Global Association between Tea Consumption and Cardiovascular Disease

Lenore Arab, David Geffen School of Medicine at UCLA

Randomized clinical trials in man of the effects tea consumption on chronic diseases are infeasible. Thus, the information gap on whether tea consumption can reduce cardiovascular disease, and if so which doses elicit which effects can only be bridged by meticulous study and analysis of the evidence from self-selected use of tea as a beverage. If high standards are used to assess the homogeneity-of-effect after controlling for potential sources of confounding, and dose response relationships are confirmed in diverse, free living populations; a high level of confidence in the findings can be achieved. Adequate control for measurement error will allow the magnitude of effect per cup of tea to be reasonably estimated. To date we have identified 18 publications from observational epidemiologic studies reporting on tea consumption and cardiovascular disease outcomes. They range across the globe from Australasia to American and European populations. They include heavy and light tea drinking populations, and habitual consumers of black, green and oolong teas. The epidemiologic studies in man support animal experiments that demonstrate a preventive effect of tea exposure on stroke outcomes, and are remarkably homogeneous. However, the evidence for other aspects of cerebrovascular disease; specifically myocardial infarction and cardiovascular disease is less consistent. An overview of these studies, meta analyses of their findings and their interpretation will be presented.

(Poly)phenolic compounds in teas and their absorption, metabolism and potential bioactivity.

Alan Crozier, School of Medicine, University of Glasgow, UK

Green tea infusions contain very high levels of a diversity of (poly)phenolic compounds with the flavan-3-ols (–)-epicatechin, (–)-epigallocatechin and (–)-epigallocatechin-3-*O*-gallate being among the major constituents (1) along with smaller amounts of chlorogenic acids and a diversity of quercetin, kaempferol and myricetin-based sugar conjugates (2). During fermentation to produce black tea major changes occur in the flavan-3-ol content of the tea leaves with monomers being converted by polyphenol oxidase activity to dimer-like theaflavins and high molecular weight thearubigins. Little was known about the structure of thearubigins until a recent pioneering, study revealed an exceedingly complex picture with black teas containing ~5000 thearubigin components with mass range between 1000 and 2100 daltons (3).

Human feeding studies with green tea have established that (–)-epicatechin is efficiently absorbed in the small intestine and appear transiently in the circulatory system as sulfated and glucuronidate metabolites. (–)-Epigallocatechin is absorbed much less readily as is (–)-epigallocatechin-3-*O*-gallate (4). Substantial amounts of a mixture of flavan-3-ol monomers pass from small to the large intestine where they are degraded by the action of the microbiota to a series of valerolactones and valeric acids which undergo side chain shortening producing phenylacetic acids. These products are absorbed into the portal vein and pass through the circulatory system before being excreted in quantities well in excess of sulfated and glucuronidated metabolites absorbed in the upper gastrointestinal tract (5). Recent *in vitro* studies indicate that colonic catabolites formed in this manner, at physiological doses, have antiglycative and neuroprotective effects (6).

The residual levels of flavan-3-ol monomers in black tea appear to be absorbed in a similar manner (7) while feeds with theaflavins have resulted in only 0.001% of intake being excreted in urine (8). It seems reasonable to assume that following ingestion the vast majority of theaflavins and thearubigins in black teas pass to the colon although, as yet, little is know about the extent to which they are degraded by the microbiota.

In view of its growing popularity, the very limited bioavailability of dihyrochalcone and flavanone *C*-glycosides in rooibos (red bush) tea will also be discussed (9).

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Interactions of black tea polyphenols with the human microbiome

John van Duynhoven[a,d,,e], Elaine Vaughan[a], Rober Kemperman[a], Laure Roger[a,f], Ewoud van Velzen[a,e], Johan Westerhuis[b,e], Age Smilde[b,e], Joel Dore [f], Tom van der Wiele[g], Justin van der Hooft[d,e], Jacques Vervoort[d,e], Ric de Vos[c,e], Richard Draijer[a], Doris Jacobs[a,e]

[a]Unilever R&D, Vlaardingen, the Netherlands; [b]University of Amsterdam, the Netherlands, [c]PRI, Wageningen, the Netherlands, [d]Wageningen University, the Netherlands, [e]Netherlands Metabolomics Centre, [f]INRA, Jouy-en-Josas, France; [g]LabMET, Gent, Belgium

