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Review

Tea, hormone-related cancers and endogenous hormone levels

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Tea is one of the most popular beverages consumed around the world, second only to water. There has been substantial interest in the potential role of tea in cancer prevention, particularly in respiratory and gastrointestinal tract cancers. Recent epidemiological data have linked tea intake to reduced risk of hormone-related cancers, including breast, ovarian and prostate cancers. Based on sparse data, there is suggestion that tea intake may influence circulating hormone levels, providing a plausible mechanism whereby tea intake may influence risk of hormone-related cancers. The major objectives of this paper are to review the epidemiological evidence on tea and risk of breast, ovarian, and prostate cancers as well as the human and non-human studies on tea and circulating hormone levels. We pay special attention to some of the limitations of the human studies and discuss future research needs.

Keywords: Cancer / Hormone / Hormone-related cancer / Polyphenols / Tea

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1 Introduction

Tea is derived from the leaf of the plant *Camellia sinensis*. Approximately 20% of the world's tea is consumed as green tea, which is popular in Japan and parts of China, whereas 78% of tea is consumed as black tea, which is the main tea beverage in the US, UK and Europe. The remaining 2% of tea production is oolong tea, which is consumed mainly in Southern China and Taiwan. Leaves meant for green tea are picked by the same method as those picked for black tea. In the processing of green tea, fresh tea leaves are steamed or heated immediately after harvest, resulting in minimal oxidation of the naturally occurring polyphenols in the tea leaves. In the processing of black tea, the tea leaves are dried and crushed upon harvesting to encourage oxidation, which converts the indigenous tea polyphenols (primarily catechins and gallocatechins) to other polyphenols (mainly theaflavins and thearubigens). An intermediate stage of enzymatic oxidation yields oolong tea [1 – 4].

There has been substantial interest in the potential role of tea in cancer protection, particularly cancers of the lung, stomach, and colorectum. In addition, recent epidemiological data have linked tea intake to reduced risk of hormone-related cancers, including breast, ovarian, and prostate cancers [5 – 7]. Tea is the major source of flavonoids in Western populations. Some flavonoids have been found to exhibit steroid hormone activities, although tea catechins were not specifically tested in this study [8]. Thus, tea intake may influence risk of hormone-related cancers via hormonal mediated pathways including the lowering of circulating estrogen, and through the modulation of enzymes that play important roles in the biosynthesis and metabolism of estrogen [9 – 14]. The first part of this report presents a brief update of the epidemiological evidence on tea and risk of hormone-related cancers, highlighting some of the limitations of the existing data. The specific studies are not discussed because they have been described in prior reviews and meta-analysis [15 – 17]. The second part of the report reviews in detail the human and non-human studies evaluating the hormonal effects of tea.

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Abbreviations: CI, confidence interval; **EGCG**, epigallocatechin gallate; **FSH**, follicular stimulating hormone; **LH**, luteinizing hormone; **OR**, odds ratio; **SHBG**, sex hormone binding globulin

2 Epidemiological evidence on tea and risk of hormone-related cancers

2.1 General remarks

The vast majority of published studies on tea and hormone-related cancers were conducted in Western populations who consumed mainly black tea. In this report, we assume that results on tea are specific to black tea if the studies were conducted in Western populations. In contrast, in studies conducted in Asian populations, results were usually presented for green tea and black tea separately. However, in Japan and some parts of coastal China (*e.g.* Shanghai, Hangzhou), black tea intake is rare among tea drinkers (*i.e.* consumed by less than 5% of study subjects) [7, 18]. Thus, one needs to be cautious in the interpretation of study results on black tea and cancer risk/circulating hormone levels in these populations. There are relatively few populations who consume considerable amounts of both black and green tea; Asian American in Los Angeles County is such a population [6]. It should be noted that to date, published cohort and case-control studies on tea generally were not designed primarily to examine the relationship between tea intake and cancer risk, thus, assessment of intake frequency and amount was often relatively crude, and most of the time, duration of regular intake was not asked. Additionally, the published studies were quite varied in terms of the covariates that were adjusted for in the analyses (Tables 1 and 2).

