might be a more suitable parameter than BMI with regard to visceral fat accumulation and atherosclerosis and that adiponectin, an anti-atherogenic protein, might be an important predictor for MS.

Previous studies showed that adiponectin was closely associated with visceral fat accumulation and insulin resistance and that low levels of adiponectin were linked to components of MS [10,18-27]. Adiponectin has been shown to have potential inhibitory activities of the following three atherogenic cellular phenomena: (1) monocyte adhesion to endothelial cells by the expression of adhesion molecules; (2) oxidized LDL uptake of macrophages through scavenger receptors; and (3) proliferation of migrating smooth muscle cells by the action of platelet-derived growth factors or heparin-binding endothelial growth factor-like growth factor [29]. These anti-atherosclerotic and anti-inflammatory functions of adiponectin are thought to be associated with atherosclerosis [30-32] and to play a key role in the prevention of MS [29]. Other previous studies showed that lower adiponectin levels are associated with MS, diagnosed on the basis of modified NCEP-ATP III guidelines [5], in an urban area in Southern India [33] and that adiponectin level might be useful for diagnosis of MS in obese Japanese children [34].

The ratios of subjects with MS in this study were 12.9% in males and 5.7% in females. We have reported that the ratio of Japanese male subjects with MS in the early 1990s, diagnosed on the basis of modified NCEP-ATP III guidelines, was about 25% [35,36]. Since subjects undergoing treatment for hypertension or diabetes were excluded in this study, it is thought that the ratio of subjects with MS in this study is lower than the actual ratio. In all subjects, including subjects undergoing treatment for hypertension or diabetes, the ratios of subjects with MS were 24.4% in males and 8.9% in females in this study. In 2005, the International Diabetes Federation announced a new worldwide definition of MS, emphasizing the importance of central obesity with modifications according to ethnic group [6]. Further investigation using the new criteria for Japanese MS is needed to clarify the proportion of Japanese with MS.

Adiponectin concentrations in subjects positive for VFA or for LA were lower than those in subjects negative for VFA or for LA in both males and females. On the other hand, there were no significant differences between adiponectin concentrations in subjects positive for H-BP and those negative for H-BP and between adiponectin concentrations in subjects positive for H-FPG and those negative for H-FPG both in males and females. In a previous study, adiponectin concentration in subjects with essential hypertension was lower than that in normotensive healthy subjects [26]. It has also been reported that adiponectin level increases with aging [37-39]. Since blood pressure is known to increase with aging, this increase in adiponectin level with aging is thought to offset the difference between adiponectin concentrations in subjects positive for H-BP and those negative for H-BP. In the present study, adiponectin level had a tendency to decrease in both male and female subjects positive for H-FPG, and there was almost statistical significance between the difference in adiponectin levels in male subjects positive for H-FPG and those negative for H-FPG ($P = 0.051$). Since the number of excluded subjects undergoing treatment for diabetes was large, only 9.6% of the males and 4.6% of the females had H-FPG. This large number of excluded subjects might be the reason why there was no significant difference between adiponectin concentrations in subjects positive for H-FPG and those negative for H-FPG.

In previous studies, thiazolidinediones [40,41], temocapril and candesartan [42], which are used for treating diabetes and hypertension, were found to increase the serum level of adiponectin. Therefore, subjects undergoing treatment for diabetes or hypertension were excluded in this study. Although it is not clear whether lipid lowering-properties would influence serum adiponectin concentration, subjects undergoing treatment for hyperlipidemia, which was present only in females, were not excluded in this study. After exclusion of the female subjects receiving antilipotropic drugs, 15.5% of the female subjects were positive for LA, and results of analysis excluding female subjects receiving antilipotropic drugs were similar to the results

presented in this report.

One limitation of this study is that it was a cross-sectional study. More prospective studies may be needed to clarify the relationship between adiponectin concentration and prevention of MS.

In conclusion, the results of this study suggest that the plasma level of adiponectin, an adipocyte-derived anti-atherogenic protein, is low in subjects with MS diagnosed by the new criteria for Japanese and might be an important predictor for MS.

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8. 大崎国民健康保険加入者コホート研究平成18年度研究成果および大崎市民コホート研究の概要

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A．大崎国民健康保険加入者コホート研究の現況

1．はじめに

本コホートの対象は宮城県大崎保健所管内の1市13町に居住し、平成6年8月31日時点で40～79歳であった国民健康保険加入者全員54,996人である。平成6年10月から12月にかけてベースライン調査を行い（健診データは平成7年6月～9月）、52,029人（94.6%）から回答を得た。このうち平成6年12月までに死亡、または転出した774人を除いた51,255人について、平成7年1月から入院・入院外別の医療機関受診回数・入院日数と医療費に関するデータ、および死因・転出・がん罹患データを収集し続けている。

2．フォローアップ状況

平成7年1月1日より観察開始し、現在のところ表1に示すようなフォローアップ状況である。

表1．フォローアップ状況

医療費データ：平成17年12月31日まで完了（11年分）
死亡・転出データ：平成17年12月31日まで完了（11年分）
死因データ：平成13年12月31日まで完了（7年分）
がん罹患データ：平成13年12月31日まで完了（7年分）

医療費データには入院・入院外別の医療機関受診回数・入院日数と医療費が含まれている。宮城県国民健康保険団体連合会から医療費データおよび死亡・転出データの提供を受けている。死因データについては、現在、人口動態調査調査票の目的外使用を申請中である。また、がん罹患データは、平成15年12月31日まで追跡を延長中である。

B．大崎国民健康保険加入者コホート研究平成18年度研究成果

大崎国民健康保険加入者コホート研究の平成18年度研究成果は、以下の通りである。

	著者	Title	Publish
1	Kuriyama S, et al.	Green tea consumption and mortality due to cardiovascular disease, Cancer, and all-causes in Japan: the Ohsaki Study.	JAMA 2006; 296: 1255-1265.
2	Kikuchi N, et al.	No association between green tea and the risk of prostate cancer in Japanese men: the Ohsaki Cohort Study.	Br J Cancer 2006; 95: 371-373.
3	Shimazu T, et al.	Dietary patterns and cardiovascular mortality in Japan: a prospective cohort study.	Int J Epidemiol (in press).
4	菊地信孝、他.	からだの痛みと自殺完遂リスクに関する前向きコホート研究:大崎コホート研究.	第17回日本疫学会学術総会.
5	中谷直樹、他.	飲酒と自殺リスクに関する前向きコホート研究：大崎コホート研究.	第17回日本疫学会学術総会.
6	曽根稔雅、他.	生きがいと死亡リスクに関する前向きコホート研究：大崎コホート研究.	第17回日本疫学会学術総会.
7	島津太一、他.	体重変化と死亡リスクに関する前向きコホート研究：大崎コホート研究.	第17回日本疫学会学術総会.
8	柿崎真沙子、他.	睡眠時間と死亡リスクに関する前向きコホート研究：大崎コホート研究.	第17回日本疫学会学術総会.

１．緑茶摂取と全死因死亡、循環器疾患死亡、がん死亡リスクに関する前向きコホート研究

【目的】緑茶ポリフェノールの循環器疾患やがんに対する防御作用が、細胞レベルや動物実験で盛んに報告されてきた。しかしながら同効果のヒトにおける証拠は少ない。本研究の目的は、緑茶摂取と全死因死亡、死因別死亡リスクとの関連を前向きコホート研究デザインで検討することである。

【方法】1994 年に宮城県大崎保健所管内に居住する国民健康保険加入者全員（40 歳-79 歳）に自記式調査票を配布し、51,255 人（95%）より有効回答を得た。全死因については、2005 年末まで 11 年間追跡、死亡原因については、2001 年末までの 7 年間追跡し、全死因死亡は 4,209 例、循環器疾患死亡は 892 例、がん死亡は 1,134 例であった。緑茶摂取頻度を回答し、ベースライン調査時にがん、心筋梗塞、脳血管障害の既往がなかった 40,530 人を解析対象者とした。

緑茶摂取頻度を<1 杯/日、1-2 杯/日、3-4 杯/日、≥5 杯/日の 4 群に分け、全死因死亡、死因別死亡リスクとの関連を Cox 比例ハザードモデルにて解析した。共変量は、年齢、職業、教育歴、BMI、スポーツを行う時間、1 日歩行時間、糖尿病・高血圧・胃潰瘍既往歴、喫煙、飲酒、総エネルギー摂取、米飯・みそ汁・大豆製品・肉類・魚・乳製品・果物・野菜摂取量、ウーロン茶・紅茶・コーヒー摂取頻度である。

【結果】男女とも緑茶を多く摂取するほど全死因死亡リスクが統計学的に有意に低下し、リスクの低下は特に女性で顕著であった。女性での緑茶摂取頻度<1 杯/日の群に対する全死因死亡の多変量補正相対危険度（95%信頼区間）は、1-2 杯/日、3-4 杯/日、≥5 杯/日で、0.98（0.84-1.15）、0.82（0.70-0.95）、0.77（0.67-0.89）（p for trend <0.001）であった。循環器疾患死亡ではこうした関連がより強くみられ、リスクは男性で 22%、女性で 31%、それぞれ低下した。循環器疾患の中では脳血管障害で特にリスクの低下がみられ、脳血管障害の中では脳梗塞でリスクの低下が顕著であった。一方、緑茶摂取とがん死亡リスクとは関連がみられなかった（表）。

【結論】緑茶摂取は、全死因死亡、循環器疾患死亡リスクの低下と関連していた。一方、緑茶摂取とがん死亡リスクとは、関連がみられなかった。

Green Tea Consumption and Mortality Due to Cardiovascular Disease, Cancer, and All Causes in Japan
The Ohsaki Study

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Context Green tea polyphenols have been extensively studied as cardiovascular disease and cancer chemopreventive agents in vitro and in animal studies. However, the effects of green tea consumption in humans remain unclear.

