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Inhibition of Carcinogenesis by Tea Constituents

Jihyeung Ju, **Gang Lu**, **Joshua D. Lambert**, and **Chung S. Yang***
Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, USA

Abstract

The possible cancer preventive activity of tea has received much attention in recent years. The inhibitory activities of tea and tea constituents against carcinogenesis at different organ sites have been demonstrated in many animal models. The effect of tea consumption on human cancers, however, remains inconclusive. The mechanisms of action of tea polyphenols, especially EGCG, the most abundant and active catechin, have been extensively investigated. Most of the studies, however, were based on cell culture systems, and these mechanisms need to be evaluated and verified in animal models or humans in order to gain more understanding on the effect of tea consumption on human cancer. Human intervention trials are warranted to determine the possible prevention of cancer of specific sites by preparation of tea constituents.

Keywords

Tea; inhibition of carcinogenesis; mechanisms for cancer inhibitory activity

Introduction

Tea, made from the dried leaves of plant *Camellia sinensis*, is the second most widely consumed beverage worldwide next to water. Green tea, black tea, and oolong tea are the three major forms of tea. Black tea constitutes 78% of tea produced worldwide; whereas green and oolong tea constitute about 20% and 2%, respectively. Green tea is produced by steaming or pan-frying fresh tea leaves, which inactivates the enzymes and prevents the oxidation of tea constituents. A typical brewed green tea (2g of tea leaves in 200 ml of hot water) contains 500-700 mg of water extractable materials, of which 30-40% (by dry weight) are catechins. (–)-Epigallocatechin-3-gallate (EGCG), (–)-epigallocatechin (EGC), (–)-epicatechin-3-gallate (ECG), and (–)-epicatechin (EC) are the major catechins in tea. Black tea is produced by a process known as fermentation, in which the tea leaves are crushed to promote enzymatic oxidation and subsequent condensation of tea polyphenols, leading to the formation of oligomeric polyphenols (theaflavins) and polymeric polyphenols (thearubigins). Black tea contains 2-6% theaflavins, >20% thearubigins, and 3-10% catechins in the water-extractable materials. Tea leaves also contain 2-5% caffeine in the water-extractable material of green, oolong, and black tea.

*Corresponding author: Dr. Chung S. Yang, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 164 Frelinghuysen Road, Piscataway, NJ 08854-8020, Phone: 732-445-3400 x248; Fax: 732-445-0687, E-mail: csyang@rci.rutgers.edu.

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This chapter reviews animal studies on the inhibitory effect of tea constituents against tumorigenesis, possible mechanisms of action of tea constituents that may be applicable to human situations, and epidemiological studies on tea and cancer in humans. Results from our own laboratory are discussed in more detail to serve as examples in this field of research.

Inhibition of Tumorigenesis in Animal Models and Possible Mechanisms

Tea and its constituents have been demonstrated in many animal models to inhibit tumorigenesis in different organs sites including the lung, oral cavity, esophagus, stomach, small intestine, colon, skin, prostate, mammary glands, liver, pancreas, and bladder. Some of the results have been reviewed previously [1-8]. Table 1 summarizes the results of 120 studies published since the year 1991. The following is a review on studies of specific organ sites.

Lung tumorigenesis

Out of total 21 studies on the effect of tea on lung tumorigenesis, 19 studies showed inhibitory effects.

Administration of green tea, black tea, EGCG, or theaflavins during initiation or promotion stages was shown to significantly decrease (4-methylnitrosamino)-1-(3-pyridyl)-1-butanon (NNK)-induced lung tumorigenesis in rats, mice, or hamsters [9-17]. Treatment with green or black tea for 60 weeks also inhibited the spontaneous formation of lung tumors in A/J mice [18]. Oral administration of green tea infusion reduced the number of lung colonies of mouse Lewis lung carcinoma cells in a metastasis system [19]. These results suggest that tea preparations may be preventive agents for all stages of lung carcinogenesis.