2.2 Breast cancer

Since the mid-1980s, the association between black tea intake and breast cancer risk has been investigated in at least 16 studies [6, 18–32]; all but three [6, 18, 22] of these studies were conducted in Western populations. In a meta-analysis that included 13 of these studies, Sun *et al.* [17] found that the association between black tea and breast cancer risk differed between cohort and case-control studies (results from two case-control studies [31, 32] were not included because they were subsequently presented in another study [29] and the study by Adebamowo *et al.* [19] was published after the journal review of the Sun *et al.* report was completed). Specifically, black tea intake was positively associated with breast cancer risk in five cohort studies (summary odds ratio (OR) = 1.15, 95% confidence interval (CI) = 1.02–1.31) but was inversely associated with risk in eight case-control studies (summary OR = 0.91, 95%, CI = 0.84–0.98) [17]. Inclusion of the new results from the Nurses Health Study II [19] did not materially alter the summary OR from the meta-analysis (revised summary OR = 1.12, 95% CI = 1.01–1.25 for the six cohort studies). The potential etiologic implications from the inconsistent findings on black tea and breast cancer between the cohort and case-control studies are unclear at this time. However, the black tea and breast cancer finding in the cohort studies are supported by results from cross-sectional studies in which black tea intake is associated with higher circulating levels of estrogen [13] and prolactin [33] (see Section 3.1).

Only four studies, three cohort studies from Japan [18, 22] (two cohort study results were reported in one paper) and a population-based case-control study we conducted in Los Angeles [6] have investigated the relationship between green tea intake and breast cancer risk. In the same meta-analysis, Sun *et al.* [17] found that breast cancer risk was significantly reduced (OR = 0.77, 95% CI = 0.61–0.97) in association with green tea intake but the risk reduction was weaker in the cohort studies (OR = 0.84, 95% CI = 0.65–1.09). A reduced risk of breast cancer recurrence among incident breast cancer cases also has been linked to green tea [34–36].

2.3 Ovarian cancer

There is currently little evidence that tea intake is associated with risk of ovarian cancer (Table 1). The association between black tea intake and risk of ovarian cancer has been investigated in US Caucasians [30, 37–39], Italians [31, 40] and Australians [41]. Black tea intake was unrelated to risk in these Western populations (Table 1). On the other hand, the study conducted in Hangzhou, a primarily green tea drinking population, suggested an inverse relationship between green tea drinking and ovarian cancer risk [7]. In this hospital-based study, the risk of ovarian cancer was significantly reduced with overall tea intake at a weekly or more frequent basis. Consumption higher than the once a week level did not confer further reduction in risk for ovarian cancer (Table 1). Zhang *et al.* [7] interpreted their results to show risk reduction associated with intake of green tea as well as with black or oolong tea. However, due to the very low intake of black or oolong tea in this population (2.8% of cases and 6.0% of controls drank black tea or oolong tea at least weekly), we believe the results are meaningful only for green tea intake. Zhang and colleagues [42, 43] also reported that green tea intake favorably enhanced survival in a small cohort of around 300 patients with epithelial ovarian cancer in Hangzhou, China.

2.4 Prostate cancer

Epidemiological data on tea intake in relation to prostate cancer risk are mixed (Table 2). Most but not all studies conducted in Western populations found no significant association between black tea and prostate cancer risk. The null-finding studies included three cohort studies conducted in the UK [7, 44] and Canada [45], and three case-control studies conducted in the US [46], Canada [47], and

