Effects of Green Tea Intake on the Development of Coronary Artery Disease

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Background Green tea, a popular beverage in Japan, contains many polyphenolic antioxidants, which might prevent atherosclerosis. This study was designed to determine whether the consumption of green tea is proportionately associated with a decreased incidence of coronary artery disease (CAD) and the cardiovascular and cerebrovascular prognosis.

Methods and Results The study group comprised 203 patients who underwent coronary angiography (109 patients with significant coronary stenosis and 94 patients without). Predictors for CAD were analyzed and the patients' cardiovascular and cerebrovascular events were followed. Green tea consumption was significantly higher in patients without CAD than in those with CAD (5.9 ± 0.5 vs 3.5 ± 0.3 cups/day; $p < 0.001$). An inverse relationship between the intake of green tea and the incidence of CAD was observed ($p < 0.001$). The green tea intake per day was an independent predictor for CAD based on a multivariate logistic regression analysis (odds ratio: 0.84 and 95% confidence interval: 0.76–0.91). In contrast, the green tea intake was not a predictor of cardiovascular and cerebrovascular events based on the Cox proportional hazard model.

Conclusions Green tea consumption was associated with a lower incidence of CAD in the present study population in Japan. Therefore, the more green tea patients consume, the less likely they are to have CAD. (*Circ J* 2004; 68: 665–670)

Key Words: Antioxidant; Coronary artery disease; Green tea

The oxidative modification of low-density lipoprotein (LDL) is a key event in early atherogenesis and it is responsible for cholesterol accumulation in the arterial wall.¹ Because of the important role played by oxidized LDL, antioxidants may prevent the initiation and progression of coronary atherosclerosis and also reduce the incidence of coronary artery disease (CAD). Considerable epidemiologic, biochemical, and clinical evidence has accumulated in support of this hypothesis;^{2–5} but the findings remain controversial.⁶ Flavonoids are a group of polyphenolic antioxidants present in fruits, vegetables, and beverages such as tea and wine. The dietary flavonoid intake is inversely related to the rate of mortality from CAD.^{7,8} Despite a high intake of saturated fat in the French diet, the mortality rate from CAD in France is much lower than in other industrialized countries.⁹ The consumption of red wine, which contains a high concentration of flavonoids, may be one explanation for this French paradox.^{10,11}

In Japan, the rate of cigarette smoking is still very high. Specifically, 32.7% of the adult Japanese population smoked in 2001, as reported by a Japan Tobacco, Inc news release. The LDL from cigarette smokers has been shown to be more susceptible to oxidative modification than LDL from nonsmokers.¹² Nevertheless, the mortality rates from

CAD are much lower in Japan than in industrialized Western countries.¹³ The relatively lower plasma LDL concentration may account, in part, for the low CAD mortality rate. Furthermore, people in Japan drink green tea, which contains a high concentration of flavonoids, including catechins. Because green tea is made by steaming, not fermenting, fresh tea leaves, it contains more antioxidants than fermented teas such as oolong or black tea. In a recent study from the USA, tea consumption was inversely associated with cardiovascular mortality and overall mortality after acute myocardial infarction.⁸ However, so far only a few studies have suggested a weak inverse relationship between green tea intake and CAD.¹⁴ The 3 aims of this study were first, to clarify whether the consumption of green tea is associated with a decreased incidence of CAD in stable patients, second, to determine the relationship between the frequency of CAD and the total green tea intake, and third, to investigate whether the green tea intake is associated with future either cardiovascular or cerebrovascular events.

Methods

Patients

The study comprised 203 consecutive patients who underwent elective coronary angiography (CAG) between July 1, 1997 and December 31, 1997 in the Department of Medicine, Chiba Hokusoh Hospital, Nippon Medical School. Most of the patients underwent CAG because of typical or atypical chest pain, or abnormal ST–T changes; 7 underwent CAG during diagnostic catheterization for cardiomyopathy, and 1 underwent CAG during an assessment of valvular disease. Of the 203 patients, 109 had

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Table 1 Patient Characteristics