Black tea is one of the most consumed beverages and accounts for a significant part of polyphenol intake in the world population. Black tea polyphenols mainly (60-70%) exist as high-molecular weight species such as theaflavins and thearubigins that are poorly absorbed in the upper digestive tract and predominantly persist to the colon. There they can undergo massive bioconversions by the resident colonic microbiota, but can in their turn also modulate gut microbial diversity. Both polyphenol bioconversion products as well as shifts in gut microbial diversity can impact on the human host. These strong and symbiotic interactions between the gut microbiome and the human host have led to the recognition of humans as superorganisms. Due to practical and ethical constraints one can mostly not get a direct experimental view on dietary induced events in the colon microbiota. Hence, besides performing controlled human intervention studies, we also made extensive use of validated vitro gut models. In order to study the complex interactions between dietary polyphenols and the human superorganism we developed and implemented a suite of measurement technologies and modelling tools. The *in vitro* impact of black tea polyphenols on the composition of the colonic microbiota can now well be assessed by microbiomics technologies. In order to capture the large chemical diversity of polyphenol bioconversions in the superorganism we implemented platforms for targeted and untargeted profiling and for *de novo* identification of hitherto unidentified metabolites. Nutrikinetic modeling of longitudinally acquired metabolic profiles has been proven critical for defining nutritional phenotypes related to gut microbial bioconversion capacity and establishing relations between gut microbial functionality and circulating metabolites. Bottom-up as well as top-down approaches now need to be pursued to link gut microbial diversity to functionality in nutritional phenotypes and ultimately to bioactivity of polyphenols. This will pave the way for personalization of nutrition based on gut microbial functionality of individuals or populations.

Tea Consumption and Risk of Cardiovascular Disease

Lenore Arab, David Geffen School of Medicine at UCLA

Randomized clinical trials in man of the effects tea consumption on chronic diseases are infeasible. Thus, the information gap on whether tea consumption can reduce cardiovascular disease, and if so which doses elicit which effects can only be bridged by meticulous study and analysis of the evidence from self-selected use of tea as a beverage. If high standards are used to assess the homogeneity-of-effect after controlling for potential sources of confounding, and dose response relationships are confirmed in diverse, free living populations; a high level of confidence in the findings can be achieved. Adequate control for measurement error will allow the magnitude of effect per cup of tea to be reasonably estimated. To date we have identified 18 publications from observational epidemiologic studies reporting on tea consumption and cardiovascular disease outcomes. They range across the globe from Australasia to American and European populations. They include heavy and light tea drinking populations, and habitual consumers of black, green and oolong teas. The epidemiologic studies in man support animal experiments that demonstrate a preventive effect of tea exposure on stroke outcomes, and are remarkably homogeneous, with individuals consuming >or=3 cups of tea per day having a 21% lower risk of stroke than those consuming <1 cup per day (absolute risk reduction, 0.79; CI, 0.73 to 0.85) [1] . However, the evidence for other aspects of cerebrovascular disease; specifically myocardial infarction and cardiovascular disease is less consistent. Heterogeneity of effect is seen for cardiovascular disease incidence and mortality. Findings are more consistent across countries for the subclass of disease such as coronary artery disease stenosis confirmed by upon catheterization, where a 70% reduction in risk among tea drinkers was seen in a high tea consuming country(OR 0.30; CI 0.15-0.65)[2]. Myocardial infarction incidence is also lower in countries with significant consumption levels such as the Netherlands and Japan but not Sweden where tea consumption is low, and not where the outcome is prognosis[3]. Questions remain of the residual confounding due to the association between tea consumption and healthy lifestyles in many western countries.

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Attention benefits of tea

Suzanne Einother

Sensation, Perception & Behaviour

Unilever R&D Vlaardingen, The Netherlands

Abstract for the 5th International Symposium on Tea & Health.

Tea has historically been associated with cognitive benefits such as mental clarity and concentration. Recent findings attribute these benefits to caffeine and theanine, two constituents of tea (Bryan, 2008).

Performance benefits of tea were initially identified in two open-label studies (Hindmarch et al., 1998; 2000), comparing tea to water and coffee with or without caffeine over the course of a day. Results showed improvements in performance and alertness after caffeine, as well as tentative evidence of beneficial effects of tea over caffeinated water.

