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Tea consumption and breast cancer risk in a cohort of women with family history of breast cancer

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Abstract

Laboratory studies have observed chemopreventive effects of black and green tea on breast cancer development, but few epidemiologic studies have identified such effects. We investigated the association between tea consumption and breast cancer risk using data from 45,744 U.S. and Puerto Rican women participating in the Sister Study. Frequency and serving size of black and green tea consumption were measured at cohort enrollment. Breast cancer diagnoses were reported during follow-up and confirmed by medical record review. Multivariable Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI). We further investigated potential variation according to estrogen receptor (ER) status, menopausal status, and body mass index (BMI). Overall, 81.6% and 56.0% of women drank black or green tea, respectively. A total of 2,809 breast cancer cases were identified in the cohort. The multivariable model suggested an inverse association between black (≥5 vs. 0 cups/week: HR=0.88, 95% CI 0.78, 1.00, *p-trend*=0.08) and green tea (≥5 vs. 0 cups/week: HR=0.82, 95% CI 0.70, 0.95, *p-trend*<0.01) consumption and breast cancer risk. We did not observe differences by ER characteristics, menopausal status, or BMI. In conclusion, our study suggests drinking at least 5 cups of green or black tea per week may be associated with decreased breast cancer risk.

Keywords

Tea; Breast cancer; Epidemiology

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Introduction

Breast cancer remains the most commonly diagnosed malignant tumor among women in the United States, with an estimated 268,600 invasive and 62,930 in situ diagnoses in 2019.[1] In addition to its high incidence, side effects and high cost associated with breast cancer treatment support the need for primary prevention.[2,3]

Tea is one of the most popular beverages worldwide. Green tea and black tea are produced from the leaves of the plant *Camellia sinensis*.[4] Many types of organic chemical compounds are found in black and green tea, including multiple types of natural polyphenols.[5] These chemicals may have anti-tumorigenic properties.[6,7] For instance, *in vitro*, clinical, and epidemiologic studies suggest that (−)-epigallocatechin-3-gallate (EGCG), the main polyphenol in green and black tea,[8] may be beneficial for cancer prevention.[7,9] Mittal et al. [10] reported that EGCG increased apoptosis in breast carcinoma MCF-7 cells, which represent estrogen receptor (ER) positive tumors, without causing adverse effects on the growth of normal mammary cells.

However, beneficial effects of tea consumption for breast cancer have not been consistently observed in epidemiologic studies.[11–13] To date, 15 cohort studies have reported the association between tea consumption and breast cancer risk. Of these, one obtained a statistically significant and positive association (1 cup/d: RR=1.12, 95% CI 1.01–1.24)[14] and two reported borderline (>3 cups/day: RR=0.79, 95% CI 0.62–1.01)[15] or significant (≥150 ml/day: RR=0.43, 95% CI 0.20–0.94)[16] inverse associations. The remaining estimates were not significant; however, based on the direction of the effect estimate, six appeared null, four reported positive associations, and four reported inverse associations. Inconsistent results may be due, in part, to chemical heterogeneity between tea types or etiological heterogeneity between breast cancer subtypes. In general, green tea has a higher level of EGCG than black tea[8], whereas black tea contains higher concentrations of caffeine.[17] Thus, studies ignoring differences in chemical constitution may obscure potential chemopreventive effects. Additionally, interpretation of the prior literature is limited by the differing levels of baseline risk in previous study populations. Most published cohort studies investigating green tea and breast cancer were conducted in Asian countries with differing tea consumption habits and breast cancer risk compared to U.S. populations, warranting further investigation in a U.S. sample.[12,13,18,19]

Some etiologic factors may contribute to specific subtypes of breast cancer. For example, laboratory evidence suggests EGCG may inhibit ER activity and thereby differentially affect ER-specific breast cancer risk.[20,21] One previous study reported that the association between green tea and breast cancer risk differed by menopausal status in 1,545 Chinese women (premenopausal: odds ratio (OR)=0.69, 95% confidence interval (CI)=0.35–1.35; postmenopausal: OR=1.82, 95% CI=1.07–3.10 for regular green tea consumption vs. never tea consumption).[22] Lastly, obesity is strongly associated with oxidative stress and steroid hormone metabolism, each of which may contribute to breast cancer development.[23–25] However, few previous epidemiologic studies have considered these potential sources of heterogeneity simultaneously.

To examine the association between different types of tea and breast cancer risk, we used data from the Sister Study.[26]

Methods

The Sister Study is a prospective cohort study supported by the National Institute of Environmental Health Sciences (NIEHS) that enrolled 50,884 women between the ages of 35 and 74 across the United States and Puerto Rico from 2003 to 2009.[26] Detailed information on cohort procedures have been published.[26] In brief, participants were recruited during 2003–2009 through breast cancer support and advocacy groups, women's volunteer organizations, hospitals, mammography centers, churches, unions, and trade organizations via online and print media. Eligible women were free of breast cancer but had a sister who had been diagnosed with breast cancer at enrollment. All participants provided written informed consent. Following the enrollment interview and home visit, women are contacted annually to update information. Study retention is high, as of September 15, 2017, 90.5% of women completed their most recent follow-up activity.[27] Study protocols were approved by the Institutional Review Boards of the NIEHS and the Copernicus Group. This analysis was completed with data release 6.0 (9/15/2016).

Data collection

At enrollment, green and black tea consumption during the past 12 months was measured by the self-administered Block 98 food frequency questionnaire (FFQ).[28,29] The modified Block FFQ assesses 110 food items[30] across beverages, fruits and vegetables, bread and cake, cookies and crackers, butter and margarine, milk and dairy products, rice, beans, pasta, red and processed meat, chicken, fish and seafood, fried foods, eggs, sweets, salty snacks and popcorn, and pastries and sandwiches. Specifically, frequency of consumption and amount of food intake at each time were asked. Within the FFQ, participants reported their frequency of tea consumption and the cups consumed each time. Frequency was reported at 9 levels, ranging from "never" to "everyday." Participants reported how many cups of tea they consumed each time as "1 cup, 2 cups, 3–4 cups, or 5 or more cups." The FFQ did not differentiate between hot or iced tea or measure cup size. Alcohol and coffee consumption and red meat intake (e.g. pork, beef, lamb) were also measured by the FFQ.[28] Caffeine from soda and black tea, as well as total energy intake, was calculated from the FFQ by NutritionQuest.[31] Caffeine levels of regular and decaffeinated coffee, as well as caffeine in green tea, were assigned by the researcher based on the United States Department of Agriculture (USDA) Food Composition Databases[32] as 95.2 mg caffeine per cup of regular coffee, 2 mg caffeine per cup of decaffeinated coffee, and 24.8 mg caffeine per cup of green tea. On average, one cup of black tea contains 47.2 mg caffeine.[32] Health Eating Index Scores (1999–2000) developed by the USDA to reflect diet quality were calculated based on FFQ.[33]

Breast cancer diagnosis was self-reported via annual health updates, detailed follow-up questionnaires, telephone calls, e-mails, or correspondence with the Sister Study helpdesk. Participants who reported a new breast cancer diagnosis (both invasive and non-invasive) were contacted approximately 6 months after diagnosis for additional information about the

diagnosis and treatment, and to request permission to access their medical records.[34,35] Medical records were reviewed by trained abstractors to verify the breast cancer diagnosis, tumor characteristics, and treatment details. Medical records were obtained for>80% of the participants with a breast cancer diagnosis.[36] ER status of the tumor was abstracted from pathology reports when available (79.7%) and by self-report otherwise. Agreement between self-reports and medical records was high (99.3% for ER+ and 83.1% for ER− breast cancer).[35]

Menopausal status was queried at enrollment and during follow-up. Women were considered postmenopausal if they were ≥12 months from last menses or reported having bilateral oophorectomy; had a hysterectomy and were older than 55; had chemotherapy, radiation, or other treatment that permanently stopped their period prior to spontaneous menopause; or were currently taking ovarian suppressing medications and were older than 55 years.

At enrollment, weekly energy expenditures were calculated in metabolic equivalents (MET) and total physical activity was obtained by summing the MET-hours/week of all sports, physical exercise, and daily activity reported. Sleep duration was self-reported at enrollment as the average hours of sleep per day. Participants were also asked for information about the total income from all household members and the highest level of school completed. Height and weight were measured at home visits by trained examiners. Measurements were taken three times and obtained numbers were rounded to the nearest quarter inch for height and whole pound for weight,[37] and body mass index (BMI) was calculated as weight(kg)/ height(m^2). History of birth control pill use was self-reported. Pre-existing cancer (excluding non-melanoma skin cancer) before enrollment were self-reported and received validation via medical record review. Breast cancer histories of first degree female relatives, which included mother, full and half sister, and daughter, were asked at baseline. Age and race/ ethnicity were self-reported.

