

Does tea prevent cancer? Evidence from laboratory and human intervention studies^{1–4}

Joshua D Lambert

ABSTRACT

Tea (*Camellia sinensis*) is a widely consumed beverage and has been extensively studied for its cancer-preventive activity. Both the polyphenolic constituents as well as the caffeine in tea have been implicated as potential cancer-preventive compounds; the relative importance seems to depend on the cancer type. Green tea and the green tea catechin have been shown to inhibit tumorigenesis at a number of organ sites and to be effective when administered either during the initiation or postinitiation phases of carcinogenesis. Black tea, although not as well studied as green tea, has also shown cancer-preventive effects in laboratory models. A number of potential mechanisms have been proposed to account for the cancer-preventive effects of tea, including modulation of phase II metabolism, alterations in redox environment, inhibition of growth factor signaling, and others. **In addition to the laboratory studies, there is a growing body of human intervention studies suggesting that tea can slow cancer progression and modify biomarkers relevant to carcinogenesis.** Although available data are promising, many questions remain with regard to the dose-response relations of tea constituents in various models, the primary mechanisms of action, and the potential for combination chemoprevention strategies that involve tea as well as other dietary or pharmaceutical agents. The present review examines the available data from laboratory animal and human intervention studies on tea and cancer prevention. These data were evaluated, and areas for further research are identified. *Am J Clin Nutr* 2013;98(suppl):1667S–75S.

INTRODUCTION

Tea (*Camellia sinensis*, Theaceae) is the second most popular beverage in the world (1). Although all tea is derived from the same plant, different processes result in green, black, and oolong tea; these teas differ in terms of appearance, flavor, and chemistry (1, 2). Green tea is characterized by high concentrations of catechins, with (–)-epigallocatechin-3-gallate (EGCG)⁵ being the most abundant (**Figure 1**). Black tea, by contrast, contains high amounts of theaflavins (Figure 1) and thearubigins, which account for the characteristic color and flavor of this beverage (2).

There is growing evidence from laboratory, epidemiologic, and human intervention studies that tea can exert beneficial disease-preventive effects. Various studies have indicated preventive effects of tea against cardiovascular disease, metabolic syndrome, neurodegenerative disease, and cancer (3–6). The cancer-preventive effects of tea have been shown in laboratory models of a number of different cancer types including cancers of the

gastrointestinal tract, lung, prostate, breast, and skin (reviewed in references 6–9). Although published laboratory studies have been nearly all positive with regard to the cancer-preventive effects of tea, epidemiologic studies have been more mixed. These results likely represent the impact of confounding variables such as lifestyle factors, inaccurate assessment of tea consumption, genetic variability, and others. There is a small but increasing amount of clinical data supporting the cancer-preventive effects of tea (10, 11). Although these data are promising, many questions remain with regard to dose-response relations, the relative efficacy of green compared with black compared with oolong teas, the underlying mechanism or mechanisms of action, and the spectrum of cancer-preventive activity.

A number of potential mechanisms of action have been proposed to account for the cancer-preventive effects of tea and tea constituents (**Figure 2**). Among these are binding to and inhibition of specific high-affinity molecular targets, induction of oxidative stress, and enhancement of endogenous antioxidant response/phase II metabolism (12–14). Although some of these

¹ From the Center of Excellence for Plant and Mushroom Foods for Health, the Department of Food Science, Pennsylvania State University, University Park, PA.

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⁴ Address correspondence to JD Lambert, The Department of Food Science, The Pennsylvania State University, 332 Food Science Building, University Park, PA 16802. E-mail: jdl134@psu.edu.

⁵ Abbreviations used: AcEGCG, peracetylated (–)-epigallocatechin-3-gallate; COX2, cyclooxygenase 2; DMBA, 7,12-dimethylbenzanthracene; DSS, dextran sulfate sodium; EGCG, (–)-epigallocatechin-3-gallate; Erk, extracellular responsive kinase; GST, glutathione S-transferase; IGF, insulin-like growth factor; IGF1BP, insulin-like growth factor binding protein; NNK, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; PBP, polymeric black tea polyphenol; PPE, polyphenon E; RXR, retinoid X receptor; 8-OHdG, 8-hydroxy-2’-deoxyguanosine.