Table 1. Studies on tea and risk of ovarian cancer

Study/Location	Sample size[a)]	Tea intake	Relative risk/ 95% CI	Tea intake in controls	Covariates adjustment[b)]
Byers [39]	274 ca	None	1.00	14%	1
USA	1034 hco	1 – 2 cups/day	1.11	73%	
		3+ cups/day	0.84	13%	
			P trend > 0.1		
Miller [38]	290 ca	None	1.0[c)]	58%	1 – 9 & others
USA	376 cancer co	1 – 2 cups/day	0.7 (0.5 – 1.0)	28%	
	480 non-cancer co	3 – 4	1.1 (0.6 – 2.1)	8%	
		5+	0.7 (0.3 – 1.6)	5%	
		None	1.0[d)]	54%	
		1 – 2 cups/day	0.8 (0.6 – 1.2)	26%	
		3 – 4	0.8 (0.5 – 1.4)	12%	
		5+	0.5 (0.2 – 1.0)	6%	
La Vecchia [31]	742 ca	None	1.0	83%	1 – 5
Italy	6147 hco[e)]	≥ 1 cup/day	1.2 (1.0 – 1.4)	17%	
Kuper [37]	563 ca	Rarely	1.0	62%	1, 2
USA	523 pco	≥ weekly	1.1 (0.8 – 1.4)	38%	
Tavani [40]	1031 ca	Never	1.0	49%	1 – 3, 5 – 8, 10 & others
Italy	2411 hco	= 1 cup./mo	0.9 (0.8 – 1.1)	51%	
Zhang [7]	254 ca	All teas			
China	652 hco[f)]	Never/seldom	1.0	25%	1 – 9 & others
		Once/week	0.44 (0.3 – 0.7)	16%	
		2 – 6 times/week	0.37 (0.2 – 0.6)	16%	
		Once/day	0.39 (0.3 – 0.6)	43%	
			P trend < 0.01		
		Green tea only			
		Never/seldom	1.0[g)]	29%	
		Once/week	0.42 (0.3 – 0.7)	13%	
		2 – 6 times/week	0.40 (0.2 – 0.7)	15%	
		Once/day	0.43 (0.3 – 0.6)	43%	
			P trend < 0.01		
Jordan [41]	696 ca	0 cups/day	1.0	14%	1, 3, 5 – 10
Australia	786 pco	< 1	1.3 (0.9 – 1.9)	16%	
		1	1.1 (0.7 – 1.7)	14%	
		2 – 3	1.4 (1.0 – 2.0)	32%	
		4+	1.1 (0.8 – 1.6)	24%	
			P trend = 0.53		
Zheng [30]	107 ca[h)]	Never/monthly	1.0	58%	1, 3, 4, 6, 8 & others
USA		Weekly	0.5 (0.3 – 0.9)	24%	
		1 cup/day	1.0 (0.5 – 1.8)	9%	
		≥2 cups/day	1.0 (0.5 – 1.9)	9%	
			P trend = 0.64		

a) Sample size: ca = cases, hco = hospital controls, pco = population/community controls.
b) Covariates adjusted for included: (1) age, (2) area/center, (3) education, (4) smoking, (5) coffee, (6) body size, (7) oral contraceptives, (8) parity, (9) alcohol, (10) energy.
c) Cancer controls were used.
d) Non-cancer controls were used; tea intake was unknown in 2% of controls.
e) Controls included 3625 women and 2522 men. The distribution of tea intake was presented for men and women combined (*i.e.* 6147 controls).
f) Controls included 340 hospital visitors, 261 non-cancer hospital outpatients, and 51 from the community.
g) The 'all tea results' were based on 252 cases and 652 controls. The 'green tea results' were based on 237 cases and 569 controls who were green tea drinkers only.
h) From a prospective cohort study.

Table 2. Studies on tea and risk of prostate cancer

Study/Location	Sample size[a)]	Tea intake	Relative risk/ 95% CI	Tea intake in controls/cohort	Covariates adjustment[b)]
Heilbrun [50]	147 ca	Almost never	1.0	51%	1
Japanese in	7833 men	<2/week	0.8	26%	
Hawaii		2–4/week	0.4	8%	
		daily	0.6	15%	
			P trend = 0.02		
Kinlen[c)] [44]	185 ca	0–3 cups/day	0.60	16%	1
United	14 085 men	4–6 cups/day	0.81	45%	
Kingdom		7–9 cups/day	1.00	29%	
		10+ cups/day	0.82	11%	
			P trend = 0.30		
Ellison [45]	145 ca	0 mL/day	1.0	19%	1, 6, 7
Canada	3400 men	>0–250	1.22 (0.7–2.1)	23%	
		>250–500	1.27 (0.8–2.2)	19%	
		>500–750	1.00 (0.6–1.7)	21%	
		>750	1.03 (0.6–1.8)	18%	
La Vecchia [31]	107 ca	None	1.0	83%	1–6
Italy	6147 hco[d)]	≥1 cup/day	0.9 (0.5–1.7)	17%	
Slattery [46]	362 ca	<= 67 years			None[e)]
Utah, USA	685 pco	0 cups/week	1.00	63%	
		1–5 cups/week	0.75 (0.5–1.2)	17%	
		>5 cups/week	1.06 (0.7–1.6)	20%	
			P trend = 0.94		
		>67 years			
		0 cups/week	1.0	69%	
		1–5 cups/week	0.90 (0.5–1.8)	9%	
		>5 cups/week	o.90 (0.6–1.4)	22%	
			P trend = 0.57		
Jain [49]	617 ca	0 g/day	1.00	26%	1, 8
Canada	637 pco	>0–500	0.89 (0.7–1.2)	54%	
			0.70 (0.5–0.99)	20%	
			P trend = 0.05		
Villeneuve [47]	1623 ca	None	1.0	24%	1, 4, 5, 6 &
Canada	1623 pco	Up to 1cup/day	1.0 (0.8–1.2)	39%	others
		1– <4 cups/day	1.2 (0.9–1.5)	25%	
		4+ cups/day	1.1 (0.8–1.5)	12%	
			P trend = 0.11		
Sharpe [48]	399 ca	<weekly	1.0	32%	1, 3, 4, 6, 7,
Canada	476 pco	Weekly	1.6 (1.0–2.5)	14%	9, 10
		Daily	1.8 (1.3–2.6)	54%	
			P trend = <0.05		
Jian [5]	130 ca	<1 cup/day	1.00	28%	1, 3, 4, 7
Hangzhou,	274 hco	1–3	0.53 (0.3–0.9)	29%	
China		>3	0.27 (0.2–0.5)	43%	
			P trend <0.01		