Objective To investigate the associations between green tea consumption and all-cause and cause-specific mortality.

Design, Setting, and Participants The Ohsaki National Health Insurance Cohort Study, a population-based, prospective cohort study initiated in 1994 among 40 530 Japanese adults aged 40 to 79 years without history of stroke, coronary heart disease, or cancer at baseline. Participants were followed up for up to 11 years (1995-2005) for all-cause mortality and for up to 7 years (1995-2001) for cause-specific mortality.

Main Outcome Measures Mortality due to cardiovascular disease, cancer, and all causes.

Results Over 11 years of follow-up (follow-up rate, 86.1%), 4209 participants died, and over 7 years of follow-up (follow-up rate, 89.6%), 892 participants died of cardiovascular disease and 1134 participants died of cancer. Green tea consumption was inversely associated with mortality due to all causes and due to cardiovascular disease. The inverse association with all-cause mortality was stronger in women ($P=.03$ for interaction with sex). In men, the multivariate hazard ratios of mortality due to all causes associated with different green tea consumption frequencies were 1.00 (reference) for less than 1 cup/d, 0.93 (95% confidence interval [CI], 0.83-1.05) for 1 to 2 cups/d, 0.95 (95% CI, 0.85-1.06) for 3 to 4 cups/d, and 0.88 (95% CI, 0.79-0.98) for 5 or more cups/d, respectively ($P=.03$ for trend). The corresponding data for women were 1.00, 0.98 (95% CI, 0.84-1.15), 0.82 (95% CI, 0.70-0.95), and 0.77 (95% CI, 0.67-0.89), respectively ($P<.001$ for trend). The inverse association with cardiovascular disease mortality was stronger than that with all-cause mortality. This inverse association was also stronger in women ($P=.08$ for interaction with sex). In women, the multivariate hazard ratios of cardiovascular disease mortality across increasing green tea consumption categories were 1.00, 0.84 (95% CI, 0.63-1.12), 0.69 (95% CI, 0.52-0.93), and 0.69 (95% CI, 0.53-0.90), respectively ($P=.004$ for trend). Among the types of cardiovascular disease mortality, the strongest inverse association was observed for stroke mortality. In contrast, the hazard ratios of cancer mortality were not significantly different from 1.00 in all green tea categories compared with the lowest-consumption category.

Conclusion Green tea consumption is associated with reduced mortality due to all causes and due to cardiovascular disease but not with reduced mortality due to cancer.

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TEA IS THE MOST CONSUMED BEVERAGE in the world aside from water. Three billion kilograms of tea are produced each year worldwide.[1] Because of the high rates of tea consumption in the global population, even small effects in humans could have large implications for public health.[2] Tea is generally consumed in the forms of green, oolong, and black tea, all of which originate from the leaves of the plant *Camellia sinensis*. Among teas, green tea polyphenols have been extensively studied as cardiovascular disease (CVD) and cancer chemopreventive agents.[3-6] Although substantial evidence from in vitro and animal studies indicates that green tea preparations inhibit CVD and carcinogenic processes, the possible protective role of green tea consumption against these diseases in humans remains unclear.

If green tea does protect humans against CVD or cancer, it is expected that consumption of this beverage would substantially contribute to the prolonging of life expectancy, given that CVD and cancer are the 2 leading causes of death worldwide.[7] To date, 4 studies[8-11] have examined the association between green tea consumption and mor-

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tality, but their sample sizes were small and the results were inconsistent.

We therefore designed this prospective analysis to examine the association between green tea consumption and mortality due to all causes, CVD, and cancer within a large population-based cohort study of 40 530 persons in Miyagi Prefecture in northeastern Japan, where green tea is widely consumed. Within this region, 80% of the population drinks green tea and more than half of them consume 3 or more cups/d.[12]

METHODS

Study Cohort

The details of the Ohsaki National Health Insurance (NHI) Cohort Study have been described in previous reports.[13-15] In brief, we delivered a self-administered questionnaire, including items on dietary intake (a 40-item food frequency questionnaire [FFQ]), between October and December 1994 to all NHI beneficiaries aged 40 to 79 years living in the catchment area of Ohsaki Public Health Center, Miyagi Prefecture, in northeastern Japan. Ohsaki Public Health Center, a local government agency, provides preventive health services for residents of 14 municipalities in Miyagi Prefecture. Of 54 996 eligible individuals, 52 029 (95%) responded.

To ascertain the date of and reason for withdrawal from the NHI, we started the prospective collection of NHI withdrawal history files on January 1, 1995. We excluded 774 participants who had withdrawn from the NHI before the baseline questionnaire survey. Thus, 51 255 participants ultimately formed the study cohort. The study protocol was reviewed and approved by the ethics committee of Tohoku University School of Medicine. We considered the return of self-administered questionnaires signed by the participants to imply their consent to participate in the study.

For current analysis, we excluded participants who died before the collection of NHI withdrawal history files (n=37) and those with missing data on green tea consumption frequency (n=6821), as well as those who reported extreme daily energy intake (n=444; sex-specific cutoffs for upper 0.5%, 3573.5 kcal/d for men and 2289.0 kcal/d for women; for lower 0.5%, 350.5 kcal/d for men and 200.0 kcal/d for women). We also excluded participants who reported a baseline history of cancer (n=1481), myocardial infarction (n=1149), or stroke (n=793), since the presence of these diseases at baseline could have affected their diet and lifestyle. Consequently, our analysis involved 40 530 participants.

Exposure Data

The questionnaire included items about the frequency of recent average consumption of 4 beverages (green tea, oolong tea, black tea, and coffee) and 36 items about food, as well as items regarding the consumption of alcohol and tobacco, personal and family history of disease, job status, level of education, body weight, height, engaging in sports or exercise, and time spent walking per day. The FFQ did not cover a specific period of time but asked about "everyday diet." The frequency of green tea consumption was divided into 5 categories: never, occasional, 1 to 2 cups/d, 3 to 4 cups/d, and 5 or more cups/d. Within the study region, the volume of a typical cup of green tea is 100 mL.

We conducted a validation study of the FFQ, in which 113 participants provided four 3-day food records within a period of 1 year and subsequently responded to the questionnaire. The results showed that the Spearman rank coefficient for the correlation between the amounts of green tea consumed according to the questionnaire and the amounts consumed according to the food records was 0.71 for men and 0.53 for women; the correlation between consumption measured by the 2 questionnaires administered 1 year apart was 0.63 for men and 0.64 for women.[16]

Because only 7% of the participants said they never drank green tea and only 19% said they drank it only occasionally, data from these respondents were collapsed into the single category of less than 1 cup/d for the purpose of this analysis. We examined the daily consumption of 40 food items, total energy, and nutrients from the FFQ responses by converting the selected frequency category for each food to a daily intake, using portion sizes based on the median values observed in four 3-day diet records. The FFQ used in this study has a high reproducibility and reasonably good validity in assessing the usual levels of intake of nutrients, foods, and food groups among our study population.[16]

Follow-up

The end points were all-cause mortality and cause-specific mortality. To follow up the participants for mortality and migration, we reviewed the NHI withdrawal history files. When a participant was withdrawn from the NHI system because of death, emigration, or employment, the date of withdrawal and its reason were coded on the NHI withdrawal history files. Because we were unable to obtain subsequent information on the participants who withdrew from the NHI, we discontinued follow-up of participants who withdrew from the NHI system because of emigration or employment.

For decedents identified as described herein, we investigated cause of death by reviewing the death certificates filed at Ohsaki Public Health Center. Cause of death was coded by trained physicians according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)*.[17] We identified deaths from CVD as *ICD-10* codes I00-I99, coronary heart disease as *ICD-10* codes I20-I25, stroke as *ICD-10* codes I60-I69, cerebral infarction as *ICD-10* code I63, cerebral hemorrhage as *ICD-10* code I61, subarachnoid hemorrhage as *ICD-10* code I60, cancer as *ICD-10* codes C00-C97, gastric cancer as *ICD-10* code C16, lung cancer as *ICD-10* code C34, and colorectal cancer as *ICD-10* codes C18-C21. None of the participants died of unknown causes. Because the Family Registra-

tion Law in Japan requires registration of death, death certificates confirmed all deaths that occurred in the study area, except participants who died after emigration from the area.

