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Is Green Tea Drinking Associated With a Later Onset of Breast Cancer?

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Abstract

Background—Studies have found that tea polyphenols inhibit aromatase. Due to the substantial difference in levels of estrogens between pre- and post-menopausal women, the relationship between tea consumption and breast cancer risk may depend on menopausal status.

Methods—We examined this hypothesis in the Shanghai Women's Health Study, a population-based cohort study of 74,942 Chinese women.

Results—We found a time-dependent interaction between green tea consumption and age of breast cancer onset (p for interaction, 0.03). In comparison with non-tea drinkers, women who started tea-drinking at 25 years of age or younger had a hazard ratio (HR) of 0.69(95% CI:0.41–1.17) to develop premenopausal breast cancer. On the other hand, compared with non-tea drinkers, women who started tea drinking at 25 years of age or younger had an increased risk of postmenopausal breast cancer with an HR of 1.61(95% CI:1.18–2.20). Additional analyses suggest regularly drinking green tea may delay the onset of breast cancer.

Conclusions—Further studies are needed to confirm our findings.

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Keywords

Green tea; later onset; breast cancer; Aromatase

INTRODUCTION

Tea, particularly green tea, has received great attention due to its antioxidant and anti-telomerase, along with numerous other tumor inhibitory properties[1–6]. These potential anti-cancer mechanisms have been largely based on *in vitro* results[6] using (−)-epigallocatechin-3-gallate (EGCG), one major tea polyphenol. However, EGCG has low bioavailability systemically[7] as well as in mammary tissues after oral intake6. Thus, instead of a direct effect on mammary cells, the activity of tea components may mainly be through an indirect mechanism in the prevention of breast cancer6.

Substantial evidence suggests estrogen plays a critical role in breast carcinogenesis[8–10]. Several cohort studies found that high circulating estrogen concentration was associated with an increased risk of postmenopausal breast cancer[10–15]. A recent nested case-control study within the Nurses' Health Study II reported that high levels of follicular, but not luteal total or free, estradiol were related to an elevated risk of premenopausal breast cancer[16]. Interestingly, green tea consumption was significantly associated with decreased levels of saliva estradiol[17] and follicular, but not luteal serum estradiol[18,19] in premenopausal women. Green tea consumption, but not black tea, was also associated with reduced levels of estrone and estradiol among postmenopausal women[20]. Green tea's estrogen reduction activity may result from tea polyphenols inhibiting aromatase, the key enzyme converting androgens to estrone or estradiol[21]. Contrary to these promising observations, epidemiologic studies have generally not supported an association between tea drinking and breast cancer. In accordance with an earlier meta-analysis, a recent meta-analysis observed[22] a non-significant inverse association between green tea and breast cancer risk in three cohort studies, and only in one case-control study the inverse association reached statistical significance[22,23].

Only two case-control studies evaluated the association of green tea drinking with breast cancer risk by menopausal status[24,25]. The trend of the associations were similar in pre- and post-menopausal women whereas significantly inverse association was only found in premenopausal women[24]. To the best of our knowledge, no previous cohort studies on green tea have reported results by menopausal status22،23،26،[27]. Due to substantial variation in aromatase, estrogens, and androgen levels between pre- and post-menopausal women, the effect of tea on breast cancer risk may depend on the menopausal status and lifetime tea exposure. To evaluate this hypothesis, we assessed the association of breast cancer risk with lifetime green tea exposure by menopausal status using data from the Shanghai Women's Health Study (SWHS), a population-based cohort study of Chinese women.

METHODS

The Shanghai Women Health's Study

Detailed methods of the Shanghai Women's Health Study (SWHS) are previously published[28]. Briefly, 74,942 Chinese women aged 40 to 70 years were interviewed from March 1997 to May 2000 (92% participation). Trained interviewers elicited information on demographic characteristics, medical history, anthropometrics, usual dietary habits, physical activities, and other lifestyle factors. Measurements were performed at the in-person interview for weight, height, and circumferences of the waist and hips. The study was approved by all relevant institutional review boards in China and the United States.

