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Evaluation of breast cancer risk associated with tea consumption by menopausal and estrogen receptor status among Chinese women in Hong Kong

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Abstract

Purpose: Experimental studies implicate tea and tea polyphenols may be preventive against breast cancer, but evidence from epidemiological studies has been inconsistent. We conducted a hospital-based case-control study to evaluate the role of tea especially green tea in breast cancer etiology.

Methods: We consecutively recruited 756 incident breast cancer cases and 789 hospital controls who had completed information on tea consumption. We calculated odds ratios (ORs) for tea consumption using unconditional multivariable logistic regression. We further conducted stratified analyses to assess whether the effect of tea consumption varied by menopausal status and estrogen receptor (ER).

Results: Overall, 439 (58.1%) breast cancer cases and 434 (55.0%) controls reported habits of regular tea drinking, showing an adjusted OR of 1.01 (95%CI: 0.78–1.31) and 1.20 (95%CI: 0.80–1.78) for any tea and green tea drinking, respectively. Regular tea drinking was significantly

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Disclosure

The authors have declared no conflicts of interest.

associated with a lower risk for breast cancer in pre-menopausal women (OR=0.62, 95%CI: 0.40–0.97) but an increased risk in post-menopausal women (OR=1.40, 95%CI: 1.00–1.96). The positive association among postmenopausal women was strongest among ER-negative green tea drinkers (OR=2.99, 95% CI: 1.26–7.11).

Conclusions: Tea or green tea drinking was not associated with overall breast cancer risk, which may be masked by the differential effect in pre- and post-menopausal women.

Keywords

tea consumption; breast cancer; menopausal status; estrogen receptor status

Introduction

Breast cancer is the most commonly diagnosed invasive malignancy and the leading cause of cancer death in women worldwide [1]. In Hong Kong, newly diagnosed breast cancer cases have tripled from 852 in 1983 to 3,508 in 2012, and the incidence rate continues to rise [2]. However, compared to women in Western countries, rates in most Asian populations including Hong Kong are still much lower, which may reflect the still lower prevalence of known risk factors associated with Westernized lifestyle especially among older Asian women. On the other hand, it has also been hypothesized that some unique dietary habits such as soy intake and green tea consumption may have protective effect, which may also contribute to lower breast cancer rates in Asian populations.

Green tea is one of the most popular beverages in China. Evidences from in vitro and in vivo studies suggested that green tea polyphenols (catechins) and its major compound — epigallocatechin-3-gallate (EGCG) are potentially cancer chemo-protective agents [3, 4] with notable anti-carcinogenic effects [5, 6]. Green tea consumption has been associated with reduced risks for several types of cancer including breast, esophagus[7], colorectum[8], prostate[9], ovary[10], and lung[11] cancer. For breast cancer, results have not always been consistent, with associations seen in all directions (null, increased risk, or decreased risk) [12–14]. Most of these studies analyzed breast cancer as a single disease entity, however, it is well known that breast cancer risk factors vary by menopausal status (such as obesity) and tumor estrogen receptor (ER) status [15, 16]. Therefore, the goal of this study was to assess whether the association between tea drinking and breast cancer risk was modified by menopausal or ER status in a breast cancer case-control study conducted among Chinese women in Hong Kong.

Materials and methods

Study population

The methods of this case-control study have been described previously[17]. Briefly, this hospital-based case-control study was conducted among Chinese women in Hong Kong. Newly diagnosed primary breast cancer (ICD-10 code 50) cases aged 20–84 years were consecutively identified from three local hospitals in Hong Kong between November 2011 and May 2014, and were interviewed within three months after the breast cancer diagnosis. All cases were histologically confirmed including all stages of breast cancer. Controls were

randomly selected from the same hospital within four weeks after cases were identified and frequency matched to cases by 5-year age groups. Controls were affected with a variety of diseases such as diseases in digestive, genitourinary, respiratory, or circulatory system but not physician-diagnosed cancer at any site. In total, we recruited 767 eligible cases and 792 eligible controls with response rates over 90% for both cases and controls.