Statistical Analysis

For all-cause mortality, from January 1, 1995, to December 31, 2005, we prospectively counted the number of person-years of follow-up for each participant, from the beginning of follow-up until the date of death, the date of withdrawal from the NHI, or the end of follow-up, whichever occurred first. For cause-specific mortality, we followed up the participants for up to 7 years (1995-2001). The difference in follow-up times for all-cause mortality and cause-specific mortality results from the different sources of information. All-cause mortality data were obtained from the NHI withdrawal history files, which are provided every month and have no information on cause of death. Obtainment of cause-of-death data requires permission from the Japanese Ministry of Health, Labour, and Welfare to use the National Vital Statistics Database. Seven years of follow-up is the most up-to-date assessment of cause-of-death data in the study area as of August 1, 2006.

Cox proportional hazards regression analysis was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and cause-specific mortality according to green tea consumption categories and to adjust for potentially confounding variables, using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, NC). For all models, the proportional hazards assumptions were tested and met through addition of time-dependent covariates to the models. Dummy variables were created for green tea consumption categories. The lowest category of green tea consumption was used as a reference category. The *P* values for the analysis of linear trends were calculated by scoring the categories, from 1 for the lowest category to 4 for the highest, entering the number as a continuous term in the regression model. In the analyses for oolong tea or black tea as a main exposure, individuals with missing data were excluded (n=9679 for oolong tea and n=10 140 for black tea).

We considered the following variables as potential confounders a priori: age at baseline (continuous variable), job status (employed or unemployed), years of education (<10, 10-12, or ≥13), body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, or ≥30.0),[18,19] engaging in sports or exercise (<1 h/wk, 1-2 h/wk, or ≥3 h/wk), time spent walking (<1 h/d or ≥1 h/d), history of hypertension (yes or no), history of diabetes mellitus (yes or no), history of gastric ulcer (yes or no), smoking status (never, former, currently smoking 1-19 cigarettes/d, or currently smoking ≥20 cigarettes/d), alcohol consumption (never, former, current ethanol intake of <45.6 g/d, or current ethanol intake of ≥45.6 g/d), daily total energy intake (continuous variable), daily rice consumption (<3 bowls, 3 bowls, 4 bowls, or ≥5 bowls), daily consumption of miso (soybean paste) soup (yes or no), daily consumption of soybean products, total meat, total fish, dairy products, total fruits, and total vegetables (for each food, continuous variable), and consumption of oolong tea, black tea, or coffee (never or occasionally, 1-2 cups/d, or ≥3 cups/d). To correct the estimates for socioeconomic status, the models were adjusted for job status and the number of years of education. In addition to engaging in sports or exercise, time spent walking was used as a measure of physical activity because it is the most common type of physical exercise among middle-aged and older individuals in rural Japan. The validity and reproducibility of the question on time spent walking has been reported elsewhere.[20] Alcohol consumption was classified in terms of *go*, a traditional Japanese unit of measure equal to approximately 180 mL of sake and containing 22.8 g of ethanol. Interactions between green tea consumption and confounders were tested through addition of cross-product terms to the multivariate model.

To minimize the possibility that diet or lifestyle factors had changed in response to subclinical disease, we repeated all analyses after excluding participants who had died in the first 3 years of follow-up. To ensure that the estimates were not biased by multicollinearity, the age- and sex-adjusted HRs for the green tea consumption categories were also calculated and compared with the multivariate adjusted HRs. All reported *P* values are 2-tailed, and the differences at $P<.05$ are considered statistically significant.

RESULTS

Baseline characteristics of the participants by green tea consumption category are shown in TABLE 1 and TABLE 2. Participants who consumed green tea more often tended to be older and were more likely to be unemployed, to engage in sports or exercise, and to have a history of hypertension and diabetes mellitus and were less likely to walk, for both men and women. Men were also more likely to have a history of gastric ulcer and women to be obese. Men and women were both also more likely to consume individual foods or beverages such as miso (soybean paste) soup, soybean products, total fish, dairy products, total fruits, total vegetables, oolong tea, and black tea, but less likely to consume coffee. There were no apparent associations between smoking status or alcohol drinking and green tea consumption categories.

Over 11 years of follow-up, among 374 174 accrued person-years, the total number of deaths was 4209. The follow-up rate was 86.1%. TABLE 3 shows the association between green tea consumption and the HRs and associated 95% CIs of mortality due to all causes. We found that green tea consumption was inversely associated with mortality due to all causes and that the inverse association was more pronounced in women ($P=.03$ for

Table 1. Baseline Characteristics of Men According to Green Tea Consumption*

Characteristics	Green Tea Consumption, Cups/d				P Value†
	<1 (n = 5801)	1-2 (n = 4325)	3-4 (n = 3895)	≥5 (n = 5039)	
Age, mean (SD), y	57.6 (10.7)	57.8 (10.8)	60.3 (10.3)	61.8 (9.9)	<.001
Job status					
Employed	3844 (85.1)	2904 (84.7)	2476 (79.3)	3129 (78.2)	<.001
Unemployed	673 (14.9)	523 (15.3)	647 (20.7)	870 (21.8)	
Years of education					
<10	3475 (62.6)	2366 (56.7)	2212 (58.7)	3017 (61.8)	<.001
10-12	1700 (30.6)	1461 (35.0)	1214 (32.2)	1488 (30.5)	
≥13	375 (6.8)	346 (8.3)	342 (9.1)	374 (7.7)	
Body mass index‡					
<18.5	179 (3.3)	138 (3.3)	99 (2.6)	189 (3.9)	.007
18.5-22.9	2397 (43.5)	1812 (43.8)	1714 (45.6)	2092 (43.2)	
23.0-24.9	1446 (26.2)	1125 (27.2)	1004 (26.7)	1356 (28.0)	
25.0-29.9	1379 (25.0)	967 (23.4)	871 (23.2)	1128 (23.3)	
≥30.0	113 (2.1)	92 (2.2)	68 (1.8)	76 (1.6)	
Sports/exercise, h/wk					
<1	3950 (73.0)	2808 (69.5)	2454 (67.4)	3132 (66.7)	<.001
1-2	743 (13.7)	655 (16.2)	599 (16.5)	712 (15.2)	
≥3	717 (13.3)	575 (14.2)	589 (16.2)	855 (18.2)	
Walking duration, h/d					
<1	2687 (49.9)	2059 (50.8)	1956 (53.6)	2404 (51.1)	.006
≥1	2700 (50.1)	1993 (49.2)	1694 (46.4)	2297 (48.9)	
History of hypertension					
Yes	1240 (21.4)	1001 (23.1)	984 (25.3)	1229 (24.4)	<.001
No	4561 (78.6)	3324 (76.9)	2911 (74.7)	3810 (75.6)	
History of diabetes mellitus					
Yes	392 (6.8)	280 (6.5)	305 (7.8)	369 (7.3)	.07
No	5409 (93.2)	4045 (93.5)	3590 (92.2)	4670 (92.7)	
History of gastric ulcer					
Yes	1114 (19.2)	851 (19.7)	797 (20.5)	1106 (22.0)	.003
No	4687 (80.8)	3474 (80.3)	3098 (79.5)	3933 (78.1)	
Smoking status					
Never	1150 (21.6)	809 (20.4)	719 (19.9)	821 (17.6)	<.001
Former	1300 (24.4)	963 (24.3)	1018 (28.1)	1330 (28.5)	
Current, <20 cigarettes/d	927 (17.4)	713 (18.0)	647 (17.9)	877 (18.8)	
Current, ≥20 cigarettes/d	1943 (36.5)	1478 (37.3)	1236 (34.1)	1632 (35.0)	
Alcohol drinking					
Never	928 (16.8)	608 (14.8)	562 (15.1)	905 (18.8)	<.001
Former	197 (3.6)	119 (2.9)	117 (3.1)	171 (3.6)	
Current, <45.6 g/d ethanol	4176 (75.8)	3256 (79.2)	2957 (79.4)	3586 (74.6)	
Current, ≥45.6 g/d ethanol	210 (3.8)	129 (3.1)	88 (2.4)	144 (3.0)	
Total energy intake, mean (SD), kcal/d	1783.5 (612.2)	1812.8 (603.7)	1852.2 (589.7)	1905.0 (592.8)	<.001
Daily dietary consumption					
Rice, ≥4 bowls	1951 (34.0)	1419 (33.1)	1281 (33.3)	1726 (34.7)	.34
Miso (soybean paste) soup	4933 (86.5)	3819 (89.5)	3506 (91.4)	4581 (92.4)	<.001
Soybean products, mean (SD), g	46.5 (28.7)	50.0 (28.3)	52.7 (27.6)	56.8 (27.0)	<.001
Total meat, mean (SD), g	22.5 (19.2)	23.2 (18.6)	22.9 (17.4)	23.1 (18.9)	<.001
Total fish, mean (SD), g	55.2 (35.5)	57.5 (34.8)	61.2 (34.3)	66.6 (34.7)	<.001
Dairy products, mean (SD), g	119.0 (98.9)	127.8 (98.5)	130.1 (98.8)	134.6 (99.6)	<.001
Total fruits, mean (SD), g	63.6 (53.1)	71.0 (54.9)	77.8 (55.5)	90.1 (58.3)	<.001
Total vegetables, mean (SD), g	61.8 (42.9)	66.7 (43.1)	72.4 (43.3)	77.5 (46.0)	<.001
Oolong tea, ≥3 cups/d	181 (3.7)	88 (2.7)	99 (3.5)	149 (4.1)	<.001
Black tea, ≥3 cups/d	20 (0.4)	24 (0.8)	48 (1.7)	50 (1.4)	<.001
Coffee, ≥3 cups/d	798 (14.9)	497 (13.3)	370 (11.1)	495 (11.8)	<.001

*Data are expressed as No. (%) unless otherwise indicated.
†*P* values calculated by analysis of variance or χ^2 test.
‡Body mass index was calculated as weight in kilograms divided by height in meters squared.

