Vitamin C Intake and Risk of Ischemic Heart Disease in a Population with a High Prevalence of Smoking

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Key words: vitamin C intake, Ischemic heart disease, case-control study, Republic of Korea

Objective: Epidemiological data on the relationship between vitamin C intake and ischemic heart disease (IHD) risk are limited in the Asian population, with a high prevalence of smoking. This study aims to investigate the association between vitamin C intake and the incidence of non-fatal IHD in Korean men.

Methods: The case group consisted of 108 patients with electrocardiogram-confirmed myocardial infarction or angiographically confirmed coronary artery disease (CAD) who were admitted to a university teaching hospital in Seoul, Korea. The controls were 142 age-matched patients admitted to the departments of ophthalmology and orthopedic surgery at the same hospital. Vitamin C intake was assessed by a nutritionist using a semi-quantitative food frequency method, and body mass index (BMI), tobacco use and past history of cardiovascular disease were determined by examination and interview.

Results: After controlling for cardiovascular risk factors, including BMI, smoking, past history of hypertension, past history of hyperlipidemia, dietary intakes of energy, total fat (or subtype of fat), cholesterol, \( \beta \)-carotene, and vitamin E, the odds ratio (OR) of non-fatal IHD was 0.34 (95% confidence interval (CI) 0.13–0.90) in the highest tertile of vitamin C intake compared with those in the lowest tertile. In a subgroup analysis, which compared nonsmokers in the highest tertile of vitamin C intake to current smokers in the lowest tertile of vitamin C intake, the odds ratio of developing non-fatal IHD was 0.12 (95% CI 0.02–0.77).

Conclusion: This study suggests that higher intake of vitamin C is associated with the decreased risk of non-fatal IHD in a population with a high prevalence of smoking.

INTRODUCTION

The concept of the relationship between diet and ischemic heart disease (IHD) has changed considerably over the past two decades because of critical breakthroughs in our understanding of the mechanisms of the disease. Biochemical, clinical and epidemiologic evidence suggests that oxidants are involved in the development and clinical expression of coronary heart disease and that these antioxidants may contribute to lowering the disease risk [1–3]. One such antioxidant nutrient of considerable interest is vitamin C. Carr et al. [1] reported a significant inverse association between vitamin C intake and cardiovascular disease risk in 7 of 12 prospective cohort studies.

In Korea, cardiovascular disease (CVD) has emerged as the leading cause of death. Even though mortality due to IHD is relatively low compared to that of Western countries, its rate rapidly increased between 1984 and 1993, stabilizing thereafter. In 1999, the age-adjusted death rates for men and women were 11.9 and 7.5 per 100,000. These rates were 3.8 and 3.6 times higher than the rates in 1984 for men and women, respectively [4]. Average daily vitamin C intake, estimated from 24-hour recall, of Koreans was 76.2 mg in 1988 and increased to 123.1 mg in 1998 [5]. Although, average vitamin C intake was higher than the Korean recommended dietary allowance (RDA) (70 mg/day for healthy, nonsmoking adults), 18.1% consume less than 75% of the RDA [6].

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Cigarette smoking is an important risk factor for IHD and has also been shown in Koreans [7, 8]. Korean men have the highest prevalence of smoking in the world. Although the prevalence of smoking among Korean men was 64.9% in 1998 and has since declined, it still remains very high [4]. A significant amount of research indicates that smokers have a higher requirement for vitamin C than nonsmokers [1, 2]. Smokers show significantly higher intakes of energy, total fat and saturated fatty acid, and lower intakes of vitamin C, vitamin E, β-carotene and polyunsaturated fat than nonsmokers. In addition to dietary intake, smokers have lower plasma vitamin C levels than nonsmokers, because smoking increases the turnover of and decreases the absorption of vitamin C. Some of these differences may further exacerbate the deleterious effects of cigarette smoking on coronary heart disease [9].

However, little information is available on the relationship between vitamin C intake and the incidence of IHD in population with a high prevalence of smoking. In this study, we investigated the association between vitamin C intake and the incidence of IHD in Korean men. This is of particular concern given the growing incidence of IHD in this area of the world.

**MATERIALS AND METHODS**

**Subjects**

Cases and controls were selected from the Cardiovascular Center at a university teaching hospital in Seoul admitted during the period October, 1995 to July, 1996. The cases were 108 male patients with a first acute myocardial infarction (MI) (50 patients) or new diagnosis of angina pectoris (58 patients). The inclusion criteria for the cases were (1) younger than 75 years of age, (2) onset of symptoms developed within a month of admission, (3) acute MI confirmed by electrocardiogram (ECG) of cardiac enzyme measurement, (4) angina pectoris confirmed by coronary angiogram (50% or more occlusion in at least one of three main coronary arteries). One hundred and forty two controls, matched by age within 10 years, were selected from male patients admitted to the department of ophthalmology (69 patients) and orthopedic surgery (73 patients). The inclusion criteria for the controls were (1) younger than 75 years of age, (2) confirmed normal ECG’s when were admitted to hospital, (3) no past history of myocardial infarction or angina pectoris.

