Chapter 16
An Evidence-based Perspective of *Camellia Sinensis* (Green Tea) for Cancer Patients

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Abstract *Camellia sinensis*, Theaceae (green tea) and its major polyphenolic constituent, (-)-epigallocatechin-3-gallate (EGCG) have been extensively studied for their preventive activity against cancer. Studies in animal models of carcinogenesis have shown that green tea and EGCG can inhibit the development of cancer in various organ systems at the initiation, promotion and progression stages. This inhibition of tumorigenesis is associated with decreased cell proliferation, increased apoptosis, and inhibition of angiogenesis. Various mechanisms of action have been proposed based on studies with human cell lines and cell-free systems. These mechanisms include induction of oxidative stress, inhibition of key enzyme systems, inhibition of growth factor signaling and others. Few of these mechanisms have been clearly demonstrated to play a role in the prevention of cancer by tea *in vivo*. Although a large number of epidemiological studies have been conducted on the relationship between tea consumption and cancer risk, the results remain mixed. Very few human intervention studies have been conducted, yet at least one demonstrated that tea has promise for the prevention of prostate cancer. Further controlled intervention studies are needed to clearly test the cancer preventive effects of green tea in high risk human subjects. Additionally, carefully designed, mechanism-based animal model studies in conjunction with biochemical and immunohistochemical studies of human samples will be critical for unraveling the key underlying mechanisms of action. Although there is promise for green tea as a cancer chemopreventive agent, considerable work is needed to fully realize its potential impact on public health.

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16.1 Introduction

Camellia sinensis, Theaceae (green tea) is a beverage with worldwide popularity second only to water. Currently per capita consumption of tea worldwide exceeds 105 L (Wolf et al. 2008). Although all tea is derived from the leaves of *C. sinensis*, there is significant variation in the processing of the leaves which results in the three major types of commercially-available tea beverage: green tea, oolong tea, and black tea. These differences in processing affect the color, flavor, and phytochemistry (Balentine et al. 1997).

Green tea accounts for approximately 20% of world consumption and is prepared by pan-frying or steaming fresh tea leaves in order to inactivate polyphenol oxidase and other enzymes. Chemically, green tea is characterized by the presence of large amounts of flavan-3-ols or catechins (Fig. 16.1). The four major catechins are (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epicatechin (EC). A typical cup of green tea (2.5 g of leaves in 250 ml water) contains 240–320 mg of catechins and 20–50 mg of caffeine (Balentine et al. 1997). EGCG is the most abundant catechin and may represent 30–50% of the extracted catechins.

By contrast, in the preparation of black tea, leaves are crushed and allowed to undergo a polyphenol oxidase-mediated oxidation known as "fermentation". This process results in the polymerization of the catechins to form higher molecular weight compounds including theaflavins and thearubigins. These higher molecular weight compounds represent 3–6% and >20% of the water extractable material in black tea, respectively, and are responsible for the characteristic orange-brown color of black tea (Yang et al. 2002). Approximately 80% of tea consumed worldwide is consumed as black tea.

Oolong tea, which represents approximately 2% of world consumption, is intermediate to green tea and black tea in terms of processing. The leaves are allowed to undergo a partial oxidation which results in the formation of interesting higher molecular weight compounds, but allows greater preservation of the monomeric catechins (Yang et al. 2002).

Tea and tea polyphenols have been extensively studied for their potential beneficial biological effects. Numerous studies have suggested that tea and tea preparations may be useful for the prevention of chronic disease including: type 2 diabetes, cardiovascular disease, neurodegenerative disease, and cancer (Wolfram 2007; Yang et al. 2007; Grove and Lambert 2010). To a greater or lesser extent, each of these potential indications is supported by data generated by *in vitro* or *in vivo* laboratory studies, epidemiological studies, or human intervention studies. In most cases, unequivocal data supporting efficacy for disease prevention by tea in humans is lacking.

Numerous *in vitro* studies have been conducted and they have been extensively reviewed (Siddiqui et al. 2007; Halder et al. 2008; Tachibana 2009; Yang et al. 2009). In this chapter, I will discuss the evidence for the prevention of cancer by green tea and green tea polyphenol (GTP). I will focus on studies in laboratory animal models, human epidemiological studies, and human intervention studies. The potential mechanisms suggested by studies in animal models and human subjects will be dis-

