and vegetables were 0.57 ($P = 0.05$) and 0.51 ($P < 0.05$) in men and 0.74 ($P < 0.001$) and 0.41 ($P = 0.069$) in women, respectively. Our questionnaire was designed to measure an individual’s relative intake of food and nutrients rather than absolute values. The estimates calculated for fruit and vegetables may have been overestimated by our questionnaire, because the estimates were −5–12% higher for fruit and 44–45% higher for vegetables on the FFQ than those based on the diet records.

Exercise was assessed by asking study participants to specify the average number of hours per week that they had spent performing various kinds of activities during the previous year. The reported time spent at each activity weekly was multiplied by its typical energy expenditure requirements, expressed as a metabolic equivalent (MET) and added to yield a MET h/wk score. The details are described elsewhere (30).

Follow-up and outcomes. All deaths in Takayama and their causes during the follow-up period (1992–99) were ascertained using data from the office of National Vital Statistics. The Statistics and Information Department of the Japanese Ministry of Health and Welfare obtains information on death and codes the causes of death using the International Classification of Diseases, Tenth Revision (ICD10). Permission to inspect information on death and codes the causes of death using the International Classification of Diseases, Tenth Revision (ICD10) was obtained from the residential registers of the city. During the follow-up period, 640 (4.5%) men and 506 (3.0%) women moved out of Takayama. This study was approved by the ethics board of the Gifu University School of Medicine.

The primary endpoint for our analysis was CVD mortality. For the category of CVD-related atherosclerosis, we selected ischemic heart disease (ICD10 codes I20, I21, I24, and I25) and cerebrovascular disease (ICD10 codes I60–64, I67, and I69). For this analysis, we excluded subjects who had reported on the baseline questionnaire that they had a history of cancer (186 men and 540 women), stroke (253 men and 154 women), or ischemic heart disease (633 men and 707 women). Thus, the final analytic population at the baseline consisted of 29,079 subjects (13,355 men and 15,724 women).

Statistical analysis methods. To evaluate the association of the intake of fruit and vegetables with death from CVD, we computed the hazard ratios (HR) and their 95% CI of death from CVD during the period of our study using Cox proportional hazard models. For each subject, person-years of follow-up were accumulated from the beginning of the study (September 1, 1992) until the date of death from CVD or any other cause, the date when an individual moved out of Takayama, or the final date of the study (December 31, 1999), whichever came first. Estimates of food and nutrients were adjusted for individual total energy by using the residual method proposed by Willett (31). The energy-adjusted intake of fruit and vegetables was categorized by the quartiles on the basis of their distribution among the total study population at the baseline. The HR and their 95% CI for CVD mortality in the 2nd, 3rd, and highest category of intake of fruit and vegetables were computed compared with the lowest one.

To identify any potential confounders, we adopted not only the variables that changed the risk estimate of CVD mortality in the univariate analysis but also those that have the obvious and well-known effect of fruit and vegetables on CVD. In the multivariate analysis of model 2, the associations of fruit and vegetable intake with CVD mortality were examined by adjusting for age, total energy, and nondietary factors, including marital status, years of education, BMI, smoking status, alcohol consumption, exercise (MET-h/wk), menopausal age, and history of diabetes and hypertension. Saturated fat was a potential confounder in previous studies (32,33). In our cohort, sodium intake was significantly and positively associated with deaths from stroke (34) and protein intake was marginally and inversely associated with the rate of CVD in the present analysis. Therefore, in the analysis of model 3, total protein, saturated fat, and sodium intakes were further included in the model as covariates. Statistical testing for linear trends was performed on continuous variables of intake. All statistical analyses were performed using SAS programs (version 9.1.3; SAS Institute). Because latent CVD might have contributed to changes in dietary habits, we further repeated the analysis after excluding the subjects who had died from CVD (66 men and 70 women) during the first 2 y of follow-up.

