RESEARCH PAPER

Green tea improves metabolic biomarkers, not weight or body composition: a pilot study in overweight breast cancer survivors

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Abstract

Background: Overweight status after breast cancer treatment may increase a woman's risk for recurrent disease and/or early onset cardiovascular disease. Green tea has been proposed to promote weight loss and favourably modify glucose, insulin and blood lipids. This pilot study tested the effect of daily decaffeinated green tea consumption for 6 months on weight and body composition, select metabolic parameters and lipid profiles in overweight breast cancer survivors.

Methods: The effect of daily decaffeinated green tea intake on weight, body composition and changes in resting metabolic rate, energy intake, glucose, insulin, homeostasis model assessment – insulin resistance (HOMA-IR) and lipids was evaluated in overweight breast cancer survivors. Participants had a mean weight of 80.2 kg; body mass index (BMI) 30.1 kg m^{-2}; and body fat 46.4%. Participants ($n = 54$) were randomised to 960 mL of decaffeinated green or placebo tea daily for 6 months.

Results: Mean (SD) tea intake among study completers ($n = 39$) was 5952 (1176) mL week^{-1} and was associated with a significant reduction in energy intake ($P = 0.02$). Change in body weight of -1.2 kg (green tea) versus $+0.2$ kg (placebo) suggests a weight change effect, although this was not statistically significant. Decaffeinated green tea intake was associated with elevated high-density lipoprotein (HDL) levels ($P = 0.003$) and nonsignificant improvements in the HDL/LDL ratio and HOMA-IR (-1.1 ± 5.9: green tea; $+3.2 \pm 7.2$: herbal).

Conclusions: Intake of decaffeinated green tea for 6 months was associated with a slight reduction in body weight and improved HDL and glucose homeostasis in overweight breast cancer survivors.

Introduction

Epidemiologic and animal studies support the health benefits of habitual green tea consumption, which include anti-obesity properties (Zaveri, 2006); a reduced risk of cardiovascular disease (Wolfram, 2007); decreased levels of oxidative stress (Cabrera *et al.*, 2006); as well as anti-proliferative (Cabrera *et al.*, 2006), anti-inflammatory (Dona *et al.*, 2003) and anti-diabetic effects (Matsumoto *et al.*, 1993). Thus, daily green tea consumption may be an effective adjuvant therapeutic approach for modifying metabolic-related disease risk, particularly in overweight people.

A number of mechanisms have been proposed by which green tea and its constitutive polyphenolic catechins may modulate body weight (Lin & Lin-Shiau, 2006; Wolfram *et al.*, 2006; Moon *et al.*, 2007). For example, green tea and its extracts have been shown to induce carbohydrate malabsorption (Zhong *et al.*, 2006); down-regulate fatty acid synthase (Zhang *et al.*, 2006; Moon *et al.*, 2007); suppress pancreatic and gastric lipase (Chantre & Lairon, 2002); induce thermogenesis (Shixian *et al.*, 2006; Diepvens *et al.*, 2007); incite sympathetic nervous system activity and lipolysis (Dulloo *et al.*, 2000); reduce adipocyte differentiation (*Wolfram et al.,* 2006); and alter the satiety response (Westerterp-Plantenga *et al.*, 2006; Kao *et al.*, 2000). A small number of human clinical trials testing hypotheses related to green tea and weight control have been conducted and, although the available studies are indicative of an overall anti-obesity effect, the findings across studies have been inconsistent (Dulloo *et al.*, 1999; Tsuchida *et al.*, 2002; Chan *et al.*, 2006). One possible explanation for the inconsistent results may be differences in the amount of constitutive green tea catechin/polyphenols in the study populations and thus illustrates the need for further studies to determine the appropriate dosing strength required to stimulate anti-obesity effects. Additionally, the use of caffeinated versus decaffeinated green tea in some studies may further complicate the interpretation of the effect of green tea intake on weight loss because the caffeine together with epigallocatechin gallate (EGCG), the main catechin in green tea, may have a beneficial synergistic effect, or perhaps a confounding effect.