Women with the following characteristics were excluded from analysis: 1) had missing data on breast cancer status (n=118, 0.2%); 2) cancer diagnosis or end of follow-up occurred prior to completion of study enrollment activities (n=17, <0.1%); 3) age at cancer diagnosis or end of follow-up was missing (n=30, <0.1%); 4) had missing data for black or green tea consumption frequency (n=469 only missing for black tea, 0.9%; n=598 only missing for green tea, 1.2%; n=1,512 missing both teas, 3.0%); or 5) had missing data for any potential confounder (n=2,396, 4.7%). After these exclusions, records from 45,744 (89.9%) women contributed to analyses.

Statistical analysis

Tea consumption (cups/week) was calculated by multiplying the frequency of consumption (times per week) by the serving size (cups consumed each time). Tea consumers with missing serving size information (N=1,103, 3.0% of black tea consumers; N=939, 3.8% of green tea consumers) were assigned a serving size of 1 cup as that was the most common serving size reported by black (57.4%) and green (73.2%) tea consumers. Black tea consumption was categorized to approximate quartiles as: never drinker, <1, 1-<5, and ≥5 cups/week. Green tea consumption was categorized in the same way for consistency.

Alcohol consumption was measured by calculating drinks consumed per week and categorized as 0, <1, 1-<7, and ≥7 drinks/week to align with previous reports from the Behavioral Risk Factor Surveillance System.[38] Red and cured meat consumption during the past 12 months was measured by FFQ as ounce-equivalents per day.[39,40] BMI categories were defined on the basis of guidelines used in WHO as underweight/normal weight (<24.9 kg/m^2), pre-obesity (25.0–29.9 kg/m^2), obesity class I (30.0–34.9 kg/m^2), obesity class II (35.0–39.9 kg/m^2), and obesity class III (≥40 kg/m^2).[41] Meat consumption, total energy intake, physical activity, and healthy eating index were categorized to approximate quartiles. Average daily sleep hours was categorized into 3 levels (<7, 7-<8, and ≥8 hours/day) based on thresholds published by the National Sleep Foundation.[42] The number of first degree female relatives with breast cancer was categorized as 1, 2, or ≥3 relatives and analyzed as an ordinal variable (1, 2, 3).[43]

Kaplan-Meier curves were used to visualize breast cancer incidence according to tea consumption levels. Specifically, we chose a common starting age at age 36 years for the Kaplan-Meier estimates where we required at least 200 women to be at risk in each tea consumption group in order to obtain stable estimates. Log-rank tests were performed to test if the incidence of different consumption levels were different. Univariate and multivariable Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for the association of black or green tea consumption with breast cancer risk. Age was used as the time scale in the above analyses and left truncation was accounted for. Using age as the time scale inherently adjusted for age in the Cox model. Women entered the risk set at the age of study enrollment and contributed person-time until age at breast cancer diagnosis, age at death, or age at last study contact, whichever occurred first. Tests for trend were conducted by treating the median value in each category of tea consumption as a continuous variable in the model,[44] and $p\text{-}trend<0.05$ indicated a significant linear trend. Tests for overall associations with black or green tea consumption were conducted by Wald test with 3 degrees of freedom for the 4 categories (0, <1, 1-<5, and ≥5 drinks/week). The proportionality assumption of the Cox model was examined based on scaled Schoenfeld residuals;[45,46] there was no evidence of violation. We applied a restricted cubic spline with 3 knots in the multivariable Cox model to depict the potential non-linear relationship between tea and breast cancer risk.

Covariates included in the multivariable model as potential confounders were chosen based on *a priori* knowledge regarding their relation with tea consumption and/or breast cancer. Covariates were included as follows: race (non-Hispanic white, non-Hispanic black, and other), BMI (<25, 25-<30, 30-<35, 35-<40, and ≥40 kg/m^2), education (high school or less, some college or undergraduate, and graduate school), annual household income (<$50,000, $50,000-<$100,000, and ≥$100,000), smoking status (never, former, current), alcohol consumption (0, <1, 1-<7, and ≥7 drinks/week), total energy intake (<1,197.2, 1,197.2-<1,545.6, 1,545.6-<1,961.2, and ≥1,961.2 kcal/day), physical activity (<27.1, 27.1-<44.4, 44.4-<67.2, and ≥67.2 MET-hours/week), meat consumption (<0.70, 0.70-<1.23, 1.23-<2.01, and ≥2.01 ounce-equivalent/day), total caffeine intake (<31.6, 31.6-<105.8, 105.8-<205, and ≥205 mg/day), healthy eating index (<54, 54-<63, 63-<71, and ≥71), average daily sleep duration (<7, 7-<8, ≥8 hours/day), ever used birth control pill (no vs. yes), personal cancer history (no vs. yes), and number of first degree relatives with breast cancer

(1, 2, and ≥3).[47,48] Black and green tea consumption were mutually-adjusted in multivariable models. Caffeine was chosen as a covariate to focus on potential direct chemopreventive effects from polyphenols in tea, rather than associations that are potentially mediated by caffeine intake.[7,20,49]

EGCG has been shown to downregulate ER activity, suggesting chemopreventive effects of tea on breast cancer may differ by ER expression.[20] Thus, we used joint Cox regression models to examine whether associations between tea consumption and breast cancer risk differed by ER status.[50] In joint Cox models, each person contributed to 2 potential event (ER+ and ER− breast cancer) times as competing risks in our analysis, and parameters of ER + cancer (β_1) and ER− cancer (β_2) were estimated simultaneously by stratifying on breast cancer subtypes defined by ER status (ER+ and ER−) and using a robust variance estimator to account for the correlation between survival times of the two subtypes.

To investigate the association between tea consumption and premenopausal breast cancer, only premenopausal person-time was included in the analysis; women who became postmenopausal without breast cancer diagnosis were censored at their age of menopause. For postmenopausal breast cancer risk models, women who were menopausal at enrollment entered the risk set at their age of study enrollment; otherwise, they entered the risk set at the age when they became postmenopausal during follow-up. Wald tests with robust variance estimators were used to examine potential interaction between tea and menopausal status on breast cancer risk in analyses that accounted for clustering of women who contributed to both pre- and postmenopausal person-time. This analysis assumed that tea consumption levels at enrollment remained constant throughout follow-up.

We conducted a subgroup analysis by obesity defined by BMI (<30 kg/m^2 vs. ≥30 kg/m^2). Interaction terms between tea consumption and BMI were used to evaluate potential modification according to obesity status using Wald tests.

Four sets of sensitivity analysis were conducted to verify the robustness of association pattern in primary analysis. First, we generated a lag period of 6 months in order to exclude women diagnosed with breast cancer shortly after enrollment to reduce the potential for undiagnosed breast cancer to influence tea consumption patterns. Second, we restricted the analysis to women without missing value of serving size. Third, we applied joint Cox models for competing risks to examine potential heterogeneity in risk estimates for invasive breast cancer and ductal carcinoma in situ (DCIS), the most common form of in situ breast cancer. Fourth, we compared the association of tea consumption in subgroups stratified by number of first degree relatives with breast cancer (1 vs. >1).

Two-sided P values <0.05 were considered to be statistically significant. Statistical analyses were conducted with Stata 13.0 (College Station, TX: StataCorp, LLP) and SAS v9.4 (SAS Institute Inc., Cary, NC).

Data availability

Data for this analysis are available upon request. See the Sister Study website at https://sisterstudy.niehs.nih.gov/English/coll-data.htm for information on requesting study data.

Results

Of the 45,744 women contributing to the analysis, the mean age at enrollment was 55.4 (SD 8.9) years. The median follow-up time was 8.6 years and 2,809 women were diagnosed with breast cancer during follow-up. Table 1 presents participants' sociodemographic and health-related characteristics at enrollment and age-adjusted HRs for breast cancer. In age-adjusted models, having a postmenopausal BMI ≥25 kg/m^2 (vs. <25 kg/m^2), completing graduate school (compared to high school or less), having an annual household income ≥$100,000 per year (compared to <$50,000), being a former (vs. never) smoker, high-level meat consumption (≥2.01 ounce-equivalent/day compared to <0.70 ounce-equivalent/day), higher total energy consumption (≥1,961.2 compared to <1,197.2 kcal/day), personal cancer history, and number of first degree relatives with breast cancer were associated with higher breast cancer risk.