a) Sample size: ca = cases, hco = hospital controls, pco = population/community controls.
b) Covariates adjusted for included: (1) age, (2) area/center, (3) education/income, (4) smoking, (5) coffee, (6) body size, (7) alcohol, (8) energy, (9) race/ethnicity, (10) respondent status.
c) Observed to expected ratios of deaths by categories of tea intake are shown.
d) Controls included 3625 women and 2522 men. The distribution of tea intake was presented for men and women combined (*i. e.* 6.147 controls).
e) Crude ORs were presented because adjustment for other factors did not change the results.

Northern Italy [31]. One case-control study conducted in Montreal, Canada, reported a statistically significant positive association between tea intake and prostate cancer risk [48] while a statistically significant inverse association between tea intake and risk of prostate cancer was reported in another Canadian study that was conducted in British Columbia, Ontario and Quebec [49]. Two studies conducted among Asian men [5, 50] reported statistically significant reduction in prostate cancer risk with increasing tea intake. Residents of Hangzhou, China, is a primarily green tea drinking population (see Section 2.3 above), thus the findings of Jain *et al.* [5] mainly pertain to green tea drinking in relation to prostate cancer risk. In the cohort study of Japanese men in Hawaii [50], the authors only reported on the relationship between black tea intake and prostate cancer risk (Table 2).

2.5 Summary

There is compelling evidence from experimental rodent models that green tea catechins fed in the diet are associated with a reduction in mammary tumor incidence among carcinogen challenged animals [51 – 53]. However, the effects of black tea on mammary tumor incidence in experimental rodent models are less consistent. Although black tea extract appeared to lower mammary tumor incidence in dimethylbenzoic acid-treated rats, this was only observed when rats were also fed a high-fat diet and not a regular diet [54]. In another study, the beneficial effects of black tea (1.5%) on mammary tumor incidence in rodent models are weaker and less consistent than the effects related to green tea (1.5%) [53]. Since 1.5% green tea contains 13 times more tea catechin than 1.5% black tea, the weaker effects of black tea may be related to the lower amounts of tea catechin [53]. Additional studies, particularly in relation to the effects of black and green tea on blood circulating estrogens may help to clarify the black tea- and green tea-breast cancer associations (see Section 3.1). In support of some of the human data, there is compelling evidence in experimental rodent models that both green tea and black tea reduce prostate tumor burden in carcinogen-treated animals [55 – 57]. We are not aware of experimental rodent models of tea intake and risk of ovarian cancers. However, epigallocatechin gallate (EGCG), a major constituent of green tea, showed growth inhibitory effects in three different ovarian cancer cell lines [58].

As reviewed above, epidemiological studies show that breast cancer risk is unlikely to be influenced by black tea intake but that risk may be reduced in association with green tea intake, based on results from one case-control study and three cohort studies. The overall evidence suggests no association between black tea intake and risk of ovarian cancer. A single study reported an inverse association between green tea intake and risk of ovarian cancer; confirmation of these results is needed. Although not entirely consistent, the overall data suggest no significant association between black tea drinking and prostate cancer risk. A single case-control study in China provides limited evidence of a protective effect of green tea on prostate cancer development. Epidemiological studies published to date generally were relatively crude in their assessment of tea intake, and few of them collected information on duration or other relevant parameters of exposure. Furthermore, adjustment of potential confounders, both dietary and non-dietary, was not performed in some of the published studies (Tables 1 and 2) and among those, which did, it was not uniformly executed across the studies, which may partly explain the discrepancies across the studies.