Exposure measurements

In-person interviews were conducted by trained interviewers using a standardized questionnaire that covered demographic characteristics, lifestyle factors, body mass index (BMI), reproductive history, occupational history, history of benign breast cancer disease, hormone replace therapy, family cancer history in the first-degree relatives, and diet habits including lifetime history of tea consumption.

Each participant was asked whether she had a habit of drinking tea regularly. Regular tea drinker was defined as drinking at least one cup of any type of tea (e.g., green tea, black tea and Oolong tea) per week for at least 6 months continuously. Those who have drunk less than one cup of tea per week were defined as non-tea drinkers. Further information on the type of tea, drinking frequency (cups/day) and duration (drinking years) was collected among regular tea drinkers. The starting age of tea drinking was derived by subtracting years of tea intake from age at interview.

We extracted data from hospital medical records to obtain ER status (for cases only) and verified disease diagnoses for cases and controls. We assessed the data quality of self-reporting tea consumption by re-interviewing 25% of the cases and controls about 6 weeks after initial interviews, and results from the two interviews showed a good agreement (Kappa=0.69).

The study protocol was approved by both the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committees and the Kowloon West Cluster. Written informed consents were obtained for both cases and controls prior to the interview.

Statistical analysis

We used t-test and Chi square tests to compare the distribution of basic characteristics in cases and controls for categorical and continuous variables, respectively. Unconditional multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer risk associated with tea consumption habits, with the adjustment of well-established breast cancer risk factors including age at diagnosis, age at menarche, age at first birth, parity, education attainment, hormone replacement therapy, BMI and first-degree family history of breast cancer. The selection of these covariates was based on significant associations at $P < 0.05$ in the univariate analysis.

Tea consumption variables (including green tea) were categorized as follows: tea drinking status (tea drinker vs non-drinker), frequency (<1 cup/day, 1~3 cups/day, >3 cups/day), duration (15 years, 30 years, >30 years) and drinking starting age (20 years old, 20~50 years old, 50 years old). Similar to pack-years for smoking, we applied the cumulative exposure index of “cup-years”, which was defined as 1 cup of tea per day for 1 year. Cup-

years was calculated by multiplying the number of cups of tea per day by the number of years of tea drinking. These categories were chosen based on the distribution of the control group. Participants who consumed none of any kind of tea (i.e., non-tea drinkers) served as the reference category for all regression analyses. Multivariable logistic regression analysis was also performed to examine risks associated with duration and starting age of tea consumption. Stratified multivariable logistic regression analyses were conducted according to menopausal status (pre- or post-menopausal at diagnosis for cases or at interview for controls) and ER status (for cases only).

We used age 50 years as a surrogate for menopausal status (the median age at menopause is 49.5 years for cases and 49.6 years for controls) for women with missing data for menopausal status, which represents 5% of all participants. Trend tests for dose-response relationships with years of tea consumption were computed by treating categorical predictors as continuous variables in logistic regression models. Statistical tests at the $P<0.05$ level were considered significant.

Results

This report was based on a total of 756 breast cancer cases and 789 controls who had completed information on tea consumption. Table 1 showed the distribution of selected breast cancer risk factors among study subjects. The median age at diagnosis for case (54.0 years) was comparable to age at interview for controls (53.5 years). Compared with controls, breast cancer cases had significantly younger age at menarche, later age at first birth, lower parity, higher proportion of first-degree family history of cancer, and higher BMI value at the time of diagnosis/interview. There were no significant differences in the distribution of cigarette smoking, alcohol drinking, education attainment, hormone replacement therapy, and menopausal status. Among all 580 breast cancer cases with known ER status, 444(76.6%) of them were classified as ER+ breast cancer cases, while 136(23.4%) were ER – cases.

