



## 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 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 postmenopausal 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.

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### 1. 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 3508 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

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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.

## 2. Materials and methods

### 2.1. 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.

### 2.2. 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.

### 2.3. 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 ( $\leq 15$  years,  $\leq 30$  years, >30 years) and drinking starting age ( $\leq 20$  years old, 20–50 years old,  $\geq 50$  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.

## 3. 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 shows 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)

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