Tea consumption and oxidative stress: a cross-sectional analysis of 889 premenopausal women from the Sister Study

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Abstract

In experimental and clinical studies, green or black tea consumption has been shown to reduce oxidative stress. However, these studies involved high levels of tea consumption and may not reflect patterns in the general population. Here, we examined the association between black or green tea consumption and oxidative stress in a cross-sectional study of 889 premenopausal US women aged 35–54 years. Tea consumption was measured using the Block-98 FFQ. Urinary 8-iso-PGF$_{2\alpha}$ (F$_2$-IsoP) and 2,3-dinor-5,6-dihydro-15-F$_{2t}$-isoprostane (15-F$_{2t}$-IsoP-M) were used as biomarkers of oxidative stress. These compounds were measured by MS and normalised to creatinine. Linear regression was used to calculate the geometric mean differences (GMD) and 95% CI for log-transformed urinary F$_2$-IsoP or 15-F$_{2t}$-IsoP-M in relation to black or green tea consumption. We further examined whether adjusting for caffeine impacted associations between tea and oxidative stress. Geometric means of urinary F$_2$-IsoP and 15-F$_{2t}$-IsoP-M were 1·44 (95% CI 1·39, 1·49) and 0·71 (95% CI 0·69, 0·73) ng/mg creatinine, respectively. Overall, green tea consumption was not associated with urinary F$_2$-IsoP or 15-F$_{2t}$-IsoP-M. High-level black tea consumption ($\geq$5 cups/week compared with 0) was associated with higher 15-F$_{2t}$-IsoP-M concentrations (adjusted GMD = 0·10, 95% CI 0·02–0.19) but not F$_2$-IsoP. Adjusting for caffeine nullified the association between black tea and 15-F$_{2t}$-IsoP-M. Our findings do not support the hypothesis that dietary tea consumption is inversely associated with oxidative stress.

Key words: Tea: Oxidative stress: Epidemiology: Women's health

Oxidative stress describes an imbalance of oxidant/antioxidant networks that results in the disruption of redox signalling and/or molecular damage[1–3]. In humans, persistent oxidative stress can lead to oxidation of lipids, alteration of protein function and mutation of DNA[4–7]. These disruptions may contribute to the pathogenesis of cancer, diabetes and neurodegenerative disease[8–10]. To detect increases in oxidative stress, oxidation products of lipids are often used as biomarkers[11]. Urinary 8-iso-PGF$_{2\alpha}$ (F$_2$-IsoP) and its primary metabolite, 2,3-dinor-5,6-dihydro-15-F$_{2t}$-isoprostane (15-F$_{2t}$-IsoP-M), are stable biomarkers of lipid peroxidation[12,13]. Several studies have reported higher levels of specific urinary F$_2$-IsoP in medical conditions including cancer and CVD[14–16].

Tea is a popular and accessible beverage worldwide[17] and may have beneficial health effects for diabetes, CVD and cancer[18–20]. Green tea and black tea contain polyphenols[21] that have potential antioxidant properties[22]. For example, the polyphenol epigallocatechin-3-gallate (EGCG) is a natural antioxidant found in green and black tea[23,24]. To experimentally study the anti-oxidative effects of tea (green tea, black tea and green tea extract)[25–28], participants were assigned to high levels of tea consumption for a short period of time (e.g. 4 cups of green tea/d for 8 weeks or placebo beverage). Participants in the intervention group drinking green tea had lower levels of blood malondialdehyde (MDA), a biomarker of oxidative stress[25]. Participants assigned to receiving one capsule (379 mg) of green tea extract per d for 3 months had a higher total antioxidant status compared with placebo[26]. A third study reported that black tea consumption (4 cups/d for 6 months) reduced lipid peroxidation among thirty-four female former smokers[28]. These findings support a potential inverse association between tea consumption and oxidative stress.

Abbreviations: 15-F$_{2t}$-IsoP-M, 2,3-dinor-5,6-dihydro-15-F$_2$t-isoprostane; F$_2$-IsoP, 8-iso-PGF$_{2\alpha}$.

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However, in the general population, tea consumption patterns may reflect longer durations of lower consumption levels. It is unknown whether these patterns also translate to benefits for oxidative stress. Here, we conducted a cross-sectional analysis of 889 premenopausal women to examine the association between tea consumption and oxidative stress.

Methods

Data for this analysis come from the National Institute of Environmental Health Sciences (NIEHS) Sister Study. Study participants (n 50 884) aged 35–74 years were enroled between 2003 and 2009 across the USA and Puerto Rico[29]. To be eligible, participants had at least one sister who had been diagnosed with breast cancer, but no personal history of breast cancer. All participants provided written consent at enrolment. Study protocols were approved by the Institutional Review Board of the NIEHS, the National Institutes of Health and the Copernicus Group.

Population for analysis

Within the Sister Study, 1367 women were identified (456 cases, 911 controls) for a nested case–control study investigating oxidative stress and breast cancer risk among premenopausal women. To be eligible for the nested case assigned control study, participants had to meet the following criteria: aged 54 and younger, premenopausal status (at least one menstrual cycle in the previous 12 months or hysterectomy with ≥1 ovary conserved) and have an available blood and urine sample from enrolment. Controls were matched to cases with a ratio of 2:1 on the basis of age and enrolment year and were free of breast cancer at the time of their matched case's diagnosis. For this analysis, information from the 911 controls was used. We further excluded women missing data of black and green tea consumption levels (n 22), which yielded 889 participants for this study.

