REVIEW

Green tea and breast cancer

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The identification of modifiable lifestyle factors that could reduce the risk of breast cancer is a research priority. Despite the enormous chemopreventive 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 remain 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 observational studies and areas of further investigations are discussed.

Keywords:
Breast cancer / Circulating hormone levels / Green tea / Insulin-like growth factor / Mammographic density

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 sixfold variation in incidence between high-risk regions (e.g. Europe and North America) and low-risk regions (e.g. Asia) [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 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 chemopreventive 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 (IGF), 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.

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Abbreviations: ***COMT,*** catechol-*O*-methyltransferase; **DMBA,** 7,12-dimethylbenz[a] anthracene; **EC,** epicatechin; **ECG,** epicatechin gallate; **EGC,** epigallocatechin; **EGCG,** epigallocatechin gallate; **ERα⁻,** estrogen receptor alpha negative; **IGF,** insulin-like growth factor; **IGFBP,** IGF-binding protein; **JPHCPS,** Japan Public Health Center-based Prospective Study; **OR,** odds ratio; **PMD,** percent mammographic density

2 Epidemiologic evidence for green tea and breast cancer risk

Since the early 2000s, 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 5604 cases and 5487 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, information was obtained on amount of intake, age started, as well as years of green tea intake [18]. These prospective cohort studies totaling 2067 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).

In vitro studies show cytotoxic effects of EGCG toward breast cancer cells regardless of estrogen receptor status [19]. Few of the epidemiologic studies have investigated the relationship between green tea and breast cancer risk by hormone receptor status. In the cohort study by Iwasaki et al., 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 among cases 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

Table 1. Characteristics of epidemiologic studies on green tea and breast cancer

Study		# Cases/ controls	# Levels	Lowest versus (vs) highest exposure	Percent in lowest versus highest exposure (non cases)	RR (95% CI)
Case-control studies (5604 cases, 5487 controls): combined OR = 0.70 (95% CI = 0.61–0.79)						
Wu [10, 12]	Los Angeles	1280/1164	4	Not regularly vs 240 mL/day	43% vs 12%	0.60 (0.44–0.81)
Zhang [11]	Zhejiang, China	953/943	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 (2067 cases): combined OR = 1.06 (95% CI = 0.93–1.20)						
Nagano [14]	Hiroshima Japan	270	3	0 to 1 times/day vs 5+times/day	15% 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	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 years	70% vs 8%	1.25 (0.96–1.62)
Iwasaki [13]	Japan	581	6	<1 cup/week vs 5+cups/day	12% vs 27%	1.12 (0.81–1.56)

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) or 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]. For example, a very small percentage of participants in JPHCPS had detectable plasma levels of the four polyphenols despite the fact that 75% of cohort participants reported they despite the fact that daily green tea drinkers and 54% drank at least three or more cups of green tea daily [13].

In Shanghai Women's Health Study, 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)-γ-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. The incorporation of biomarkers of green tea intake 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. It is hypothesized that 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 nondrinkers 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 modify 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 five or more cups per day versus four or fewer cups daily [28]. In the second study the comparison was between those who consumed three or more cups per day versus those who consumed zero to two cups per day [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 and breast cancer risk or established breast cancer-related endpoints such as endogenous hormone levels or mammographic density. However, 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, IGF and adiponectin have been investigated as biomarkers of breast cancer risk. If an association between these individual biomarkers and green tea intake is in the direction similar to the relationship between these biomarkers and breast cancer risk, this would strengthen the evidence for green tea as a chemopreventive agent for

breast cancer and provide 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 population-based 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 nonusers 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 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 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

Table 2. Adjusted geometric mean concentration of circulating biomarkers by green tea intake and in Asian American control women in Los Angeles County

		Green tea			
		None $n = 98$	≤ 120 mL/day ($\sim <1$ cup/day) $N = 53$	>120 mL/day (>1 cup/day) $N = 68$	P Trend
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

a) Model 1: All values are adjusted least square means; model adjusted for age, Asian ethnicity, birthplace, and age at menopause.
b) Model 2: As in model 1 and additionally adjusted for number of births and body mass index.

to endogenous hormones and use of exogenous hormones. High mammographic 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 et al. [46] conducted a cross-sectional study among 3315 Chinese women in Singapore who were participants of two population-based cohort studies, the Singapore Chinese Health Study and the nationwide Singapore Breast Screening Project. As part of the Singapore Chinese Health Study, women aged 45–74 years were enrolled during 1993–1998 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 Singapore Breast Screening Project 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 energy intake. This difference in PMD between daily green tea drinkers and non-tea drinkers remained statistically significant after further adjustment for intake of soy. 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, $P = 0.003$). However, 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 IGFs