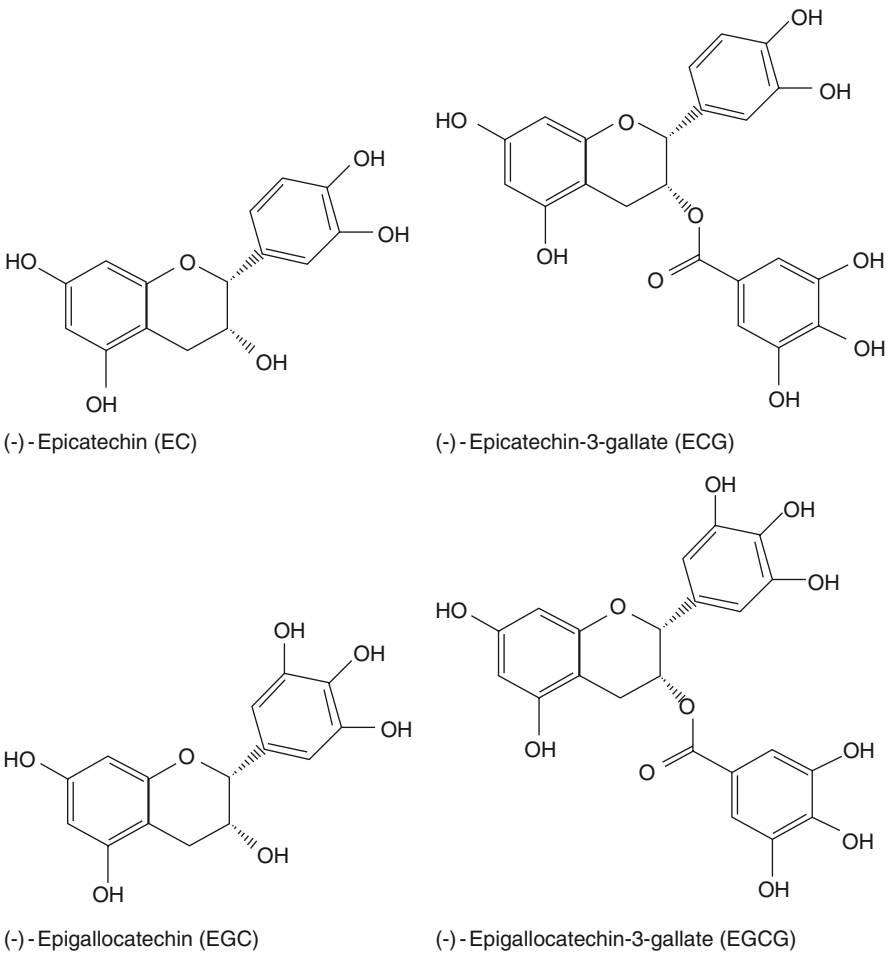

Fig. 16.1 The structure of the major tea catechins

cussed, and supporting *in vitro* data will be presented. I will also discuss the emerging evidence for toxicity resulting from high oral doses of GTP and the implications of this toxicity for the potential usefulness of green tea as a cancer preventive agent in humans. This chapter is meant to inform readers new to the field, to point out areas in need of further study, and to stimulate new efforts to more fully determine the efficacy and mechanism of action of green tea as a cancer preventive agent.

16.2 Evidence of Cancer Prevention from Animal Studies

Green tea and GTP have been shown to inhibit carcinogenesis in a number of animal models of cancer of the oral cavity, gastrointestinal tract, liver, lung, prostate, mammary gland, and skin (reviewed in Yang et al. 2002; Chung et al. 2003; Saleem et al.

2003; Lambert et al. 2005; Ju et al. 2007). In the present chapter, I will summarize some recent studies, with an emphasis on those reporting potential mechanistic biomarkers. Most reports have focused on the polyphenols in tea, although there is emerging evidence indicating the potential role of caffeine as a cancer preventive agent in tea in some models (Huang et al. 1997; Chung 1999; Lu et al. 2006).

16.2.1 Green Tea and GTP

Kaur et al. (2007) have recently reported that 0.05% green tea catechins prevent mammary tumorigenesis in TAg mouse model of spontaneous mammary tumorigenesis. Treatment for 25 weeks increased mean survival time by 4.8% compared to water-treated controls and reduced tumor burden by 25%. Inhibition of tumorigenesis was associated with increased tumor cell apoptosis as well as decreased levels of the oxidative DNA damage compared to water-treated controls.

A number of studies have examined the effect of GTP against colon carcinogenesis. The effect of Polyphenon E (PPE, a defined catechin mixture containing 65% EGCG) and EGCG on the development of aberrant crypt foci (ACF) in carcinogen-treated rats have been examined. Treatment of rats with dietary PPE (0.12–0.24%) for 8 weeks following injection with azoxymethane (AOM) dose-dependently decreased ACF multiplicity by 16.3–36.9% (Xiao et al. 2008). Decreases in ACF multiplicity were associated with decreased nuclear β-catenin, cyclin D_1, and retinoid X receptor α staining.

Obesity and metabolic syndrome are suggested to be risk factors for colon cancer development. A recent study of AOM-treated C57BL/KsJ-*db/db* (*db/db*) mice reported that treatment with 0.1% EGCG for 7 weeks reduced the total number of ACF and the number of β-catenin positive ACF by 33% and 57%, respectively (Shimizu et al. 2008). These reductions were associated with decreased levels of β-catenin, cyclooxygenase (COX)-2, and cyclin D_1 protein in the colonic mucosa. EGCG treatment also decreased colonic levels of total and phosphorylated IGF-1 (insulin-like growth factor-1) receptor. Conversely, EGCG treatment increased plasma levels of IGF-1 binding protein (IGFBP)-3, a negative regulator of IGF-1 signaling. The authors suggest that this modulation of IGF-1 signaling may represent the underlying mechanism for the cancer preventive activity of EGCG in this model.

IGF-1 signaling has also been suggested as a potential target of green tea in a mouse model of prostate cancer. Oral GTP have been shown to inhibit prostate cancer in the transgenic adenocarcinoma of the mouse prostate (TRAMP) mouse model. Treatment with 0.1% GTP for 24 weeks delayed tumor development, reduced prostate weight, and decreased tumor cell proliferation (Gupta et al. 2001). Western blot and immunohistochemical analysis showed that GTP treatment decreased the IGF-1 to IGFBP-3 ratio in tumor tissue by 70–83%. PI3 K (phosphotidylinositol-3-kinase) and phosphorylation of ERK (extracellular responsive kinase) 1/2 and AKT were also reduced (Adhami et al. 2004). IGF-1 signaling has been shown to play an important role in metastasis and has been shown to increase MMP (matrix

metalloproteinase) expression. Adhami et al. (2004) have shown that GTP treatment reduces the expression of MMP-2 and MMP-9 by 68% and 60%, respectively.

GTP has not been shown to have universally beneficial effects in animal models of carcinogenesis. A recent study by Kim et al. (2007) suggests that, under certain conditions, these compounds may have a deleterious effect. The authors report that in the dextran sulfate sodium (DSS) mouse model of acute colitis, treatment with 0.5% and 1% GTP enhanced the inflammatory response. Mice treated with these doses of GTP had significant body weight loss, enhanced colon shortening and increased levels of interleukin (IL)-1β compared to mice treated with 2% DSS only. By contrast, treatment with 0.01% GTP had no negative effect on body weight and decreased IL-1β levels compared to DSS-treated mice. These results may be specific to this model, or they may indicate that under conditions of high oxidative stress (e.g. colitis) higher doses of GTP can exacerbate inflammation and oxidative stress. This would be support previous *in vitro* studies demonstrating the pro-oxidant effect of EGCG under cell culture conditions (Hou et al. 2005). Further studies are needed to more thoroughly assess the potential utility of GTP for the prevention of colitis and colitis-associated carcinogenesis.

16.2.2 Caffeine

Several studies have shown the potential role for caffeine in the cancer preventive activity of tea in several animal models. A study in 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced A/J mice showed that caffeine may play a key role in the cancer preventive effects of green tea (Lu et al. 2006). Treatment of adenoma-bearing A/J mice with caffeine (0.044%) or PPE (0.5%) as the sole source of drinking fluid for 12 weeks reduced progression of adenoma to adenocarcinoma. Incidence of adenocarcinoma was reduced by 48% and 52% in caffeine and PPE-treated mice, respectively. Adenocarcinoma multiplicity was also reduced by 49% and 63% in caffeine and PPE-treated mice, respectively. Immunohistochemistry revealed that inhibition of progression was associated with decreased phosphorylation of c-jun and ERK 1/2, and increased apoptotic index in treated tumor cells.

