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Green Tea and Breast Cancer

Anna H Wu¹ and Lesley M Butler²

¹Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California 90089

²Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO. 80523-1681

Abstract

The identification of modifiable lifestyle factors that could reduce the risk of breast cancer is a research priority. Despite the enormous chemo preventive potential of green tea and compelling evidence from animal studies, its role in breast cancer development in humans is still unclear. Part of the uncertainty is related to the relatively small number of epidemiological studies on green tea and breast cancer and that the overall results from case-control studies and prospective cohort studies are discordant. In addition, the mechanisms by which green tea intake may influence risk of breast cancer in humans remains not well studied. We review the human studies that have evaluated the relationship between green tea intake and four biomarkers (sex steroid hormones, mammographic density, insulin-like growth factor, adiponectin) that are believed to be important in breast cancer development. Results from these biomarker studies are also inconclusive. Limitations of human studies and areas of further investigations are discussed.

Keywords

green tea; breast cancer; circulating hormone levels; mammographic density; insulin-like growth factor; adiponectin

1. Introduction

Green tea accounts for approximately 20% of the world's tea production; it is the main tea beverage consumed in Japan and parts of China but it is rarely consumed in Europe and North America where black tea is the common tea beverage. Breast cancer is the most common cancer worldwide, with a 6-fold variation in incidence between high-(e.g., Europe and North America) and low-risk (e.g., Asia) regions [1]. Green tea intake may be a relevant factor for the lower incidence of breast cancer in Asian populations because it is not only a common exposure, but it also has many purported beneficial properties; and there are supportive evidence of its protective effects in some epidemiological studies [2–4] Black tea intake, in contrast, appears to be unrelated to breast cancer risk in Asian and western

Correspondence should be addressed to: Anna H. Wu, USC/Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, Los Angeles, CA 90089-9175. Telephone: (323) 865-0480, Fax: (323) 865-0139; annawu@usc.edu.

Conflict of Interest

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populations [4]. Green tea is rich in tea catechins, namely epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin (EC), and epicatechin gallate (ECG), which have many cancer chemo preventive attributes including anti-oxidation, anti-inflammatory, anti-proliferative, and anti-angiogenic [5]. In addition, EGCG has been found to exhibit steroid hormone activities [6–8] and may influence breast cancer risk via hormonal mediated pathways. In the first part of this paper, we present an update of the epidemiological evidence on green tea and breast cancer. We then summarize the human studies that have evaluated the relationship between green tea intake and select biomarkers (sex steroid hormones, mammographic density, insulin-like growth factor, adiponectin) that have been established or are suspected to be important in breast cancer development. Third, we provide a brief review of animal studies on green tea and breast cancer.

2. Epidemiologic evidence for green tea and breast cancer risk

Since the early 2000's, intake of green tea and breast cancer risk has been investigated in three case-control studies [9–11]. Two population-based studies conducted among Asian-Americans in Los Angeles County [10, 12] and in Shanghai, China [9], and one hospital-based study was conducted in Zhejiang Province, China [11]. These three studies showed significant breast cancer risk reduction with regular green tea intake after adjustment for soy and other potential confounding factors (Table 1). In two of these case-control studies, detailed characteristics of green tea intake was assessed, and the inverse association was observed with greater frequency and amount of green tea intake, as well as number of years of green tea drinking [9, 11]. The combined odds ratio (OR) from these case-control studies totaling 5,602 cases and 5,483 controls is 0.70 (95% CI=0.61–0.79) for women who drank green tea regularly compared to non-green tea drinkers (Table 1).

Intake of green tea and breast cancer risk has been investigated in five prospective cohort studies that were conducted in Japan [13–15], Singapore [16, 17], and Shanghai, China [18]. The assessment of green tea intake was relatively crude in three of the studies, as it was based only on frequency of intake at the time of study enrollment [14–16]. More complete assessment was used in the Japan Public Health Center-based Prospective Study (JPHCPS); it asked about frequency and amount of green tea intake at baseline and then also re-assessed intake of the two main types of green tea consumed Japan in the five-year follow-up questionnaire [13]. In the Shanghai Women's Health Study (SWHS), information was obtained on amount of intake, age started, as well as years of green tea intake [18]. These prospective cohort studies totaling 2,067 breast cancer cases show no association between breast cancer risk and green tea intake; the combined OR is 1.06 (95% CI=0.93– 1.20) for women who drank green tea regularly compared to non-green tea drinkers (Table 1).

Few of the epidemiologic studies have investigated the relationship between green tea and breast cancer risk by hormone receptor status although in vitro studies show cytotoxic effects of EGCG toward breast cancer cells regardless of estrogen receptor status [19]. In the cohort study by Iwasaki and coworkers, green tea intake was unrelated to risk of breast cancer regardless of hormone receptor status [13]. In contrast, unpublished results from our case-control study of Asian Americans in Los Angeles County [12] showed an inverse association with green tea intake for breast cancers that are positive for estrogen receptor/

progesterone receptor status as well as for cancers that are negative for both hormone receptors.

Reasons for the differences in results between the case-control and cohort studies are not apparent. Although selective recall bias among breast cancer cases in case-control studies cannot be ruled out, we believe this is unlikely the explanation because the tea-breast cancer association appeared specific to green tea whereas black tea intake was unrelated to breast cancer risk [4]. There is no reason for selective recall bias of only green tea but not black tea intake in case-control studies since there is little awareness of health-related effects of tea on cancer in the study populations where these studies were conducted. Difference in the green tea-breast cancer association by menopausal status has been suggested as a possible explanation. Results from a case-control [9] and a prospective cohort study [18] from Shanghai, China, showed that any benefit of green tea is present only in premenopausal women. However, two other studies showed no differences in results by menopausal status. Green tea intake was significantly inversely associated with breast cancer risk in both pre- and postmenopausal Asian American women in Los Angeles County [12]. In contrast, green tea was unrelated to breast cancer risk in both pre- and postmenopausal women in Japan [13]. Given that the proportion of postmenopausal women is substantially higher in the cohort studies than in the case-control studies, a difference in the green tea-breast cancer association by menopausal status, if confirmed, may help explain the combined null result in cohort studies. Further investigation of the green tea-breast cancer association in prospective studies that are powered to evaluate the possible effect modification by menopausal status is needed.

