Review

The Role of Tea in Human Health: An Update

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Tea is an important dietary source of flavanols and flavonols. *In vitro* and animal studies provide strong evidence that tea polyphenols may possess the bioactivity to affect the pathogenesis of several chronic diseases, especially cardiovascular disease and cancer. However, the results from epidemiological and clinical studies of the relationship between tea and health are mixed. International correlations do not support this relationship although several, better controlled case-referent and cohort studies suggest an association with a moderate reduction in the risk of chronic disease. Conflicting results between human studies may arise, in part, from confounding by socioeconomic and lifestyle factors as well as by inadequate methodology to define tea preparation and intake. Clinical trials employing putative intermediary indicators of disease, particularly biomarkers of oxidative stress status, suggest tea polyphenols could play a role in the pathogenesis of cancer and heart disease.

Key teaching points:

- Tea is a rich source of polyphenolic flavonoids which exhibit potent antioxidant activity *in vitro* and *in vivo*. The flavonoid content of tea depends upon the type of tea and preparation method.
- Contrasting results have arisen from human studies of the relationship between tea and health, particularly the risk for cardiovascular disease and cancer. A limited number of studies suggest a beneficial impact of tea intake on bone density, cognitive function, dental caries and kidney stones.
- Randomized clinical trials examining the effect of tea on putative intermediary biomarkers, e.g., homocysteine for heart disease and 8-hydroxy-2′-deoxyguanosine for cancer, and physiological responses like brachial artery dilation suggest a potential health benefit from tea consumption.
- Human studies examining the effects of tea on health must carefully define tea preparation and intake (including amount, frequency and timing) and control or adjust for confounding by socioeconomic and lifestyle factors.

INTRODUCTION

People have been brewing tea made from the leaves of the *Camellia sinensis* plant for almost 50 centuries. Although health benefits have been attributed to tea consumption since the beginning of its history, scientific investigations of this beverage and its constituents has been underway for less than three decades. Epidemiological surveys have associated tea drinking with reduced risk of cardiovascular diseases (CVD) and cancer, while studies in cell cultures and animal models indicate a potentially beneficial effect of tea on Phase I and II hepatic enzymes, gene transcription, cell proliferation and other molecular functions. Within the last few years, clinical studies have revealed several physiological responses to tea which may be relevant to the promotion of health and the prevention or treatment of some chronic diseases. Some apparent inconsistencies between studies on tea and health now suggest improved research approaches which may resolve them. This article is intended to contribute to this effort by critically reviewing the most recent human studies, i.e., epidemiological studies and clinical trials, examining the relationship between tea and health. While elucidating the molecular mechanisms of

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action of tea polyphenols is critical to understanding this relationship, this topic has been recently reviewed elsewhere [1–10].

BACKGROUND

After water, tea is the most popularly consumed beverage worldwide with a per capita consumption of ~120 mL/day. Black tea is consumed principally in Europe, North America and North Africa (except Morocco) while green tea is drunk throughout Asia; oolong tea is popular in China and Taiwan. All tea is produced from the leaves of the tropical evergreen *C. Sinensis*. There are three main types of tea with black tea made via a post-harvest "fermentation," an auto-oxidation catalyzed by polyphenol oxidase. After picking, leaves for green tea are steamed to inactivate polyphenol oxidase prior to drying. Oolong tea is produced by a partial oxidation of the leaf, intermediate between the process for green and black tea. Approximately 76% to 78% of the tea produced and consumed worldwide is black, 20% and 22% is green and less than 2% is oolong.

Tea is a rich source of polyphenolics, particularly flavonoids. Flavonoids are phenol derivatives synthesized in substantial amounts (0.5% to 1.5%) and variety (more than 4000 identified), and widely distributed among plants [11]. The major flavonoids present in green tea include catechins (flavan-2-ols) such as epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG). In black tea the polymerized catechins such as theaflavins and thearubigens predominate (Fig. 1). The relative catechin content of tea is dependent upon how the leaves are processed prior to drying as well as geographical location and growing conditions.

The flavonoid concentration of any particular tea beverage depends upon the type of tea (e.g., blended, decaffeinated instant) and preparation (e.g., amount used, brew time, temperature). Decaffeinating reduces slightly the catechin content of black tea, while herbal infusions (often called "herbal teas") contain neither catechins nor caffeine [12]. The highest concentration of flavonoids are found in brewed hot tea (541–692 μg/mL) [13], less in instant preparations (90–100 μg/mL) and lower amounts in iced and ready-to-drink tea [14]. The addition

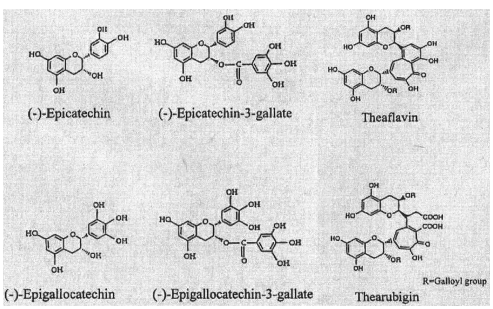

Fig. 1. Major flavonoids present in green, black and oolong teas.