Oxidative stress measurement

At Sister Study enrolment, participants self-collected approximately 60 ml of first-morning void urine in a study-provided collection cup[29]. Participants refrigerated the samples without preservative until they were picked up by study examiners who shipped the samples on ice to the study repository[30]. On receipt, urine samples were aliquoted and stored at –80°C. In 2012, samples were retrieved and urinary concentrations of F_2-IsoP and 15-F_{2t}-IsoP-M were measured using GC/negative ion chemical ionisation MS at the Eicosanoid Core Laboratory at Vanderbilt University Medical Center. The mean storage time of urinary samples was 8·3 years. Protocols for chemical analysis and procedures have been described in detail[31–34]. A total of seventy-seven batches were run; each batch contained eighteen samples from study subjects (twelve controls and six cases) and two quality control (QC) samples. The CV for QC duplicates was 16·0 and 12·5 % for F_2-IsoP and 15-F_{2t}-IsoP-M, respectively[35]. Urinary levels of F_2-IsoP and 15-F_{2t}-IsoP-M were adjusted for creatinine (ng/mg creatinine) to correct for urine diluteness.

Exposure and covariate measurement

During an enrolment home visit, trained examiners measured height and weight without shoes. These measurements were taken three times and values were rounded to the nearest quarter inch for height and whole pound for weight[36]. BMI was calculated as weight (kg)/height (m)^2. Black and green tea consumption during the past 12 months was measured by the self-administered Block 98 FFQ at study enrolment[37]. Within the FFQ, participants reported their frequency of tea consumption and the cups consumed each time[29]. Frequency was reported at nine levels, ranging from 'never' to 'everyday'. Participants reported how many cups of tea they consumed each time as '1 cup, 2 cups, 3–4 cups or 5 or more cups'. Regular (non-decaffeinated) coffee consumption was measured using the same methods described above. Healthy eating index, dietary fruit and vegetable intake and dietary β-carotene, vitamin C, and vitamin E intake were obtained via information collected in self-administered FFQ. Total energy intake and caffeine from beverages (soda and black tea) and dietary sources were calculated from the FFQ by Nutrition-Quest[38]. We assigned caffeine levels to coffee (regular and decaffeinated) and green tea on the basis of data from USDA Food Composition Databases[39,40]. Each cup of regular coffee was assigned 95·2 mg caffeine, each cup of decaffeinated coffee 2 mg caffeine, and each cup of green tea 24·8 mg caffeine. On average, one cup of black tea contains 47·2 mg caffeine[39].

A validated series of questions were used for measurement of physical activity[41,42]. Weekly energy expenditures at enrolment were calculated as metabolic equivalents (MET), and total physical activity was calculated by summing the MET-h/week of all sports, physical exercise and daily activity self-reported at enrolment. Participants were also asked for information about the total annual income from all household members and the highest level of school they had completed as well as their age and race/ethnicity.

Statistical analysis

Tea consumption was categorised into four levels (0, <1, 1–<5 and ≥5 cups/week). The consumption value was obtained by multiplying the frequency of consumption (times/week) and serving size (cups consumed each time) together. Cut-off points were determined based on the distribution of tea consumption among women who reported drinking black tea to approximate tertiles. Non-consumers were identified *a priori* as the reference group. The same cut-off points were used for green tea consumption for consistency. Tea consumers with missing serving size information (twenty-two for black tea, twenty-four for green tea) were assigned a serving size of one cup per serving (the most common serving size for black (56·7 %) and green (76·0 %) tea consumption). For coffee consumption, one and two cups per serving were about equally common (37·0 and 38·5 %, respectively), and coffee consumers with missing

serving size information (n 13) were also assigned as drinking one cup per serving. Coffee consumption was categorised into four levels: 0, <10, 10– <15 and ≥15 cups/week. Caffeine intake was categorised based on approximate quartiles (<33·9, 33·9– <111·2, 111·2– <205·2 and ≥205·2 mg/d). BMI categories were defined based on WHO guidelines as underweight/ normal weight (<24·9 kg/m^2), pre-obesity (25·0–29·9 kg/m^2), obesity class I (30·0–34·9 kg/m^2), obesity class II (35·0– 39·9 kg/m^2) and obesity class III (≥40 kg/m^2)[43]. The healthy eating index, dietary fruit and vegetable intake and dietary β-carotene, vitamin C, vitamin E, total energy intake and physical activity were categorised to approximate quartiles.