Table 2. Baseline Characteristics of Women According to Green Tea Consumption*

Characteristics	Green Tea Consumption, Cups/d				P Value†
	<1 (n = 4901)	1-2 (n = 4478)	3-4 (n = 4944)	≥5 (n = 7147)	
Age, mean (SD), y	58.9 (10.8)	60.1 (10.5)	61.6 (9.7)	62.7 (9.2)	<.001
Job status					
Employed	2086 (55.8)	1842 (52.7)	1710 (44.7)	2319 (42.8)	<.001
Unemployed	1656 (44.3)	1656 (47.3)	2119 (55.3)	3097 (57.2)	
Years of education					
<10	2709 (59.2)	2303 (54.5)	2558 (54.3)	3949 (58.2)	<.001
10-12	1527 (33.4)	1560 (36.9)	1739 (36.9)	2277 (33.5)	
≥13	340 (7.4)	366 (8.7)	410 (8.7)	564 (8.3)	
Body mass index‡					
<18.5	211 (4.6)	155 (3.6)	190 (4.0)	247 (3.6)	<.001
18.5-22.9	1856 (40.3)	1697 (39.8)	1924 (40.8)	2579 (37.8)	
23.0-24.9	1107 (24.1)	1086 (25.5)	1162 (24.6)	1705 (25.0)	
25.0-29.9	1244 (27.0)	1194 (28.0)	1286 (27.2)	2031 (29.8)	
≥30.0	183 (4.0)	131 (3.1)	159 (3.4)	265 (3.9)	
Sports/exercise, h/wk					
<1	3376 (76.7)	2917 (73.0)	3144 (70.4)	4656 (72.7)	<.001
1-2	586 (13.3)	665 (16.7)	784 (17.6)	998 (15.6)	
≥3	441 (10.0)	413 (10.3)	539 (12.1)	753 (11.8)	
Walking duration, h/d					
<1	2454 (55.7)	2315 (56.4)	2659 (59.0)	3794 (58.6)	.002
≥1	1952 (44.3)	1793 (43.7)	1847 (41.0)	2686 (41.5)	
History of hypertension					
Yes	1205 (24.6)	1221 (27.3)	1410 (28.5)	2134 (29.9)	<.001
No	3696 (75.4)	3257 (72.7)	3534 (71.5)	5013 (70.1)	
History of diabetes mellitus					
Yes	252 (5.1)	204 (4.6)	262 (5.3)	410 (5.7)	.05
No	4649 (94.9)	4274 (95.4)	4682 (94.7)	6737 (94.3)	
History of gastric ulcer					
Yes	531 (10.8)	515 (11.5)	547 (11.1)	763 (10.7)	.56
No	4370 (89.2)	3963 (88.5)	4397 (88.9)	6384 (89.3)	
Smoking status					
Never	3380 (87.4)	3239 (91.5)	3649 (92.9)	5008 (89.2)	<.001
Former	113 (2.9)	84 (2.4)	90 (2.3)	151 (2.7)	
Current, <20 cigarettes/d	238 (6.2)	145 (4.1)	142 (3.6)	315 (5.6)	
Current, ≥20 cigarettes/d	138 (3.6)	73 (1.2)	45 (1.2)	142 (2.5)	
Alcohol drinking					
Never	2883 (72.2)	2707 (73.9)	3071 (75.8)	4297 (73.8)	<.001
Former	77 (1.9)	43 (1.2)	46 (1.1)	80 (1.4)	
Current, <45.6 g/d ethanol	1007 (25.2)	903 (24.7)	926 (22.9)	1431 (24.6)	
Current, ≥45.6 g/d ethanol	27 (0.7)	8 (0.2)	9 (0.2)	15 (0.3)	
Total energy intake, mean (SD), kcal/d	1188.3 (366.4)	1231.3 (349.1)	1268.9 (331.2)	1310.2 (331.6)	<.001
Daily dietary consumption					
Rice, ≥4 bowls	507 (10.5)	380 (8.6)	403 (8.3)	615 (8.7)	<.001
Miso (soybean paste) soup	4026 (84.0)	3904 (88.9)	4407 (90.5)	6335 (90.4)	<.001
Soybean products, mean (SD), g	42.7 (24.3)	46.9 (23.2)	49.5 (22.0)	51.1 (21.5)	<.001
Total meat, mean (SD), g	15.7 (14.1)	16.0 (13.0)	16.2 (12.5)	16.3 (13.7)	.07
Total fish, mean (SD), g	47.2 (30.6)	50.1 (30.4)	53.6 (29.1)	57.0 (29.8)	<.001
Dairy products, mean (SD), g	140.8 (102.3)	151.3 (100.9)	157.0 (100.0)	155.0 (101.4)	<.001
Total fruits, mean (SD), g	96.9 (64.8)	110.0 (64.0)	119.1 (62.9)	127.0 (63.3)	<.001
Total vegetables, mean (SD), g	71.5 (47.0)	80.8 (47.3)	84.9 (46.6)	88.6 (48.4)	<.001
Oolong tea, ≥3 cups/d	311 (7.7)	161 (4.9)	231 (6.4)	369 (7.1)	<.001
Black tea, ≥3 cups/d	17 (0.4)	24 (0.8)	40 (1.1)	82 (1.6)	<.001
Coffee, ≥3 cups/d	550 (12.6)	350 (9.2)	308 (7.6)	388 (6.7)	<.001

*Data are expressed as No. (%) unless otherwise indicated.
†*P* values calculated by analysis of variance or χ^2 test.
‡Body mass index was calculated as weight in kilograms divided by height in meters squared.

interaction with sex). In men, the multivariate HRs of mortality due to all causes associated with different green tea consumption frequencies were 1.00 (reference) for less than 1 cup/d, 0.93 (95% CI, 0.83-1.05) for 1 to 2 cups/d, 0.95 (95% CI, 0.85-1.06) for 3 to 4 cups/d, and 0.88 (95% CI, 0.79-0.98) for 5 or more cups/d, respectively ($P=.03$ for trend). The corresponding data in women were 1.00, 0.98 (95% CI, 0.84-1.15), 0.82 (95% CI, 0.70-0.95), and 0.77 (95% CI, 0.67-0.89), respectively ($P<.001$ for trend). We included a variety of potential confounders in our multivariate models; however, the results did not change substantially even after adjustment for these variables. Comparison between the age- and sex-adjusted model and multivariate model suggested that the estimates were not biased by multicollinearity. When we excluded the 1018 participants who died in the first 3 years of follow-up, the results also did not change substantially.

Over 7 years of follow-up, among 252 101 total accrued person-years, the total number of deaths was 2931 (892 from CVD and 1134 from cancer). The follow-up rate was 89.6%. TABLE 4 shows the association between green tea consumption and the HRs and associated 95% CIs of mortality due to CVD and cancer. We found that green tea consumption was inversely associated with mortality due to CVD but not with that due to cancer. The inverse association with CVD mortality was stronger than that with all-cause mortality and the inverse association was also more pronounced in women ($P=.08$ for interaction with sex). In women, compared with those who consumed less than 1 cup/d of green tea, those who consumed 5 or more cups/d had a 31% lower risk of CVD death. In contrast, the association between green tea consumption and cancer mortality was substantially different. The HRs of cancer mortality were not significantly different from 1.00 in all green tea consumption categories compared with the lowest-consumption (referent) category.

We further investigated the association between green tea consumption and specific CVD and cancer mortality (TABLE 5, TABLE 6, and TABLE 7). In men, green tea consumption was significantly associated with reduced mortality due to stroke. In women, green tea consumption also was significantly associated with reduced mortality due to stroke, especially cerebral infarction. Compared with women who consumed less than 1 cup/d of green tea, those who consumed 5 or more cups/d had 42% and 62% lower risk of death due to stroke and cerebral infarction, respectively. In both men and women, the multivariate HRs of gastric, lung, and colorectal cancer mortality were mostly above unity but not statistically significant.