Results

At baseline, participants with the highest consumption of fruits and vegetables tended to be older and were less likely to be current tobacco and alcohol users and more likely to be married and educated and to have hypertension and diabetes (Table 1). During 201,156 person-years of follow-up over 7 y (median follow-up period of 7.33 y), 384 deaths (200 men and 184 women) occurred due to CVD, i.e. 269 cases of cerebrovascular disease (137 men and 132 women) and 115 cases of ischemic heart disease (63 men and 52 women). In Table 1, we show the servings per day for the consumption of fruit and vegetables. The serving size was determined as 77 g for vegetables and 80 g for fruits (35).

In model 1, after adjustment for age and total energy, mortality from CVD was not associated with total fruit or vegetable intake for men (Table 2). In a multivariate analysis after controlling for nondietary factors (model 2) or after additional controlling for dietary factors (model 3), the results were not substantially altered. In women, HR decreased for the highest compared with the lowest quartile of total vegetable intake (HR = 0.68; 95% CI, 0.44–1.07) in model 2. Although the estimate was not significant (P = 0.09), the linear trend for vegetable intake and the risk of death from CVD was significant (P-trend = 0.02). In the analysis after exclusion of the subjects who had died due to CVD within the first 2 y of this study, the association of vegetable intake with CVD death was somewhat attenuated, but the linear trend was still significant (P-trend = 0.04).

In the stratified analysis according to tobacco use, vegetable intake was somewhat more inversely associated with CVD mortality in men who had never smoked; the HR and 95% CI of CVD deaths in men with the lowest intake were 0.48 (95% CI, 0.13–1.73), 0.91 (95% CI, 0.32–2.65), and 1.19 (95% CI, 0.62–3.59) for the 2nd to the highest quartiles of vegetable intake, respectively, after excluding CVD deaths during the first 2 y of follow-up. On the other hand, in smokers, the corresponding

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HR were 0.89 (95% CI, 0.48–1.63), 1.14 (95% CI, 0.65–2.00), and 1.24 (95% CI, 0.73–2.11), respectively. However, the interaction between smoking and vegetable intake for the risk of death from CVD was not significant ($P = 0.53$).

We repeated the analysis between premenopausal and postmenopausal women. The HR of CVD death for the top quartile of fruit and vegetable consumption compared with the lowest was 0.60 (0.15–2.67) and 0.88 (0.15–5.30) in premenopausal women and 0.90 (0.57–1.43) and 0.70 (0.43–1.13) in postmenopausal women, respectively.

We also conducted a subgroup analysis in younger (<60 y) and older (≥60 y) subjects, because there were relatively few older people who ate few vegetables and relatively many who ate more vegetables. In men, the HR (95% CI) of the risk of CVD with the highest compared with the lowest quartile of vegetable intake were 0.45 (0.16–1.23) and 1.16 (0.74–1.83) in younger and older subjects, respectively. In women, the HR (95% CI) of CVD with the highest compared with the lowest quartile of vegetable intake were 0.34 (0.06–1.55) and 0.65 (0.40–1.05) in younger and older subjects, respectively.

**Discussion**

In this population-based prospective cohort study, we observed a significant trend between vegetable intake and risk of death due to CVD in women but not in men. Compared with women who consumed the lowest amount of vegetables, those women who consumed the highest were at a lower risk of CVD mortality. The inverse association between fruit and death from CVD in women...
Table 2: HR and 95% CI of mortality from CVD according to fruit and vegetable intake

