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Tea and health: preventive and therapeutic usefulness in the elderly?

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Abstract

Purpose of review—To update the growing literature suggesting that tea and its constituent flavonoids are inversely related to the risk of chronic diseases common among the elderly.

Recent findings—Results are provided from recent observational studies and clinical trials on the relationship of tea and tea catechins to body weight control and energy metabolism, impaired glucose tolerance and diabetes, cardiovascular disease, bone mineral density, cognitive function and neurodegenerative disease, and cancer. The evidence for the efficacy and potency of tea and tea extracts in benefiting these outcomes ranges from compelling for cardiovascular disease to equivocal at best for some forms of cancer.

Summary—Although randomized clinical trials of tea have generally been of short duration and with small sample sizes, together with experimental and epidemiological studies, the totality of the data suggests a role for tea in health promotion as a beverage absent in calories and rich in phytochemicals. Further research is warranted on the putative benefits of tea and the potential for synergy among its constituent flavonoids, L-theanine, and caffeine.

Keywords

cancer; cardiovascular disease; catechins; elderly; tea; weight control

Introduction

Intake of polyphenols, especially flavonoids, has been inversely associated with the incidence of chronic disease. Tea is a major source of dietary flavonoids, particularly the catechins (flavan-3-ols). The daily total flavonoid intake of tea consumers in the USA has been reported as over 20 times that of nonconsumers, with older adults more likely to be tea drinkers [1]. A growing body of research describes many putative benefits of tea and catechins, including antiatherogenic, antibiotic, anticarcinogenic, antidiabetic, anti-inflammatory, antioxidant, immune enhancing, and antiviral effects. This review briefly summarizes recent human studies investigating health outcomes of tea relevant to older adults.

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Body weight control and energy metabolism

There may be a putative role for tea, a noncaloric beverage, in weight loss/maintenance through actions on metabolic rate and/or glucose and lipid absorption [2-4]. However, several recent studies have provided contrasting outcomes in this area. Employing a randomized, double-blind, placebo-controlled clinical trial (RCT) with a crossover design, Rudelle *et al.* [5] tested a beverage formulated with green tea catechins, caffeine, and calcium and found that it increased 24-h resting energy expenditure (REE) by 106 kcal (4.6%) in 31 healthy, young, lean individuals; the specific contribution of each ingredient to this outcome was not evaluated. Similarly, in a 12-week RCT, Auvichayapat *et al.* [6] provided a green tea extract (GTE, 750 mg) containing 141 mg catechins to 60 sedentary and overweight (BMI: 27.7) individuals consuming a 2000 kcal/day diet and reported an increase in REE and a decrease in body weight despite no change in food intake.

In contrast, in a crossover RCT with six middle-aged men (BMI: 29.9), Boschmann and Thielecke [7] found that a 2-day treatment with 300mg epigallocatechin gallate (EGCG)/day had no effect on REE, though postprandial fat oxidation was increased. In another crossover RCT with 12 young men (BMI: 23.9) during a 30-min cycling exercise at 60% of maximal oxygen consumption, Venables *et al.* [8] reported that a single bolus of GTE (366mg EGCG) had no effect on total energy expenditure, but found that lipolysis (measured by circulating glycerol) increased.

Nagao *et al.* [9•] reported that supplementation of green tea (583mg catechins) in a 12-week RCT decreased body weight, BMI, body fat ratio, body fat mass, waist circumference, hip circumference, and area of visceral and subcutaneous fat in 240 middle-aged Japanese individuals (BMI: 26.8). However, Hill *et al.* [10••] found that EGCG (300mg/day) did not provide any benefit beyond that achieved by an aerobic exercise program (45 min walking at 75% of heart rate, three times per week) in total body fat, abdominal fat, waist circumference, and waist : hip ratio in a 12-week RCT of 38 postmenopausal women (BMI: 31.4). Consistent with this finding are the results from an RCT by Diepvens *et al.* [11] in which GTE supplementation for 3 months did not promote weight loss beyond that achieved by a low-calorie diet in 46 middle-aged women (BMI: 27.7). Similarly, Fukino *et al.* [12] found no benefit from 2-month supplementation with GTE (456mg catechins) on body weight, BMI, or body fat in 60 Japanese individuals (BMI: 25.7) with borderline diabetes. Thus, tea and GTE do not appear to posses a potent efficacy on body weight reduction, though they may have a short-term impact on energy metabolism.

