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ORIGINAL PAPER

Green and black tea intake in relation to prostate cancer risk among Singapore Chinese

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Abstract
Purpose Tea is one of the most commonly consumed beverages worldwide. To date, observational data from prospective cohort studies investigating the relationship between green and black tea intake and prostate cancer risk are sparse and equivocal. In a population-based, prospective cohort study of Chinese men in Singapore, we investigated the relationship between green and black tea intake and prostate cancer risk.
Methods Tea consumption data for 27,293 men were collected at baseline (between 1993 and 1998) using a validated food frequency questionnaire. After an average of 11.2 years of follow-up, 298 men had developed prostate cancer. Proportional hazards regression methods were used to assess the associations between tea intake and prostate cancer risk.
Results There was no association between daily green tea intake and prostate cancer risk, compared with no green tea intake [hazard ratio (HR) = 1.08; 95 % confidence interval (CI) 0.79, 1.47]. For black tea, a statistically significant positive association and trend were observed for daily intake compared with no black tea intake (HR = 1.41, 95 % CI 1.03, 1.92; p for trend <0.01)
Conclusions Few prospective data are available from populations that have both a high level and wide range of black and green tea intake; this study represents a unique opportunity to evaluate their individual effects on prostate cancer risk. Our findings support the notion that green tea intake does not protect against prostate cancer and that black tea intake may increase prostate cancer risk.

Keywords Black tea · Diet · Green tea · Prospective cohort · Prostate cancer · Singapore Chinese

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Introduction

Worldwide, prostate cancer is the second-most frequently diagnosed cancer [1]. There are few established risk factors for prostate cancer other than older age, a positive family history, and African-American race/ethnicity [2]. The Singapore population is uniquely suited for identifying

lifestyle and dietary factors related to clinically significant prostate cancers, as articulated below.

Singapore is a historically low-risk population where population-wide prostate-specific antigen (PSA) screening is not used to identify asymptomatic disease [3, 4]. The age-adjusted incidence rate among Chinese in Singapore has increased over 250 % within only two decades, from 7.6 per 100,000 populations in 1983–1987 to 27.2 per 100,000 in 2004–2008 [5, 6]. These temporal trends are likely the result of a birth cohort effect influenced by Singapore's transition in the mid-1960s from a developing to a developed country and the resulting increase in income and education level [7, 8]. The marked increase in prostate cancer incidence has occurred concurrently with an incorporation of western influences, including diet, into the Singapore lifestyle, and a decreased intake of dietary factors thought to protect against prostate cancer, such as green tea [9, 10].

All tea is made from the leaves of *Camellia sinensis*. Green tea is made by steaming or heating fresh tea leaves immediately after harvest, resulting in minimal oxidation of the naturally occurring polyphenols in the tea leaves (e.g., catechins and gallocatechins). In contrast, black tea is made by drying and crushing the tea leaves to encourage oxidation. This results in the conversion of the naturally occurring polyphenols to other polyphenols (e.g., theaflavins and thearubigens) [11].

Green and black tea may have different effects on prostate carcinogenesis. Epigallocatechin-3-gallate (EGCG), the major green tea catechin, was shown to inhibit prostate tumor growth and increase survival in mice [12, 13]. Tea catechins such as EGCG account for 30–42 % of dry green tea weight, but only 3–10 % of dry black tea weight [14, 15]. In addition, black and green tea differentially affects circulating hormone levels [16, 17] that may be involved in the development of prostate cancer [18].

Prospective observational data do not support a protective effect for green or black tea intake [9], although preliminary results from a randomized clinical trial suggest that green tea catechins may protect against prostate cancer development [19, 20]. One possible reason for the inconsistent results between prospective observational studies and experimental studies are that three of the four prospective studies were conducted in Japan, where the high prevalence of green tea intake does not allow for comparison with an "unexposed" group of non-green tea drinkers.

We investigated the relationship between black and green tea intake and prostate cancer risk among 27,293 men in the Singapore Chinese Health Study, a population-based prospective cohort study. We hypothesized that green tea would be inversely associated with prostate cancer risk, while black tea would have no association. The high level and wide variation (e.g., 33 % consume no tea and 15 % consume black or green tea daily) of both green and black tea intake in our study population allows for an examination of the individual effects of black and green tea consumption on prostate cancer risk.

