Published in final edited form as:
Cancer Prev Res (Phila). 2012 March ; 5(3): 393–402. doi:10.1158/1940-6207.CAPR-11-0407.

Effect of 2 month controlled green tea intervention on lipoprotein cholesterol, glucose, and hormone levels in healthy postmenopausal women

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Abstract

There have been no controlled intervention studies to investigate the effects of green tea on circulating hormone levels, an established breast cancer risk factor. We conducted a randomized, double-blind, placebo-controlled intervention study to investigate the effect of the main green tea catechin, epigallocatechin gallate (EGCG), taken in a green tea extract, Polyphenon E (PPE). Postmenopausal women (n=103) were randomized into three arms: placebo, 400 mg EGCG as PPE, or 800 mg EGCG as PPE as capsules per day for 2 months. Urinary tea catechin and serum estrogen, androgen, lipid, glucose-related markers, adiponectin, and growth factor levels were measured at baseline and at the end of months 1 and 2 of intervention. Based on urinary tea catechin concentrations, compliance was excellent. Supplementation with PPE did not produce consistent patterns of changes in estradiol (E2), estrone (E1), or testosterone (T) levels. Low density lipoprotein (LDL)-cholesterol decreased significantly in both PPE groups but was unchanged in the placebo group; the change in LDL-cholesterol differed between the placebo and PPE groups (P=0.02). Glucose and insulin levels decreased nonsignificantly in the PPE groups but increased in the placebo group; statistically significant differences in changes in glucose (P=0.008) and insulin (P=0.01) were found. In summary, green tea (400 and 800 mg EGCG as PPE; ~5–10 cups) supplementation for 2 months had suggestive beneficial effects on LDL cholesterol concentrations and glucose-related markers.

Keywords

green tea; hormones; lipids; glucose; intervention

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Introduction

Approximately 20% of the world's tea is consumed as green tea, and there is evidence that green tea has preventive properties against breast carcinogenesis in animal and *in vitro* models (1, 2). However, the question remains whether these chemopreventive properties are observed in women. An inverse association between green tea intake and breast cancer risk has been consistently seen in case-control studies conducted among Asian Americans in Los Angeles County and in China (meta-analysis RR=0.70, 95% CI=0.61–0.79), but not in prospective studies conducted in Japan, China and Singapore (meta-analysis RR=1.06, 95% CI=0.93–1.20) (see review (3)). In these case-control studies, the baseline group comprised of women who were never or seldom green tea drinkers whereas in the prospective studies, the baseline group included women who were non-daily or non-weekly green tea consumers. Thus, the difference in the definition of unexposed group between the prospective studies and case-control studies may have contributed, in part, to the differences in results (3). In cross-sectional studies we conducted among Chinese women in Singapore, regular green tea drinkers showed significantly lower estrone levels (4) and lower mammographic percent density than non-regular tea drinkers (5). We found that black tea drinking was unrelated to estrogen levels or mammographic percent density (4, 5), and an overview of epidemiological studies found that black tea drinking was also unrelated to breast cancer risk (6). In rodent studies, green tea extract and epigallocatechin gallate (EGCG), the main green tea catechin, had inhibitory effects on aromatase activity (7, 8). We hypothesized that green tea intake may influence breast cancer risk *via* hormonal pathways.

Green tea but not black tea appears to have cardioprotective properties (9, 10). Recent meta-analyses have reported significantly reduced risk of coronary artery disease (10) and concentrations of low-density lipoprotein (LDL)-cholesterol (9) in association with green tea, but not black tea, intake. There are a considerable amount of animal data demonstrating that green tea may have favorable effects on glucose and insulin sensitivity but the results in humans are less consistent (11, 12). Healthy profiles in lipids and glucose levels may have favorable effects on breast cancer risk as there is accumulating evidence that breast cancer risk in postmenopausal women is elevated in relation with a history of metabolic syndrome (13, 14) and diabetes (15) even after adjustment for body mass index.

To follow-up on our cross-sectional findings of a potential effect of green tea on circulating hormone levels, we have conducted a double-blind randomized intervention study using Polyphenon E (PPE), a defined, decaffeinated green tea polyphenol mixture containing EGCG, which has been found to be safe and well tolerated in humans (16). We investigated the effects of two doses of a daily green tea capsule (400 mg EGCG as PPE, 800 mg EGCG as PPE; hereafter referred to as 400 mg PPE, 800 mg PPE) versus a daily placebo capsule for 2 months. The primary endpoints of interest were circulating concentrations of estrogen, androgen, and sex hormone-binding globulin (SHBG). The secondary endpoints included selected liver enzymes, lipids, glucose-related markers, growth factors, and adiponectin.