A total of 439 (58.1%) breast cancer cases and 434 (55.0%) controls reported regular tea drinking habits (Table 2). More cases than controls reported a history of drinking green tea (16.1% vs 12.3%, $P=0.03$). Compared with non-tea drinkers, regular tea (OR: 1.01; 95%CI: 0.78–1.31; $P=0.92$) or green tea drinkers (OR: 1.20; 95%CI: 0.80–1.78; $P=0.38$) were not associated with the overall breast cancer risk (Table 3). The results did not change much after additional adjusted for coffee intake (data not shown). There appeared to be a trend that heavy green tea drinking (>3 cups/day) was associated with increased breast cancer risk (OR: 1.53; 95%CI: 0.71–3.28; P for trend=0.24), but the association was not statistically significant. However, no dose-response relationship was observed for cumulative tea or green tea consumption. Compared with non-drinkers, there was a decreased risk for breast cancer among those who drank tea for 10–29 cup-years (OR: 0.88; 95%CI: 0.62–1.26) but an increased tendency for breast cancer risk among those who drank tea for more than 30 cup-years (OR: 1.24; 95%CI: 0.88–1.76). However, none of those results were of statistical significance.

We further conducted stratified analyses by menopausal status, ER, and tea starting age. Interestingly, tea intake was associated with a decreased risk of breast cancer in pre-menopausal women (OR=0.62, 95%CI: 0.40–0.97, $P=0.04$) but an increased risk in post-menopausal women (OR=1.40, 95%CI: 1.00–1.96, $P=0.05$). A similar pattern was observed among green tea drinkers (Table 3). Further, risks associated with tea especially green tea drinking also seem to be modified by the age onset of tea drinking, with a protective effect for women who started drinking tea/green tea before age 20 years and an increased risk for those who started after age 50 years (Table 3). When we stratified the analysis by both menopausal and ER status, we found that the increased risk was the strongest for ER-negative post-menopausal green tea drinkers (OR=2.99, 95%CI: 1.26–7.11, $P=0.01$; Table 4).

Discussion

Results from this case-control study did not provide evidence for an association between regular tea or green tea drinking and the overall breast cancer risk among Hong Kong Chinese women. However, we found that tea particularly green tea drinking was associated with a reduced risk among pre-menopausal women but an increased risk among postmenopausal women. This association may be modified by ER and tea drinking starting age, which collectively may explain the inconsistent associations between tea drinking and overall breast cancer risk observed in most previous studies.

Evidence shows that pre- and post-menopausal breast cancer vary greatly in clinical behaviors, histopathologic characteristics and molecular alterations, and may develop through different etiologic pathways [18, 19]. In this study, tea consumption was associated with a decreased risk of breast cancer in pre-menopausal women but an increased risk in post-menopausal women. Our data is consistent with previous findings from a prospective study conducted among Chinese women (The Shanghai women's health study) in which the reduced breast cancer risk associated with green tea consumption was restricted to pre-menopausal women and women who started drinking tea before age 25 years [20].

A number of potential mechanisms underlying the protective effect of green tea drinking have been proposed, including hormone-related (such as blocking the binding of estrogen to its receptors and inhibiting aromatase) and hormone-independent (anti-proliferation) activities [21, 22]. Green tea has been shown to slow the proliferation of mammary tumor cells through the inhibition of vascular endothelial growth factor (VEGF) expression [23]. We hypothesize that the growth inhibitory effect might be particularly important early in life when breast epithelial cells undergo rapid proliferation. Experimental evidence in mouse models supports this hypothesis by demonstrating that green tea catechin inhibited mammary tumorigenesis in a dose-dependent manner before the carcinogen was given but not in the post-initiation stage [24].