Cohort follow-up and outcome ascertainment—The SWHS participants were tracked for cancer occurrence by biennial follow-up surveys and annual record linkage to the population-based Shanghai Cancer Registry and death certificates collected by the Shanghai Municipal Center for Disease Control and Prevention. The response rates for the follow-up survey were 99.8% (2000–2002), 98.7% (2002–2004), and 96.7% (2004–2007). All cancer cases were verified by home visits and medical record review. In order to allow for the delay in records processing, the date of the last follow-up was set as Dec, 31, 2005 for study participants, 6 months after the most recent record linkage (June 30, 2005).

Exposure Measurement

Tea consumption—At baseline, every participant was asked whether she ever drank tea three times or more per week for at least 6 months. If the participant answered 'yes', she was considered a regular tea drinker. She was then asked whether she still currently drank tea regularly, the age she started, and the type of tea she mainly drank, as well as the amount of dry tea leaves she consumed each month. If she was not a current regular tea drinker, she was asked at what age she stopped regularly consuming tea.

Urinary excretion of tea polyphenols—Measurements of tea polyphenols were carried out by liquid chromatography photo-diode array electrospray mass spectrometry (LC/PDA/ESI-MS) as established recently by Dr. Franke's laboratory29. Epicatechin, epigallocatechin, and their metabolites M4 and M630 were measured by HPLC with electrospray ionization (negative mode) high resolution tandem mass spectrometry (model TSQ, Thermo, San Jose, CA) similar to our earlier reports31⁻33. In a validation study among 683 non-case SWHS participants, we compared the tea leaves consumed, derived from questionnaire data, with the urinary excretion level of epigallocatechin, a specific tea polyphenol. Epicatechin or other tea-related polyphenols were not used in this validation study because they could also be derived from other sources of fruits and vegetables, such as apples.

Covariates—A wide array of covariates assessed at the baseline survey, including those derived from a validated food frequency questionnaire[34] were evaluated as potential confounding factors.

Statistical Analysis

Excluded from the analyses were 1,490 subjects with a history of cancer at baseline, 132 subjects with unreasonably high or low energy intake (<500 or >3,500 kcal/day, n = 132), and 10 subjects who moved away from Shanghai immediately after the baseline survey. Due to power concerns, we limited our analyses to green tea by excluding 381 subjects who regularly drank only black or oolong tea. As a result, a total of 72,861 subjects were included in the final analyses.

We estimated the main associations using HR in time-dependent Cox proportional hazard regression models[35], using age at entry and age at onset or age at censor as a time-scale with additional control for birth cohort effects by stratifying on birth cohort[36]. Other confounding factors are listed in the footnote of Table 3. To provide consistency to previous studies, we selected the potential confounding factors based on adjustment in published reports or risk factors in our previous studies. To examine the appropriateness of the proportional hazard assumption for Cox regression models, variables have been examined using log-log survival curves, Schoenfeld residual plots, and tests for time-dependent interactions. We conducted stratified analyses using the menopausal status at diagnosis or censoring. We have carried out stratified analyses by the following three strata: 1) both tea consumption and breast cancer diagnosis occurred prior to menopause; 2) tea consumption began prior to menopause, but breast cancer occurred following menopause; and 3) both tea consumption initiation and breast

cancer diagnosis occurred following menopause. Tests for multiplicative interaction were evaluated by the likelihood ratio test. Tests for trend across exposure categories were performed by entering the categorical variables as a continuous variable in the model. *P* values of < 0.05 (2-sided probability) were interpreted as being statistically significant. Statistical analyses were conducted by using SAS statistical software (version 9.1; SAS Institute, Cary, NC).

RESULTS

After an average of 7.3 years of follow-up, 614 breast cancer patients were identified. Regular tea drinkers comprised 29.5% of study participants, 98.2% of whom were green tea drinkers. Compared to non-tea drinkers (See Table 1), green tea drinkers were more likely to be premenopausal, smokers, alcohol drinkers, to have exposure to passive smoking, to take ginseng supplement, to have higher income and higher educational attainment, and to have a higher daily dietary intake of total energy, fruits, vegetables, fish, and soy isoflavones.

We examined the association between urinary excretion of epigallocatechin (nmol/mg creatinine), a specific tea polyphenol, and green tea consumption among healthy women selected from the SWHS. We found urinary epigallocatechin increased with the amount of consumed green tea leaves in a dose-response manner (Table 2).