Kaplan-Meier curves suggested differences in breast cancer risk across tea consumption levels were statistically significant for green tea (*log-rank p<0.01*), but not black tea (*log-rank p=0.25*) (Figure 1A and B). Table 2 presents HRs for associations between tea consumption and breast cancer risk. Black tea consumption (81.6 %) was more frequently reported than green tea (56.0 %). Overall, 25.2% and 8.9% of women drank ≥5 cups/week of black and green tea, respectively. In multivariable models, green tea consumption was inversely associated with breast cancer risk (*p-overall*<0.01). Drinking at least 5 cups of green tea per week was associated with a lower risk of breast cancer (HR=0.82, 95% CI 0.70, 0.95 for ≥5 vs. 0 cups/week of green tea; *p-trend*<0.01). The association with black tea were less consistent, with no apparent overall association (*p-overall*=0.25) but a pairwise inverse association between drinking ≥5 cups/week (HR=0.88, 95% CI 0.78, 1.00) compared to not drinking black tea and a marginally significant trend across categories (*p-trend*=0.08). The fitted curves (Figure 2A and B) of the restricted cubic spline also suggested that higher tea consumption levels were associated with a lower cancer risk, although the association was only statistically significant for green tea

There were 2,043 ER+ and 357 ER− breast cancers in our sample. Associations between black and green tea consumption and ER-defined breast cancer risk were not statistically different (*p-heterogeneity=0.84* for black tea; *p-heterogeneity=0.98* for green tea) (Table 3). Similar to associations with breast cancer risk overall (Table 2), we observed inverse associations between green tea and ER+ (*p-overall*<0.01) and ER− (*p-overall*=0.01) breast cancer risk and a significant trend with increasing consumption for ER+ risk (≥5 vs. 0 cups/week, HR=0.81, 95% CI 0.68, 0.97, *p-trend*<0.01). Associations between black tea consumption and cancer risk were not statistically significant for either ER+ (≥5 vs. 0 cups/week, HR=0.89, 95% CI 0.77, 1.03, *p-trend*=0.16) or ER− (≥5 vs. 0 cups/week, HR=0.86, 95% CI 0.63, 1.17, *p-trend*=0.24) breast cancer, although the HR in the highest consumption category was 0.86–0.89 across ER types.

Table 4 presents effect measures of black and green tea consumption by menopausal status. A total of 545 premenopausal and 2,160 postmenopausal breast cancer cases were included in our analysis. Interactions between menopausal status and tea consumption were not statistically significant (*p-interaction=0.87* for black tea, *p-interaction=0.22* for green tea)

(Table 4). Neither black nor green tea consumption appeared to be associated with premenopausal breast cancer risk. Green tea consumption was inversely associated with postmenopausal breast cancer risk (HR=0.77, 95% CI: 0.64, 0.91 for ≥5 vs. 0 cups per week of green tea; *p-trend*<0.01; *p-overall*<0.01). Suggested inverse associations with black tea consumption were limited to the highest category of consumption, and were not statistically significant (HR=0.88, 95% CI 0.76, 1.02 for ≥5 vs. 0 cups/week of black tea; *p-trend=0.16; p-overall=0.38*).

Breast cancer risk associations were not statistically different between non-obese and obese women (*p-interaction=0.80* and *0.63* for black and green tea, respectively, Table 5). Inverse associations with green tea (HR=0.76, 95% CI 0.63, 0.91 for ≥5 vs. 0 cups/week of green tea; *p-trend<0.01; p-overall<0.01*), and possibly black tea (HR=0.85, 95% CI 0.73, 0.99 for ≥5 vs. 0 cups/week of black tea; *p-trend=0.047; p-overall=0.18*), were only apparent among non-obese (BMI <30 kg/m^2) women. These associations were largely null in the obese strata (Table 5).

The 4 sets of sensitivity analyses (Supplementary Tables 1–4) yield similar results to primary analysis and did not find heterogeneity between invasive cancer and DCIS (*p-heterogeneity=0.54* for black tea; *p-heterogeneity=0.85* for green tea). The number of first degree relatives with breast cancer did not modify the association either (*p-interaction=0.64* for black tea; *p-interaction=0.84* for green tea).

Discussion

In our study, frequent green tea consumption, as compared to never consuming, was associated with a lower risk of breast cancer, with some evidence for inverse associations with black tea as well. Associations between tea consumption and breast cancer risk were not statistically different by ER status, menopausal status, or BMI. However, since some subgroups have small sample sizes, it is possible that the non-significant interaction could be due to the lack of sufficient power.

Two recent published meta-analyses investigated associations between tea consumption and breast cancer risk and reported null summary associations for black tea (RR=1.00, 95% CI=0.91–1.10)[51] and green tea (RR=0.97, 95% CI=0.86–1.11)[52] across 13[51] and 5[52] cohort studies, respectively. However, in the meta-analysis of black tea, 4 studies did not specifically clarify tea type in the original analysis and 3 classified non-herbal tea as black tea (although green tea is also a type of non-herbal tea). These 2 meta-analyses involved 14 cohort studies in total, 10 of which combined non-tea consumers and infrequent tea consumers in the reference group, which could obscure potential associations with low-dose black or green tea consumption.

The inverse association we observed may be due, in part, to the polyphenols (e.g. EGCG) found in green and, to a lesser extent, black tea.[8,53] A previous animal study fed female mice on solution containing radio-labeled EGCG and found that mammary gland levels of EGCG substantially increased after 24 hours of ingestion.[54] This indicates the potential for polyphenols in tea to be absorbed and transported in the human body. Hong et al.[49] reported

that EGCG induced breast tumor cell apoptosis and inhibited tumorigenesis in MDA−MB−231 breast cancer cells by inactivating the β−catenin signaling pathway.[55] Laboratory research reported anti-mutagenic effects of polyphenols in non-herbal tea.[56,57] This evidence supports the potential for tea consumption to prevent breast cancer by inhibiting tumor initiation. Green or black tea may also reduce breast cancer risk by inhibiting tumor promotion. Studies[58–60] of EGCG support a role in inhibition of angiogenesis through suppression of vascular endothelial growth factor (VEGF). Angiogenesis is an important factor for solid tumor growth since vascular networks facilitate nutrient transport and waste product removal.[61] Usually, solid tumors like early-stage breast cancer need new blood vessels to proliferate larger than one micrometer in size;[62] therefore, green and black tea, which are rich in EGCG, may reduce breast cancer risk by inhibiting angiogenesis and tumor proliferation. Antioxidant properties of green and black tea may also contribute to inverse associations with breast cancer risk. *In vitro* studies found that EGCG in green and black tea could lower oxidative stress-induced molecular damage and lower the risk of cancer development.[63,64]

The clear definition and categorization of tea, which considered potential dose-response, is a strength of our analysis. We used data from a national cohort study with a larger overall sample size and number of breast cancer cases as compared to previous studies, which increased precision. Moreover, conducting additional sensitivity analyses further validated results in primary analysis. However, some limitations should be considered. At enrollment, black and green tea consumption, as well as other dietary and lifestyle characteristics, were self-reported, which may have introduced measurement error and introduced the potential for residual confounding if this information was collected imperfectly. However, we anticipate measurement error would be non-differential with respect to breast cancer status as exposure and covariate information was reported prior to diagnosis.[65] Women reported their dietary consumption during the past 12 months, which is used in the current analysis as an indicator of more long-standing adult consumption patterns. In addition to frequency and serving size, the duration of tea consumption may also play an important role in cancer prevention; however, this information was not available. The potential lack of sufficient power in subgroup analysis makes it necessary to further verify interactions in future studies.

In conclusion, our study suggests that drinking 5 or more cups of green or black tea per week, compared to none, is associated with an approximately 15% lower risk of breast cancer. Tea is an inexpensive, accessible, and safe beverage; however, randomized trials are needed to confirm the inverse association of green or black tea consumption with breast cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	body mass index
CI	confidence interval
DNA	deoxyribonucleic acid
EGCG	(−)-epigallocatechin-3-gallate
ER	estrogen receptor
FFQ	food frequency questionnaire
HR	hazard ratio
MET	metabolic equivalent
NIEHS	National Institute of Environmental Health Sciences
SD	standard deviation
USDA	United States Department of Agriculture
VEGF	vascular endothelial growth factor
WHO	World Health Organization

References

1. Cancer Facts & Figures 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf [Last accessed July 1st 2019].
2. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. N Engl J Med. 2001;344(26):1997–2008. [PubMed: 11430330]
3. Will BP, Berthelot JM, Le Petit C, Tomiak EM, Verma S, Evans WK. Estimates of the lifetime costs of breast cancer treatment in Canada. Eur J Cancer. 2000;36(6):724–735. [PubMed: 10762744]
4. Lin JK, Liang YC, Lin-Shiau SY. Cancer chemoprevention by tea polyphenols through mitotic signal transduction blockade. Biochem Pharmacol. 1999;58(6):911–915. [PubMed: 10509743]
5. Lambert JD. Does tea prevent cancer? Evidence from laboratory and human intervention studies. Am J Clin Nutr. 2013;98(6 Suppl):1667S–1675S. [PubMed: 24172300]
6. Zhang D, Kaushiva A, Xi Y, Wang T, Li N. Non-herbal tea consumption and ovarian cancer risk: a systematic review and meta-analysis of observational epidemiologic studies with indirect comparison and dose-response analysis. Carcinogenesis. 2018;39(6):808–818. [PubMed: 29579174]
7. Chen D, Wan SB, Yang H, Yuan J, Chan TH, Dou QP. EGCG, green tea polyphenols and their synthetic analogs and prodrugs for human cancer prevention and treatment. Adv Clin Chem. 2011;53:155–177. [PubMed: 21404918]
8. Lee KW, Lee HJ, Lee CY. Antioxidant activity of black tea vs. green tea. J Nutr. 2002;132(4):785; author reply 786. [PubMed: 11925478]
9. Thangapazham RL, Singh AK, Sharma A, Warren J, Gaddipati JP, Maheshwari RK. Green tea polyphenols and its constituent epigallocatechin gallate inhibits proliferation of human breast cancer cells in vitro and in vivo. Cancer Lett. 2007;245(1–2):232–241. [PubMed: 16519995]
10. Mittal A, Pate MS, Wylie RC, Tollefsbol TO, Katiyar SK. EGCG down-regulates telomerase in human breast carcinoma MCF-7 cells, leading to suppression of cell viability and induction of apoptosis. Int J Oncol. 2004;24(3):703–710. [PubMed: 14767556]