Materials and Methods

Subjects

Recruitment for the study commenced in May 2006 and ended in January 2008. Subjects were identified through flyers and newsletters that were distributed on our university campus and at the University of Southern California (USC) Health Fair. To be eligible for inclusion, subjects had to be postmenopausal (≥1 year since the last menstrual period), 45 years of age or older, and non-current users of menopausal hormone therapy (*i.e.*, stopped use ≥6 mo before entering study). Women were excluded if they were regular (i.e., at least once per week) green tea or black tea drinkers, had a history of allergic reactions to tea

compounds, had elevated liver enzymes, had a history of cancer, or were currently participating in another dietary intervention study. We conducted telephone pre-screening interviews with 326 interested women; 176 passed the telephone screening questions. Of these 176 women, 58 were subsequently excluded for various reasons (35 had elevated liver enzymes; 6 had preexisting medical conditions including previous cancer, 5 were not postmenopausal, and 12 withdrew consent). Of the 118 women enrolled in the study, 10 were later excluded (8 had adverse events: 3 in the placebo group [abdominal cramp, epigastric pain, and back pain/heart burn]; 4 in the 400 mg PPE group [constipation, gall stone, rectal bleeding, and hip and back pain] and 1 in the 800 mg PPE group [back pain]), one was noncompliant and drank tea during the intervention, and one did not wish to continue on the study). In total, 108 women completed 2 months of intervention. The final analysis included 103 women (32 in the placebo group, 37 in the 400 mg PPE group, and 34 in the 800 mg PPE group) as we excluded 5 women (3 in the placebo, and 2 in the 800 mg PPE group) as their baseline, month 1 or month 2 estrogen concentrations suggested that they were using menopausal hormones.

The study protocol was approved by the USC Institutional Review Board. Written informed consent was obtained from all study participants.

Study Drugs

Polyphenon E (PPE) is a green tea catechin extract that was produced by Mitsui Norin, Ltd (Shizuoka, Japan). This standardized tea polyphenol preparation contained 80% to 98% total catechins by weight with epigallocatechin gallate (EGCG) as the main component accounting for 50% to 75% of the material. Other catechins included epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and gallocatechin gallate (GCG) which are present at levels of 12% or less. Green tea has a higher content of these catechins than black tea, and its effects against cancer has been attributed to the presence of these polyphenolic compounds, particularly EGCG, as it major constituents (17). PPE contained small quantities of caffeine (<2%) and can be considered a decaffeinated product. PPE was administered in a hard gelatin capsule and each PPE capsule contained 200 mg EGCG, 37 mg EGC, 31 mg EC and other green tea polyphenols. Placebo capsules were hard gelatin capsules containing pregelatinized starch, colloidal silicon dioxide, and magnesium stearate. Participants in the three arms (placebo, 400 mg EGCG as PPE, 800 mg EGCG as PPE) were asked to take four capsules daily, two capsules with breakfast and two capsules with dinner (study drug packages were labeled AM and PM) for 2 months.

Baseline assessment and data and sample collection

At the initial screening interview, a blood specimen was obtained to determine participants' eligibility status, which included being postmenopausal (blood follicle stimulating hormone >25 mIU/ml) and having normal liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP)). Within about 2 weeks, a baseline visit was made during which we administered a baseline questionnaire that asked about menstrual, reproductive, and menopausal factors and obtained a fasting blood specimen for blood hormone levels and other biomarkers of interest. Body weight, blood pressure measurements, and blood samples were obtained at baseline and after 1 and 2 months of the intervention at the General Clinical Research Center (GCRC) of the University of Southern California. A 30 ml sample of venous blood was collected in sterile vacutainers before 10 am from each participant after fasting for a minimum of 12 hours. Serum and plasma were separated by centrifugation (2500 × g, 15 min, 4°C). Participants were asked to collect an overnight urine specimen into plastic bottles that contained 1 g ascorbic acid during the night before the blood draw at baseline and after 1 and 2 months of

intervention. Urine specimens collected at each time point were separated into “10 ml” aliquots and stored at −20°C.

Urinary tea catechin measurement

Urine samples from each participant (baseline, month 1, month 2) were identified by unique codes and were assayed in a single batch. Urinary concentrations of EGC, and 4′-O-methyl-epigallocatechin (MeEGC), EC, 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone (M4), and 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone (M6), the respective metabolites of EGC and EC were determined in the laboratory of Dr. Yang using validated methods (18, 19). Urinary creatinine (Cr) level was determined on each sample using a validated method (20). EGCG is not reported as this is not detectable in human urine (21).

Blood lipid, glucose, growth factors, hormone and other analyses

A standard lipid panel (total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglycerides), insulin, glucose, glycosylated hemoglobin (HbA_{1c}) and liver enzymes (ALT, AST, ALP) were measured at the Clinical Core Laboratory at the Los Angeles County/USC Medical Center. Estradiol (E2), estrone (E1), testosterone (T), androstenedione (A4), SHBG, insulin-like growth factor (IGF)-1, IGF binding protein (BP)-3, and adiponectin concentrations were measured in the Reproductive Endocrine Research Laboratory at USC, under the direction of Dr. Frank Stanczyk. All samples from an individual were included in the same batch run and each batch included samples from the three study arms. Radioimmunoassays, previously validated in his laboratory (22–24) were used to measure plasma levels of E2, E1, T and A4. Prior to quantification, the steroids were first extracted with hexane:ethyl acetate (1:1) and then separated from each other and interfering metabolites by the use of Celite column partition chromatography. The assay sensitivities for the respective steroids are 2 pg/ml, 4 pg/ml, 15 pg/ml, and 30 pg/ml, respectively, and the interassay coefficients of variation range from 8 to 13%. Intraassay coefficients for these assays were around 8%. Adiponectin was measured by using the Human Adiponectin RIA Kit from Millipore (St. Charles, MO). IGF-1, IGFBP3, and SHBG were quantified by direct solid-phase, chemiluminescent immunoassays, using the Immulite 2000 (Siemens Healthcare Diagnostics, Deerfield, IL).