Materials and methods

Study population

The design of the Singapore Chinese Health Study has been previously described in detail [21]. Briefly, the cohort consists of 27,959 men and 35,298 women recruited between April 1993 and December 1998, who were permanent residents or citizens of Singapore aged 45–74 years and resided in government-built housing estates (86 % of the Singapore population resided in such facilities) at the time of enrollment. We restricted the study to individuals belonging to the two major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese. For these analyses, we used data from the 27,293 men who did not have a history of cancer diagnosis at baseline, based on self-report and computer-assisted record linkage analysis with the population-based Singapore Cancer Registry database. The nationwide cancer registry has been in place since 1968 and has been shown to be comprehensive in its recording of cancer cases [22]. The Institutional Review Boards at the National University of Singapore and the University of Pittsburgh have approved this study.

Identification of incident prostate cancer cases among cohort members was accomplished by record linkage of the cohort database with the Singapore Cancer Registry database. To date, <1 % ($n = 446$) of cohort members have been lost to follow-up due to migration out of Singapore. As of 31 December 2007 (an average of 11.2 years of follow-up), 298 cohort participants had developed prostate cancer. Staging was determined through comprehensive chart reviews by a single urology oncologist (ASW). Cases that had radical prostatectomy were staged according to pathologic criteria ($n = 57$), as defined by The American Joint Committee on Cancer [23]. The remaining cases were staged according to clinical criteria by D'Amico risk group categories [24]. Early disease included cases with pathologically staged organ-confined disease (T1–T2), or clinically staged organ-confined disease and with either D'Amico good or intermediate risk. Locally advanced disease included cases with pathologically staged extracapsular (T3–T4) or nodal involvement (N1), or clinically staged extra-prostatic extension or regional nodal disease, or clinically organ-confined disease and with D'Amico high risk. Metastatic disease was defined as those with evidence of distant metastases, based on clinical

information. In summary, 124 (41.6 %) cases had localized disease and 162 (54.4 %) had advanced (i.e., locally advanced or metastatic) disease at diagnosis. The remaining 12 (4.0 %) cases did not have sufficient information for the determination of disease stage. Gleason sum scores were available for 271 (90.9 %) of cases and used to categorize cancers into high grade (scores 7–10) and low grade (scores 2–6).

Exposure assessment

Enrollment in the cohort entailed completing a baseline, in-person interview in the participant's home. The questionnaire elicited information on smoking, diet, demographics, current physical activity, occupational exposure, and medical history. We used a 165-item quantitative food frequency questionnaire (FFQ), developed for and validated in this population, to assess usual diet over the past year [21]. Comparison means between the FFQ and 24-h recall responses for the major macro- and micronutrients were within 10 % deviation of each other and thus very comparable [21]. Subjects were asked to identify their intake frequency, in cups consumed, of green and black tea separately over the past 12 months from nine predefined responses: never or hardly ever, 1–3 times a month, once a week, 2–3 times a week, 4–6 times a week, once a day, 2–3 times a day, 4–5 times a day, and 6 or more times a day. Subjects also indicated their intake frequency of coffee, alcohol, and soft drinks from the same nine predefined categories.

Statistical methods

Demographic and lifestyle characteristics were compared across green and black tea intake frequencies. Person-years of follow-up were counted from the date of recruitment to the date of diagnosis of prostate cancer, death, migration out of Singapore, or 31 December 2007, whichever occurred first. Hazard ratios (HRs) for prostate cancer and their corresponding 95 % confidence intervals (CIs) for green and black tea consumption were calculated using Cox proportional hazards regression methods.

The linear trend tests for associations between tea intake and prostate cancer risk were based on ordinal values of intake frequency (i.e., none, monthly, weekly, daily). Age at baseline interview (years), year of baseline interview (1993–1995, 1996–1998), dialect group (Hokkien, Cantonese), level of education (none/primary, ≥secondary), body mass index (BMI) (quartiles, kg/m^2), and cigarette smoking history (never, former, current) were included in multivariable regression models to adjust for possible confounding on the association between tea consumption and prostate cancer risk [25, 26]. Additional inclusion of the following covariates individually did not change the parameter estimate for green or black tea intake on prostate cancer risk by >10 %, and thus, they were not included in final adjusted models: physical activity, family history of prostate cancer, self-reported history of diabetes at baseline, vitamin/mineral supplement use, and intake of calcium, saturated fat, caffeine, coffee, lycopene, total soy isoflavones, red meat, preserved meat, total vegetables, and total energy. We also examined whether the association between tea intake and prostate cancer risk varied by education level, an indicator of socioeconomic status, by assessing the fitness of including interaction terms in adjusted models using the likelihood ratio test. We also examined whether smoking history or soy isoflavone intake were effect modifiers of the tea-prostate cancer association, given their previously observed biologic interactions with tea components [27, 28]. Statistical computing was conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). All p values were two-sided and considered statistically significant if <0.05.