Two subsequent randomized placebo controlled studies (De Bruin et al., 2011) investigated the effects of black tea on test of attention and a self-report measure of alertness. In the first study, participants consumed two cups of black tea, with a cumulative amount of 100mg caffeine and 46mg L-theanine, and a placebo tea (coloured and flavoured water). Results indicated that accuracy on the Attention Switching task was improved after tea as compared to the placebo, as well as performance on two of the four subtasks from the Intersensory Attention task.. Finally, participants felt more alert after tea consumption. In a replication of this study, participants consumed 3 cups of tea of a slightly weaker tea blend (cumulative amount of 90mg caffeine and 36mg L-theanine). Again, accuracy on the Attention Switching task was improved after tea as compared to placebo, and participants reported feeling more alert. Tea did not significantly affect performance on the Intersensory Attention task.

In addition, two recent studies provided a broader perspective on tea's effects on psychological wellbeing. A cross-sectional study showed that participants who consumed more tea felt less tired and reported higher levels of subjective work performance (Bryan et al., 2012). Furthermore, tea consumption can positively affect mood and may improve creative problem solving, as compared to water (Einother et al., 2012).

In sum, these studies clearly demonstrate that black tea helps to improve cognitive functioning, and in particular attention.

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Abstract

Effects of black tea with and without a fat load on vascular function in mildly hypertensive volunteers

Davide Grassi, Richard Draijer, Giovambattista Desideri, Theo Mulder, Claudio Ferri

Introduction. Endothelial dysfunction has been supposed to be the first step of atherosclerosis. Endothelial dysfunction may be an early biomarker for the development of cardiovascular disease and a predictor of future cardiovascular events. Flavonoids are a class of compounds occurring in different plant foods. Major dietary sources include fruits and vegetables, tea, red wine and chocolate. Recent studies in healthy subjects reported positive effects of both acute and chronic black tea consumption on endothelium-dependent flow-mediated dilation (FMD). Further, we recently observed black tea ingestion dose-dependently improved FMD and decreased peripheral arterial stiffness in healthy volunteers. In contrast, lipemia following a fatty meal occurs several times per day and a fat-rich meal decreased FMD.
Aim: To assess the effect of black tea with and without a fatty meal on FMD, digital volume pulse (DVP) and office blood pressure (BP) in never treated grade 1 hypertensive patients without additional cardiovascular risk factors.
Methods. According to a randomized, double-blind, controlled, cross-over design, 19 grade 1 hypertensives were assigned to receive 150 mg tea flavonoids or placebo twice a day for eight days. Wash-out between treatments was of 13 days. On day 7 all measurements were performed in a fasted state while on day 8 patients consumed ultra-heat-treated whipping cream (1 gram fat per kg body weight) approximately 30 minutes after consuming the test product. FMD, DVP and BP measurements were measured basally and repeated at 1, 2, 3 and 4 hours after consumption of the test product.
Results: After 1-week, tea ingestion improved FMD ($p<0.0001$). One cup of tea further increased FMD at 1, 2, 3 and 4 hours after consumption with acute improvement and maximal response 2 hours after intake ($p<0.0001$). Fat challenge significantly decreased FMD, while tea consumption counteracted FMD impairment by the fat challenge ($p<0.0001$). Tea improved reflection index (small vessel tone; $p<0.0001$) and stiffness index (large arterial stiffness; $p<0.0001$) with additional effects after acute tea consumption (1, 2, 3 and 4 hours), with and without fat load. Further, tea decreased systolic and diastolic BP with and without a fat load (all $p<0.0001$). Tea intake significantly increased the number of circulating blood endothelial progenitor cells ($p<0.005$).
Conclusions: We observed for the first time that black tea may have beneficial effects on BP and vascular function and attenuated, or completely prevented, the abnormalities in endothelial function, peripheral arterial hemodynamics and BP caused by an acute oral fat load in never-treated hypertensive patients. Considering that the ingestion of the main daily meal has been considered a possible trigger for acute myocardial infarction, our findings are of clinical relevance and interest.

Abstract (Lay press)

Effects of black tea with and without a fat load on vascular function in mildly hypertensive volunteers

Atherosclerosis is the main cause of death and disease in US. An impaired vasodilation with dysfunction of the arterial function precedes and cause atherosclerosis and recent studies in healthy subjects reported positive effects of both acute and chronic black tea consumption on arterial function and vasodilation, as investigated by the gold standard technique, i.e. flow-mediated dilation (FMD).