Chung *et al.* [12] showed that the inhibitory effect of caffeine (680 ppm) on NNK-induced lung tumorigenesis in rats was similar to that of 2% black tea (containing 680 ppm caffeine). In a previous study with A/J mice, however, pure EGCG was shown to be slightly more effective than caffeine in inhibiting lung tumorigenesis [10]. Black tea polyphenols have lower bioavailability than green tea polyphenols, and the contribution of caffeine could account for the inhibition of lung tumorigensis by black tea in rats.

In our recent study, the oral administration of 0.5% Polyphenon E (PPE, a standardized green tea polyphenol preparation containing 65% EGCG, 25% other catechins, and 0.6% caffeine) or 0.044% caffeine in the drinking fluid for 32 weeks was found to inhibit the progression of lung adenomas to adenocarcinomas in A/J mice that had been treated with a single dose of NNK 20 weeks earlier [17]. Immunohistochemical (IHC) analysis showed that PPE and caffeine treatment inhibited cell proliferation in adenocarcinomas, enhanced apoptosis in adenocarcinomas and adenomas, and decreased levels of c-Jun and phospho-Erk1/2. In the normal lung tissues, neither agent had a significant effect on cell proliferation or apoptosis.

Lu *et al.* [20] recently analyzed the gene expression changes caused by the administration of green tea or PPE to chemically-induced mouse model for lung tumorigenesis. They found that 88 genes that were differentially expressed in tumors (from the normal tissues) were reversed by the treatment and suggested that these genes may be used as markers for tea exposure.

Tumorigenesis of digestive tract

Inhibitory effects of tea against tumorigenesis in the digestive tract including oral cavity, esophagus, stomach, small intestine, and colon have been shown in 27 out of 33 studies.

The inhibitory effects of tea and tea polyphenols on intestinal tumorigenesis in mice have been consistently observed in different laboratories [21-24]. We showed that administration of EGCG at 0.02% to 0.32% in drinking fluid dose-dependently inhibited small intestinal tumorigenesis in *Apc*$^{Min/+}$ mice, but caffeine did not have such an effect [24]. Western blot analysis indicated that the EGCG administration resulted in increased levels of E-cadherin as well as decreased levels of β-catechin in the nucleus, c-Myc, phospho-Akt, and phospho-Erk in the tumors [24]. In another study with *Apc*$^{Min/+}$ mice, PPE (0.12% in diet) was found to decrease intestinal tumor multiplicity by 70.5%, but ECG (0.08% in drinking fluid) had no significant inhibitory effect. [25]. IHC analysis showed that PPE or EGCG treatment increased apoptosis but decreased cell proliferation as well as levels of phospho-Akt and nuclear β-catenin. Green tea administration (0.6% in drinking fluid) inhibited the formation of azoxymethane (AOM)-induced aberrant crypt foci in CF-1 mice on a high-fat diet [26]. EGCG (0.1% in drinking fluid) administration decreased tumor incidence and the number of tumors per tumor-bearing mouse in AOM-treated CF-1 mice [27].

The effects of tea preparation on colon tumorigenesis in rats, however, have not been consistent [28-34]. The lack of a consistent protective effect against colon carcinogenesis is rather surprising because the intestine is considered to be a promising site for chemoprevention with polyphenols that have low systemic bioavailability. EGCG has only limited systemic bioavailability after oral ingestion. Even the absorbed EGCG is excreted mostly into the intestine through the bile. Our recent animal study showed that PPE at 0.24% in the diet significantly inhibited AOM-induced ACF and colon tumor formation in rats by 37% and 55%, respectively (unpublished results).

Skin carcinogenesis

There are a total of 24 studies demonstrating inhibition of tumorigenesis during the initiation, promotion, or progression stages by oral administration or topical application of different tea preparations.