**Methods**

A trained interviewer interviewed cases and controls in the hospital. Variables measured were sociodemographic characteristics, cigarette smoking, leisure time physical exercise, alcohol consumption and past history of cardiovascular disease. Height and weight were measured at hospital admission, and the body mass index (BMI) was calculated. Cigarette smoking history involved questions about current or past use of cigarettes, and to be classified as an ex-smoker, a patient had to report having quit smoking at least one year prior to the time of the admission. Aspirin use was not investigated since it is not used widely in Korea.

Dietary data were obtained by a nutritionist using a semi-quantitative food frequency questionnaire (FFQ) containing 93 food items, as reported previously [8]. Each subject was asked to state the number of meals eaten and the usual portion size over the previous year. Consumption frequency was measured on a nine-grade scale: never, once a month, twice a month, once a week, three times a week, five times a week, once a day, twice a day, three times a day. The questionnaire also included a specific question about the type of fat used for cooking. This information was also used in the appropriate recipes. During the interview, food models and reference utensils were shown to subjects to help them estimate portion size. The participants were interviewed within a week of admission to the hospital and were asked to describe their usual dietary patterns before diagnosis of any known coronary disease. When it was apparent that a patient had substantially changed his usual dietary pattern within the past year, we excluded him from the analysis.

Nutrient intake based on this information was calculated using Korean food composition tables, while fatty acids were calculated according to other published data [6, 10, 11]. To calculate the daily nutrient intake, the nutrient content of each food item was multiplied by the frequency of its daily consumption and all items summed. However, trans fatty acid and folate intake could not be estimated because of the incomplete database in Korea. The dietary method adopted was validated by a pilot study, which was carried out on 31 men who visited the hospital for health screening. Nutrient intakes estimated from FFQ were compared with estimated nutrient intakes from two three-day dietary records, and the results showed that the method provided a reasonable measure of vitamin C as well as total and specific types of fat [12].

**Statistical Analysis**

Dietary vitamin C intake from food sources was categorized into tertiles, which were based on the distribution of controls, and the risk of non-fatal IHD in the highest and middle tertiles was compared with the risk of non-fatal IHD in the lowest tertile. The association between vitamin C intake and the risk of non-fatal IHD was determined by multivariate logistic regression analysis. Also, we constructed a score variable for vitamin C intake by awarding 1, 2 and 3 to the corresponding tertile. Trend testing was performed by treating this score variable as a continuous variable in the regression models. Statistical significance ($p < 0.05$) was the guideline for selecting independent variables to be included in the final logistic regression model. The fiber intake was highly correlated with
the vitamin C intake (r = 0.84), and the change in the likelihood due to inclusion of the fiber intake was not significant. Therefore, the fiber intake was not included in the final logistic regression model in accordance with the parsimonious principle. No significant interactions were found between vitamin C intake and smoking status, between vitamin C intake and BMI or between smoking status and BMI. Therefore, we excluded these interaction terms from the logistic regression model. The analyses were adjusted for BMI (≥25 kg/m², <25 kg/m²), smoking (>20 cigarettes/day, ≤20 cigarettes/day, ex-smoker, nonsmoker), a past history of hypertension, a past history of hyperlipidemia, energy, total fat or fatty acids, cholesterol, and other antioxidants (β-carotene, vitamin E). We also performed the same analysis upon subjects that did not use vitamin supplements. Finally, logistic regression was performed after excluding patients admitted to the department of ophthalmology in order to examine whether or not the inclusion of patients admitted to the department of ophthalmology could minimize the protective effect of vitamin C intake on the risk of non-fatal IHD. Statistical analysis was performed using statistical analysis system (SAS) software (Release 8.1; SAS Institute, Cary, NC).

RESULTS

Vitamin C tertiles, defined as vitamin C intake derived from food <141.8 mg, 141.8 mg–220.2 mg, ≥220.2 mg were used for the analysis. Details of the association between vitamin C intake and selected baseline characteristics are presented in Table 1. At higher vitamin C intake, men had higher BMIs and had a lower past history of hyperlipidemia. Dietary intakes of β-carotene, vitamin E and fiber as well as polyunsaturated fatty acid (PUFA) and polyunsaturated fatty acid/saturated fatty acid (P/S) were also higher at higher vitamin C intake.