Results

The study population consisted of non-tea drinkers (33.3 %), green tea-only drinkers (23.1 %), black tea-only drinkers (20.9 %), and drinkers of both tea types (22.8 %). Of the green or black tea-only drinkers, 20.6 and 12.4 %, respectively, consumed more than one cup of tea per day. Compared with non-tea drinkers, those who drank tea more frequently, regardless of the type of tea, tended to be more educated, more physically active, less likely to smoke, more likely to report weekly supplement use, and more likely to consume alcohol (Table 1).

There was no association with daily green tea intake and prostate cancer risk (Table 2). For black tea intake, there was a statistically significant trend with increasing intake and risk of prostate cancer. Consuming black tea on a daily basis was associated with a statistically significant 41 % increase in prostate cancer risk, compared with no black tea intake. When daily black tea drinkers were further divided into 1 cup/day and 2 or more cups/day groups, the point estimate for 2 or more cups/day was attenuated and lost statistical significance.

To evaluate whether the adverse effect observed for daily black tea intake is consistent with an early- or late-acting effect on prostate cancer risk, we conducted stratified analyses by stage of disease at diagnosis (e.g., localized and advanced) and by median duration of follow-up among cases (e.g., <8 and ≥8 years) (Table 3). The positive association for black tea intake versus no black tea intake and prostate cancer risk was confined to cases with longer duration of

Table 1 Distribution of selected factors by tea intake in the Singapore Chinese Health Study

	Frequency of green tea intake			Frequency of black tea intake		
	None/monthly	Weekly	Daily	None/monthly	Weekly	Daily
Person-years	199,726	58,205	46,791	199,327	59,670	45,725
Mean age (SD), years	57 (8)	56 (8)	56 (8)	57 (8)	56 (8)	56 (8)
% with none or primary education only	64.3	56.9	58.3	65.0	56.0	56.1
% any weekly physical activity	40.3	48.4	49.5	40.9	48.7	46.8
% never smokers	41.1	45.9	42.5	40.2	47.4	44.3
Mean body mass index (SD), kg/m^2	22.8 (3.2)	23.4 (3.2)	23.6 (3.2)	22.9 (3.2)	23.2 (3.2)	23.1 (3.2)
Weekly supplement use, % yes	4.4	5.7	5.6	4.3	5.9	5.5
Alcohol intake, % non-drinkers	70.0	65.3	66.6	69.2	66.6	68.1

SD standard deviation

Table 2 Hazard ratios (HRs) and 95 % confidence intervals (CIs) for tea intake and prostate cancer risk in the Singapore Chinese Health Study

	Green tea intake			Black tea intake		
	Cases, *n*	HR (95 % CI)[a]	HR (95 % CI)[b]	Cases, *n*	HR (95 % CI)[a]	HR (95 % CI)[c]
None	153	1.0 (ref)	1.0 (ref)	156	1.0 (ref)	1.0 (ref)
Monthly	33	1.06 (0.73, 1.55)	1.07 (0.73, 1.56)	22	1.17 (0.75, 1.84)	1.17 (0.75, 1.83)
Weekly	58	1.09 (0.80, 1.47)	1.09 (0.80, 1.48)	67	1.40 (1.05, 1.87)	1.40 (1.05, 1.86)
Daily	54	1.08 (0.79, 1.47)	1.08 (0.79, 1.48)	53	1.41 (1.03, 1.92)	1.41 (1.03, 1.92)
1 cup/day	29	1.22 (0.82, 1.82)	1.22 (0.82, 1.82)	40	1.51 (1.06, 2.13)	1.50 (1.06, 2.13)
≥2 cups/day	25	0.95 (0.62, 1.45)	0.95 (0.62, 1.45)	13	1.17 (0.67, 2.07)	1.17 (0.67, 2.07)
p for trend[d]		0.6	0.6		<0.01	<0.01
p for trend[e]		0.7	0.7		0.01	0.01

SD standard deviation

[a] Adjusted models include variables for age, dialect group, interview year, education, body mass index and smoking history

[b] Adjusted models include the covariates listed under (b) and black tea intake

[c] Adjusted models include the covariates listed under (b) and green tea intake

[d] Calculated from the model with four categories of tea intake: none, monthly, weekly, daily

[e] Calculated from the model with five categories of tea intake: none, monthly, weekly, 1 cup/day, ≥2 cups/day

follow-up, especially those diagnosed with localized disease. Thus, our findings are consistent with an early-acting adverse effect of black tea on prostate cancer risk, given that the strongest positive association was observed for localized disease among those with longer duration of follow-up. We observed the same findings when we conducted the analyses stratified by disease grade (e.g., low and high) and by median duration of follow-up among cases (e.g., <8 and ≥8 years) (data not shown).