Surprisingly, we found that tea particularly green tea drinking was associated with increased breast cancer risk among post-menopausal women and the highest risk was seen in women with ER-negative tumors. It is not completely surprising for an exposure to have opposite effect in pre- and post-menopausal women; similar differential effect has been reported for

parity and obesity. Recent genomic studies using integrated tumor profiling analyses found distinct molecular characteristics in pre-menopausal compared to post-menopausal breast tumors, such as unique mutation rates and signatures, expression and methylation patterns, and oncogenic pathways [25]. Green tea and its major compounds have been shown to influence growth signaling pathways, apoptosis, angiogenesis, and lipid metabolism. It is possible that the interplay of these pathways may exert different actions in pre- and post-menopausal tumors with different genomic features. In addition, it is also possible that green tea may have different effect on hormone related pathways in pre- and post-menopausal women, which should be investigated by biomarker analyses in prevention trials. The association between green tea consumption and increased risk among post-menopausal women was also seen in the Shanghai women's health study, which was attributed to the delaying cancer onset among those who started drinking green tea at early ages [20]. We did not directly collect information on tea starting age and therefore were not able to address this issue. Nevertheless, large well-designed epidemiologic studies are needed to further evaluate the relationship between green tea consumption and delayed breast cancer onset with the careful control for other risk factors and tumor subtypes that also influence breast cancer onset.

Our stratified analysis according to the combination of menopausal and ER status has limited power because of small sample size, although our data suggests that the green tea association might be further complicated by ER status. Green tea drinking did not protect breast cancer risk for pre-menopausal women with ER-negative tumors and it was associated with 3-fold increased risk among ER-negative postmenopausal women. This finding, if confirmed, will improve our knowledge of tea drinking on breast cancer risk, which may have important implications in targeted prevention.

Only two previous studies have looked at tea consumption and breast cancer risk in the context of both menopausal and ER status. Both studies reported that tea consumption was not associated with breast cancer risk according to either menopausal or ER status. However, both studies were conducted among Western women [26, 27]. While black tea is popular in the United States, United Kingdom and Europe, green tea is the most frequently consumed tea in Japan and China[28, 29]. Although all tea originates from the same plant, *Camellia sinensis*, the properties of these teas differ because of different processing procedures [29, 30]. As a result, green tea, which is processed to prevent fermentation and oxidation, has much higher levels of antioxidant polyphenols than black tea[30]. In addition, genetic variants in genes involved in the metabolism of tea catechins, folate pathways, and reactive oxygen species (ROS) production have been suggested to modify tea-breast cancer association [31–33] and the frequency of these variants may vary in different populations. So far, the association between tea intake and breast cancer risk was primarily observed in Asian populations, which is likely due to population variations in the prevalence of green tea consumption and genetic structures.

Our study has a number of limitations. First, tea consumption was assessed after the diagnosis of breast cancer and is therefore sensitive to recall bias. In order to minimize recall bias, we recruited only incident cases rather than prevalent cases. All cases were ascertained with histological confirmation to minimize the misclassification of cases. The distribution of

tumor characteristics in our study population is comparable to those from the Hong Kong Cancer Registry, which has a nearly complete coverage of breast cancer cases in Hong Kong. Second, the use of controls from hospital patients may be a concern since dietary habits of hospital controls may differ from those of the general population due to health consciousness or diseases, particularly among those with diseases in the digestive system. We recruited hospital controls with a broad range of diagnoses to address this potential question and sensitivity analyses indicated that the tea-breast cancer association remained almost unchanged after excluding control subjects with digestive diseases. Third, confounding effect from coffee drinking poses another concern for the current study but the frequency of coffee drinkers amongst the cases (27.8%) and controls (28.1%) was similar. In addition, we conducted the sensitive analysis by further classifying subjects into women who drank tea only, either tea or coffee, and both tea and coffee. Breast cancer risk in these three subgroups was similar, suggesting coffee drinking is unlikely a significant confounder in our analysis. Fourth, our study is small and has limited power in looking into the tea associations in different subtypes. The magnitude of most associations presented in this paper were small, which need to be confirmed in larger Asian breast cancer studies.