of milk or water (e.g., to iced tea) can reduce the flavonoid concentration per serving; however, this effect may be offset by a fixed serving size (e.g., a tea bag) and recipes generally recommend using 50% more tea when preparing iced tea to allow for dilution (*Recommendations for the Preparation of Iced and Hot Tea*, The Tea Association of the U.S.A., Inc. in cooperation with The National Restaurant Association, 2000). Research results are largely consistent in demonstrating that the addition of milk to tea does not interfere with catechin absorption [15–17]. Milk may affect the antioxidant potential of tea, depending upon its fat content, the volume added and the method used to assess this parameter [15,18–21]. Importantly, data regarding tea preparation are rarely collected in epidemiological studies, and this situation may account for some of the contrasting outcomes from different studies. Investigations employing standardized tea or tea extracts and controlling tea preparation can help clarify the putative health effects of tea.

ANTIOXIDANT CAPACITY OF TEA *IN VITRO* AND *IN VIVO*

In Vitro Antioxidant Capacity

Tea flavonoids have been found, *in vitro*, to enhance gap junctional communication, stimulate B cell proliferation and inhibit hepatic cytochrome P450-dependent enzymes [2]. However, the principal hypothesis associated with the putative health benefits of tea is linked to the antioxidant properties of its constituent flavonoids [11]. In addition to directly quenching reactive oxygen species, tea flavonoids can chelate metal ions like iron and copper to prevent their participation in Fenton and Haber-Weiss reactions [22,23]. The antioxidant capacity of teas and tea polyphenols has been assessed by several methods [18,22,24–27]. Using the Oxygen Radical Absorbance Capacity (ORAC) assay, Cao *et al.* [24] found both green and black tea have much higher antioxidant activity against peroxyl radicals than vegetables such as garlic, kale, spinach and Brussels sprouts. Using the Ferric Reducing Ability of Plasma (FRAP) assay, Langley-Evans [18] found the total antioxidant capacity of green tea to be more potent than black tea. Using the Tocol Equivalent Antioxidant Capacity (TEAC) assay, Rice-Evans *et al.* [25] ranked epicatechin and catechin among the most potent of 24 plant-derived polyphenolic flavonoids they evaluated. The antioxidant capacity of flavonoids determined *in vitro* is dependent upon the type of assay employed and does not reflect factors such as bioavailability and metabolism. Thus, *ex vivo* tests of antioxidant capacity would appear to better represent the physiological impact of tea.

Ex Vivo Antioxidant Capacity

Recently, several clinical trials have demonstrated that a single dose of tea improves plasma antioxidant capacity of healthy adults within 30 to 60 minutes after ingestion (Table 1).

Table 1. The effect of tea consumption on antioxidant capacity and biomarkers of oxidative stress

Assay	Results	Type of Tea	Daily Quantity	Duration	Reference
FRAP	↑ 4%	Green	20 g dry leaves/500 mL (300 mL consumed)	20 minutes	[28]
FRAP	↑ 3%	Green tea solids	2 g/300 mL (equivalent to 3 c)	30 minutes	[15]
FRAP	↑ 2%	Black tea solids	2 g/300 mL (equivalent to 3 c)	30 minutes	[15]
TAS	↑ 7.0%	Green	5 g dry leaves/300 mL	60 minutes	[29]
TRAP	↑ 16–19%	EGCG	400 mg		[30,31]
PCOOH	↓ 39%	Green tea catechins	254 mg	60 minutes	[32]
8-OHdG (urine, WBC)	↓ 40–500%	Green	6 c	7 days	[33]
MDA (urine)	↓ 50–300%				
2,3 DHBA (urine)	↓ 50%				
Oxidative DNA damage (lymphocytes)	↓ 13%	Not specified	6 c	2 weeks	[34]
MDA (plasma)	↓ 22%	Green tea extract	10 c (equivalent)	4 weeks	[35]

FRAP = Ferric Reducing Ability of Plasma, TAS = Total Antioxidant Status, TRAP = Total Radical Antioxidant Parameter, PCOOH = phosphotidylcholine, 8-OHdG = 8-hydroxy-2′-deoxyguanosine, DHBA = 2,3-dihydroxybenzoic acid, MDA = malondialdehyde, EGCG = epigallocatechin-3-gallate.

A significant rise in plasma antioxidant capacity ($p < 0.001$) was detected with the FRAP assay after 300 mL of either brewed green tea made with 20 g of dry leaves/500 mL water [28] or 2 g of green or black tea solids (equivalent to three cups of tea) were consumed [15,21]. Similarly, plasma antioxidant activity increased ($p < 0.001$) when assessed by an assay employing 2,2′-azino-di-2-ethyl-benzthiazoline sulphonate (ABTS+) after subjects consumed 300 mL of a green tea preparation made with 5 g of dry leaves [29]. Total Radical Antioxidant Parameter (TRAP) values in plasma increased after subjects consumed 400 mg of green tea extract containing EGCG [30,31]. The concentration of phosphotidylcholine hydroperoxide (PCOOH), an index of lipid peroxidation, was attenuated ($p < 0.05$) after subjects consumed 254 mg of green tea catechins [32]. In general, the rise in plasma antioxidant capacity peaks about one to two hours after tea ingestion and subsides shortly thereafter.