Log-log survival curves (See Figure 1) were plotted to evaluate the appropriateness of the proportional hazard assumption for Cox regression models. Two curves (non-tea drinkers vs. green tea drinkers) crossed over. The test for time-dependent interactions between green tea drinking and age at breast cancer onset was statistically significant (p for interaction, 0.03). The interaction between menopausal status and tea drinking was also statistically significant (p for interaction, 0.05). This is consistent with the observation that the intersection was around age 50 (very close to the mean menopausal age) in the log-log plot. Likewise, Schoenfeld residual plots (not shown) indicated a violation of proportional hazard assumption for green tea drinking. Therefore, Cox proportional hazards models stratified by menopausal status were utilized to investigate the green tea drinking and breast cancer risk association in subsequent analyses. The stratified analyses were also in accordance with our hypothesis of a differing effect of green tea by life-time exposure window.

In the analyses stratified by menopausal status, drinking green tea tended to be associated with a reduced breast cancer risk among premenopausal women, particularly among those with moderate consumption, earlier age of tea consumption initiation, and with longer years of consumption, although the associations were not statistically significant (Table 3). Among postmenopausal women, breast cancer risk increased with the amount of green tea consumption. Breast cancer risk was significantly elevated with an earlier age of initiation and longer years of consumption, particularly for those starting younger than 25 years or those with at least 23 years of consumption.

Due to the significant time-dependent interaction between green tea consumption and age of breast cancer onset, we conducted additional analyses to compare the age of breast cancer onset between green- tea drinkers and non-drinkers, stratified by combination of menopausal status at breast cancer diagnosis and tea drinking status (Table 4). We found among premenopausal breast cancer patients who both began drinking tea and were diagnosed with breast cancer prior to menopause, age of breast cancer onset was significantly later (P=0.03) among green-tea drinkers (mean age=48.3) than among non-drinkers (mean age=47.5). Likewise, among postmenopausal breast cancer patients who both began drinking tea and were diagnosed with breast cancer after menopause, age of breast cancer onset was also significantly later (P<0.01) among green-tea drinkers (mean age=62.7) than among non-drinkers (mean age=60.8). On the other hand, among postmenopausal breast cancer patients who began drinking tea prior to

menopause, and were diagnosed with breast cancer after menopause, age of breast cancer onset was not significantly different between green-tea drinkers and non-drinkers.

DISCUSSION

Results from this large, population-based prospective study suggest that the association between green tea consumption and breast cancer risk differed by onset age and menopausal status. Unlike black tea[22], very few studies have examined green tea drinking and breast cancer risk. All four previous case-control studies, including one conducted among Asian Americans[37] and three conducted among Chinese women[24,25,38], found a significantly reduced risk of breast cancer associated with green-tea drinking. On the other hand, three cohort studies all conducted in Japan[39,40] did not find a significant association with green tea drinking, with an overall RR of 0.85 (95% CI: 0.66–1.09). A recent nested case-control study conducted in Singapore also did not find an association[41]. Thus, the results from previous studies on green tea and breast cancer risk have been inconsistent.

Our observations of differing associations between green-tea drinking and breast cancer by menopausal status and age of onset may provide one possible explanation for the inconsistencies reported in previous studies. It is possible that overall RRs associated with tea consumption derived from cohort studies may be influenced by the proportion of postmenopausal women at baseline as well as factors related to age of onset, such as average age tea drinking began, average age at baseline, and length of follow-up years. For example, in the pooled analysis of two cohort studies conducted in Japan, the combined RR was 0.84 (95% CI: 0.57–1.24)(≥5 cups daily vs. <1 cup daily)40. Cohort 1 was substantially older at baseline and more postmenopausal than Cohort 240. The RR (95%CI) was 1.17 (0.67–2.05) for the Cohort 1 whereas the corresponding RR (95%CI) was 0.61 (0.36–1.06) for the Cohort 2. In addition, two Japanese studies of breast cancer recurrence may also provide some indirect support. The first Japanese study42 found that an increased green tea consumption was associated with fewer axillary lymph node metastases among premenopausal stage I and II breast cancer patients. In the first and the second Japanese survival cohorts42,43, green tea drinking was also associated with decreased recurrence of stage I and II breast cancer. These findings indicate that instead of totally eliminating cancer initiation, green tea may primarily delay cancer progression. Therefore, it will be very interesting to examine whether green tea drinking may delay or prevent breast cancer recurrence in further studies.

