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The safety of green tea extract supplementation in postmenopausal women at risk for breast cancer: results of the Minnesota Green Tea Trial

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ABSTRACT

Green tea is thought to provide health benefits, though adverse reactions to green tea extract (GTE) have been reported. We conducted a randomized, double-blind, placebo-controlled study of GTE on breast cancer biomarkers, including mammographic density, in which 1075 postmenopausal women were randomly assigned to consume GTE containing 843 mg (-)-epigallocatechin-3-gallate (EGCG) or placebo daily for one year. There were no significant differences in % of women with adverse events (AEs, 75.6% and 72.8% of the GTE group and placebo group, respectively) or serious AEs (2.2 % and 1.5% of GTE and placebo groups, respectively). Women on GTE reported significantly higher incidence of nausea ($P < 0.001$) and dermatologic AEs ($P = 0.05$) and significantly lower diarrhea incidence ($P = 0.02$). More women in the GTE group experienced an alanine aminotransferase (ALT) elevation compared with placebo group ($n = 36$, (6.7%) vs. $n = 4$, (0.7%); $P < 0.001$). There were no statistically significant differences between groups in frequencies of other AEs. Overall, AEs were mainly mild and transient, indicating that daily consumption of GTE containing 843 mg EGCG is generally well tolerated by a group of predominantly Caucasian postmenopausal women. However, 6.7% of GTE consumers experienced ALT elevations, with 1.3% experiencing ALT-related serious AEs.

1. Introduction

Green tea is one of the world's most popular beverages and has been associated with a number of health benefits, including prevention of obesity (Huang et al., 2014), cardiovascular disease (Hodgson and Croft, 2010), neurodegenerative diseases (Andrade and Assuncao, 2012), and several site-specific cancers, including breast cancer (Yuan, 2013). These beneficial effects are primarily attributed to the chemical properties of tea catechins, of which (−)-epigallocatechin-3-gallate (EGCG) is the most abundant (50–75% of total catechin content) and biologically active form (Kao

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; COMT, catechol-O-methyltransferase; CTCAE, Common Terminology Criteria for Adverse Events; EGCG, (−)- epigallocatechin-3-gallate; GTE, green tea extract; SAE, serious adverse event.

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et al., 2000). Other important components include epigallocatechin (EGC), epicatechin-3-gallate (ECG), epicatechin (EC), flavonols, and phenolic acids (Yang et al., 2011).

Tea is produced from the leaves of the *Camellia sinensis* plant and is classified into green, black, and oolong varieties based on the distinct processing techniques used for each type. To produce green tea, fresh tea leaves are steamed or heated immediately after harvest to minimize oxidation reactions, which results in maintenance of a high content of catechins, the main polyphenolic constituents in green tea. In contrast, black tea is produced by crushing and fermenting tea leaves after harvest to enhance oxidation and conversion of catechins primarily to the aflavins and the arubigens, which are responsible for the color and flavor characteristics of black tea. Worldwide, green tea accounts for approximately 20% of total tea production (Sang et al., 2011).

Several studies and case reports have described adverse events (AEs) associated with high-dose GTE preparations. Hepatotoxicity, gastrointestinal (GI) complaints (abdominal bloating, dyspepsia, flatulence, nausea, and vomiting), and central nervous system symptoms (agitation, dizziness, headache, and insomnia) are the most commonly reported AEs (Mazzanti et al., 2009; Patel et al., 2013; Sarma et al., 2008). In light of this information, the United States Pharmacopeia (USP) conducted a safety review in 2008 and found 216 AE case reports following the use of multiple GTE preparations, including 34 reports of liver damage. Doses ranged from 0.7 to 3 g catechins per day, and most individuals recovered after termination of use. However, whether or not the hepatotoxicity was due specifically to the GTE was unclear in most cases due to differences in methods of GTE extraction, concomitant medication use, or the presence of additional herbal compounds in the product. The USP concluded that significant safety issues are minimal if GTEs are formulated correctly and used as directed, and suggested, but did not require, a warning to be placed on any green tea extract marketed as a dietary supplement (Sarma et al., 2008).