Information on the mechanisms of action underlying these effects is limited. A metabolomic investigation by Van Dorsten *et al.* [13] suggested that tea modifies oxidative energy metabolism and biosynthetic pathways in humans, increasing the urinary excretion of citric acid cycle intermediates and reducing alanine and lactate, products of anaerobic glycolysis. They also found that tea increased fatty acid oxidation (acetate and β-hydroxybutyrate) in plasma. These effects may be mediated in part through the inhibition of catechol *O*-methyl-transferase activity by tea catechins, increasing the half-life of norepinephrine, a mediator of thermogenesis.

Impaired glucose tolerance and diabetes

Tea intake may also influence the impaired glucose tolerance associated with obesity and the metabolic syndrome. Evidence from in-vitro and animal models suggests catechins can prevent hyperglycemia by increasing insulin activity and protecting β-cells against oxidative damage. However, in the Mediterranean Islands Study (MEDIS) of 542 older adults (65–100 years), Polychronopoulos *et al.* [14] observed an inverse association between tea consumption and serum glucose in lean but not in obese individuals, after adjusting for age, sex, smoking, physical activity status, diet, and other clinical parameters. In contrast, examining the National Health and Nutrition Examination Survey III (NHANES III) data from 14 900 Americans, MacKenzie *et al.* [15] found no association between tea intake and the incidence of type 2 diabetes. In their RCT, Hill *et al.* [10••] also found no benefit of EGCG on fasting glucose, insulin, or lipid profiles. Further, Ryu *et al.* [16] found that drinking green tea (9 g) for 4 week did not improve glucose or insulin status in 45 middle-aged people with type 2 diabetes. Fukino *et al.* [12] also found no effect of 2-month supplementation with GTE (456mg catechins) on serum glucose level or insulin sensitivity in a crossover RCT of 60 borderline diabetic patients, though fasting glycosylated hemoglobin (HbA1c) decreased 4%. Similarly, in a 3-month RCT, Mackenzie *et al.* [17] found no effect of GTE and black tea extract (375 mg containing 150 and 75 mg of green and black tea catechins, respectively) on plasma glucose, insulin, or HbA1c in 47 type 2 diabetic patients. In contrast, Bryans *et al.* [18••] reported an acute benefit of black tea (1 g) on plasma glucose and insulin compared with a placebo or matched caffeinated drink during an oral glucose tolerance test in 16 healthy individuals. Thus, further research is warranted to determine whether tea or tea catechins may influence glucose and insulin homeostasis in a clinically meaningful manner.

Cardiovascular disease

Several recent articles have reviewed the relationship between tea and cardiovascular disease (CVD) [19-25]. In the prospective cohort of the French Three-City Study with 6597 noninstitutionalized participants of at least 65 years of age, an inverse association between tea drinking and carotid plaques was observed; compared with nontea drinkers, women with intakes of at least 3 cups/day had a lower prevalence [odds ratio (OR): 0.68; 95% confidence interval (CI): 0.54–0.86] of carotid plaques but had no difference in carotid artery intima–media thickness [26]. In a RCT of 37 nonsmoking, tea-drinking European men (18–55 years), supplementation with a black tea extract (4.2 g/day) for 6 weeks decreased monocyte-induced, neutrophil-induced, and leucocyte-induced platelet aggregation and reduced plasma C-reactive protein (CRP), though no changes were observed in total antioxidant capacity (by the Trolox Equivalent Antioxidant Capacity assay) or sP-selectin [27]. Similarly, in Taiwan, in an RCT, hemodialysis patients supplemented with green tea catechins (455 mg/day) for 5 months were found to have a reduced plasma CRP, soluble intercellular adhesion molecule-1, monocyte chemoattractant protein-1, TNF-α, lipid peroxides, hypochlorite, and hydrogen peroxide, parameters that returned to baseline values 2 months after the intervention [28]. In a substudy of this report, a single dose of tea catechins administered prior to hemodialysis decreased the elevation of proinflammatory cytokines resulting from the treatment. In a 4-week RCT of 29 Japanese individuals, GTE

(500 mg/day) was considered an effective antioxidant due to its action of lowering oxidized low-density lipoprotein cholesterol [29]. In contrast to these studies, in a 6-month RCT of 28 individuals more than 55 years of age with CVD or diabetes, Mukamal *et al.* [30] found no effect of dehydrated black tea (6 g/day) on CVD biomarkers, including inflammation, lipids, hemoglobin, adhesion molecules, prothrombotic and fibrinolytic parameters, or low-density lipoprotein cholesterol oxidizability.