Another interesting observation is that previous case-control studies are more likely to find an inverse association or a stronger inverse association than cohort studies[22]. Although the difference could be due to recall bias in case-control studies, recall bias on tea drinking habits is considered to be less serious than dietary factors. Also, in a case-control setting, every eligible case from all age groups in the target population is recruited in a very short period of time. Thus, follow-up time is not relevant in the estimation of overall OR in the case-control study. In this regard, the association estimates from case-control and cohort design could be different. The Shanghai Breast Cancer Study (SBCS) is a large-scale population-based case-control study conducted in urban Shanghai where the SWHS is being conducted. We also found in the SBCS that drinking green tea was weakly, but significantly, related to a reduced breast cancer risk [24].

We found log-log survival curves for green tea drinkers and non-drinkers cross over around menopausal age. The exact mechanism is still unclear and the following is one possible interpretation. Among premenopausal women, estrogens are converted from androgens mainly via aromatase in ovary although they are also through aromatase in fat tissues in a small amount; whereas among postmenopausal women this process is predominantly dependent on aromatase distributed in fat tissues. As a result, levels of estrogen are much higher in premenopausal

women than postmenopausal women. It is conceivable that tea drinking may be more potent among premenopausal women in decreasing estrogen levels compared to that among postmenopausal women. As a result, a larger reduction in risk associated with drinking tea would be expected among premenopausal women than among postmenopausal women. In the current study, age of breast cancer onset was significantly later for breast cancer patients who drank green tea than for those who did not, among premenopausal women who began drinking tea and were diagnosed with breast cancer before menopause, and among postmenopausal women who both began drinking tea and were diagnosed with breast cancer after menopause. On the other hand, we found that among postmenopausal breast cancer patients, green tea drinkers who started before menopause had comparable age of onset to the nondrinkers. One possible explanation for the findings is that, for breast cancer patients who drank green tea before menopause, the effect of green tea drinking may be primarily through delaying the onset from before menopause to after menopause. In other words, some of the breast cancer patients diagnosed after menopause would have had breast cancer before menopause if they had not been drinking green tea before menopause. This may explain why green tea drinking was associated with an increased risk of postmenopausal breast cancer for those who started tea drinking before menopause (Data not shown). However, the detailed mechanisms remain unclear. We are conducting further biomarker studies to explore other possible explanations.

Other than polyphenols, many other tea components, such as caffeine, may also possess chemopreventive effects. However, very few women in our study population drank coffee regularly whereas tea contains much lower caffeine than coffee[6,26,27].

Our study has several strengths. These include a population-based prospective design, large sample size, and high rates for baseline participation and follow-up, which minimize potential differential recall bias or selection bias inherent to many case-control studies. We have also specifically designed a questionnaire to capture the amount of tea consumption and lifetime duration patterns. The dose-response relationship between urinary excretion of epigallocatechin and amount of consumed tea leaves indicates tea consumption information is valid. In addition, the study population has a unique exposure pattern; 98.2% of tea drinkers are green tea drinkers and thus black tea drinkers were excluded from the analysis. We adjusted for many potential confounding factors. However, we cannot totally exclude the possibility that some unknown residual confounding may still remain.

Future studies are necessary to confirm our finding. Our hypothesis, if confirmed, may help in the understanding of the mechanism for tea and other chemopreventive agents when they only delay the onset of cancer.