The results of the multivariate analysis are shown in Table 2. Vitamin C intake was found to be inversely related to risk of non-fatal IHD after adjustment for non-dietary variables. After additional adjustment for energy, cholesterol and total fat (in Model 2), and PUFA and saturated fatty acid (SFA) instead of total fat (in Model 3), the above associations were retained. The odds ratios (ORs) for the highest versus the lowest tertile were 0.26 (95% confidence interval (CI) 0.11–0.65; p for trend = 0.00) for model 2, 0.25 (95% CI: 0.10–0.62; p for trend = 0.00) for model 3. Further adjustment for β-carotene and vitamin E led to only slight changes in the observed associations (OR 0.36, 95% CI 0.13–0.97, p for trend = 0.05 for Model 4; OR 0.34, 95% CI 0.13–0.90, p for trend = 0.04 for Model 5).

Logistic analysis was performed after adding the past history of diabetes, alcohol consumption, exercise and omega-3 fatty acid intake to the models. However, none of these variables was found to be significantly related to non-fatal IHD. In addition, none of these variables was capable of altering the significance of the relationship between the vitamin C intake and non-fatal IHD.

In additional analysis of subjects that did not use vitamin supplements, after adjusting for non-dietary risk factors and energy, cholesterol and total fat (in Model 2) or fatty acid intake (in Model 3) showed a significant difference between the highest tertile and the lowest tertile. However, after additionally adjusting for β-carotene and vitamin E (in Model 4 and Model 5), these risks were attenuated and no longer significant (Table 3).

After excluding patients admitted to the department of ophthalmology, the odds ratios of non-fatal IHD in the highest tertile of vitamin C intake were similar to those of the overall population. These odds ratios were 0.34 (95% CI 0.13–0.90, p = 0.04 for Model 5). When further adjusting for BMI, total fat, smoking, body mass index (BMI) and fiber intake, the odds ratios were 0.25 (95% CI 0.10–0.62, p = 0.05 for Model 3).

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Table 1. Diet and Lifestyle Characteristics by Tertiles of Vitamin C Intake

<table>
<thead>
<tr>
<th>Vitamin C intake tertile</th>
<th>&lt;141.8 mg</th>
<th>&lt;220.2 mg</th>
<th>≥220.2 mg</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C (mg)</td>
<td>103.6</td>
<td>175.2</td>
<td>285.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (year)</td>
<td>53.0</td>
<td>53.7</td>
<td>52.2</td>
<td>0.36</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.7</td>
<td>24.7</td>
<td>24.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>63.0</td>
<td>56.3</td>
<td>45.1</td>
<td>0.22</td>
</tr>
<tr>
<td>Regular exercise (%)</td>
<td>30.4</td>
<td>31.0</td>
<td>36.6</td>
<td>0.67</td>
</tr>
<tr>
<td>Current drinkers (%)</td>
<td>59.3</td>
<td>67.8</td>
<td>54.9</td>
<td>0.57</td>
</tr>
<tr>
<td>Past history of hypertension (%)</td>
<td>18.5</td>
<td>29.9</td>
<td>25.4</td>
<td>0.51</td>
</tr>
<tr>
<td>Past history of hyperlipidemia (%)</td>
<td>21.7</td>
<td>18.4</td>
<td>15.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Average intake of Energy (kJ)</td>
<td>8532.2</td>
<td>9784.1</td>
<td>11253.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total fat (% of energy)</td>
<td>22.8</td>
<td>23.3</td>
<td>23.5</td>
<td>0.67</td>
</tr>
<tr>
<td>PUFA (% of energy)</td>
<td>5.1</td>
<td>5.1</td>
<td>5.5</td>
<td>0.12</td>
</tr>
<tr>
<td>SFA (% of energy)</td>
<td>7.1</td>
<td>7.2</td>
<td>7.2</td>
<td>0.91</td>
</tr>
<tr>
<td>P/S</td>
<td>0.77</td>
<td>0.74</td>
<td>0.84</td>
<td>0.05</td>
</tr>
<tr>
<td>Cholesterol (mg/1000 kcal)</td>
<td>133.4</td>
<td>139.4</td>
<td>131.4</td>
<td>0.02</td>
</tr>
<tr>
<td>β-carotene (μg)</td>
<td>3321.7</td>
<td>4399.0</td>
<td>8315.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vitamin E (mg)</td>
<td>12.9</td>
<td>15.9</td>
<td>20.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>6.5</td>
<td>8.9</td>
<td>12.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

PUFA = polyunsaturated fatty acid, SFA = saturated fatty acid, P/S = polyunsaturated fatty acid/saturated fatty acid.
tertile of vitamin C intake compared with those in the lowest tertile ranged from 0.28 to 0.47, a little higher than those obtained from logistic models that included patients admitted to the department of ophthalmology, as shown Table 2 (the odds ratios: 0.25–0.36).