Repeated consumption of tea and encapsulated tea extracts for one to four weeks has been demonstrated to decrease biomarkers of oxidative status. In a trial of 40 male smokers in China and 27 men and women (smokers and non-smokers) in the United States, oxidative DNA damage, lipid peroxidation and free radical generation were reduced (p-values not reported) after consuming ~6 cups a day of green tea for seven days [33]. Similarly, ten patients with Type 2 diabetes consuming a high flavonoid diet for two weeks, including six cups a day of black tea, had a significant reduction ($p = 0.037$) in oxidative damage to lymphocyte DNA [34]. Plasma malondialdehyde, another indicator of lipid peroxidation, was reduced ($p < 0.05$) in 20 healthy women, 23 to 50 years of age, consuming a high linoleic acid diet and administered an encapsulated tea extract (equivalent to 10 cups a day of green tea) for four weeks; however, no changes were noted relative to the placebo in urinary 8-isoprostaglandin $F_{2\alpha}$ and blood oxidized glutathione [35]. These latter results may be confounded by the consumption of up to 560 mL/day of black tea by some subjects in both the control and treatment groups.

CARDIOVASCULAR DISEASE

Coronary Heart Disease

Hertog and his colleagues [36–39] have observed an inverse association between flavonol intake and CVD in Europe, where black tea, together with apples and onions, contributes substantially to total flavonol consumption. Epidemiological evidence, particularly from a 10-to-15 year follow-up of cohorts of 550–800 men from the Zutphen Study in the Netherlands, reveals a strong inverse association between flavonol intake and coronary heart disease (CHD) mortality [36,37] and stroke incidence [38]. Consistent with these observations, an inverse correlation between flavonol intake and CHD mortality was found after the 25 year follow-up of 12,763 men from Seven Countries Study [39]. Similarly, men and women from the Boston Area Health Study who consumed one or more cups a day of tea in the previous year had a 44% lower risk of myocardial infarction than those who drank no tea [40]. The outcome of this case control study (n = 338/group) was independent of other coronary risk factors, and a significant linear trend across levels of tea intake was observed ($p = 0.012$). Nakachi *et al.* [41], employing a cohort of 8,552 Japanese citizens reported significant reduction in risk of death from CVD mortality among men (RR [relative risk] = 0.58; 95% CI [confidence interval]: 0.34–0.99) and a beneficial trend among women (RR = 0.82, 95% CI: 0.49–1.38) consuming more than ten cups a day of green tea. Although tea type is often not reported, it can be presumed the results from European and American cohorts are derived from consumption of black tea.

Conversely, Hertog *et al.* [42] reported no association of

flavonol or tea intake with ischemic heart disease incidence in a 14-year follow-up of 334 men, 45 to 59 years of age, conducted in Caerphilly, Wales, and a positive association with total mortality (RR: 1.4; 95% CI: 1.0–2.0; $p = 0.014$). Also, results from the 11,567 men and women, 40 to 59 years of age, participating in the Scottish Heart Health Study revealed a slight positive association between increased tea consumption and coronary morbidity and all-cause mortality [43]. The discrepancy between the outcome of these studies and those described above may be due largely to the confounding presented by socioeconomic and lifestyle factors associated with tea drinking in the respective national cohorts. For example, tea consumption was positively associated with a lower social class and less healthy lifestyle (i.e., higher prevalence of smoking and higher fat intake) in the Welsh [42] and Scottish [43] studies. In contrast, those who drink tea in the Netherlands tend to be more educated, have a lower body mass index, smoke less and consume less fat, alcohol and coffee [36–38].

Peters *et al.* [44] have recently provided a meta-analysis of tea consumption in relation to CHD as well as myocardial infarction and stroke based on ten cohort and seven case-control studies. The various measures of tea consumption were transformed to a common measure by assuming one cup = 8 oz = 237 mL. While most studies suggested a decrease in the rate of CVD outcomes with increasing tea consumption, the study-specific effect estimates for CHD and stroke were too heterogeneous to summarize simply (homogeneity $p < 0.001$ and <0.02, respectively) due largely to geographical differences. The incidence rate of myocardial infarction was estimated from seven studies to decrease by 11% with an increase in tea consumption of three cups a day (RR = 0.89, 95% CI: 0.79–1.01). However, these authors caution that bias toward preferential publication of smaller studies may affect these results.

Atherosclerosis

Tea consumption has been inversely associated with the development and progression of atherosclerosis. In the prospective Rotterdam Study of 3,454 adults, 55 years of age or older, and followed for two to three years, Geleijnse *et al.* [45] examined aortic atherosclerosis via X-ray measurement of calcified deposits in the abdominal aorta. The odds ratio (OR) for drinking 125–250 mL (1–2 cups) of tea daily was 0.54 (95% CI: 0.32–0.92) and decreased to 0.31 (95% CI: 0.16–0.59) when >500 mL/day (more than four cups) were consumed [45]. Sasazuki *et al.* [46] determined atherosclerosis by coronary arteriography in 512 Japanese patients over 30 years of age and reported a protective effect of tea among those not being treated for diabetes. In this subgroup of 262 men, the odds ratio of significant stenosis was 0.5 (95% CI: 0.2–1.2) for those consuming two to three cups of green tea and 0.4 (95% CI: 0.2–0.9) for those drinking four or more cups a day compared to subjects consuming one cup a day or less.