<table>
<thead>
<tr>
<th>Fourth</th>
<th>Median intake</th>
<th>CVD deaths</th>
<th>Person-years</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 3*</th>
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<tbody>
<tr>
<td></td>
<td>servings/d</td>
<td>n</td>
<td>n</td>
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<td>Men</td>
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<td>Total fruit</td>
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<tr>
<td>1 (low)</td>
<td>0.3</td>
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<td>22,872</td>
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<td>1.00</td>
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<td>2</td>
<td>0.7</td>
<td>54</td>
<td>22,829</td>
<td>1.09 (0.73–1.62)</td>
<td>1.11 (0.75–1.65)</td>
<td>1.09 (0.73–1.62)</td>
<td>1.10 (0.70–1.74)</td>
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<td>3</td>
<td>1.3</td>
<td>42</td>
<td>22,820</td>
<td>0.85 (0.56–1.29)</td>
<td>0.90 (0.59–1.39)</td>
<td>0.90 (0.58–1.38)</td>
<td>0.93 (0.57–1.52)</td>
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<tr>
<td>4 (high)</td>
<td>2.6</td>
<td>59</td>
<td>22,515</td>
<td>1.16 (0.78–1.71)</td>
<td>1.20 (0.80–1.79)</td>
<td>1.16 (0.77–1.74)</td>
<td>1.27 (0.81–2.01)</td>
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<td>P-trend</td>
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<tr>
<td>1 (low)</td>
<td>2.2</td>
<td>38</td>
<td>23,063</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>2</td>
<td>3.4</td>
<td>33</td>
<td>22,860</td>
<td>0.68 (0.43–1.08)</td>
<td>0.70 (0.44–1.11)</td>
<td>0.68 (0.42–1.09)</td>
<td>0.61 (0.46–1.43)</td>
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<td>3</td>
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<td>53</td>
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<td>0.89 (0.58–1.36)</td>
<td>0.83 (0.52–1.32)</td>
<td>0.86 (0.63–1.85)</td>
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<td>4 (high)</td>
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<td>76</td>
<td>22,304</td>
<td>0.84 (0.56–1.25)</td>
<td>0.91 (0.60–1.36)</td>
<td>0.81 (0.49–1.34)</td>
<td>1.02 (0.57–1.82)</td>
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<td>P-trend</td>
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<td>Women</td>
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<td>Total fruit</td>
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<tr>
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<td>52</td>
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<td>1.00</td>
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<tr>
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<td>0.9</td>
<td>48</td>
<td>27,638</td>
<td>0.67 (0.65–1.45)</td>
<td>0.98 (0.64–1.50)</td>
<td>0.99 (0.65–1.50)</td>
<td>0.95 (0.59–1.52)</td>
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<tr>
<td>3</td>
<td>1.5</td>
<td>35</td>
<td>27,562</td>
<td>0.75 (0.49–1.41)</td>
<td>0.74 (0.47–1.17)</td>
<td>0.74 (0.47–1.18)</td>
<td>0.71 (0.42–1.18)</td>
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<tr>
<td>4 (high)</td>
<td>2.7</td>
<td>51</td>
<td>27,463</td>
<td>1.07 (0.71–1.55)</td>
<td>1.01 (0.67–1.53)</td>
<td>0.99 (0.66–1.50)</td>
<td>0.83 (0.51–1.34)</td>
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<td>P-trend</td>
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<tr>
<td>1 (low)</td>
<td>2.5</td>
<td>43</td>
<td>27,496</td>
<td>1.00</td>
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<td>3.6</td>
<td>47</td>
<td>27,621</td>
<td>0.87 (0.59–1.35)</td>
<td>0.84 (0.54–1.31)</td>
<td>0.80 (0.50–1.28)</td>
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<tr>
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<td>4.8</td>
<td>49</td>
<td>27,480</td>
<td>0.82 (0.54–1.23)</td>
<td>0.82 (0.53–1.26)</td>
<td>0.78 (0.47–1.25)</td>
<td>0.83 (0.47–1.47)</td>
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<tr>
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<td>7.4</td>
<td>45</td>
<td>27,524</td>
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<td>0.77 (0.41–1.46)</td>
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<tr>
<td>P-trend</td>
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1 Highest vs. lowest quartile.
2 Using continuous variables.
3 Adjusted for age and total energy.
4 Adjusted for age, total energy, marital status, years of education, BMI, smoking status (never, former, current), alcohol intake, exercise, history of hypertension or diabetes mellitus (non-diabetic factors), and menopausal status.
5 Adjusted for the above nondiabetic confounders and dietary confounders (total protein, saturated fat, and sodium intake).
6 Excluded CVD deaths in the first 2 y of the study.

was not significant (P-trend = 0.11). In men, fruit or vegetable consumption was not associated with CVD mortality, even after excluding the cases in which individuals died from CVD in the first 2 y of follow-up.

