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Original Contribution

Green Tea Consumption and Prostate Cancer Risk in Japanese Men: A Prospective Study

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The incidence of prostate cancer is much lower in Asian than Western populations. Given that environmental factors such as dietary habits may play a major role in the causation of prostate cancer and the high consumption of green tea in Asian populations, this low incidence may be partly due to the effects of green tea. The JPHC Study (Japan Public Health Center-based Prospective Study) was established in 1990 for cohort I and in 1993 for cohort II. The subjects were 49,920 men aged 40–69 years who completed a questionnaire that included their green tea consumption habit at baseline and were followed until the end of 2004. During this time, 404 men were newly diagnosed with prostate cancer, of whom 114 had advanced cases, 271 were localized, and 19 were of an undetermined stage. Green tea was not associated with localized prostate cancer. However, consumption was associated with a dose-dependent decrease in the risk of advanced prostate cancer. The multivariate relative risk was 0.52 (95% confidence interval: 0.28, 0.96) for men drinking 5 or more cups/day compared with less than 1 cup/day ($p_{trend} = 0.01$). Green tea may be associated with a decreased risk of advanced prostate cancer.

Camellia sinensis; catechin; Japan; men; neoplasm staging; prospective studies; prostatic neoplasms; tea

Abbreviations: CI, confidence interval; EGCG, (−)-epigallocatechin-3-gallate; JPHC Study, Japan Public Health Center-based Prospective Study; PHC, Public Health Center; RR, relative risk.

Although the incidence of prostate cancer is much lower in Asian men than in Western men (1), the incidence of latent or clinically insignificant prostate cancer in autopsy studies among men from Asian countries and from the United States is similar (1–3). Moreover, migration data show that the incidence increases in men migrating from areas of low incidence to areas of higher incidence (4, 5). These results suggest that the etiology of prostate cancer may involve dietary, lifestyle, and environmental factors. A large number of experimental studies have shown that tea and its constituents have preventive effects against the development of prostate cancer, including antioxidant properties against free radicals, induction of apoptosis, inhibition of cell growth, and the arrest of cell cycle progression (6, 7). Teas are made from a leaf extract of the plant *Camellia sinensis* and classified into two main types, depending on the manufacturing process: green tea, which is nonfermented, and black tea, which is fermented (8). In general, green tea has a higher content of catechins, such as (−)-epigallocatechin-3-gallate (EGCG), which play an important role in cancer prevention, than does black tea (9). Given the high consumption of green tea in Asia, it has been suggested that the low incidence of prostate cancer in Asia may be partly due to the effects of green tea.

Although the preventive effects of green tea on prostate cancer have been reported in many laboratory studies (6), results from epidemiologic studies researching the association

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between teas in general (including both black and green teas) or green tea alone and prostate cancer have been inconsistent. In a case-control study in southeast China, the risk of prostate cancer decreased with increasing frequency of green tea consumption in a dose-dependent manner (10). Similarly, in a case-control study in Canadian men, general tea consumption was associated with a decreased risk of prostate cancer (11), and green tea consumption was further associated with a modest reduction in risk in a case-control study in Japan (12). To the contrary, however, other case-control studies in Italy, Utah, and Canada found no difference in risk for prostate cancer between general tea drinkers and nondrinkers (13–15). Among prospective studies, moreover, no association was reported between green tea consumption and prostate cancer in Japanese men (16, 17), while risk was conversely increased with green tea consumption in a cohort of men of Japanese ancestry in Hawaii (18).

This inconsistency might be explained as follows. First, subjects in some of these previous studies did not commonly drink green tea, but rather black tea. Second, almost all of these previous studies did not analyze by cancer stage, notwithstanding that the effects of green tea on prostate cancer may differ between localized and advanced cancer (10, 14).

Here, we investigated the relation between green tea consumption and risk of prostate cancer according to stage in a large prospective study among Japanese, who generally consume green tea.

MATERIALS AND METHODS

Study population

This cohort was part of the Japan Public Health Center-based Prospective Study (JPHC Study), which was established in 1990 for cohort I and in 1993 for cohort II. The study design has been described in detail previously (19). Cohort I consisted of five Public Health Center (PCH) areas (Iwate, Akita, Nagano, Okinawa, and Tokyo), and cohort II consisted of six PHC areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka) across Japan. The study population was defined as all residents aged 40–59 years in cohort I and 40–69 years in cohort II at the start of the respective baseline survey. In the present analysis, the Tokyo subjects were not included in data analyses because incidence data for them were not available. Initially, we defined a population-based cohort of 65,802 men. After initiation of the study, 143 subjects were found to be ineligible and were excluded because of non-Japanese nationality ($n = 31$), late report of emigration occurring before the start of the follow-up period ($n = 107$), duplicate enrollment ($n = 2$), incorrect birth data ($n = 1$), and self-reported prostate cancer at baseline ($n = 2$), leaving 65,659 men eligible for participation. This study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan.