Elevated plasma total homocysteine is an independent risk factor for atherosclerosis and CVD and, while generally responsive to vitamins B6, B12 and folate, may also be affected by tea intake. Olthof *et al.* [47] recently tested the consumption of 4 g/day of black tea solids (equivalent to 1 L of strong black tea) for seven days in 20 healthy, young adults, 24 ± 8 years of age and found their mean plasma total homocysteine increased 11% (1.1 μmol/L; 95% CI: 0.6–1.5). However, the potential effect of caffeine on homocysteine was not evaluated. This is relevant as Jacques *et al.* [48], in a cohort study of 1,960 adults, 28 to 82 years of age, identified a positive association between plasma homocysteine and caffeine intake (p for trend <0.001), but an inverse association with tea after adjusting for coffee consumption. These latter findings concur with the results of the Hordaland Homocysteine Study of more than 16,000 Norwegian adults, 40 to 67 years of age [49] and the observations by de Bree *et al.* [50] among 3,025 Dutch adults, 20 to 65 years of age, in which a strong inverse relation between tea and plasma total homocysteine concentration was also established.

Hypertension

Elevated blood pressure can accelerate the atherosclerotic process, and evidence linking reduced blood pressure with tea consumption has been reported in studies of green tea polyphenols in hypertensive animals [51] and among black tea drinkers in Norway [52]. However, more recent studies do not support a hypotensive effect of tea. Green tea intake in the year prior to a self-administered questionnaire was unrelated to blood pressure in a study of 3,336 Japanese men, 48 to 56 years of age [53]. Five cups of either green or black tea daily for one week did not significantly alter the ambulatory blood pressure of 13 normotensive Australian men [54], nor did six cups a day of black tea for four weeks in a study of 57 men and women in the United Kingdom [55]. Small increases in blood pressure, 3–5 mm Hg diastolic and 6–11 mm Hg systolic for green and black tea, respectively, were noted when compared to caffeine alone, 30 minutes after ingestion in the Australian study, but this effect was transient and absent at 60 minutes [54].

Endothelial Cell Function

Impaired endothelium-derived nitric oxide activity contributes to the pathogenesis of atherosclerosis and, in coronary circulation, has been linked with future CVD events. Further, this endothelial dysfunction is associated with increased oxidative stress and may be reversed by antioxidant interventions. Recently, Duffy *et al.* [56] randomized 50 patients with CHD to freshly brewed black tea and water in a cross-over design and assessed endothelium-dependent flow-mediated dilation of the brachial artery using high-resolution vascular ultrasound. Both acute (two hours after 450 mL) and chronic (900 mL/day after four weeks) consumption of tea improved flow-mediated dilation ($p < 0.001$) in association with increased plasma catechin concentration. No effects were observed with an equivalent

dose of caffeine (200 mg) or on endothelium-independent nitroglycerin-mediated dilation. As flow-mediated dilation is blunted in CHD patients relative to healthy subjects, these results suggest that tea reverses endothelial vasomotor dysfunction.

LDL Oxidation

Dietary antioxidants may slow atherogenesis by reducing the oxidative modification of low density lipoprotein cholesterol (LDL) and associated events such as foam cell formation, endothelial cytotoxicity and induction of proinflammatory cytokines [3]. The susceptibility of LDL to oxidative modification is readily inhibited *in vitro* by extracts of black and green tea [57–62]. However, *ex vivo* studies in healthy volunteers have shown little or no inhibition of LDL oxidation (Table 2). Recently, Hodgson *et al.* [63] reported a greater lag time before LDL oxidation for both black and green tea compared to water, but these changes within a healthy cohort of 20 men were either borderline ($p = 0.05$ for black tea) or not significant ($p = 0.17$ for green tea). Although van het Hof *et al.* [64] observed an accumulation of tea catechins in LDL of 18 healthy adults, 18 to 64 years of age, after daily consumption of eight cups of black tea, green tea or black tea with milk for three days, the concentration attained was not sufficient to enhance LDL resistance to Cu^{2+}-induced oxidation. However, Miura *et al.* [65] did detect an increase in lag time ($p < 0.05$) among 22 healthy young men after they consumed green tea extract equivalent to seven to eight cups a day for seven days; it may be noteworthy that plasma β-carotene was higher ($p < 0.01$) in the tea group after the intervention.

The discrepancy between the effect of tea *in vitro* and *ex vivo* on the susceptibility of LDL to oxidation may be due to the inability to achieve concentrations *in vivo* as great as those obtained with the former methods [57]. However, recent bioavailability studies indicate that tea catechins can accumulate in the body at concentrations comparable to those employed *in vitro* by several laboratories. For example, van het Hof *et al.* [64] found five cups of green or black tea (at one cup every two hours) elevated total plasma catechin levels to 1.0 and 0.30 μmol/L, respectively, and up to 0.077 μmol/L in LDL. EC concentrations of 0.08–1.25 μmol/L from green tea extracts are able to inhibit formation of conjugated dienes [66] and increase lag time [67]. While the maximum concentration of intact flavonoids in plasma rarely exceeds 1 μmol/L after consumption of 10–100 mg of a single compound [68], higher plasma concentrations can be maintained with repeated ingestion over time [64,69].