Green tea consumption has been consistently inversely associated with cardiovascular disease (Jochmann *et al.*, 2008), most likely because of its anti-inflammatory (Dona *et al.*, 2003) and antioxidant effects (Osada *et al.*, 2001). Epidemiological studies indicate that the daily intake of green tea is associated with a significant reduction in mortality from cardiovascular disease (Kuriyama *et al.*, 2006). The results of one clinical study suggest that daily intake of green tea may significantly decrease plasma oxidised low-density lipoprotein (LDL) concentrations (Inami *et al.*, 2007); a significant risk factor for cardiovascular disease. Furthermore, green tea may favourably modulate blood glucose homeostasis and, as such, may be an appropriate dietary modification to promote reductions in glucose and insulin among people with diabetes or insulin resistance as previously demonstrated (Venables *et al.*, 2008). However, this has not been consistently confirmed (Mackenzie *et al.*, 2007), perhaps because the effect is dependent on the dose administered (Islam & Choi, 2007). Proposed biological mechanisms for these beneficial effects include the inhibition of hepatic gluconeogenesis (Collins *et al.*, 2007), inhibition of glucose uptake in the brush border membranes of the small intestine (Shimizu *et al.*, 2000) and enhanced insulin activity (Anderson & Polansky, 2002). Human clinical trials have not consistently corroborated this anti-diabetic activity, although studies in animal models have provided evidence supporting a role for the green tea polyphenols in the absorption and utilisation of glucose (Sabu *et al.*, 2002).

Obesity, and its related co-morbidities, results in a poorer prognosis for both pre- and postmenopausal breast cancer survivors (Coates *et al.*, 1999; Pasanisi *et al.*, 2006; Lipscombe *et al.*, 2008). Overweight status has been suggested to increase the risk for breast cancer recurrence in most (Rock & Demark-Wahnefried, 2002), but not all (Caan *et al.*, 2006), studies, as well as increase the risk for co-morbid conditions such as metabolic syndrome (Sinagra *et al.*, 2002), cardiovascular disease (McTiernan, 2005) and diabetes (Fox *et al.*, 2006). This pilot study tested the effect of daily decaffeinated green tea consumption for 6 months on body weight and body composition in overweight breast cancer survivors. Secondary endpoints included testing changes in select metabolic parameters and lipids in women randomised to decaffeinated green tea versus an herbal placebo tea.

Materials and methods

Study population

This pilot study was conducted among overweight/obese women residing in Southern Arizona who had completed primary treatment(s) for invasive, early stage (I–III) breast cancer at least 12 months prior and no more than 10 years prior to study enrolment. To be eligible for participation, women had to demonstrate a body mass index (BMI) in the range 25–40 kg m^{-2}, have received chemotherapy (neo-adjuvant or adjuvant with any medically-prescribed agent/regime) for treatment of invasive breast cancer, aged 18–80 years at the time of study enrolment, have reported no current use of tobacco (past 12 months) and have no chronic illness such as diabetes, cardiovascular disease (or to be taking medications to control blood glucose and/or blood lipids) or cancer other than the previously treated breast cancer, and also had to be willing to refrain from all weight loss diets and supplements for a study period of 6 months. Subjects were also required to successfully complete a 2-week run-in period consisting of daily intake of 960 mL of herbal tea. All subjects must have completed the consent process prior to study enrolment. This study was approved by the University of Arizona Human Subjects Committee prior to initiation.

Study design

Using a randomised, double-blind, placebo-controlled design, this pilot study sought to test the hypothesis that daily decaffeinated green tea consumption in comparison with herbal placebo tea consumption for a period of 6 months would result in significant reductions in body weight and improvements in metabolic parameters among overweight breast cancer survivors. All subjects who successfully completed the run-in period were randomised to either decaffeinated green tea or herbal placebo tea. Randomisation was completed using a table of random numbers, independent of study personnel, at the Biometry Shared Service at the Arizona Cancer Center. The investigators and subjects were blinded to the tea compositions until all subjects had completed the trial and data analysis was underway.

Materials

This study used decaffeinated green tea and herbal tea product provided by Unilever, Lipton (Unilever Bestfoods Company North America, Englewood, NJ, USA). The green tea bags comprised between 550–700 mg tea solids, providing an average catechin dose of 58.91 mg bag^{-1} and 32.21 mg EGCG per bag. Caffeine content averaged 6.68 mg bag^{-1}. The citrus-based herbal placebo tea used in the study was specifically manufactured for use in tea intervention trials of this nature and contained no EGCG. Blinded taste testing prior to study initiation showed that people ($n = 6$) were unable to correctly differentiate green tea from herbal tea product.