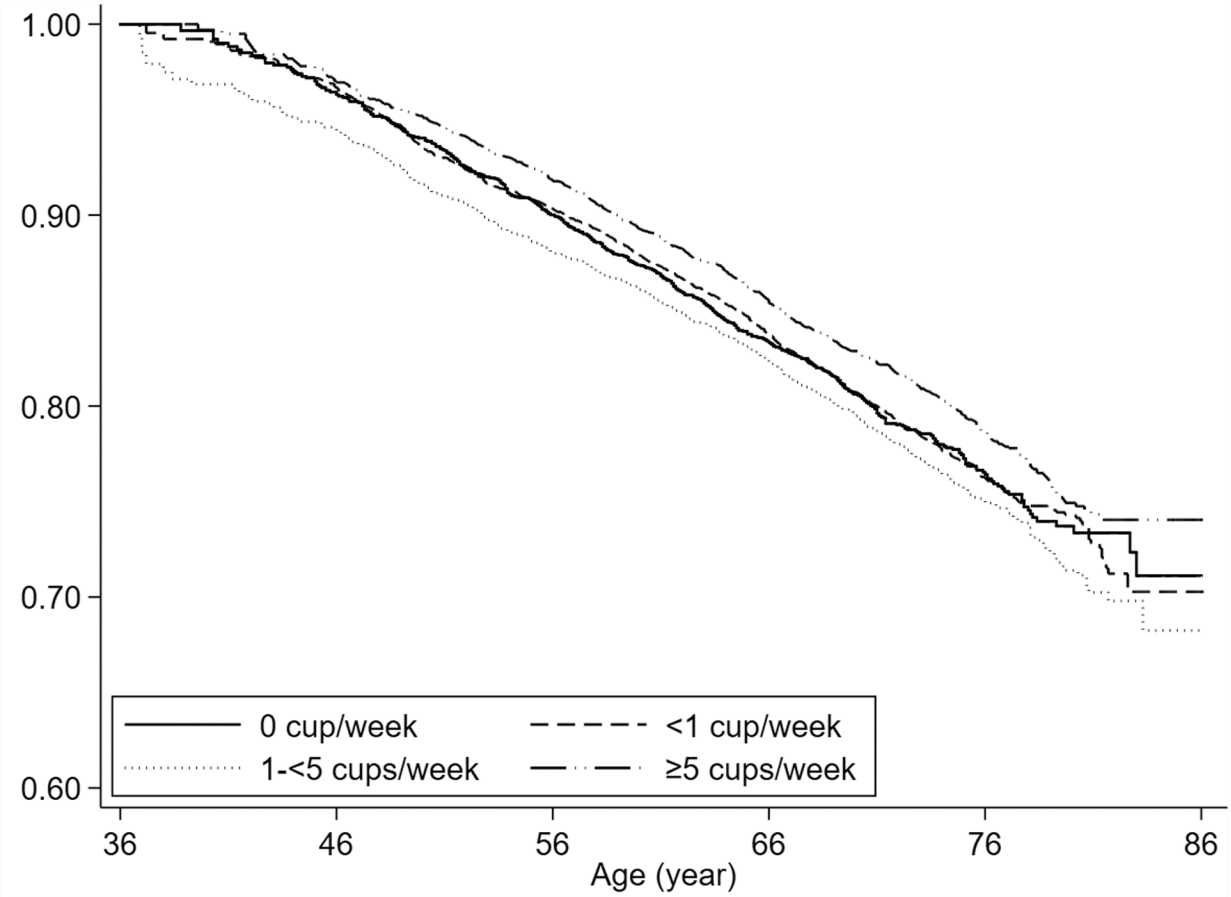
11. Boggs DA, Palmer JR, Stampfer MJ, Spiegelman D, Adams-Campbell LL, Rosenberg L. Tea and coffee intake in relation to risk of breast cancer in the Black Women's Health Study. Cancer Causes Control. 2010;21(11):1941–1948. [PubMed: 20680436]
12. Key TJ, Sharp GB, Appleby PN, et al. Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. Br J Cancer. 1999;81(7):1248–1256. [PubMed: 10584890]
13. Suzuki Y, Tsubono Y, Nakaya N, Suzuki Y, Koizumi Y, Tsuji I. Green tea and the risk of breast cancer: pooled analysis of two prospective studies in Japan. Br J Cancer. 2004;90(7):1361–1363. [PubMed: 15054454]
14. Larsson SC, Bergkvist L, Wolk A. Coffee and black tea consumption and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort. Cancer Causes Control. 2009;20(10):2039–2044. [PubMed: 19597749]
15. Fagherazzi G, Touillaud MS, Boutron-Ruault MC, Clavel-Chapelon F, Romieu I. No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study. Public Health Nutr. 2011;14(7):1315–1320. [PubMed: 21466740]
16. Hirvonen T, Mennen LI, de Bree A, et al. Consumption of antioxidant-rich beverages and risk for breast cancer in French women. Ann Epidemiol. 2006;16(7):503–508. [PubMed: 16406814]
17. Henning SM, Niu YT, Lee NH, et al. Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement. American Journal of Clinical Nutrition. 2004;80(6):1558–1564. [PubMed: 15585768]
18. Iwasaki M, Inoue M, Sasazuki S, et al. Green tea drinking and subsequent risk of breast cancer in a population-based cohort of Japanese women. Breast Cancer Res. 2010;12(5):R88. [PubMed: 22889409]
19. Nagano J, Kono S, Preston DL, Mabuchi K. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). Cancer Causes Control. 2001;12(6):501–508. [PubMed: 11519758]
20. Farabegoli F, Barbi C, Lambertini E, Piva R. (−)-Epigallocatechin-3-gallate downregulates estrogen receptor alpha function in MCF-7 breast carcinoma cells. Cancer Detect Prev. 2007;31(6):499–504. [PubMed: 18061364]
21. Yiannakopoulou EC. Interaction of green tea catechins with breast cancer endocrine treatment: a systematic review. Pharmacology. 2014;94(5–6):245–248. [PubMed: 25471334]
22. Li M, Tse LA, Chan WC, et al. Evaluation of breast cancer risk associated with tea consumption by menopausal and estrogen receptor status among Chinese women in Hong Kong. Cancer Epidemiol. 2016;40:73–78. [PubMed: 26680603]
23. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004;114(12):1752–1761. [PubMed: 15599400]
24. Keaney JF, Jr., Larson MG, Vasan RS, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. Arterioscler Thromb Vasc Biol. 2003;23(3):434–439. [PubMed: 12615693]
25. Lee JD, Cai Q, Shu XO, Nechuta SJ. The Role of Biomarkers of Oxidative Stress in Breast Cancer Risk and Prognosis: A Systematic Review of the Epidemiologic Literature. J Womens Health (Larchmt). 2017;26(5):467–482. [PubMed: 28151039]
26. Sandler DP, Hodgson ME, Deming-Halverson SL, et al. The Sister Study Cohort: Baseline Methods and Participant Characteristics. Environ Health Perspect. 2017;125(12):127003. [PubMed: 29373861]
27. Sister Study Cohort Status: Data Release 7. https://sisterstudy.niehs.nih.gov/English/images/SIS-CohortStatus-DR7-508.pdf [Last accessed Sept 18th 2019].
28. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol. 1986;124(3):453–469. [PubMed: 3740045]
29. Zhang D, Ferguson K, Troester M, et al. Tea consumption and oxidative stress: a cross-sectional analysis of 889 premenopausal women from the Sister Study. Br J Nutr. 2018:1–23.
30. Petimar J, Park YM, Smith-Warner SA, Fung TT, Sandler DP. Dietary index scores and invasive breast cancer risk among women with a family history of breast cancer. Am J Clin Nutr. 2019;109(5):1393–1401. [PubMed: 30968114]

