Lack of Long-Term Effect of Vitamin C Supplementation on Blood Pressure

Mi Kyung Kim, Satoshi Sasaki, Shizuka Sasazuki, Shunji Okubo, Masato Hayashi, Shoichiro Tsugane

Abstract—In a double-blinded randomized controlled trial, we investigated the long-term effect of vitamin C supplementation on blood pressure. A total of 439 Japanese subjects with atrophic gastritis initially participated in the trial using vitamin C and β-carotene to prevent gastric cancer. Before and on early termination of β-carotene supplementation, 134 subjects dropped out of this trial, whereas 120 and 124 subjects took the vitamin C supplement daily at either 50 mg or 500 mg, respectively, for 5 years. Before supplementation, neither systolic nor diastolic blood pressure was significantly related with the serum vitamin C concentration. This relationship was unchanged after adjustment for age, body mass index, and alcohol intake or after stratification by gender. After 5 years, systolic blood pressure significantly increased in groups, regardless of vitamin C dose, compared with baseline. Systolic blood pressure in the high-dose group (500 mg daily) increased from 125.4 to 131.7 mm Hg (5.88 mm Hg increase; 95% confidence interval [CI], 3.11 to 8.65). This value was similar with that of the low-dose group (5.73 mm Hg increase; 95% CI, 2.62 to 8.83) and of the dropout group (4.52 mm Hg increase; 95% CI, 1.26 to 7.77). There was no difference in change of diastolic blood pressure among the 3 groups. In conclusion, we observed no reduction in blood pressure with long-term moderate doses (500 mg/d) of vitamin C supplementation in a high-risk population for stomach cancer and stroke. (Hypertension. 2002;40:●●●●●●●●.)

Key Words: vitamins ▪ blood pressure ▪ antihypertensive agents ▪ clinical trials

The hypothesis that antioxidant vitamins may exert potential protective effects against cardiovascular disease has long been the focus of considerable research. Several biologic mechanisms have been proposed to explain the association of vitamin C and cardiovascular disease, including an antioxidative effect on LDL, lowering of blood pressure (BP), serving as a marker of other preventive factors or healthy behaviors, and possibly other as yet unknown mechanisms. Several observational epidemiologic studies have raised the possibility that agents with antioxidant properties (including the dietary antioxidants β-carotene, vitamin C, and vitamin E) might play a potential role in reducing the risk of cardiovascular disease through lowering BP.

Several cross-sectional epidemiologic studies suggested that vitamin C status was inversely associated with BP and that a high intake of vitamin C was related to a reduced incidence of stroke and myocardial infarction. Randomized trials are the best way to determine whether a relationship is causal and whether an intervention has therapeutic relevance. Although some but not all findings from intervention trials have suggested vitamin C and/or fruit and/or vegetables have a BP-lowering effect, the scientific evidence is scarce, especially in Asian populations. In addition, previous reports from intervention trials have several limitations: short-term intervention, small number of subjects, not being community-based, or not being randomized. Moreover, in Japan, with its high prevalence of hypertension, few studies have been conducted on the relationship between vitamin C status and BP.

Based on proposed biological mechanisms and previous reports on vitamin C and BP, we hypothesized that serum vitamin C might be inversely associated with BP, and that if vitamin C affects BP, vitamin C supplementation could actually reduce it. Therefore, we examined the effect of 500 mg of vitamin C compared with 50 mg of vitamin C on BP in a double-blinded randomized controlled trial.

Methods

Study Population
Target subjects were Japanese men and women, age 40 to 69 years, living in a village within the Yokote Public Health Center district in Akita Prefecture, one of the regions with the highest mortality from gastric cancer and stroke in Japan. They regularly participated in annual screening programs for circulatory diseases conducted by each municipality under the National Health and Welfare Services Law for the Aged. The rationale, design, and methods of the study; the characteristics of the participants; and the measures of compliance have been described in detail elsewhere.