	CAD (n=109)	No CAD (n=94)	p value
Age (years)	60.0 (0.9)	57.5 (1.1)	0.08
Male/female	89 (81.7%)/20 (18.3%)	55 (58.5%)/39 (41.5%)	<0.001
Hypertension	64 (58.7%)	40 (42.5%)	0.03
Diabetes mellitus	27 (24.8%)	15 (16.0%)	0.16
Hyperlipidemia	71 (65.1%)	56 (59.6%)	0.47
Hyperuricemia	33 (30.3%)	17 (18.1%)	0.05
Obesity	29 (26.6%)	17 (18.1%)	0.18
Smoking	74 (67.9%)	42 (44.7%)	0.001
Family history of CAD	36 (33.0%)	31 (33.0%)	1.00
Plasma lipids			
TC (mg/dl)*	207.9 (3.9)	204.8 (4.0)	0.81
LDL-C (mg/dl)*	129.1 (3.1)	125.9 (4.3)	0.93
HDL-C (mg/dl)*	46.6 (1.2)	51.5 (1.5)	0.02
TG (mg/dl)†	165.0 (9.0)	142.9 (8.1)	0.10

Data are reported as the mean (SE) or number (%).

CAD, coronary artery disease; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides.

*To convert mg/dl to mmol/L, multiply by 0.0259, †to convert mg/dl to mmol/L, multiply by 0.0113.

significant coronary stenoses (89 men, 20 women; mean age: 60.0±0.9 years) and 94 patients did not (55 men, 39 women; mean age: 57.5±1.1 years). The patients who had previously undergone coronary interventions, such as percutaneous transluminal coronary angioplasty, were considered to have significant coronary stenosis.

Coronary Angiography

Coronary angiography was performed using the Judkins method. At least 3 views of the right coronary artery and 4 views of the left coronary artery were obtained. Angiograms were interpreted by the consensus of 3 experienced cardiologists, who were unaware of the clinical data, using a semiquantitative grading system recommended by the American Heart Association.¹⁵ Significant coronary stenosis was defined as a stenosis >50% in the left main trunk or >75% in the other major coronary arteries. Patients with CAD were defined as patients with at least 1 significant coronary stenosis.

Risk Factors

Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or treatment with antihypertensive drugs. Brachial blood pressure was measured at least 3 times using a calibrated mercury sphygmomanometer while the patient was supine. Hyperlipidemia was defined as a serum total cholesterol concentration >220 mg/dl (5.698 mmol/L) or triglyceride concentration >150 mg/dl (1.695 mmol/L), or treatment with lipid-lowering agents. Diabetes mellitus was defined according to World Health Organization criteria.¹⁶ Hyperuricemia was defined as a uric acid concentration >7.5 mg/dl in men or >6.0 mg/dl; in women, or drug therapy. The patients who smoked regularly during the previous 12 months were classified as smokers. The height and weight of each patient was measured, from which the body mass index (BMI) was calculated. Obesity was defined as a BMI ≥25.0 kg/m².¹⁷

Lipids

Fasting blood samples were obtained during the hospitalization for CAG. The total cholesterol concentration was determined using the cholesterol oxidase-3,5-dimethoxy-

N-ethyl-N-(2-hydroxy-3-sulfopropyl)-aniline method. The high-density lipoprotein cholesterol (HDL-C) concentration was measured using the enzymatic selective inhibition method and the triglyceride concentration was measured using the enzymatic method. LDL-cholesterol concentration was calculated using Friedewald's method.¹⁸ None of the patients had type III hyperlipidemia.

Assessment of the Intake of Green Tea and Other Beverages

All patients were interviewed just before CAG regarding their typical daily intake of green tea, vitamin supplementation, and the consumption of other beverages including red wine. Tea intake is reported as cups/day (1 cup=120 ml). This study was approved by the Institutional Review Board of the hospital. Informed consent was obtained from all patients.

Cardiovascular and Cerebrovascular Events

The occurrences of cardiovascular and cerebrovascular events and all causes of death were followed up through October 30, 2003. The cardiovascular events included myocardial infarction and unstable angina. The cerebrovascular events included cerebral infarction, transient ischemic attack, which needed hospitalization, and cerebrovascular hemorrhage. The diagnosis of each disease and cause of death was verified from the medical records.

Statistical Analysis

The sample size was based on the assumption from our preliminary study that the average intake of green tea of the patients with CAD was 4±4 cups/day and without CAD was 6±4 cups/day. According to that estimation, we deduced the minimal sample size for this study to be 170 with 0.05 of two-sided and 90% of power. Continuous variables were reported as the mean±SE and analyzed by the Wilcoxon rank-sum test. Categorical variables were analyzed using Fisher's exact probability test. The relationship between the daily intake of green tea and the incidence of CAD was analyzed using the Cochran-Mantel-Haenszel test. An analysis of variance was determined for the relationships between daily green tea intake and age or plasma lipid concentration. The predictors of CAD were analyzed by