Baseline survey

A self-administered questionnaire, which included green tea consumption and other lifestyle factors, was distributed to all eligible registered residents in 1990 for cohort I and in 1993–1994 for cohort II. Completed questionnaires were collected from 50,436 men (response rate, 77 percent). Information on the frequency and amount of green tea intake was obtained by use of the answer categories of almost none, 1–2 days/week, 3–4 days/week, 1–2 cups/day, 3–4 cups/day, and $\geq$5cups/day. Exposure was categorized by approximate quartile ($<$1 cup/day, 1–2 cups/day, 3–4 cups/day, $\geq$5 cups/day), with the category of $<$1 cup/day including those who consume almost none, 1–2 days/week, and 3–4 days/week. The validity of green tea consumption was assessed among subsamples using 28-day dietary records. Spearman's correlation coefficients between green tea consumption from the questionnaire and from dietary records were 0.57 for cohort I (20) and 0.37 for cohort II (21). In the validation study, the median value of green tea was 150 ml based on dietary records. Dietary factors in the questionnaire used in this study have been provided elsewhere (22).

Follow-up

Subjects were followed from the baseline survey until December 31, 2004. Changes in residence status including survival were identified annually through the residential registry in each area or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Among questionnaire respondents at baseline, 5,517 (10.9 percent) died, 3,017 (6.0 percent) moved out of a study area, and 91 (0.2 percent) were lost to follow-up during the study period. Generally, mortality data for the residents included in a residential registry are forwarded to the Ministry of Health, Labor, and Welfare and coded for inclusion in the national vital statistics. Residency and death registration are required by the Basic Residential Register Law and Family Registry Law, respectively, and the registries are believed to be complete. Here, information on the cause of death for those who had not moved out of the original area was based on death certificates from the respective PHC.

The occurrence of cancer was identified by active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries, with permission from the local governments responsible for the registries. Cases were confirmed from medical records, 94 percent of which included pathologic diagnoses, and were coded by use of the *International Classification of Diseases for Oncology*, Third Edition (23). Death certificate information was used as a supplementary information source, with 1.5 percent of cases of prostate cancer first notified by death certificate. The proportion of case patients with prostate cancer ascertained by death certificate only was 1.2 percent. These ratios were considered satisfactory for the present study.

We excluded men with incomplete information on green tea consumption ($n = 516$). For the present analysis, the earliest date of diagnosis was used in subjects with multiple primary cancers at different times. A total of 404 newly diagnosed prostate cancer cases were identified by December 31, 2004. Finally, a total of 49,920 men, including 404 prostate cancer patients, were used in the analysis.

Definition of localized and advanced prostate cancer

Cancer registration in our study required the entry of local staging, with the Gleason score used as supplementary information only. Cases were therefore classified as advanced cases (extraprostatic or metastatic cancer involving lymph nodes or other organs, 25 percent of total), localized cases (cancer confined within prostate, 54 percent of total), and undetermined cases (21 percent of total). The distribution of local staging in our study was similar to that in Japan overall (24). Moreover, cases for which local staging information was not available (83 undetermined cases) were divided into localized and advanced cancer by use of information on Gleason score or degree of differentiation. We added 11 cases with a high Gleason score of 8–10 or poor differentiation to the advanced cancer cases group. These criteria were selected to allow the identification of cases with a high likelihood of poor prognosis. Further, we added 53 cases with a low Gleason score of $\leq$7 or well or moderate differentiation to the localized cancer group (25). Finally, we confirmed 271 localized, 114 advanced, and 19 undetermined (5 percent of total) cases.