Inter-individual variations in the bioavailability of tea polyphenols can be substantial and may be due, in part, to differences in colonic microflora and genetic polymorphisms among the enzymes involved in polyphenol metabolism [68]. The effect of tea drinking may also differ by genotype, e.g., individuals with the E2 allele of ApoE possess a reduced plasminogen activator inhibitor (PAI-1) activity following consumption of black tea ($p = 0.007$, n = 7) [70]. Importantly, tea may affect cardiovascular function through mechanisms of action unrelated to LDL oxidation, such as via endothelial function. Kang *et al.* [71] have also demonstrated significant antithrombotic effects of tea flavonoids.

CANCER

Evidence for the anticarcinogenic potential of tea polyphenols has been provided by numerous *in vitro* and experimental studies describing their action to bind directly to carcinogens, induce Phase II enzymes such as UDP-glucuronosyl transferase and inhibit heterocyclic amine formation. Molecular mechanisms, including catechin-mediated induction of apoptosis and cell cycle arrest, inhibition of transcription factors NF-kB and AP-1 and reduction of protein tyrosine kinase activity and c-*jun* mRNA expression have also been suggested as relevant chemopreventive pathways for tea [72]. Some epidemiological studies also support a protective role of tea against the development of cancer. Studies conducted in Asia, where green tea is consumed frequently and in large amounts, tend to show a beneficial effect on cancer prevention [2,41]. For example, a prospective nine year study among 8,552 Japanese adults observed consumption of ten or more cups of green tea a day delayed cancer onset by 8.7 years in females and three years in males when compared to patients consuming fewer than three cups a day [73]. Protective effects appear to be observed less frequently in European populations where intake of black tea predominates [2]. Importantly, the putative chemopreventive effect of tea also varies by the specific type of cancer.

Table 2. The effect of tea on the inhibition of the susceptibility of LDL to oxidative modification

Type of Tea	Daily Quantity	Duration	Significance	Reference
Green	7.6 g leaves/400 mL	60 minutes	NS	[63]
Black	7.6 g leaves/400 mL	60 minutes	$p = 0.05$	[63]
Green or Black	8 c (0.5 g solids/150 mL each)	3 days	NS	[64]
Green Tea Extract	600 mg (equivalent to 7–8 c, 100 mL each)	7 days	$p < 0.05$	[65]
Black	1500 mL (5 × 3.3 g bag/300 mL)	7 days	NS	[57]
Green or Black	6 c (900 mL)	4 weeks	NS	[59]
Green Tea Extract	3.6 g (equivalent to 18 c)	4 weeks	NS	[59]
Green or Black	6 c (900 mL)	4 weeks	NS	[60]

Breast Cancer

The incidence of breast cancer appears unrelated to tea consumption in recent studies conducted in the United States [74], the Netherlands [75] and Italy [76]. In contrast, a Japanese study of 472 stage I and II breast cancer patients found an inverse correlation ($p < 0.05$) between the consumption of green tea and the rate of recurrence after seven years [77]. The relative risk of recurrence was 0.564 (95% CI: 0.350–0.911) and the recurrence rate was 16.7% for patients consuming five or more cups a day *versus* 24.3% for those drinking four or fewer. Green tea may favorably alter estradiol and sex hormone-binding globulin levels associated with the risk of breast cancer [78].

Esophageal Cancer

While some studies have associated green tea consumption with an increased risk of esophageal cancer, this effect appears due to the scalding beverage temperatures common to these specific cohorts [79].

Lung Cancer

Mendilaharsu *et al.* [80] reported that consumption of two or more cups of black tea a day reduced the risk of lung cancer by 66% in a case control study of 855 male smokers in Uruguay. In contrast, earlier studies show no chemopreventive action by black tea on lung cancer [74,75,81], although Goldbohm *et al.* [75] did observe an inverse association ($p < 0.001$) prior to adjustment for smoking status. While a recent case control study of 1,164 Hawaiians linked intake of flavonoid-rich foods, including onions, apples and white grapefruit, with protection against lung cancer, a clear association between tea drinking and lung cancer was not observed [82].

Stomach Cancer

A weak, inverse association between intake of black tea and stomach cancer was observed in a prospective cohort study of 120,852 people in the Netherlands [74]. A significant reduction in risk of stomach cancer was found in a population-based case-control study among 944 Polish women who drank tea daily, although this relationship was absent in men [83]. It is noteworthy that black tea theaflavins can induce apoptosis and inhibit the growth of human stomach cancer cells in a time and dose dependent manner [84].