Further analyses were undertaken involving combinations of factors (i.e., smoking status) that may influence the vitamin C intake level. A positively strong association was seen at higher smoking levels. Compared to current smokers in the lowest vitamin C tertile, the ORs of non-fatal IHD among ex-smoking men and among non-smoking men in the highest vitamin C tertile were 0.24 (95% CI 0.07–0.88) and 0.12 (95% CI 0.02–0.77) respectively (Fig. 1).

**DISCUSSION**

We observed an inverse association of vitamin C intake with risk of non-fatal IHD in Korean men. For dietary vitamin C the relation remained significant after adjustment for BMI, smoking, past history of hypertension, past history of hyperlipidemia, energy, total fat, SFA, PUFA, β-carotene and vitamin E. Our results are consistent with those of several other studies [16–19] that found dietary vitamin C or plasma vitamin C to be associated with a protective effect against IHD. Knekt et al. [20] reported an inverse association between the vitamin C intake and IHD among women, but not among men. However, others have observed no association between high vitamin C intake or high plasma vitamin C and IHD [21–27]. Klipstein-Grobusch et al. (>126 mg/day) [25], Kushi et al. (>196 mg/day) [26], and Enstrom et al. (>250 mg/day) [27] reported no additional reduction in risk of IHD associated with a relatively high vitamin C intake. Furthermore, Levine et al. [28] suggested that because plasma and circulating cells become saturated between 200 mg and 400 mg of vitamin C, increasing vitamin C intake over this amount might have no additional effect on disease risk. However, we found that higher vitamin C intake compared with those in the lowest tertile ranged from 0.28 to 0.47, a little higher than those obtained from logistic models that included patients admitted to the department of ophthalmology, as shown Table 2 (the odds ratios: 0.25–0.36).

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C intake (≥220 mg/day) was significantly associated with a decreased risk of non-fatal IHD. The difference between our study and other studies may have resulted from the difference in the range of vitamin C intake or plasma concentrations and the prevalence of smoking.

Smokers have a higher vitamin C requirement than nonsmokers, due to their lower dietary intakes [9, 29, 30], and their higher metabolic turnovers of vitamin C [31]. Smokers in general have poorer diets than nonsmokers; they eat more fat and SFA and consume fewer antioxidants and fiber than nonsmokers. Although the RDA of vitamin C for smokers is 125 mg in U.S.A. [32], Schectman et al. [33] proposed that smokers should consume more than 200 mg of vitamin C, and Kallner et al. [31] suggested that at least 140 mg of vitamin C is required by smokers to reach serum vitamin C concentrations comparable with those of nonsmokers. The prevalences of smokers in Western studies, which showed no protective effects of vitamin C on IHD, were 20% to 31% [25], 12% to 22% [26] and 38% [27], and these were much lower those in Asian countries, which showed 63% for China (1996) and 53% for Japan (in 1998) [34]. The high smoking prevalence in Korea [4] makes it an important risk factor. The percentage of current smokers in this study was 64.8% for cases and 48.6% for controls. Therefore, the protective effects of higher vitamin C intake (≥220 mg/day) in this study may suggest that there is a possibility of biological interaction between vitamin C intake and smoking.

Recognized risk factors for IHD were evident in this study [8]. Men who reported the following risk factors had higher risks of IHD than men without these risk factors: BMI (≥25 kg/m²), OR 2.26; 95% CI 1.27–4.01), current smoking (>20 cigarettes/day, OR 10.51; 95% CI 3.61–30.56) and total fat intake (OR 1.08; 95% CI 1.02–1.14). Because the data we collected are observational, we evaluated whether those association with IHD could be explained by other healthy lifestyle practices among men with the highest tertile of vitamin C intake. In our study, men with the highest tertile of vitamin C had a lower smoking rate, and different PUFA, P/S and cholesterol intakes as well as a past history of hypertension and hyperlipidemia. The information we collected on blood pressure, serum triglyceride and serum cholesterol levels after admission was not used because these could have been modified by cardiovascular event or treatment. Instead of these variables, we used a past history of hyperlipidemia and hypertension. To account for the effects of potentially confounding lifestyle factors, we adjusted for dietary and non-dietary risk factors. When non-dietary risk factors were adjusted, the association between vitamin C intake and risk of non-fatal IHD was similar to that obtained when only age was adjusted. On the other hand, when dietary variables were additionally adjusted by multiple regression, the intake of total fat or subtype of fat were found to have more important confounding effects. This actually strengthened the association between vitamin C intake and non-fatal IHD (OR 0.26; 95% CI 0.11–0.65 controlling for total fat, OR 0.25; 95% CI 0.10–0.62 controlling for fat subtype). In our study, alcohol intake, exercise, the history of diabetes and omega-3 fatty acid intake were not risk factors for non-fatal IHD. This was unexpected. It is possible that the power of this study was insufficient to detect the differences in these factors between the cases and controls. Further research will be needed to determine whether or not these factors are associated with non-fatal IHD in a population with a high prevalence of smoking.