Received April 2, 2002; first decision April 25, 2002; revision accepted September 10, 2002.
Eligibility required diagnosis with atrophic gastritis; no past history of gastric cancer or related surgery; no previous history of liver cancer, cirrhosis, or of other cancers within the past 5 years; no abnormal liver function (aspartate aminotransferase > 100 U/L, alanine aminotransferase > 100 U/L, or alkaline phosphatase > 800 U/L); no use of diet supplements containing β-carotene or vitamin C; and no expectation of moving outside the study area within 1 year. Previous studies have shown a significant association between serum pepsinogen (PG) levels and endoscopically diagnosed atrophic gastritis. Serum PG levels have recently been considered reasonable indicators of atrophic gastritis. Based on the above criteria, we discontinued the treatment of any patient with atrophic gastritis. Thirty-three people were ineligible because they had previous histories of gastric cancer or related surgery; no previous history of cirrhosis, liver cancer, or other cancers within the past 5 years; and no expectation of moving outside the study area within 1 year. Of the 1231 individuals screened, 1214 provided serum for PG measurement, and 635 of them (52%) were diagnosed with chronic atrophic gastritis. Thirty-three people were ineligible because they failed to meet the additional eligibility criteria. Of the remaining 602 eligible individuals, 439 (73%) consented to take part in the trial. Out of 439 persons initially participating in the study, 134 subjects dropped out before and on modification of the study protocol based on a National Cancer Institute report that indicated that 2β-carotene trials had shown no benefit or potential harm from the supplement. Of the 305 remaining participants, 244 completed this study (Figure 1). In addition, because the study aim was to examine the 5-year effect of vitamin C supplementation on BP among those who completed the supplementation of vitamin C throughout the study period, those 61 subjects (24 on low dose and 37 on high dose) who dropped out for personal reasons after the protocol modification were excluded from the main analysis.

Conduct of the Trial
At the outset, in September 1995, we randomized the participants into 4 treatment groups using a 2×2 factorial design, whereby 0 or 15 mg/day β-carotene and 50 or 500 mg/day vitamin C were supplemented in a double-blind manner. Because of possible harm, we discontinued the β-carotene supplementation but continued the prescription of vitamin C for 5 years on March 1996. Informed consent was obtained from individuals willing to take part in the modified trial, and they were provided with new capsules containing vitamin C only (50 or 500 mg/day). Compliance with treatment was constantly encouraged and monitored by nurses, who interviewed the participants and recorded pill counts every 3 months (compliance rate, 80%). We also monitored adverse effects using a questionnaire at every visit. The study protocol was approved by the institutional review boards of the National Cancer Center and Hiraka General Hospital.

Measurements
Trained nurses measured the subject’s BP at baseline and during an annual visit for a regular screening program using a sphygmomanometer OKOSE-300 model (Matsuyoshi & Co) according to a common protocol. A single BP measurement was performed in this trial, and only 1 nurse was involved in the measurement each year. Subjects sat in silence for at least 2 minutes before the BP measurement, with their legs uncrossed and their arms crossed at heart level. All measurements were conducted by persons blinded to the intervention assignment.

At recruitment and after supplementation, participants provided information on their weight, height, and demographic details such as marital and occupational status, education attainment, smoking status, alcohol consumption, disease history, family history of disease, and general health status. Body mass index was computed as body weight (kg) divided by the square of body height (m²). Participants also completed a 138-item semiquantitative food frequency questionnaire (FFQ) to provide information on their food habits and usual consumption of food and beverage during 1 year, at enrollment in the trial and after supplementation (fifth year). The design of the FFQ was described in detail elsewhere. In a validation study of this FFQ, the median correlation coefficients between the intakes obtained from FFQ and those obtained from 28-day semi-weighted dietary records were 0.52 and 0.41 for 15 nutrients and 0.38 and 0.32 for 19 food groups in 102 men and 113 women, respectively. The energy-adjusted correlation coefficients for sodium intake were 0.41 in men and 0.48 in women (data not shown).

Fasting blood samples collected on entering the study in 1995 and at 5 years in 2000 were analyzed for serum vitamin C and lipids. Serum concentrations of total cholesterol, triglycerides, and HDL cholesterol were analyzed immediately after blood sampling. For vitamin C measurement, serum samples were stabilized by addition of meta-phosphoric acid and stored at −80°C before analysis, in which measurements were performed simultaneously (February 1997 for serum sample at baseline and November 2000 for serum sample at 5 years, respectively).