To our knowledge, there have been 6 prospective cohort studies of dietary fruit and vegetable consumption in relation to the risk of CVD in Western countries. In Japan, we found 2 prospective cohort studies in which the relationship between dietary fruit and vegetable intake and CVD was assessed (24,25). In 1 study conducted between 1980 and 1998, the daily consumption of green-yellow vegetables and fruit was associated with a lower risk of stroke mortality in atomic bomb survivors. However, the estimates of fruit and vegetable intake were based on a limited number of foods listed in the questionnaire (24). Another study conducted between 1995 and 2002 indicated that high consumption of fruit, but not vegetables, was associated with lower risk of CVD (25). In that study, as well as ours, a validated questionnaire using various kinds and items as foods was used.

Three of the 6 studies conducted in Western countries indicated that the intake of fruit and vegetables was significantly and inversely associated with CVD mortality (19,21,23). In these reports, the HR (95% CI) were 0.54 (0.34–0.86), 0.73 (0.58–0.92), and 0.70 (0.55–0.89). The other 3 found that there tended to be an inverse association between fruit and vegetable intake and the risk of CVD (P = 0.09–0.15) (18,20,22). These findings suggested a modest inverse association between fruit and vegetable intake and the risk of CVD. In our study, in which fruit and vegetable intake were treated separately, there were modest inverse associations with death of CVD in women, which are consistent with the results from these previous studies. In men, we did not find a significant association between mortality from CVD and fruit intake; however, vegetable intake reduced the risk of CVD. Considering the modest strength of the associations previously reported, our results of vegetable intake in men were not contradictory with those from previous studies.

The difference in the results between men and women may involve an interaction with cigarette smoking. In a previous study (18), inverse associations between fruit and vegetable intake and CVD mortality was stronger in individuals who had never smoked; therefore, there might be an interaction between the fruit and vegetable consumption and smoking status in the present analysis. Because in our cohort, the proportion of smokers in men was larger than in women, this difference might be responsible for the lack of significant differences in the former. The interaction of smoking and serum carotenoid concentrations with the development of diabetes has also been reported by Hozawa et al. (36). They suggested that cigarette smoking modified carotenoid metabolism and may have influenced the risk of diabetes. Another possibility is that the significant inverse trend of...
association between fruit and vegetable consumption and the risk of CVD in women might be influenced by an interaction with a sex hormone. Premenopausal women, who produce ovarian hormones in abundance, are protected from CVD and the rates of CVD for men exceed those for women at all ages (37). In our study, the HR of CVD deaths for fruit and vegetable intake in premenopausal women were lower than those in postmenopausal women.

We also considered the possibility that men had lower fruit and vegetable intakes or reported their diet less accurately than women. However, the intake of fruits as well as vegetables did not differ greatly between men and women. As reported in “Materials and Methods,” the results from the validity study of our FFQ were similar for men and women.

Our current study has several methodological advantages. The participants of our study were residents in a community in Japan. In addition, the study was prospective. Thus, we were able to reduce the likelihood of a recall bias and avoid a selection bias. Small loss of this cohort during the follow-up period (3.9%), and high participation rate (85.3%) at the baseline also were an advantage of our study.

On the other hand, our study had several limitations: for example, the use of mortality data rather than incidence data. We could not determine whether fruit and vegetable intake was related to incidence, survival, or both. Although our main interest in this study was CVD mortality, it was desirable to examine which type of CVD was related to dietary fruit and vegetable intake. If this present study had been large enough, we could have conducted a worthwhile analysis of fruit and vegetable intake and the mortality from ischemic stroke, cerebral hemorrhage, and ischemic heart disease separately.

The duration of follow-up may have been too short to assess the relationship between diet and death from CVD. The FFQ, like all methods of dietary assessment, is subject to measurement error. In addition, the dietary assessment was conducted only at baseline. Although we reported the analysis after excluding the individuals who had died from CVD during the first 2 y of follow-up, the change in diet during the follow-up may have affected the results.

In conclusion, our results suggest that high fruit and vegetable intake is associated with a modest reduction in CVD in Japanese women. To more accurately assess the association of fruit and vegetable consumption with death from CVD, larger studies that can include more intake categories are needed.

**Literature Cited**

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