Geometric means and 95 % CI of urinary F_2-IsoP and 15-F_{2t}-IsoP-M were calculated for each level of tea consumption and by other covariates. The distribution of urinary F_2-IsoP and 15-F_{2t}-IsoP-M concentrations was right skewed; thus, a natural log transformation was applied for these biomarkers to approximate normality. Univariate geometric mean difference and adjusted geometric mean difference (aGMD) and 95 % CI of urinary F_2-IsoP and 15-F_{2t}-IsoP-M were calculated using linear regression of the natural log-transformed values. To calculate aGMD of F_2-IsoP or 15-F_{2t}-IsoP-M across tea consumption levels, the linear regression model adjusted for age (35– <40, 40– <45, 45– <50 and ≥50 years), race (non-Hispanic white, non-Hispanic black and other), BMI (BMI, <25, 25– <30, 30– <35, 35– <40 and ≥40 kg/m^2), education (high school or less, some college or undergraduate and graduate school), annual income (0– <\$50 000, \$50 000– <\$100 000 and ≥\$100 000), smoking status (never, former and current), healthy eating index (<53, 53– <63, 63– <72 and ≥72), dietary fruit (<0·6, 0·6– <1·1, 1·1– <2 and ≥2 servings/d) and vegetable intake (<1·6, 1·6– < 2·7, 2·7– <4·3 and ≥4·3 servings/d), dietary β-carotene (<2427·2, 2427·2– <4106·1, 4106·1– <6942·3 and ≥6942·3 μg/d), vitamin C (<55·3, 55·3– <84·1, 84·1– <121·9 ≥121·9 mg/d) and vitamin E intake (<5·6, 5·6– <7·6, 7·6– <10·1 ≥10·1 mg/d), total energy intake (<5148·0, 5148·0– <6396·1, 6396·1– <8263·0 and ≥8263·0 kJ/d) and physical activity (<28·11, 28·11– <44·16, 44·16– <65·99, ≥65·99 MET-h/week) were used as potential confounders[44]. We also evaluated the impact of additional adjustment for caffeine (<33·9, 33·9– <111·2, 111·2– <205·2 and ≥205·2 mg/d)[45,46]. The assumptions of the linear regression (linearity, independence, multivariate normality and homoscedasticity) were examined by scatterplots of urinary F_2-IsoP or 15-F_{2t}-IsoP-M $v.$ tea consumption and plots of the residuals $v.$ fitted values of the regression model; results did not suggest that assumptions were violated.

Subgroup analyses were conducted to address potential effect modification of associations between tea and F_2-IsoP or 15-F_{2t}-IsoP-M according to overweight (BMI <25 kg/m^2 $v.$ BMI ≥25 kg/m^2) and regular coffee consumption (drinker $v.$ non-drinker). Interaction terms between tea consumption and the covariates were included in multivariable linear regressions, and log-likelihood ratio tests were used to assess whether the interaction terms were statistically significant.

We did not adjust for multiple comparisons as our analysis was hypothesis driven[47–49]. Two-sided P values <0·05 were considered to be statistically significant. All statistical analyses

were conducted with Sister Study data release 6.0 using Stata 13.0 (StataCorp, LLP).

Results

Of the 889 participants in our analysis, the average age at baseline was 47·28 (SD 4·45) and the majority were non-Hispanic white (87·3 %). The geometric means of urinary F_2-IsoP and 15-F_{2t}-IsoP-M were 1·44 (95 % CI 1·39, 1·49) and 0·71 (95 % CI 0·69, 0·73) ng/mg creatinine, respectively. Table 1 presents geometric means and mean differences of urinary F_2-IsoP and 15-F_{2t}-IsoP-M according to participant characteristics. Both F_2-IsoP and 15-F_{2t}-IsoP-M decreased slightly as age increased, but the differences were not statistically significant. Average F_2-IsoP and 15-F_{2t}-IsoP-M levels among non-Hispanic black women were lower compared with white women. Levels of both F_2-IsoP and 15-F_{2t}-IsoP-M were positively associated with BMI and inversely associated with higher income and physical activity. Current smokers had higher levels of both F_2-IsoP and 15-F_{2t}-IsoP-M compared with never smokers, but associations were statistically significant only for 15-F_{2t}-IsoP-M. Inverse but non-significant associations with education were also observed for 15-F_{2t}-IsoP-M but not F_2-IsoP. High-level coffee consumption (≥15 cups/week) was not associated with F_2-IsoP or 15-F_{2t}-IsoP-M. Total energy intake was positively associated with F_2-IsoP or 15-F_{2t}-IsoP-M. Associations with the healthy eating index, vegetable intake and vitamin C were not statistically significant for F_2-IsoP and 15-F_{2t}-IsoP-M. Higher fruit intake and dietary β-carotene were inversely associated with F_2-IsoP and 15-F_{2t}-IsoP-M, respectively, but not with both markers. Dietary vitamin E appeared inversely associated with both biomarkers, but only estimates of 15-F_{2t}-IsoP-M were statistically significant.

Associations between black and green tea consumption and caffeine intake with urinary oxidative stress measures are shown in Table 2. Black tea consumption was more common than green tea consumption; 18·6 % of women reported never drinking black tea, while 45·9 % of women reported never drinking green tea. The highest level of consumption, ≥5 cups/week, was reported by 24·9 and 7·6 % of women for black and green tea consumption, respectively. Overall, black and green tea consumption were not associated with F_2-IsoP levels (Table 2). However, mean concentrations of 15-F_{2t}-IsoP-M were higher for black tea consumption of 5 cups/week or more compared with 0 cups/week (aGMD = 0·10, 95 % CI 0·02, 0·19). High-level green tea consumption (≥5 cups/week compared with 0) was not significantly associated with 15-F_{2t}-IsoP-M (aGMD = 0·09, 95 % CI –0·02, 0·20).