Statistical analysis

Person-years of follow-up were calculated for each person from the date of the baseline survey until the date of prostate cancer diagnosis, date of emigration from the study area, or date of death, whichever came first; if none of these occurred, follow-up was through the end of the study period (December 31, 2004). Subjects who were lost to follow-up were censored on the last confirmed date of their presence in the study area. The relative risks and 95 percent confidence intervals of prostate cancer according to green tea consumption were calculated by the Cox proportional hazards model, adjusted for age, study area (10 PHC areas), smoking status, alcohol consumption, body mass index, men who live with their wife, and coffee, black tea, and miso soup consumption according to the SAS PHREG procedure in SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina). The questionnaires used with the JPHC Study cohort I and cohort II differed slightly with respect to food items, method of expression, and frequency categories (excluding green tea, black tea, coffee, and miso soup consumption). Thus, for adjustments that included food items, the following statistical methods were used. For analysis of the further covariates of fruits, green or yellow vegetables, dairy food, soy food, and genistein, we calculated separate estimates for cohort I and cohort II and then analyzed the combined result using a fixed-effects model. In the test for heterogeneity using an inverse variance method, the two cohorts were not heterogeneous ($p = 0.95$). The covariates used in the model were age at enrollment, study area (10 PHC areas), smoking status (never, former, and current smokers), alcohol consumption (non-, former, or occasional drinkers, 1–149 g/week, $\geq$150 g/week), body mass index (continuous), men who live with their wife (yes/no), coffee consumption (almost none, $\geq$1 time/week, $\geq$1 cup/day), black tea consumption (almost none, $\geq$1 time/week, $\geq$1 cup/day), miso soup consumption ($<$4 times/week, one bowl/day, two bowls/day, $\geq$3 bowls/day), consumptions of fruits (g/day), green or yellow vegetables (g/day), dairy food (g/day), and soy food (g/day), and genistein (mg/day). Respective consumption of fruits, green or yellow vegetables, dairy food, and soy food was calculated by use of the frequency and portion size of each food from the questionnaire, while values for genistein were calculated by a specially developed food composition table for isoflavones in Japanese foods (26, 27).

P_{trend} values were assessed by assigning ordinal values for categorical variables. All p values are two sided, and statistical significance was determined at the $p < 0.05$ level.

RESULTS

Subjects' characteristics at baseline according to category of green tea consumption are shown in table 1. Participants with higher green tea consumption tended to be older, to smoke more, to have a higher likelihood of living with their wife, to consume more miso soup, fruits, vegetables, and soy food, and to consume less coffee.

Table 2 shows relative risks and 95 percent confidence intervals for prostate cancer by green tea consumption. Consumption was not associated with all cases of prostate cancer, and relative risks did not change substantially after adjustment for all potential confounding factors (for highest vs. lowest: relative risk (RR) = 0.89, 95 percent confidence interval (CI): 0.65, 1.21; $p_{\text{trend}} = 0.43$). We next classified the data according to prostate cancer stage. No statistically significant association was seen between green tea consumption and localized prostate cancer risk (for highest vs. lowest: RR in model 2 = 1.04, 95 percent CI: 0.72, 1.52; $p_{\text{trend}} = 0.54$). In contrast, however, green tea consumption was associated with a decreased risk of advanced prostate cancer in a dose-dependent manner ($<$1 cup/day: reference; 1–2 cups/day: age- and area-adjusted RR = 1.12, 95 percent CI: 0.65, 1.94; 3–4 cups/day: RR = 0.86, 95 percent CI: 0.50, 1.47; $\geq$5 cups/day: RR = 0.60, 95 percent CI: 0.34, 1.06; $p_{\text{trend}} = 0.03$). This association was strengthened to statistical significance when adjustment was made for all potential confounding factors (for highest vs. lowest: RR = 0.52, 95 percent CI: 0.28, 0.96). Tests for linear trends were also strengthened ($p_{\text{trend}} = 0.01$).

DISCUSSION

In this prospective cohort study among Japanese men, green tea consumption was associated with a decreased risk of advanced prostate cancer. In contrast, no association was observed between consumption and localized prostate cancer. To our knowledge, this is the first prospective study to investigate the association between green tea and prostate cancer according to stage and to identify the preventive effects of green tea on advanced prostate cancer. Although green tea and its constituents have shown protective effects on prostate cancer in many experimental studies (6, 7), previous epidemiologic studies researching the association between teas or green tea and prostate cancer have been inconsistent. One reason for this inconsistency is that most

TABLE 1. Baseline characteristics of study subjects according to green tea consumption, JPHC* Study, 1990–2004