Fig 1. Relationship between green tea intake and coronary artery disease (CAD): the more green tea patients consume, the less likely they are to have CAD ($p<0.001$).

univariate and multivariate logistic regression analyses using the following parameters: gender, hypertension, diabetes mellitus, obesity, smoking habits, family history of CAD, age, daily intake of green tea, triglyceride, LDL- and HDL-C concentrations. The predictors of cardiovascular and cerebrovascular events were analyzed by the Cox proportional hazards regression analysis using the following parameters: gender, hypertension, diabetes mellitus, obesity, smoking habits, family history of CAD, left ventricular ejection fraction, number of diseased coronary vessels, age, daily intake of green tea, triglyceride, LDL- and HDL-C concentrations, and HMG-CoA reductase inhibitors and the anti-platelet drug intake. Gender, hypertension, diabetes mellitus, obesity, smoking habits, and family history of CAD were analyzed as categorical variables, and age, daily intake of green tea, left ventricular ejection fraction, number of diseased coronary vessels and triglyceride, LDL- and HDL-C concentrations were analyzed as continuous variables. A value for $p<0.05$ was considered statistically significant. Statistical analyses were performed using SAS for Windows version 6.12 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

Table 1 summarizes the baseline characteristics of the patients. The percentage of men, the incidence of hypertension and the frequency of smoking were all significantly higher in the group of patients with CAD than in the group without CAD. The HDL-C concentration was significantly higher in the patients without CAD than in the patients with CAD.

Daily Intake of Green Tea and Other Beverages

The mean daily intake of green tea in patients with CAD was 3.5 ± 0.3 cups/day compared with 5.9 ± 0.5 cups/day in patients without CAD ($p<0.001$). The relationship between green tea intake and the number of patients with CAD is shown in Fig 1. The data indicate that the more green tea that patients drink, the less likely they are to have CAD ($p<0.001$). The patient characteristics and the daily green tea intake are summarized in Table 2. The mean daily intake of green tea was significantly higher in women than in men. There was no relationship between age or plasma

Table 2 Patient Characteristics and Daily Green Tea Intake

	No. of patients	Green tea intake (cups/day)	p value
Gender			
Male	144	4.3 (0.3)	0.04
Female	59	5.3 (0.5)	
Hypertension			
+	104	4.3 (0.3)	0.55
0	99	5.0 (0.5)	
Diabetes mellitus			
+	42	3.9 (0.6)	0.08
0	161	4.8 (0.3)	
Hyperlipidemia			
+	127	5.1 (0.4)	0.06
0	76	3.8 (0.3)	
Hyperuricemia			
+	50	4.7 (0.6)	0.76
0	153	4.6 (0.3)	
Obesity			
+	46	3.8 (0.5)	0.10
0	157	4.8 (0.3)	
Smoking			
+	116	4.3 (0.4)	0.09
0	87	5.0 (0.4)	
Family history of CAD			
+	67	4.6 (0.5)	0.85
0	136	4.6 (0.4)	

Data are reported as the mean (SE) or number. CAD, coronary artery disease.

lipid concentration and the daily intake of green tea. Sixty-eight patients drank alcohol either everyday or every other day. There was no significant difference in HDL-C between drinkers and non-drinkers (51.0 ± 1.8 mg/dl and 48.0 ± 1.2 mg/dl, respectively, $p=0.16$; data not shown). None of the patients took vitamin supplements, such as vitamin E or C, and none of the patients regularly drank red wine or black tea.

Predictors of Coronary Disease

The predictors of CAD were identified by logistic regression analysis (Table 3). Based on a univariate analysis, the significant predictors of CAD were male gender, hypertension, smoking habits, green tea intake and HDL-C concentration. The green tea intake and HDL-C concentra-

Table 3 Predictors of Coronary Artery Disease Based on Univariate and Multivariate Logistic Regression Analyses