Caffeine intake was not associated with F_2-IsoP. As compared with the lowest quartile (<33·9 mg/d), higher levels of caffeine intake were positively associated with 15-F_{2t}-IsoP-M, but there was no consistent increase across quartiles. Additional adjustment for caffeine intake attenuated the association between black tea and 15-F_{2t}-IsoP-M towards the null (Table 2). Associations between tea

Table 1. Characteristics of study participants and estimates of urinary 8-iso-PGF$_{2\alpha}$ (F$_2$-IsoP) or 2,3-dinor-5,6-dihydro-15-F$_{2t}$-isoprostane (15-F$_{2t}$-IsoP-M) by covariates*
(Numbers and percentages; geometric means (GM) and 95% confidence intervals)

	n 889		F$_2$-IsoP						15-F$_{2t}$-IsoP-M					
Characteristics	n	%	GM	95% CI†	uGMD	95% CI‡	aGMD	95% CI§	GM	95% CI†	uGMD	95% CI‡	aGMD	95% CI§
Age (years)														
35–<40	61	6·9	1·61	1·41, 1·83		Ref.		Ref.	0·75	0·67, 0·83		Ref.		Ref.
40–<45	177	19·9	1·43	1·33, 1·53	−0·13	−0·28, 0·02	−0·09	−0·24, 0·05	0·72	0·67, 0·77	−0·04	−0·17, 0·09	−0·01	−0·13, 0·11
45–<50	377	42·4	1·44	1·36, 1·51	−0·11	−0·25, 0·03	−0·07	−0·20, 0·07	0·73	0·70, 0·76	−0·03	−0·15, 0·09	0·00	−0·11, 0·12
≥50	274	30·8	1·41	1·32, 1·51	−0·13	−0·28, 0·01	−0·08	−0·22, 0·06	0·68	0·65, 0·72	−0·10	−0·23, 0·02	−0·06	−0·18, 0·05
Race														
Non-Hispanic white	776	87·3	1·45	1·40, 1·51		Ref.		Ref.	0·72	0·69, 0·74		Ref.		Ref.
Non-Hispanic black	56	6·3	1·25	1·09, 1·44	−0·14	−0·28, 0·00	−0·23	−0·37, −0·09	0·65	0·58, 0·74	−0·09	−0·21, 0·03	−0·18	−0·29, −0·06
Other	57	6·4	1·42	1·27, 1·60	−0·02	−0·16, 0·12	−0·01	−0·15, 0·13	0·73	0·65, 0·81	0·01	−0·11, 0·13	0·01	−0·10, 0·12
BMI (kg/m^2)														
<25	406	45·7	1·29	1·23, 1·36		Ref.		Ref.	0·63	0·60, 0·65		Ref.		Ref.
25–<30	246	27·7	1·46	1·38, 1·55	0·13	0·04, 0·21	0·11	0·03, 0·20	0·70	0·67, 0·74	0·12	0·05, 0·19	0·10	0·03, 0·17
30–<35	122	13·7	1·50	1·37, 1·65	0·15	0·05, 0·26	0·10	−0·01, 0·20	0·79	0·74, 0·85	0·24	0·16, 0·33	0·17	0·08, 0·26
35–<40	67	7·5	1·71	1·49, 1·97	0·27	0·14, 0·40	0·19	0·05, 0·32	0·94	0·84, 1·05	0·41	0·30, 0·52	0·36	0·25, 0·47
≥40	47	5·3	2·23	1·90, 2·63	0·54	0·39, 0·69	0·46	0·30, 0·62	1·17	1·06, 1·30	0·63	0·51, 0·76	0·57	0·44, 0·70
Missing	1	0·1	6·08	–					1·85	–				
Education level														
High school or less	107	12·0	1·57	1·41, 1·76		Ref.		Ref.	0·84	0·77, 0·91		Ref.		Ref.
Some college or undergraduate	543	61·1	1·42	1·36, 1·48	−0·09	−0·20, 0·02	0·02	−0·09, 0·14	0·72	0·69, 0·75	−0·14	−0·24, −0·05	−0·03	−0·12, 0·06