Conney *et al.* [35-37] demonstrated inhibitory effects of orally administered tea, decaffeinated tea, and caffeine against UVB-induced skin tumorigenesis in mice and a close association between inhibition of carcinogenesis and reduction of adipose tissue by tea and caffeine [35]. Decaffeinated green tea or decaffeinated black tea was found to be much less effective in inhibiting the tumor formation and reducing fat levels, and adding caffeine to the decaffeinated green or black tea restored the inhibitory effects. When tea polyphenols are administered orally, their low bioavailability in the skin may limit the inhibitory effect; the contribution of caffeine present in tea to inhibiting carcinogenesis could become more important. Topical application of EGCG and caffeine to the skin was shown to decrease, by a similar extent, the incidence, multiplicity, and size of tumors induced by UVB treatment in SKH-1 mice [38,39].

Prostate tumorigenesis and transplanted prostate tumor growth

There are a total of six studies on the effect of tea on prostate cancer. Four studies were in xenograft models where human prostate cancer cells were inoculated in immune deficient mice, and the tumor growth was inhibited by oral or i.p. administration of tea extracts or polyphenols [40-43].

Gupta *et al.* [44] reported that oral infusion of the polyphenolic fraction isolated from green tea (0.1% as drinking fluid) significantly inhibited tumor incidence and burden in the prostate

as well as metastases to distant sites in an autochthonous transgenic adenocarcinoma of the mouse prostate (TRAMP) model. In a follow-up study [45], the treatment was found to decrease insulin-like growth factor (IGF)-1, phosphor-Akt, and -Erk 1/2 levels, but increase IGF binding protein-3 (IGFBP-3) levels in the prostate cancer of TRAMP mice. Caporali *et al.* [46] reported similar inhibitory activity of orally administered green tea catechins on prostate tumor formation in the TRAMP model. They showed that levels of clusterin (a protein involved in apoptosis and down-regulated in the prostate during cancer progression) were sustained by the administration [46].

It is not clear whether tea polyphenols inhibit prostate carcinogenesis by a direct action of tea polyphenols that are bioavailable to prostate or by an indirect action such as by affecting androgen metabolism or by affecting circulating serum IGF-1 levels, as observed by Gupta *et al.* [44].

Mammary tumorigenesis

There are a total of 12 studies on the effect of tea on mammary tumorigenesis, and 8 of the studies showed inhibitory effects. The reason for a lack of inhibition in 4 of the studies is not clear. One possible factor is the suspected low bioavailability of tea polyphenols in the mammary tissues, and the observed inhibitory effect of tea on mammary tumorigenesis may be due to an indirect action of tea. For example, Rogers *et al.* [47] showed no significant inhibitory effect of black tea administered during the promotion stage of 7,12-dimethylbenz *[a]*anthracene-induced mammary tumorigenesis in rats on AIN76 diet. However, in rats on a high fat diet, a reduction of the tumor number and size by black tea was found. The results suggest that black tea may decrease tumorigenesis indirectly by affecting fat absorption and metabolism that may influence estrogen metabolism.

Mechanistic Studies on the Activities of EGCG in Cell Lines

Many studies on the mechanisms of action of EGCG and other catechins have been conducted in cell lines, and this topic has been reviewed previously [4,48,49]. The proposed mechanisms include inhibition of MAP kinases and the PI3K/AKT pathway, inhibition of NFκB- and AP-1-mediated transcription, inhibition of growth factor-mediated signaling, inhibition of proteinase activities, and other activities. The concentrations of EGCG required to observe these biological effects *in vitro*, however, usually exceed the concentrations achievable in plasma and tissues by 10- to 100-fold, and questions remain concerning the relevance of these *in vitro* observations to the mechanisms of the cancer-preventive activities *in vivo* [49].