Intervention and adherence

Women were asked to consume 960 mL of green tea daily. Specific instructions for tea preparation were provided by the study coordinator during the initial clinic visit. To review, individual tea bags were placed in the provided tea mug and 240 mL of boiling water was added and allowed to steep for a period of 3 min. The tea bag was then removed from the cup and stored in a provided bag to track compliance to tea intake. Subjects were asked to consume the tea product four times daily and up to two doses were allowed at any single dosing (two bags in 500 mL of boiling water).

Adherence was assessed using daily tea logs where participants recorded the number of tea bags consumed daily. In addition, participants returned all used and unused tea bags to the clinic during their regularly scheduled monthly visits. Overall compliance among study participants from both groups was good, with a mean (SD) tea consumption among women completing the study of 24.8 (4.9) bags week^{-1} [5952 (1176) mL week^{-1}].

Outcome assessments

Anthropometrics

The primary outcomes for this research were changes in body weight and body composition. All measures were assessed at baseline, prior to randomisation to tea assignment and again at 6 months post-treatment. Body weight, height and waist and hip circumference were measured following standardised protocols (Khosla & Lowe, 1967; Lean *et al.*, 1995). Body composition measurements (mean percentage body fat and lean mass) were assessed using dual energy X-ray absorptiometry (DXA) (GE/LUNAR PRODIGY, software, version 6.5 and 6.7; GE Medical Instruments, Madison, WI, USA) in accordance with standardised procedures under the direction of a certified radiation technician at the Body Composition Laboratory of Dr. Scott Going (Department of Physiology, University of Arizona).

Resting energy expenditure

Secondary endpoint assessments included changes in resting metabolic rate (RMR), dietary energy and macronutrient intake, fasting lipids, glucose, insulin, and homeostasis model assessment – insulin resistance (HOMA-IR). Resting energy expenditure (REE) (Herman *et al.*, 2005) was assessed by the respiratory gas exchange method using an open-circuit indirect calorimeter (DeltaTrac™ MBM-100; SensorMedics, Yorba Linda, CA, USA). Briefly, subjects arrived at the clinic between 06.00 h and 07.30 h in a fasting state, having not participated in any physical activity during the previous 12 h. The measurement was taken in a darkened room, which was maintained at constant temperature in the range 22–23 °C. Subjects remained in a supine position on a recliner with no voluntary skeletal muscle activity; a 30-min rest period was completed prior to measurement. A minimum of 5 min in 'steady state' was required; measures were then taken every 5 min over a 2-h period. The average of VO_2 and VCO_2 from a 5-min equilibrated period with least variation was used to calculate REE via Weir formula: energy expenditure = $1.44 \times [3.941 \times$ oxygen consumption (VO_2 mL min^{-1}) + $1.106 \times$ carbon dioxide production (VCO_2 in mL min^{-1})] $- 2.17 \times$ urinary nitrogen.

Dietary intake

Dietary intake was estimated using repeated administrations of the validated Arizona Food Frequency Questionnaire (AFFQ) (baseline and 6 months) (Ritenbaugh *et al.*, 1997; Thomson *et al.*, 2003). The AFFQ is a scannable 153 food/beverage item questionnaire, comprising a

regionally-appropriate modification of the food frequency component of the validated Block NCI Health Habits and History Questionnaire, and includes responses on serving sizes and frequency of intake using a Likert-type scale from more than three times daily to rarely/never. Nutrient analyses of the AFFQ were completed by the Behavioral Measurement Shared Services at the Arizona Cancer Center using the proprietary METABOLIZE Software Program specifically developed by programming professional staff of the University of Arizona for the quantification of nutrient intake derived from the AFFQ. Questionnaires were reviewed for completeness by the study personnel and participants were contacted by telephone to ascertain missing data. Questionnaires missing more than five items were considered to be incomplete and participants were contacted to complete these. Using this approach, there were no FFQs missing more than five items; all FFQs were included in the analysis. METABOLIZE, the AFFQ analysis program, is a four-module system of programs that reduces data from scanned questionnaires to individual nutrients per day. The database used to quantify nutrient intake from the AFFQ was derived from the Continuing Survey of Food Intake by Individuals 1994–1996, 1998 (CSFII) and the Nutrient Database for Standard Reference (NDS-R) (versions 11–13) (USDA, 2000).

Physical activity

Physical activity was assessed at baseline and 6 months using the validated Arizona Activity Frequency Questionnaire (AAFQ) (Staten *et al.*, 2001), a 1-month adaptation of the validated Minnesota Leisure Time Physical Activity Questionnaire (Taylor *et al.*, 1978). The AAFQ is a scannable questionnaire that provides output in hours per day at each activity level, hours in load-bearing activities, hours in social activities, and hours in each major activity category, as well as the number of activities reported for each category. The AAFQ groups physical activity by leisure, recreational, household, occupational and 'other' activity categories.