Graduate school	239	26·9	1·42	1·33, 1·52	−0·10	−0·22, 0·03	0·06	−0·07, 0·18	0·65	0·62, 0·69	−0·25	−0·35, −0·14	−0·09	−0·19, 0·02
Annual household income ($)														
<50 000	144	16·2	1·64	1·50, 1·80		Ref.		Ref.	0·83	0·76, 0·90		Ref.		Ref.
50 000–<100 000	364	40·9	1·54	1·46, 1·63	−0·05	−0·15, 0·04	0·00	−0·10, 0·10	0·76	0·72, 0·79	−0·08	−0·17, 0·00	0·00	−0·08, 0·08
≥100 000	360	40·5	1·29	1·23, 1·35	−0·24	−0·34, −0·14	−0·13	−0·23, −0·02	0·63	0·60, 0·66	−0·27	−0·35, −0·18	−0·09	−0·18, −0·01
Missing	21	2·4	1·11	0·90, 1·38					0·76	0·63, 0·91				
Smoking history														
Never	545	61·3	1·41	1·36, 1·47		Ref.		Ref.	0·70	0·67, 0·72		Ref.		Ref.
Former	267	30·0	1·42	1·33, 1·52	−0·01	−0·09, 0·07	−0·01	−0·08, 0·07	0·70	0·67, 0·74	0·01	−0·06, 0·07	0·00	−0·07, 0·06
Current	77	8·7	1·69	1·50, 1·92	0·16	0·03, 0·29	0·04	−0·09, 0·17	0·88	0·79, 0·97	0·24	0·14, 0·35	0·10	0·00, 0·21
Regular (not decaffeinated) coffee consumption (cups/week)														
0	279	31·4	1·53	1·44, 1·63		Ref.		Ref.	0·73	0·69, 0·78		Ref.		Ref.
<10	257	28·9	1·37	1·28, 1·46	−0·12	−0·21, −0·03	−0·07	−0·15, 0·02	0·69	0·66, 0·73	−0·06	−0·13, 0·02	0·00	−0·07, 0·07
10–<15	203	22·8	1·37	1·28, 1·48	−0·12	−0·22, −0·03	−0·09	−0·19, 0·00	0·69	0·64, 0·73	−0·06	−0·15, 0·02	−0·05	−0·12, 0·03
≥15	143	16·1	1·49	1·36, 1·62	−0·06	−0·16, 0·05	−0·04	−0·14, 0·07	0·76	0·71, 0·81	0·03	−0·06, 0·12	0·04	−0·05, 0·12
Missing	7	0·8	1·39	0·97, 2·00					0·63	0·44, 0·92				
Total energy intake (kJ/d)														
<5148·0	222	25·0	1·41	1·32, 1·51		Ref.		Ref.	0·70	0·66, 0·75		Ref.		Ref.
5148·0–<6396·1	223	25·1	1·40	1·31, 1·50	−0·02	−0·12, 0·08	0·02	−0·09, 0·13	0·68	0·64, 0·72	−0·03	−0·12, 0·05	0·03	−0·06, 0·12
6396·1–<8263·0	221	24·9	1·46	1·36, 1·56	0·03	−0·07, 0·12	0·10	−0·03, 0·22	0·74	0·69, 0·78	0·05	−0·04, 0·13	0·12	0·02, 0·22
≥8263·0	223	25·0	1·48	1·38, 1·58	0·02	−0·07, 0·12	0·18	0·03, 0·32	0·73	0·69, 0·78	0·05	−0·04, 0·13	0·16	0·04, 0·28
Physical activity (MET-h/week)														
<28·11	221	24·9	1·68	1·57, 1·81		Ref.		Ref.	0·82	0·77, 0·87		Ref.		Ref.
28·11–<44·16	221	24·9	1·40	1·31, 1·49	−0·18	−0·27, −0·08	−0·12	−0·22, −0·03	0·70	0·66, 0·74	−0·16	−0·25, −0·08	−0·10	−0·18, −0·02
44·16–<65·99	221	24·9	1·43	1·34, 1·53	−0·17	−0·27, −0·07	−0·09	−0·18, 0·01	0·70	0·66, 0·74	−0·17	−0·25, −0·09	−0·10	−0·18, −0·02
≥65·99	221	24·9	1·27	1·19, 1·36	−0·29	−0·39, −0·20	−0·16	−0·25, −0·06	0·65	−0·61, 0·69	−0·24	−0·33, −0·16	−0·12	−0·20, −0·04
Missing	5	0·4	1·34	0·86, 2·09					0·76	0·54, 1·07				