Statistical Analysis
Preliminary analyses were performed in an intention-to-treat fashion (439 subjects). The same analyses were also performed among those who completed this trial (378 subjects). However, there were no substantial differences in any baseline characteristics or overall conclusions between the 2 results.

Descriptive statistics were calculated and examined on baseline characteristics, nutrient intake, and food consumption. Comparisons between high- and low-dose groups were examined by t test or 1-way ANOVA for continuous variables. Comparisons of continuous variables between the 2 supplementation groups and the dropout group were examined by 1-way ANCOVA followed by a Duncan test. ANCOVA was also used to adjust for possible differences owing to the potentially confounding variables. Comparisons of categorical variables among groups were performed with Fisher’s exact test. The Statistical Analysis System, version 6.12 (SAS Institute Inc), was used for data analysis.

Results
We present data on 244 intervention group participants who completed the vitamin C supplementation for 5 years and on 134 subjects who dropped out before modification of the study protocol. At the time of rerandomization after modification of the study protocol, baseline characteristics did not differ between the 500-mg assigned group (n=161) and the 50-mg assigned group (n=144). Also, as shown in Table 1, baseline characteristics were not greatly different between the high- and low-dose groups, except for mean age. The mean and standard deviations in systolic BP (SBP) and diastolic BP (DBP), as well as in serum vitamin C levels, did not statistically differ between the high- and low-dose groups or among the 3 groups (2 completed groups and dropout group). Sodium and salt intake were

Figure 1. Profile of a randomized controlled trial.
not different between groups and did not differ according to the BP level. The inclusion of 61 subjects who dropped out after the protocol modification did not affect this study finding.

**Relationship With BP and Serum Vitamin C at Baseline**

We examined the associations between BP and serum vitamin C concentration and other selected factors among groups (2 completed groups and dropout group; data not shown). When both sexes were combined, both SBP and DBP were positively related to age, body mass index, and serum triglyceride levels; however, this was not true of men, in whom SBP was positively related to age only. Neither SBP nor DBP was significantly related with serum vitamin C concentration in men and/or women. This relationship was unchanged after adjustment for age, body mass index, and alcohol intake. We have also examined the possible association between BP and serum vitamin C when including and excluding current smokers; the magnitude of the correlation coefficients did not remain significant nor did it differ markedly between the 2 results. The same analysis was performed among the study subjects, excluding those who had taken antihypertensives medication. Neither SBP nor DBP was significantly corre-
lated with serum vitamin C, whether those given antihypertensives were included or not. In addition, the serum vitamin C concentration was negatively correlated with alcohol intake in male subjects.

### Effects of Long-term Vitamin C Supplementation on BP

Baseline SBP and DBP did not differ between the high- and low-dose groups or among the 3 groups in both sexes. Table 2 shows mean changes in BP during the 5-year supplementation. After vitamin C supplementation, SBP, but not DBP, significantly increased in all 3 groups compared with the baseline, regardless of the vitamin C dose. SBP in the high-dose group (500 mg vitamin C daily) increased from 125.4 to 131.7 mm Hg (5.88 mm Hg increase; 95% confidence interval [CI], 3.11 to 8.65). This value was similar to that of the low-dose group (5.73 mm Hg increase; 95% CI, 2.62 to 8.83) and the dropout group (4.52 mm Hg increase; 95% CI, 1.26 to 7.77). These increments were clearly significant in female subjects but not in men.