Topical application or oral administration of caffeine has been shown to inhibit skin tumor formation and induced tumor cell apoptosis in ultraviolet light B-treated SKH-1 mice (Huang et al. 1997; Lou et al. 1999). Irradiation of these mice for 20 weeks increases risk of skin tumor formation and results in the formation of cellular patches in the epidermis that are immunoreactive to antibodies that recognize mutated *p53* (Lu et al. 2005). These patches represent a possible precancerous lesion. Discontinuation of UVB-treatment results in a disappearance of these patches over time, and treatment with topical caffeine has been shown to enhance this disappearance (Kramata et al. 2005; Lu et al. 2005).

A recent study by Castro et al. (2008) has reported that green tea and caffeine, but not decaffeinated green tea or EGCG, reduces dibenzo[*a,l*]pyrene (DBP)-induced transplancental carcinogenesis in mice. Treatment of pregnant B6129SF1 mice with

DBP induces aggressive T-cell lymphoma in the off-spring that results in premature death post-partum. Pre-treatment with 0.5% green tea or the equivalent amount of caffeine or EGCG for 17 days prior to injection with DBP significantly increased the survival of the pups post-partum. Caffeine increased the surviving fraction from 7.7% to 23% compared to water-treated controls. The authors found that caffeine induced cytochrome P450 (CYP)1B1 activity in the liver of the mother, and hypothesized that this may reduce the bioavailability DBP and therefore reduce lymphoma formation in the offspring.

16.2.3 Effects on In Vivo Antioxidants and Carcinogen Metabolism

Studies have suggested that GTP can inhibit the expression and activity of carcinogen activating enzymes such as CYP and increase the expression of detoxification enzymes. In some cases, these studies may suggest generalized mechanisms for the prevention of cancer. In others, the effects may be specific for chemical carcinogen-induced cancers.

Krishnan et al. (2005) have shown that pretreatment of Swiss mice with 1% tea polyphenols blunted benzo[a]pyrene (B[a]P)-induced increase in expression of CYP1A1 and 1A2. This is likely due to interference at the aromatic hydrocarbon receptor level. Western blot analysis showed that B[a]P-induced expression of these two isoforms were decreased by 55–58% and 79–86% by tea polyphenols in the liver and lung, respectively. Conversely, long-term treatment with green tea resulted in increased expression of hepatic CYP1A1 and 1A2 in rats in the absence of carcinogen treatment (Sohn et al. 1994; Xu et al. 1996). It has been suggested that these effects on CYP1A1 and 1A2 activity is likely due to the caffeine (Chen et al. 1996).

Treatment of piglets with 0.2% green tea extract (45% EGCG) for 3 weeks increased glutathione conjugation of aflatoxin (AF)B_1 by small intestinal microsomes in *ex vivo* studies (Tulayakul et al. 2007). Maliakal et al. (2001) have reported that treatment of female Wistar rats with 2% green tea solution for 4 weeks was shown to increased glutathione-*S*-transferase (GST) activity in the liver. Other studies, however, found no effect (Liu et al. 2003). More recently, oral gavage treatment with EGCG (200 mg/kg) has been shown to upregulate gene expression of γ-glutamyltransferase, glutamate cysteine ligase, and hemeoxygenase 1 in C57bl/6 J mice in a nuclear factor (erythroid-derived 2)-like (Nrf2)-dependent fashion (Shen et al. 2005).

Although green tea and GTP have been historically regarded as antioxidant, and they are powerful chemical antioxidants which can chelate transition metals and directly quench free radicals, it is possible that they function by a more indirect mechanism (Lambert and Elias 2010). In the absence of pre-existing oxidative stress, the tea polyphenols may generate a low level of reactive oxygen species that stimulate upregulation of the endogenous antioxidant systems by mechanisms such as the antioxidant response element/Nrf2 signaling pathway. Indeed, Yuan et al.

(2007a) have recently reported that treatment of colon cancer xenograft-bearing nude mice with dietary EGCG caused dose-dependent upregulation of Nrf2 expression in orthotopically-implanted colon tumors. Shen et al. (2005) have reported similar results in the small intestine and liver of non-tumor-bearing C57bl/6 J mice.

Recent studies have lent support to the hypothesis that EGCG exerts some of its anticancer effects *via* pro-oxidative mechanisms (Azam et al. 2004; Sang et al. 2005; Maeta et al. 2007). H_2O_2 has previously been shown to play a role in the growth inhibitory and pro-apoptotic effects of EGCG and EGC against human lung cancer cells (Yang et al. 1998, 2000). In these studies, EGCG and EGC dose-dependently generated H_2O_2 and induced apoptosis in both transformed bronchial epithelial cells and lung cancer cells. Inclusion of exogenous catalase ablated the pro-apoptotic effects of EGCG. A similar role for H_2O_2 was observed in other cancer cell lines (Weisburg et al. 2004; Chan et al. 2006).

EGCG, given either orally or by intraperitoneal injection, has recently been reported to induce oxidative stress selectively in human lung cancer xenografts in nude mice (Li et al. 2010). Tumors derived from EGCG-treated mice had higher levels of phosphorylated histone 2A.X, 8-hydroxy-2-deoxyguanosine (8-OHdG) and metallothionein I/II. These markers correlated with tumor growth inhibition, and represent both direct oxidative stress as well as the inducible cellular response to oxidative stress.

The end result of decreased carcinogen activation and increased detoxification induced by tea may be the prevention of DNA damage. Tea and tea components have been shown to inhibit carcinogen-induced DNA damage *in vitro*. For example, co-treatment of human leukocytes with EGCG (2 μM) and bleomycin (20 μg/ml) resulted in a 50% decrease in bleomycin-induced DNA damage compared to treatment with bleomycin alone (Glei and Pool-Zobel 2006). It has also been reported that green tea extract can dose-dependently protect Chang liver cells from B[a]P-induced DNA damage (Yen et al. 2004). Similar protective effects have been observed *in vivo*.

Pre-treatment of C57bl/6 Big Blue *lacI* transgenic mice with 2% green tea prior to a single dose of B[a]P was shown to reduce characteristic GC to TA transversions in the liver by 54% compared to water-treated controls (Jiang et al. 2001). In contrast, green tea administration did not inhibit DNA adduct formation in the lungs of NNK-treated A/J mice even though tea did reduce tumorigenesis (Shi et al. 1994). Lin et al. (2003) have reported that pre-treatment of rats with 3% green tea extract as the sole source of drinking fluid for 10 days reduced PhIP-DNA adduct formation. PhIP-DNA adducts were reduced by 50–63% in the colon, heart, lung, and liver, respectively by green tea treatment.