Metabolic parameters

Fasting glucose and insulin were quantified according to manufacturer's instructions using the One Touch Ultra Mini blood glucose monitoring system (Lifescan, Milpitas, CA, USA) and human insulin specific radioimmunoassay (RIA) kit (HI-14K; Linco Research, St Charles, MO, USA), respectively. The insulin RIA intra-assay coefficient of variation was 1.8%. Fasting lipids including total cholesterol, high-density lipoprotein (HDL), LDL and triglycerides (TG) were measured at baseline (prior to tea intervention) and again at 6 months utilising the Cholestech LDX System (Hayward, CA, USA) in accordance with the manufacturer's instructions.

Statistical analysis

Measures of central tendency were computed and frequencies and distributions produced for demographic and clinical characteristics of the study participants and checked for missing values, normalcy and outliers, where appropriate, using the Shapiro–Wilk statistic for the normality test and Pearson's chi-square test for skewness and kurtosis. At all study time points, triplicate anthropometric measures and RMR were averaged and the mean was used in analyses. Baseline measurement values for anthropometry, dietary intake, physical activity and energy expenditure were subtracted from follow-up values to produce measures of change. Compliance with green or herbal tea use was calculated as the average of monthly tea bag counts derived from bag return rates. The HOMA-IR was computed by the standard equation: $HOMA\text{-}IR = (insulin_{0(uU\,ml^{-1})} \times glucose_{0(mmol\,l^{-1})})/22.5$ (Bonora *et al.*, 2000).

To examine differences in demographic and clinical characteristics and 6-month changes in anthropometric measures, dietary intake, energy expenditure and metabolic parameters between green tea and herbal tea groups, independent group Student *t*-tests were carried out. The significance of changes from baseline to 6 months was tested with paired *t*-tests. The alpha level considered significant was set at $P < 0.05$. All statistical computation was carried out using SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Study attrition

A total of 74 women were consented for participation, with 54 successfully completing the run-in period. Reasons for run-in failure included intolerance or dislike of the tea product, difficulty consuming the tea beverage on a regular basis, personal reasons, and unwillingness to discontinue other organised approaches to weight loss throughout the study. Of the 54 women randomised, 29 were assigned to the green tea group and 25 to the herbal tea group, all of which provided complete anthropometric, clinical, dietary and demographic information for the study at baseline. At the 6-month measurement, six women randomised to green tea and nine randomised to herbal tea were lost to follow-up, for primary outcomes, including four who did not provide reasons for study discontinuation. Intolerance or dislike of tea product was reported by four subjects and difficulty adhering to study protocol as a result of busy schedules was reported by three subjects. For secondary biomarker outcomes, there was further reduction in sample size as a result of insufficient sample volume, refusal or difficult blood draws.

Comparison of demographic and anthropometric measures of women completing the 6-month visit and those who did not revealed no statistically significant differences between completers and noncompleters with respect to clinical, demographic and lifestyle data. Potential differences between completers classified as being overweight or obese were not assessed as a result of the small sample size.

Demographic and clinical characteristics

The demographic and clinical characteristics of the study population at baseline are presented in Table 1. On average, subjects entered the study with a body weight of 80.2 kg, BMI of 30.1 kg m^{-2} and a waist-to-hip ratio of 0.8. All had received chemotherapy and 56.4% also received radiation therapy to treat their breast cancer.

Women randomised to the herbal group had a slightly lower BMI (28.7 kg m^{-2} versus 31.0 kg m^{-2}; $P = 0.10$) and greater frequency of stage II disease (75.0% of group versus 45.5% of green tea group subjects; $P = 0.09$).