31. Nutrient Analysis Data Overview (2008) https://docs.sssepistudies.org/studies/sisterstudy/Baseline/NA_placeholder.pdf [Last accessed July 10th 2018].
32. Mitchell DC, Knight CA, Hockenberry J, Teplansky R, Hartman TJ. Beverage caffeine intakes in the U.S. Food Chem Toxicol. 2014;63:136–142. [PubMed: 24189158]
33. Basiotis PP CA, Gerrior SA, Juan WY, Lino M, . The Healthy Eating Index: 1999–2000. Washington, DC: United States Department of Agriculture, Center for Nutrition Policy and Promotion 2002.
34. Kim S, Shore DL, Wilson LE, et al. Lifetime use of nonsteroidal anti-inflammatory drugs and breast cancer risk: results from a prospective study of women with a sister with breast cancer. BMC Cancer. 2015;15:960. [PubMed: 26673874]
35. Confirmation of Breast Cancer Diagnosis. https://sisterstudy.niehs.nih.gov/English/brca-validation.htm [Last accessed July 1st 2019].
36. White AJ, Nichols HB, Bradshaw PT, Sandler DP. Overall and central adiposity and breast cancer risk in the Sister Study. Cancer. 2015;121(20):3700–3708. [PubMed: 26193782]
37. Lin CJ, DeRoo LA, Jacobs SR, Sandler DP. Accuracy and reliability of self-reported weight and height in the Sister Study. Public Health Nutr. 2012;15(6):989–999. [PubMed: 22152926]
38. Behavioral Risk Factor Surveillance System. https://www.cdc.gov/brfss/annual_data/2017/pdf/codebook17_llcp-v2-508.pdf [Last accessed May 1st 2018].
39. Guo J, Wei W, Zhan L. Red and processed meat intake and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat. 2015;151(1):191–198. [PubMed: 25893586]
40. Lo JJ, Park YM, Sinha R, Sandler DP. Association between meat consumption and risk of breast cancer: Findings from the Sister Study. Int J Cancer. 2019.
41. World Health Organization (2017) Body mass index - BMI. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi [Last accessed July 10th 2018].
42. Girschik J, Heyworth J, Fritschi L. Self-reported sleep duration, sleep quality, and breast cancer risk in a population-based case-control study. Am J Epidemiol. 2013;177(4):316–327. [PubMed: 23324334]
43. Brewer HR, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. Family history and risk of breast cancer: an analysis accounting for family structure. Breast Cancer Res Treat. 2017;165(1):193–200. [PubMed: 28578505]
44. Larsson SC, Giovannucci EL, Wolk A. Coffee Consumption and Risk of Gallbladder Cancer in a Prospective Study. J Natl Cancer Inst. 2017;109(3):1–3.
45. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. Biometrika. 1994;81(3):515–526.
46. Xue X, Xie X, Gunter M, et al. Testing the proportional hazards assumption in case-cohort analysis. BMC Med Res Methodol. 2013;13:88. [PubMed: 23834739]
47. Katapodi MC, Lee KA, Facione NC, Dodd MJ. Predictors of perceived breast cancer risk and the relation between perceived risk and breast cancer screening: a meta-analytic review. Prev Med. 2004;38(4):388–402. [PubMed: 15020172]
48. Tilburt JC, James KM, Sinicrope PS, et al. Factors influencing cancer risk perception in high risk populations: a systematic review. Hered Cancer Clin Pract. 2011;9:2. [PubMed: 21595959]
49. Hong OY, Noh EM, Jang HY, et al. Epigallocatechin gallate inhibits the growth of MDA-MB-231 breast cancer cells via inactivation of the beta-catenin signaling pathway. Oncol Lett. 2017;14(1):441–446. [PubMed: 28693189]
50. Xue X, Kim MY, Gaudet MM, et al. A comparison of the polytomous logistic regression and joint cox proportional hazards models for evaluating multiple disease subtypes in prospective cohort studies. Cancer Epidemiol Biomarkers Prev. 2013;22(2):275–285. [PubMed: 23292084]
51. Wu Y, Zhang D, Kang S. Black tea, green tea and risk of breast cancer: an update. Springerplus. 2013;2(1):240. [PubMed: 23750333]
52. Gianfredi V, Nucci D, Abalsamo A, et al. Green Tea Consumption and Risk of Breast Cancer and Recurrence-A Systematic Review and Meta-Analysis of Observational Studies. Nutrients. 2018;10(12).

53. Stoner GD, Mukhtar H. Polyphenols as cancer chemopreventive agents. J Cell Biochem Suppl. 1995;22:169–180. [PubMed: 8538195]
54. Suganuma M, Okabe S, Oniyama M, Tada Y, Ito H, Fujiki H. Wide distribution of [3H](−)-epigallocatechin gallate, a cancer preventive tea polyphenol, in mouse tissue. Carcinogenesis. 1998;19(10):1771–1776. [PubMed: 9806157]
55. Yang CS, Wang H. Cancer Preventive Activities of Tea Catechins. Molecules. 2016;21(12).
56. Bunkova R, Marova I, Nemec M. Antimutagenic properties of green tea. Plant Foods Hum Nutr. 2005;60(1):25–29. [PubMed: 15898356]
57. Gupta S, Chaudhuri T, Seth P, Ganguly DK, Giri AK. Antimutagenic effects of black tea (World Blend) and its two active polyphenols theaflavins and thearubigins in Salmonella assays. Phytother Res. 2002;16(7):655–661. [PubMed: 12410547]
58. Basini G, Bianco F, Grasselli F. EGCG, a major component of green tea, inhibits VEGF production by swine granulosa cells. Biofactors. 2005;23(1):25–33. [PubMed: 15817996]
59. Wang CC, Xu H, Man GCW, et al. Prodrug of green tea epigallocatechin-3-gallate (Pro-EGCG) as a potent anti-angiogenesis agent for endometriosis in mice. Angiogenesis. 2013;16(1):59–69. [PubMed: 22948799]
60. Xu H, Becker CM, Lui WT, et al. Green tea epigallocatechin-3-gallate inhibits angiogenesis and suppresses vascular endothelial growth factor C/vascular endothelial growth factor receptor 2 expression and signaling in experimental endometriosis in vivo. Fertil Steril. 2011;96(4):1021–1028. [PubMed: 21821246]
61. Nishida N, Yano H, Nishida T, Kamura T, Kojiro M. Angiogenesis in cancer. Vasc Health Risk Manag. 2006;2(3):213–219. [PubMed: 17326328]
62. Folkman J Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971;285(21):1182–1186. [PubMed: 4938153]
63. Anderson RF, Fisher LJ, Hara Y, et al. Green tea catechins partially protect DNA from (.)OH radical-induced strand breaks and base damage through fast chemical repair of DNA radicals. Carcinogenesis. 2001;22(8):1189–1193. [PubMed: 11470748]
64. Leanderson P, Faresjo AO, Tagesson C. Green tea polyphenols inhibit oxidant-induced DNA strand breakage in cultured lung cells. Free Radic Biol Med. 1997;23(2):235–242. [PubMed: 9199885]
65. Jurek AM, Greenland S, Maldonado G, Church TR. Proper interpretation of non-differential misclassification effects: expectations vs observations. Int J Epidemiol. 2005;34(3):680–687. [PubMed: 15802377]

What's new

Previous epidemiologic studies of tea and breast cancer risk have largely ignored heterogeneous chemical constituents across different types of tea or potential variation by breast cancer subtype. Our research considered these issues and reports a modest inverse association between black and green tea consumption and breast cancer risk that did not vary according to estrogen receptor status of the tumor.