In general, if an effect can be observed *in vitro* at concentrations lower or similar to those observed *in vivo*, then the event may occur *in vivo*. Inhibition of telomerase and matrix metalloproteinases has been demonstrated with rather low concentrations of EGCG (IC_{50} in the range of 0.5–1 μM). EGCG has also been found to bind to 67-kDa laminin receptor, Bcl-2, vimentin, and glucose-regulated protein 78 with high affinity [50-53]. However, there are big differences between the effective concentrations determined with pure enzymes and those in cell lines or tissues, possibly due to the nonspecific binding of EGCG to many proteins and the limited amount of EGCG that can enter the cells. When a small amount of pure enzyme is used in an enzymatic assay, inhibition may be observed with nanomolar concentrations of EGCG, but it may take much higher concentrations of EGCG to inhibit the activity in cell lines or tissues. This point is illustrated in the inhibition of 20 s proteasome chymotryptic activities by EGCG; i.e. the IC_{50} observed in a cell-free system was 0.1–0.2 μM, but it was 1–40 μM in tumor cell lines [54]. EGCG was reported to bind to the 67-kDa laminin receptor with a K_d of 0.04 μM, to vimentin with a K_d of 3.3 nM, and interact with Bcl-2 with a K_i of 0.33 μM [50-52]. In all these studies, there were experiments demonstrating the biological relevance of the effects in their specific experimental systems, but it required much higher concentrations

of EGCG to cause growth inhibition and induce apoptosis. The general applicability of these mechanisms for cancer prevention is still not known.

Another concern in the use of redox-sensitive compounds in a cell culture system is the oxidation and stability of the compound. When added to the cell culture medium, EGCG is oxidized to produce superoxide radical and H_2O_2 [55]. We have demonstrated that, depending on the cell lines and culture conditions, the EGCG-induced apoptosis can be completely or partially blocked by the addition of catalase in the culture medium, suggesting that the apoptosis is mediated by H_2O_2 [49]. Autooxidation of EGCG generated reactive species may inactivate epidermal growth factor receptor in cells in culture [55]. In a recent study on EGCG-induced gene expression changes using DNA microarrays [56], we found that the suppression of gene expression of the bone morphogenic protein-signaling pathway by EGCG was not affected by catalase, and was therefore considered to be hydrogen peroxide independent. On the other hand, many gene and cellular pathways, including genes of the transforming growth factor **β** signaling pathway were hydrogen peroxide dependent [56]. It is not clear whether the EGCG autooxidation-induced effects occur inside animal tissues, because these tissues are endowed with anti-oxidative enzymes and are usually under lower oxygen partial pressure (< 40 mm Hg) than the cell culture medium (152 mm Hg). This point was discussed in our previous publications [49,55] and reviewed by Khan *et al.* [57].

Based on the above discussions, we summarize our understanding of the mechanisms of cancer prevention by EGCG as follows: 1) multiple mechanisms are likely to be involved in different experimental systems; 2) some of the proposed mechanisms based on studies in cancer cell lines may not be relevant to cancer prevention; 3) mechanisms of cancer prevention need to be demonstrated in relevant models or human tissues; and 4) many of the observed effects are probably secondary events or downstream events and it is important to identify the direct targets of EGCG action.

Studies on Tea and Human Cancer

The relationship between tea consumption and human cancer risk has been reviewed in many articles. In 1991, the Working Group of the International Agency for Research on Cancer (IARC) reviewed the effects of tea on cancers of different sites and concluded that “there is inadequate evidence for the carcinogenicity in human and experimental animals of tea drinking” [58]. In 1993, Yang and Wang reviewed more than 100 published papers and paid more attention to the possible cancer preventive effects of tea consumption [1]. This review summarized that, while some studies showed a negative association between tea consumption and cancer risk, others showed no association or positive association. It was suggested that the protective effect of tea may depend on the different etiological factors involved in different cancer types and even for the same cancer types in different geographical areas. Similar conclusions have been reached in subsequent reviews [59-62].

In the present article, we reviewed approximately 150 epidemiological studies regarding the association between tea consumption and human cancer risks of the colorectum, lung, stomach, esophagus, breast, kidney, bladder, prostate, ovary, pancreas and other sites. The results are summarized in Table 2.

Colorectal cancer

The relationship between tea consumption and colorectal cancer risk has been the topic of several reviews [63-66]. Most of the reviews concluded that the studies did not provide consistent evidence to support the hypothesis that tea is a chemopreventive agent and that a negative association may be stronger in observational epidemiological studies of rectal cancer than colon cancer [65,66]. Sun *et al.* [67] recently performed a meta-analysis on eight published

studies with usable data. Reduced risk of colorectal cancer with intake of green tea was found (OR= 0.82, 95% CI=0.69–0.98); however, no association was found with black tea (OR = 0.99, 95% CI = 0.87–1.13).