In this regard, an uncorrect with high fat content can occur even several times per day and is known to induce a marked and repeated damage at the vascular level, particularly by decreasing the vasodilatory ability.

Thus, in our more recent studies we evaluated for the first time the effect of black tea with and without a fatty meal on FMD and blood pressure levels in never-treated grade 1 hypertensive patients without additional cardiovascular risk factors.

Main results showed that black tea ingestion (1 week) improved FMD ($p<0.0001$). As expected, the fat challenge significantly decreased FMD. Black tea consumption counteracted FMD impairment by the fat challenge ($p<0.0001$). Tea also reduced systolic and diastolic BP with and without a fat load (all $p<0.0001$). Of note, we also observed that black tea intake significantly increased the number of circulating blood endothelial progenitor cells, i.e. of protective circulating cells, ($p<0.005$).

In conclusion, we observed for the first time that black tea exerts beneficial effects on BP and vascular function and attenuated, or completely prevented, the acute vascular abnormalities induced by fats. The main responsible for this benefits are likely to be the flavanols contained in black tea.

Considering that an “junk diet”, rich in fats an/or glucose, is considered as a trigger for acute myocardial infarction and stroke, our findings are of clinical relevance.

Summary Rick Hursel

Targeting overweight and obesity is essential since excessive weight has become a major health problem in the 21st century. The presentation focuses on triggers for increasing energy expenditure such as green tea and caffeine, which may be able to promote weight loss or prevent excessive weight gain, separately or synergistically.

First, the impact of green tea on body weight regulation will be reviewed, addressing the short-term effects, long-term effects and mechanisms of action. Ingredients for obesity management including caffeine and different teas such as green, white and oolong tea increased on average energy expenditure with 4-5% and fat oxidation with 10-16% and they may counteract the decrease in metabolic rate that is present during weight loss. A daily increase in thermogenesis of approximately 300-400 kJ can eventually lead to substantial weight loss.

Second, two meta-analyses will be discussed; one of these evaluated short-term effects of catechin-caffeine mixtures on energy expenditure and fat oxidation and the other meta-analysis evaluated long-term effect of catechin-caffeine mixtures on body-weight loss and weight maintenance. Different outcomes of the effect of catechin-caffeine mixtures have been reported in studies with subjects differing in ethnicity and habitual caffeine intake. Therefore, these meta-analyses elucidated whether a catechin-caffeine mixture indeed plays a role in body-weight regulation. A catechin-caffeine mixture and caffeine-only treatment showed a stimulating effect on energy expenditure and a catechin-caffeine mixture also showed a stimulating effect on fat oxidation compared with placebo. 24h energy expenditure and fat oxidation were increased on average with 0.5kJ/mg and 0.02g/mg for catechin-caffeine mixtures and 0.4kJ/mg and 0.01g/mg for the caffeine-only treatment. It was also shown that catechin-caffeine mixtures have a positive effect on weight loss and on weight maintenance. Catechins significantly promoted body-weight loss or prevented weight gain after weight loss with approximately 1.3 kilogram. Moreover, it also showed that habitual caffeine intake and ethnicity, due to different COMT polymorphisms, might be moderators.

Third, catechin-caffeine mixtures and protein separately were able to increase diet-induced thermogenesis. Hence, a combination of both was examined to study the acute effect of milk-protein on green tea induced thermogenic effect of food, as well as on the long-term effect where its contribution to weight maintenance after weight loss was assessed. In the short-term, consumption of milk-protein inhibited the effect of green tea on diet-induced thermogenesis. In the long-term, catechin-caffeine mixture, as well as a high-protein diet improved weight-maintenance independently, via multiple pathways such as thermogenesis, fat oxidation, sparing fat free mass, and for the high-protein diet through satiety. Nevertheless, a possible synergistic effect failed to appear, most presumably by formations of protein-polyphenol complexes that reduce the absorption.

Prevention of weight gain after weight loss and during weight maintenance, can be achieved when certain metabolic targets such as sustained satiety, sustained energy expenditure, sparing of fat free mass are stimulated, together resulting in a high energy inefficiency. These requirements need to be fulfilled despite being in negative energy balance, since successful weight loss or weight maintenance depends on the combination of the three.