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Figure 1.
Evaluation of proportional hazard assumption

Table 1

Baseline Lifestyle Factors and Demographics by Drinking of Green Tea, the Shanghai Women's Health Study, 1996–2004

Baseline Characteristic	Green Tea Drinking		
	Non-drinkers	Regular Drinkers	P values
Number of Cancer-free Participants	51,354	21,507	
Age (years), mean ± SD	52.3 ± 9.3	50.8 ± 8.2	<0.01
Average income per subject in family, %			
Low	30.3	21.3	
Middle	40.0	36.5	
High	29.8	42.2	<0.01
Education, %			
Elementary or below	25.5	11.6	
Middle School	37.7	36.0	
High School	25.8	33.0	
College or above	11.0	19.4	<0.01
Family history of breast cancer, %	1.8	1.9	0.38
Ever diagnosed with fibroadenoma, %	3.1	3.9	<0.01
Use of hormone replacement therapy, %	3.3	4.2	<0.01
Age at menarche (years), mean ± SD	15.0 ± 1.7	14.7 ± 1.7	<0.01
Postmenopausal, % 52.3	41.0		<0.01
Age at menopause (years), mean ± SD	48.6 ± 4.3	48.5 ± 4.5	0.12
Age at first live birth, (years), mean ± SD	25.4 ± 4.2	26.1 ± 3.8	<0.01
Smokers, former and current, %	2.3	4.0	<0.01
Exposure to passive smokers, %	79.4	82.9	<0.01
Alcohol drinkers, current and past, %	1.5	3.9	<0.01
Physically active, %	35.0	35.2	0.64
Body mass index (kg/m^2), mean ± SD	23.9 ± 3.4	24.1 ± 3.4	<0.01
Waist-to-hip Ratio, mean ± SD	0.81± 0.05	0.81± 0.05	<0.01
Taking ginseng regularly, %	27.4	32.8	<0.01
Mean dietary intake			
Daily energy intake (kcal/day), mean ± SD	1667.4 ± 395.7	1689.1 ± 388.9	<0.01
Fruit intake (g/day), mean ± SD	253.2 ± 177.5	289.6 ± 179.1	<0.01
Vegetable intake (g/day), mean ± SD	288.3 ± 165.9	313.4 ± 174.9	<0.01
Red meat intake (g/day), mean ± SD	49.8 ± 35.8	53.4 ± 36.7	<0.01
Fish intake (g/day), mean ± SD	48.2 ± 43.4	56.0 ± 46.4	<0.01
Isoflavone intake (g/day), mean ± SD	29.9 ± 22.3	31.4 ± 22.2	<0.01

Table 2

The association of urinary epigallocatechin with green tea intake amount among healthy women, within the Shanghai Women's Health Study (SWHS), 1997–2006

The amount of green tea leaves consumed (gram/day)	Urinary excretion of epigallocatechin (nmol/mg creatinine)
None	0.12 (0.08,0.36)*
≤ 1.7	0.12 (0.03–0.61)*
≤ 3.3	0.16 (0.12–1.20)*
≤ 5.0	0.25 (0.12, 1.85)*
> 5.0	0.96 (0.12, 5.16)*
	P for trend, <0.01

*Median (25^{th}, 75^{th} percentiles) for urinary epigallocatechin (a specific tea polyphenol; nmol/mg creatinine) for non-drinkers and current green tea drinkers in a subset of 683 non-cancer women within SWHS.

Table 3

Person-year, hazard ratios (HR), and 95% confidence intervals for breast cancer by green tea exposure, the Shanghai Women's Health Study, 1996–2004

Green tea exposure	Events	Person-years	HR[1] (95% confidence interval)
		All subjects	
Intake of green tea regularly			
No	418	373,369	1.00
Yes	196	159,216	1.05 (0.88–1.26)
Dosage of green tea intake (g/day)			
≤ 1.67	60	45,137	1.07 (0.81–1.42)
≤3.33	62	54,957	0.98 (0.75–1.29)
≤5.00	28	24,198	1.00 (0.68–1.48)
>5.00	46	34,915	1.18 (0.86–1.61)
P for trend			0.47
Age green tea intake began (years)			
>40	45	36,158	1.06 (0.78–1.45)
≤ 40	45	42,955	0.89 (0.65–1.23)
≤ 30	39	32,441	1.00 (0.71–1.40)
≤ 25	67	47,653	1.23 (0.94–1.61)
P for trend			0.30
Years of green tea intake (years)			
≤ 10	60	52,480	1.00 (0.76–1.31)
≤16	28	29,055	0.85 (0.58–1.25)
≤ 23	39	32,661	1.04 (0.74–1.45)
> 23	69	45,010	1.25 (0.96–1.62)
P for trend			0.23
		Premenopausal women	
Intake of green tea regularly			
No	130	168,660	1.00
Yes	59	89,210	0.84 (0.61–1.15)
Dosage of green tea intake (g/day)			
≤ 1.67	22	24,019	1.05 (0.65–1.70)
≤ 3.33	15	31,196	0.63 (0.37–1.09)
≤ 5.00	7	13,786	0.66 (0.31–1.42)
>5.00	15	20,210	1.01 (0.59–1.74)
P for trend			0.33
Age green tea intake began (years)			
>40	8	10,006	1.36 (0.66–2.80)
≤ 40	21	28,437	0.88 (0.55–1.42)
≤ 30	13	21,160	0.79 (0.44–1.40)
≤ 25	17	29,608	0.69 (0.41–1.17)