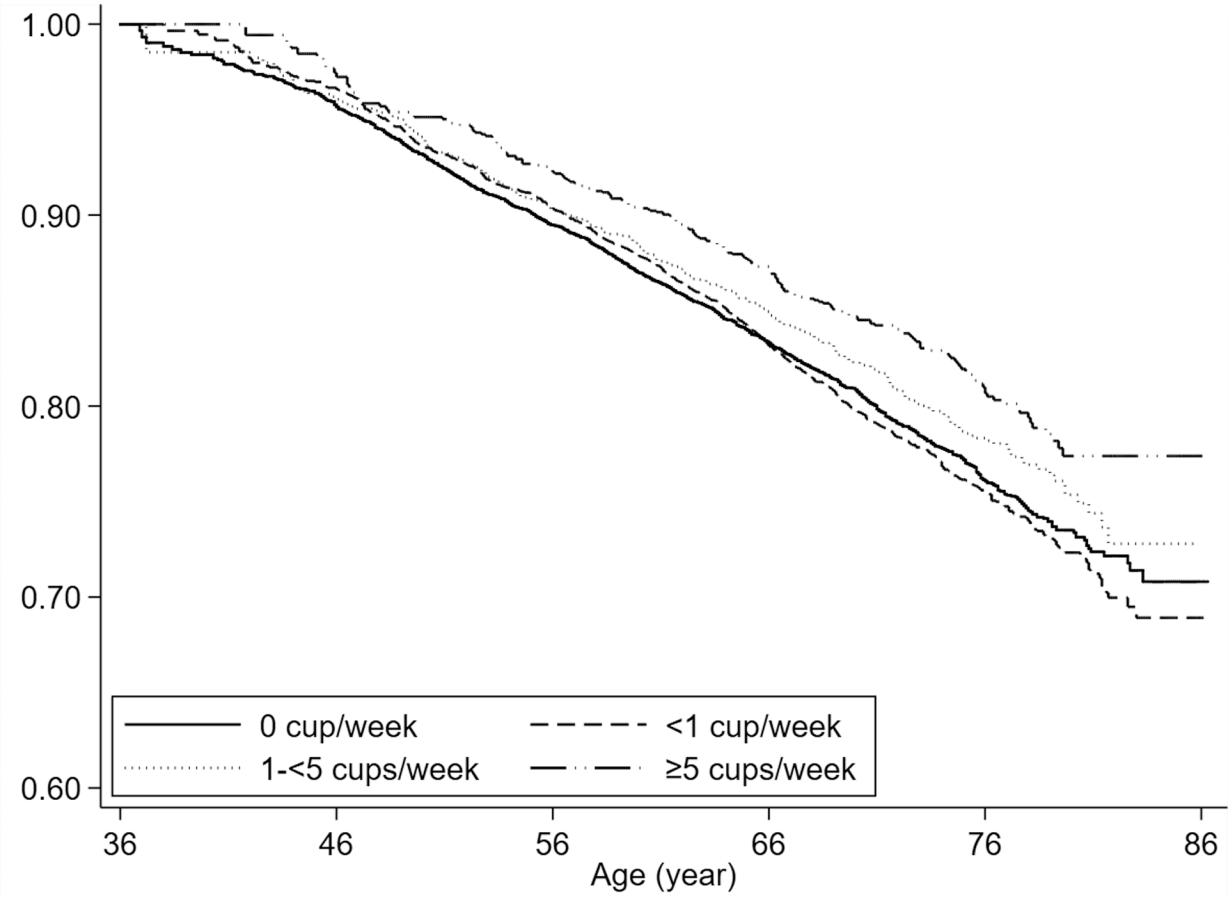


Figure 1A and 1B.

Kaplan-Meier curves for black (Figure 1A) and green tea (Figure 1B) consumption. Age was used as the time scale in the figure. The vertical axis indicated the probability of being free of breast cancer.

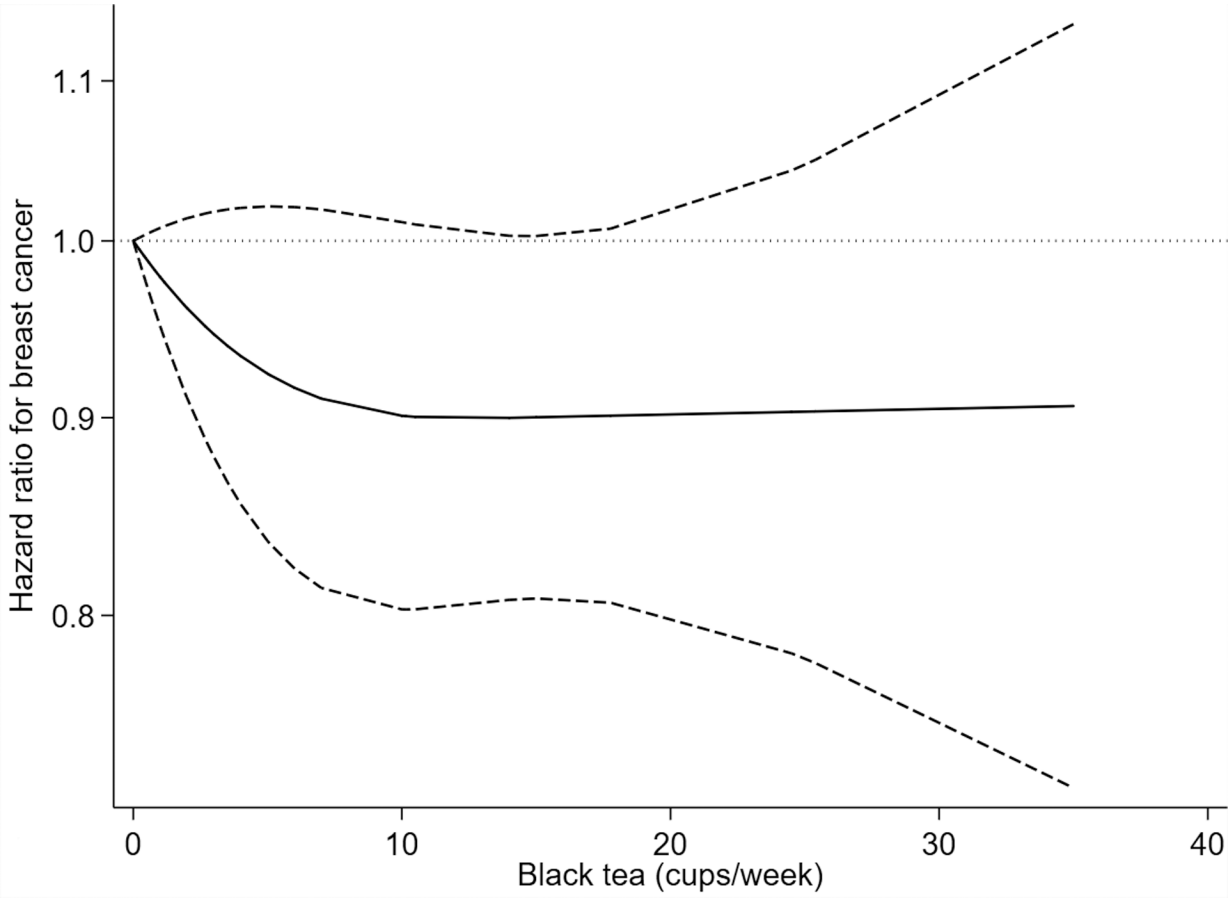


Figure 2A.

Restricted cubic spline showing the hazard ratio for breast cancer with increasing black tea consumption compared to no black tea consumption adjusted for green tea, race, body mass index, education, income, smoking status, alcohol consumption, energy intake, physical activity, meat consumption, sleep duration, caffeine intake, healthy eating index, history of birth control pill utilization, personal cancer history, and number of first degree relatives with breast cancer. The dashed lines are the 95% confidence intervals.

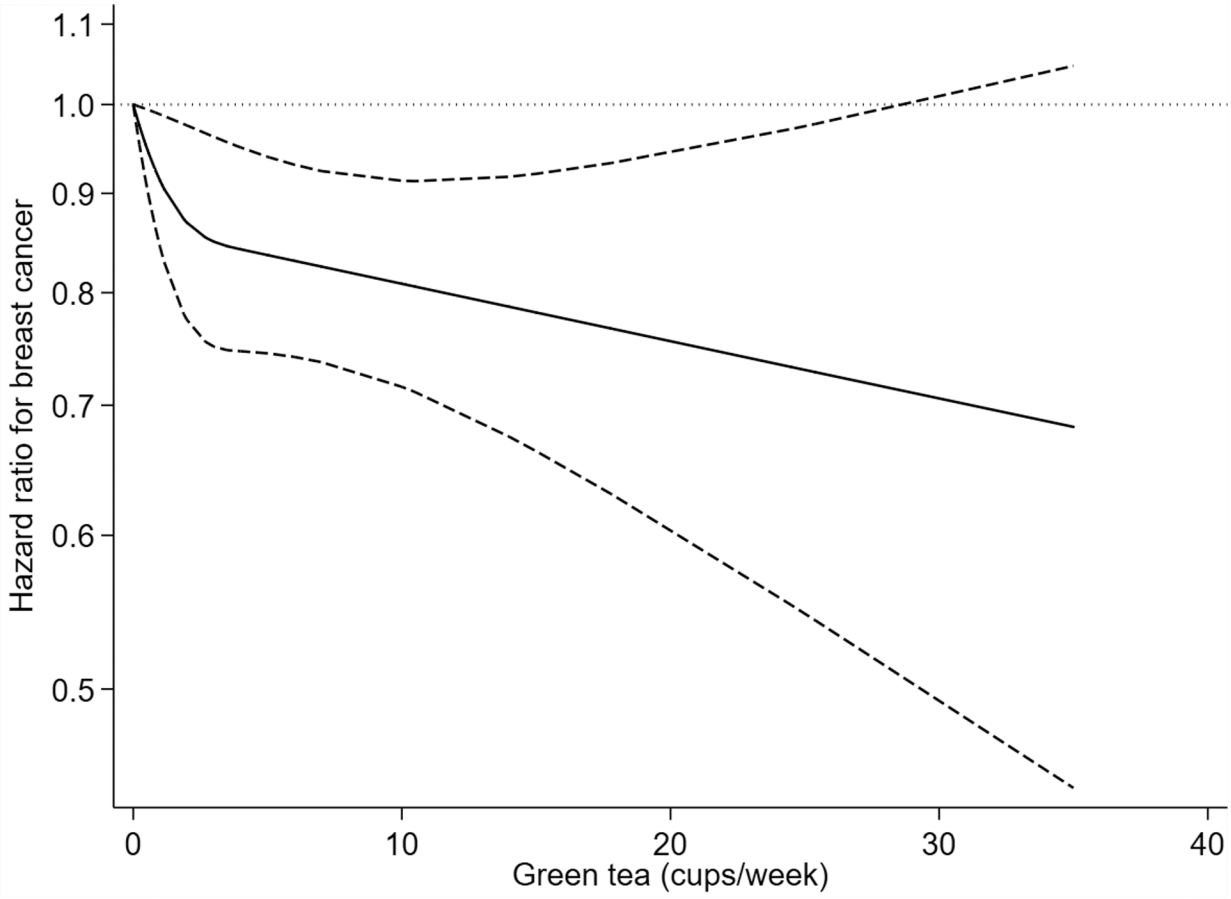


Figure 2B.