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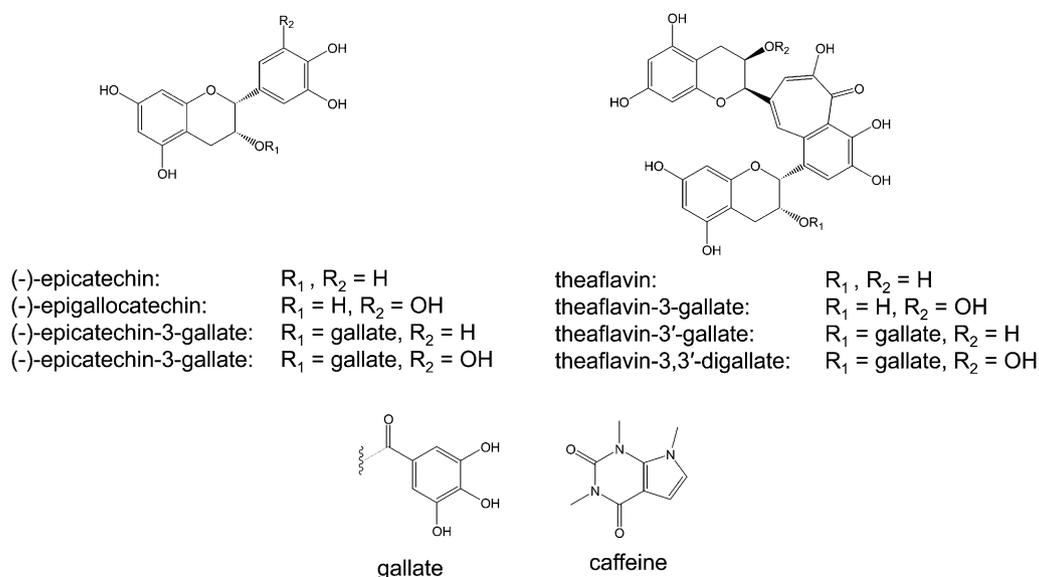


FIGURE 1. Structures of the major putative cancer-preventive compounds in tea.

mechanisms have been shown to occur *in vivo*, many are based on studies in cell lines or using purified enzymes. The results of such studies must be interpreted with caution because the concentrations of compounds used *in vitro* are often not physiologically relevant, the systems do not account for biotransformation, and the tea polyphenols are oxidatively unstable under cell culture conditions.

In the present review, I discuss the currently available laboratory and human intervention studies with regard to the cancer-preventive effects of tea. Emphasis is placed on *in vivo* studies because these inherently take issues of bioavailability and toxicity into account; studies with mechanistic endpoints will be highlighted. This review serves to raise critical questions with regard to the cancer-preventive effects of tea and spur further research in this area.

CANCER-PREVENTIVE EFFECTS OF TEA

Human intervention studies

Prevention of cancer progression

The number of human studies directly examining the effect of tea supplementation on cancer progression is limited. As might be expected, studies that have examined early-stage disease have been promising, whereas those that have dealt with late-stage disease have largely yielded negative results. These data indicate that tea and tea compounds likely lack sufficient potency to serve as first-line chemotherapeutic compounds but do have a role to play in both primary prevention and prevention of cancer recurrence.

Bettuzzi et al (10) reported that supplementation with 600 mg green tea catechins/d reduced prostate cancer prevention in subjects

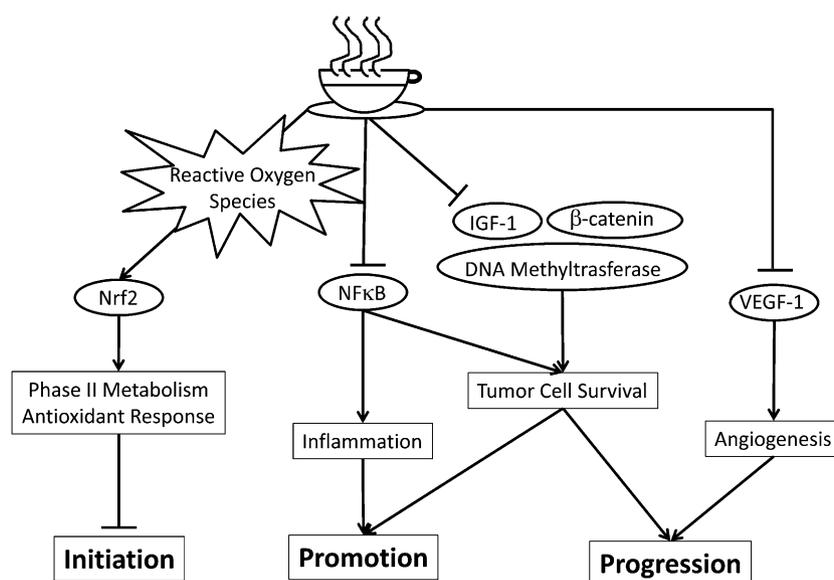


FIGURE 2. Potential mechanisms for the cancer-preventive effects of tea. IGF-1, insulin-like growth factor I; NFκB, nuclear transcription factor κB; Nrf2, nuclear factor-E2-related factor; VEGF-1, vascular endothelial growth factor 1.