Higher level of education was a statistically significant, positive risk factor for prostate cancer in these data (HR = 2.64; 95 % CI 1.63, 4.27; *p* for trend <0.001; for more than a secondary-level education verses no formal education). In stratified analyses by education level, the positive association with prostate cancer risk for daily black tea versus no black tea intake was confined to men with higher education level (*p* for interaction = 0.1). The HR was 1.88 (95 % CI 1.18, 3.00, *p* for trend <0.01) among men with at least a secondary-level education (person-years = 118,592 and cases = 122) and 1.15 (95 % CI 0.74, 1.77, *p* for trend = 0.3) among men with no formal or primary education (person-years = 186,130 and cases = 176). There was no difference in the distribution of prostate cancer by stage of disease (χ^2 *p* value = 0.99) or disease grade (χ^2 *p* value = 0.3) with increasing levels of education.

Soy isoflavone intake and smoking history did not modify the black tea-prostate cancer association in these data (data not shown). Daily green tea versus no green tea intake was not associated with prostate cancer risk, regardless of stage of disease, age at baseline or education level (data not shown). We also evaluated whether there were main effects

Table 3 Hazard ratios (HRs) and 95 % confidence intervals (CIs) for black tea intake in relation to prostate cancer by duration of follow-up and stage of disease in the Singapore Chinese Health Study

	<8 years of follow-up			≥8 years of follow-up		
	Cases, *n*	HR (95 % CI)[a]	*p* for trend	Cases, *n*	HR (95 % CI)[a]	*p* for trend
All cases						
None	85	1.0 (ref)		71	1.0 (ref)	
Monthly	8	0.83 (0.40, 1.72)		14	1.58 (0.89, 2.80)	
Weekly	31	1.27 (0.84, 1.92)		36	1.57 (1.05, 2.35)	
Daily	20	1.05 (0.64, 1.71)	0.5	33	1.82 (1.20, 2.75)	0.002
Localized disease						
None	32	1.0 (ref)		30	1.0 (ref)	
Monthly	4	1.08 (0.38, 3.06)		4	1.04 (0.37, 2.96)	
Weekly	13	1.41 (0.74, 2.69)		14	1.41 (0.74, 2.66)	
Daily	10	1.40 (0.69, 2.87)	0.2	17	2.16 (1.19, 3.93)	0.01
Advanced disease						
None	51	1.0 (ref)		36	1.0 (ref)	
Monthly	4	0.70 (0.25, 1.94)		8	1.81 (0.84, 3.90)	
Weekly	17	1.16 (0.67, 2.02)		21	1.85 (1.08, 3.17)	
Daily	10	0.86 (0.44, 1.70)	0.9	15	1.66 (0.91, 3.04)	0.03

[a] Adjusted models include variables for age, dialect group, interview year, education, BMI, and smoking history

of other (non-tea) beverage intake on prostate cancer risk. We observe no associations with daily versus no intake of coffee, alcohol, or soft drinks (data not shown).

Discussion

Prostate cancer incidence has more than tripled within the last two decades among Singapore Chinese men. This dramatic increase may be attributed in part to changes in frequency of dietary and lifestyle prostate cancer risk and/or preventative factors that accompanied Singapore's relatively recent transition from a developing to a developed country [10]. Major changes in the gene pool or the detection of pre-clinical disease are not major contributing factors, because there has been little migration into or out of Singapore and PSA screening for asymptomatic prostate cancer is not widely practiced in Singapore.

Using data from a large prospective cohort of Singapore Chinese men, we investigated the relationship between green and black tea intake and prostate cancer risk. Our findings do not support a protective effect of green tea on prostate cancer risk. Despite the abundant experimental evidence supporting the inhibitory effects of green tea catechins on prostate cancer development [29], our finding is consistent with results from a recent meta-analysis of prospective cohort studies that evaluated green tea–prostate cancer associations [9].

Three of the four previous prospective cohort studies found no association between green tea intake and prostate cancer risk. These studies were conducted in Japan [30, 31] and among Japanese Americans [32]. In the fourth study, no overall association was reported among a cohort of 49,920 Japanese men; however, among the 114 prostate cancer cases with advanced disease, there was an inverse association between green tea consumption and prostate cancer risk for men who consumed ≥5 cups of green tea per day compared with those who consumed <1 cup per day [relative risk (RR) = 0.52; 95 % CI 0.28, 0.96] [33]. We did not observe an association with daily green tea intake versus no tea intake for advanced prostate cancer ($n = 162$).