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Table 1. *Continued*

Characteristics	n	%	GM	95 % CI†	uGMD	95 % CI‡	aGMD	95 % CI§	GM	95 % CI†	uGMD	95 % CI‡	aGMD	95 % CI§
			F$_2$-IsoP						**15-F$_{2t}$-IsoP-M**					
Healthy eating index (0–100)														
<53	213	24.0	1.54	1.42, 1.66		Ref.		Ref.	0.77	0.72, 0.82		Ref.		Ref.
53–<63	230	25.9	1.54	1.44, 1.64	0.00	−0.10, 0.09	0.08	−0.02, 0.18	0.75	0.71, 0.79	−0.03	−0.12, 0.05	0.02	−0.06, 0.11
63–<72	223	25.1	1.35	1.27, 1.44	−0.12	−0.22, −0.03	0.06	−0.06, 0.18	0.68	0.64, 0.72	−0.14	−0.22, −0.05	0.00	−0.10, 0.10
≥72	223	25.1	1.34	1.26, 1.44	−0.14	−0.23, −0.04	0.13	−0.01, 0.26	0.66	0.62, 0.70	−0.17	−0.25, −0.08	0.03	−0.09, 0.14
Dietary fruit intake (servings/d)														
<0.6	210	23.6	1.62	1.51, 1.73		Ref.		Ref.	0.78	0.73, 0.82		Ref.		Ref.
0.6–<1.1	212	23.9	1.51	1.40, 1.63	−0.05	−0.15, 0.05	−0.04	−0.15, 0.06	0.73	0.69, 0.78	−0.07	−0.16, 0.02	−0.01	−0.09, 0.08
1.1–<2	203	22.8	1.40	1.31, 1.48	−0.13	−0.23, −0.03	−0.09	−0.22, 0.04	0.71	0.67, 0.76	−0.08	−0.17, 0.01	0.01	−0.09, 0.12
≥2	264	29.7	1.29	1.21, 1.37	−0.21	−0.31, −0.12	−0.13	−0.27, 0.00	0.65	0.62, 0.69	−0.19	−0.27, −0.11	−0.01	−0.13, 0.10
Dietary vegetable intake (servings/d)														
<1.6	202	22.7	1.63	1.51, 1.75		Ref.		Ref.	0.75	0.71, 0.80		Ref.		Ref.
1.6–<2.7	240	27.0	1.45	1.36, 1.55	−0.10	−0.20, −0.01	−0.09	−0.20, 0.03	0.76	0.72, 0.80	0.01	−0.08, 0.09	0.09	0.00, 0.19
2.7–<4.3	221	24.9	1.40	1.31, 1.49	−0.15	−0.25, −0.05	−0.09	−0.24, 0.06	0.67	0.64, 0.71	−0.11	−0.20, −0.03	0.05	−0.07, 0.17
≥4.3	226	25.4	1.31	1.22, 1.40	−0.22	−0.32, −0.12	−0.05	−0.23, 0.13	0.67	0.63, 0.71	−0.13	−0.22, −0.04	0.12	−0.03, 0.26
Dietary β-carotene intake (μg/d)														
<2427.2	222	25.0	1.63	1.52, 1.74		Ref.		Ref.	0.80	0.75, 0.84		Ref.		Ref.
2427.2–<4106.1	222	25.0	1.49	1.38, 1.60	−0.07	−0.17, 0.02	0.01	−0.11, 0.13	0.75	0.71, 0.80	−0.06	−0.15, 0.02	−0.04	−0.14, 0.06
4106.1–<6942.3	222	25.0	1.42	1.32, 1.52	−0.13	−0.23, −0.04	−0.02	−0.18, 0.13	0.67	0.64, 0.72	−0.18	−0.27, −0.10	−0.13	−0.26, −0.01
≥6942.3	223	25.1	1.25	1.17, 1.33	−0.26	−0.36, −0.16	−0.13	−0.31, 0.05	0.64	0.60, 0.68	−0.22	−0.31, −0.14	−0.16	−0.31, −0.01
Dietary vitamin C intake (mg/d)														
<55.3	221	24.9	1.60	1.48, 1.72		Ref.		Ref.	0.77	0.73, 0.82		Ref.		Ref.
55.3–<84.1	223	25.1	1.48	1.39, 1.58	−0.06	−0.16, 0.03	0.00	−0.11, 0.11	0.75	0.71, 0.79	−0.04	−0.13, 0.04	0.02	−0.07, 0.11
84.1–<121.9	222	25.0	1.38	1.29, 1.48	−0.14	−0.24, −0.04	−0.01	−0.14, 0.12	0.67	0.63, 0.71	−0.15	−0.23, −0.06	−0.03	−0.13, 0.08
≥121.9	223	25.1	1.30	1.22, 1.39	−0.20	−0.30, −0.11	−0.04	−0.20, 0.12	0.67	0.63, 0.72	−0.14	−0.22, −0.06	−0.01	−0.14, 0.12
Dietary vitamin E intake (mg/d)														
<5.6	217	24.4	1.54	1.43, 1.65		Ref.		Ref.	0.77	0.73, 0.82		Ref.		Ref.
5.6–<7.6	225	25.3	1.44	1.33, 1.55	−0.07	−0.17, 0.03	−0.03	−0.15, 0.08	0.70	0.66, 0.74	−0.11	−0.19, −0.02	−0.09	−0.18, 0.01
7.6–<10.1	222	25.0	1.46	1.37, 1.57	−0.06	−0.15, 0.04	−0.04	−0.17, 0.09	0.71	0.67, 0.76	−0.08	−0.17, 0.00	−0.10	−0.21, 0.01
≥10.1	225	25.3	1.33	1.25, 1.41	−0.16	−0.26, −0.06	−0.13	−0.29, 0.03	0.67	0.63, 0.72	−0.14	−0.22, −0.05	−0.18	−0.31, −0.05

uGMD, univariate geometric mean difference; aGMD, adjusted geometric mean difference; Ref., reference; MET, metabolic equivalent of task.

* Geometric mean difference and 95 % CI were calculated on the basis of natural logarithm of F$_2$-IsoP and 15-F$_{2t}$-IsoP-M.

† GM was calculated using the whole sample (n 889).

‡ Univariate models were restricted to participants without missing values of the covariates and had the same size as adjusted models (n 856).

§ aGMD was calculated in multivariable model adjusting for all variables in Table 1.