We prospectively examined the associations between biomarkers of tea consumption and the risk of developing colorectal cancer among a cohort of 18,244 men in Shanghai, China, with 16 years of follow-up. EGC, 4′-*O*-methyl-EGC (4′-MeEGC) and EC, and their metabolites in baseline urine samples were measured on 162 incident colorectal cancer cases and 806 matched controls. Individuals with high prediagnostic urinary EGC and 4′-MeEGC levels had a lower risk of colon cancer. [68].

Lung cancer

Clark *et al.* [69] reviewed 15 epidemiological studies of tea consumption and lung cancer and discussed the related bias-producing factors. As with all epidemiological studies on lung cancer, the possible confounding effect of smoking or second hand smoking is a serious problem. In some recent studies, a protective effect of tea consumption against lung cancer was only observed in specific subpopulations. For example, green tea was protective in individuals with the OGG1 Cys (326) allele [70] and nonsmoking women [71], and black tea in nonsmoking women [72,73]. These results point out the importance of considering genetic polymorphism and specific risk factors in future studies. A phase II chemoprevention trial is currently being conducted by a consortium of cancer centers and universities in Canada and the US in former heavy smokers using PPE [74].

Stomach and esophageal cancers

Fourteen cohort studies and 23 case-control studies have been performed on the relationship between tea drinking and stomach cancer since 1966. Results from early case-control studies on the possible stomach cancer preventive activities of tea encouraged many other studies in this topic. The results from cohort studies, however, have been disappointing. Of the eight cohort studies on green tea, two studies indicated a reduced risk in stomach cancer [75,76]. Of six studies on black tea, one study showed increased risk of stomach cancer [77]. The other studies showed no association between tea consumption and stomach cancer risk. A nested case-control study in the Shanghai cohort showed that prediagnostic urinary EGC was inversely associated with gastric cancer (OR=0.52, 95% CI = 0.28-0.97) after adjustment for possible confounding factor [75]. In a review by Hoshiyama *et al.* [78], five out of eight case-control studies showed that tea consumption was associated with a significant risk reduction and two studies showed a non-significant risk reduction. Among six prospective studies, one showed a non-significant risk reduction, but the other five showed no association.

There have been three cohort studies and ten case-control studies on the relationship between tea consumption and esophageal cancer since 1974. The effects of tea consumption on esophageal cancer are inconsistent. The inconsistency can be mostly attributed to the temperature of the tea preparations [79], as consumption of hot food or beverage is known to be a risk factor in esophageal cancer [80]. It was further indicated that the higher the temperature of the tea or beverage, the greater the risk [81].

Breast Cancer

In a meta-analysis that included three cohort and one case-control studies on green tea, Sun *et al.* [82] found that breast cancer risk was significantly reduced (OR = 0.78, 95% CI = 0.61–0.98) with green tea intake but the risk reduction was weaker in the cohort studies (OR = 0.85, 95% CI =0.66–1.09). Black tea intake was positively associated with breast cancer risk in five cohort studies (OR=1.15, 95% CI=1.02–1.31), but inversely associated with the risk in eight case-control studies (OR = 0.91, 95% CI = 0.84–0.98). In another meta-analysis that included

five cohort and two case-control by Seely *et al.* [83], drinking 5 or more cups of green tea a day showed a non-statistically significant trend towards the prevention of breast cancer.

Wu *et al.* [84] observed that the breast cancer risk reduction by green tea intake was only found in women with low activity allele of catechol-*O*-methyltransferase, which may result in increased tea catechin bioavailability. Another study [85] showed that green tea consumption was associated with a reduced risk of breast cancer in women possessing the high activity angiotensin-converting enzyme, but not the low activity enzyme. These studies suggest that the cancer preventive effect of green tea consumption is likely to be affected by genetic polymorphism.