Does Tea Prevent Cancer? An Update on Laboratory and Clinical Studies.

Joshua D. Lambert, PhD
Department of Food Science
The Pennsylvania State University

Tea (*Camellia sinensis*, Theaceae) is the second most commonly consumed beverage in the world and is consumed as one of three processed types- green, oolong, and black, which differ in terms of their sensory qualities as well as their chemical composition. Studies have focused on both tea extracts as well as purified compounds. (-)-Epigallocatechin-3-gallate (EGCG), the most abundant polyphenol in green tea; theaflavins, the characteristic polyphenols in black tea; and caffeine have been the most extensively studied. \

Laboratory studies have shown that tea and tea constituents, both polyphenols and to a lesser extent caffeine, have cancer preventive activity in a number of animal models and at different stages of the carcinogenic process. For example dietary administration of green tea extract inhibits 4-(methylnitrosamino)- 1-(3-pyridyl)-1-butanone (NNK)-induced lung tumorigenesis in mice. In most studies that have examined the issue, the polyphenols have been reported to be the major active constituents in tea, although in some models, for example ultraviolet light-induced skin carcinogenesis, caffeine has been shown to exert potent cancer preventive activity. Recent animal model studies have focused on the potentiation of the cancer preventive effects of tea by other dietary compounds or pharmaceutical agents. For example, dietary administration of green tea polyphenols in combination with atorvastatin resulted in a greater than additive reduction in tumor number and volume in NNK-treated mice compared to either treatment alone. Our laboratory has observed that treatment of mice with EGCG in combination with inhibitors of catechol-o-methyltransferase enhances the *in vitro* bioactivity of EGCG and improves the bioavailability of unmethylated EGCG in mice.

A number of potential mechanisms have been proposed for the cancer preventive activities of tea and tea components based on *in vitro* studies. These mechanisms remain largely untested *in vivo*, although there are some exceptions including induction of phase II drug metabolizing enzymes and modulation of insulin-like growth factor signaling. Interestingly, there is increasing evidence to suggest that polyphenol-induced oxidative stress may play a role in the anticancer activity of EGCG. Our laboratory and others have demonstrated that EGCG-induced oxidative stress is critical for inhibition of cell growth and induction of apoptosis: inclusion of exogenous antioxidants such as superoxide dismutase stabilize EGCG and reduce its growth inhibitory effects under cell culture conditions. More recently, it has been reported that orally-administered EGCG can induce oxidative stress in human lung cancer xenografts in mice without affecting the liver or small intestine. These results suggest some selectivity for the pro-oxidant effects of tea: selectively that likely depends on molecular differences between tumor cells and normal cells. Further study is needed to fully elucidate the role of oxidative stress and other potential mechanisms in mediating the cancer preventive effects of tea.

Whereas tea has been widely studied in the laboratory for its cancer preventive activity, there is limited data with regard to hard cancer endpoints. Most human studies have focused on the modulatory effects of tea on biomarkers related to cancer (e.g. induction of endogenous antioxidant systems). A pilot study in Italy reported that daily supplementation with 600 mg green tea polyphenols reduced the progression prostate intraepithelial neoplasia to prostate

cancer in 30 subjects by 90% compared to placebo. Similar and larger studies are needed to effectively test the cancer preventive efficacy of tea and tea constituents in human subjects.

In conclusion, although there is ample laboratory data demonstrating the preclinical cancer preventive activity of tea and tea constituents, the underlying mechanism(s) of action remain unclear and the efficacy of tea for cancer prevention in humans remains to be conclusively demonstrated.