In our case-control study, cases were selected with newly developed acute MI as confirmed by ECG, enzyme, cardiac pain, and angina pectoris were confirmed by angiography, while controls were selected from patients at the departments of ophthalmology and orthopedic surgery. The use of incident cases helped to avoid the possibility that cases may have modified their dietary pattern because of a previous diagnosis.

![Fig. 1. Odds ratios of non-fatal ischemic heart disease by tertiles of vitamin C intake at different smoking statuses (Model included BMI (≥25 kg/m²), past history of hypertension, past history of hyperlipidemia, energy, polyunsaturated fatty acid, saturated fatty acid, cholesterol, β-carotene, and vitamin E intake).](image-url)
of IHD. However, this study was limited in terms of selecting the controls admitted to the department of ophthalmology since they might have had low antioxidant level and intake. The distributions of controls admitted to the department of ophthalmology were 54 for cataract, 7 for glaucoma, 7 for retinopathy, and 5 for other eye diseases, and the patients admitted to the department of orthopedic surgery were 27 for trauma, 14 for degenerative disease and 32 for inflammatory disease. After excluding the patients admitted to the department of ophthalmology, the main result on the relationship between the vitamin C intake and the risk of non-fatal IHD was not changed. Therefore, the inclusion of ophthalmologic patients among our controls does not seem to minimize the protective effect of vitamin C intake. In order to reduce the potential for recall bias, a highly structured questionnaire was used, and the dietary interview was performed within a week of hospitalization using food models and reference utensils. Moreover, the cases and controls were blind to the study hypothesis, as were the interviewers. However, the recall bias might not have been eliminated perfectly in our study design. Care should be taken when interpreting the effect of the vitamin C intake on non-fatal IHD.

This relationship between vitamin C intake and IHD may also be affected by other potentially important micronutrients; for example, foods rich in vitamin C also contain β-carotene and vitamin E [35], and people taking vitamin supplements are generally more health-conscious than others, although those with vitamin deficiencies may be ill or have detrimental health habits. When adjusted for other antioxidants, the above associations were not changed, though a little attenuated (OR 0.34, 95% CI 0.13–0.90). The supplemental use of vitamins has also been shown to be related to IHD mortality [36, 37]. We requested details of the type and dose of multivitamin and vitamin C supplementations in the FFQ; however, the effect of vitamin supplements could not be analyzed in detail because of the low prevalence of vitamin supplement use (8.8%; 22 of 250 subjects). When we conducted additional analyses after excluding subjects who had used multivitamins and vitamin C supplements, the association between vitamin C intake and the risk of non-fatal IHD remained significant, except when we additionally controlled for β-carotene and vitamin E, which, in themselves, showed no significant inverse association. One limitation to our study is the effect of the fiber intake. We could not exclude this effect because of the multicollinearity between the vitamin C intake and fiber intake.

Although no significant statistical interaction was found between vitamin C intake and smoking status in this study, we conducted further analyses involving combinations of the two risk factors (vitamin C intake and smoking status). When the two factors were examined in combination, the risk of non-fatal IHD (OR 0.12; 95% CI 0.02–0.77) was lowest among those that had the highest intake of vitamin C intake and were nonsmokers. This can be explained by the following biological interaction: Smoking may cause an increased turnover of vitamin C because it induces oxidative stress; this would lower vitamin C concentrations and increase cardiovascular disease risk [30, 38]. On the basis of such a mechanism, it would appear that smokers in particular, may benefit from increased vitamin C intake.

CONCLUSION

This study indicates the importance of vitamin C intake as well as smoking cessation on the prevention of IHD in developing countries, where the prevalence of smoking is high. In addition, this finding suggests that the effect of vitamin C intake on non-fatal IHD incidence may differ according to the degree of oxidative stress induced by factors such as smoking. Randomized trials are needed to provide recommended dietary allowances of vitamin C in a population with a high prevalence of smoking.

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