We conducted further stratified analyses of CVD mortality examining

Table 3. Cox Proportional Hazard Ratios (HRs) for 11-Year Mortality Due to All Causes by Green Tea Consumption in Japanese Adults

Mortality Outcomes	Green Tea Consumption, Cups/d				*P* Value for Trend
	<1	1-2	3-4	≥5	
			Total Participants		
No. of person-years	97 127	80 416	82 121	114 510	
No. of deaths	1109	872	920	1308	
Age- and sex-adjusted HR (95% CI)	1.00	0.94 (0.86-1.03)	0.88 (0.80-0.96)	0.83 (0.77-0.90)	<.001
Multivariate HR (95% CI)*	1.00	0.96 (0.87-1.05)	0.90 (0.82-0.98)	0.84 (0.77-0.92)	<.001
Multivariate HR (95% CI)†	1.00	0.95 (0.85-1.05)	0.92 (0.83-1.02)	0.85 (0.77-0.94)	.001
			Men		
No. of person-years	53 348	39 678	35 984	47 273	
No. of deaths	747	541	584	796	
Age-adjusted HR (95% CI)	1.00	0.96 (0.86-1.07)	0.95 (0.86-1.06)	0.89 (0.81-0.99)	.03
Multivariate HR (95% CI)*	1.00	0.93 (0.83-1.05)	0.95 (0.85-1.06)	0.88 (0.79-0.98)	.03
Multivariate HR (95% CI)†	1.00	0.94 (0.82-1.07)	0.97 (0.85-1.10)	0.88 (0.78-1.00)	.07
			Women		
No. of person-years	43 779	40 738	46 137	67 238	
No. of deaths	362	331	336	512	
Age-adjusted HR (95% CI)	1.00	0.91 (0.78-1.05)	0.75 (0.65-0.87)	0.74 (0.64-0.84)	<.001
Multivariate HR (95% CI)*	1.00	0.98 (0.84-1.15)	0.82 (0.70-0.95)	0.77 (0.67-0.89)	<.001
Multivariate HR (95% CI)†	1.00	0.96 (0.81-1.15)	0.86 (0.72-1.02)	0.80 (0.68-0.94)	.003

Abbreviation: CI, confidence interval.
*The multivariate HR has been adjusted for age (continuous variable), sex (among total participants), job status (employed vs unemployed), years of education (<10, 10-12, or ≥13), body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, or ≥30.0), engaging in sports or exercise (<1, 1-2, or ≥3 h/wk), walking duration (<1 vs ≥1 h/d), history of hypertension, diabetes mellitus, and gastric ulcer (for each disease, yes or no), smoking status (never, former, currently smoking <20, or currently smoking ≥20 cigarettes/d), alcohol drinking (never, former, currently drinking <45.6 g/d, or currently drinking ≥45.6 g/d ethanol), total energy intake per day (continuous variable), daily consumption of rice (<3, 3, 4, or ≥5 bowls), daily consumption of miso (soybean paste) soup (yes or no), daily consumption of soybean products, total meat, total fish, dairy products, total fruits, and total vegetables (for each food, continuous variable), and consumption of oolong tea, black tea, and coffee (for each beverage, never or occasionally, 1-2 cups/d, or ≥3 cups/d).
†Participants who died in the first 3 years of follow-up were excluded from this analysis.

subgroups defined by traditional CVD risk factors and dietary factors. The results in all subgroups showed the same inverse relationship between green tea consumption and CVD mortality, with no interactions noted. Although the interaction was not significant, the inverse association between green tea consumption and CVD mortality appeared to be more pronounced in participants who had never smoked. Among current smokers (n=11 614), the multivariate HRs of mortality due to CVD associated with different green tea consumption frequencies were 1.00 (reference) for less than 1 cup/d, 0.79 (95% CI, 0.55-1.14) for 1 to 2 cups/d, 0.81 (95% CI, 0.56-1.17) for 3 to 4 cups/d, and 0.86 (95% CI, 0.62-1.18) for 5 or more cups/d, respectively (P=.43 for trend). The corresponding data among never smokers (n=18 775) were 1.00, 0.85 (95% CI, 0.62-1.16), 0.69 (95% CI, 0.51-0.95), and 0.75 (95% CI, 0.56-1.00), respectively (P=.03 for trend).

Table 4. Cox Proportional Hazard Ratios (HRs) for 7-Year Mortality Due to Cardiovascular Disease and Cancer by Green Tea Consumption in Japanese Adults

Mortality Outcomes	Green Tea Consumption, Cups/d				*P* Value for Trend
	<1	1-2	3-4	≥5	
			Total Participants		
No. of person-years	65 656	54 443	55 290	76 712	
Cardiovascular disease mortality					
No. of deaths	261	186	182	263	
Age- and sex-adjusted HR (95% CI)	1.00	0.83 (0.69-1.00)	0.70 (0.58-0.85)	0.67 (0.57-0.80)	<.001
Multivariate HR (95% CI)*	1.00	0.87 (0.72-1.06)	0.77 (0.63-0.93)	0.74 (0.62-0.89)	<.001
Multivariate HR (95% CI)†	1.00	0.76 (0.59-0.97)	0.77 (0.60-0.98)	0.74 (0.59-0.92)	.01
Cancer mortality					
No. of deaths	256	229	265	384	
Age- and sex-adjusted HR (95% CI)	1.00	1.08 (0.91-1.29)	1.13 (0.95-1.34)	1.11 (0.95-1.30)	.21
Multivariate HR (95% CI)*	1.00	1.11 (0.93-1.34)	1.16 (0.97-1.38)	1.11 (0.94-1.31)	.25
Multivariate HR (95% CI)†	1.00	1.12 (0.89-1.41)	1.17 (0.94-1.46)	1.11 (0.90-1.37)	.36
			Men		
No. of person-years	36 003	26 885	24 250	31 718	
Cardiovascular disease mortality					
No. of deaths	149	103	98	131	
Age-adjusted HR (95% CI)	1.00	0.91 (0.71-1.17)	0.79 (0.61-1.02)	0.73 (0.58-0.92)	.005
Multivariate HR (95% CI)*	1.00	0.88 (0.68-1.14)	0.84 (0.64-1.09)	0.78 (0.61-1.00)	.05
Multivariate HR (95% CI)†	1.00	0.82 (0.59-1.16)	0.91 (0.65-1.27)	0.87 (0.64-1.19)	.49
Cancer mortality					
No. of deaths	179	142	175	243	
Age-adjusted HR (95% CI)	1.00	1.04 (0.84-1.30)	1.21 (0.98-1.48)	1.16 (0.96-1.41)	.08
Multivariate HR (95% CI)*	1.00	1.02 (0.82-1.28)	1.18 (0.95-1.46)	1.11 (0.90-1.36)	.22
Multivariate HR (95% CI)†	1.00	1.02 (0.77-1.35)	1.13 (0.86-1.48)	1.04 (0.80-1.35)	.66
			Women		
No. of person-years	29 653	27 558	31 040	44 995	
Cardiovascular disease mortality					
No. of deaths	112	83	84	132	
Age-adjusted HR (95% CI)	1.00	0.74 (0.55-0.98)	0.61 (0.46-0.81)	0.62 (0.48-0.80)	<.001
Multivariate HR (95% CI)*	1.00	0.84 (0.63-1.12)	0.69 (0.52-0.93)	0.69 (0.53-0.90)	.004
Multivariate HR (95% CI)†	1.00	0.68 (0.47-0.98)	0.65 (0.45-0.93)	0.61 (0.44-0.85)	.006
Cancer mortality					
No. of deaths	77	87	90	141	
Age-adjusted HR (95% CI)	1.00	1.14 (0.84-1.55)	0.97 (0.72-1.32)	1.00 (0.75-1.32)	.68
Multivariate HR (95% CI)*	1.00	1.27 (0.93-1.74)	1.09 (0.79-1.49)	1.07 (0.80-1.44)	.97
Multivariate HR (95% CI)†	1.00	1.34 (0.90-1.98)	1.22 (0.83-1.79)	1.20 (0.83-1.73)	.53

Abbreviation: CI, confidence interval.

*The multivariate HR has been adjusted for age (continuous variable), sex (among total participants), job status (employed vs unemployed), years of education (<10, 10-12, or ≥13), body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, or ≥30.0), engaging in sports or exercise (<1, 1-2, or ≥3 h/wk), walking duration (<1 vs ≥1 h/d), history of hypertension, diabetes mellitus, and gastric ulcer (for each disease, yes or no), smoking status (never, former, currently smoking <20, or currently smoking ≥20 cigarettes/d), alcohol drinking (never, former, currently drinking <45.6 g/d, or currently drinking ≥45.6 g/d ethanol), total energy intake per day (continuous variable), daily consumption of rice (<3, 3, 4, or ≥5 bowls), daily consumption of miso (soybean paste) soup (yes or no), daily consumption of soybean products, total meat, total fish, dairy products, total fruits, and total vegetables (for each food, continuous variable), and consumption of oolong tea, black tea, and coffee (for each beverage, never or occasionally, 1-2 cups/d, or ≥3 cups/d).