with high-grade prostate intraepithelial neoplasia. This placebo, double-blind study with $n = 30$ per arm found that after 1 y, only 9% of men in the green tea-supplemented group had progressed to prostate cancer, whereas 30% of men in the placebo group had progressed. An update by the same group was published 1 y after suspension of the intervention (15). The authors found that there was a significantly higher proportion of cancer-free subjects in the former green tea catechin-supplemented group than in the former placebo group. These results indicate that green tea catechins can induce a robust response in precancerous tissues and that this effect is durable even after cessation of treatment.

A recent phase II study examined the efficacy of green tea against oral premalignant lesions (11). Treatment with 500–1000 mg/m² caffeine-containing green tea extract for 12 wk resulted in a complete or partial response in 14 of 28 subjects (all green tea doses combined) compared with 2 of 11 placebo subjects ($P = 0.09$). Biomarker analysis showed that vascular endothelial growth factor and cyclin D₁ expression were downregulated in clinically responsive green tea extract-treated subjects compared with nonresponders.

Shimizu et al (16) examined the preventive effects of green tea extract on the recurrence of metachronous colorectal adenomas in polypectomy patients. Supplementation of patients up to 2.5 g green tea extract/d for 12 mo reduced adenoma recurrence from 31% in the placebo group to 15% in the green tea-supplemented group.

Studies in more advanced stage cancer have resulted in largely negative findings. For example, a phase I study of green tea extract (0.5–3 g/m²) in subjects with advanced lung cancer ($n = 17$) showed no objective response in cancer progression (17). No grade III or IV toxicities were induced by green tea treatment, and the maximum tolerated dose was established at 3 g/m².

Modulation of carcinogenesis-relevant biomarkers

Although the number of human studies examining hard endpoints (eg, tumor progression, tumor volume) for carcinogenesis is limited, there is a growing body of data related to the effects of tea on carcinogenesis-relevant biomarkers in human subjects. These biomarkers provide insight into the potential mechanisms by which tea and tea constituents might prevent cancer. Many of these studies have focused on the modulation of oxidative stress or carcinogen metabolism by tea components.

A randomized phase II clinical trial examined the impact of decaffeinated green or black tea consumption on urinary markers of oxidative stress in smokers (18). Treatment over 4 mo with 4 cups green tea/d (146 mg polyphenols/cup) reduced urinary concentrations of 8-hydroxy-2'-deoxyguanosine (8-OHdG) by 31% compared with baseline. No reduction was observed in smokers consuming black tea. Stratification of these data on the basis of polymorphisms in glutathione *S*-transferase (GST) T-1 and GSTM-1 showed the importance of this enzyme in the protective effects of EGCG (19). Green tea decreased the concentrations of urinary 8-OHdG in GSTT-1- and GSTM-1-positive subjects, but no effect was observed in GSTM-1- and GSTT-1-negative individuals.

Similar results were observed in a study in a Chinese population at increased risk of liver cancer because of aflatoxin exposure (20). In this placebo-controlled phase IIa study, treatment of subjects ($n = 42$ per arm) with increasing concentrations of green tea

polyphenols (0.5 or 1 g/d) for 3 mo dose-dependently increased urinary excretion of (–)-epigallocatechin and (–)-epicatechin and decreased urinary 8-OHdG concentrations, indicating an amelioration of oxidative stress. A more recent study by the same group found that green tea polyphenol treatment increased the concentrations of *N*-acetylcysteine-conjugated aflatoxin metabolites in a dose-dependent manner (21). Treatment over 3 mo with 1000 mg green tea polyphenols/d increased urinary excretion of these metabolites by 14-fold compared with baseline.

Animal model studies

Numerous studies have investigated the potential cancer-preventive effects of tea using animal models of carcinogenesis. Tea has been shown to inhibit carcinogenesis when administered before or only during initiation, only during the postinitiation period, or during the entire experiment. Increasingly, these studies are mechanistic in nature and incorporate multiple doses of tea or tea compounds. Such improvements in study design have resulted in improved quality of preclinical data. In this section, results of the most widely studied cancer types are highlighted. Emphasis has been placed on studies with mechanistic endpoints.