	Green tea consumption (cups/day)				$p_{difference}$†
	<1	1–2	3–4	≥5	
No. of subjects	12,940	11,772	13,176	12,031	
Proportion (%)‡	25.9	23.6	26.4	24.1	
Mean age (years)	49.7 (7.4)§	50.8 (7.9)	52.3 (8.1)	53.9 (7.8)	<0.001
Body mass index, ≥25 (%)‡	23.8 (3.0)	23.5 (2.8)	23.3 (2.8)	23.3 (2.8)	<0.001
Current smoker (%)‡	51.3	52.8	51.6	54.0	<0.001
Regular drinker (%)‡	63.9	68.6	66.3	61.2	<0.001
Men who live with their wife, yes (%)‡	80.6	86.6	88.4	87.9	<0.001
Coffee, daily (%)‡	42.6	47.3	40.2	30.5	<0.001
Black tea, daily (%)‡	2.6	3.2	2.9	2.5	<0.001
Miso soup, daily (%)‡	61.7	68.3	72.6	78.4	<0.001
Fruits, daily (%)‡	17.7	22.8	26.3	30.7	<0.001
Green or yellow vegetables, daily (%)‡	37.8	36.5	40.2	47.1	<0.001
Dairy food, daily (%)‡	33.2	37.2	36.8	36.6	<0.001
Soy food, daily (%)‡	78.6	82.4	86.2	90.2	<0.001

* JPHC Study, Japan Public Health Center-based Prospective Study.

† $p_{difference}$ values of characteristics between categories of green tea consumption were calculated by analysis of variance and the chi-square test for homogeneity.

‡ All variables except for age were standardized to the age distribution (categorized by 5-year intervals) of the entire cohort.

§ Numbers in parentheses, standard deviation.

of the studies included populations that drink black tea predominantly. In a case-control study among Canadian men, tea consumption was associated with a statistically significant 30 percent decrease in prostate cancer risk (11). In contrast, no association with prostate cancer (RR = 0.9) was seen in men with a tea-drinking habit compared with non-tea drinkers in Italy (13), while drinking more than 5 cups of tea per week was not associated with a decreased risk of prostate cancer (RR = 0.90) in Utah (14). Moreover, a population-based case-control study in Canada found no difference in risk for prostate cancer between tea drinkers and non-tea drinkers (RR = 1.1 in men drinking ≥4 cups per day) (15).

However, this inconsistency in the effects of black tea on prostate cancer has also been seen in studies on green tea and prostate cancer among populations who mainly consume green tea. In a case-control study in southeast China, an increasing frequency of green tea consumption dose dependently decreased the risk of prostate cancer (10). Ten or more cups of green tea per day produced a modest reduction in the risk of prostate cancer (RR = 0.67) in a case-control study in Japan (12). In two prospective studies among Japanese men, no association was reported between green tea consumption and prostate cancer (16, 17). In contrast, Severson et al. (18) reported a nearly 50 percent increase in risk in relation to green tea intake in a prospective cohort study among men of Japanese ancestry in Hawaii. However, no studies have examined the association between green tea consumption and prostate cancer risk with regard to cancer stage. Given our finding that the effects of green tea differ according to cancer stage, this lack of classification by stage may be another reason for the inconsistency among studies. Our study showed that green tea was associated with a decrease in the risk of advanced prostate cancer only. This result is not inconsistent with a previous paper on the preventive effects of green tea on prostate cancer in China, where prostate cancer is typically diagnosed at an advanced stage (10).

This result is also supported by several mechanisms of cancer pathogenesis. Green tea and its constituents, such as EGCG, induce apoptosis, inhibit cell growth, and arrest progression of the cell cycle (6). In addition, EGCG has been found to inhibit tumor cell invasion and the expression of matrix metalloprotease, which is reported to be overexpressed in angiogenesis and essential in penetrating the basement membrane barriers (6, 7, 28). High levels of matrix metalloprotease 2 in plasma have been correlated with metastasis in prostate cancer patients (29), and increased expression of matrix metalloprotease 2 has been correlated with a high Gleason score and aggressive prostate cancer (30). In animal models, Gupta et al. (31) demonstrated that oral infusion of green tea polyphenols inhibits prostate carcinogenesis in transgenic adenocarcinoma of the mouse prostate (TRAMP), a model for prostate cancer that closely mimics progressive forms of human disease (32), and Caporali et al. (33) similarly reported that oral feeding of tea polyphenol to these mice prevented prostate cancer development. Moreover,

TABLE 2. Relative risk of prostate cancer according to green tea consumption, JPHC* Study, 1990–2004