Endothelial dysfunction, often assessed by flow-mediated vasodilation (FMD) of the brachial artery, is a physiological risk factor of CVD. Confirming earlier observations in other trials, green and black tea increased FMD to the same extent in 21 women more than 60 years of age [31]. In a crossover RCT of 14 men and women (30 years), Alexopoulos *et al.* [32] found green tea improved FMD, whereas the same amount of caffeine found in the tea was without effect on FMD; plasma CRP, IL-1β and IL-6, antioxidant status, and resting brachial artery diameter were not changed by the tea intervention. In a RCT of 15 postrenal transplant patients, a population at high risk for endothelial dysfunction, 2 h after consuming black tea (10 g), FMD improved [33]. In a crossover RCT of 16 postmenopausal women, a single dose of freshly brewed black tea (5 g) enhanced FMD significantly after 2 h [34], about the time tea catechins reach their maximal concentration in plasma. However, in contrast to most other reports, this study also found that the addition of milk to the tea negated the vasodilatory effect of tea.

Bone mineral density

A few early reports suggest tea may increase bone mineral density (BMD) in elderly populations. More recently, Devine *et al.* [35••] assessed tea intake in a cross-sectional analysis of a 5-year RCT of calcium supplementation in women (>70 years) in Western Australia. Areal BMD, a measure of hip structure, was found to be 2.8% greater in tea drinkers than nondrinkers. Further, nontea drinkers lost 4.0%, whereas green or black tea drinkers lost 1.6% of total hip, trochanter, and intertrochanter BMD, though no trend was found with the amount of tea consumption. In Japan, Muraki *et al.* [36•] reported a 10% greater BMD among green tea drinkers than nondrinkers in a cross-sectional analysis of 632 women (>60 years). However, as previously documented in case reports, obsessive tea drinking (10–40 cups/day) can lead to toxic concentrations of serum fluoride in which increased BMD is not associated with a reduced risk of fractures [37].

Cognitive function and neurodegenerative disease

In-vitro and animal model studies suggest green tea catechins may have neuroprotective actions via their modulation of antioxidant capacity, mitochondrial function, or signal transduction [38]. Although evidence in human studies is limited, recently Ng *et al.* [39••] examined data from the Chinese cohort in the Singapore Longitudinal Ageing Study. Comparing the 2-year follow-up ($n = 1438$) to baseline values ($n = 2501$), intake of black or oolong tea occasionally or of at least 1 cup/day was associated with a lower cognitive impairment (OR: 0.55; 95% CI: 0.38–0.79 and OR: 0.46; 95% CI: 0.31–0.68, respectively) and cognitive decline (OR: 0.81; 95% CI: 0.59–1.11 and OR: 0.68; 95% CI: 0.49–0.94, respectively). Green tea intake was also inversely associated with cognitive impairment (OR:

0.42; 95% CI: 0.25–0.69), but not with cognitive decline, possibly due to the small number of green tea drinkers in this cohort.

A prospective cohort study (n = 29 335; 25–74 years) in Finland [40] examined the association between black or green tea consumption and the risk of Parkinson's disease and found an inverse relationship for intakes of at least 3 cups/day (hazard ratio: 0.41; 95% CI: 0.20–0.83). With 157 cases of Parkinson's disease, the prospective Singapore Chinese Health Study (n = 63 257; 45–74 years) [41] revealed an inverse relationship between the highest tertile of black tea intake and nontea drinkers [relative risk (RR): 0.29; 95% CI: 0.13–0.67] but no association among green tea drinkers. In contrast, no association was observed between tea intake and risk or progression of Parkinson's disease in two studies conducted in Israel [42,43].