Several studies conducted in Japan and China have shown a protective effect of green tea on stomach cancer [6], with the greatest effect among those with the highest levels of consumption [85,86]. These observations have been confirmed by Inoue [87] in a case-referent study of 22,834 Japanese where a high intake (seven or more cups a day) of green tea was associated with a 31% reduction in the risk of stomach cancer. Consistent with these data, in a cross-sectional study Shibata *et al.* [88] found high consumption (more than ten cups a day) of green tea among 636 Japanese in a farming village reduced the risk (OR = 0.63, 95% CI: 0.43–0.93) of precancerous chronic atrophic gastritis, even after adjustment for *Helicobacter pylori* and lifestyle factors associated with the condition. On the other hand, Hamajima *et al.* [89] found the equivalent of ten cups a day of green tea polyphenols for one year was no more effective than one to two cups a day in improving serum pepsinogen levels (reflecting stomach atrophy), a risk factor for stomach cancer. Another prospective study of 26,311 Japanese adults 40 years of age or older found no protective effect of green tea against stomach cancer [90]. However, the highest category of green tea consumption (five or more cups) among this cohort was lower than that utilized for other Asian cohorts, so the potential effect of greater intake, e.g., more than seven to ten cups a day, could not be distinguished. Importantly, other risk factors of gastric cancer, such as smoking and consumption of pickled vegetables, were also associated with increased tea intake and may have confounded this study's results.

Colorectal Cancer

Several experimental studies indicate a strong chemopreventive action of tea and tea flavonoids against cancers of the gastrointestinal tract, particularly colorectal cancers. In a consistent manner, green tea appears to have a protective effect on colorectal cancers in several studies conducted in Japan and China [6]. Interestingly, green tea polyphenols reduced the synthesis of prostaglandin E_2 synthesis in rectal mucosa by 50% within four hours of consumption [91]. In contrast, black tea showed little or no effect on colon cancer incidence in studies from the Netherlands [75] and Sweden [92], and a positive effect in a Finnish cohort from the Alpha-Tocopherol and Beta-Carotene trial [93]. In this latter population, compared with persons who did not drink tea, those who consumed less than one cup a day increased their risk of colon cancer by 40%, and those with an intake one cup or more a day doubled their risk, although tea had no impact on the incidence of rectal cancer [93]. As noted above, the effects of tea drinking on some forms of cancer, including colorectal cancer, may be seriously confounded by strong correlations with social class and lifestyle factors [94].

Bladder and Kidney Cancers

A case-control study of 882 Japanese by Ohno *et al.* [95] indicated a protective effect of green tea on bladder cancer, particularly among women. In a follow-up study of this cohort, Wakai *et al.* [96] found patients who drank green tea had a substantially better five-year survival rate than those who did not. In contrast, green tea consumption was not related to risk of bladder cancer in a prospective study of 38,540 Japanese survivors of the atomic bomb [97]. While a population-based, case-control study of 4,000 Americans indicated intake of more than five cups of tea a day was associated with a 30% reduction

in risk of bladder cancer, there was no evidence of a dose-response relationship and no association with risk of kidney cancer [98]. A case-control study conducted in Taiwan suggested an increased risk of bladder cancer with tea consumption, although none of the calculated odds ratios was statistically significant [99].

Prostate Cancer

In vitro, tea inhibits the 5-α-reductase mediated conversion of testosterone to 5-α-dihydrotestosterone and suggests a potential mechanism of action in prostate cancer [100]. Jain *et al.* [101] recently found a 30% reduction in risk of prostate cancer with tea intakes >500 mL/day in a case-control study of 1,254 Canadians. However, no association between tea intake and prostate cancer was observed in a retrospective cohort study of the 1970–1972 Nutrition Canada Survey participants. In this study, subjects who drank >500 mL/day of tea experienced the same risk as those who reported no tea consumption (RR = 1.02, 95% CI: 0.62–1.65) [102]. Although these observations are most relevant to black tea, it is worth noting evidence by Paschka *et al.* [103] that the green tea catechin EGCG induces apoptosis in human prostate cancer cells.

Skin Cancer

Animal and human studies have revealed a consistent, protective effect of tea polyphenols against chemical- and ultraviolet light (UV)-induced skin cancer. Zhao *et al.* [104] reported the topical application of a standardized green tea extract 30 minutes prior to the administration of psoralen plus UVA radiation reduced the photochemical damage associated with this treatment for psoriasis. Similarly, Katiyar *et al.* [105,106] found topical application of EGCG inhibited the UVB-induced infiltration of leukocytes and subsequent generation of reactive oxygen and nitrogen species in human skin as well as maintained gluthatione status. Similarly, Elmets *et al.* [107] found tea catechins inhibited the UVB-induced erythema response and DNA damage in a dose dependent manner, with EGCG and ECG being the most potent agents. Administration of standardized black tea extracts before or after UVB irradiation was also effective in reducing the induction of phototoxicity and inflammation in human skin [108]. Hakim *et al.* [109] observed an inverse association between tea consumption and the occurrence of squamous cell carcinoma of the skin in a population-based, case-control study of 450 older adults in Arizona. After administering a detailed tea intake questionnaire and adjusting for brewing time, drinking hot black tea reduced the risk of this skin cancer by 67% (OR = 0.33; 95% CI: 0.12–0.87). Interestingly, a six month clinical trial in 118 patients with recalcitrant atopic dermatitis (a non-tumor lesion) showed more than half the subjects obtained moderate to marked improvement after consuming 1 L/day of oolong tea (10 g) [110].