	Green tea consumption (cups/day)										
	<1		1–2			3–4			≥5			p_{trend}
	No.	Relative risk	No.	Relative risk	95% confidence interval	No.	Relative risk	95% confidence interval	No.	Relative risk	95% confidence interval	
						All cases (n = *404*)						
Cases	76		83			114			131			
Age and area adjusted†		1.00		1.04	0.75, 1.42		1.00	0.74, 1.35		0.92	0.69, 1.24	0.49
Mutivariate (model 1)‡		1.00		0.98	0.70, 1.37		0.95	0.69, 1.30		0.90	0.66, 1.23	0.48
Mutivariate (model 2)§		1.00		0.96	0.68, 1.35		0.94	0.68, 1.30		0.89	0.65, 1.21	0.43
						Localized cases (n = *271*)¶						
Cases	49		48			74			100			
Age and area adjusted†		1.00		0.92	0.61, 1.38		1.00	0.69, 1.45		1.06	0.75, 1.51	0.57
Mutivariate (model 1)‡		1.00		0.83	0.54, 1.27		0.95	0.64, 1.40		1.07	0.73, 1.55	0.48
Mutivariate (model 2)§		1.00		0.81	0.52, 1.25		0.93	0.63, 1.37		1.04	0.72, 1.52	0.54
						Advanced cases (n = *114*)#						
Cases	26		29			32			27			
Age and area adjusted†		1.00		1.12	0.65, 1.94		0.86	0.50, 1.47		0.60	0.34, 1.06	0.03
Mutivariate (model 1)‡		1.00		1.10	0.62, 1.96		0.83	0.47, 1.47		0.56	0.31, 1.00	0.02
Mutivariate (model 2)§		1.00		1.10	0.61, 1.97		0.83	0.47, 1.48		0.52	0.28, 0.96	0.01

* JPHC Study, Japan Public Health Center-based Prospective Study.

† Calculated from a proportional hazards regression analysis of the two cohorts together and adjusted for age and area.

‡ Calculated from a proportional hazards regression analysis of the two cohorts together and adjusted for age, area, smoking status, alcohol consumption, body mass index, marital status, and coffee, black tea, and miso soup consumption.

§ Calculated from the weighted average of results from separate proportional hazards regressions fitted to the individual cohorts and further adjusted for fruits, green or yellow vegetables, dairy food, soy food, and genistein consumption.

¶ Localized cases were defined as cancer confined within the prostate. If information on local staging was not available, localized cases were considered as cases with a Gleason score of ≤7 (or well or moderate differentiation).

Advanced cases were defined as extraprostatic or metastatic cancer involving lymph nodes or other organs. If information on local staging was not available, advanced cases were defined as cancer with a Gleason score of 8–10 (or poor differentiation).

oral EGCG decreased testosterone levels in an animal experiment (34), and EGCG repressed transcription of the androgen receptor gene, *AR*, and thereby inhibited the effect of androgen on prostate cancer (35). Given that androgen receptor genes are amplified in at least one third of advanced prostate cancers cases (36), advanced prostate cancer may be more sensitive to the effects of green tea on testosterone or androgen receptor than is localized prostate cancer. These reports indicate the biologic plausibility of our result that green tea decreased the risk of advanced prostate cancer only. Nevertheless, the number of advanced prostate cancers was relatively small, and the occurrence of this result by chance cannot be ruled out.

The major strength of the present study was its prospective design. Collection of green tea consumption data before the subsequent diagnosis of prostate cancer allowed us to avoid recall bias. Other strengths were its high response rate (approximately 80 percent) and negligible loss to follow-up (0.2 percent). Moreover, we were able to adjust possible confounding factors to remove associations with other substances. A high intake of green tea is associated with some substances that may have contributed to the risk of prostate cancer. In this study, the association between green tea and advanced prostate cancer was strengthened after adjustment for several confounding factors.

Several limitations of the study also warrant mention. First, we did not collect information on whether men had undergone screening for prostate cancer. It is possible that men who have health check-ups are more health conscious and may drink more green tea, which would attenuate the results for localized prostate cancer and obscure any preventive effects on localized prostate cancer. Second, misclassification of exposure due to changes in green tea consumption during the study period might have occurred, because the exposure assessment was done at a single point. Third, we have no information on the methods used to brew the tea, such as infusion time or strength. These inaccurate measurements of green tea consumption may lead to random misclassification. If present, however, such misclassification would tend to underestimate the true relative risk. Finally, misclassification may have occurred when local-stage cases with a high Gleason score of 8–10 were classified as localized but as advanced when stage information was missing. Unfortunately, we were unable to classify

cases by Gleason score only, because this was collected as supplementary information and available in only a relatively small number of cases (23 percent of total).

In conclusion, we observed that green tea dose dependently decreased the risk of advanced prostate cancer. Although this result is supported by many animal studies, further studies are required to confirm the preventive effects of green tea on prostate cancer, including well-designed clinical trials in humans.

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