Restricted cubic spline showing the hazard ratio for breast cancer with increasing green tea consumption compared to no green tea consumption adjusted for black tea, race, body mass index, education, income, smoking status, alcohol consumption, energy intake, physical activity, meat consumption, sleep duration, caffeine intake, healthy eating index, history of birth control pill utilization, personal cancer history, and number of first degree relatives with breast cancer. The dashed lines are the 95% confidence intervals.

Table 1.

Participant characteristics at enrollment, Sister Study, 2003–2009

Characteristics	Total cohort N (%)	Breast cancers[1] N (%)	Person-year	Age-adjusted HR (95% CI)	P[4]
Total N	**45,744**	**2,809**	**384,008.4**		
Age (year)					
35-<45	6,075 (13.3)	282 (10.0)	52333.8	REF	0.74
45-<55	16,116 (35.2)	915 (32.6)	137247.8	1.08 (0.88, 1.32)	
55-<65	16,081 (35.2)	1,063 (37.8)	134230.7	1.04 (0.81, 1.33)	
≥65	7,472 (16.3)	549 (19.6)	60196.1	0.98 (0.73, 1.33)	
Race					
Non-Hispanic white	38,709 (84.6)	2,429 (86.5)	330548.3	REF	0.86
Non-Hispanic black	3,756 (8.2)	195 (6.9)	28114.1	0.99 (0.86, 1.15)	
Other	3,279 (7.2)	185 (6.6)	25346	1.04 (0.90, 1.21)	
BMI (kg/m^2)[2] (premenopausal at enrollment)					
<25	7,036 (43.7)	400 (44.5)	61489.5	REF	0.70
25-<30	4,594 (28.6)	272 (30.3)	39195	1.05 (0.90, 1.22)	
30-<35	2,480 (15.4)	130 (14.5)	20870.9	0.94 (0.77, 1.14)	
35-<40	1,149 (7.1)	55 (6.1)	9554.5	0.87 (0.66, 1.15)	
≥40	826 (5.1)	42 (4.7)	6642.9	0.96 (0.70, 1.32)	
(postmenopausal at enrollment)					
<25	10,759 (36.3)	629 (32.9)	91279.1	REF	<0.01
25-<30	9,771 (33.0)	633 (33.1)	81059.1	1.12 (1.00, 1.25)	
30-<35	5,351 (18.1)	387 (20.3)	43570	1.29 (1.13, 1.46)	
35-<40	2,347 (7.9)	161 (8.4)	18939.3	1.26 (1.06, 1.50)	
≥40	1,415 (4.8)	100 (5.3)	11249.4	1.35 (1.09, 1.66)	
Education level					
High school or less	6,854 (15.0)	380 (13.5)	55859.9	REF	0.01
Some college or undergraduate	27,815 (60.8)	1,674 (59.6)	233345.4	1.10 (0.98, 1.23)	
Graduate school	11,075 (24.2)	755 (26.9)	94803.1	1.21 (1.07, 1.37)	
Annual household income ($)					
0-<50,000	11,441 (25.0)	692 (24.6)	93190.7	REF	0.06
50,000-<100,000	18,795 (41.1)	1,129 (40.2)	158920.5	1.02 (0.93, 1.13)	
≥100,000	15,508 (33.9)	988 (35.2)	131897.2	1.12 (1.01, 1.23)	
Smoking history					
Never	25,738 (56.3)	1,516 (54.0)	217064.7	REF	0.04
Former	16,252 (35.5)	1,093 (38.9)	136265.8	1.10 (1.01, 1.19)	
Current	3,754 (8.2)	200 (7.1)	30677.9	0.96 (0.83, 1.12)	
Alcohol consumption (drinks/week)					
0	8,464 (18.5)	498 (17.7)	69148.5	REF	0.11
<1	16,231 (35.5)	948 (33.8)	136247.3	1.01 (0.90, 1.12)	
1-<7	14,828 (32.4)	955 (34.0)	125974.4	1.11 (0.99, 1.23)	

Characteristics	Total cohort N (%)	Breast cancers[1] N (%)	Person-year	Age-adjusted HR (95% CI)	P[4]
Total N	**45,744**	**2,809**	**384,008.4**		
≥7	6,221 (13.6)	408 (14.5)	52638.2	1.09 (0.96, 1.24)	
Caffeine intake (mg/day)					
<31.6	11,283 (24.7)	687 (24.5)	95056.2	REF	0.89
31.6-<105.8	11,405 (24.9)	695 (24.7)	95405.1	1.01 (0.91, 1.12)	
105.8-<205.0	11,501 (25.1)	700 (24.9)	96919	0.99 (0.89, 1.10)	
≥205.0	11,555 (25.3)	727 (25.9)	96628.1	1.03 (0.93, 1.15)	
Total energy intake (kcal/day)					
<1,197.2	11,370 (24.9)	670 (23.8)	94436.1	REF	<0.01
1,197.2-<1,545.6	11,412 (24.9)	656 (23.4)	96186.5	0.97 (0.87, 1.08)	
1,545.6-<1,961.2	11,503 (25.1)	709 (25.2)	97333.4	1.03 (0.93, 1.15)	
≥1,961.2	11,459 (25.1)	774 (27.6)	96052.4	1.16 (1.05, 1.29)	
Physical activity (MET-hour/week)					
<27.1	11,436 (25.0)	718 (25.6)	95593.6	REF	0.30
27.1-<44.4	11,397 (24.9)	725 (25.8)	95587.6	1.01 (0.91, 1.12)	
44.4-<67.2	11,492 (25.1)	696 (24.8)	96821.3	0.95 (0.86, 1.06)	
≥67.2	11,419 (25.0)	670 (23.8)	96005.9	0.92 (0.83, 1.02)	
Meat consumption (ounce-equivalent/day)[3]					
<0.70	11,260 (24.6)	665 (23.7)	93702.1	REF	<0.01
0.70-<1.23	11,466 (25.1)	682 (24.3)	96587.9	1.01 (0.91, 1.12)	
1.23-<2.01	11,503 (25.1)	675 (24.0)	96872.3	1.01 (0.91, 1.12)	
≥2.01	11,515 (25.2)	787 (28.0)	96846.1	1.19 (1.07, 1.32)	
Healthy eating index score (0–100)					
<54	11,441 (25.0)	715 (25.5)	94914.6	REF	0.50
54-<63	11,485 (25.1)	686 (24.4)	95821.9	0.94 (0.85, 1.05)	
63-<71	10,434 (22.8)	629 (22.4)	87989.9	0.93 (0.83, 1.03)	
≥71	12,384 (27.1)	779 (27.7)	105282	0.94 (0.85, 1.04)	
Sleep duration (hours/day)					
<7	13,138 (28.7)	777 (27.7)	108782.3	0.94 (0.86, 1.03)	0.22
7-<8	17,358 (38.0)	1,116 (39.7)	147273.1	REF	
≥8	15,248 (33.3)	916 (32.6)	127953	0.93 (0.85, 1.02)	
Personal cancer history at baseline[5]					
No	43,317 (94.7)	2,612 (93.0)	364615	REF	<0.01
Yes	2,427 (5.3)	197 (7.0)	19393.4	1.34 (1.16, 1.55)	
Ever used birth control pill					
No	7,027 (15.4)	456 (16.2)	58237.7	REF	0.86
Yes	38,717 (84.6)	2,353 (83.8)	325770.7	1.01 (0.91, 1.12)	
Number of first degree female relatives with breast cancer					
1	33,566 (73.4)	1,810 (64.5)	282615	REF	<0.01

Characteristics	Total cohort N (%)	Breast cancers[1] N (%)	Person-year	Age-adjusted HR (95% CI)	P[4]
Total N	**45,744**	**2,809**	**384,008.4**		
2	10,706 (23.4)	849 (30.2)	89425.3	1.45 (1.34, 1.58)	
≥3	1,472 (3.2)	150 (5.3)	11968.1	1.86 (1.58, 2.20)	

Abbreviation: NIEHS: The National Institute of Environmental Health Sciences, BMI: body mass index, MET: metabolic equivalent of task, HR: hazard ratio, CI: confidence interval

[1] Breast cancer included invasive breast cancer and non-invasive cancer

[2] Menopausal status at enrollment. For BMI, the sum of the column did not equal the total sample because of missing data of menopausal status

[3] This included cured meat and red meat.