16.2.4 Green Tea in Combination with Other Compounds

The idea of using combinations of different agents, which work *via* different mechanisms, for enhanced chemopreventive effect is growing as an area of research inter-

est. A relatively small number of studies have been conducted with GTP, but these have included combination with other dietary components as well as drugs.

Green tea in combination with the turmeric-derived polyphenol, curcumin, has yielded promising results for the prevention of cancer. Li et al. (2002) have reported that the combination of oral green tea and topically-applied curcumin reduced tumorigenesis in the 7,12-dimethylbenz[a]anthracene-induced hamster model of oral cancer. Hamsters treated with the combination had a reduction in visible tumors and tumor volume of 52.4% and 69.8%, respectively, compared to water-treated controls. The combination enhanced apoptotic index and reduced angiogenesis.

More recently, the same combination was shown to inhibit carcinogenesis in the 1,2-dimethylhydrazine (DMH)-induced rat model of colon carcinogenesis (Xu et al. 2010). Dietary treatment of rats with 0.1% tea catechins (80% EGCG, 15% EGC, and 5% ECG, EC) and 0.1% curcumin for 32 weeks reduced tumor multiplicity and tumor volume by 64.5% and 36.6%, respectively, compared to rats fed a control diet. By contrast, treatment with 0.2% catechins or 0.2% curcumin as single agents had no significant effect on either parameter. The effects appear to be the result of a reduction in tumor cell proliferation and enhanced apoptosis in the tumors of combination-treated rats. Although statistical analysis was not conducted, the results appear to be additive rather than synergistic.

Mechanistically, it is unclear how the combination of green tea and curcumin results in enhanced chemopreventive activities. If the effects are truly synergistic, the enhancement may result from the combination of the direct chemopreventive effects of the single agent, and, an enhancement in the bioavailability of the tea catechins.

Previous studies have shown that the tea catechins are substrates for multidrug resistance-associated proteins (MRP)-1 and -2 (Hong et al. 2003; Vaidyanathan and Walle 2003). MRP-2 is expressed on the apical membrane of the enterocytes and pumps compounds from the interior of the epithelium back into the intestinal lumen. Curcumin has been shown to inhibit this efflux transporter (Wortelboer et al. 2005; Chearwae et al. 2006). It is conceivable, although purely speculative at this point, that curcumin could reduce the efflux of catechins from the enterocytes of DMH-treated rats, enhance the bioavailability of these compounds, and thereby enhance the bioactivity of the combination. Such a hypothesis remains to be tested.

Green tea catechins, in combination with the cholesterol-lowering drug atorvastatin, have been shown to have synergistic inhibitory effects against lung cancer cells in culture, and to have enhanced lung cancer preventive effects *in vivo* (Lu et al. 2008). Treatment of NNK-induced A/J mice with 0.25% PPE and 200 ppm atorvastatin for 20 weeks significantly reduced both lung tumor multiplicity and lung tumor burden by 55.8% compared to treatment with either agent alone. Inhibition of tumorigenesis was associated with decreased expression of the anti-apoptotic protein myeloid leukemia cell differentiation protein (Mcl)-1 and an increase in the apoptotic index in the tumor cells. *In vitro* studies by the same group showed that co-treatment of human lung cancer cells with PPE and atorvastatin synergistically inhibited cell growth and induced apoptosis. These effects were again accompanied by decreased expression of Mcl-1 and increased apoptosis. Combination treatment also reduced the expression of cyclin D_1 and cyclin-dependent kinase-4 and -6.

Previous *in vitro* studies have shown that EGCG is able to bind directly to the BH-3 domain of members of the Bcl-2 family of proteins, of which Mcl-1 is a member (Leone et al. 2003). Using a combination of binding studies, NMR, and molecular modeling studies, Leone et al. (2003) found that EGCG can potently bind to and inhibit the activity of Bcl-X_L with an inhibitory constant value of 490 nM. Based on molecular modeling studies, the gallate ester was found to essential for inhibitory activity. It is possible that the effects observed in the NNK-treated A/J mouse and the human lung cancer cells *in vitro* are downstream effects of this direct binding, but further studies using site-directed mutagenesis and *in vivo* binding assays are needed to more fully understand the role of this potential mechanism.

The combination of GTP and the selective cyclooxygenase (COX)-2 inhibitor, celecoxib, have shown enhanced anticancer effects against human androgen-sensitive prostate cancer xenografts in nude mice (Adhami et al. 2007). Time to euthanizable tumor volume (mean = 1,300 mm^3) was increased from 28 days in control mice to 48 days in mice treated with the combination of GTP (0.1% in the drinking fluid) and celecoxib (5 mg/kg, ip, once daily). Mice treated with either celecoxib or GTP had intermediate rates of tumor growth. Biochemical analysis showed that combination treatment had significantly reduced plasma IGF-1 levels and significantly increased plasma IGFBP-3 levels compared to the control mice. Analysis also showed an increase in the ratio of BAX:BCL-2 and PARP cleavage in the tumors of combination-treated mice indicating an increase in apoptosis in the tumors. The results of this study are interesting, although a clear mechanistic hypothesis to explain the results was not presented.

Many other potential combinations of green tea and other chemopreventive agents remain to be explored. Studies by our laboratory and others have suggested that enhancement of tea polyphenol bioavailability, either by inhibition of Phase II metabolism, inhibition of protein-mediated efflux, or modulation of gastrointestinal motility may represent a means to enhance cancer preventive activity (Hong et al. 2003; Vaidyanathan and Walle 2003; Lambert et al. 2004). Additionally, EGCG has been reported to inhibit a number of key cellular pathways *in vitro*. Among these potential targets is the proteasome (Dou 2009). Proteasome inhibitors have been suggested for use in combination with other chemotherapeutic drugs (e.g. gemcitabine) for enhanced anticancer effects (Bold et al. 2001). Such results suggest several novel GTP-based combinations that could be explored.