Antihypertensive medications may affect the BP level. Participants began to take antihypertensives after randomization was 9 in the high-dose group and 11 in the low-dose group. As shown in Table 2, to discriminate the effect of vitamin C with antihypertensive medications on the BP level, we performed a subgroup analysis. Even when excluding those on antihypertensives, increases in SBP remained significant in all 3 groups. For DBP, the changing pattern was different from that of SBP. There was no difference in DBP change in any group, regardless of taking or not taking antihypertensives. However, in the low-dose group, DBP decreased in male subjects (−5.79 mm Hg), whereas it increased in female subjects (2.47 mm Hg). Figure 2 shows the yearly changes in BPs for the supplementation group. The changing modality of the high-dose group was not different from that of the low-dose group. The same analyses were repeated on an intention-to-treat group basis (including 61

### Table 2. Comparison of Mean Changes in BP During 5-Year Vitamin C Supplementation

<table>
<thead>
<tr>
<th>Group</th>
<th>High-Dose Group</th>
<th>Low-Dose Group</th>
<th>Dropout Group</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>n=124</td>
<td>n=120</td>
<td>n=134</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>5.88 (3.11–8.65)</td>
<td>5.73 (2.62–8.83)</td>
<td>4.52 (1.26–7.77)</td>
<td>0.92</td>
<td>0.69</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>0.17 (−1.61–1.95)</td>
<td>−0.28 (−2.31–1.74)</td>
<td>−0.96 (−2.86–0.93)</td>
<td>0.98</td>
<td>0.52</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>3.17 (−0.68–7.02)</td>
<td>−2.00 (−7.41–3.41)</td>
<td>7.27 (0.04–14.5)</td>
<td>0.4</td>
<td>0.16</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>0.93 (−1.71–3.56)*‡</td>
<td>−5.79 (−8.97–2.62)a</td>
<td>−2.73 (−6.47–1.02)a</td>
<td>0.009</td>
<td>0.03</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>7.34 (3.60–11.1)k</td>
<td>9.59 (6.02–13.2)</td>
<td>3.31 (−0.23–6.84)</td>
<td>0.54</td>
<td>0.04</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>−0.24 (−2.62–2.15)</td>
<td>2.47 (0.07–4.88)</td>
<td>−0.19 (−2.40–2.03)</td>
<td>0.09</td>
<td>0.17</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nonuser</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>5.72 (3.02–8.43)</td>
<td>6.42 (3.05–9.79)</td>
<td>3.90 (0.50–7.30)</td>
<td>0.88</td>
<td>0.39</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>0.91 (−0.94–2.77)</td>
<td>0.05 (−2.22–2.32)</td>
<td>−1.09 (−3.13–0.95)</td>
<td>0.79</td>
<td>0.30</td>
</tr>
<tr>
<td>User§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>6.88 (−5.21–19.0)</td>
<td>2.57 (−5.83–11.0)</td>
<td>11.33 (−1.34–24.0)</td>
<td>0.82</td>
<td>0.62</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>−4.50 (−10.3–1.25)</td>
<td>−1.81 (−6.57–2.95)</td>
<td>0.44 (−4.58–5.47)</td>
<td>0.38</td>
<td>0.57</td>
</tr>
</tbody>
</table>

*P values for comparison between high- and low-dose groups by ANCOVA after adjustment for age, gender, BMI, alcohol intake, and vitamin C intake.
†P values for comparison among the 3 groups by ANCOVA after adjustment for age, gender, BMI, alcohol intake, and vitamin C intake.
‡Means sharing the different superscripts (a and b) are significantly different from each other.
§Users were defined as those who took antihypertensives throughout the study period.

Figure 2. Systolic and diastolic blood pressures at baseline and during each intervention year, according to the 2 treatment groups.
subjects), but the result did not differ substantially from current analysis (excluding 61 subjects).

This study also examined the effect of vitamin C supplementation on the BP in smokers and nonsmokers. However, there were no significant differences in change of BP during 5-year supplementation between the 2 treatment groups according to smoking status.

**Discussion**

The main finding of the present study was that 5-year vitamin C supplementation reduced neither SBP nor DBP in a group of subjects with atrophic gastritis. Our result does not support previous studies showing that vitamin C supplementation may reduce SBP and DBP. In addition, after vitamin C supplementation, SBP, but not DBP, significantly increased in all 3 groups, regardless of the vitamin C dose, compared with the baseline. Because the subjects of our intervention study have been monitored for 5 years, these increments of BP may be owing to aging rather than to the effect of vitamin C supplementation. Our second finding was that serum vitamin C concentrations were inversely associated with neither SBP nor DBP at baseline, even though several plausible mechanisms have been proposed. These results did not support previous reports that serum or plasma vitamin C concentrations were inversely associated with the SBP and DBP.