3 Tea and endogenous hormones

3.1 Human studies

There is now compelling evidence that endogenous hormones, including estrogens and androgens, play a critical role in the etiology of breast cancer [59] and may have a role in the development of ovarian cancer [60] and prostate cancer [61]. Thus, we are interested in determining whether tea intake influences endogenous estrogen and androgens since data in support of a modulating effect of tea on blood hormone levels would lend credibility to the epidemiological findings on tea and cancer risk.

In this section we review findings from observational (cross-sectional) studies that have evaluated the hormonal effects of tea in men and in pre-menopausal and post-menopausal women. We paid special attention to whether the findings on tea and hormone levels can be explained by potential confounding factors including caffeine intake, soy intake, smoking, alcohol use, body size, and other factors since the determinants of tea intake varied in different populations. Tea drinking in Western populations is generally associated with a healthier lifestyle and diet and tea intake tends to be higher in lean, educated subjects who are more likely to be nonsmokers and have lower intake of alcohol, coffee, and fat [21, 62]. However, in Asian populations, tea intake is not necessarily associated with a healthier lifestyle/diet. In fact, tea intake has been reported to be positively associated with heavier cigarette smoking and higher intake of alcohol and coffee [63, 64].

We identified studies by a computerized search of the MEDLINE English language literature on tea and estrogen/androgen/hormone published from January 1966 through May 2005. We also reviewed the reference lists of the relevant publications to identify additional studies. We included studies that presented results specifically on tea and endo-

Table 3. Cross-sectional studies on tea and endogenous hormone levels

Study	Age N	Tea intake	Hormone	
			Estradiol[a)]	SHBG[a)]
Nagata [65]	21 – 42	Green tea	–0.35 (day 11)	0.16 (day 11)
Japan	N = 50		$p = 0.02$	$p = 0.10$
			0.03 (day 22)	0.25 (day 22)
			$p > 0.05$	$p = 0.05$
		Black tea	–0.11 (day 11)	–0.10 (day 11)
			0.19 (day 22)	–0.09 (day 22)
		Oolong tea	0.003 (day 11)	0.08 (day 11)
			0.20 (day 22)	–0.03 (day 22)
			Estradiol	Prolactin (μg/L)[b)]
Geleijnse [33]	55+	Tea (mL/day)	Not measured	
Rotterdam	N = 577[d)]	0 ($n = 175$)		2.46
		> 0 to 250 ($n = 73$)		2.75
		> 250 – 500 ($n = 74$)		2.86
		> 500 ($n = 215$)		2.86
		P trend		0.03
			Estradiol[b)] (pg/mL)	SHBG (nmol/L)[b)]
Lucero [66]	36 – 45	Tea (cups/day)		
USA	N = 498	< 1 ($n = 332$)	3.44	4.23
		≥ 1 ($n = 156$)	3.42	4.36
		P value	> 0.05	> 0.05
			Estradiol[c)] (pg/mL)	Estrone (pg/mL)[c)]
Wu [70]	50 – 74	Tea		
Singapore Chinese	N = 144	Occasionally (n = 83)	13.4	30.2
		Weekly (n = 35)	12.9	29.7
		Daily (n = 26)	12.7	31.6
		P trend	0.51	$p = 0.51$
Wu [13]	50 – 74	Black only, daily ($n = 4$)	18.7	44.6
Singapore Chinese	N = 130	Black only, wkly ($n = 15$)	14.2	33.0
		Non-irregular ($n = 84$)	13.7	29.5
		Green only, wkly ($n = 12$)	12.3	25.1
		Green only, daily ($n = 15$)	12.7	26.3
		P trend	0.03	0.02

a) Spearman correlation coefficients are presented.
b) Age-adjusted geometric mean levels.
c) Adjusted for age, time of blood draw, body size, soy intake, age at menarche and parity.
d) 40 women were exluded from the analysis.

genous estrogen levels (and other sex-steroid hormones) but did not include studies that presented results only on total caffeine intake in which tea intake contributed to the intake of caffeine.