16.3 Evidence of Cancer Prevention from Human Studies

16.3.1 Epidemiological Studies

A large number of epidemiological studies have been conducted on the potential cancer preventive activities of tea (Blot et al. 1996; Kohlmeier et al. 1997; Arab and Il'yasova 2003; Borrelli et al. 2004; Hoshiyama et al. 2005; Shukla 2007; Tsu-

gane and Sasazuki 2007). Although some studies have shown an inverse correlation between tea consumption and cancer risk, others have found no association. In general, case-control studies have been more positive than prospective cohort studies. The inconsistencies in these studies may be due to differences in the type of tea consumed; smoking status, alcohol consumption, and other lifestyle factors; accuracy in assessment of tea consumption; and genetic variability in study populations. In the present review, we will discuss the association between green tea and the three most common cancers in the United States (lung, breast, and prostate) as well as gastrointestinal cancers.

16.3.1.1 Lung Cancer

The literature on epidemiological studies on tea and lung cancer prevention was recently reviewed (Arts 2008). Twenty studies were reviewed and included both prospective cohort ($n=6$) and case-control studies ($n=14$), and considered green tea ($n=10$), black tea ($n=8$), and other/any tea type ($n=2$). Overall, 4 of the 20 studies found a significant inverse correlation, whereas the majority of the remaining studies found no effect of a non-significant reduced risk. Among never-smokers, (reported in 7 studies) a protective effect was observed in 4 studies (two green tea and two black tea).

A recent population-based cohort study (Ohsaki National Insurance Cohort) examined the relationship between green tea and lung cancer risk in a cohort of 41,440 Japanese men and women (Li et al. 2008). Even after adjusting for smoking status, the authors could find no significant association between tea consumption and lung cancer risk.

Several recent studies have demonstrated an association between lung cancer risk and tea consumption in selected populations. For example, Bonner et al. (2005) have reported that green tea was protective in individuals with the 8-oxoguanine glycosylase (OGG1) Cys (326) allele. Protective effects have also been observed for green in nonsmoking women (Zhong et al. 2001; Kubik et al. 2004).

16.3.1.2 Breast Cancer

A meta-analysis of epidemiological studies (three cohort and one case-control study) on the relationship between green or black tea intake and breast cancer risk has reported a combined reduction odds ratio (OR)=0.78 (95% confidence interval (CI): 0.61–0.98) (Sun et al. 2006a). The protective effect of tea was observed most-strongly in the case-control study, whereas much weaker (or no) protective effects were observed in the cohort studies. A more recent meta-analysis of seven epidemiological studies focused on green tea consumption and breast cancer risk found similar results with regard to breast cancer incidence (Ogunleye et al. 2010). A somewhat reduced risk (pooled risk ratio (RR)=0.81, 95% CI: 0.75–0.88) was observed in case-control studies, whereas no association was observed in cohort

studies. Interestingly, there was a significant reduction in risk of breast cancer recurrence (RR = 0.73, 95% CI: 0.56–0.96), although this conclusion is based on only two studies and is somewhat premature.

In a hospital-based case-control study (n = 1,009 cases and 1,009 controls) in southeast China, a dose-dependent reduction in risk of breast cancer was associated with increased intake of green tea (Zhang et al. 2007). Multivariant adjusted OR of developing breast cancer were 0.87 (95% CI = 0.73–1.04), 0.68 (95% CI = 0.54–0.86), 0.59 (95% CI = 0.45–0.77), and 0.61 (95% CI = 0.48–0.78) for intake of <250 g, 250–500 g, 500–750 g, and >750 g of green tea leaves per year.

A case-control study of Asian-American women in Los Angeles county suggests that genetic polymorphism in catechol-O-methyltransferase (COMT) may represent a modifying factor in the breast cancer preventive effects of tea (Wu et al. 2003). In this study of 1,152 women (589 cases and 563 age-matched controls), the authors found that whereas green tea had no protective effect (OR = 0.86, 95% CI = 0.46–1.62) in women with two high activity alleles of COMT, a protective effect was observed in women with one or more low activity allele of COMT (OR = 0.42, 95% CI = 0.22–0.80). Based on the role of COMT in the metabolism (and inactivation) of the tea catechins (Zhu et al. 2000; Lu et al. 2003; Chen et al. 2005; Bai et al. 2007), the authors hypothesized that the protective effect was due to slower metabolism and increased exposure to biologically active tea compounds in women with one or more low activity allele of COMT. The role of this polymorphism in modulating the protective effects of tea against other cancer should be investigated further.

For the most part, the results of prospective studies of tea and breast cancer have been less positive. A report on two cohorts of women in rural northern Japan (total n = 35,004) showed no reduction in relative risk of breast cancer associated consumption of ≥5 cups of green tea per day compared to consumption of <1 cup per day (RR = 0.84, 95% CI = 0.57–1.24) (Suzuki et al. 2004). Similar results were also reported as part of the Nurses' Health Study which involved 85,987 subjects and 22 years of follow-up (Ganmaa et al. 2008).

By contrast a prospective study of 50,633 first-time outpatient visitors as part of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center found a significant inverse relationship between breast cancer recurrence and intake of three or more cups of green tea regardless of initial tumor grade (hazard ratio (HR) = 0.69, 95% CI = 0.47–1.00) (Inoue et al. 2001). This study would suggest that selection of high risk populations (i.e. cancer survivors) for study might yield a more clearly beneficial effect of tea.

16.3.1.3 Prostate Cancer

Cohort-based epidemiological studies on tea and prostate cancer have yielded largely negative results (Lee et al. 2009). For example, a prospective cohort study of 19,561 men in Japan found no significant association between consumption five or more cups of tea per day and prostate cancer risk (HR = 0.85, CI: 0.5–1.43) (Kikuchi et al. 2006). Although a small number of case-control studies have yielded posi-

tive results, overall, these studies have also been largely negative (Lee et al. 2009). Whereas two hospital-based case control studies in Japan (140 cases and 140 controls) and China (130 cases and 274 controls) found a significant inverse correlation between tea consumption and prostate cancer, three population-based case-control studies in Canada and the United States reported no association (Ellison 2000; Sharpe and Siemiatycki 2002; Jian et al. 2004; Sonoda et al. 2004). These differences may be the result of higher prevalence of green tea intake in China and Japan compared to a higher intake of black tea in the United States and Canada.

A study which may shed light on the design of future epidemiological studies of tea and prostate cancer is a prospective cohort study conducted with 49,920 Japanese men (The Japanese Public Health Center study). This study found no association between green tea consumption and incidence of localized prostate cancer, but did find a significant dose-dependent inverse correlation between incidence of advanced prostate cancer and consumption of five or more cups of green tea per day (RR = 0.52, CI: 0.28–0.96) (Kurahashi et al. 2008). The authors also reported a significant trend for increased tea consumption being inversely correlated with invasive prostate cancer ($P = 0.01$). These data suggest that although tea may not be useful for the prevention of primary prostate cancer in men, it may prevent the progression of localized prostate cancer to invasive prostate cancer. This hypothesis has been borne out by a recent controlled intervention study by Bettuzzi et al. discussed below.