Mechanisms of Action of Tea Polyphenols

Mario Lorenz, PhD
Charité-Universitätsmedizin Berlin, Germany

Tea polyphenols have attracted much attention as potential beneficial agents in a variety of human diseases. Human intervention studies are on the way where tea polyphenols are applied as beverages or as isolated compounds. Although promising experimental and clinical data demonstrate protective effects, still limited information is available on how these beneficial effects of tea polyphenols are mediated at the cellular level. For the elaboration of human studies and to understand their mode of action, the elucidation of molecular targets for tea polyphenols at the cellular level is inevitable. Owing to the scientific interest in beneficial properties of tea in cancer, neurological disorders, cardiovascular and other human diseases, a diverse spectrum of different cell types for molecular actions of tea polyphenols is involved. In addition, green and black tea that contain different biologically active compounds are consumed in distinct geographical regions. Evidence is accumulating that catechins in green tea as well as theaflavins and thearubigins from black tea are the substances responsible for the physiological effects of tea. The green tea catechin EGCG (epigallocatechin-3-gallate) is generally considered to be the biologically most active compound *in vitro*. The modification of the activity of various growth factors, transcription factors and protein kinases is a common mechanism involved in the molecular effects of tea polyphenols. By affecting the activity of receptor and intracellular signal transduction pathways, the major ingredients of green and black tea exert a variety of beneficial impacts in diverse cell types. Surprisingly, they frequently result in opposing effects. Whereas in fast-proliferating, activated cells (e.g. tumor cells) tea polyphenols inhibit the activity of intracellular signaling cascades (leading to cell cycle arrest and apoptosis), in primary, resting cells these pathways are activated. These apparently contradictory cellular effects provide the rationale for the potential use of tea polyphenols both against cancer and diseases without uncontrolled cell proliferation. In neurodegenerative disorders, besides their antioxidant effects, tea polyphenols interfere with the formation of toxic amyloids and even convert mature fibrils into non-toxic intermediates by direct binding to unfolded polypeptides or mature aggregates at the extracellular level.

Many human diseases are characterized by sustained inflammatory processes. Tea polyphenols exert direct and indirect antioxidant effects at the cellular level. These include direct scavenging of free radicals, chelating of metal ions, inhibition of cellular ROS generating enzymes and cytokine production at one hand and induction of intracellular free radical scavenging enzymes on the other hand. However, also the generation of reactive oxygen species by tea polyphenols was observed in a number of *in vitro* experiments. The extent of biological activity of tea polyphenols depends on their chemical structure. Overall, catechins and theaflavins containing a galloyl group at their 3 position proved to be physiologically most potent. The contribution of various other tea ingredients is less well understood. Many cell culture studies used much higher concentrations of tea polyphenols as can be achieved *in vivo* after tea consumption. Whereas this approach is able to detect many molecular targets at the cellular level, it also raises questions about the biological relevance of the observed effects for the *in vivo* situation.

Although an impressive progress has been made in recent years in the elucidation of molecular targets of tea polyphenols in diverse cell types, many questions still remain unresolved. Attempts to attribute functional effects *in vivo* to specific molecular signal transduction pathways affected at the cellular level are still at the beginning.

Green Tea and Bone Health: From Bench to Clinical Trial

Chwan-Li Shen, PhD, CCRP

Texas Tech University Health Sciences Center
Lubbock, Texas

Osteoporosis, a degenerative bone disease, is characterized by low bone mass and microstructural deterioration of bone tissue that results in bone fragility and an increased susceptibility to fractures, especially of the hip, spine and wrist [1]. The trend of increased life expectancy is accompanied with an increase in the prevalence of osteoporosis and concomitant complications in the elderly population [1]. Bone is a dynamic organ that is constantly renewed through a process of remodeling and modeling involving bone resorption by osteoclasts and bone formation by osteoblasts [2]. Oxidative stress (excessive reactive oxygen species) is considered to be responsible for contributing to the etiology of various degenerative diseases, including osteoporosis [3-5]. Recent research has suggested that bone mineral density is positively associated with tea consumption that may optimize bone health. The bioactive components in tea may benefit bone health in terms of maintaining higher bone mineral density [6-8] and reducing fracture risk [9,10]. Specifically, green tea appeared to benefit bone health more than other kinds of tea (e.g., black, oolong). The abilities of green tea bioactive components to increase indices of bone formation (osteoblastogenesis) and to decrease indices of bone resorption (osteoclastogenesis) has been suggested by previous *in-vitro* studies, in terms of green tea's impact in osteoblastic and osteoclastic activity, respectively [11]. The previous animal studies support that green tea polyphenols (extract of green tea) may benefit bone health by mitigating bone loss/preserving bone mass, by attenuating micro-architectural deterioration, or by improving bone strength due to aging, aging plus sexual hormone deficiency, chronic inflammation, and obesity [12]. In addition, we recently reported that 6-month supplementation of green tea polyphenols significantly increased serum bone-specific alkaline phosphatase (bone formation biomarker) concentration at 1 month, elevated the change of bone-specific alkaline phosphatase/tartrate-resistant acid phosphatase (bone resorption biomarker) ratio at 3months, and improved muscle strength at 6 months in postmenopausal women with low bone mass [13]. The beneficial effects of green tea and its bioactive components on bone health appear to be mediated via anti-oxidant or anti-inflammatory pathways and their signaling mechanisms along with various types of cells [11, 12]. These significant beneficial effects on bone suggest that green tea polyphenols may serve as an effective dietary supplement to mitigate bone loss in patients with low bone mass. It is worthy to point out that even though green tea and their metabolites are found to be useful in treating bone loss, there is a gap in knowledge still needed to explore in terms of how to translate animal observation to human populations [12]. All animal evidence only shows an increase in bone mineral density and bone strength without testing anti-fracture capacity, and these animal data mainly focus on long bones while the published epidemiological human data are for spine and hip. In addition, there is still limited report supporting bone mineral density increment and anit-fracture effect of green tea from longitudinal studies. In future human studies, green tea and its active ingredients should be given for long-term periods, the bioavailability should be monitored via validated biomarkers, and efficacy in terms of bone mass and micro-architecture should be evaluated through advanced imaging technology in order to ensure their possible benefits in treating osteoporosis [12].