Lung cancer

A number of studies have indicated that green tea and green tea polyphenols can inhibit 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung carcinogenesis when given either during the initiation stage, throughout the entire course of the experiment, or only during the postinitiation period (22–24). Lu et al (25) reported that administration of 0.5% polyphenon E (PPE; containing 65% EGCG and 0.044% caffeine) to NNK-induced A/J mice reduced progression of lung adenomas to adenocarcinomas; adenocarcinoma incidence and multiplicity were reduced by 52% and 63%, respectively, compared with NNK-induced controls. PPE treatment increased the apoptosis index (2.6-fold increase) and inhibited cell proliferation (56% inhibition) in adenocarcinomas compared with NNK-induced controls. These effects correlated with decreased phosphorylation of c-Jun and extracellular responsive kinase (Erk) 1/2 in tumor cells. Although similar effects on cancer cell apoptosis and cell proliferation were observed after treatment with pure caffeine, caffeine was not able to recapitulate the effects of PPE on adenocarcinoma incidence and multiplicity.

More recently, the cancer-preventive effects of green tea polyphenols given via alternative routes of administration have been explored. The delivery of tea polyphenols to lung via aerosol has been hypothesized as a means of overcoming the relatively poor oral bioavailability of these compounds, reducing the effective dose, and potentially limiting any side effects. Daily aerosol treatment of benzo[a]pyrene-induced A/J mice with 4.19 mg/kg body weight PPE reduced lung tumor multiplicity by 53% compared with control mice after 20 wk (26). Interestingly, both purified EGCG and EGCG-depleted PPE were ineffective.

Although widely regarded as antioxidants, recent studies have suggested that tea polyphenols may exert their cancer inhibitory effects via prooxidative mechanisms (reviewed in references 12 and 27). A study by Li et al (28) recently showed that these prooxidative effects may play a role in the inhibition of lung cancer growth *in vivo* by EGCG. Treatment of H1229 human lung cancer xenograft-bearing mice with EGCG dose-dependently

inhibited tumor growth: at the 0.5% dose amount, the final tumor mass was 57% lower than in water-treated control mice. Decreases in tumor growth correlated with dose-dependent increases in tumor cell apoptosis and oxidative stress (measured as 8-OHdG and histone 2A.X phosphorylation). These oxidative effects were specific to tumor cells, and no increases were observed in the liver or small intestine. Further studies are needed to determine how EGCG increases tumor cell oxidative stress.

Black tea and black tea constituents, although less well studied, have also shown inhibitory effects against chemical-induced lung cancer. Treatment of NNK-induced Fischer 344 rats with 2% black tea as the sole source of drinking fluid resulted in a 60% decrease in lung tumor incidence (29). Interestingly, a concentration of caffeine equivalent to 2% black tea solids (0.068%) resulted in a similar effect on tumor incidence. These results, coupled with the previously mentioned study by Lu et al (25) suggest a role for caffeine in the lung cancer-preventive effects of tea.

Studies in NNK-induced A/J mice have shown that treatment with purified theaflavins (0.1%) during the postinitiation phase dose-dependently reduced lung adenoma incidence (23%) and multiplicity (34%) compared with controls. In the same model, short-term studies showed that treatment with 0.3% theaflavins as the sole source of drinking fluid resulted in a 36% decrease in NNK-induced bronchiolar cell hyperplasia compared with water-treated controls (30).

A black tea polyphenol fraction has recently been shown to have lung cancer-preventive activity. Roy et al (31) showed that oral administration of 0.1–0.2% black tea polyphenols in drinking fluid reduced the incidence of alveolar carcinoma in diethylnitrosamine-induced Swiss albino mice. These cancer-preventive effects were related to black tea polyphenol-mediated decreases in the phosphorylation of Akt and the expression of cyclooxygenase 2 (COX2), as well as inhibition of nuclear transcription factor κ B. Another study showed that orally administered black polyphenols can induce the expression of phase II metabolic enzymes and antioxidant-responsive genes in the lung via an Nrf2 (nuclear factor-E2-related factor)-mediated pathway (32). These gene changes may underlie some of the observed cancer-preventive effects of black tea polyphenols *in vivo*. Given the very poor oral bioavailability of the theaflavins and thearubigins, it is interesting that these compounds apparently affect carcinogenesis at a distal organ such as lung (33). Further studies are needed to determine whether these effects are a result of some indirect mechanism of the theaflavins (eg, modulation of the gut microflora) or of the presence of some collection of microbial metabolites that have better bioavailability and retain biological activity.