The custom of tea drinking has traditionally been associated with a calming effect, though only recently has research been conducted in this area with particular attention devoted to the regulation by tea catechins and L-theanine (typically comprising 1–2% of the dry weight of tea) of cortisol production [44]. In a RCT of 75 nonsmoking men, Steptoe *et al.* [45•] reported that drinking a cup of black tea extract (1050 mg, 68 mg flavonoids) for 6 weeks did not change responses to performing behavioral tasks, but lowered posttask cortisol concentrations and increased the subjective evaluation of relaxation during the recovery period compared with a caffeine-matched placebo. These results suggest that tea may diminish posttask-related stress. In a RCT of 24 young adults, Haskell *et al.* [46] examined acute effects of either 250mg L-theanine, 150mg caffeine, or their combination on cognition and mood and found that L-theanine alone increased reports of 'headache' and decreased numeric working ability, but the combination led to faster simple reaction time and numeric working memory reaction time as well as improved sentence verification accuracy than caffeine alone. Testing 50mg L-theanine in a RCT of 35 young adults, Nobre *et al.* [47] found the treatment increased mental alertness or arousal assessed by electroencephalographic measurement of alpha waves. In contrast, in a RCT of 48 young adults, Rogers *et al.* [48] found 200mg L-theanine had no effect on mental arousal and did not antagonize 250mg caffeine-induced jitteriness and alertness. In a crossover RCT of 16 healthy individuals with acute doses of placebo, L-theanine (100mg), and/or caffeine (50mg), Kelly *et al.* [49] found a beneficial, synergistic effect of these two constituents of tea on behavioral and electrophysiological indices of visuospatial attentional deployment.

Cancer

A substantial body of in-vitro and animal model research suggests mechanisms by which tea and tea catechins may promote chemoprevention [50-52]. For example, green tea can induce phase 2 detoxification enzymes [53] and Chow *et al.* [54•] recently demonstrated in a RCT of 42 healthy adults that supplementation for 4 weeks with GTE (200mg EGCG/day) increased lymphocyte glutathione-*S*-transferase-π among those in the lowest tertile of basal activity. Poor expression of this enzyme has been linked to preneoplastic and neoplastic disorders. Employing a RCT with 116 volunteers at risk for hepatocellular carcinoma in southern China, Tang *et al.* [55••] supplemented volunteers for 3 months with placebo, 500, or 1000mg/day GTE (98.5% purity) and found that the urinary excretion of aflatoxin B_1-

mercapturic acid, a biomarker of phase 2 detoxification, increased between seven-fold and 17-fold in the treatment groups. Procarcinogenic aflatoxin B_1-albumin adducts, urinary aflatoxin M_1 and serum aflatoxin B_1, were also decreased by the GTE. In contrast, some in-vitro studies [56••,57,58] suggest a potential procarcinogenic mechanism of tea catechins via actions to reduce folate status. In the only human study available to date examining this effect, Alemdaroglu *et al.* [56••] tested a GTE (51mg catechins) and black tea extract in a crossover RCT on the bioavailability of 5mg folic acid in seven healthy individuals and found that only the GTE significantly reduced serum folate. Nonetheless, recent observational studies suggest either a potential benefit or null outcome without increased risk from tea intake for cancer of the breast, colon/rectum, liver, ovaries, prostate, skin, and stomach as well as leukemia (see reviews [59-62]).

Breast cancer

In a case–control study in Southeast China of 1009 patients with histologically confirmed breast cancer [63], the OR declined from 0.87 (95% CI: 0.73–1.04) to 0.61 (95% CI: 0.48–0.78) with increasing annual intake of green tea consumption. As in similar studies, a variety of socioeconomic, lifestyle, and dietary characteristics were also associated with tea drinking. In contrast, in the prospective Nurses' Health Study [64], green tea intake was not associated with the risk of invasive breast cancer among 5272 documented patients (30–55 years in 1976).

Ovarian cancer

A meta-analysis of nine studies published before 2006 found no association between tea consumption and risk of ovarian cancer [65]. More recently, Song *et al.* [66] observed that green tea consumption, but not black or decaffeinated tea, was inversely associated with ovarian cancer in a study of 781 cases of primary invasive or borderline epithelial ovarian tumors with an OR of 0.82 (95% CI: 0.66–1.04) and 0.46 (95% CI: 0.26–0.84) among those consuming less than 1 and more than 1 cup/day, respectively. However, a case–control study of 414 women with ovarian cancer [67] revealed a RR of 0.70 (95% CI: 0.51–0.97) among those drinking at least 2 cups/day of black tea. A weak inverse trend for risk of ovarian cancer and green or black tea intake with age was observed in 280 cases among a cohort of 2083 women (55–69 years in 1986) in The Netherlands, but its statistical significance was lost after adjusting for smoking, oral contraceptive use, and number of children [68].