In conclusion, our findings are consistent with a previous study conducted among Chinese women showing that tea especially green tea consumption may have dual effect on breast cancer risk according to menopausal status and/or onset of tea drinking. Our study suggested that the tea-breast cancer association may be further modified by hormone receptor expression. Future larger studies with the detailed annotation of tea drinking habits, other breast cancer risk factors, genetic variants, as well as tumor subtype information are needed to determine the complex relationship between tea drinking and breast cancer risk.

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Table 1.

Distribution of selected breast cancer risk factors in breast cancer cases and controls participating in the Hong Kong breast cancer case-control study^a

Risk factors	Cases (n=756)	Controls (n=789)	P value^b
Age at interview (years) Median (P25, P75)	54.0 (48.0, 63.0)	53.5 (46.0, 61.0)	0.01
Age at menarche (years)	13.6±2.0	13.9±2.3	0.02
Age at first birth (years)	26.5±4.8	25.5±4.7	<0.01
Body mass index (kg/m ²)	23.5±3.7	23.0±3.9	0.01
Parity			0.03
0	133 (17.6)	139 (17.6)	
1–2	419 (55.4)	404 (51.2)	
3	179 (23.7)	238 (30.2)	
Missing	25 (3.3)	8 (1.0)	
Hormone replacement therapy			0.07
Yes	17 (2.2)	31 (3.9)	
No	717 (94.8)	751 (95.2)	
Missing	22 (2.9)	7 (0.9)	
First-degree family cancer history			<0.01
Yes	277 (36.6)	214 (27.1)	
No	468 (61.9)	567 (71.9)	
Missing	11 (1.5)	8 (1.0)	
Oral contraceptives use			0.33
Yes	252 (33.3)	289 (36.6)	
No	480 (63.5)	496 (62.9)	
Missing	24 (3.2)	4 (0.5)	
Cigarette smoking			0.58
Yes	52 (6.9)	60 (7.6)	
No	704 (93.1)	729 (92.4)	
Alcohol drinking			0.51
Yes	32 (4.2)	39 (4.9)	
No	724 (95.8)	750 (95.1)	
Education			0.47
Primary school	281 (37.2)	280 (35.5)	
High school	341 (45.1)	374 (47.4)	
College or above	93 (12.3)	112 (14.2)	
Missing	41 (5.4)	23 (2.9)	
Menopausal status			0.96
Pre-menopausal	269 (35.6)	283 (35.9)	
Post-menopausal	449 (59.4)	475 (60.2)	
Missing	38 (5.0)	31 (3.9)	
Estrogen receptor status			
ER+	444 (76.6)		

Risk factors	Cases (n=756)	Controls (n=789)	<i>P</i> value^b
ER–	136 (23.4)		

Values expressed as mean±SD or number (percent).

^aSubjects with missing values were excluded from the analyses.

^bTwo-sided t-test for continuous variables and chi-squared test for categorical variables were used in the comparison of breast cancer cases and hospital controls.

Table 2

Tea drinking pattern and overall breast cancer risk among Hong Kong Chinese women.

	Case		Control		<i>P</i> value	Adjusted OR ^a
	n	%	n	%		
Total No.	756	100	789	100		
Non-tea drinkers ^b	317	41.9	355	45.0		1.00
Tea drinkers ^c	439	58.1	434	55.0	0.92	1.01 (0.78–1.31)
Green tea	122	16.1	97	12.3	0.38	1.20 (0.80–1.78)
Black tea	217	28.7	212	26.9	0.66	1.07 (0.79–1.46)
Oolong tea	159	21.0	137	17.4	0.32	1.19 (0.85–1.67)
Unspecified	60	7.9	75	7.9	0.34	0.80 (0.50–1.27)

^a Adjusted for age at interview, age at menarche, age at first birth, parity, hormone replacement therapy, first-degree family history and body mass index.