Dietary intake and physical activity

Comparison of dietary and physical activity data across treatment groups at 6 months (Table 2) showed an average reduction in energy intake, primarily reported as carbohydrate calories, in subjects randomised to the green tea intervention, and such a change in intake was not reported among women assigned herbal tea. Assignment to the decaffeinated green tea beverage resulted in a significant reduction in caffeine intake at 6 months, whereas caffeine intake in the herbal tea group increased by 50 mg day^{-1} over the same time period, resulting in a

Table 1 Baseline demographics, clinical and lifestyle characteristics of breast cancer survivors participating in the green tea study ($n = 39$)

	All mean (SD)	Green tea ($n = 23$)	Placebo tea ($n = 16$)	P-value*
Age (years)	57.1 (8.2)	56.6 (8.1)	57.8 (8.5)	0.66
Height (cm)	163.5 (5.4)	162.4 (5.5)	165.0 (5.2)	0.15
Weight (kg)	80.2 (13.3)	81.9 (15.3)	77.8 (9.8)	0.34
BMI (kg m^{-2})	30.1 (4.2)	31.0 (4.3)	28.7 (3.8)	0.10
% Body fat from DXA	46.4 (4.6)	47.1 (4.7)	45.5 (4.4)	0.29
Waist-to-hip ratio	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.40
RMR (kJ day^{-1})	5315.0 (719.8)	5377.7 (832.8)	5214.5 (510.6)	0.50
Weight (kg) at 18 years	55.8 (7.4)	55.0 (7.3)	56.9 (7.7)	0.44
Weight (kg) 1 year prior to diagnosis for cancer	72.4 (14.5)	74.1 (16.5)	69.8 (10.9)	0.37
Weight (kg) at diagnosis for cancer	74.0 (15.5)	75.9 (17.8)	71.2 (11.4)	0.36
Alcohol (g day^{-1})	3.5 (5.2)	3.3 (4.9)	3.7 (5.7)	0.84
				Chi-square P-value*
Tobacco (%)				
None	59.00	60.90	56.30	0.77
Past	41.00	39.10	43.80	
Ethnicity (%)				
White	92.30	95.70	87.50	0.35
Other	7.70	4.30	12.50	
Education (%)				
Post college, college	50.00	52.20	6.60	0.69
Some college	39.50	34.80	46.70	
High school graduate	10.50	13.00	46.70	
Breast cancer stage (%)				
Stage I	28.90	45.50	6.30	0.09
Stage II	57.90	45.50	75.00	
Stage III	13.20	9.00	18.70	
Breast cancer treatment (%)				
Chemotherapy	100.00	100.00	100.00	1.00
Radiation	56.40	60.90	50.00	0.50
Hypertension (%)	15.40	21.70	6.30	0.19
Elevated cholesterol (%)	33.30	34.80	31.30	0.82

BMI, body mass index; DXA, dual X-ray absorptiometry; RMR, resting metabolic rate.
*Tests for difference between tea groups.

Table 2 Dietary intake and physical activity characteristics of breast cancer survivors participating in the green tea study (n = 39)

	Green tea (n = 23)				Placebo tea (n = 16)				
	Baseline	6 months	Δ	P for change*	Baseline	6 months	Δ	P for change*	P for groups[†]
Energy[‡] (kJ day^{-1})	7030.8 (3050.9)	5934.3 (2251.5)	−1096.5 (2059)	0.02	6315.2 (2343.6)	6352.8 (2000.4)	37.7 (1933.5)	0.95	0.11
Fat[‡] (g day^{-1})	56.8 (25.5)	50.4 (22.3)	−6.4 (12.6)	0.02	47.1 (19.1)	46.6 (19.3)	−0.4 (18.6)	0.93	0.25
Protein[‡] (g day^{-1})	66.0 (25.3)	56.9 (19.5)	−9.1 (16.6)	0.02	67.7 (23.5)	67.6 (21.2v	−0.1 (19.3)	0.98	0.14
Carbohydrates[‡] (g day^{-1})	230.7 (117.2)	188.0 (81.2)	−42.7 (87.7)	0.03	208.6 (98.5)	205.9 (86.7)	−2.7 (82.2)	0.9	0.18
Caffeine[‡] (mg)	133.3 (114.6)	97.2 (87.4)	−36.0 (71.7)	0.02	116.7 (71.6)	174.8 (147.4)[‡]	50.0 (126.2)	0.16	0.03
Total energy expenditure[‡] (kJ day^{-1})	8945 (1434)	8895 (1530)	−50 (1142)	0.95	8867 (1282)	8790 (1095)	−78 (1280)	0.95	0.95

*From baseline to 6 months.
[†]Difference in change in dietary intake between tea groups.
[‡]Dietary intake and total energy expenditure estimated with the Arizona Food Frequency Questionnaire and Arizona Activity Frequency Questionnaire, respectively.