Prostate cancer

The relationship between tea consumption and prostate cancer has been reviewed [86-89] and the possibility that green tea has greater chemopreventive potential than black tea is worth considering [89]. A recent double-blind study by Bettuzzi *et al.* [90] followed 200 individuals with high-grade prostate intraepithelial neoplasia (PIN) receiving either 600 mg of green tea catechins daily or placebo (100 individuals in each group) 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%. No side or adverse effect was associated with the treatment. These results are very exciting, and the impact would be tremendous if the results could be reproduced in similar trials with larger numbers of subjects.

The above review of the literature indicates that a clear conclusion on the cancer preventive activity by tea consumption in humans cannot be reached. This is true even for specific types of cancer. Studies conducted in Asia, where green tea is consumed frequently, tend to show a beneficial effect on cancer prevention. Protective effects appear to be observed less frequently in European populations where intake of black tea predominates. Overall, more results on preventive effects were found in cancers of the gastrointestinal tract than other types of cancers, and in case-control studies than cohort studies.

Concluding Remarks

The above reviewed animal studies demonstrated the broad cancer preventive activities of tea constituents in different organs. Results from human studies, however, are not consistent. The differences between animal and human studies may be related to the fact that the doses of tea used in animal studies are generally higher than those consumed by humans and that the experimental conditions in animal studies are generally optimized for the detection of a protective effect. On the other hand, the results of epidemiological studies are affected by the lack of accuracy in measuring the quantity of tea consumption, the different etiological factors for cancer in different populations, the individual differences (such as genetic polymorphism), the lifestyles associated with tea consumption in different cultures, and other confounding factors. More clear-cut results may be obtained when the quantity of tea consumption can be measured more accurately, the etiological factors are better known and the status of smoking, drinking of alcoholic beverage, and relevant genetic polymorphism are considered. Large cohort studies on this topic are needed.

Even though the results from epidemiological studies on tea and cancer prevention are not conclusive, tea constituents could still be used for cancer prevention (treatment of precancers) at selected organ sites if such activity can be demonstrated in human intervention trials. In this direction, the study by Betuzzi *et al.* [90] is very encouraging. More studies of this type as well as oral and colon cancer prevention trials with well defined preparations of tea constituents in sufficient number of subjects at risk fro these cancers would be of great importance.

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Table 1

Number of animal studies showing protective or no protective effects of tea on tumor formation in different organs[a]

Site	Protective effect	No protective effect
Lung	19 (1)	2
Oral cavity	3	-
Esophagus	4	-
Stomach	7	-
Small intestine	6	1
Colon	7 (2)	5
Skin	24 (1)	-
Prostate	2 (4)	-
Breast	8 (5)	4
Liver	7	1
Bladder	2 (1)	-
Pancreas	2 (1)	-
Thyroid	1	-

[a]The number of xenograft studies is in parentheses.

Table 2

Number of studies on tea consumption and the risk of human cancers

		Cohort studies				Case-control studies			
		Risk reduction	No association in risk	Risk increase	Total	Risk reduction	No association in risk	Risk increase	Total
Colon	G	1	4	0	5	4	2	1	7
	B	2	6	1	8	4	11	1	16
Lung	G	0	2	0	2	2	3	1	6
	B	0	6	2	8	5	4	0	9
Stomach	G	2	6	0	8	7	7	1	15
	B	0	5	1	6	4	5	0	9
Esophageal	G	0	0	2	2	3	2	2	7
	B	0	1	0	1	2	1	0	3
Breast	G	2	4	0	6	3	0	0	3
	B	0	7	0	7	1	9	0	10
Prostate	G	1	0	0	1	1	0	0	1
	B	1	2	0	3	1	3	0	4
Ovarian	G	1	0	0	1	1	0	0	1
	B	1	2	0	3	0	6	0	6
Pancreatic	G	0	1	0	1	1	0	0	1
	B	0	4	0	4	1	3	0	4
Kidney and Bladder	G	0	1	0	1	0	1	2	3
	B	1	3	1	5	2	4	1	7
Other	G	0	1	0	1	1	0	1	2
	B	2	3	0	5	1	2	0	3

G, green tea; B, black tea