Statistical analysis

When necessary, data were transformed logarithmically to achieve approximate normal distributions for statistical analysis. Results were converted back to the original scale for reporting purposes. Statistical tests were performed by using the general linear model approach. We computed geometric mean values by group at baseline for the biomarkers of interest (blood concentrations of lipids, glucose, liver enzymes, E2, E1, T, A4, SHBG, adiponectin, IGF-1 and IGFBP-3) and used ANOVA to assess the differences for statistical significance. Previous studies have found tea polyphenols to inhibit aromatase activity (7, 8). Given that the main source of estrogens in postmenopausal women is the peripheral conversion of androgens by the aromatase enzyme in which T is converted to E2 and A4 is converted to E1, we also investigated the ratios of T/E2 and A4/E1 in this intervention study. Because results for month 2 were generally very similar to those for month 1, we used the average of the two results as an estimate of the effect of intervention. Within each of the three groups, Student’s paired-sample t-test was used to compare hormonal, lipid, and growth factor biomarkers at baseline and the average biomarker concentrations at the end of month 1 and month 2. We show the percent change between baseline values and the average values at month 1 and 2 within each group and the corresponding P values. Using ANOVA, we tested whether the individual changes differed between the placebo group and the two PPE groups combined. We also tested whether the individual changes differed between the 400 mg and 800 mg PPE groups. P values less than 5% are considered statistically

significant and all P values quoted are 2-tailed. All analyses were performed using the statistical software package SAS 9.1 (SAS Institute, Cary, NC).

Results

Study group characteristics are presented in Table 1. Participants in the placebo group were slightly younger (average 57.7 years) than those in the 400 mg PPE (59.6 years) and 800 mg PPE groups (62.0 years) (P_{2df}=0.062). Women in the 3 groups did not differ significantly in terms of race/ethnicity, age at menarche, parity, age at natural menopause, baseline weight or body mass index (BMI). There were no significant differences in changes in body weight or BMI after 2 months of intervention between the placebo and PPE groups. There were no baseline differences in the 3 liver enzymes tested (ALP, AST, and ALT). The placebo and PPE groups did not differ significantly in differences in changes in these three liver enzymes (Table 1). The two PPE groups did not differ significantly in the percent changes in ALP and AST. While ALT levels declined in the 400 mg PPE group but increased in the 800 mg PPE group (P=0.011), levels in the 800 mg PPE group remained low during the 2 months of intervention (23.7 U/l).

Baseline tea catechin levels (EGC, Me-EGC, M4, and M6) were low and did not differ significantly between the 3 groups. Although baseline EC levels were low, there were differences between the 3 groups (P=0.039) (Table 2). In association with the 2 months of intervention, all five tea catechins increased significantly in the 800 mg PPE group (P<0.001). Four of the catechins (EGC, EC, M4, M6) also increased significantly in the 400 mg PPE group but the increase in Me-ECG was borderline statistically significant (P=0.089). In contrast, all five tea catechins remained largely unchanged in the placebo group. The increases in EGC and EC were significantly larger in the 800 mg than in the 400 PPE group but the changes in metabolites (Me-EGC, M4 and M6) did not differ significantly between the two PPE groups. The differences in changes in all five catechins differed significantly between the placebo and the two PPE groups (Table 2).

Participants in the 3 groups did not differ significantly in baseline concentrations of estrogen (E1, E2), androgen (T, A4), or SHBG (Table 3). There were no significant changes in concentrations of E1, E2, T, and A4 concentrations between baseline and with intervention in any of the 3 groups (all paired t-tests within groups >0.05). Differences in the changes of E2, E1, T, and A4 did not differ significantly between the placebo group compared to the two PPE groups (Table 3). Although there were suggestive differences in the ratio of total T to total E2 with PPE intervention, this was due largely to an increase in the ratio of T/E2 in the placebo group (P=0.06) and little to no change in the PPE groups. There were no significant differences in the change in the ratio of A4/E1 between the placebo and PPE groups (data not shown). Changes in SHBG levels differed significantly between the two PPE groups (P=0.008); this was due to a significant decrease in the 400 mg PPE (−6.8%, P=0.002) and a small increase in the 800 mg PPE (1.5%). The difference in changes in SHBG levels did not differ significantly between the placebo and the 800 mg PPE groups (P=0.50) but they differed significantly between the placebo and the 400 mg PPE groups (P=0.018); this difference remained after adjustment for changes in weight.