Table 3 Body composition measures of breast cancer survivors participating in the green tea study (n = 39)

	Green tea (n = 23)				Placebo tea (n = 16)				
	Baseline	6 months	Δ	P for change*	Baseline	6 months	Δ	P for change*	P for groups[†]
Weight (kg)	81.9 (15.3)	80.7 (14.9)	−1.2 (4.1)	0.18	77.8 (9.8)	78.0 (9.1)	0.2 (2.5)	0.73	0.23
BMI (kg m^{-2})	31.0 (4.3)	30.5 (4.2)	−0.5 (1.5)	0.14	28.7 (3.8)	28.8 (3.7)	0.0 (1.0)	0.84	0.22
% Body fat	47.2 (4.8)	46.5 (5.6)	−0.6 (2.9)	0.31	45.5 (4.4)	45.9 (5.1)	0.4 (2.0)	0.4	0.21
Lean mass (kg)	40.34 (5.59)	40.16 (5.07)	−0.18 (1.65)	0.62	39.23 (2.50)	39.09 (2.30)	−0.14 (1.31)	0.68	0.93
Waist circumference (cm)	92.4 (9.6)	91.5 (10.9)	−0.9 (4.9)	0.37	93.6 (14.2)	90.4 (9.5)	−3.2 (7.6)	0.14	0.28
Hip circumference (cm)	113.3 (9.2)	112.5 (9.8)	−0.8 (6.9)	0.58	111.6 (9.6)	112.2 (9.1)	0.6 (3.2)	0.51	0.49
Waist-to-hip ratio	0.82 (0.07)	0.81 (0.08)	−0.00 (0.05)	0.94	0.83 (0.10)	0.80 (0.07)	−0.03 (0.07)	0.08	0.12
RMR (kJ day^{-1})	5415.4 (832.8)	5448.9 (1272.2)	33.5 (853.7)	0.85	5193.6 (523.1)	5151.7 (975.1)	−41.9 (912.3)	0.71	0.68

BMI, body mass index; RMR, resting metabolic rate.
*From baseline to 6 months.
[†]Difference in change in dietary intake between tea groups.

statistically significant difference in change in caffeine intake across treatment groups at 6 months (P = 0.03). No significant change in physical activity was shown.

Anthropometrics

Table 3 represents the analysis of change across tea treatment groups for body weight and related anthropometric measurements. Specifically, mean body weight was reduced by 1.2 kg at 6 months with green tea consumption, whereas assignment to the herbal tea group was associated with a slight rise in mean body weight of 0.2 kg over the same time period. These changes were not significant (P = 0.23). Similarly, BMI was reduced by 0.5 kg m^{-2} and percent body fat by 0.6 compared to decaffeinated green tea intake; these same measures remained stable or were slightly increased in the herbal

tea group, although these differences were not statistically significant.

Metabolic parameters

Table 4 represents changes in blood metabolic biomarkers, including lipids (total cholesterol, TG, LDL, HDL), glucose, insulin and HOMA-IR in response to 6 months of regular decaffeinated green tea or herbal tea consumption. Of interest, blood lipid values showed improvements in LDL cholesterol in all subjects over time, regardless of tea group assignment. Furthermore, HDL levels were significantly increased only in the green tea group between baseline and 6 months (P = 0.003), resulting in positive shifts in the HDL/LDL ratio with decaffeinated green tea compared to herbal tea consumption (data not shown). In the green tea group, a decrease in mean (SD) fasting

Table 4 Lipid, blood glucose, insulin and insulin growth factor (IGF) biomarker measures of breast cancer survivors participating in green tea study