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Cancer Prevention by Green Tea: Evidence from Epidemiological Studies

Jian-Min Yuan, MD, PhD
University of Pittsburgh Cancer Institute
Pittsburgh, Pennsylvania

Green tea contains high concentrations of tea polyphenols including (-)-epigallocatechin-3-gallate (EGCG) at the highest concentration. Both tea extracts and EGCG have shown inhibitory effect against the development, progress, and growth of carcinogen-induced tumors in animal models at various organ sites including the oral-digestive tract, lung, prostate, mammary glands, and urinary bladder. Although epidemiological studies have provided inconclusive results on the effect of green tea consumption against the development of cancers in humans overall, the inverse association between high consumption of green tea and risk of oral-digestive tract cancers is more consistently observed in studies with adequate control for potential confounders. Green consumption was associated with statistically significantly reduced risk of esophageal cancer in men and women who did not consume ether alcohol or tobacco or (1). Biomarker studies showed that individuals with high levels of tea polyphenols in urine samples collected many years before cancer diagnosis experienced significantly reduced risk of esophageal, gastric and colon cancers (2, 3). Randomized clinical trial showed that oral supplementation of green tea extract significantly reduced the size or progression of precancerous lesion of oral cavity in patients (4, 5). A randomized phase II clinical trial supported a protective role of green tea extract against the liver damage by aflatoxin exposure and hepatitis B, two established risk factors for liver cancer, suggesting a protective role of liver cancer (6). Epidemiological studies also have demonstrated an inverse, albeit moderate, association between green tea consumption and lung cancer. Intake of 2 cups of green tea per day would result in a statistically significant, approximately 20% decrease in the risk of developing lung cancer (7). This protective effect of green tea consumption on lung cancer was more pronounced in nonsmokers than in smokers (8). Although observational studies do not support a beneficial role of tea intake against the development of prostate cancer, a phase II clinical trials have demonstrated an inhibitory effect of green tea extract against the progression of prostate pre-malignant lesions to malignant tumors, and the protective effect lasted for at least 2 years after termination of green tea supplementation (9, 10). Evidence from epidemiological studies that examined the association between green tea consumption and risk of breast cancer was inconsistent. An inverse association was reported in case-control studies whereas a null association was found in prospective cohort studies (11). Given the important role of O-methylation by catechol-O-methyltransferase (COMT) in the conjugation reaction of tea catechins, several studies examined the modifying role of *COMT* genotype on the green tea-breast cancer association and also produced inconsistent results (12, 13). There is no sufficient evidence that supports a protective role of green tea intake on the development of urinary bladder cancer. The difference between results from animal and human studies is likely to be due to (a) the relatively weak cancer preventive effect in humans because the lower quantities of green tea consumed by a healthy individual as compared to the doses used in animal studies, and (b) the confounding factors in the epidemiological studies that could reduce or even mask the true protective effect of green tea whereas in animal experimental studies the conditions are well controlled to maximize the likelihood to detect a protective effect. Future prospective observational studies with biomarkers of exposure and phase III clinical trials are required to provide definitive evidence for the hypothesized beneficial effect of tea consumption on cancer development in humans.

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