Two of the above mentioned prospective studies also used biomarkers of green tea intake to complement self-reported assessment of green tea intake pattern [13, 18]. These investigators conducted nested case-control studies within their respective cohorts to evaluate the relationship between pre-diagnostic circulating tea polyphenol levels and breast cancer risk. In JPHCPS, plasma polyphenol levels were compared between 144 newly diagnosed breast cancer patients and 288 individually matched control women. Breast cancer risk was unrelated to individual tea polyphenol (EGC, EC, EGCG, and ECG) and total plasma tea polyphenol levels which was the sum of four tea polyphenols [20]. While these results based on plasma tea polyphenol agree with their previous results based on self-reported tea intake [13], correlation coefficients between plasma levels and green tea intake were low, ranging between 0.16 for EC and 0.23 for EGC. Previous studies have found low bioavailability of tea catechins in humans [21–23]. This may explain, in part, the low percent of participants in JPHCPS showing detectable plasma levels of the four polyphenols when 75% of cohort participants reported they were daily green tea drinkers and 54% drank at least 3 or more cups of green tea daily [13].

In SWHS, urinary concentrations of total tea polyphenol (flavanol) as well as individual tea polyphenols (EGC, EC) and metabolites of EC and EGC (metabolites M4 and M6) were compared between 353 incident breast cancer cases and 701 individually matched control women [24]. Although levels of total and specific tea polyphenols (EC, EGC) and metabolites of EC [5-(3',4',5'-trihydroxy-phenyl)--valerolactone (M4)] and EGC [5-(3',4',-dihydroxy-phenyl)- γ -valerolactone (M6)], and the methylated form of EGC [4'-MeECG]

were significantly higher in controls than in cases, there was no significant trend of decreasing risk with increasing level of any of these polyphenols and metabolites. In addition, while urinary excretion of tea polyphenols (EC, EGC, EGC_4M, M4, M6) increased with increasing self-reported amount of tea consumed among control women, a similar relationship was not observed among breast cancer patients. Thus, the incorporation of biomarkers of green tea in epidemiological studies is clearly important but our current understanding of the relationship between self-reported intake of green tea and endogenous levels of green tea (urine and plasma) in women with breast cancer and those without breast cancer is incomplete. These results raise the possibility that the bioavailability of tea polyphenols may be influenced by factors other than the amount of green tea consumed, such as genetic variability in the metabolism of green tea.

Variations in genes involved in the metabolism of tea catechins may modify the green tea-breast cancer association. O-methylation by catechol-O-methyltransferase (*COMT*) is one important conjugation reaction of tea catechins [25, 26]. In our study of breast cancer among Asian Americans in Los Angeles County, we found that the *COMT* rs4680 genotype affected the relationship between green tea intake and breast cancer risk. Specifically, the inverse association between tea intake and breast cancer risk was observed only among women possessing at least one low activity *COMT* allele whereas risk of breast cancer did not differ between tea drinkers and non drinkers who were homozygous for the high-activity *COMT* allele [27]. However, results from the Shanghai Breast Cancer Study did not find any evidence that *COMT* rs4680 genotype modified the green tea-breast cancer relationship [9]. Antioxidative properties of green tea polyphenols may also influence breast cancer risk via other pathways. Genetic polymorphisms of methylenetetrahydrofolate reductase (*MTHFR*) and thymidylate synthase (*TYMS*) genes in the folate pathway [17] and angiotensin-converting enzyme (*ACE*) in the angiotensin-II pathway [16], have been found to influence the green tea-breast cancer association in the Singapore Chinese Health Study. These results have not been confirmed in other studies of green tea and breast cancer.

In addition to the above mentioned studies on green tea and risk of breast cancer development, two studies conducted in Japan suggest that green tea consumers with stage I or II breast cancer experienced a lower risk of recurrence than women with low daily intake of green tea. However, intake levels were uniformly high in these two studies. In one study, the comparison was between breast cancer patients who consumed 5 or more cups per day versus 4 or few cups daily [28] whereas the comparison was between those who consumed 3 or more cups per day versus those who consumed 0–2 cups per day in another study [29]. The relevance of these findings to populations with substantially lower green tea intake is unclear.

We are not aware of published intervention studies that have investigated the effects of green tea or catechins on established breast cancer related endpoints such as endogenous hormone levels or mammographic density although there are some data on these relationships from cross-sectional studies (see below).

3. Green tea and biomarkers of breast cancer risk

Sex steroid hormones and mammographic density and more recently, insulin-like growth factor and adiponectin, have been investigated as biomarkers of breast cancer risk. An association between these individual biomarkers and green tea intake that is in a direction similar to the relationship between these biomarkers and breast cancer risk would strengthen the evidence for green tea as a chemopreventive agent for breast cancer by providing a biological basis for the association between green tea intake and breast cancer risk.

3.1 Circulating estrogens and androgens

A substantial body of evidence has implicated sex hormones in the etiology of breast cancer; showing that circulating estrogen and androgen concentrations are associated with risk of breast cancer development [30–33]. Tea polyphenols have sex hormone-related activities that include preventing the binding of estrogen to its receptor in breast cancer cells [34, 35], suppression of androgen receptor expression in prostate cancer [36], strong inhibition of *COMT*-mediated O-methylation of catechol estrogens [37], and the inhibition of aromatase, the key enzyme mediating the conversion of androgens to estrogens [6–8].