Baseline blood concentrations of cholesterol (total, LDL, HDL) and triglycerides were not significantly different in the 3 groups (Table 4). Total cholesterol decreased in the 400 mg PPE (−5.0%, P=0.012) and 800 mg PPE (−3.1%, P=0.045) groups but not in the placebo group (−0.2%, P=0.90). The change in total cholesterol between the placebo group and the two PPE groups was borderline statistically significant (P=0.072). LDL-cholesterol decreased 7.9% in the 400 mg PPE (P=0.007) and 6.6% in the 800 PPE groups (P=0.012) but increased slightly in the placebo group (0.5%); the difference in change in LDL-

cholesterol between the placebo and the two PPE group was statistically significant (P=0.021). Intervention with PPE was not associated with significant changes in HDL-cholesterol or triglyceride levels.

Baseline glucose, insulin, and HbA_{1c} concentrations did not differ significantly between the 3 groups (Table 4). Glucose levels decreased nonsignificantly in the 400 mg PPE (−1.3%) and 800 mg PPE (−2.6%) groups, but increased in the placebo group (2.7%, P=0.052). The difference in change in glucose concentrations between the placebo and the two PPE groups was statistically significant (P=0.008). Insulin levels decreased nonsignificantly in the 400 mg (−2.6%) and 800 mg (−5.8%) PPE groups, but increased in the placebo group (19.7%, P=0.059). The difference in change in insulin concentrations between the placebo and the two PPE groups was statistically significant (P=0.010). Levels of HbA_{1c} decreased slightly in both PPE groups; the difference in change did not differ significantly between the placebo group and the PPE groups (P=0.26). The three groups did not differ significantly in baseline concentrations of IGF-1 on in the change in this biomarker. Baseline IGFBP-3 and adiponection also did not differ significantly between the three groups, there were suggestive differences of borderline statistical significance in the changes between the placebo and the PPE groups.

Discussion

In this 2-month double-blind randomized trial among postmenopausal women, 2 doses of green tea in capsules of PPE (400 mg EGCG as PPE, and 800 mg EGCG as PPE) were compared to placebo capsules in order to examine their short-term effects on circulating hormones, lipids, glucose, insulin, HbA_{1c}, adiponectin, and growth factor concentrations. Based on urinary tea catechin concentrations, compliance in the 2 PPE and placebo groups appears excellent. Urinary catechin levels remained low in the placebo group, but increased significantly during the intervention in both PPE groups; levels were intermediate in the 400 mg group and highest in the 800 mg group. Although there was not a proportionate increase in urinary EGC levels in the 400 mg group, more EGC became methylated in the 400 PPE group, possibly because of enzyme saturation at this level and a smaller proportion of EGC was converted to 4′-MeEGC in the 800 mg PPE group. In fact, the sum of EGC and 4-MeECG in the 400 mg PPE group was about half of the levels in the 800 mg PPE group. The urinary EGC concentrations in the 800 mg PPE group are akin to levels found in habitual green tea drinkers in Shanghai (25). Although baseline EC levels differed significantly between the 3 groups, EC is not a specific marker of tea consumption and is found in numerous other dietary sources such as apples, wine and chocolate (26, 27). Our overall results suggest that 400 mg and 800 mg PPE supplementation had beneficial effects on lipid and glucose profiles and may possibly influence the ratio of testosterone to estradiol.

Supplementation with 400 mg and 800 mg PPE did not produce consistent patterns of changes in serum estradiol, estrone, or testosterone levels. Although estradiol and testosterone decreased 6.3% and 6.9%, respectively, in the 800 mg PPE group, an unexplained 6.6% reduction in estradiol was found in the placebo group making it difficult to interpret the changes observed in the 800 mg PPE group. Similar reductions in estradiol and testosterone were not found in the 400 mg PPE group. Because the number of years after menopause appeared to differ between the three arms, we further adjusted for years stopped menstruating and the results remained largely similar. Although there was a suggestive difference in the ratio of total testosterone to total estradiol between the placebo and PPE groups, this was due largely to a change in the placebo group. Additional studies will be needed to clarify if green tea supplementation in humans influences aromatase activity (7). We found significant differences in the change in SHBG levels between the

groups, but this is likely a chance finding since the decrease in SHBG was only found in the 400 mg PPE but not in the 800 mg PPE group. The difference in change in SHBG levels between the 400 mg PPE and placebo group remained even after adjustment for changes in weight (data not shown). We are not aware of other data from controlled intervention studies on the effects of green tea on circulating hormone levels. The strongest evidence of a hormonal effect of green tea came from a small cross-sectional study we conducted among Chinese women in Singapore in which we observed a 13% reduction in estrone levels (P=0.03) and a borderline statistically significant reduction in estradiol levels among regular green tea drinkers compared to nondrinkers (4). However, this inverse association between green tea intake and circulating levels of estradiol, estrone, and testosterone were not confirmed in a cross-sectional study we conducted among Asian-American women in Los Angeles County (3).