Variable	No. of patients with CAD	Univariate		Multivariate	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Gender					
Female	20	1.00		1.00	
Male	89	3.16 (1.69–6.05)	<0.001	1.77 (0.76–4.13)	0.18
Hypertension					
0	45	1.00		1.00	
+	64	1.92 (1.10–3.38)	0.02	1.52 (0.78–2.99)	0.22
Diabetes mellitus					
0	82	1.00		1.00	
+	27	1.73 (0.87–3.57)	0.12	1.19 (0.53–2.71)	0.68
Obesity					
0	80	1.00		1.00	
+	29	1.59 (0.86–2.96)	0.14	1.16 (0.56–2.42)	0.69
Smoking habits					
0	35	1.00		1.00	
+	74	2.62 (1.49–4.67)	0.001	1.99 (0.95–4.20)	0.07
Family history of CAD					
0	73	1.00		1.00	
+	36	1.00 (0.56–1.81)	0.99	0.84 (0.42–1.68)	0.63
Age		1.03 (1.00–1.05)*	0.08	1.03 (1.00–1.07)*	0.10
Green tea intake		0.83 (0.76–0.90) [†]	<0.001	0.84 (0.76–0.91) [‡]	0.001
TG		1.00 (1.00–1.01) [‡]	0.08	1.00 (1.00–1.01) [‡]	0.28
LDL-C		1.00 (1.00–1.01) [‡]	0.54	1.01 (1.00–1.02) [‡]	0.21
HDL-C		0.97 (0.95–0.99) [‡]	0.01	0.99 (0.96–1.02) [‡]	0.60

CAD, coronary artery disease; CI, confidence interval; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

*Per 1-year old increment; [†]per 1-cup/day increment; [‡]1-mg/dl increment.

tion were inversely related to CAD. The only independent variable identified by multivariate regression analysis was the green tea intake ($p<0.001$). The odds ratio for green tea intake per cup/day was 0.84. Green tea intake was inversely associated with the presence of CAD.

Gender Difference in Predictors of Coronary Disease

The percentage of men was significantly higher in the group of patients with CAD than in the group without CAD. We analyzed the data in each gender to exclude any gender-related bias. In male patients, the green tea intake was significant higher in those without CAD than with CAD, 6.1 ± 0.6 cups/day and 3.2 ± 0.3 cups/day, respectively ($p<0.001$). In female patients, green tea intake was higher in those without CAD than with CAD, but not significantly, 5.7 ± 0.6 cups/day and 4.5 ± 0.9 , respectively ($p=0.27$). The predictors of CAD were analyzed by logistic regression analysis in each gender. In male patients, the only independent variable identified by multivariate regression analysis was green tea intake (odds ratio (OR): 0.81, 95% confidence interval: 0.72–0.91). In female patients, there was no independent variable identified by multivariate regression analysis.

Cardiovascular and Cerebrovascular Events

The mean follow up period was 4.9 ± 0.1 years and the follow up rate was 93.4%. The number of cardiovascular events was 38: 34 with unstable angina, 1 non-fatal myocardial infarction, 1 fatal myocardial infarction, and 2 sudden cardiac deaths. The number of cerebrovascular events was 7, and all of them were ischemic stroke. According to age-, coronary risk factors-, and medication-adjusted Cox proportional hazards regression analyses, there was no significant relationship between the occurrence of cardiovascular and cerebrovascular events, cardiovascular death and green tea consumption, $p=0.097$ and $p=0.891$, respectively. There

was also no significant relationship between cardiovascular events and green tea consumption in either all patients or in the patients with cardiovascular disease ($p=0.137$ and $p=0.172$, respectively). Among the patients with CAD, the mean green tea consumption in patients with cardiovascular events was 3.7 ± 0.5 cups/day and without events was 3.4 ± 0.4 cups/day ($p=0.67$).

Discussion

The present study showed a strong inverse association between green tea consumption and CAD. Furthermore, we demonstrated that higher the green tea intake, the less CAD occurred. There have been few reports concerning the relationship between green tea intake and angiographically proven CAD. Hirano et al reported only 29% of patients drank >3 cups green tea/day.¹⁴ Approximately 50% of Japanese aged over 40 years usually drink ≥ 4 cups/day.^{19,20} In the present study, 47% of the patients drank >3 cups/day, which is comparable with the general Japanese population. The lack of an association between green tea consumption and CAD in Hirano's report may be due to their subjects' low average intake of green tea. Sasagaki et al analyzed the data in each gender group, and green tea consumption was inversely associated with CAD only in men without diabetes mellitus, but not in women.²¹ We also analyzed the data in each gender and found a significant relationship between the green tea intake and CAD in men alone. No significant relationship was observed between green tea intake and CAD in women, but the green tea consumption tended to be higher in women without CAD than in those with CAD. The lack of an association in women in the present study may be related to the low number of female patients. After adjusting for gender, age, and coronary risk factors in all patients in the multivariate logistic analysis, green tea consumption was analyzed as a predictor of

CAD. Green tea consumption was inversely associated with CAD unrelated to gender.