Green tea exposure	Events	Person-years	HR[1] (95% confidence interval)
P for trend			0.12
Years of green tea intake (years)			
≤ 10	28	31,791	1.07 (0.70–1.63)
≤ 16	9	19,346	0.58 (0.30–1.15)
≤ 23	14	21,919	0.85 (0.48–1.48)
> 23	8	16,155	0.63 (0.29–1.35)
P for trend			0.12
		Postmenopausal women	
Intake of green tea regularly			
No	288	284,711	1.00
Yes	137	113,232	1.17 (0.94–1.45)
Dosage of green tea intake (g/day)			
≤ 1.67	38	33,090	1.07 (0.76–1.51)
≤ 3.33	47	39,067	1.19 (0.87–1.63)
≤ 5.00	21	17,140	1.20 (0.77–1.88)
>5.00	31	23,926	1.26 (0.86–1.85)
P for trend			0.11
Age green tea intake began (years)			
>40	37	32,886	1.04 (0.73–1.47)
≤ 40	24	27,970	0.88 (0.57–1.34)
≤ 30	26	21,286	1.14 (0.75–1.73)
≤ 25	50	31,082	1.61 (1.18–2.20)
P for trend			0.01
Years of green tea intake (years)			
≤ 10	32	35,423	0.92 (0.64–1.34)
≤ 16	19	17,968	1.06 (0.66–1.70)
≤ 23	25	21,229	1.16 (0.76–1.77)
> 23	61	38,604	1.42 (1.06–1.89)
P for trend			0.02

[1]Adjusted for age, educational achievement (categorical), income (categorical), family history of breast cancer, history of fibroadenoma, body mass index (continuous), waist-to-hip ratio (continuous), physically active (yes, no), smoking status (ever, never), alcohol consumption status (ever, never), passive smoking status (ever, never), ginseng intake (ever, no), age at menarche (continuous), age at first live birth (continuous), menopausal status (pre-, post-), age at menopause (continuous), use of hormone replacement therapy, and dietary intake of total energy, fruits, vegetables, red meat, fish, and isoflavones.

Table 4

Age of breast cancer diagnosis (Case only) by green tea exposure, stratified by combination of menopausal status and age green tea drinking began, the Shanghai Women's Health Study, 1996–2004

Green tea exposure	**Premenopausal (Starting green tea drinking and breast cancer diagnosis before menopause)**		
Drinking green tea regularly (Breast cancer cases only)	**Case number**	**Age of diagnosis**	**P value for T test**
No	130	47.5 (0.2)[1]	
Yes	59	48.3 (0.3)[1]	0.03[2]
	Starting green tea drinking before menopause, but breast cancer diagnosis after menopause		
Drinking green tea regularly (Breast cancer cases only)	Case number	Age of diagnosis	P value for T test
No	288	60.8 (0.1)[1]	
Yes	120	60.8 (0.2)[1]	0.98[2]
	Starting green tea drinking and breast cancer diagnosis after menopause		
Drinking green tea regularly (Breast cancer cases only)	Case number	Age of diagnosis	P value for T test
No	288	60.8 (0.1)[1]	
Yes	17	62.7 (0.5)[1]	<0.01[2]

[1] Least square mean (standard error).

[2] Adjusted P values.