	Green tea*					Placebo tea*					P for groups‡
	Baseline	6 months	P for change†	Δ	Baseline adjusted Δ	Baseline	6 months	P for change†	Δ	Baseline adjusted Δ	
Total cholesterol (mmol L^{-1})	5.9 (1.0)	5.6 (1.0)	0.16	−0.3 (0.9)	−0.4 (0.8)	6.9 (1.3)	6.3 (1.6)	0.11	−0.6 (1.2)	−0.4 (1.2)	0.93
Triglycerides (mmol L^{-1})	1.8 (1.0)	1.6 (2.1)	0.16	−0.2 (0.8)	−0.2 (0.7)	1.7 (0.9)	1.5 (0.8)	0.4	−0.1 (0.5)	−0.2 (0.5)	0.92
LDL (mmol L^{-1})	3.8 (0.9)	3.4 (1.1)	0.07	−0.5 (1.1)	−0.5 (0.9)	4.7 (1.1)	3.9 (1.3)	0.05	−0.7 (1.2)	−0.4 (1.2)	0.77
HDL (mmol L^{-1})	1.3 (0.39)	1.4 (0.4)	0.003	0.1 (0.2)	0.1 (0.2)	1.4 (0.4)	1.6 (0.4)	0.1	0.2 (0.4)	0.2 (0.3)	0.33
Glucose (mmol L^{-1})	6.5 (1.3)	6.7 (1.0)	0.47	0.2 (1.3)	0.1 (0.9)	7.0 (1.2)	7.0 (1.0)	0.96	0.0 (1.3)	0.2 (1.0)	0.62
Insulin (pmol L^{-1})	154.2 (148.6)	128.5 (68.1)	0.33	−25.7 (118.8)	−6.9 (53.5)	91.7 (27.1)	154.9 (139.6)	0.11	63.2 (138.9)	34.7 (138.9)	0.3
HOMA-IR	6.9 (7.4)	5.8 (3.4)	0.42	−1.1 (5.9)	−0.2 (2.7)	4.1 (1.6)	7.4 (7.4)	0.12	3.2 (7.2)	2.0 (7.3)	0.28

LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMO-IR, homeostasis model assessment – insulin resistance.

*n = 21, 20, 21, and 19 for green tea and n = 13, 14, 14, 14 for placebo tea for lipids, glucose, insulin, and HOMA-IR, respectively; P = 0.34 and P = 0.18 for difference at baseline between intervention groups in glucose and insulin, respectively.

†From baseline to 6 months within tea group.

insulin concentrations of −25.7(118.8) pmol L^{-1} was demonstrated between baseline and 6 months, whereas fasting insulin levels increased by 63.2 (138.9) pmol L^{-1} in the placebo tea group, resulting in a nonsignificant between group difference in change scores. Additionally, HOMA-IR scores were improved, although not significantly with green tea intake as compared to herbal (−1.1 ± 5.9, 3.2 ± 7.2, respectively).

Discussion

The results of this pilot study indicate improvements in metabolic status with daily decaffeinated green tea consumption for 6 months without a significant reduction in body weight, BMI or body fat in overweight breast cancer survivors. Specifically, decreases in LDL cholesterol, accompanied by increases in HDL cholesterol associated with green tea consumption, suggest a metabolic shift consistent with a reduction in cardiovascular risk in this population. Furthermore, decreases in insulin and in the HOMA-IR score were demonstrated with green tea consumption. Although beyond the scope of this research, these reductions may be clinically relevant if they were to be associated with decreasing the risk for type 2 diabetes over time (Haffner et al., 1996; Bonora et al., 2000; Jayagopal et al., 2002; Garcia-Estevez et al., 2003; Bakris et al., 2004; Wallace et al., 2004). While the expected changes in weight and body composition were not statistically significant, the metabolic trends support the use of decaffeinated green tea as a potentially clinically relevant dietary approach for reducing the risk of the development of various metabolic-related diseases for which overweight breast cancer survivors are particularly vulnerable.

In the present study, adherence data suggested that compliance was extremely good among those remaining in the study at 6 months (>94% in both groups); however, 960 mL of green tea per day provided, on average, 236 mg total catechins, comprising an intake level lower than that used in a study by Chantre & Lairon (2002) demonstrating weight-reducing effects and also comprising an intake approximately 50% lower than that used by Nagao et al. (2009) demonstrating a loss of central adiposity in overweight adults with type 2 diabetes mellitus. In support of this dosage level, Diepvens et al. (2006) demonstrated modest weight changes similar to this trial in a study of overweight female subjects with a green tea extract providing only 134 mg total catechins per day. Further confounding these results, intake in the fasting versus nonfasting state was not closely controlled for; and this factor can significantly alter the bioavailability of tea catechins (Chow et al., 2007).

The use of a green tea product relatively low in caffeine content may have compromised the efficacy of the green

tea intervention to modulate body weight. As reported by Dulloo et al. (2000), a demonstrated rise in RMR with green tea extract was apparent when green tea polyphenol intake was combined with caffeine. The tea catechins and caffeine appeared to act synergistically by targeting different enzymatic response along the norepinephrine–cyclic AMP axis. The relative importance of caffeine on weight loss is unclear. In a pilot clinical trial conducted by Dulloo et al. (1999), a significant increase in energy expenditure in relation to green tea was demonstrated in healthy males, independent of caffeine. In addition, a 12-week green tea leaf supplement trial conducted among obese Thai adults showed a rise in resting energy expenditure that was associated with a significant difference in weight loss compared to placebo (Auvichayapat et al., 2008). In the present study population, only small changes in RMR were shown, regardless of tea assignment, and the changes were not associated with a change in body weight.