Table 2. Association between tea consumption or caffeine intake and urinary 8-iso-PGF$_{2a}$ (F$_2$-IsoP) or 2,3-dinor-5,6-dihydro-15-F2t-isoprostane (15-F$_{2t}$-IsoP-M)*
(Numbers and percentages; geometric means (GM) and 95 % confidence intervals)

Characteristics	n 889		F$_2$-IsoP						15-F$_{2t}$-IsoP-M					
	n	%	GM	95 % CI†	uGMD	95 % CI‡	aGMD	95 % CI§	GM	95 % CI†	uGMD	95 % CI‡	aGMD	95 % CI§
Black tea (cups/week)														
0	165	18·6	1·50	1·38, 1·63		Ref.		Ref.	0·71	0·66, 0·75		Ref.		Ref.
<1	311	35·0	1·39	1·32, 1·47	−0·07	−0·17, 0·03	−0·06	−0·15, 0·04	0·70	0·67, 0·74	0·00	−0·09, 0·08	0·04	−0·04, 0·12
1–<5	187	21·0	1·38	1·28, 1·48	−0·08	−0·19, 0·03	−0·09	−0·20, 0·01	0·68	0·64, 0·73	−0·04	−0·13, 0·06	−0·01	−0·10, 0·08
≥5	221	24·9	1·51	1·40, 1·62	0·01	−0·09, 0·12	0·01	−0·10, 0·11	0·76	0·71, 0·81	0·08	−0·02, 0·17	0·10	0·02, 0·19
Missing	5	0·5	1·62	0·81, 3·24					0·63	0·34, 1·15				
Green tea (cups/week)														
0	408	45·9	1·47	1·40, 1·55		Ref.		Ref.	0·72	0·69, 0·75		Ref.		Ref.
<1	315	35·4	1·45	1·37, 1·54	0·00	−0·08, 0·07	0·03	−0·05, 0·10	0·72	0·68, 0·76	0·00	−0·07, 0·06	0·05	−0·01, 0·12
1–<5	96	10·8	1·29	1·17, 1·43	−0·12	−0·24, −0·01	−0·03	−0·14, 0·08	0·66	0·61, 0·72	−0·09	−0·19, 0·01	0·01	−0·09, 0·10
≥5	67	7·6	1·41	1·24, 1·60	−0·04	−0·18, 0·09	0·06	−0·07, 0·19	0·70	0·64, 0·78	−0·02	−0·14, 0·10	0·09	−0·02, 0·20
Missing	3	0·3	1·17	0·24, 5·77					0·67	0·21, 2·16				
Caffeine intake (mg/d)														
<33·9	222	25·0	1·42	1·33, 1·52		Ref.		Ref.	0·67	0·64, 0·71		Ref.		Ref.
33·9–<111·2	223	25·1	1·46	1·36, 1·57	0·03	−0·07, 0·13	0·03	−0·07, 0·13	0·74	0·69, 0·79	0·09	0·00, 0·17	0·09	0·01, 0·17
111·2–<205·2	221	24·9	1·38	1·29, 1·48	−0·03	−0·13, 0·06	−0·02	−0·11, 0·08	0·69	0·65, 0·74	0·03	−0·06, 0·11	0·05	−0·03, 0·13
≥205·2	223	25·0	1·49	1·39, 1·59	0·03	−0·07, 0·12	0·01	−0·09, 0·11	0·75	0·71, 0·79	0·10	0·02, 0·18	0·08	0·00, 0·16
Black tea (cups/week)‖														
0								Ref.						Ref.
<1							−0·05	−0·15, 0·04					0·03	−0·05, 0·11
1–<5							−0·09	−0·20, 0·02					−0·02	−0·11, 0·07
≥5							0·01	−0·10, 0·12					0·08	−0·01, 0·17
Green tea (cups/week)‖														
0								Ref.						Ref.
<1							0·03	−0·05, 0·10					0·05	−0·02, 0·11
1–<5							−0·03	−0·15, 0·08					−0·01	−0·10, 0·09
≥5							0·05	−0·08, 0·19					0·07	−0·04, 0·18

uGMD, univariate geometric mean difference; aGMD, adjusted geometric mean difference; Ref., reference.
* Geometric mean difference and 95 % CI were calculated on the basis of natural logarithm of F$_2$-IsoP and 15-F$_{2t}$-IsoP-M.
† GM was calculated using the whole sample (n 889).
‡ Univariate models were restricted to participants without missing values of the covariates (black tea: n 858, green tea: n 861, caffeine: n 863).
§ The multivariable model adjusted for age, race, smoking status, BMI, physical activity, household income, education level, energy intake, healthy eating index, dietary fruit, vegetable, β-carotene, vitamin C and vitamin E intake (black tea: n 858, green tea: n 861, caffeine: n 863).
‖ The multivariable model additionally adjusted for caffeine intake.

consumption and urinary F$_2$-IsoP or 15-F$_{2t}$-IsoP-M were not modified by overweight (online Supplementary Table S1) or regular coffee consumption (online Supplementary Table S2).

Discussion

Our analysis did not provide support for an inverse association between dietary tea consumption and urinary F$_2$-IsoP or 15-F$_{2t}$-IsoP-M, high-quality biomarkers of oxidative stress. Green tea consumption was not associated with either F$_2$-IsoP or 15-F$_{2t}$-IsoP-M. Black tea consumption was not associated with F$_2$-IsoP; however, drinking at least 5 cups of black tea/week (compared with none) was associated with higher 15-F$_{2t}$-IsoP-M concentrations before adjustment for caffeine.