Prostate cancer

A number of studies have shown the cancer-preventive effects of tea in animal models of prostate cancer (reviewed in references 8 and 34). Both genetic and xenograft models have been examined. The results of these studies have been largely positive, and a number of potential mechanisms of action have been suggested, including modulation of oxidative stress, inhibition of growth factor signaling, or modification of epigenetic factors.

Green tea polyphenols have shown preventive effects in the transgenic adenocarcinoma of the mouse prostate model. Gupta

et al (35) showed that oral consumption of 0.1% green tea polyphenols for 24 wk significantly increased tumor-free survival from 0% to 50% at 40 wk and reduced tumor growth by 42%. Green tea polyphenol treatment also enhanced tumor cell apoptosis by 10-fold and decreased tumor cell proliferation. Further studies showed that the cancer-preventive effects appear to be due to green tea-mediated reductions in the expression of insulin-like growth factor (IGF) I and increases the expression of the IGF binding protein (IGFBP) 3, resulting in a 83% decrease in the ratio of IGF-I to IGFBP-3 (36). This effect correlated with a significant decrease in PI3K (phosphatidylinositol 3-kinase)-induced Akt and Erk 1/2 phosphorylation.

More recently, it has been reported that oral administration of brewed green tea exerted an antitumor effect in severe combined immunocompromised mice bearing LAPC4 human prostate cancer xenografts (37). Treatment over 2 wk significantly delayed tumor growth: tumors were 80% smaller at day 8 in tea-treated mice compared with controls. Tea treatment reduced the expression of DNA methyltransferase-1 by 50% at both the mRNA and protein level. Green tea treatment also decreased markers of DNA and protein oxidation. On the basis of the results of this study, it appears that oral green tea exerts its anticancer effect through a combination of epigenetic and antioxidant mechanisms. Whether these are, in fact, 2 separate mechanisms or are somehow related remains to be determined.

There are limited animal model data with regard to prostate cancer inhibitory effects of black tea and theaflavins. In a study of CWR22Rv1 human androgen-responsive prostate cancer xenograft-bearing *nu/nu* mice, green tea polyphenols, black tea extract, and purified theaflavins significantly delayed tumor growth (38). Tumor volume in control mice reached 1200 mm³ in 26 d, whereas mice treated with green tea polyphenols, black tea extract, and theaflavins did not reach this volume until 54, 42, and 38 d, respectively. These effects were correlated with increased tumor cell apoptosis and decreased tumor concentrations of vascular endothelial growth factor. All treatments significantly reduce serum prostate-specific antigen concentrations compared with control (66–83% reduction). These results indicate the potential prostate cancer inhibitory effects of black tea and support future studies in this area.

Skin cancer

Studies in both chemical as well as UV-light induced non-melanoma skin carcinogenesis have indicated the potential cancer-preventive activity of both green and black tea. Topical application of EGCG has been shown to inhibit UVB-induced photocarcinogenesis and immunosuppression (39). More recently, the same group reported that orally administered green tea polyphenols (0.2–0.5%) can reduce UVB-induced immunosuppression by >50% compared with water-treated controls (40). Green tea polyphenol-treated mice also had reduced numbers of pyrimidine-dimer positive cells (59%) and enhanced DNA repair. In xeroderma pigmentosum complement group A-deficient mice, which lack nucleotide excision repair capabilities, green tea polyphenols had no effects on UVB-induced immunosuppression or DNA damage.

Studies in the UVB complete carcinogenesis model have indicated that caffeine plays an important role in the skin cancer-preventive effects of tea. Oral administration of green tea or

black tea dose-dependently inhibited tumor incidence, multiplicity, and tumor volume in UVB-treated mice, with green tea being more potent than black tea (41). By contrast, decaffeinated green and black teas lacked skin cancer-preventive activity. Orally administered caffeine exerted significant skin cancer-preventive effects, and these effects correlated with an enhancement of UV-induced skin cell apoptosis and p53- and p21-positive cells (42). Caffeine has been shown to inhibit the ataxia telangiectasia and Rad3-related protein/checkpoint kinase 1 pathway in tumor cells and induce mitotic catastrophe and cancer cell death in this model (43, 44).

Although oral EGCG was ineffective in this model, topical application of the compound did reduce tumor multiplicity by 66% and induced tumor cell apoptosis (45). This disparity may be the result of the relatively poor oral bioavailability of EGCG, a problem overcome by direct topical application.