Consumption of green tea catechins has been shown to improve numerous cardiovascular risk factors (Yang et al., 2004; Kuriyama et al., 2006; Shimazu et al., 2007; Nantz et al., 2009). The improvements in HDL as well as the HDL/LDL ratio associated with decaffeinated green tea intake among overweight breast cancer survivors are consistent with the results obtained in other trials among overweight patients with no history of cancer. For example, a double-blind, multicentre study in Japanese men and women with visceral-type obesity demonstrated significant improvements in body weight, systolic blood pressure and LDL cholesterol in subjects consuming 583 mg catechins daily for 12 weeks compared to the control group (Nagao et al., 2007). Another randomised, double-blind, controlled clinical trial of overweight/obese women who received 400 mg of a green tea extract in capsule form for 12 weeks showed significant decreases in TG and LDL cholesterol as well as significant increases in HDL compared to the placebo control group (Hsu et al., 2008). By contrast, a shorter duration feeding trial with approximately 642 mg total catechins daily intake resulted in no change in lipid parameters between intervention and control (mineral water) groups after 4 weeks. A subsequent in vitro study suggested that doses of catechins necessary to provide resistance of LDL to oxidation greatly exceed doses that would be achievable with usual tea intake (van het Hof et al., 1997). The favourable shift in lipids shown in some studies, including the present study, may be explained by the longer duration of tea administration and the selection of a study population demonstrating elevations in cardiovascular risk factors, including hyperlipidaemia, at the time of study entry.

The insulin-modulating effects of green tea in this study are supported by epidemiological studies that indicate a dose-dependent, inverse relationship between green tea intake and the risk of diabetes (Iso et al., 2006), although a direct effect of the tea consumption has not been demonstrated in association based studies. The modest difference in change in HOMA-IR between baseline and 6 months by tea treatment group demonstrated in this trial suggests that green tea consumption may improve insulin sensitivity although the mechanism of the green tea effect is unclear. This study demonstrated a nonsignificant reduction in carbohydrate intake in the green tea arm that might explain some of the effects observed for insulin and measures of insulin sensitivity. In contrast to these results, a trial of obese adult males was unable to demonstrate a significant change in oral glucose tolerance test in response to 8 week supplementation with 800 mg EGCG compared to placebo (Iso et al., 2006), while the Nagao trial of type 2 diabetics showed a significant improvement in insulin secretion in patients who received green tea (583 mg catechins) versus placebo tea (96 mg catechins) daily for 12 weeks (Nagao et al., 2007). Additional research in a larger sample is needed to determine if the effect on insulin is directly mediated by the green tea and its constituents or if green tea consumption appreciably alters macronutrient intake and satiety for specific food components to modify insulin sensitivity.

Due to the small sample size of this pilot study, elucidation of the results is limited as randomisation resulted in an unequal distribution of demographic and clinical characteristics upon study commencement. There were more women with stage II and stage III disease in the placebo group, while more women who received radiation therapy were randomised to the intervention group. Although these differences were not considered to be statistically significant, it is possible that they may have modified these results. Additionally, high attrition and lower catechin exposure compared to other trials further reduces interpretation of possible effects of green tea on body weight in this population.

Overweight/obesity and cardiovascular morbidity are common among women treated for breast cancer and remain a significant clinical concern (Herman et al., 2005; Whiteman et al., 2005; Abrahamson et al., 2006; Dignam et al., 2006). Green tea has been associated with modulation of obesity, diabetic, and cardiovascular risk factors and is recognised as a low toxicity approach to cancer chemoprevention (Anderson & Polansky, 2002; Moyers & Kumar, 2004; Kuriyama et al., 2006). While the findings of this pilot intervention trial support daily consumption of decaffeinated green tea with lower catechin exposure to improve lipid profiles and possibly improve insulin sensitivity in a population of overweight breast cancer survivors, these results do not support an effect of 960 mL daily consumption of decaffeinated green tea on weight

loss in overweight breast cancer survivors. Future efforts that include delivery of concentrated green tea extracts in capsular form, preferably in a fasting state, will likely enhance adherence as well as allow testing of the efficacy of higher doses of tea catechin on body weight to confirm the low dose effects on metabolic parameters observed herein, are also warranted.

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