16.3.1.4 Esophageal, Stomach, and Colon Cancer

Historically, tea consumption has been considered a risk factor for esophageal cancer. Nevertheless, of the publications reporting a positive association between tea consumption and esophageal cancer, nearly all have been attributed to the hot temperature of tea (Yang and Wang 1993).

In a population-based case-control study of 133 stomach cancer cases, 166 chronic gastritis cases, and 433 healthy controls in Yangzhong, China, an inverse association was observed between green tea drinking and risk of chronic gastritis and stomach cancer. ORs of green tea consumption were 0.52 (95% CI: 0.29–0.94) and 0.49 (95% CI: 0.31–0.77) for stomach cancer and chronic gastritis, respectively. The results provide support for earlier studies showing a protective effect of green tea against stomach cancer. This study represents the first report of the protective effect of green tea against chronic gastritis. Since this populations suffering from this condition are at increased risk of stomach cancer, this finding may be of importance in designing intervention strategies for stomach cancer and its pre-malignant lesions in high-risk populations (Setiawan et al. 2001).

A population-based case-control study was conducted in Taixing City in 2000 in which 206 patients with primary stomach cancer were recruited (Mu et al. 2005). In the same study, over 200 cases with esophageal cancer and 200 cases with liver cancer were also recruited. Green tea drinking was associated with decreased risk of stomach cancer, with an adjusted OR of 0.59 (95% CI: 0.34–1.01). Tea concentration was categorized into three levels: low (tea leaves were less than 25% of the

volume of the cup), moderate (tea leaves were between 25–50% of the volume of the cup, and high volume of tea leaves was more than 50% of cup volume). Based on these categories, a strong dose-response relationship was observed between increased green tea concentration and decreased risk of stomach cancer (*P* value for the trend was 0.01).

A case-control study in Montevideo, Uraguay (240 cases, 960 controls) of incidence of gastric cancer and its relationship to diet found a significant decrease in OR of gastric cancer associated with tea intake (De Stefani et al. 2004). A dose-dependent decrease was observed in gastric cancer risk with OR = 0.43 (95% CI: 0.27–0.69) for the middle tertile and 0.13 (95% CI: 0.05–0.32) for the highest tertile of consumption. The protective effect of tea appeared to be more pronounced in men (OR = 0.23, 95% CI: 0.13–0.41) than in women (OR = 0.47, 95% CI: 0.25–0.88).

A meta-analysis in 2006 of 25 studies on the association between tea consumption and colon cancer risk concluded that there was insufficient evidence to suggest a protective effect against cancer (Sun et al. 2006b). This has also generally been the conclusion of prospective cohort studies and some of the case-control studies. Several recent case-control studies, however, suggest that a more careful determination of tea consumption may allow detection of a protective association.

The associations between validated biomarkers of specific tea exposure and the risk of colorectal cancer among a cohort of 18,244 men in Shanghai, China, with 16 years of follow-up was prospectively examined (Yuan et al. 2007b). EGC, 4'-*O*-methyl-epigallocatechin (4'-*O*-MeEGC), EC, and their ring-fission metabolites were measured in baseline urine samples from 162 incident colorectal cancer cases and 806 matched controls. Compared with undetectable EGC, odds ratios for colon cancer in the lowest, intermediate and highest tertile of detectable EGC were 0.64 (95% CI: 0.33–1.24), 0.60 (95% CI: 0.30–1.20), and 0.40 (95% CI: 0.19–0.83), respectively. A similar inverse relation between 4'-*O*-MeEGC and colon cancer also was observed. The strongest protective effect was seen for regular tea drinkers who showed high levels of urinary EGC and 4'-MeEGC. No association between urinary levels of EC or its metabolite and colon cancer risk was observed.

16.3.2 Human Intervention Studies

Several human studies have been conducted examining the effects of dietary catechins on cancer. Although most have dealt with surrogate biomarkers of cancer such as effects on oxidative stress markers and carcinogen metabolism, at least two studies on cancer progression have been conducted.

For example, Hakim et al. (2003) have reported that supplementation of heavy smokers (>10 cigarettes per day) with four cups of decaffeinated green tea (73.5 mg catechins per cup) per day for 4 months reduced urinary 8-OHdG levels by 31% compared to control. In a second study, that examined the effect of genotype, this antioxidant effect was found to be dependent on GST μ1 and θ1 status: a protective effect was only in GST μ1 and θ1 positive individuals (Hakim et al. 2004). This

GST dependence suggests that the antioxidant effects *in vivo* may work indirectly *via* endogenous antioxidant systems.

Similarly, other studies have suggested a role for modulation of endogenous antioxidant systems and Phase II metabolism in the protective effects of green tea. A study in China has reported that 3 month treatment with 500 or 1,000 mg/day GTP increased urinary excretion of the mercapturic acid conjugated of AFB_1 by 10-fold and 8.4-fold, respectively compared to baseline (Tang et al. 2008). Schwartz et al. (2005) have also reported that heavy smokers treated with green tea (400–500 mg green tea powder per cup) 5 times per day for 4 weeks had 50% lower levels of B[a]P-DNA adducts and 8-OHdG compared to control subjects. In another study of healthy volunteers reported that treatment for 4 weeks with 800 mg/day PPE increased GST-π activity in blood lymphocytes (Chow et al. 2007). These results may provide a mechanistic explanation for the enhanced formation of the mercapturic acid metabolite of AFB_1.

In contrast to studies of Phase II metabolism, studies in humans have yielded less impressive results on the modulation of CYP expression and activity by tea. Treatment of human volunteers with 800 mg PPE for 4 weeks did not significantly alter the activity of CYP1A2, CYP2D6, or CYP2C9 (Chow et al. 2006). Another study has reported that treatment of healthy volunteers with 844 mg decaffeinated green tea extract (59% EGCG) for 14 days did not significantly affect CYP3A4 or CYP2D6 activity (Donovan et al. 2004). These results raise questions about the relevance of the observed CYP-modulating effect in animal studies to human disease (Sohn et al. 1994; Xu et al. 1996; Krishnan et al. 2005).