Oral administration of green or black tea polyphenols (0.1–0.2%) dose-dependently reduced 7,12-dimethylbenzanthracene (DMBA)-induced skin carcinogenesis in Swiss albino mice (46). Green and black tea polyphenols delayed induction of a first tumor by 30–44% and reduced tumor incidence (13–33%) and tumor multiplicity (17–50% reduction). Black tea polyphenols showed superior activity in this model. Cancer-preventive effects correlated with increased tumor cell apoptosis: tumor cell concentrations of Bax, Apaf1, Caspase 3, and Parp increased, whereas tumor concentrations of Bcl-2 decreased.

Intestinal and colon cancers

A number of studies have examined the inhibitory effect of tea on intestinal and colon cancers. In the APC^{min/+} mouse model, EGCG dose-dependently inhibited intestinal tumor multiplicity (47). At oral doses of 0.08% and 0.16% in drinking fluid, EGCG reduced tumor multiplicity by 37% and 47%, respectively. By contrast, 0.044% caffeine had no inhibitory effect. Tumor inhibition was associated with decreased β -catenin signaling and enhanced tumor cell apoptosis.

Later, Volate et al (48) found that 0.6% green tea as the sole source of drinking fluid decreased colon tumor multiplicity by 28% in azoxymethane-treated APC^{min/+} mice. Green tea treatment reduced the number of cyclin D₁-positive and β -catenin-positive small tumors but had no effect on COX2 expression; changes in protein expression correlated with changes in mRNA levels. Concentrations of retinoid X receptor (RXR) α in adenomas were decreased by azoxymethane treatment. These decreases were due to DNA hypermethylation of the RXR α promoter. Green tea treatment enhanced RXR α protein concentrations and appeared to accomplish this via inhibition of RXR α promoter methylation.

The results of studies on green tea and EGCG in the dextran sulfate sodium (DSS)-induced model of colitis have shown mixed results. At lower doses, green tea polyphenol treatment can act as an antiinflammatory agent (49). Higher doses of EGCG, however, can actually enhance toxicity (50). Treatment of ICR mice with 1% green tea polyphenols concomitant to treatment with 5% DSS induced nephrotoxicity as indicated by increased kidney weight and serum creatinine concentrations. Green tea polyphenol treatment also decreased the expression of NADPH:quinone oxidoreductase-1 and heat shock protein 90 in the kidney. The underlying mechanisms for this toxicity are unclear but indicate

that care should be taken in determining the appropriate upper limit of safety to green tea polyphenols in different disease contexts.

Oral administration of polymeric black tea polyphenols (PBPs), a fraction rich in thearubigins, inhibited colon cancer in 1,2-dimethylhydrazine-induced Sprague-Dawley rats. PBPs reduced tumor incidence and multiplicity (51). Mechanistically, the authors reported that PBPs enhanced the expression of NADPH:quinone oxidoreductase-1 and GST in an Nrf2-dependent manner. PBP treatment also decreased β -catenin signaling in tumor cells. These data suggests that PBP is able to blunt carcinogenesis in this model both via an antioxidant mechanism as well as by targeting proliferative signals in the tumor cells directly.

Potential for combination effects

A growing number of studies have reported the potential synergistic cancer inhibitor effects of tea and tea components in combination with pharmaceutical agents. This represents a promising new direction that has the potential to increase preventive efficacy and decrease effective concentrations of each agent. A number of studies have shown synergistic growth inhibition or induction of apoptosis by the combination of tea polyphenols and chemotherapeutic agents in cell culture. Although interesting, these studies remain somewhat preliminary with regard to their relevance to in vivo cancer prevention and treatment (52–54). Given the uncertainties related to the bioavailability of tea polyphenols and the possibility for artifacts of cell culture including autooxidation to affect the results, the present review focuses on those combinations that have been examined in in vivo model systems.

Lu et al (55) reported that oral administration of PPE (0.25%) in combination with atorvastatin (200 ppm) produced greater than additive preventive effects in NNK-induced lung tumor progression. Compared with NNK-treated controls, mice treated with PPE and atorvastatin had a 56% reduction in tumor multiplicity and 54% reduction in tumor burden. Neither PPE (0.25%) nor atorvastatin (200 ppm) as single agents had a significant effect on these variables. Molecular analysis showed that combination treatment significantly decreased the expression of the antiapoptotic protein Mcl-1 and increased the apoptotic index in tumor cells.