Two cross-sectional studies suggest that green tea intake was associated with lowering circulating estrogen levels in premenopausal women in Japan [38] and postmenopausal Chinese women in Singapore [39]. We are not aware of additional published studies on green tea and sex hormones in women since our review of this topic [40]. Unpublished data from a cross-sectional study of Asian American women provide additional support that green tea drinking may influence circulating hormone concentrations. Participants were control subjects in a case-control study of breast cancer in Asian-Americans in Los Angeles County and donated blood specimens at the completion of their in-person interview [41]. The cross-sectional analysis was conducted in a randomly selected group of control women who reported that they reached menopause naturally and were non-users of menopausal hormones at the time of blood donation. Table 2 shows that adjusted geometric mean concentrations of circulating estrone, estradiol, free estradiol, androstenedione, testosterone, and sex hormone-binding globulin (SHBG) did not differ significantly by green tea intake in Asian American women. Although our results suggest that free testosterone concentrations differed significantly by green tea intake; highest among non-green tea drinkers, intermediate among those who drank <1 cup per day, and lowest among those who drank more than a cup of green tea per day (P trend=0.04), this association weakened after further adjustment for parity and body mass index (kg/m^2) ($P=0.17$). Black tea drinking was unrelated to concentrations of sex hormone levels in this group of Asian-American women (data not shown). Unfortunately sample size of this and previous cross-sectional studies on green tea and hormone levels [38, 39] were small. Confirmation of these findings on green tea and effects on estrogen and androgen levels is needed.

3.2 Mammographic density

Mammographic density is a well-established breast cancer risk factor [42, 43]. Substantial evidence shows that mammographic density is influenced by markers of exposure to endogenous hormones and use of exogenous hormones. High mammo-graphic density may

reflect an increased rate of cellular proliferation due to the increased number of epithelial cells [44]. In a spontaneous tumor model [C3]1/SV40 mice model], green tea administration (0.5% Polyphenon E) showed antiproliferative and antiangiogenic effects on both ductal and stromal epithelial cells [45], suggesting that green tea intake may influence breast tissue density.

Wu and colleagues [46] conducted a cross-sectional study among 3,315 Chinese women in Singapore who were participants of two population-based cohort studies, the Singapore Chinese Health Study (SCHS) and the nationwide Singapore Breast Screening Project (SBSP). As part of the SCHS, women ages 45 to 74 years were enrolled during 1993 to 1998 and completed a face-to-face structured interview and provided information on medical and family history, menstrual and reproductive factors, other lifestyle factors including detailed diet history using a validated dietary food frequency questionnaire [47]. Mammograms from SBSP were retrieved and they were assessed for density using a highly reproducible computer-assisted method. In brief, we found that daily green tea drinkers showed statistically significantly lower percent mammographic density (PMD) (19.5%) than non-tea drinkers (21.7%, $P=0.002$) after adjustment for covariates including age at mammography, body mass index, education, menopause status, parity, and total calories. This difference in PMD between daily green tea drinkers and non-tea drinkers remained statistically significant after further adjustment for intake of soy. Although our results suggest that this difference in mammographic density was observed mainly among postmenopausal women (PMD was 20.6% in non-tea drinkers, 18.4% in daily green tea drinkers, $P=0.003$), we had limited ability to study this relationship in premenopausal women since they accounted for only 9% of the participants in our analysis. The effect of tea on mammographic density was specific to green tea, as black tea intake was unrelated to PMD [46].

3.3 Insulin-like growth factors (IGF)

IGF-1 is a peptide which stimulates mitosis and inhibits apoptosis [48]. Around 99% of IGF-1 circulates bound to IGF binding proteins, with most bound to IGF binding protein 3 (IGFBP-3). There is accumulating evidence that pre-diagnostic circulating levels of IGF-1 and IGFBP3 may influence risk of breast cancer development. In a pooled analysis of 17 prospective studies, IGF-1 was significantly positively associated with breast cancer risk in both pre- and postmenopausal women. IGFBP-3 levels were also significantly positively associated with risk in postmenopausal women although this was not observed in premenopausal women [49]. In a study of female SCID mice, serum IGF-1 levels decreased by 19% in association with green tea infusion (1.5 g leaf/100 mL water) suggesting that green tea may inhibit breast tumor growth in part by modulating IGF-1 signaling pathway [50].

Maruyama and coworkers evaluated the relationship between circulating IGF levels and dietary factors in a cross-sectional study of 10,336 (4961 women, 5385 men) participants of the Japan Collaborative Cohort Study (JCCS) [51]. In age-adjusted analyses, IGF-1 levels were associated with the percentage of men and women who reported they were 'high' (5 times or more per week) green tea consumers: 59.3% of men in the lowest quartile of IGF-1 (< 91 ng/mL) compared to 71.2%, 70.5%, and 68.6% in the second, third, and fourth quartiles of IGF-1, respectively (P trend=0.01) were 'high' green tea consumers. A similar pattern

between the percentage of 'high' green tea consumers and IGF-1 level was found in women (P trend=0.04). IGFBP-3 levels were unrelated to the percentage of 'high' green tea consumers in both women and men. In contrast, the percentage of 'high' green tea consumers was lower with increasing IGF-II levels in men (P trend=0.02) and in women (P trend=0.12). Although this cross-sectional study was large and evaluated the relationship between many foods and nutrients and circulating IGF levels, the analyses only adjusted for age and did not consider other potential confounders (e.g., height, weight). Using '5 times or more per week' to define high intake of green tea in a Japanese population may be too crude since over two-thirds of the subjects were classified as 'high' green tea consumers.

Among Asian-American control women in Los Angeles County (Table 2), concentrations of circulating IGF-1 and IGFBP3 were unrelated to green tea intake. IGF-1 levels were 114.5, 112.3, 117.6 (P trend=0.67), respectively among non-green drinkers, green tea drinkers of <1 cup per day, and green tea drinkers of >1 cup per day. The corresponding IGFBP3 levels were 4.1, 4.3, and 4.4 (P trend=0.16). These results were unchanged when we further adjusted for other covariates including parity, and body mass index. Black tea intake was unrelated to IGF-1 and IGFBP3 levels in Asian American women (data not shown). IGF-2 concentrations were not measured in our cross-sectional study.