Relatively few studies have examined cancer incidence or progression directly. A double-blind study in Italy, followed 200 individuals with high-grade prostate intraepithelial neoplasia receiving either 600 mg of green tea catechins daily or placebo ($n=100$ per arm) for 12 months. Only 3% of the patients in the catechin treatment group developed prostate cancer, whereas the rate of cancer development on the placebo group was 30% (Bettuzzi et al. 2006). No adverse effect was associated with the treatment.

The efficacy of green tea extract was examined in a recent placebo-controlled Phase II trial against oral precancerous lesions (Tsao et al. 2009). Patients were evaluated and randomized into four groups ($n=9$ per arm): placebo, 500, 750, or 1,000 mg green tea extract. Patients were treated for 12 weeks and response was determined. Although there was no statistically significant effect of green tea extract on oral precancerous lesions, there was a trend for increased positive response to treatment (50% of patients had a partial or complete response) and decreased disease progression (28% of patients had disease progression from baseline) compared to placebo (18.2% response, 45% progression from baseline).

An earlier Phase I study of green tea extract in patients with advanced lung cancer found that a dose of up to 3 g/m^2/day for 16 weeks was well-tolerated by produced no objective response in tumor size (Laurie et al. 2005). Although the results of this study were negative, the study size was small ($n=17$) and the disease stage was likely inappropriate since most dietary components lack necessary efficacy to affect late-stage cancer of any type.

16.4 Protection Against Chemotherapy Side-effects

Based on the putative antioxidant effects and the ability of green tea to stimulate the expression of endogenous antioxidant systems, it has been hypothesized that green tea may alleviate some side-effects associated with cytotoxic cancer chemotherapy. Indeed several animal model studies with common chemotherapeutic agents have borne this out. Treatment of Wistar rats with 3% green tea as the sole source of drinking fluid beginning 5 days before cisplatin injection and continuing for the duration of the study reduced nephrotoxicity compared to water-treated controls (Khan et al. 2009). Blood urea nitrogen levels were reduced by 42%, and levels of catalase and superoxide dismutase were increased by 37% and 50%, respectively compared to water-treated control.

Another study found that green tea (1% as drinking fluid) prevented irinotecan-induced small intestinal toxicity in mice (Wessner et al. 2007). Mice treated with irinotecan only had decreased ratio of reduced to oxidized glutathione. Green treatment prevented this reduction. Green tea treatment did not however reduce irinotecan-induced lipid peroxidation or inflammation in the small intestinal mucosa. Further studies are necessary to clearly delineate the protective effect of green tea against irinotecan-mediated toxicity.

More recently, Sato et al. (2010) have reported that orally administered green tea reduced doxorubicin-mediated spermatogenic disorders. Treatment of male mice with low dose doxorubicin reduced sperm concentration, sperm motility, and decreased Sertoli cell index compared to untreated controls. Co-administration of 200 or 500 mg/kg GTE *via* the diet ameliorated spermatotoxicity, increased sperm motility, and prevented decreased in the Sertoli cell index. These effects correlated with an increase in telomerase activity in the testes compared to doxorubicin-treated controls.

There is significant work that remains to be done in the area of green tea as palliative therapy for cancer patients. There have been no *in vivo* studies on chemotherapy-induced alopecia or immunosuppression. Further, only a small number of clinically-used classes of chemotherapy agents have been examined.

16.5 Potential Toxicity of High-dose Oral GTP

Green tea enjoys a long history of use as a beverage and is generally regarded as safe. Moreover, numerous human intervention and bioavailability studies using low to moderate doses of green tea preparations or EGCG have reported no serious adverse effects (Lee et al. 2002; Bettuzzi et al. 2006; Chow et al. 2006). One effect of the increasing number of reports describing the potential anti-obesity, and other beneficial effects of tea and tea polyphenols has been a proliferation of green tea-based dietary supplements. Sales of green tea-based dietary supplements in the US totaled (USD) 5.6 million in 2005, an increase of 94% from 2004 (Blumenthal et al.

2006). Green tea supplements typically contain 200–400 mg EGCG and recommending dosing of 1–2 capsules up to three times daily. This results in a total recommended dose that may be up to 2,400 mg/day. Although there have been no reported adverse effects associated with green tea beverage consumption, green tea based dietary supplements represent a different dosage form, and have the potential deliver a much higher dose of catechins than green tea beverages. Indeed, studies from our laboratory have shown that oral bolus dosing results in greatly increased peak plasma concentrations of EGCG compared to dietary administration of the same total daily dose (Lambert et al. 2006). Treatment of mice with a single oral bolus dose of 500 mg/kg EGCG result in peak plasma concentrations of 898 ng/ml, whereas the same total daily dose given *via* the diet result in plasma concentrations of 231 ng/ml.

Since 1999, there have been 34 case studies linking consumption of green tea-based supplements to hepatotoxicity (Mazzanti et al. 2009). In most cases, elevations in serum transaminase levels, as well as increased serum bilirubin, were observed. Histological examination revealed inflammatory, cholestatic, or necrotic liver damage depending on the subject. No clear determinants for the type of pathology observed have been reported. In approximately 20% of these reported case studies, additional liver damage following re-challenge with the same preparation was observed. This suggests a causal relationship between hepatotoxicity and green tea. Generally, incidence of toxicity have been related to the use of concentrated extracts or "pill or capsule" dosage forms, however, there is a report of a 45-year old man who developed jaundice and elevated serum alanine aminotransferase (ALT) following six cups/day green tea infusion for 4 months (Jimenez-Saenz and Martinez-Sanchez Mdel 2006). The reasons for this difference in sensitivity are unclear, but may be related to intra-individual differences in the detoxification of GTP.

Laboratory studies of green tea-derived preparations in rodents and dogs have generally supported the potential toxicity of those preparations at high doses (Isbrucker et al. 2006; Galati et al. 2006). Oral administration of Teavigo or PPE (standardized tea polyphenol preparations) for 13 or 9 weeks, respectively, to Beagle dogs resulted in dose-dependent toxicity and death (Isbrucker et al. 2006). Vomiting and diarrhea were observed throughout both studies. In addition, 500 mg/kg, po Teavigo caused proximal tubule necrosis and elevated serum bilirubin in all dogs treated. Most male dogs (two of three) had elevated serum aspartate aminotransferase levels. Female dogs (two of three), but not male dogs, had liver necrosis. Oral administration of 2,000 mg/kg, ig Teavigo to rats resulted in lethality in 80% of animals treated (Isbrucker et al. 2006). Histological analysis revealed hemorrhagic lesions in the stomach and intestine.