A study of MCF7 human breast cancer xenografts in ovariectomized female *nu/nu* mice showed a beneficial interaction between green tea and tamoxifen (56). Mice treated with 0.25% green tea and subcutaneous tamoxifen implants (2 mg/pellet) had a 81% reduction in final tumor compared with controls. The combination effect appeared to be largely additive. Molecular analysis showed that the combination significantly reduced markers of angiogenesis (50% reduction) and significantly increased markers of necrosis and apoptosis. Combination treatment also reduced the number of estrogen receptor-positive cells in treated tumors. Another study in C3H/OuJ mice, which spontaneously develop mammary tumors, found similar beneficial interactions between green tea and tamoxifen (57). Whereas treatment with green tea extract (1%) as the sole source of drinking fluid or implanted tamoxifen pellets (10 mg/mouse) significantly delayed tumor formation and reduced tumor multiplicity (~73% reduction), the combination prevented the development of tumors over the course of the experiment.

Adhami et al (58) showed that the combination of green tea polyphenols and selective COX2 inhibitors more effectively

inhibit the growth of CWR22Rv1 human prostate xenograft growth in *nu/nu* mice. Tumors in mice treated with oral green tea polyphenols (0.1%) and celecoxib (10 mg/kg, intraperitoneally) reached 1300 mm³ after 48 d, whereas mice in the control group reached the same volume in only 27 d. Both agents as single treatments had inhibitory activity, but the effect was not as dramatic. Analysis of the ratio of serum IGF-I to IGFBP-3 was reduced by >6-fold in combination-treated mice compared with control mice.

EGCG was examined in combination with doxorubicin-containing nanoparticles in mice bearing Erlich's ascites tumors (59). Treatment with the combination of EGCG (20 mg/kg, intragastrically) and doxorubicin containing nanoparticles (1.5 mg/kg, intravenously) significantly increased mean survival time and reduced ascites-induced body weight compared with either treatment alone. Other studies have shown that EGCG can improve the activity of doxorubicin and taxanes against metastatic prostate cancer in immune-compromised mice (60, 61). Although both studies reported positive results with regard to metastasis and tumor growth, both used intraperitoneal injection as the route of delivery for EGCG. This limits the translatability of these results in human subjects.

The impact of tea on glioblastoma and other forms of brain cancer has not been widely studied. An interesting recent study by Chen et al (62) examined the impact of EGCG in combination with temozolomide on the survival of mice bearing orthotopically implanted glioblastoma cells. Daily treatment with temozolomide (5 mg/kg, intragastrically) in combination with EGCG (50 mg/kg, intragastrically) increased survival to 78 d compared with 27 d in vehicle-treated controls. By contrast, EGCG had no effect as a single agent and temozolomide increased survival to only 58 d as a single agent. These results are promising, but further studies are needed to better understand the underlying mechanism for these enhanced effects and to more fully understand the potential effects of tea in combination with standard therapy on various forms of brain cancer.

More limited data exist for combinations of tea polyphenols and other dietary components. Bose et al (63) reported the preventive effects of an EGCG/fish-oil combination in APC^{Min/+} mice. Treatment of mice with the combination of 0.16% EGCG and 12% fish oil reduced tumor multiplicity by 53% compared with controls, whereas the single agents had no significant effect. Tumor inhibition correlated with nuclear β -catenin positivity in tumor cells as well as decreased prostaglandin E₂ concentrations in the tumors. These results suggest that the combination can modify tumor cell proliferation and aberrant arachidonic acid metabolism, thus ameliorating tumorigenesis.

A recent study of black tea polyphenols in combination with resveratrol showed enhanced cancer-preventive activity in a DMBA/phorbol ester mouse model of skin cancer (64). Treatment with 0.2% black tea polyphenols in drinking fluid and 50 μ mol resveratrol/L topically increased tumor-free survival from 0% to 72%. In tumor-bearing mice, tumor burden was reduced by 5-fold compared with controls. Molecular analysis showed that the combination decreased phosphorylated Erk, p38, and Jun kinase concentrations in tumor tissue.

NOVEL FORMULATIONS AND NEW DERIVATIVES OF TEA POLYPHENOLS

Alternative formulations and derivatives of the tea polyphenols have been explored as strategies for enhancing the bioavailability

and cancer-preventive efficacy of these compounds. My laboratory and others have reported that acetylation can enhance the oral bioavailability and in vitro anticancer effects of EGCG (65, 66). More recently, peracetylated EGCG (AcEGCG) has been shown to inhibit DSS-induced colitis and colon carcinogenesis in mice (67). Dietary administration of 0.085% AcEGCG or the molar equivalent dose of EGCG (0.05%) resulted in a reduction in lymphoid nodules and an increase in colon length, both markers of antiinflammatory activity, compared with DSS-treated mice (67). Interestingly, AcEGCG was more effective than the equivalent dose of EGCG. Only AcEGCG was effective at reducing aberrant crypt foci multiplicity (40% reduction compared with DSS-treated mice). In longer-term experiments, only AcEGCG reduced tumor multiplicity.