†Participants who died in the first 3 years of follow-up were excluded from this analysis.

The multivariate HRs of all-cause mortality according to green tea, oolong tea, and black tea consumption frequencies are compared in TABLE 8. Green tea consumption was associated with reduced mortality. In contrast, a weak or null association was observed between consumption of black tea or oolong tea and the HRs of all-cause mortality. We were unable to examine the associations between oolong tea or black tea and CVD or cancer mortality because of insufficient numbers of cases of disease among the higher-consumption categories of those beverages.

COMMENT

On the basis of a large, population-based, prospective cohort study, we found significant inverse associations of green tea consumption with mortality due to all causes and due to CVD. Compared with participants who consumed less than 1 cup/d of green tea, those who consumed 5 or more cups/d had a risk of all-cause and CVD mortality that was 16% lower (during 11 years of follow-up) and 26% lower (during 7 years of follow-up), respectively. These inverse associations of all-cause and CVD mortality were primarily observed in women, although the inverse association for green tea consumption was observed in both sexes. In contrast, null results were observed in the association between green tea consumption and cancer mortality.

Sato et al[8] found a significant inverse association between green tea consumption and stroke mortality in 5910 participants over a 4-year period. Nakachi et al[9,11] reported an observed association between increased consumption of green tea and significantly lower risk of CVD death among 8552 individuals with a follow-up period of 11 to 13 years. Our findings were consistent with these results. In contrast, Iwai et al[10] did not observe significant association between green tea consumption and all-cause mortality, but the results were consistent with an inverse association between green tea consumption and all-cause mortality. The study had a much smaller sample size (2855 participants with 9.9 years of follow-up), and nonsignificant results might be due to low statistical power. Nakachi et al[9,11] also demonstrated that green tea consumption was associated with reduced mortality due to cancer, in contrast with our findings.

The reason for the discrepancy between men and women for the associa-

Table 5. Cox Proportional Hazard Ratios (HRs) Among All Participants for 7-Year Mortality Due to Cardiovascular Disease and Cancer Subtypes by Green Tea Consumption in Japanese Adults

Mortality Outcomes	Green Tea Consumption, Cups/d				*P* Value for Trend
	<1	1-2	3-4	≥5	
Coronary heart disease					
No. of deaths	58	47	43	61	
Multivariate HR (95% CI)*	1.00	1.04 (0.70-1.56)	0.90 (0.60-1.36)	0.86 (0.59-1.26)	.34
Stroke					
No. of deaths	145	99	102	126	
Multivariate HR (95% CI)*	1.00	0.84 (0.65-1.09)	0.78 (0.60-1.01)	0.63 (0.49-0.82)	<.001
Cerebral infarction					
No. of deaths	65	41	48	43	
Multivariate HR (95% CI)*	1.00	0.77 (0.52-1.15)	0.81 (0.55-1.19)	0.49 (0.33-0.73)	.001
Cerebral hemorrhage					
No. of deaths	34	30	33	40	
Multivariate HR (95% CI)*	1.00	1.10 (0.66-1.82)	1.15 (0.70-1.89)	0.98 (0.60-1.58)	.94
Subarachnoid hemorrhage					
No. of deaths	21	13	12	26	
Multivariate HR (95% CI)*	1.00	0.71 (0.35-1.44)	0.57 (0.27-1.17)	0.78 (0.42-1.43)	.42
Gastric cancer					
No. of deaths	44	44	38	67	
Multivariate HR (95% CI)*	1.00	1.33 (0.86-2.04)	1.00 (0.64-1.58)	1.17 (0.78-1.76)	.72
Lung cancer					
No. of deaths	49	41	46	82	
Multivariate HR (95% CI)*	1.00	1.03 (0.67-1.58)	1.05 (0.69-1.59)	1.18 (0.81-1.72)	.36
Colorectal cancer					
No. of deaths	30	24	36	42	
Multivariate HR (95% CI)*	1.00	1.04 (0.59-1.82)	1.45 (0.87-2.41)	1.10 (0.67-1.82)	.54

Abbreviation: CI, confidence interval.
*The multivariate HR has been adjusted for age (continuous variable), sex, job status (employed vs unemployed), years of education (<10, 10-12, or ≥13), body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, or ≥30.0), engaging in sports or exercise (<1, 1-2, or ≥3 h/wk), walking duration (<1 vs ≥1 h/d), history of hypertension, diabetes mellitus, and gastric ulcer (for each disease, yes or no), smoking status (never, former, currently smoking <20, or currently smoking ≥20 cigarettes/d), alcohol drinking (never, former, currently drinking <45.6 g/d, or currently drinking ≥45.6 g/d ethanol), total energy intake per day (continuous variable), daily consumption of rice (<3, 3, 4, or ≥5 bowls), daily consumption of miso (soybean paste) soup (yes or no), daily consumption of soybean products, total meat, total fish, dairy products, total fruits, and total vegetables (for each food, continuous variable), and consumption of oolong tea, black tea, and coffee (for each beverage, never or occasionally, 1-2 cups/d, or ≥3 cups/d).

tions of green tea consumption and risk of all-cause and CVD mortality is uncertain. One possibility is the residual confounding by cigarette smoking. Men were more likely to smoke (Table 1 and Table 2), and the inverse associations between green tea consumption and CVD mortality appeared to be more pronounced in participants who had never smoked, although tests for interaction between green tea consumption categories and smoking in the analyses of CVD mortality yielded nonsignificant results. These results suggest that higher rates of smoking may mask the association of green tea consumption with CVD mortality among men.

Our finding of an inverse association between green tea consumption and CVD mortality appeared to be a threshold effect rather than a dose-response relationship, such that persons who consume at least 1 cup/d may receive some benefit. There may be differences in dietary intake and health characteristics besides green tea consumption between the lowest fourth and the highest three fourths of the distribution, suggesting that the observed association may be somehow explained by selection bias. However, in our models we adjusted for various potential confounders, and the estimates did not change substantially from the age- and sex-adjusted estimates.

Our results for CVD mortality may be partly explained by the effect of green tea on CVD risk profile. Previous studies have suggested that green tea may have beneficial effects on CVD risk profile, such as hypertension and obesity.[21,22] However, the present results of stratified analysis show that inverse associations were also evident among lean participants and among those who had no history of hypertension. Therefore, mechanisms other than the effects on traditional CVD risk factors might play a role. Green tea polyphenols, especially (-)-epigallocatechin-3-gallate, might explain the observed association with reduced all-cause and CVD mortality, irrespective of CVD risk profiles.[23,24] A number of biological mechanisms, including radical scavenging and antioxidant properties, have been proposed for the beneficial effects of green tea in different models of chronic disease.[3-6] The present inverse association between green tea consumption and cerebral infarction mortality, but not cerebral hemorrhage, indicates that green tea polyphenols

Table 6. Cox Proportional Hazard Ratios (HRs) Among Men for 7-Year Mortality Due to Cardiovascular Disease and Cancer Subtypes by Green Tea Consumption in Japanese Adults

Mortality Outcomes	Green Tea Consumption, Cups/d				*P* Value for Trend
	<1	1-2	3-4	≥5	
Coronary heart disease					
No. of deaths	37	29	27	36	
Multivariate HR (95% CI)*	1.00	1.03 (0.62-1.71)	0.96 (0.57-1.62)	0.91 (0.56-1.48)	.66
Stroke					
No. of deaths	79	53	59	58	
Multivariate HR (95% CI)*	1.00	0.85 (0.60-1.22)	0.97 (0.68-1.37)	0.65 (0.45-0.93)	.04
Cerebral infarction					
No. of deaths	37	23	33	23	
Multivariate HR (95% CI)*	1.00	0.78 (0.45-1.34)	1.16 (0.71-1.91)	0.58 (0.33-1.00)	.15
Cerebral hemorrhage					
No. of deaths	21	15	17	21	
Multivariate HR (95% CI)*	1.00	0.91 (0.46-1.78)	1.08 (0.56-2.09)	1.01 (0.53-1.91)	.88
Subarachnoid hemorrhage					
No. of deaths	10	5	3	5	
Multivariate HR (95% CI)*	1.00	0.58 (0.19-1.73)	0.37 (0.10-1.38)	0.37 (0.11-1.27)	.08
Gastric cancer					
No. of deaths	32	30	30	46	
Multivariate HR (95% CI)*	1.00	1.29 (0.78-2.16)	1.19 (0.71-2.00)	1.20 (0.74-1.95)	.55
Lung cancer					
No. of deaths	43	29	34	60	
Multivariate HR (95% CI)*	1.00	0.88 (0.54-1.42)	0.97 (0.61-1.54)	1.14 (0.75-1.73)	.46
Colorectal cancer					
No. of deaths	22	18	21	23	
Multivariate HR (95% CI)*	1.00	1.09 (0.57-2.09)	1.23 (0.66-2.29)	0.88 (0.47-1.63)	.74

Abbreviation: CI, confidence interval.