^b Non-drinkers referred to those who did not drink any kind of tea.

^c A subset of participants (14.6% of cases and 10.2% of controls) reported drinking more than one kind of tea which were counted separately.

Table 3

Associations between tea drinking habits and breast cancer risk stratified by intensity, frequency, starting age, menopausal, and ER status.

	Non-drinkers ^a		Regular tea drinkers		Regular green tea drinkers	
	Cases/controls	OR(95%CI) ^b	Cases/controls	OR(95%CI) ^b	Cases/controls	OR(95%CI) ^b
Tea consumption	317/355	1.00	439/434	1.01 (0.78–1.31)	122/97	1.20 (0.80–1.78)
Intake (cups/d)						
<1			245/241	0.96 (0.67–1.37)	40/24	1.08 (0.52–2.25)
1–3			136/112	0.95 (0.68–1.31)	53/49	1.20 (0.71–2.03)
>3			43/58	1.25 (0.85–1.84)	26/20	1.53 (0.71–3.28)
<i>p</i> -trend				0.48		0.24
Intake years(y)						
15			245/241	1.03 (0.77–1.38)	75/57	1.41 (0.87–2.27)
30			136/112	1.27 (0.87–1.86)	30/21	1.00 (0.48–2.07)
>30			43/58	0.66 (0.39–1.14)	11/13	0.85 (0.29–2.50)
<i>p</i> -trend				0.81		0.46
Cumulative tea consumption (cup-years)						
9			136/132	1.03 (0.72–1.48)	38/23	1.42 (0.67–3.01)
10–29			119/131	0.88 (0.62–1.26)	35/33	1.19 (0.67–2.10)
30			160/137	1.24 (0.88–1.76)	40/31	1.29 (0.71–2.32)
<i>p</i> -trend				0.44		0.27
Menopausal status						
Premenopausal	131/136	1.00	153/169	0.62 (0.40–0.97)	51/43	0.69 (0.35–1.35)
Postmenopausal	186/219	1.00	286/265	1.40 (1.00–1.96)	71/54	1.82 (1.07–3.10)
Estrogen receptor status						
ER+	185/355	1.00	259/434	0.94 (0.69–1.28)	67/97	0.99 (0.60–1.63)
ER–	54/355	1.00	82/434	1.16 (0.74–1.84)	29/97	2.03 (1.08–3.84)
Starting age of drinking						
20			41/59	0.65 (0.37–1.16)	5/11	0.44 (0.11–1.83)
20–50			283/275	1.05 (0.79–1.40)	90/70	1.24 (0.80–1.92)
50			100/76	1.26 (0.82–1.96)	21/9	1.93 (0.73–5.08)
<i>p</i> -trend				0.36		0.17

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Non-drinkers referred to those who did not drink any kind of tea.
Adjusted for age at interview, age at menarche, age at first birth, parity, hormone replacement therapy, first-degree family history and body mass index.

Table 4
Associations between tea consumption and breast cancer risk stratified by combined menopausal and ER status

Tea	Pre-menopausal				Post-menopausal			
	Controls (N=305)		Cases(N=212)		Controls (N=484)		Cases(N=368)	
	No.	OR(95%) ^a	No.	OR(95%) ^d	No.	OR(95%) ^a	No.	OR(95%) ^d
Non-drinkers	136	74	1.00	25	1.00	111	29	1.00
Tea drinkers	169	85	0.63(0.37–1.08)	28	0.58 (0.27–1.24)	174	54	1.85 (1.00–3.42)
Green teadrinker	43	29	0.61 (0.25–1.49)	12	1.22 (0.43–3.43)	38	17	2.99 (1.26–7.11)

^aNon-drinkers referred to those who did not drink any kind of tea.

^bAdjusted for age at interview, age at menarche, age at first birth, parity, hormone replacement therapy, first-degree family history and body mass index.