In a second study by the same group, AcEGCG was shown to potentially inhibit DMBA/phorbol ester-induced skin tumorigenesis in mice (68). Topical application of AcEGCG (1 or 5 μ mol/mouse per day) more effectively inhibited tumor incidence and multiplicity than the corresponding dose of EGCG. Inhibition was related to a decrease in the mitotic index of tumor cells and a decrease in PI3K/Akt signaling and the activity of protein kinase D.

Alternative formulation of tea polyphenols, for example as nanoparticles, has been shown to improve the cancer-preventive effects of these compounds. Siddiqui et al (69) reported that encapsulation of EGCG in polylactic acid-polyethylene glycol nanoparticles improved the growth inhibitory potency of EGCG in PC3 human prostate cancer xenograft-bearing immune compromised mice. Encapsulated EGCG (100 μ g EGCG equivalent) reduced tumor growth to the same extent as 1 mg of unencapsulated EGCG (50% reduction in final tumor volume); encapsulated EGCG more effectively reduced serum prostate-specific antigen concentrations than unencapsulated EGCG.

The efficacy of EGCG-gold nanoparticles was evaluated in mice bearing subcutaneous bladder cancer implants (70). The treatment of mice with 2 mg EGCG complexed to gold nanoparticles after tumor implantation reduced final tumor volume by 83%, whereas uncomplexed EGCG had no significant effect. EGCG-gold nanoparticles were also shown to have antitumor effects in PC3 xenograft-bearing mice; these effects were mediated by uptake via the laminin receptor (71). Although the results are interesting, the authors used intratumoral injection as the route of administration. This limits the application to cancer prevention as well as the interpretation with regard to the underlying mechanisms by which tea polyphenols might affect cancer in human subjects.

CONCLUSIONS AND SUGGESTIONS FOR FUTURE STUDIES

There is a considerable, and growing, body of data derived from laboratory animal model and human intervention studies showing the cancer-preventive effects of tea and tea constituents. Both the polyphenolic components as well as caffeine have been implicated as the cancer-preventive substances. A number of potential molecular mechanisms have been proposed, including modulation of oxidative environment, enhanced expression of phase II metabolic pathways, inhibition of growth factor signaling, and others. Moreover, there are a number of studies that have shown the potential enhancement of tea cancer-preventive activity by

combination with pharmaceutical agents or other dietary components. Further work remains including the following:

1. Further studies are needed to refine the proposed mechanisms of action and to determine which mechanisms are relevant in which cancer types. Although it is unlikely that the tea polyphenols have a single, specific molecular target, it is equally unlikely that all of the proposed mechanisms are of equal physiologic importance. Many of the observed molecular effects may be secondary to some earlier primary event. Additional animal model studies at earlier time points are needed to determine these earliest events.
2. Research is needed to develop additional preventive combinations involving tea and pharmaceutical or dietary components. This work should be driven by rational mechanistic hypotheses based on available data. For example, our laboratory has examined the effect of other dietary components on the bioavailability of EGCG. The results of these studies may be useful in guiding future cancer-prevention studies.
3. There is a dearth of information about the biological activity of the metabolites of the tea polyphenols. Although the tea polyphenols are extensively metabolized, there are only a handful of *in vitro* studies that have investigated the cancer-preventive activity of these metabolites. Given the observed cancer-preventive effects of green and black tea despite the low bioavailability of the catechins and the very low bioavailability of the theaflavins, these metabolites likely play an important role in the overall cancer-preventive effects of tea. Further *in vitro* and *in vivo* studies are needed to address this issue.
4. Finally, although the number of human intervention studies on the cancer-preventive effects of tea is growing, available data remain scarce and relatively limited in scope. Further studies using relevant biomarker endpoints and multiple-dose designs in high-risk populations are needed. Such studies are needed over a broad range of cancer types to more carefully assess the spectrum of cancer-preventive activity for tea and to establish the relevant effective dose and dosing schedule.

Although the data regarding the cancer-preventive effects of tea are growing and remain promising, they are still not definitive. Future studies are needed if the scientific community is going to answer the question, "Does tea prevent cancer?"

The author had no conflicts of interest to declare.

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