A number of studies have described the relationship between vitamin C and BP in several countries, including the United States,\(^{16,25}\) Finland,\(^{26}\) and Japan.\(^{11,27}\) In contrast to the present study, most cross-sectional studies\(^{11,25–27}\) indicated that ascorbic acid status was significantly inversely correlated with both SBP and DBP. In a Japanese community study of 919 men and 1266 women age \(\geq 40\) years, the level of BP was associated inversely with the serum vitamin C concentration.\(^{11}\)

The proposed protective effect of vitamin C against hypertension could be affected by both dietary\(^{16,28,29}\) and nondietary factors\(^{28}\) associated with vitamin C status in humans. Serum vitamin C is a biomarker not only of the intake of vegetables and fruits but also of healthy behavior that may affect BP.\(^{28,29}\) The circulating concentration of vitamin C is known to be influenced by various dietary and lifestyle factors, including body weight, alcohol, and smoking habits.\(^{28–30}\) Alcohol consumption in particular was negatively linked to the serum vitamin C concentration\(^{28}\) and positively related to SBP and DBP.\(^{31}\) Therefore, to reach a reliable conclusion about the BP–vitamin C relationship, adequate statistical adjustments should be made, at least for important known confounding variables. Actually, in the present study, before any adjustment for possible confounders, there was an inverse correlation between serum vitamin C and DBP. After that adjustment, however, a significant relationship no longer existed.

Although the data from analytic observational studies\(^{1,2,6–8}\) (both the dietary intake and blood-based study) are compatible with possible cardiovascular benefits of antioxidant vitamins, observational studies are unable to control for the potential effects of unknown or unmeasured confounding variables that may explain all or part of any observed associations. Because of these limitations inherent in all observational studies, only randomized trials of sufficient sample size, dose, duration of treatment, and follow-up can establish conclusively whether antioxidant vitamins actually reduce BP and, in the long run, decrease cardiovascular disease risk.

Underpowered intervention trials may have increased the inherent risk of false-positive results. To date, several randomized trials have also been performed that were designed specifically to test the effect of antioxidant vitamins\(^{10,16,17,32}\) or fruit/vegetables\(^{8}\) on BP. However, most of them were relatively short-term trials.\(^{9,10,16,17,32}\) With only a small sample,\(^{16,17,32}\) or did not control other dietary and nondietary factors that might affect BP.\(^{16,17,32}\) Publication bias may seriously compromise assessment of treatment effectiveness of vitamin C on BP. Therefore, one should pay special attention when presenting and interpreting findings.

Although a food-based approach allows for the additive effects of different protective dietary factors and the potential synergy of biological interactions that further enhance those desired protective effects, a single-nutrient intervention would be useful to determine whether a particular nutrient plays a major regulatory role. Few intervention studies have focused on the association of vitamin C and BP.\(^{10,16,17,32}\) In their depletion-repletion study (provided 9 and 117 vitamin C mg/day, respectively), Block et al\(^{10}\) found that low plasma levels of ascorbic acid, measured after 1 month on a vitamin C–depleted diet, were associated with higher levels of BP. Other dietary factors may influence BP. Trials of vegetarian diets have shown that vegetarians tend to have a lower BP than that of nonvegetarians.\(^{31}\) Dietary factors of vegetarian diets to lower BP may be attributed to their high intake levels of fiber, potassium, magnesium, and calcium, together with their low levels of fat. The Dietary Approaches to Stop Hypertension (DASH) trials were able to substantially lower BP.\(^{8}\)

The advantages of the present study over previous intervention trials based on relatively short-term intervention include the following: examination of the long-term effect of vitamin C supplementation and the fact that it is a double-blind, randomized controlled, and population-based trial means the confounding effects of unknown or unmeasured factors can be avoided, and the long-term effect of vitamin C supplementation may be observed, thereby reducing error and bias in recalling past exposure.