Prostate cancer

A variety of research approaches have suggested that tea may protect against prostate cancer [69]. In a prospective cohort study of 49 920 Japanese men (40–69 years) [70], green tea intake was associated with a reduction in risk of advanced prostate cancer (RR: 0.52; 95% CI: 0.28–0.96) but when all stages of the cancer were included, no statistically significant trends were noted. A case–control study of 130 elderly men in Hangzhou, China revealed a reduced risk of prostate adenocarcinoma linked to green tea consumption with a decline in OR from 0.45 (95% CI: 0.25–0.82) to 0.13 (95% CI: 0.05–0.32) with intakes from 0.3–2.9 to more than 5 g/day, respectively [71•]. Further, combined intake of tea and lycopene was more protective than tea alone, reducing the OR to 0.21 (95% CI: 0.08–0.57) and 0.03 (95% CI: 0.01–0.16) for middle and high tertiles of tea intake, respectively [71•].

Digestive system and liver cancers

Despite several animal model studies indicating tea can potently reduce cancers of the digestive system and liver, recent prospective cohort studies in Japan found no relationship between tea intake and pancreatic cancer [72] or mortality from pancreatic cancer [73]. In a nested case–control study of 494 patients [74•], the highest tertile of plasma (-)-epicatechin-3-gallate (ECG, >10 ng/ml) was associated with decreased risk of gastric cancer (OR: 0.25; 95% CI: 0.08–0.73) in women, whereas no association was noted for other tea catechins. Conversely, increasing plasma ECG and EGCG were associated with an increased risk for gastric cancer in men. However, the percentage of current smokers was more than 38 and less than 10 for men and women, respectively, so further adjustment for potential confounding is warranted to support the validity of these results. Although tea may reduce the risk of lung cancer only among nonsmokers [59], a meta-analysis of 14 trials in Cochrane library, accounting for 6123 cases, did not support the hypothesis that green tea prevents gastric cancer [75]. Consistent with the experimental evidence suggesting a beneficial impact of tea on the risk for colon cancer [76], a recent report from the Shanghai Women's Health Study cites a RR of 0.64 (95% CI: 0.42–0.98) and 0.48 (95% CI: 0.25–0.92) among those women (40–70 years) consuming green tea at 1–4 g and at least 5 g/day, respectively [77].

Skin cancer

As suggested by plausible mechanisms of action [78], tea consumption at least 2 cup/day was inversely associated with skin carcinoma (OR: 0.65; 95% CI: 0.44–0.96) in a case–control study of 770 patients with basal cell carcinoma and 696 with squamous cell carcinoma [79]. A long duration of tea consumption (47 years) was also associated with reduced squamous cell carcinoma (OR: 0.49; 95% CI: 0.29–0.83).

Leukemia

In a case–control study including 107 patients with leukemia in Hangzhou, China, inverse trends were found between drinking tea for at least 20 years (OR: 0.20; 95% CI: 0.06–0.60) and intake of at least 1 cup/day (OR: 0.40; 95% CI: 0.19–0.82) [80].

Conclusion

There has been a remarkable increase in research on the role of tea in health promotion and disease prevention with over 300 new reports in each of the last several years. Tea appears to be a healthful beverage choice based simply on its absence of calories and rich source of flavonoids, particularly catechins. Indeed, Popkin *et al.* [81] have proposed a guidance system that ranks beverages from lowest to highest value based on caloric and nutrient contents and related health benefits and risks. They proposed water as the preferred beverage to fulfill daily hydration needs, immediately followed in decreasing value by tea and coffee. The American College of Cardiology Foundation Task Force [82] now recommends moderate tea intake as part of nutritional advice for risk reduction in CVD. Nonetheless, while the impact of tea on cardiovascular function is compelling, the evidence for its other putative benefits ranges markedly between various outcomes. No recent studies have directly examined the potential efficacy of tea as a therapeutic agent for the amelioration of a

disease. Recent studies suggesting an effect of L-theanine, an amino acid unique to tea, on cognitive performance should encourage new research in this area. Further, few RCTs have directly compared types of tea, so additional research is required to determine the relative importance to health outcomes of the different polyphenol profiles presented by green, oolong, and black tea.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 97).

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