We were unable to identify any studies in men. We identified four studies [13, 33, 65, 66] in women that investigated the association between tea intake and hormone levels in a cross-sectional manner (Table 3). Three [13, 65, 66] of the four studies were conducted to identify lifestyle determinants of blood estrogen levels and many relevant potential confounders were adjusted for in the analysis. In addition to estradiol, other hormones including estrone, androstenedione [13], follicular stimulating hormone (FSH), luteinizing hormone (LH) [66], and sex hormone binding globulin (SHBG) were measured [65, 66] in these studies. One study measured only prolactin on the basis that serum prolactin levels can be used as a marker of estrogenic activity [33]. Two of the studies were conducted in pre-menopausal women [65, 66] and two in post-menopausal women [13, 33]. One study each in pre- and post-menopausal women was conducted in Western populations [33, 66]. In the two studies conducted in Western populations, results were presumed to reflect intake of black tea, the main tea type con-

sumed in the study populations. In the two studies conducted in Asian populations, results were presented separately for black tea and green tea [13, 65].

Nagata *et al.* [65] investigated the relationship between intake of green tea, black tea, and oolong tea in Gifu, Japan by studying 50 healthy premenopausal women in college, ages 21 – 42 years old, who had no history of diabetes or endocrine diseases, and were non-users of oral contraceptives. As part of the study, each subject completed a validated self-administered questionnaire, which asked about frequency of intake of 169 food items, menstrual and reproductive histories, and other lifestyle factors. For intake of coffee (caffeinated and decaffeinated), green tea, black tea, oolong tea, and cola, participants chose one of nine possible response categories for the frequency questions. Intake of green tea was high (mean 397.7 mL/day), intake of oolong tea was intermediate (mean 142.5 mL/day), whereas intake of black tea was low (mean 21.8 mL/day) (the authors did not specify whether the mean intake was presented for all subjects or for drinkers of the specific type of tea). Green tea intake was significantly inversely associated with follicular (day 11) (Spearman correlation coefficient (r) = -0.35, $p = 0.02$) but not with luteal (day 22) serum estradiol level after adjustment for age, body mass index and menstrual cycle length. This inverse association with follicular serum estradiol remained statistically significant after further adjustment for intake of fat and fiber, determinants of estradiol levels in this population [67]. Green tea intake was also positively correlated with follicular and luteal SHBG levels; the luteal phase finding was strengthened ($r = 0.31$, $p = 0.05$) upon further adjustment for intake of fat and fiber (Table 3). In further analysis, Nagata *et al.* [65] reported a significant inverse association between bioavailable follicular estrogen (ratio of estradiol to SHBG) levels and green tea intake ($r = -0.32$, $p = 0.04$). In contrast, serum estradiol and SHBG levels were not significantly correlated with intake of black tea or oolong tea. Although total caffeine intake and blood estradiol levels were not significantly correlated in this population, intake of total caffeine was positively associated with serum SHBG levels during the follicular ($r = 0.29$) and the luteal phase ($r = 0.32$, $p < 0.05$). The inverse correlations between green tea and estradiol and the positive correlations between green tea and SHBG remained after adjustment for intake of caffeine. Thus, in this cross-sectional study, green tea's inverse relationship with estradiol level and its positive relationship with SHBG level seemed credible given that many of the potentially confounding variables were adjusted for in the analysis. However, confirmation of these results is essential given the small study sample size (50 subjects). In addition, there are no apparent reasons for the inverse association to be found only with the follicular phase estradiol and not with the luteal phase estradiol levels. Finally, soy intake, also inversely associated with serum estradiol levels in this population [68], was not adjusted for in the analysis.

Lucero *et al.* [66] conducted an analysis to examine the effects of caffeine on female hormones among women ages 36 – 45 years old, who were participants of the Harvard Study of Moods and Cycles designed to identify correlates of depression in women. The 498 women included in the caffeine-hormone analysis represented those who were in the 'nondepressed' subgroup, were non-users of exogenous hormones, and had completed a baseline food frequency questionnaire. Although early follicular (day 3) estradiol levels increased significantly with increasing intake of caffeinated coffee and total caffeine intake (coffee, tea, cola, and caffeinated soft drinks) in this report, tea intake was not significantly associated with levels of estradiol, SHBG, FSH and LH after adjustment for age. Estradiol was 2% lower, SHBG was 4% higher, FSH was 4% lower and LH levels were 10% higher in daily (≥ 1 cup/day) compared to non-daily (< 1 cup/day) tea drinkers; none of the differences were statistically significant (Table 3). Given that the results in this study are presumably related to black tea intake, these findings are compatible with the results on black tea in pre-menopausal Japanese women [65].