*The multivariate HR has been adjusted for age (continuous variable), job status (employed vs unemployed), years of education (<10, 10-12, or ≥13), body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, or ≥30.0), engaging in sports or exercise (<1, 1-2, or ≥3 h/wk), walking duration (<1 vs ≥1 h/d), history of hypertension, diabetes mellitus, and gastric ulcer (for each disease, yes or no), smoking status (never, former, currently smoking <20, or currently smoking ≥20 cigarettes/d), alcohol drinking (never, former, currently drinking <45.6 g/d, or currently drinking ≥45.6 g/d ethanol), total energy intake per day (continuous variable), daily consumption of rice (<3, 3, 4, or ≥5 bowls), daily consumption of miso (soybean paste) soup (yes or no), daily consumption of soybean products, total meat, total fish, dairy products, total fruits, and total vegetables (for each food, continuous variable), and consumption of oolong tea, black tea, and coffee (for each beverage, never or occasionally, 1-2 cups/d, or ≥3 cups/d).

might directly affect atherosclerosis itself, irrespective of traditional CVD risk profiles.

We observed weak or null relationships between black tea or oolong tea and mortality. The discrepancy between green tea and other teas might indicate the specific role of substances rich in green tea. However, the smaller varia-

Table 7. Cox Proportional Hazard Ratios (HRs) Among Women for 7-Year Mortality Due to Cardiovascular Disease and Cancer Subtypes by Green Tea Consumption in Japanese Adults

Mortality Outcomes	Green Tea Consumption, Cups/d				*P* Value for Trend
	<1	1-2	3-4	≥5	
Coronary heart disease					
No. of deaths	21	18	16	25	
Multivariate HR (95% CI)*	1.00	1.04 (0.54-2.01)	0.79 (0.40-1.56)	0.77 (0.42-1.44)	.31
Stroke					
No. of deaths	66	46	43	68	
Multivariate HR (95% CI)*	1.00	0.79 (0.53-1.16)	0.61 (0.41-0.90)	0.58 (0.41-0.84)	.002
Cerebral infarction					
No. of deaths	28	18	15	20	
Multivariate HR (95% CI)*	1.00	0.76 (0.41-1.39)	0.47 (0.24-0.89)	0.38 (0.21-0.69)	<.001
Cerebral hemorrhage					
No. of deaths	13	15	16	19	
Multivariate HR (95% CI)*	1.00	1.33 (0.61-2.90)	1.32 (0.61-2.82)	0.98 (0.46-2.09)	.87
Subarachnoid hemorrhage					
No. of deaths	11	8	9	21	
Multivariate HR (95% CI)*	1.00	0.80 (0.32-2.03)	0.71 (0.29-1.75)	1.05 (0.49-2.26)	.81
Gastric cancer					
No. of deaths	12	14	8	21	
Multivariate HR (95% CI)*	1.00	1.32 (0.59-2.94)	0.64 (0.26-1.63)	1.08 (0.50-2.33)	.84
Lung cancer					
No. of deaths	6	12	12	22	
Multivariate HR (95% CI)*	1.00	1.83 (0.68-4.96)	1.46 (0.54-3.95)	1.59 (0.63-4.05)	.54
Colorectal cancer					
No. of deaths	8	6	15	19	
Multivariate HR (95% CI)*	1.00	0.98 (0.32-2.97)	1.96 (0.78-4.95)	1.49 (0.60-3.71)	.26

Abbreviation: CI, confidence interval.
*The multivariate HR has been adjusted for age (continuous variable), job status (employed vs unemployed), years of education (<10, 10-12, or ≥13), body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, or ≥30.0), engaging in sports or exercise (<1, 1-2, or ≥3 h/wk), walking duration (<1 vs ≥1 h/d), history of hypertension, diabetes mellitus, and gastric ulcer (for each disease, yes or no), smoking status (never, former, currently smoking <20, or currently smoking ≥20 cigarettes/d), alcohol drinking (never, former, currently drinking <45.6 g/d, or currently drinking ≥45.6 g/d ethanol), total energy intake per day (continuous variable), daily consumption of rice (<3, 3, 4, or ≥5 bowls), daily consumption of miso (soybean paste) soup (yes or no), daily consumption of soybean products, total meat, total fish, dairy products, total fruits, and total vegetables (for each food, continuous variable), and consumption of oolong tea, black tea, and coffee (for each beverage, never or occasionally, 1-2 cups/d, or ≥3 cups/d).

Table 8. Cox Proportional Hazard Ratios (HRs) for 11-Year Mortality Due to All Causes by Type of Tea Consumption in Japanese Adults

Mortality Outcomes	Tea Consumption, Cups/d			*P* Value for Trend
	<1	1-2	≥3	
Green tea				
No. of person-years	97 127	80 416	196 631	
No. of deaths	1109	872	2228	
Multivariate HR (95% CI)*	1.00	0.96 (0.87-1.05)	0.87 (0.80-0.93)	<.001
Oolong tea (Chinese tea)				
No. of person-years	256 266	15 909	14 715	
No. of deaths	2646	135	122	
Multivariate HR (95% CI)*	1.00	1.01 (0.84-1.21)	1.03 (0.85-1.25)	.76
Black tea				
No. of person-years	271 605	8313	2712	
No. of deaths	2750	87	33	
Multivariate HR (95% CI)*	1.00	1.00 (0.79-1.25)	1.04 (0.72-1.51)	.89

Abbreviation: CI, confidence interval.
*The multivariate HR has been adjusted for age (continuous variable), sex, job status (employed vs unemployed), years of education (<10, 10-12, or ≥13), body mass index (calculated as weight in kilograms divided by height in meters squared; <18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, or ≥30.0), engaging in sports or exercise (<1, 1-2, or ≥3 h/wk), walking duration (<1 vs ≥1 h/d), history of hypertension, diabetes mellitus, and gastric ulcer (for each disease, yes or no), smoking status (never, former, currently smoking <20, or currently smoking ≥20 cigarettes/d), alcohol drinking (never, former, currently drinking <45.6 g/d, or currently drinking ≥45.6 g/d ethanol), total energy intake per day (continuous variable), daily consumption of rice (<3, 3, 4, or ≥5 bowls), daily consumption of miso (soybean paste) soup (yes or no), daily consumption of soybean products, total meat, total fish, dairy products, total fruits, and total vegetables (for each food, continuous variable), and consumption of green tea, oolong tea, black tea, and coffee (for each beverage, never or occasionally, 1-2 cups/d, or ≥3 cups/d). Models for green tea, oolong tea, or black tea did not include these variables, respectively.

tions in the consumption of black tea or oolong tea may have contributed in part to the noted lack of association with mortality.

Our study has limitations. First, the number of cases of individual CVD and cancer was only modest at best. Therefore, our study may not have had sufficient statistical power for detecting significant results in coronary heart disease or for detecting small increases or decreases in the risk of cancer at individual sites, as associated with green tea consumption. Second, 10.4% (during 7 years of follow-up) and 13.9% (during 11 years of follow-up) of total participants were lost to follow-up. However, this proportion did not vary across the green tea consumption categories (10.6%, 9.7%, 10.2%, and 10.8% of participants from the lowest to highest green tea consumption categories, respectively, were lost to follow-up during 7 years of follow-up, and 15.2%, 14.8%, 13.4%, and 12.4% of participants, respectively, were lost to follow-up during 11 years of follow-up). Therefore, we consider it unlikely that the association between green tea consumption and mortality was substantially distorted by the effect of loss to follow-up. Third, since green tea consumption was assessed on the basis on self-administered questionnaires, some misclassification of consumption status could arise in estimating the effect of the beverage. However, this misclassification may be nondifferential and would tend to result in underestimation of the impact of green tea consumption.

Healthy or unhealthy behavior, in association with high green tea consumption, could have confounded the correlation between green tea consumption and mortality. Almost all Japanese persons consume green tea as one of their favorite beverages and it is unlikely that green tea consumption was driven by health concerns. Therefore, the possibility that the observed inverse associations between green tea and mortality were confounded by habits related to health consciousness is small. However, although we statistically controlled for a variety of potential confounding factors and conducted analysis after excluding death during the first 3 years of follow-up, and the findings were robust, we could not eliminate residual confounding. Clinical trials are ultimately necessary to confirm the protective effect of green tea on mortality.