We observed significant reductions in LDL-cholesterol in both the 400 mg and 800 mg PPE groups, but no comparable changes in HDL-cholesterol or triglyceride levels. Changes in lipid levels in association with green tea have been investigated in randomized intervention studies of 12 weeks (28–30), 8 weeks (31, 32) and 4–6 weeks duration (33–35). All three 12-weeks studies found significant reductions in LDL-cholesterol levels among those randomized to green tea; these differences between the groups were significantly different in the two larger studies (~120 subjects in each study arm) (28, 29) but not in the smaller study (~40 subjects in each study arm) (30). Results from the shorter (4–8 weeks) intervention studies are mixed but these studies were also smaller; three studies had ~45 subjects in each study arm (32, 34, 35) and two studies had ~16 in each study arm (31, 33). Three of these studies found nonsignificant reductions in LDL-cholesterol levels (6% to 11%) among those randomized to the green tea group (31, 33, 35) but these differences in changes did not differ significantly between the green tea and control groups. Small sample sizes, heterogeneous study populations including limiting study to diabetics or persons with metabolic syndrome (31, 32, 34), and using different green tea agents may have contributed to some of the differences in the findings related to LDL-cholesterol. Changes in HDL-cholesterol and triglyceride levels were also investigated in the above mentioned green tea intervention studies (27–33); no significant differences in changes in these biomarkers were found. The mechanisms by which green tea influences LDL-cholesterol levels is not known but it has been found to increase LDL receptor activity in experimental settings (36).

We observed statistically nonsignificant reductions in glucose (1.3% to 2.6%) and insulin (2.6% to 5.6%) levels in the 400 mg and 800 mg PPE groups and unexpected increases in these two biomarkers, particularly a large increase in insulin levels in the placebo group. These differences in change in glucose and insulin levels between the placebo and PPE groups were statistically significant. Glycosylated hemoglobin, a longer term indicator of blood glucose levels, decreased nonsignificantly in the two PPE arms but this difference in change did not differ between the placebo and PPE groups. There are supportive *in vitro* and animal studies suggesting that green tea catechins could improve glucose homeostasis (11, 12), but statistically significant supportive results from short-term intervention studies are lacking. Five of the above mentioned intervention studies on green tea and lipid levels also evaluated biomarkers related to glucose control (29–32, 34). Glucose levels decreased in three (29, 31, 34) of the five studies (29–32, 34); results were borderline statistically significant in one study (34). Insulin levels decreased 9% in one study (30) but negligibly (~1%) in two other studies (32, 34). HbA_{1c} levels decreased in one study (31) but increased significantly in another study (32). Thus, datafrom human studies is sparse and based largely on a few relatively small studies.

There were borderline statistically significant reductions in IGFBP-3 levels in both the 400 mg and 800 mg PPE groups; the difference in change in IGFBP-3 levels between placebo

and PPE groups was nearly statistically significant (P=0.078). We did not observe any statistically significant differences in change of IGF-1 levels between groups. We are not aware of results on IGF-1 and IGFBP-3 and green tea in intervention studies. In a cross-sectional study of healthy Asian-American women in Los Angeles County, green tea intake was unrelated to circulating IGF-1 and IGFBP-3 levels (3). In a cross-sectional study in Japan, high green tea intake was associated with high IGF-1 levels but was unrelated to IGFBP-3 levels (37). Green tea intervention did not have any significant effects on adiponectin levels in this study. This finding differs from cross-sectional results we recently reported in Asian American women in which green tea intake was associated with significantly elevated levels of adiponectin (38). Although adiponectin levels increased in association with green tea intervention in two (30, 31) of the three studies (30, 31, 34); equally large increases were also observed in the control groups and none of the changes were statistically significantly different.

The significance of our finding of beneficial effects of green tea on lipid and glucose-related markers in relation to breast cancer risk remains to be established. However, with the strong link between diabetes and risk of breast cancer and other cancers (15), beneficial effects on green tea on glucose-related markers may have clinical importance. Interestingly, EGCG, the most abundant green tea catchin, has been found to strongly inhibit hydroxyl-3-methyl-glutaryl-CoA reductase (HMGR), the rate-controlling enzyme of cholesterol synthesis (39). Lipophilic statins have been found to possess anticancer activity and inhibit mammary tumor growth (40). Although results are not all consistent, there is some support that the risk of developing breast cancer and recurrence may be influenced by use of certain statins (41, 42). It will be of interest to examine the separate and combined effects of green tea and lipid-lowering agents in relation to risk of breast cancer and other studies.