Mucosa Leukoplakia

Li *et al.* [111] conducted a double-blind, placebo-controlled trial in 59 patients with oral mucosa leukoplakia, a pre-cancerous lesion, and found oral and topical administration with a black and green tea mixture resulted in a partial regression of this lesion in 37.9% of the treated patients. Compared to the placebo control, the treatment reduced ($p < 0.01$) cell proliferation and the rate of chromosome aberration in peripheral blood lymphocytes. Yang *et al.* [112] have reported that relatively high catechin concentrations (up to 7.5, 22.0 and 43.9 μg/mL of EC, EGCG and EGC, respectively) can be achieved in the oral mucosa after drinking tea slowly. Saliva levels of EGCG, EGC and EC were two orders of magnitude higher than plasma levels within minutes of consuming two to three cups of green tea. However, the half-life of catechins in saliva was much shorter than in plasma, and encapsulated tea solids had no effect on salivary catechin level.

ORAL HEALTH

Drinking tea was associated with lower levels of dental caries in a cross-sectional study of 6,014 secondary school children in England [113]. Tea may have a beneficial impact on caries because of it natural fluoride [114]. In addition, extracts of green tea inhibit oral bacteria such as *Escherichia coli*, *Streptococcus salivarius* and *Streptococcus mutans* [115]. Oolong tea polyphenols appear to inhibit bacterial adherence to tooth surfaces by reducing the hydrophobicity of streptococci and to inhibit their cariogenicity by reducing the rate of acid production [116]. Tea decoctions prepared from a number of black and green teas also inhibit amylase activity in human saliva, reducing maltose release by 70% and effectively lowering the cariogenic potential of starch-containing foods [117]. While not directly related to oral health, it is worth noting that impetigo contagiosa, a streptococcal and staphylococcal infection of the skin, was treated by a tea liquor and ointment in 64 patients in a manner as effective as standard antibiotic therapies [118].

BONE HEALTH

Tea consumption was identified as an independent factor protecting against the risk of hip fractures in women and seven men, respectively, over age 50 in the Mediterranean Osteoporosis Study [119,120]. Consistent with this observation, Hegarty *et al.* [121] studied 1,256 British women, 65 to 76 years of age, and found that those who drank tea had greater bone mineral density than those who did not drink tea. Higher mean bone mineral density of the lumbar spine ($p = 0.004$), greater trochanter ($p = 0.004$) and Ward's triangle ($p = 0.02$) were

independent of smoking status, hormone replacement therapy, coffee drinking and the addition of milk to the tea.

THERMOGENESIS

Green tea may have thermogenic properties not attributable to its caffeine content. In a randomized clinical trial controlling for caffeine intake, Dulloo *et al.* [122], a green tea extract containing 90 mg EGCG increased the energy expenditure ($p < 0.01$) and decreased the respiratory quotient ($p < 0.001$) of ten healthy young men 24 hours after consumption. Urinary nitrogen was not affected, but 24-hour urinary norepinephrine excretion increased by 40% ($p < 0.05$) during treatment. The investigators of this study suggest a potential role of tea in the control of body weight.

COGNITIVE FUNCTION

Tea was not among the dietary sources of aluminum associated with an increased risk of Alzheimer's disease in a pilot study of geriatric residents [123]. The adjusted odds ratio for other foods containing high levels of aluminum was 8.6 ($p = 0.19$). While not determining tea intake *per se*, after a five-year follow-up Commenges *et al.* [124] found the two highest teriles of flavonoid intake among 1,367 subjects older than 65 was associated with a significant reduction ($p = 0.04$) in the risk of dementia (RR = 0.49, 95% CI: 0.26–0.92). Hindmarch *et al.* [125] reported that day-long consumption of tea improved the cognitive and psychomotor performance of healthy adults in a manner similar to coffee, but tea (which contains less caffeine) was less likely than coffee to disrupt sleep quality at night.

IRON STATUS

Black tea appears to inhibit the bioavailability of non-heme iron by 79% to 94% when both are consumed concomitantly [126]. The impact of this interaction will be dependent on the iron intake and status of the individual. Iron deficiency anemia among children in Saudi Arabia [127] and the U.K. [128] may be exacerbated by the regular consumption of tea with meals. On the other hand, this effect may be of benefit to patients with genetic hemochromatosis, as Kaltwasser *et al.* [129] observed a significant reduction in iron absorption when 18 hemochromatosis patients included with their meals a tannin-rich tea instead of water. This change in the patients' diets resulted in a reduction of the frequency of required phlebotomies. Green tea catechins may also have an affinity for iron. Recently, Samman *et al.* [130] added 0.1 mmoles green tea extract to a single meal consumed by 27 women, 19 to 39 years of age, and found a 25% reduction ($p < 0.05$) in non-heme iron absorption. Iron-induced malondialdehyde production and DNA damage were significantly reduced in Jurkat T cells grown in media supplemented with green tea extract, suggesting that catechins may also have a direct affinity for iron [131]. It is worth noting that the interaction between tea and iron can be mitigated by the addition of lemon or consuming tea between meals.