Clinical studies have found an inverse association between tea consumption and oxidative stress[25–27,50]. For example, by observing nineteen people in a 5-d experimental study, Stote et al.[50] found that green tea consumption could lower plasma levels of F$_2$-IsoP. However, subjects in this study consumed a higher level of tea (e.g. 2 servings of green tea/d for 5 d) than was commonly consumed in our population-based sample of the US women. In addition, this study enroled only nineteen

obese people at high risk of insulin resistance, which may have compromised the generalisability of their outcomes.

A cross-sectional epidemiological study[12] of 845 Chinese women observed an almost null association between any tea drinking and urinary levels of F$_2$-IsoP (geometric mean: never drinker: 1·62, ever drinker: 1·65, P = 0·72) and 15-F$_{2t}$-IsoP-M (geometric mean: never drinker: 0·56, ever drinker: 0·61, P = 0·06) after adjustment for age, education, occupation, smoking, BMI, multivitamin supplement use, fruit and vegetable intakes, plasma total carotenoids, tocopherols and retinol, assay batch and urinary tea polyphenols. However, the ever/never analysis did not consider level of consumption or potential difference between black and green tea[12]. Green and black tea differ in concentrations of polyphenols (e.g. EGCG) and caffeine[51,52]. For example, green tea has a higher level of EGCG compared with black tea[53], while black tea contains more caffeine[51]. In addition, a previous study measuring total phenol levels and antioxidant capacity of tea products sold in the USA found green tea had a higher antioxidant capacity than black tea of the same volume (436 v. 239 mg vitamin C equivalents per serving)[54]. These suggest analysis pooling all types of tea in to one category may obscure meaningful variation.

15-F_{2t}-IsoP-M is the metabolite of F_2-IsoP under β-oxidation[12]. Both black and green tea contain EGCG and caffeine which have been found to facilitate β-oxidation on the basis of laboratory evidence[55,56]. The suggested positive associations between black tea and caffeine with 15-F_{2t}-IsoP-M, but not F_2-IsoP, may be due, in part, to related increases in β-oxidation pathways. We did not observe an association between green tea and 15-F_{2t}-IsoP-M; however, there were few high-level green tea consumers in our analysis.

Our results regarding the association between caffeine and 15-F_{2t}-IsoP-M were similar to an experimental study[57] that assigned twenty participants caffeine (5 mg/kg) or placebo before physical exercise and observed a positive association between caffeine and plasma MDA using blood samples collected immediately after exercise. However, other experimental studies have reported inverse associations between caffeine intake and biomarkers of oxidative stress using other caffeine dosages or different biomarkers of antioxidant activity (e.g. plasma glutathione) or oxidative stress (e.g. 8-hydroxydeoxyguanosine)[58,59]. Due to the different study design, biomarkers used for analysis and divergent findings to date, the association between caffeine and oxidative stress deserves further investigation.

Strengths of our study included the use of a general population sample, the clear categorisation of tea type and detailed information on socio-demographic and lifestyle factors for statistical adjustment. Particularly, using a population-based sample can better reflect real-world tea consumption pattern as compared with high-level tea assignment in experimental studies. The use of urinary F_2-IsoP provided a stable biomarker of lipid peroxidation. A previous biochemical study has shown that plasma stored appropriately for at least 10 years has F_2-IsoP levels similar to freshly prepared samples[13]. Given that artefactual generation of F_2-IsoP through autoxidation of lipids only occurs in plasma and not in urine[12,13], our samples were likely to be equally or more stable. In some previous studies, MDA was used as the biomarker of oxidative stress[25,27]; however, MDA is more affected by dietary lipid consumption[60] and can be generated from non-lipid sources such as bile pigments[61], which may cause measurement error. 8-Hydroxy-2'-deoxyguanosine (8-OHdG) is another biomarker of oxidative stress which is an end product of non-enzymatic DNA oxidation[62]. However, levels of 8-OHdG can be influenced by DNA repair capacity which makes 8-OHdG an indicator of the combined effects of oxidative stress-associated damage and DNA repair capability. Furthermore, a previous study of ten healthy volunteer suggests that there is not a significant diurnal variation in urinary F_2-IsoP[63], whereas many studies suggest that diurnal variation in urinary 8-OHdG is substantial[62,64,65]. These characteristics make urinary F_2-IsoP a more desirable biomarker of oxidative stress.

Our study also has some limitations. Our sample included only premenopausal women, which may compromise the external validity for men, older women or individuals with specific medical conditions. Also, tea consumption was measured by retrospective self-report, and non-differential measurement error could be introduced. Duration of tea consumption was not available for analysis, and the antioxidant potential of green and black tea sources was not directly measured. Finally, our study is a cross-sectional analysis with one-time urinary sampling and two biomarkers of oxidative, which makes it inappropriate for casual interpretation.

Our study contributes real-world data regarding associations between tea consumption and oxidative stress. In our study, we did not observe an inverse association between green or black tea consumption and urinary F_2-IsoP. Additional studies with detailed information on the timing and duration of tea consumption, and additional measures of oxidative stress, may be warranted to inform the use of antioxidant products.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114518003732

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