Catechins are primarily metabolized through methylation, glucuronidation, sulfation, and ring fission metabolism (Lambert et al., 2007). Polymorphisms in catechol-*O*-methyltransferase (COMT), an enzyme involved in the methylation pathway, have been correlated with breast cancer risk. A G to A transition at codon 158 of *COMT* (SNP rs4680) causes a valine to methionine substitution in the cytosolic or membrane-bound form of the enzyme, resulting in a 3- to 4-fold decrease in enzymatic activity (Dawling et al., 2001). Wu et al., have shown that the breast cancer protective effect of green tea intake is more prominent in women with the homozygous low-activity (A/A) COMT genotype than those with the homozygous high-activity (G/G) genotype (Wu et al., 2003), suggesting that individuals with the low-activity COMT genotype metabolize tea catechins at a slower rate and retain these bioactive components longer in their bodies. This may contribute to prolonged exposure to beneficial compounds within green tea. At the same time, little is known about the effect of variation in COMT enzymatic activity with respect to adverse effects of green tea or GTE consumption.

Given the widespread use of green tea supplements and data suggesting benefits with respect to disease prevention, it is extremely important to clarify the AEs that can be attributed to GTE and if AE incidence is modified by variation in COMT genotype. To accomplish this, we carefully monitored AEs in a randomized, double-blind, placebo-controlled intervention study designed to evaluate the effects of oral decaffeinated GTE supplementation on biomarkers of breast cancer risk. This paper reports in detail the adverse events that occurred in the entire group of 1075 randomized participants.

2. Material and methods

2.1. Study design

A detailed description of the Minnesota Green Tea Trial (MGTT) design, eligibility criteria, study conduct, and patient flow through the trial will be published separately (Samavat et al., Cancer Causes and Control). Briefly, postmenopausal women aged 50–70 years and classified as having high mammographic density (>50% fibroglandular tissue) were recruited on the basis of their annual screening mammogram from 2009 to 2013 at 8 clinical centers in the Minneapolis-St. Paul metropolitan area. Of 1075 randomized women, 538 were assigned to receive four oral GTE capsules containing 1315 mg ± 116 total catechins per day (843 ± 44 mg as EGCG) and 537 were randomized to receive placebo for 12 months. Fig. 1 depicts the full randomization scheme. Total catechin and EGCG dosage was approximately equivalent to four 8-ounce (240 mL) cups of brewed green tea per day (Bhagwat et al., 2014). Nine hundred thirty-seven women (87.2%) completed the study. Participants were required to limit brewed green tea consumption to <1 cup/week and were instructed to take two study capsules with food, twice daily.

Participants, investigators, laboratory staff, and those monitoring clinical outcomes and adverse events were blinded to treatment assignment. The primary objectives were to determine the effects of GTE supplementation on mammographic density, circulating reproductive hormones and circulating insulin-like growth factor axis proteins. Secondary endpoints included circulating F2-isoprostanes (an established biomarker of oxidative stress), urinary estrogen metabolites, anthropometric variables, and obesity-associated hormone concentrations. Institutional Review Board (IRB) approval was obtained at each clinical center and all participants provided written informed consent.

Women with any of the following characteristics at baseline were ineligible for the present study: (1) tested positive for serological status of hepatitis B surface antigen; (2) tested positive for serological status of antibodies to hepatitis C virus; (3) baseline alanine aminotransferase (ALT) higher than 1.5 times the upper limit of normal (ULN) (defined in this study as 60 U/L); (4) any history of cancer; (5) any history of proliferative breast disease; (6) history of breast augmentation; (7) body mass index (BMI) below 18.5 or above 40 kg/m^2; weight change more than 4.6 kg during the previous 12 months; (8) current or recent (within 6 months) use of hormone replacement therapy; (9) current use of anti-inflammatory agents including methotrexate or Enbrel (etanercept); (10) current smoker; (11) regular consumption of 7 or more alcoholic beverages per week; and (12) regular consumption of 1 or more cups of green tea per week.

2.2. Study supplement

Green Tea Extract Catechin Complex (Corban complex GTB, referred to as GTE in this publication) and placebo capsules were supplied by Corban Laboratories (Eniva Nutraceutics, Plymouth, MN). Catechin analysis was performed on each batch in the laboratory of CS Yang at Rutgers University. Mean total catechin content of each GTE capsule was 328 ± 30 mg, including 211 ± 11 mg EGCG, 27 ± 30 mg EGC, 51 ± 19 mg ECG, and 27 ± 6 mg EC. Placebo capsules were identical in appearance to GTE and contained 50% (816 mg) maltodextrin, 49.5% (808 mg) cellulose, and 0.5% (8 mg) magnesium stearate. Each capsule contained less than 4 mg caffeine. Participants were instructed to consume two capsules, twice daily with morning and evening meals.