KIDNEY STONES

Although some studies have suggested tea consumption may affect the absorption of oxalates and contribute to the development of kidney stones [132], in an examination of the prospective Nurses' Health Study, a cohort of more than 81,000 women, 40 to 65 years of age, Curhan *et al.* [133] found an inverse association between tea consumption and the risk of kidney stone formation. Employing a multivariate model that adjusted simultaneously for 17 beverages and other potential risk factors, each 240 mL serving of tea consumed daily decreased the risk of developing kidney stones by 8% (CI: 1–15%).

DISCUSSION

Tea is an important dietary source of flavanols and flavonols. *In vitro* and animal studies continue to provide strong evidence that tea polyphenols may possess the capacity to affect the pathogenesis of several chronic diseases, especially cardiovascular disease and cancer. However, these experiments do not appear to readily extrapolate to human studies. The results from epidemiological studies of the relationship between tea and health are inconsistent. International correlation studies reveal the striking variation in tea consumption between countries does not consistently correlate with differences in rates of cancer or heart disease, but notable limitations are associated with this research approach. Case-control and cohort studies provide methodologically superior approaches to address this relationship but remain significantly hampered by their use of dietary assessment tools, particularly food frequency questionnaires, which rarely distinguish between the type of tea (including herbal teas) or its preparation despite the marked impact of these factors on polyphenol content and concentration. This constraint may mask the contributions of tea to the promotion of health. Conflicting results between cohort studies conducted in different countries may also arise from confounding due to marked contrasts in the socioeconomic and lifestyle factors associated with tea drinkers. However, meta-analyses provide some confidence to the observations of a beneficial impact of tea. Randomized clinical trials to test the primary prevention of chronic diseases by tea are not feasible, but some recent human studies examining the effect of tea on putative intermediary biomarkers, e.g., homocysteine for heart disease and 8-hydroxy-2′-deoxyguanosine for cancer, as well as physiological responses like brachial artery dilation,

suggest such a benefit. New human studies will benefit from the use of standardized teas and tea extracts. Evidence for the therapeutic use of tea or tea extracts, e.g., in oral leukoplakia, is provocative but very limited.

It is important to appreciate the peril of concluding too quickly that *in vitro* effects translate into *in vivo* actions. For example, the potent *in vitro* inhibition by catechins of the oxidative modification of LDL is not reflected in *ex vivo* analyses from individuals consuming substantial amounts of tea. Understanding the basis for this discrepancy will require further research into the distribution and metabolism of tea polyphenols as well as genetic polymorphisms. Alternatively, an impact of tea on risk of cardiovascular disease may be mediated instead by its action on endothelial function or its effects, demonstrated thus far only *in vitro* and in animal models, on platelets, thrombosis and hemostasis. In contrast to data on LDL oxidation, recent clinical studies consistently demonstrate an increase in the antioxidant capacity of blood which closely reflects the dose- and time-course of tea bioavailability. These *ex vivo* observations correlate closely with *in vitro* analyses of the antioxidant capacity of tea and its constituent polyphenols. To the extent that these results are relevant to the promotion of health, not only will matters like type of tea (i.e., green, oolong and black) and preparation (e.g., short *vs.* long brew time and hot *vs.* iced) be important, but so will the frequency and timing of intake as these factors directly affect the pharmacokinetics and ultimate disposition of the polyphenols within tissues.

In the face of equivocal results from human studies, the increasing knowledge about the bioactivity of tea polyphenols should encourage further clinical investigations to uncover their actual contribution to the promotion of health and prevention of chronic disease. Both *in vitro* and *in vivo* tea polyphenols act as an antioxidants. Catechins induce Phase I cytochrome P450 1A1, 1A2, and 2B1 and Phase II glucuronyl transferase and may thereby enhance the detoxification of carcinogens. Further, EGCG induces apoptosis and cell cycle arrest in human carcinomas, and EGC inhibits the proliferative response to several different animal and human cells. Tea may also possess a probiotic effect.

The Dietary Guidelines for Americans provide detailed information about healthful food patterns but offer little advice concerning beverage consumption beyond including milk within the dairy group and suggesting alcohol intake be moderate if and when it is consumed. While the totality of the evidence from research on tea is very promising, more research is necessary to fully understand its contributions to human health. While no single food item can be expected to provide a significant effect on public health, it is important to note that a modest effect between a dietary component and a disease having a major impact on the most prevalent causes of morbidity and mortality, i.e., cancer and heart disease, should merit substantial attention. While nutritional guidelines for public health should always be conservative with the potential benefits and efficacy of changes defined in the near absence of risk, there is no evidence to suggest any adverse consequence from tea consumption in an otherwise healthful diet.

Dietary recommendations must be developed such that people will accept the changes proffered and try, if only with partial success, to incorporate them into their lives. Recent human studies suggest tea may contribute to a reduction in the risk of cardiovascular disease and some forms of cancer as well as to the promotion of oral health and other physiological functions. As tea is already one of the most popular beverages worldwide, future studies, designed to accurately assess tea consumption and tea polyphenol status, should be directed to quantifying its role in the primary and secondary prevention of chronic diseases.

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