Finally, several strengths and limitations of this study should be mentioned. Participants were blinded to the tea capsule group to which they were randomly assigned. An important strength is that we had an objective marker of compliance in this study. All the above mentioned intervention studies on green tea and lipid levels (27–33) did not measure urinary or blood tea catechin levels. In addition, we used two doses of green tea supplementation (400 mg and 800 mg EGCG as PPE) that are comparable to drinking about 5–10 cups of green tea. Our results suggest that lipid and glucose changes occur with both 400 mg and 800 mg PPE doses and there were no significantly differences in changes in these biomarkers between the two PPE doses. However, there are several study limitations. The distribution of ethnicity of among the three groups was unequal although the pattern of results remained largely the same when we restricted the analysis to the Hispanic women, the largest group in this study. A study limitation is that the baseline measurement of circulating levels of the hormones, lipids, glucose and other markers were based on a single sample collection. The intervention was only for 2 months and, thus, the longer-term effects of green tea on circulating hormone levels are not addressed.

In summary, in this well-controlled, randomized, double-blinded, placebo-controlled intervention study in healthy postmenopausal women, green tea (400 and 800 mg PPE; ~5–10 cups) supplementation for 2 months had suggestive beneficial effects on LDL cholesterol concentrations and glucose-related biomarkers. Confirmation of these results in longer-term green tea intervention studies will enhance our understanding of the effects of green tea, a dietary factor of immense public health interest and potential.

Acknowledgments

We are extremely grateful to all the study participants and the data collection team at the General Clinical Research Center, particularly Martha Hernandez, Margaret Regan-Rainey and in the Department of Preventive Medicine, including Sushma Jain, June Yashiki and Jillian Wong. This work was supported by the Whittier Foundation, a

USC Cancer Center Core Support grant (2P30 CA14089-26) and a NIEHS grant (P30 ES07048), and R01CA122474 (CS Yang).

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Table 1

Characteristics of study participants at baseline and on average during 2 months of intervention

	Placebo N=32	400 mg EGCG as PPE n=37	800 mg EGCG as PPE N=34	p[1]	p[2]	p[3]
Race/ethnicity						
Whites	6	9	10			
Hispanic	16	19	20			
African-Am	5	7	3			
Asian-Am	5	2	1			
Age[4]	57.7 ± 6.29	59.6 ± 6.36	62.0 ± 9.42	0.062		
Age at menarche[4]	12.8 ± 1.50	12.8 ± 1.40	12.7 ± 1.26	0.89		
Age at menopause[4]	49.7 ± 4.97	49.8 ± 5.31	50.0 ± 4.76	0.24		
% parous	94%	86%	88%	0.60		
Weight (kg)						
Baseline	74.6 (67.8, 81.5)	77.9(72.4, 83.5)	71.6 (67.3, 75.9)	0.26		
Ave month 1–2	74.7 (67.9, 81.6)	78.4(72.8,84.0)	71.7 (67.4,76.0)			
Change (%)	0.05%	0.45%	0.13%			
P	0.82	0.009	0.58		0.30	0.26
Body mass index (BMI) kg/m^2						
Baseline	29.1(26.8, 31.4)	29.9 (27.9,31.8)	28.7 (27.2,30.4)	0.70		
Ave month 1–2	29.1(26.8, 31.4)	30.0 (28.1,32.0)	28.8 (27.2,30.5)			
Change (%)	0.02%	0.17%	0.07%			
P	0.79	0.01	0.45		0.29	0.37
Alkaline phosphatase (ALP) (U/l)						
Baseline	70.5 (65.0,76.5)	72.9 (67.6,78.7)	73.3 (67.7,79.3)	0.77		
Ave month 1–2	73.2 (67.0,79.9)	73.4 (67.6,79.7)	73.0 (67.0,79.5)			
Change%	3.8%	0.7%	−0.4%		0.09	0.60
P	0.08	0.66	0.77			
Aspartate aminotransferase (AST) (U/l)						
Baseline	24.0 (22.2,26.0)	24.4 (22.8,26.3)	23.7 (22.0,25.6)	0.85		
Ave month 1–2	23.6 (21.8,25.6)	23.5 (21.8,25.3)	24.8 (23.0,26.9)			
Change%	−1.4%	−4.0%	4.7%		0.72	0.06

	Placebo N=32	400 mg EGCG as PPE n=37	800 mg EGCG as PPE N=34	p*1*	p*2*	p*3*
P value	0.66	0.25	0.13			
Alanine aminotransferase (ALT) (U/l)						
Baseline	20.5 (18.1,23.3)	23.7 (21.1,26.6)	20.6 (18.2,23.2)	0.16		
Ave month 1–2	21.9 (19.0,25.3)	22.8 (20.0,26.1)	23.7 (20.6,27.2)			
Change (%)	6.6%	−3.5%	15.1%		0.82	0.01
P value	0.35	0.40	0.011			

*1*P value for difference between the 3 groups at baseline (ANOVA for continuous variable, 2 df)

*2*P value for difference in change between the placebo versus the two PPE groups

*3*P value for difference in change between the 400 mg and 800 mg PPE groups

*4*Means and standard deviation are shown

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Table 2

Mean (95% confidence interval) urinary tea catechin concentrations at baseline and on average during 2 months of intervention by treatment group