3.4 Adiponectin levels

Adiponectin is an adipocyte secreted hormone and has been found to predict the development of type 2 diabetes and atherosclerosis [52]. Adiponectin has been found to be an independent risk factor for breast cancer but this is by no means conclusive [53]. Results from the large nested case-control study (1,477 breast cancer cases, 2,196 matched controls) conducted within the Nurses' Health Study reported some risk reduction (OR=0.73, 95% CI=0.55–0.98) comparing postmenopausal women in the highest versus lowest quartile of adiponectin levels [54] but this result was not confirmed in two smaller nested case-control studies [55, 56]. Green tea catechins have been shown to up-regulate adiponectin expression in mouse preadipocytes [57].

Results on adiponectin levels and green tea intake are available in one short-term clinical study [58] and two cross-sectional studies [59, 60]. In a randomized controlled trial of obese men and women with metabolic syndrome, there were no significant differences in adiponectin levels between subjects randomized to green tea beverage (440 mg EGCG) ($n=11$) or green tea extract (460 mg EGCG) ($n=7$) compared to those randomized to no green tea treatment ($n=11$) [58]. However, this study was small and the intervention was relatively short (8 weeks). The association between green tea intake and adiponectin levels was evaluated in a cross-sectional study of 665 male employees in Japan who donated blood specimens at their annual health check-ups. Adiponectin levels did not differ by green tea intake after adjusting for age, smoking, body mass index and other covariates: concentrations were 6.09, 5.82, 5.99, and 6.23 $\mu\text{g/mL}$ (P trend =0.55), respectively, for non-green tea drinkers and drinkers of 1–5 times/week, 1–3 cups/day and 4+ cups/day [59]. In contrast, in a cross-sectional study conducted in Asian American women (see Section 3.1), regular weekly or daily green tea drinkers showed significantly higher adiponectin levels (13.7 $\mu\text{g/mL}$, SD 1.09) than non-green drinkers (11.0 $\mu\text{g/mL}$, SD 1.09) ($P=0.03$). This

difference remained after adjustment for age, Asian ethnicity, parity, body mass index and other covariates [60].

4. Experimental evidence in animal models

Numerous studies have investigated the effects of green tea on mammary cancer using different rodent models and a variety of green tea products including green tea mixtures as well as specific catechins [61] (Table 3). Green tea or EGCG did not have significant effects on tumor incidence or multiplicity in DMBA-induced mammary carcinogenesis when given in the post-initiation stage [62, 63] although there was some suggestion of reduced incidence when green tea (0.01%, 0.1%, and 1% green tea) was given before the carcinogen [63]. Oral administration of green tea using mouse xenograft models has shown beneficial results including delaying mammary tumor onset, reducing the tumor burden, and reducing the number of invasive tumors. [64–68] More recently, Leong and coworkers used the C3(1)/SV40 mouse model to evaluate the chemopreventive effects of green tea; this model is considered more relevant to human breast cancer development.. They found that administration of 0.5% Polyphenon E in drinking water significantly delayed tumor onset and suppressed the development of tumor growth by 40% compared to tap water-fed animals [45]. Green tea was found to significantly slow proliferation and increase ductal regression by inhibiting vascular endothelial growth factor (VEGF) expression in both ductal tumors cells and surrounding stroma cells in this study. No adverse side effects were found [45].

One of the issues of concern is that the doses of green tea or EGCG used in most of the animal studies are many times higher than the typical green tea intake levels in humans (Table 3). Thus, animal model studies that use green tea levels that are consistent with human consumption (doses of 0.05% to 0.3% green tea in animals are equivalent to about 3 to 18 cups of green tea in humans) may be particularly informative. Interestingly, a study that used a low (0.05%) green tea dose in TAg mouse model reported delayed mammary carcinogenesis [65]. In studies of Sprague-Dawley rats, all three doses of green tea (0.01%, 0.1%, or 1%) given before DMB treatment (initiation model) were associated with lower mammary tumor incidence (range was 45–50%) and multiplicity (range was 1.4 to 1.6 tumors/rat) compared to rats treated with DMBA with no green tea (tumor incidence was 60%, multiplicity was 2.6 tumors/rat) [63]. Additional animal studies that are conducted using doses of green tea or EGCG that are compatible with human intake levels will be needed.

5. Catechins and breast cancer treatment

On the basis that EGCG can prevent and inhibit breast tumorigenesis independently of hormone receptor status [19], a promising avenue of research has been conducted to examine the effects of EGCG in combination with tamoxifen and in tumors that have become resistant to tamoxifen. Sartippour and colleagues found that the combination of green tea and tamoxifen was more potent than either agent alone in suppressing breast cancer growth in mice experiments [69]. In addition, EGCG was found to enhance tamoxifen-induced cellular apoptosis in ER α -negative MDA-MB-231 [70]. Studies

conducted by Eddy and coworkers also showed that EGCG inhibited proliferation of trastuzumab-resistant human breast cancer cells and suggested that EGCG may be used in combination with trastuzumab to treat those with HER-2 over expressing breast cancers [71]. More recently, EGCG was found to reactivate ER α expression in ER α -negative MDA-MB-213 breast cancer cells via epigenetic mechanisms. This effect appeared to be enhanced when EGCG was combined with a histone deacetylase (HDAC) inhibitor [72]. Results from these studies show promise that better understanding of the anti-cancer mechanisms associated with EGCG may help to reduce not only the risk of breast cancer development but also reduce mortality by improving the effectiveness of available breast cancer treatment.