A possible explanation for the null findings for green tea and prostate cancer risk in our study and previous observational studies may be the failure to account for genetic variability in the metabolism of green tea catechins in the analyses. In a cross-sectional study conducted in Shanghai, China, we found men homozygous for low-activity associated catechol-*O*-methyltransferase (COMT) genotype to have a statistically significant 44 % lower urinary level of total tea polyphenols relative to men homozygous for high-activity COMT genotype [34]. These findings suggest that the protective properties of tea catechins against prostate carcinogenesis would be more apparent in men possessing the low-activity COMT genotype.

We reported a statistically significant positive association for daily black tea intake and prostate cancer risk, compared with no tea intake. In stratified analyses, the positive association with daily black tea intake was present mainly among men with higher education. In this

historically low-risk population that has seen a tripling of prostate cancer incidence in the past two decades [5, 6], education was shown to be a strong, statistically significant risk factor. Thus, our findings suggest that the enhanced prostate cancer risk associated with black tea drinking is most relevant among the subgroup of men most responsible for the general population's upward trend in prostate cancer incidence. This interpretation is tenuous given the relatively small number of cases in the current study and therefore awaits future confirmation. However, if confirmed, this interpretation carries obvious public health implications for prostate cancer prevention.

Of the three cohort studies that previously evaluated black tea intake and prostate cancer risk, only one, a Canadian retrospective cohort study [35] was conducted in a population with a relatively wide range of black tea intake. In this Canadian study ($n = 267$ cases), no association was observed for any versus no black tea intake and prostate cancer risk (RR = 1.13; 95 % CI 0.72, 1.76) [35]. In a Japanese prospective cohort study ($n = 110$ cases), imprecise, statistically non-significant associations were reported for occasional black tea intake (HR = 1.34; 95 % CI 0.77, 2.34) and daily black tea intake (HR = 0.60; 95 % CI 0.13, 2.68), compared with no black tea intake [31]. An inverse association with prostate cancer was reported in a US prospective cohort study of Japanese in Hawaii ($n = 149$ cases) for drinking black tea "almost daily," compared with "almost never" (RR = 0.6; 95 % CI not provided; p for trend = 0.02) [36]. The low prevalence of black tea intake among the study populations of Japanese in Hawaii and in Japan calls for caution in the interpretation of the reported associations.

Black tea, relative to green tea, contains low levels of the type of catechins that are shown to have prostate chemo-preventive properties [14]. On the other hand, the tannins prominent in black tea may have tumorigenic effects, although the animal data supporting this hypothesis are not specific for prostate carcinogenesis [37, 38]. Although our findings support an adverse effect of black tea intake on prostate cancer risk, there is no evident biologic mechanism that can explain the association.

This study had several strengths, including the use of a FFQ that was created for and validated in this population [21]. Additionally, the relatively wide variation in tea intake among the cohort provided a unique opportunity to compare the individual effects of black and green tea on prostate cancer risk. The prospective nature of our study reduced the opportunity for recall bias arising from differential misclassification of self-reported tea intake. Our ability to obtain prostate cancer diagnosis information from the Singapore Cancer Registry ensures near-complete case ascertainment. Limitations of the study include limited statistical power, especially in examining tea-prostate cancer associations in subgroup analyses, due to the relatively low incidence of prostate cancer in this population. Thus, it is possible that the positive associations for black tea among those with higher education may have been due in part to chance. There is also the possibility that the positive association reported with black tea intake was due in part to residual confounding by diet and/or lifestyle factors related to tea intake. Although the frequency of PSA screening is low in the Singapore general population, we did not have information available to evaluate whether PSA screening was related to tea intake in our study population. We observed small differences by stage of disease or disease grade among those who drank no black tea (42 % localized and 58 % advanced; 43 % low and 57 % high) and those who drank black tea daily (52 % localized and 48 % advanced; 41 % low and 59 % high), suggesting that if differences in PSA screening frequency by exposure status exist, detection bias was unlikely to influence our main finding for black tea and prostate cancer risk.

In summary, we report a positive association between black tea intake and prostate cancer risk among a prospective cohort of Chinese men in Singapore. Black tea is by far the most commonly consumed tea type worldwide, particularly among western populations, in which prostate cancer incidence is the highest [39]. It is also important to note that there is no widespread PSA screening to detect asymptomatic disease in Singapore, so risk factors identified in the present study pertain to clinically significant prostate cancer. Our results need to be confirmed in additional, large prospective studies, and through laboratory data on the biologic plausibility of our finding that black tea is a risk factor for prostate cancer, prior to translating these results into primary prevention strategies.

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