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２．緑茶摂取と前立腺がん罹患に関する前向きコホート研究

【目的】緑茶に含まれるポリフェノールの前立腺がん予防効果について動物での研究結果が複数報告されており、症例対照研究では緑茶摂取が前立腺がん罹患リスク低下に関与する可能性が示唆されているが、結果が一致しておらず、前向きコホート研究は行われていない。この仮説を、前向きコホート研究デザインで検討する。

【方法】1994 年に宮城県大崎保健所管内 1 市 13 町の国民健康保険加入者で 40－79 歳の男女に自記式質問紙を配布し、52,029 名（94.6%）から有効回答を得た。緑茶摂取項目に回答したがん既往歴のない男性でエネルギー摂取量上位 5%と下位 5%の者を除外した 19,647 名を解析対象とし、2001 年末まで 7 年間の追跡調査を行い、121 例の前立腺がん罹患症例を確認した。

緑茶摂取量を、1 杯未満/日、1 杯または 2 杯/日、3 杯または 4 杯/日、5 杯以上/日に分け、前立腺がん罹患リスクとの関連を Cox 比例ハザードモデルで解析した。解析では、年齢、BMI、飲酒、喫煙、歩行時間、婚姻状態、カロリー摂取量、カルシウム摂取量、肉摂取量で補正を行った。

【結果および考察】緑茶摂取 1 杯未満/日群に対する、1 杯または 2 杯/日群、3 杯または 4 杯/日群、5 杯以上/日群、それぞれの多変量補正相対危険度は、0.92 (0.53-1.58), 1.24 (0.76-2.03), 0.85 (0.52-1.40), (P for trend = 0.74)であった (Table)。調査開始日から３年以内の前立腺がん罹患例を除外しても結果に大きな変化はなかった。本研究結果では、緑茶摂取と前立腺がん罹患リスクとの間には有意な関連がみられなかった。

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Short Communication

No association between green tea and prostate cancer risk in Japanese men: the Ohsaki Cohort Study

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In a prospective study of 19 561 Japanese men, green-tea intake was not associated with a lower risk of prostate cancer (110 cases), the multivariate hazard ratio for men drinking ⩾5 cups compared with <1 cup per day being 0.85 (95% confidence interval 0.50–1.43, trend $P=0.81$).

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Although laboratory studies have suggested a protective effect of green-tea polyphenols against development of prostate cancer in animal models (Gupta *et al*, 1999; Saleem *et al*, 2003), few epidemiological studies have examined the association. A case–control study in China found that green-tea intake was associated with a lower risk of prostate cancer (Jian *et al*, 2004), whereas a prospective study of Japanese Americans in Hawaii and a case–control study in Japan found no such association (Severson *et al*, 1989; Sonoda *et al*, 2004). The age-standardised incidence of prostate cancer is low in Japan (12.7 per 100 000), being approximately one-tenth of that in the US (Parkin, 2002). Green-tea consumption per capita in Japan is the highest in the world (International Tea Committee, 2004). One reason for the low incidence of prostate cancer in Japan may be the high consumption of green tea. We therefore examined the association between green-tea consumption and prostate cancer incidence among men in the Ohsaki Cohort Study conducted in rural Japan.

MATERIALS AND METHODS

The details of the Ohsaki Cohort Study have been described previously (Tsuji *et al*, 1999; Anzai *et al*, 2005). Briefly, this prospective cohort study was started in 1994 and included 26 481 men aged 40–79 years living in 14 municipalities of Miyagi Prefecture (95% response rate) (Anzai *et al*, 2005). The study used a self-administered questionnaire that included items about the frequency of consumption of beverages (coffee, green tea, black tea) and food items, as well as alcohol drinking, smoking and other health-related lifestyle factors. We asked the subjects about their frequency of green-tea consumption according to five categories: never, occasionally, 1–2 cups per day, 3–4 cups per day and 5 or more cups per day. The validity of green-tea consumption was assessed by calculating Spearman correlation coefficients between the 12-day dietary records and the 40-item food-frequency questionnaire. The age- and energy-adjusted Spearman correlation coefficient in men was 0.71 (Ogawa *et al*, 2003). After exclusion of subjects with missing responses or with a prior history of cancer, 19 561 subjects remained. We followed up the vital and residential status of the subjects using population registries from 1 January 1995 to 31 December 2001. Reference to population-based cancer registries identified 110 incident cases of prostate cancer (7 years of follow-up with 121 543 person-years). During the study period, there was no mass screening programme for prostate cancer in this area.

We combined the lower two categories of green-tea consumption into the single category 'less than one cup per day' because of the small number of subjects in each category. We estimated hazard ratios (HRs) and the 95% confidence interval (CI) of prostate cancer incidence according to green-tea consumption, using the Cox proportional hazards model with adjustment for age and potential confounders. *P*-values for the test of linear trend were calculated by treating the green-tea consumption category as an ordinal variable. All *P*-values were two-tailed. This study had approximately 80% statistical power, with a two-sided α-error level of 5%, in detecting a true HR of 0.75 among the highest *vs* lowest categories of green-tea consumption.

RESULTS

Table 1 shows the characteristics of the subjects according to green-tea consumption. Subjects with a higher green-tea intake tended to be older, to have a higher calorie intake, to consume calcium and fish more frequently, and to drink coffee less frequently.

We found no significant association between green-tea consumption and the risk of prostate cancer. Multivariate HRs for prostate cancer associated with drinking 1–2, 3–4 and 5 or more cups of green-tea per day, as compared with less than one cup per day, were 0.77 (95% CI 0.42–1.40), 1.15 (0.69–1.94), and 0.85 (0.50–1.43), respectively (trend $P=0.81$) (Table 2). Exclusion of

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Table 1 Characteristics of the subjects according to green-tea consumption

Characteristic	Green-tea consumption (cups per day)			
	<1	1 or 2	3 or 4	≥5
No.	5982	4460	3397	5122
Age (years), means±s.d.	57.8±10.7	58.0±10.9	60.5±10.4	61.9±9.9
Smoking (%)				
Never	20.5	19.1	19.1	16.9
Past	24.7	24.0	27.5	27.8
Current	54.8	56.9	53.4	55.3
Alcohol drinking (%)				
Never	16.4	14.6	15.2	18.3
Past	10.5	9.8	10.2	11.5
Current	73.1	75.6	74.6	70.2
Body mass index (%)				
<18.5	8.4	7.6	6.4	7.6
18.5–24.9	65.3	67.0	68.6	67.7
≥25.0	26.3	25.4	25.0	24.7
Daily calorie intake (kcal day^{-1}), means±s.d.	1776±614	1809±602	1847±589	1902±592
Daily calcium intake (mg day^{-1}), means±s.d.	373±163	400±163	423±160	457±160
Walking duration (%)				
At least 1 h day^{-1}	49.6	48.1	45.8	48.6
Under 1 h day^{-1}	50.4	51.9	54.2	51.4
Meat consumption (%)				
Few	28.6	24.8	26.1	29.0
1–2 times/month	48.8	50.9	50.2	47.5
1–2 or more times/week	22.6	24.3	23.7	23.5
Fish consumption (%)				
Few or 1–2 times/week	35.5	31.7	26.8	22.1
3–4 times/week	32.6	34.8	36.4	33.8
Daily	31.9	33.5	36.8	44.1
Coffee consumption (%)				
Never	23.4	17.3	19.4	23.1
Occasionally	33.0	32.3	38.2	41.3
1–2	29.1	37.1	31.1	23.8
≥3	14.5	13.3	11.3	11.8
Black tea consumption (%)				
Never	68.8	63.4	63.2	66.3
Occasionally	29.1	30.6	32.6	30.2
1–2	1.7	5.3	2.5	2.1
≥3	0.4	0.7	1.7	1.4

$n=19561$. s.d. denotes standard deviation.

Table 2 HRs and 95% CIs of prostate cancer according to green-tea consumption

Variable	Green-tea consumption (cups per day)				
	<1	1 or 2	3 or 4	≥5	Trend *P*
No. of cases	29	18	31	32	
Person-years	36925	27658	24788	32172	
Age-adjusted HR	1.00	0.79 (0.44–1.43)	1.26 (0.76–2.09)	0.90 (0.55–1.50)	0.96
Multivariate HR[a]	1.00	0.77 (0.42–1.40)	1.15 (0.69–1.94)	0.85 (0.50–1.43)	0.81

HR=hazard ratio; CI=confidence interval. [a]Mulitivariate HR was adjusted for age (in years), body mass index (<18.5, 18.5–24.9 and ≥25.0), alcohol consumption (never, former and current drinking), smoking status (never, former, and current smoking), marital status (marriage at age<25, 25–29, ≥30, unmarried, separated or divorced), daily calorie intake (continuous), daily calcium intake (tertile), walking duration (<1 h day^{-1}, and ≥1 h day^{-1}), consumption frequencies of black tea and coffee (never, occasionally, 1–2, and >3 cups per day), consumption frequencies of meat (few, 1–2 times/month, 1–2 or more times/week) and consumption frequencies of fish (few or 1–2 times/week, 3–4 times/week, daily).

Epidemiology