6. Conclusions

Evidence from animal models provides convincing risk reduction effects of green tea against mammary tumors. Overall data derived from case-control studies also show a dose-dependent, statistically significant association between green tea intake and breast cancer risk reduction. However, supportive evidence from prospective cohort studies is lacking. Differences in the green tea-breast cancer association by menopausal status (a beneficial effect mainly in premenopausal women) has been suggested in some studies and the predominance of postmenopausal women in cohort studies may have contributed, in part, to the differences in results by study design. Better understanding of the mechanisms by which green tea influences breast cancer risk is needed; this may help to resolve differences in findings by menopausal status which may also explain some of the differences in results between case-control and cohort studies. Additional prospective studies that have information on green tea intake as well as pre-diagnostic circulating tea polyphenol measurements will be needed. These studies will allow sorting out potential differences in green tea bioavailability and/or metabolism between women who develop breast cancer and those who do not as well as potential modifying effects by menopausal status. Several biomarkers (mammographic density, circulating sex hormone, insulin growth factors and adiponectin concentrations) have been evaluated in association with green tea intake in cross-sectional studies. While intriguing findings have been reported in these studies, the evidence is also inconclusive and requiring confirmation in larger studies as well as in controlled clinical trial study designs.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005; 55:74–108. [PubMed: 15761078]
2. Ogunleye AA, Xue F, Michels KB. Green tea consumption and breast cancer risk or recurrence: a meta-analysis. *Breast Cancer Res Treat.* 2010; 119:477–484. [PubMed: 19437116]
3. Seely D, Mills EJ, Wu P, Verma S, Guyatt GH. The effects of green tea consumption on incidence of breast cancer and recurrence of breast cancer: a systematic review and meta-analysis. *Integr Cancer Ther.* 2005; 4:144–155. [PubMed: 15911927]

4. Sun CL, Yuan JM, Koh WP, Yu MC. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. *Carcinogenesis*. 2006; 27:1310–1315. [PubMed: 16311246]
5. Yang CS, Wang X, Lu G, Picinich SC. Cancer prevention by tea: animal studies, molecular mechanisms and human relevance. *Nat Rev Cancer*. 2009; 9:429–439. [PubMed: 19472429]
6. Satoh K, Sakamoto Y, Ogata A, Nagai F, et al. Inhibition of aromatase activity by green tea extract catechins and their endocrinological effects of oral administration in rats. *Food Chem Toxicol*. 2002; 40:925–933. [PubMed: 12065214]
7. Goodin MG, Rosengren RJ. Epigallocatechin gallate modulates CYP450 isoforms in the female Swiss-Webster mouse. *Toxicol Sci*. 2003; 76:262–270. [PubMed: 14600287]
8. Kao YH, Hiipakka RA, Liao S. Modulation of endocrine systems and food intake by green tea epigallocatechin gallate. *Endocrinology*. 2000; 141:980–987. [PubMed: 10698173]
9. Shrubsole MJ, Lu W, Chen Z, Shu XO, et al. Drinking green tea modestly reduces breast cancer risk. *J Nutr*. 2009; 139:310–316. [PubMed: 19074205]
10. Wu AH, Yu MC, Tseng CC, Hankin J, Pike MC. Green tea and risk of breast cancer in Asian Americans. *Int J Cancer*. 2003; 106:574–579. [PubMed: 12845655]
11. Zhang M, Holman CD, Huang JP, Xie X. Green tea and the prevention of breast cancer: a case-control study in Southeast China. *Carcinogenesis*. 2007; 28:1074–1078. [PubMed: 17183063]
12. Wu AH, Yu MC, Tseng CC, Pike MC. Body size, hormone therapy and risk of breast cancer in Asian-American women. *Int J Cancer*. 2007; 120:844–852. [PubMed: 17131315]
13. Iwasaki M, Inoue M, Sasazuki S, Sawada N, et al. Green tea drinking and subsequent risk of breast cancer in a population based cohort of Japanese women. *Breast Cancer Res*. 2010; 12:R88. [PubMed: 22889409]
14. 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; 12:501–508. [PubMed: 11519758]
15. Suzuki Y, Tsubono Y, Nakaya N, Koizumi Y, Tsuji I. Green tea and the risk of breast cancer: pooled analysis of two prospective studies in Japan. *Br J Cancer*. 2004; 90:1361–1363. [PubMed: 15054454]
16. Yuan JM, Koh WP, Sun CL, Lee HP, Yu MC. Green tea intake, ACE gene polymorphism and breast cancer risk among Chinese women in Singapore. *Carcinogenesis*. 2005; 26:1389–1394. [PubMed: 15802301]
17. Inoue M, Robien K, Wang R, Van Den Berg DJ, et al. Green tea intake, MTHFR/TYMS genotype and breast cancer risk: the Singapore Chinese Health Study. *Carcinogenesis*. 2008; 29:1967–1972. [PubMed: 18669903]
18. Dai Q, Shu XO, Li H, Yang G, et al. Is green tea drinking associated with a later onset of breast cancer? *Ann Epidemiol*. 2010; 20:74–81. [PubMed: 20006278]
19. Stuart EC, Scandlyn MJ, Rosengren RJ. Role of epigallocatechin gallate (EGCG) in the treatment of breast and prostate cancer. *Life Sci*. 2006; 79:2329–2336. [PubMed: 16945390]
20. Iwasaki M, Inoue M, Sasazuki S, Miura T, et al. Plasma tea polyphenol levels and subsequent risk of breast cancer among Japanese women: a nested case-control study. *Breast Cancer Res Treat*. 2010; 124:827–834. [PubMed: 20440552]
21. Chow HH, Cai Y, Hakim IA, Crowell JA, et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res*. 2003; 9:3312–3319. [PubMed: 12960117]
22. Lee MJ, Maliakal P, Chen L, Meng X, et al. Pharmacokinetics of tea catechins after ingestion of green tea and (–)-epigallocatechin-3-gallate by humans: formation of different metabolites and individual variability. *Cancer Epidemiol Biomarkers Prev*. 2002; 11:1025–1032. [PubMed: 12376503]
23. Henning SM, Niu Y, Lee NH, Thames GD, et al. Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement. *Am J Clin Nutr*. 2004; 80:1558–1564. [PubMed: 15585768]
24. Luo J, Gao YT, Chow WH, Shu XO, et al. Urinary polyphenols and breast cancer risk: results from the Shanghai Women's Health Study. *Breast Cancer Res Treat*. 2010; 120:693–702. [PubMed: 19653095]