	Placebo	400 mg EGCG as PPE	800 mg EGCG as PPE	p[1]	p[2]	p[3]
EGC[4] (μmol/g Cr)						
Baseline	0.80 (0.33,1.27)	0.78 (0.44,1.12)	0.84 (0.36,1.31)	0.98		
Ave month 1–2	0.77 (0.39,1.15)	2.25 (1.58,3.02)	8.49 (5.93, 11.0)			
Absolute change	−0.03 (−0.43,.36)	1.47 (0.70,2.24)	7.65 (5.10,10.2)			
P value	0.86	<0.001	<0.001		<0.0001	<0.0001
4′-MeEGC[4](μmol/g Cr)						
Baseline	0.19 (0.05,0.34)	0.56 (0.06,1.06)	0.38 (0.00,0.75)	0.40		
Ave month 1–2	0.47 (0.03,0.91)	7.73 (−0.5.15.9)	10.8 (7.5, 14.0)			
Absolute change	0.27 (−0.17,0.72)	7.16 (−1.1,15.4)	10.4 (7.1,13.6)			
P value	0.22	0.086	<0.001		0.013	0.48
EC[4] (μmol/g Cr)						
Baseline	1.37 (0.53,2.21)	0.74 (0.40,1.09)	2.86 (0.92,4.80)	0.039		
Ave month 1–2	1.87 (0.91,2.83)	3.49 (2.56,4.43)	13.2 (10.0,16.3)			
Absolute change	0.50 (−0.22,1.2)	2.75 (1.82,3.68)	10.33 (6.7,14.0)			
P value	0.17	<0.001	<0.001		0.0002	<0.0001
M4[4] (μmol/g Cr)						
Baseline	0.66 (0.23,1.09)	0.46 (0.09,0.83)	0.34 (0.13,0.55)	0.43		
Ave month 1–2	0.54 (0.22,0.86)	1.96 (0.95,4.1)	2.51 (0.95, 4.08)			
Absolute change	−0.12 (−0.56, 0.32)	1.50 (0.29,2.70)	2.17 (0.59,3.76)			
P value	0.59	0.011	0.009		0.009	0.47
M6[4] (μmol/g Cr)						
Baseline	19.5 (13.2,25.8)	15.2 (8.7,21.8)	19.3 (11.5,27.2)	0.60		
Ave month 1–2	18.8 (9.3,28.3)	48.0 (36.1,59.8)	57.8 (44.0,71.6)			
Absolute change	−0.68 (−8.5,7.1)	32.7 (19.0,46.4)	38.5 (26.2,50.7)			
P value	0.86	<0.001	<0.001		<0.0001	0.53

[1] P value for difference between the 3 groups at baseline (ANOVA for continuous variable, 2 df)

[2] P value for difference in change between the placebo versus the two PPE groups

[3] P value for difference in change between the 400 mg and 800 mg PPE groups

[4] EGC=epigallocatechin; EC=epicatechin; MeEGC= 4′-O-methyl-epigallocatechin; M4= 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone (metabolite of EGC); M6= 5-(3′,4′-dihydroxy-phenyl)-γ-valerolactone (metabolite of EC)

Table 3

Geometric mean (95% confidence interval) serum hormone concentrations at baseline and on average during 2 months of intervention by treatment group

	Placebo	400 mg EGCG as PPE	800 mg EGCG as PPE	p*1*	p*2*	p*3*
Estradiol (E2) (pg/ml)						
Baseline	8.2 (6.7,10.0)	9.1 (7.6,10.9)	9.6 (7.9,11.6)	0.54		
Ave month 1–2	7.7 (6.3,9.3)	9.2 (7.7,11.1)	9.0 (7.4,10.9)			
Change %	−6.6%	1.2%	−6.3%			
P value	0.084	0.81	0.16		0.26	0.17
Estrone (E1) (pg/ml)						
Baseline	32.5 (28.3,37.3)	36.8 (32.3,41.8)	36.7 (32.0,42.1)	0.36		
Ave month 1–2	31.4 (27.4,36.0)	34.9 (30.7, 39.6)	35.9 (31.4,41.1)			
Change %	−3.5%	−5.1%	−2.1%			
P value	0.29	0.15	0.61		0.89	0.58
Testosterone (T) (pg/ml)						
Baseline	184 (152, 223)	226 (190,270)	208 (172,251)	0.30		
Ave month 1–2	185 (163,278)	224 (187,298)	190 (152,264)			
Change %	3.0%	−0.8%	−6.9%			
P value	0.43	0.80	0.11		0.15	0.25
Androstenedione (A4) (pg/ml)						
Baseline	431 (367,505)	446 (384,518)	464 (397, 544)	0.80		
Ave month 1–2	418 (362,482)	470 (411,537)	462 (401, 532)			
Change %	−3.0%	5.3%	−0.6%			
P value	0.42	0.25	0.90		0.35	0.41
T/E2						
Baseline	22.4 (18.2,27.7)	24.9 (20.5,30.3)	21.7 (17.7,26.7)	0.62		
Ave month 1–2	24.7 (20.1,30.3)	24.4 (20.2,29.5)	21.7 (17.8,26.6)			
Change %	9.9%	−1.9%	0.0%			
P value	0.096	0.68	1.00		0.053	0.61
Sex hormone-binding globulin (SHBG) (nmol/l)						
Baseline	41.8 (35.6,49.0)	40.1 (34.6, 46.5)	39.0 (33.3,45.6)	0.83		
Ave month 1–2	41.6 (35.5,48.9)	37.4 (32.2, 43.4)	39.6 (33.8,46.4)			