Geleijnse *et al.* [33] conducted a cross-sectional study among post-menopausal women participants in the Rotterdam Study, a prospective study that included 1323 men and 2131 women aged 55 years or older. As part of the original cohort study, subjects completed an extensive, validated semiquantitative food frequency questionnaire and quantified their usual tea intake as the number of cups ingested per day, week, or month. A main finding from the Rotterdam study was that the risk of severe aortic atherosclerosis was significantly reduced in association with high intake of black tea; this finding was stronger in women than in men which led to the authors' conjecture that the 'phytoestrogens' in black tea may have estrogenic effects [69]. To test their hypothesis, these investigators conducted a cross-sectional study among a random sample of 577 female cohort participants to investigate the relationship between black tea intake and serum prolactin level, which was used as a marker of estrogenic activity (estrogen levels were not measured). Geleijnse *et al.* [33] reported that serum prolactin concentrations increased significantly with increasing amounts of tea consumed; serum prolactin levels were 2.46, 2.75, 2.86, and 2.86 μg/L ($p = 0.03$), respectively, in association with none, >0 to 250 mL, 250 to 500 mL, and >500 mL of tea intake per day after adjustment for age (Table 3). The association remained statistically significant with additional adjustment for body mass index, ever use of hormone, age at menopause, and parity.

While the black tea-prolactin findings are suggestive, these results were presented in the form of a letter, which pro-

vided few relevant details regarding the study methods of this substudy. In particular, it is not clear whether there were any inclusionary/exclusionary criteria although the authors mentioned they oversampled women who were non- (0 mL/day) or heavy- (>500 mL/day) tea drinkers. It is not known how many (if any) of the women were current hormone users. In addition, dietary factors (*i.e.* total energy, alcohol, coffee, and total fat) that were significantly lower among high tea drinkers and dietary factors (*i.e.* various antioxidants) that were significantly higher among high tea drinkers in the original cohort [62] were not considered in the black tea-prolactin analysis. Nevertheless, if one accepts these results at face value, the 'estrogenic' effects of black tea observed in this study resembled our findings on black tea and estrogen levels among postmenopausal Chinese women in Singapore [13] (see below).

Wu *et al.* [70] conducted a cross-sectional study among Chinese women in Singapore to identify lifestyle determinants of blood estrogen and androstenedione. Subjects were participants in the Singapore Chinese Health Study, a population-based prospective study of diet and cancer that included 63 257 Chinese women and men aged 45–74 years at baseline. At recruitment, a face-to-face structured questionnaire was administered to each subject, which included a validated dietary component in which usual intake frequencies and portion sizes for 165 food and beverage items were obtained. For coffee, black tea, green tea, and alcoholic beverages, participants chose one of nine possible response categories for the frequency questions. A year after the initiation of the cohort study, collection of blood and single-void urine specimens was obtained from a random 3% sample of study enrollees. This cross-sectional investigation on determinants of blood hormone levels included the first 149 women who were at least 50 years of age, post-menopausal at blood draw for at least 1 year, and without any history of cancer; 95% of study participants experienced a natural menopause.

In our initial report from this cross-sectional study, we found that high body mass index, early age at menarche, nulliparity/late age at first birth, and low intake of soy were independently associated with high estrogen levels. Intake of coffee and tea (black and green tea combined) was not significantly associated with blood estradiol, estrone, or androstenedione levels [70]. However, when we later observed that the risk of breast cancer was inversely associated with green tea but not with black tea intake among Asian-American women in Los Angeles County, CA [6], we re-analyzed our Singapore Chinese data on tea and blood hormone levels separately for the two types (black *vs.* green) of tea drunk in this study population [13]. In the re-analysis, we first excluded subjects who drank both black and green tea regularly because we hypothesized that the two types of tea might have opposing effects on blood hormone levels. We found reduction in circulating levels of both estrone (–13%) and estradiol (–18%) among weekly/daily green tea drinkers and increase in both estrone (+19%) and estradiol (+10%) levels among weekly/daily black tea drinkers. Both the estrone and estradiol findings were statistically significant ($p = 0.02$ and $p = 0.03$, respectively) (Table 3). A similar pattern of differences in androstenedione levels by tea intake also was found. Compared to non- and irregular tea drinkers, weekly/daily green tea drinkers had lower circulating levels of androstenedione (–12%) while weekly/daily black tea drinkers had higher (24%) circulating levels of androstenedione ($p = 0.14$) (data not shown). These findings on green tea and black tea remained statistically significant after adjustment for dietary soy, coffee drinking, body mass index, age at menarche and parity.