25. Zhu BT, Patel UK, Cai MX, Conney AH. O-Methylation of tea polyphenols catalyzed by human placental cytosolic catechol-O-methyltransferase. *Drug Metab Dispos.* 2000; 28:1024–1030. [PubMed: 10950844]
26. Zhu BT, Patel UK, Cai MX, Lee AJ, Conney AH. Rapid conversion of tea catechins to monomethylated products by rat liver cytosolic catechol-O-methyltransferase. *Xenobiotica.* 2001; 31:879–890. [PubMed: 11780762]
27. Wu AH, Tseng CC, Van Den Berg D, Yu MC. Tea intake, COMT genotype, and breast cancer in Asian-American women. *Cancer Res.* 2003; 63:7526–7529. [PubMed: 14612555]
28. Nakachi K, Suemasu K, Suga K, Takeo T, et al. Influence of drinking green tea on breast cancer malignancy among Japanese patients. *Jpn J Cancer Res.* 1998; 89:254–261. [PubMed: 9600118]
29. Inoue M, Tajima K, Mizutani M, Iwata H, et al. Regular consumption of green tea and the risk of breast cancer recurrence: follow-up study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan. *Cancer Lett.* 2001; 167:175–182. [PubMed: 11369139]
30. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst.* 2002; 94:606–616. [PubMed: 11959894]
31. Key TJ, Appleby PN, Reeves GK, Roddam A, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst.* 2003; 95:1218–1226. [PubMed: 12928347]
32. Hankinson SE, Eliassen AH. Endogenous estrogen, testosterone and progesterone levels in relation to breast cancer risk. *J Steroid Biochem Mol Biol.* 2007; 106:24–30. [PubMed: 17719770]
33. Dorgan JF, Stanczyk FZ, Kahle LL, Brinton LA. Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk. *Breast Cancer Res.* 2010; 12:R98. [PubMed: 21087481]
34. 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; 31:499–504. [PubMed: 18061364]
35. Komori A, Yatsunami J, Okabe S, Abe S, et al. Anticarcinogenic activity of green tea polyphenols. *Jpn J Clin Oncol.* 1993; 23:186–190. [PubMed: 8350491]
36. Ren F, Zhang S, Mitchell SH, Butler R, Young CY. Tea polyphenols down-regulate the expression of the androgen receptor in LNCaP prostate cancer cells. *Oncogene.* 2000; 19:1924–1932. [PubMed: 10773882]
37. Nagai M, Conney AH, Zhu BT. Strong inhibitory effects of common tea catechins and bioflavonoids on the o-methylation of catechol estrogens catalyzed by human liver cytosolic catechol-o-methyltransferase. *Drug Metab Dispos.* 2004; 32:497–504. [PubMed: 15100171]
38. Nagata C, Kabuto M, Shimizu H. Association of coffee, green tea, caffeine intakes with serum concentrations of estradiol and sex hormone-binding globulin in premenopausal Japanese women. *Nutr Cancer.* 1998; 30:21–24. [PubMed: 9507508]
39. Wu AH, Arakawa K, Stanczyk FZ, Van Den Berg D, et al. Tea and circulating estrogen levels in postmenopausal Chinese women in Singapore. *Carcinogenesis.* 2005; 26:976–980. [PubMed: 15661801]
40. Wu AH, Yu MC. Tea, hormone-related cancers and endogenous hormone levels. *Mol Nutr Food Res.* 2006; 50:160–169. [PubMed: 16470648]
41. Wu AH, Yu MC, Tseng CC, Stanczyk FZ, Pike MC. Dietary patterns and breast cancer risk in Asian American women. *Am J Clin Nutr.* 2009; 89:1145–1154. [PubMed: 19211822]
42. Boyd NF, Lockwood GA, Byng JW, Trichler DL, Yaffe MJ. Mammographic densities and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 1998; 7:1133–1144. [PubMed: 9865433]
43. Boyd NF, Rommens JM, Vogt K, Lee V, et al. Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol.* 2005; 6:798–808. [PubMed: 16198986]
44. Hawes D, Downey S, Pearce CL, Bartow S, et al. Dense breast stromal tissue shows greatly increased concentration of breast epithelium but no increase in its proliferative activity. *Breast Cancer Res.* 2006; 8:R24. [PubMed: 16646977]