	Placebo	400 mg EGCG as PPE	800 mg EGCG as PPE	p[1]	p[2]	p[3]
Change %	−0.4%	−6.8%	1.5%			
P value	0.80	0.002	0.51		0.33	0.008

[1] P value for difference between the 3 groups at baseline (ANOVA for continuous variable, 2 df)

[2] P value for difference in change between the placebo versus the two PPE groups

[3] P value for difference in change between the 400 mg and 800 mg PPE groups

Table 4

Geometric mean (95% confidence interval) serum lipid and other biomarkers at baseline and on average during 2 months of intervention by treatment group

	Placebo	400 mg EGCG as PPE	800 mg EGCG as PPE	p*1*	p*2*	p*3*
Cholesterol (mg/dl)						
Baseline	216 (203,231)	218 (205,231)	208 (195,221)	0.54		
Ave month 1–2	216 (203,229)	207 (196,219)	202 (190,214)			
Change %	−0.2%	−5.0%	−3.1%			
P value	0.90	0.01	0.045		0.072	0.44
Cholesterol LDL (mg/dL)						
Baseline	127 (114,142)	129 (117,143)	122 (110,136)	0.74		
Ave month 1–2	128 (116,141)	119 (109,130)	114 (104,126)			
Change %	0.5%	−7.9%	−6.6%			
P value	0.86	0.007	0.012		0.021	0.73
Cholesterol HDL (mg/dL)						
Baseline	61 (56,67)	62 (57,67)	59 (54,63)	0.59		
Ave month 1–2	61 (56,67)	62 (57,67)	58 (53,63)			
Change %	−0.3%	0.0%	−1.2%			
P value	0.87	0.98	0.56		0.89	0.61
Triglycerides (mg/dL)						
Baseline	106 (91,124)	107 (93,123)	108 (93,125)	0.99		
Ave month 1–2	109 (94,127)	106 (93,121)	118 (103,136)			
Change %	3.2%	−1.1%	9.8%			
P value	0.57	0.79	0.042		0.92	0.090
Glucose (mg/dL)						
Baseline	97 (91,103)	99 (94,105)	103 (97,110)	0.32		
Ave month 1–2	99 (94,105)	98 (93,103)	101 (95,106)			
Change %	2.7%	−1.3%	−2.6%			
P value	0.052	0.13	0.15		0.008	0.50
Insulin (uIU/mL)						
Baseline	7.3 (5.7, 9.5)	8.5 (6.6,10.9)	9.5 (7.4,12.3)	0.39		
Ave month 1–2	8.9 (6.9,11.5)	8.3 (6.5,10.5)	9.0 (7.0,11.5)			

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	Placebo	400 mg EGCG as PPE	800 mg EGCG as PPE	p*1*	p*2*	p*3*
Change %	19.7%	−2.6%	−5.8%			
P value	0.059	0.65	0.33		0.010	0.69
Glycosylated Hemoglobin (%) (HbA_{1c})						
Baseline	5.9 (5.7,6.2)	5.9 (5.6,6.2)	6.3 (6.0,6.5)	0.071		
Ave month 1–2	5.9 (5.6,6.2)	5.8 (5.5,6.0)	6.2 (5.9,6.5)			
Change %	−0.3%	−1.5%	−1.1%			
P value	0.71	0.044	0.10		0.26	0.71
IGF-1 (ng/ml)						
Baseline	110 (97,124)	109 (97,122)	95 (84,107)	0.15		
Ave month 1–2	110 (98,124)	109 (98,122)	94 (83,106)			
Change %	0.3%	0.1%	−0.8%			
IGFBP-3 (μg/ml)						
Baseline	3.9 (3.5,4.2)	4.0 (3.7,4.4)	3.7 (3.4,4.0)	0.37		
Ave month 1–2	3.9 (3.6,4.2)	3.9 (3.6,4.3)	3.6 (3.3,3.9)			
Change %	0.4%	−2.01%	−2.8%			
P value	0.76	0.068	0.053		0.078	0.66
Adiponectin (μg/ml)						
Baseline	17.1 (14.4,20.1)	16.4 (14.1,19.1)	17.0 (14.5,20.0)	0.93		
Ave month 1–2	18.0 (15.2,21.3)	16.3 (14.0,19.0)	16.7 (14.1,19.6)			
Change %	5.4%	−0.6%	−2.2%			
P value	0.27	0.90	0.58		0.084	0.78

*1*P value for difference between the 3 groups at baseline (ANOVA for continuous variable, 2 df)

*2*P value for difference in change between the placebo versus the two PPE groups

*3*P value for difference in change between the 400 mg and 800 mg PPE groups

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