[4] Wald test was used to calculate the overall-p value.

[5] This excluded non-melanoma skin cancer.

Table 2.

Hazard ratios and 95% confidence intervals for the association between tea consumption and breast cancer risk in the total study population

	Total cohort (n=45,744)	Breast cancer diagnoses[1] (n=2,809)	Person-years	Age-adjusted HR (95% CI)[2]	Multivariable HR (95% CI)[3]
Black tea (cups/week)					
0	8,442 (18.4%)	520 (18.5%)	69660.4	REF	REF
<1	15,588 (34.1%)	982 (35.0%)	131388.5	0.99 (0.89, 1.10)	0.94 (0.84, 1.05)
1-<5	10,207 (22.3%)	633 (22.5%)	85938.5	0.97 (0.86, 1.09)	0.93 (0.82, 1.05)
≥5	11,507 (25.2%)	674 (24.0%)	97021	0.90 (0.81, 1.01)	0.88 (0.78, 1.00)
				p-trend=0.045	*p-trend=0.08*
				p-overall=0.25	*p-overall=0.25*
Green tea (cups/week)					
0	20,129 (44.0%)	1,230 (43.8%)	169592.5	REF	REF
<1	15,664 (34.2%)	1,046 (37.2%)	131645.5	1.09 (1.00, 1.18)	1.08 (0.99, 1.18)
1-<5	5,893 (12.9%)	329 (11.7%)	49157.6	0.91 (0.81, 1.03)	0.91 (0.80, 1.03)
≥5	4,058 (8.9%)	204 (7.3%)	33612.8	0.81 (0.70, 0.94)	0.82 (0.70, 0.95)
				p-trend<0.01	*p-trend<0.01*
				p-overall<0.01	*p-overall<0.01*

Abbreviations: HR: hazard ratio, CI: confidence interval.

[1] Breast cancer included invasive and non-invasive breast cancer.

[2] Age was used as the time scale in analysis. HR is the age-adjusted hazard ratio, and the model restricted to women (N=45,744) without missing data of covariates in the multivariable model. The model only included one type of tea (either black or green tea).

[3] HR is the adjusted hazard ratio calculated from multivariable model which included black and green tea simultaneously. Variables adjusted in the multivariable model were race, body mass index, education, income, smoking status, alcohol consumption, energy intake, physical activity, meat consumption, sleep duration, caffeine intake, healthy eating index, history of birth control pill utilization, personal cancer history, and number of first degree relatives with breast cancer. The model included 45,744 women for analysis.

Table 3.

Hazard ratios and 95% confidence intervals for the association between tea consumption and breast cancer risk according to ER status.

	ER+ Breast Cancer		ER− Breast Cancer		
	No. cases/overall	**aHR (95% CI)**	**No. case/overall**	**aHR (95% CI)**	***p-heterogeneity***
Black tea (cups/week)					
0	373/8,360	REF	65/8,360	REF	
<1	721/15,454	0.96 (0.85, 1.08)	127/15,454	0.95 (0.82, 1.10)	0.84
1-<5	457/10,116	0.94 (0.82, 1.08)	85/10,116	0.92 (0.74, 1.16)	
≥5	492/11,405	0.89 (0.77, 1.03)	80/11,405	0.86 (0.63, 1.17)	
		p-trend=0.16		*p-trend=0.24*	
		p-overall=0.44		*p-overall=0.79*	
Green tea (cups/week)					
0	890/19,945	REF	156/19,945	REF	
<1	767/15,520	1.09 (0.99, 1.19)	135/15,520	1.09 (0.94, 1.25)	0.98
1-<5	240/5,844	0.91 (0.79, 1.05)	40/5,844	0.91 (0.71, 1.18)	
≥5	146/4,026	0.81 (0.68, 0.97)	26/4,026	0.82 (0.57, 1.18)	
		p-trend<0.01		*p-trend=0.26*	
		p-overall<0.01		*p-overall=0.01*	

Abbreviations: aHR: adjusted hazard ratio, CI: confidence interval, ER: estrogen receptor.

A total of 45,335 women were included in the multivariable joint Cox model.

Adjusted for race, body mass index, education, income, smoking status, alcohol consumption, energy intake, physical activity, meat consumption, sleep duration, caffeine intake, healthy eating index, history of birth control pill utilization, personal cancer history, number of first degree relatives with breast cancer, and alternate (green or black) tea type consumption.

Table 4.

Hazard ratios and 95% confidence intervals for the association between tea consumption and breast cancer risk according to menopausal status.

	Premenopausal breast cancer		Postmenopausal breast cancer		
	No. cases/overall	**aHR (95% CI)**	**No. case/overall**	**aHR (95% CI)**	***p-interaction***
Black tea (cups/week)					
0	111/2,678	REF	386/6,710	REF	
<1	200/4,638	1.01 (0.79, 1.29)	748/12,644	0.93 (0.82, 1.06)	0.87
1-<5	122/2,957	0.99 (0.75, 1.30)	493/8,341	0.93 (0.81, 1.07)	
≥5	112/3,063	0.89 (0.67, 1.19)	533/9,620	0.88 (0.76, 1.02)	
		p-trend=0.28		*p-trend=0.16*	
		p-overall=0.76		*p-overall=0.38*	
Green tea (cups/week)					
0	257/6,266	REF	935/16,265	REF	
<1	185/4,444	0.97 (0.79, 1.18)	817/12,731	1.10 (1.00, 1.21)	0.22
1-<5	63/1,628	0.90 (0.68, 1.20)	255/4,892	0.90 (0.78, 1.04)	
≥5	40/998	0.96 (0.68, 1.36)	153/3,427	0.77 (0.64, 0.91)	
		p-trend=0.78		*p-trend<0.01*	
		p-overall=0.91		*p-overall<0.01*	

Abbreviations: aHR: adjusted hazard ratio, CI: confidence interval.

Adjusted for race, body mass index, education, income, smoking status, alcohol consumption, energy intake, physical activity, meat consumption, sleep duration, caffeine intake, healthy eating index score, history of birth control pill utilization, personal cancer history, number of first degree relatives with breast cancer, and alternate (green or black) tea type consumption.

Interaction was tested by Wald test. P<0.05 indicated statistical significance.

For premenopausal breast cancer, 13,336 women were included for analysis.

For postmenopausal breast cancer, 37,315 women were included for analysis.

Table 5.

Subgroup analysis of associations between tea consumption and breast cancer risk stratified by obesity (BMI±30 kg/m^2)

	BMI<30 kg/m^2		BMI≥30 kg/m^2		
	No. cases/overall	**aHR (95% CI)**	**No. case/overall**	**aHR (95% CI)**	***p-interaction***
Black tea (cups/week)					
0	365/5,954	REF	155/2,488	REF	
<1	703/11,307	0.94 (0.82, 1.07)	279/4,281	0.94 (0.77, 1.16)	0.80
1-<5	421/6,982	0.91 (0.79, 1.06)	212/3,225	0.99 (0.79, 1.23)	
≥5	445/7,923	0.85 (0.73 0.99)	229/3,584	0.97 (0.78, 1.21)	
		p-trend=0.047		*p-trend=0.97*	
		p-overall=0.18		*p-overall=0.94*	
Green tea (cups/week)					
0	827/13,592	REF	403/6,537	REF	
<1	736/11,342	1.05 (0.95, 1.16)	310/4,322	1.14 (0.98, 1.33)	0.63
1-<5	230/4,240	0.88 (0.75, 1.02)	99/1,653	0.99 (0.79, 1.24)	
≥5	141/2,992	0.76 (0.63, 0.91)	63/1,066	0.94 (0.72, 1.24)	
		p-trend<0.01		*p-trend=0.36*	
		p-overall<0.01		*p-overall=0.28*	

Abbreviations: aHR: adjusted hazard ratio, CI: confidence interval, BMI: body mass index

Adjusted for race, education, income, smoking status, alcohol consumption, energy intake, physical activity, meat consumption, sleep duration, caffeine intake, healthy eating index score, history of birth control pill utilization, personal cancer history, number of first degree relatives with breast cancer, and alternate tea type (green or black) consumption.

Interaction was tested by Wald test. P<0.05 indicated statistical significance.

For BMI<30 kg/m^2, 32,166 women were included for analysis.

For BMI≥30 kg/m^2, 13,578 women were included for analysis.