45. Leong H, Mathur PS, Greene GL. Inhibition of mammary tumorigenesis in the C3(1)/SV40 mouse model by green tea. *Breast Cancer Res Treat.* 2008; 107:359–369. [PubMed: 17484049]
46. Wu AH, Ursin G, Koh WP, Wang R, et al. Green tea, soy, and mammographic density in singapore chinese women. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:3358–3365. [PubMed: 19064551]
47. Hankin JH, Stram DO, Arakawa K, Park S, et al. Singapore Chinese Health Study: development, validation, and calibration of the quantitative food frequency questionnaire. *Nutr Cancer.* 2001; 39:187–195. [PubMed: 11759279]
48. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer.* 2004; 4:505–518. [PubMed: 15229476]
49. Key TJ, Appleby PN, Reeves GK, Roddam AW. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. *Lancet Oncol.* 2010; 11:530–542. [PubMed: 20472501]
50. Zhou JR, Yu L, Mai Z, Blackburn GL. Combined inhibition of estrogen-dependent human breast carcinoma by soy and tea bioactive components in mice. *Int J Cancer.* 2004; 108:8–14. [PubMed: 14618609]
51. Maruyama K, Iso H, Ito Y, Watanabe Y, et al. Associations of food and nutrient intakes with serum IGF-I, IGF-II, IGFBP-3, TGF- β 1, total SOD activity and sFas levels among middle-aged Japanese: the Japan Collaborative Cohort study. *Asian Pac J Cancer Prev.* 2009; 10(Suppl):7–22. [PubMed: 20553076]
52. Swarbrick MM, Havel PJ. Physiological, pharmacological, and nutritional regulation of circulating adiponectin concentrations in humans. *Metab Syndr Relat Disord.* 2008; 6:87–102. [PubMed: 18510434]
53. Barb D, Williams CJ, Neuwirth AK, Mantzoros CS. Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. *Am J Clin Nutr.* 2007; 86:s858–s866. [PubMed: 18265479]
54. Tworoger SS, Eliassen AH, Kelesidis T, Colditz GA, et al. Plasma adiponectin concentrations and risk of incident breast cancer. *J Clin Endocrinol Metab.* 2007; 92:1510–1516. [PubMed: 17213279]
55. Gaudet MM, Falk RT, Gierach GL, Lacey JV Jr, et al. Do adipokines underlie the association between known risk factors and breast cancer among a cohort of United States women? *Cancer Epidemiol.* 2010; 34:580–586. [PubMed: 20579950]
56. Cust AE, Stocks T, Lukanova A, Lundin E, et al. The influence of overweight and insulin resistance on breast cancer risk and tumour stage at diagnosis: a prospective study. *Breast Cancer Res Treat.* 2009; 113:567–576. [PubMed: 18330696]
57. Cho SY, Park PJ, Shin HJ, Kim YK, et al. (–)-Catechin suppresses expression of Kruppel-like factor 7 and increases expression and secretion of adiponectin protein in 3T3-L1 cells. *Am J Physiol Endocrinol Metab.* 2007; 292:E1166–E1172. [PubMed: 17164435]
58. Basu A, Du M, Sanchez K, Leyva MJ, et al. Green tea minimally affects biomarkers of inflammation in obese subjects with metabolic syndrome. *Nutrition.* 2010; 27:206–213. [PubMed: 20605696]
59. Imatoh T, Tanihara S, Miyazaki M, Momose Y, et al. Coffee consumption but not green tea consumption is associated with adiponectin levels in Japanese males. *Eur J Nutr.* (Epub ahead of print).
60. Wu AH, Y M, Stanczyk F, Tseng CC, Pike MC. Anthropometric, dietary and hormonal correlates of serum adiponectin in Asian American women. *Nutrition and Cancer.* (in press).
61. Crespy V, Williamson G. A review of the health effects of green tea catechins in in vivo animal models. *J Nutr.* 2004; 134:3431S–3440S. [PubMed: 15570050]
62. Hirose M, Mizoguchi Y, Yaono M, Tanaka H, et al. Effects of green tea catechins on the progression or late promotion stage of mammary gland carcinogenesis in female Sprague-Dawley rats pretreated with 7,12-dimethylbenz(a)anthracene. *Cancer Lett.* 1997; 112:141–147. [PubMed: 9066720]
63. Tanaka H, Hirose M, Kawabe M, Sano M, et al. Post-initiation inhibitory effects of green tea catechins on 7,12-dimethylbenz(a)anthracene-induced mammary gland carcinogenesis in female Sprague-Dawley rats. *Cancer Lett.* 1997; 116:47–52. [PubMed: 9177457]

64. Baliga MS, Meleth S, Katiyar SK. Growth inhibitory and antimetastatic effect of green tea polyphenols on metastasis-specific mouse mammary carcinoma 4T1 cells in vitro and in vivo systems. *Clin Cancer Res.* 2005; 11:1918–1927. [PubMed: 15756018]
65. Kaur S, Greaves P, Cooke DN, Edwards R, et al. Breast cancer prevention by green tea catechins and black tea theaflavins in the C3(1) SV40 T, t antigen transgenic mouse model is accompanied by increased apoptosis and a decrease in oxidative DNA adducts. *J Agric Food Chem.* 2007; 55:3378–3385. [PubMed: 17407311]
66. Liao S, Umekita Y, Guo J, Kokontis JM, Hiipakka RA. Growth inhibition and regression of human prostate and breast tumors in athymic mice by tea epigallocatechin gallate. *Cancer Lett.* 1995; 96:239–243. [PubMed: 7585463]
67. Sartippour MR, Shao ZM, Heber D, Beatty P, et al. Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells. *J Nutr.* 2002; 132:2307–2311. [PubMed: 12163680]
68. Thangapazham RL, Singh AK, Sharma A, Warren J, et al. Green tea polyphenols and its constituent epigallocatechin gallate inhibits proliferation of human breast cancer cells in vitro and in vivo. *Cancer Lett.* 2007; 245:232–241. [PubMed: 16519995]
69. Sartippour MR, Pietras R, Marquez-Garban DC, Chen HW, et al. The combination of green tea and tamoxifen is effective against breast cancer. *Carcinogenesis.* 2006; 27:2424–2433. [PubMed: 16785249]
70. Chisholm K, Bray BJ, Rosengren RJ. Tamoxifen and epigallocatechin gallate are synergistically cytotoxic to MDA-MB-231 human breast cancer cells. *Anticancer Drugs.* 2004; 15:889–897. [PubMed: 15457130]
71. Eddy SF, Kane SE, Sonenshein GE. Trastuzumab-resistant HER2-driven breast cancer cells are sensitive to epigallocatechin-3 gallate. *Cancer Res.* 2007; 67:9018–9023. [PubMed: 17909003]
72. Li Y, Yuan YY, Meeran SM, Tollefsbol TO. Synergistic epigenetic reactivation of estrogen receptor-alpha (ERalpha) by combined green tea polyphenol and histone deacetylase inhibitor in ERalpha-negative breast cancer cells. *Mol Cancer.* 2010; 9:274. [PubMed: 20946668]
73. Bhide SV, Azuine MA, Lahiri M, Telang NT. Chemoprevention of mammary tumor virus-induced and chemical carcinogen-induced rodent mammary tumors by natural plant products. *Breast Cancer Res Treat.* 1994; 30:233–242. [PubMed: 7526904]
74. Kavanagh KT, Hafer LJ, Kim DW, Mann KK, et al. Green tea extracts decrease carcinogen-induced mammary tumor burden in rats and rate of breast cancer cell proliferation in culture. *J Cell Biochem.* 2001; 82:387–398. [PubMed: 11500915]