As shown in the trial diagram (Figure 1), in the present study we compared the general characteristics listed in Table 1 between the low-dose (n = 144) and high-dose (n = 161) groups at the time of rerandomization. However, no statistical differences were found between the 2 groups in baseline characteristics. Accordingly, we assumed that even after the study modification, subjects were randomly assigned to high-dose (500 mg vitamin C) and low-dose (50 mg vitamin C) groups.

Additionally, during the follow-up, 24 subjects of the 50-mg group and 37 subjects of the 500-mg group withdrew from the study. Thus, 120 subjects for 50-mg group and 124 subjects for 500-mg group completed the supplementation (completed group). Because the primary purpose of this report was to examine the long-term (5-year) effect of
vitamin C on BP among those who completed the vitamin C supplementation throughout 5 years, the results of the completed group analysis are presented here. However, the same analyses were repeated for the intention-to-treat group basis, but the results did not differ substantially.

The possible limitations of the present study may have made the present finding inapplicable to the general population. Our study subjects were serologically diagnosed with atrophic gastritis, and more than half (52%) of the screening participants were matched with this criterion. The prevalence of atrophic gastritis increased with age: 37% in years 40 to 49, 52% in years 50 to 59, and 63% in years 60 to 69. Therefore, the stomach with atrophy was not a special condition in this area and is considered an aging phenomenon. The prevalence of atrophic gastritis was 55.4% (866/1564) among screening program participants age 40 to 59 years in another village within the same Yokote Public Health Center district (data not shown). Moreover, the prevalence ranged from 9% to 27% among randomly selected men age 40 to 49 years in 5 areas across Japan, and they correlated well with age-adjusted mortality rates of gastric cancer. The highest prevalence was observed in the Yokote Public Health Center district (26%) and even in Tokyo (27%). Although the prevalence of atrophic gastritis was relatively higher in other areas, our study subjects were not a specially selected group in Japan. Nevertheless, there is a possibility that the effect of vitamin C supplementation on the BP may be affected by the presence of atrophic gastritis. However, even though gastric juice concentrations were considerably lower in patients with atrophic gastritis than in patients with a normal histological assessment, plasma and mucosal concentrations were unaffected by the presence of atrophic gastritis.

In addition, the prevalence of current smokers among male subjects in this trial was 43.8%, which is slightly lower than that (50.9%) among health check-up participants (data not shown) or that (55.8%) among men who responded to the questionnaire (response rate, 75%) in the Yokote Public Health Center district. Therefore, the trial participants may be more health conscious than people in general, as might be expected.

In conclusion, we could not observe any reduction in BP attributable to 5-year vitamin C supplementation in the high-risk population for stomach cancer and stroke.

Perspectives

Although there are a great number of observation and intervention studies showing an inverse association of vitamin C with BP, they are completely inconsistent. The present finding suggests that neither systolic nor diastolic BP was significantly related with 5-year vitamin C supplementation in a double-blinded randomized controlled trial. Therefore, this finding does not support a beneficial effect of vitamin C on BP. There are several possible reasons for the inconsistency between the results of trials: measurements of possible confounding variables, intervention duration, and sample size. To reach a reliable conclusion about the BP–vitamin C relationship, adequate statistical adjustments should be made, at least for important known confounding variables, as in this trial. In addition, most previous randomized trials were relatively short-term trials with only a small sample, or did not control for other dietary and nondietary factors that might affect BP. A high priority for future study should be randomized controlled trials with a variety of doses of vitamin C and in groups who are at higher-than-average risk of hypertension or who already have high BP. In addition, study must be undertaken to determine whether or not vitamin C supplementation has a preventive effect in developing hypertension.

Acknowledgments

This study was supported in part by Grants-in-Aid for Cancer Research and for the Second-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan, and M.K.K. was supported by a fellowship granted by the Foundation for the Promotion of Cancer Research, Japan. We are grateful to the following persons for their painstaking efforts in initiating, maintaining, modifying, and setting the 2 study protocols: Dr. Yoshitaka Tsubono of the Division of Epidemiology, Tohoku University Graduate School of Medicine; staff members of the Hiraka General Hospital; Sannai Village; the Yokote Public Health Center; and the Hiraka Medical Association.

References


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Hypertension. published online October 21, 2002;

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