Our laboratory has recently reported that high, oral dose EGCG is hepatotoxic in mice (Lambert et al. 2010). Treatment with either a single bolus (1,500 mg/kg) or repeated daily (750 mg/kg) doses of EGCG resulted in elevated ALT levels and severe, generalized liver necrosis. These effects appear to result from pro-oxidant insult as toxicity correlated with increased lipid peroxidation, elevated metallothionein, and increased histone 2A.X phosphorylation in the liver. These results build on previous observations that intraperitoneal administration of EGCG to CD-1 mice resulted in dose-dependent lethality beginning at 150 mg/kg (Galati et al. 2006).

Toxicity, especially in the liver and kidney, appears to be correlated with the bioavailability of EGCG. In the rat, where bioavailability is low (absolute bioavailability = 1.6%), toxicity is confined to the GI tract following oral administration (Chen et al. 1997). In the dog, where bioavailability is much higher, hepatotoxicity and nephrotoxicity, as well as intestinal toxicity, were observed. Toxicity was greater in fasted, than in pre-fed, dogs (Isbrucker et al. 2006). The plasma exposure (AUC_{plasma}) in the pre-fed dogs was 19.8 μg h/ml compared to 205 μg h/ml in fasted dogs following administration of 300 mg/kg, po. Recent studies in humans have also demonstrated that fasting increases the bioavailability of EGCG (Chow et al. 2005). It is unclear, however, what the safety factor of the pre-fed condition is, and whether the aforementioned human case studies involved fasting. Decreasing the biotransformation of EGCG could also result in increased exposure to unmetabolized EGCG and potentially increased hepatotoxicity.

The induction of nephrotoxicity and hepatotoxicity by green tea catechins contradicts a significant body of literature demonstrating that these compounds can protect the liver and kidney from a wide variety of toxicants. As mentioned in a previous section of this review, green tea supplementation ameliorated the nephrotoxic side effects of cisplatin in rats (Khan et al. 2009). More studies have examined the hepatoprotective effects of green tea. For example, co-treatment of ICR mice with EGCG reduced the hepatotoxic effects of carbon tetrachloride (Chen et al. 2004). These effects were correlated with an EGCG-mediated decrease in the expression of inducible nitric oxide synthase and concomitant reduction in reactive nitrogen species. Other studies have shown that green tea or green tea catechins can reduce the toxic effects of 2-nitropropane and acetaminophen among others (Sai et al. 1998; Chen et al. 2004; Oz et al. 2004). Furthermore, dietary green tea and EGCG have been shown to prevent fatty liver disease in both diet-induced and genetic animal models (Baltaziak et al. 2004; Kuzu et al. 2008; Bose et al. 2008; Bruno et al. 2008). These hepatoprotective *versus* hepatotoxic effects clearly point to the importance of dose and dosage form. Hepatotoxic effects are almost universally observed with large oral bolus or intraperitoneal doses. By contrast, hepatoprotective effects are generally observed following oral administration of lower doses (in the diet or drinking fluid) that more closely mimic typical human exposure.

These findings suggest that caution should be exercised in the use of green tea-based dietary supplements and that further studies are needed to determine the upper limit of safety for bolus dosing with tea polyphenols as well as the underlying mechanisms of toxicity.

16.6 Conclusions and Future Directions

This chapter has discussed the evidence for the cancer preventive effects of green tea that have been generated from laboratory animal models, human epidemiological studies, and human invention studies. The results of animal model studies overwhelmingly support the cancer preventive effects of GTP. Both GTP and caffeine

have shown cancer preventive activity in different models. The broad range of carcinogen and non-carcinogen-driven models, the various timing of treatment, the multitude of doses used, and differences in physiology for between the test species used (mouse, rat, hamster) make it difficult to compare potential mechanisms of action and effective doses between studies. That being said, the apparent efficacy of tea preparations under such a broad range of experimental conditions suggests that the observed effects may be general to the carcinogenic process rather than specific to a single model.

Future studies in animal models should be mechanism-driven in terms of study design and model selection. Mechanistic data obtained from *in vivo* studies avoids issues of bioavailability that typically hinder interpretation of *in vitro* studies, and simultaneously allows development of biomarkers that can be used in future human clinical trials.

These studies should utilize multiple doses of green tea preparations in order to develop data on both the maximum tolerated doses of green tea preparations as well as the potential dose-response relationships. Both types of data will aid in the development of human studies.

Finally, future animal model studies should focus on systems that are most relevant to human disease. For example, the most likely point of intervention for lung cancer prevention in smokers is following smoking cessation. Such individuals are already at elevated risk of developing lung cancer and already likely have premalignant lesions or adenomas. The NNK-treated A/J mouse model which is allowed to develop adenomas (~20 weeks after NNK treatment) prior to starting green tea treatment represents a more realistic model of human disease than the A/J mouse that is pre-treated with green tea prior to injection with NNK. Such studies will ultimately result in the most translatable data to human disease.

Future epidemiological studies should be tightly linked to exposure biomarkers for green tea consumption. Such biomarkers will allow a more accurate assessment of green tea consumption and should provide clues about the bioavailability of green tea across a study population. In addition, the use of genetic analysis for expression of key antioxidant, phase II metabolic, and other cancer related genes (e.g. *GST, COMT,* and *OGG1*) may prove invaluable in determining potentially responsive populations for future intervention studies. Such considerations must be made given the high cost of human intervention trials.

Green tea has enjoyed a long history of safe use as a beverage. Recent case-reports of hepatotoxicity linked to consumption of green tea-based dietary supplements suggest, however, that pharmacological doses of green tea in certain individuals (or populations) may have deleterious effects (Mazzanti et al. 2009). Given that cancer chemoprevention involves long-term treatment of otherwise healthy individuals with the preventive agent, it is critical that these agents have extremely low risk of adverse effects. Future studies in animal models, further controlled Phase I trials, and mechanistic studies to understand risk factors for green tea polyphenol-associated hepatotoxicity are needed.

Finally, the efficacy of green tea as a cancer preventive agent will only be established by further controlled human interventions studies of cancer incidence and

progression. These studies are costly but necessary to move beyond our current understanding.

To summarize, although the results of laboratory studies overwhelmingly support the efficacy of green tea preparation for cancer prevention, the epidemiological data remains mixed and there are only few human intervention studies. Green tea as a beverage appears to be part of a healthy diet, yet more work is needed to demonstrate its cancer prevention properties.

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