Table 1

Characteristics of epidemiologic studies on green tea and breast cancer

Study		# cases/ controls	# levels	Lowest/Highest exposure	Percent in lowest vs highest exposure	RR (95% CI)
Case-control studies (5,602 cases, 5,483 controls) Combined OR = 0.70 (95% CI=0.61–0.79)						
Wu [10, 12]	Los Angeles	1277/1160	4	Not regularly vs >240 ml/day	43% vs 12%	0.60 (0.44–0.81)
Zhang [11]	Zhejiang, China	954/943	5	Never or seldom vs 2+/day	37% vs 35%	0.57 (0.47–0.69)
Shrubsole [9]	Shanghai China	3371/3380	5	Never regular vs regular for 23 years	68% vs 8%	0.86 (0.71–1.01)
Cohort or nested case-control studies (n=2,067 cases): Combined OR =1.06 (95% CI=0.93–1.20)						
Nagano [14]	Hiroshima Japan	270	3	0–1 times/day vs 5+ times/day	14% vs 27%	1.0 (0.67–1.6)
Suzuki [15]	Japan	222	5	<1 cup/day vs 5+ cups/day	24% vs 34%	0.87 (0.59–1.28)
Inoue [17]	Singapore	380/662	3	None or < weekly vs Daily	71% vs 12%	1.00 (0.82–1.22)
Dai [18]	Shanghai, China	614	5	Not regular vs regularly for 23 year	70% vs 8%	1.25 (0.96–1.62)
Iwasaki [13]	Japan	581	5	<1 cup/week vs 5+ cup/day	12% vs 27%	1.12 (0.81–1.56)

Adjusted geometric mean concentration of circulating biomarkers by green tea intake and in Asian American control women in Los Angeles County

Table 2

		Green tea				P trend
		0	<=120 ml/day (<1 cup/d)		>120 ml/day (>1 cup/d)	
		N=98	N=53	N=68		
Estrone (pg/mL)	Model 1 ^a	35.3	39.1	36.3	0.76	
	Model 2 ^b	34.9	39.1	36.5	0.65	
Estradiol (pg/mL)	Model 1	10.6	11.2	10.7	0.89	
	Model 2	10.4	11.0	10.7	0.74	
Free estradiol (pg/mL)	Model 1	0.32	0.32	0.30	0.58	
	Model 2	0.31	0.31	0.30	0.81	
Testosterone (ng/dL)	Model 1	19.1	19.6	17.4	0.32	
	Model 2	18.3	18.7	17.2	0.50	
Free testosterone (pg/mL)	Model 1	4.4	4.1	3.4	0.04	
	Model 2	4.0	3.7	3.4	0.17	
Androstenedione (pg/mL)	Model 1	472.2	532.9	479.4	0.85	
	Model 2	451.1	515.4	472.9	0.57	
Sex hormone-binding globulin (nmol/L)	Model 1	42.2	42.8	43.5	0.77	
	Model 2	44.2	45.1	42.9	0.78	
IGF-1 (ng/mL)	Model 1	114.5	112.3	117.6	0.67	
	Model 2	111.8	111.0	116.0	0.52	
IGFBP3 (µg/mL)	Model 1	4.1	4.3	4.4	0.16	
	Model 2	4.1	4.3	4.4	0.09	

^aModel 1: All values are adjusted least square means- model adjusted for age, Asian ethnicity, birthplace, and age at menopause

^bModel 2: As in model 1 and additionally adjusted for number of births and body mass index.

Table 3

Studies on green tea catechins on mammary tumors in animal models

Study	Green tea dose/ ^a Timing of GT	Species, N/group	Incidence /latency	Effect on tumor (T) incidence (INC), size and other factors- green tea compared to control ^a	Other
Blide 1994 [73]	Catechin 2.5 mg/day/5ml water- start at age 8 months	C3H(Dax) mice	↓INC	Size/burden Weight/ Volume	NA
Liao 1995 [66]	1 mg EGCG in 0.1 water; intraperitoneal injection	BALB/c nude mice (female), 3–4/group	NA	↓size	NA
Hirose 1997 [62]	0.5% PPE, 0.5% EGCG-80; started 13 wks after DMBA (50 mg/kg) at 7 wks	Sprague-Dawley rat (female)28/group	Not different	Not different	NA
Tanaka 1997 [63]	Initiation model: GTE (1, 0.1, 0.01%) at 6 wks for 2wks; DMBA 1 wk after GTE started Post-initiation model: DMBA 1 wk, GTE (1, 0.1, 0.01%)	Sprague-Dawley rat (female) 20/group	↓INC&multiplicity in initiation model	Not different	NA
Kavanagh 2001 [74]	0.3% GT at ~wk 4 of age; DMBA (15 mg/kg) at wk 8 of age	Sprague-Dawley rat (female) 15/group	↓INC ↑latency	↓weight	NA
Sartippour 2001 [67]	Pharmanex GTX (47% EGCG, 14% ECG)	SCID mice (female) 12/group	NA	↓volume	↓proliferation ↓tumor vessel density
Zhou 2004 [50]	GT (1.5%) 2 wks then 17β- estradiol (0.72 mg, 90-day release) implant	SCID mice (female) 12/group	NA	↓weight	↓proliferation ↑apoptosis ↓tumor vessel density
Baliga 2005 [64]	GT (0.2%, 0.5% w/v)-started 7 days before tumor cells inoculation	BALB/c mice (female) 10/group	NA	↓volume	↓proliferation ↑apoptosis ↓Bcl-2 expression
Thangapazham 2007 [68]	GT (1% in water) EGCG (1 mg/ mouse oral gavage)	Athymic nude mice MDA-MB-231	↑latency	↓burden	↓proliferation ↑apoptosis NA
Kaur 2007 [65]	GT (0.01%, 0.05%), from 4 weeks of age	C3 (1) SV40 mouse 10 per group	↑survival	↓size	↑apoptosis NA
Leong 2008 [45]	0.1%, 0.3%, or 0.5% PPE in water (~65% EGCG, 10% EC, 5% EGC, 5% ECG)	C3 (1)/SV40 mouse 20 per group	↑latency	↓volume	↓proliferation ↓angiogenesis

^a GT =green tea, GTE (GTC)=green tea extract, PPE= Polyphenon E, DMBA=7, 12-dimethylbenz[a] anthracene; SCID= severe combined immune deficient, NA= not available