Japanese have a low incidence of CAD. A low plasma cholesterol concentration was considered to be one explanation, but the cholesterol concentration has increased in Japanese over the past 3 decades.²² In addition, the smoking rate is higher in Japan than in other industrialized countries. Even under these circumstances, the incidence of CAD is still low. Genetic differences could be one reason and the environment or living habits may also affect the incidence of CAD. In the Seven Countries Study, there were strong associations between serum total cholesterol and CAD mortality in the USA and Northern Europe, but much weaker associations in Japan.²³ It is difficult to explain the low incidence of CAD based on a low cholesterol concentration alone. Hertog et al reported in The Seven Countries Study that the average intake of antioxidant flavonoids is inversely associated with the mortality rate from CAD.²⁴ Japan has a higher per capita flavonoid intake than other industrialized countries, because of the high rate of tea consumption, generally green tea.²⁴ In a recent study, tea consumption was inversely associated with cardiovascular mortality and overall mortality after acute myocardial infarction.⁸ However, so far no study on green tea, which contains more antioxidants than fermented teas such as oolong or black tea, has been made in regard to the cardiovascular and cerebrovascular prognosis. Our study revealed that the green tea intake is an independent predictor for CAD. However, no relationship was found between green tea intake and cardiovascular events. This is the first report about green tea consumption and the cardiovascular prognosis in stable patients. However, the sample size was small. We need to perform further studies on a larger number of patients.

Previous studies have suggested that tea consumption decreases atherosclerosis. Tijburg et al reported that the ingestion of green tea reduced atherosclerotic plaque formation by 31% in cholesterol-fed rabbits²⁵ and Geleijnse et al reported an inverse relationship between tea intake with the presence of long (>5cm) calcified plaques in the abdominal aorta.²⁶ The ORs decreased from 0.54 for patients drinking 1–2 cups of tea to 0.31 for patients drinking more than 4 cups per day.

The strong antioxidant property of tea may be one explanation of its preventive effect on the development of CAD. Because green tea is made by steaming, not fermenting fresh tea leaves, it contains more antioxidants than fermented teas such as oolong or black tea. Green tea contains high concentrations of flavonoids, especially catechins. They have strong antioxidant properties both in vitro and in vivo^{27–31} and they inhibit the oxidation of LDL to a higher degree than vitamin E.²⁷ Ishikawa et al reported that the time required for LDL oxidation increased significantly in patients consuming 750 ml of black tea/day (5 cups/day) for 4 weeks.³¹ In the present study, the daily intake of green tea was 5.9 cups/day in patients without CAD and it was expected to have an antioxidant activity in vivo.

Improvement in endothelial dysfunction by tea may be other explanation of how it prevents the development of CAD. Endothelial dysfunction may contribute to the pathogenesis of atherosclerosis. Duffy et al reported the consumption of 900 ml black tea daily for 4 weeks reversed endothelial dysfunction in patients with CAD.³²

Green tea also has other properties that may prevent the development of CAD. Specifically, green tea has anti-

hyperlipidemic (lowering LDL-, increasing HDL-C)^{19,33,34} properties. Furthermore, green tea suppresses increased plasma glucose concentration,³⁵ and inhibits platelet aggregation.^{36,37} However, in the present study, no association was observed between green tea consumption and plasma lipid concentrations, or the presence of diabetes mellitus.

According to the univariate analysis, male, hypertension, and smoking were predictors of CAD, but diabetes mellitus was not and age had only a weak association, the reason being that the sample size of this study was small. The only independent predictor of CAD from the multivariate logistic regression analysis was the daily intake of green tea; traditional coronary risk factors were not investigated as independent predictors in this study. The reason for this may be multi-correlations among coronary risk factors in the present study population. All of the study subjects underwent CAD because of a suspected diagnosis of CAD. Patients with coronary risk factors tend to undergo exercise electrocardiography or ambulatory electrocardiography in our hospital, and of them, the patients with abnormal ST–T change usually undergo CAG. In the present study the percentages of patients with each coronary risk factor were higher than would ordinarily occur.³⁸ The high percentages of patients with multiple risk factors would cause multi-correlations among the risk factors. We need to study a larger sample size and also have more accurate information about green tea intake and the incidence of CAD among the general population.

A strong relationship was observed between green tea consumption and CAD, but we cannot rule out the possibility that patients who frequently take green tea may also prefer traditional Japanese style foods. Traditional Japanese style foods frequently contain fish, vegetables, and soybeans, which may also have anti-atherosclerotic properties.

In conclusion, the ingestion of green tea was found to be associated with a lower incidence of CAD in our study population in Japan. As a result, the higher the green tea intake, the less likely CAD is to develop.

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