IGF-1 is a peptide that stimulates mitosis and inhibits apoptosis [48]. Around 99% of IGF-1 circulates bound to IGF-binding proteins (IGFBPs), with most bound to IGFBP-3. There is accumulating evidence that pre-diagnostic circulating levels of IGF-1 and IGFBP-3 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 pre-menopausal women [49]. There are a few studies on green tea and circulating IGF levels. In a study of female severe combined immune deficient 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 et al. evaluated the relationship between circulating IGF levels and dietary factors in a cross-sectional study of participants (4961 women, 5385 men) of the Japan Collaborative Cohort Study [51]. In age-adjusted analyses, IGF-1 levels were associated with the percentage of men who reported they were ''high'' (five times or more per week) green tea consumers: 59.3% of men in the lowest quartile of IGF-1 ($\leq$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). 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-2 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 ''five 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 IGFBP-3 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 IGFBP-3 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 IGFBP-3 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 (1477 breast cancer cases, 2196 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 in humans are available in one short-term intervention study [58] and two cross-sectional studies [59, 60]. In the 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 wk). 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 checkups. 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 μg/mL (P trend = 0.55), respectively, for non-green tea drinkers and drinkers of one to five times/week, one to three cups/day and four+ 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 μg/mL, SD 1.09) than non-green drinkers (11.0 μg/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 (Table 3) [61]. Green tea or EGCG did not have significant effects on tumor incidence or multiplicity in 7,12-dimethylbenz[a] anthracene (DMBA)-induced mammary carcinogenesis when given in the post-initiation stage [62, 63] although there was some suggestion of reduced incidence when green tea at various levels (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 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 0.05–0.3% green tea in animals are equivalent to about three 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 DMBA treatment (initiation model) were associated with lower mammary tumor incidence (range was 45–50%) and reduced multiplicity (range was 1.4 to 1.6 tumors/rat) compared to DMBA treated rats 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 estrogen receptor alpha negative ($ER\alpha^-$) MDA-MB-231 [70]. Studies conducted by Eddy et al. 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 overexpressing breast cancers [71]. More recently, EGCG was found to reactivate ERα expression in $ER\alpha^-$ MDA-MB-213 breast cancer cells via epigenetic mechanisms. This effect appeared to be enhanced when EGCG was combined with a histone deacetylase inhibitor [72]. Results from these studies show promise that better understanding of the anti-cancer mechanisms associated with EGCG may not only help to reduce the risk of breast cancer development but also reduce mortality by improving the effectiveness of available breast cancer treatment.

6 Concluding remarks

Animal models provide convincing evidence of risk reduction effects of green tea against mammary carcinogenesis. Overall data derived from case-control studies

Table 3. Studies on green tea catechins on mammary tumors in animal models

Study	Green tea dose/day[a] Timing of GT	Species, N/group	Effect on tumor (T) incidence (INC), size, and other factors- green tea compared to control[a]			
			Incidence/ latency	Size/burden weight/volume	Proliferation/ apoptosis	Other
Bhide [73]	Catechin 2.5 mg/day/5 mL water- start at age 8 months	C3H(Jax) mice 20/group	↓ INC	↓ Burden	NA	NA
Liao [66]	1 mg EGCG in 0.1 mL water; intraperitoneal injection	BALB/c nude mice (female), three to four/group	NA	↓ Size	NA	NA
Hirose [62]	0.5% PPE, 0.5% EGCG-80; started 13 wk after DMBA (50 mg/kg) at age 7 wk	Sprague-Dawley rat (female) 28/ group	Not different	Not different	NA	NA
Tanaka [63]	Initiation model: GTE (1, 0.1, 0.01%) at age 6 wk for 2 wk; DMBA 1 wk after GTE started. Post-initiation model: at age 7 wk given DMBA, 1 wk later given GTE (1, 0.1, 0.01%)	Sprague-Dawley rat (female) 20/ group	↓ INC and Multiplicity in initiation model	Not different	NA	NA
Kavanagh [74]	0.3% GT at age wk 4; DMBA (15 mg/kg) at age 8 wk	Sprague-Dawley rat (female) 15/ group	↑latency	↓ Weight	NA	NA
Sartippour [67]	Pharmanex GTX (47% EGCG, 14% ECG)	SCID mice (female) 12/group	NA	↓ Volume	↓ Proliferation	↓ Tumor vessel density
Zhou [50]	GT (1.5%) 2 wk then 17β-estradiol (0.72 mg, 90-day release) implant	SCID mice (female) 12/group	NA	↓ Weight	↓ Proliferation ↑ apoptosis	↓ Tumor vessel density
Baliga [64]	GT (0.2%, 0.5% w/v)- started 7 days before tumor cells inoculation	BALB/c mice (female) ten/group	NA	↓ Volume	↓ Proliferation ↑ apoptosis	↓ Bcl-2 expression
Thangapazham [68]	GT (1% in water) EGCG (1 mg/0.1mL mouse oral gavage)	Athymic nude mice MDA-MB-231	↑Latency ↓INC	↓ Burden	↓ Proliferation ↑ apoptosis	NA
Kaur [65][b]	GTC (0.01%. 0.05%), from 4 wk of age	C3(1) SV40 mouse ten per group	↑Survival	↓ Size	↑ Apoptosis	NA
Leong [45][c]	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; SCID, severe combined immune deficient; NA, not available.
b) ↑survival only for 0.05% GTC group.
c) ↑latency only for 0.5% PPE group.

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. A better understanding of the mechanisms by which green tea influences breast cancer risk is needed; this may help to resolve 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, and levels of circulating sex hormone, insulin growth factors, and adiponectin) have been evaluated in association with green tea intake in primarily 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 randomized clinical trial study designs.

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