In summary, there exist limited data from cross-sectional studies on tea and hormone levels in women and no comparable data in men. The overall data in women suggest that green tea intake may be inversely related to blood estrogen levels while black tea intake may be positively related to blood estrogen levels. There are many limitations with cross-sectional data, most important of which is that causal inferences cannot be drawn from the observed associations in the data. In addition, the possibility of publication bias (*i.e.* null finding reports are less likely to be published) cannot be ruled out. There is a need for large, better quality data from population-based cross-sectional and intervention studies in both women and men. As reviewed below, the non-human data on tea intake and endogenous hormones also are inconsistent.

3.2 Non-human studies

The effects of tea catechin on circulating androgen levels in rodent models have been investigated in at least four studies in male rats [57, 71–73]; one of these investigations also studied female rats [72]. Three of the four studies in male rats showed increases in total testosterone levels in association with tea intake. In one study of male F344 rats 8 weeks of age, the control group received water and the two experimental groups received 2% solutions of black or green tea for 6 weeks, respectively [71]. Compared to control animals, circulating total testosterone levels increased in the black tea (+18%) and green tea (+32%) groups; smaller increases in free testosterone levels also were found (+2% and +19%, respectively). The differences between treated and control rats in total or free testosterone levels were not statistically significant in this study that included only four rats per treatment group. In a second study, polyphenone-60 (P-60), a green tea catechin extract, was given in the diet (0, 1.25 and 5%) to male F344 rats for 2, 4, and 8 weeks of duration, beginning at

age of 5 weeks [73]. Circulating testosterone levels increased significantly by fourfold in the group treated with a P-60 dose of 5% compared to the control group after 8 weeks of treatment, whereas increases in levels were nonsignificant after 4 weeks of treatment at the 5% dose or after 4 or 8 weeks of treatment in the lower dose (1.25%) group. In a third study, Zhou *et al.* [57] investigated the separate and combined effects of tea and soy on prostate tumor progression by inoculating intraprostatically severe combined immune deficient (SCID) male mice with LNCaP human prostate cancer cells. Mice treated with black tea alone had nonsignificantly higher serum testosterone levels (+34%) but lower dihydrotestosterone (DHT) levels (–72%) compared to control animals. Mice treated with green tea alone showed nonsignificantly higher serum testosterone (+74%) and higher DHT levels (+194%) compared to controls. These investigators suggested that black tea might have bioactive components that inhibited the conversion of testosterone to DHT, presumably via inhibition of 5α-reductase. However, it is not obvious why these components would be lacking in green tea since a previous study have found that EGCG and ECG were potent inhibitors of both the type 1 and type 2 5α-reductase [74] and levels of EGCG and ECG are known to be higher in green tea than in black tea [75]. In a fourth study, Kao *et al.* [72] investigated the effects of green tea in adult male and female Sprague Dawley rats. Testosterone levels decreased (–19%) nonsignificantly when male rats were given EGCG orally for 7 days but significantly (–70%) when EGCG was injected. Estradiol levels also decreased nonsignificantly (–34%) in female rats who were treated with EGCG for 7 days. In contrast, EC did not influence testosterone and estrogen levels significantly in either male or female rats in this study [72].

4 Conclusions

Limited results on ECGC and blood estradiol levels in female rats [72] are compatible with findings on green tea and estradiol levels observed in cross-sectional studies conducted in pre-menopausal [65] and postmenopausal women [13]. Altogether, the animal and human data consistently point to lower blood estrogens and lower breast cancer risk in association with green tea exposure. Limited laboratory and epidemiological data on black tea intake in relation to circulating estrogens and breast cancer risk suggest an association with increased circulating estrogens and possibly a modest increase in breast cancer risk. At present, available experimental/human evidence on tea intake, whether green or black tea, and risk of ovarian or prostate cancers is severely limited and inconclusive.

Design considerations for future epidemiological studies should include the following: relatively wide exposure ranges in black tea and/or green tea drinking in the study population, information on lifetime tea intake patterns, and inclusion of potential confounding and modifying genetic and environmental (dietary and non-dietary) factors. Cross-sectional studies that examine the associations between hormone levels and black and green tea, separately, in men and women with diverse intake patterns are also needed. Short-term tea intervention studies designed to examine changes in circulating hormones/metabolites in response to green tea and black tea intake separately would be informative.

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