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Review

Chemoprevention of lung cancer by tea

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Tea is the second only to water as the most consumed beverage in the world. Both green and black teas have been studied for their health benefits for a variety of diseases, particularly cancer. Lung cancer is the predominant cause of cancer mortality in developed countries. Smokers' risk of lung cancer is 20 times that of persons who have never smoked. Epidemiological studies on the cancer-preventive effects of tea produce inconsistent results, which could in part be attributed to the lack of a universal standard for tea preparations. However, most animal studies indicate that tea has strong chemopreventive effects against lung tumorigenesis. The reported mechanisms for chemopreventive activity of green tea are antioxidation, induction of phase II enzymes, inhibition of TNFα expression and release, inhibition of cell proliferation, and induction of apoptosis. Cell cycle arrest and apoptosis induced by green tea are probably the two most significant factors. Future studies are needed to determine how green tea affects the genes associated with cell cycle regulation and apoptosis during the mouse lung carcinogenesis process.

Keywords: AP-1 / Epidemiology / Lung cancer / Mouse models / Tea

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1 Introduction

Tea is the second only to water as the most consumed beverage in the world. Green tea, which accounts for 80% of the world's tea, is primary consumed in Asian nations. Black tea, which accounts for only 18% of total tea consumption, is predominantly consumed in Western nations. Black, green, and oolong teas are made from the leaves of the *Camellia sinensis* plant [1]. White tea is made from both the leaves and the buds [2]. Although green and black teas are made from the leaves of the same plant, differences in the processing of the leaves result in differing chemical compositions. By dry weight, a cup of green tea is typically 30–40% catechins (also known as polyphenols). These catechins include epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) [3]. EGCG is the major catechin in green tea [4]. Green tea is not fermented, but black tea is. The fermentation process converts many of the catechins found in green tea to thearubigins and theaflavins. In contrast to green tea, by dry weight, a cup of black tea is only 3–10% catechins, 2–6% theaflavins, and >20% thearubigins [3]. Black tea contains more caffeine than green tea [5]. Both green and black teas have been studied for their potential health benefits for a variety of diseases, particularly cancer and heart disease. EGCG is thought to be responsible for much of the cancer-preventive effect of green tea. A single cup of green tea contains up to 200 mg EGCG [4]. Tea has incredible potential as a chemopreventive agent due to its low cost, wide availability, and low toxicity.

Lung cancer is the predominant cause of cancer mortality in developed countries. Five-year survival is less than 10% [6]. Exposure to tobacco is involved in 90% of lung carcinomas. Smokers' risk of lung cancer is 20 times that of persons who have never smoked [7]. About half of all the people who have ever smoked are currently nonsmokers, but many others are unable or unwilling to quit smoking [8]. Former smokers are still susceptible to the development of lung cancer [9]. In fact, over 50% of new lung cancer cases develop in former smokers [10]. For millions of current and former smokers, tea could provide a cheap and easy way to

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Abbreviations: BP, benzo(a)pyrene; **cAMP,** adenosine 3′, 5′-cyclic monophosphate phosphodiesterase; **EGCG**, epigallocatechin-3-gallate; **EPA,** environmental protection agency; **NDEA**, *N*-nitrosodiethylamine; **NNK,** 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

prevent or delay cancer onset. However, the efficacy and safety of tea as a chemopreventive agent must be adequately established. This review attempts to examine the available research on tea's potential as a lung cancer chemopreventive agent.

2 Epidemiology

As shown in Table 1, epidemiological studies on the cancer-preventive effects of tea produce inconsistent results. Some studies found no meaningful association between tea drinking and lung cancer [11–16], others found increased risks of up to nearly 200% [17, 18], while others yet found reduced risks [19–23]. A subset of studies did suggest that tea consumption may reduce the risk of human lung, skin, breast, and gastrointestinal cancers [4, 24, 25]. A prospective cohort study over 10 years in Japan showed that the consumption of ten or more cups of green tea *per* day delayed the onset of cancer in both smokers and nonsmokers [26]. Another study [27] showed that the reduction of gastric cancer was found only in people who consumed ten or more cups of tea *per* day. The inconsistent results seen in the epidemiological studies could result from a number of factors including inaccurate assessment of tea usage due to dependence on recall for classification, the different lifestyles associated with tea consumption in various cultures, lack of accounting of pack years smoked, differing composition of teas used in different areas, and genetic variability among subjects. In addition, differing results were seen depending on sex [21], smoking status [22], amount of tea consumption [21], type of tea consumed [18], and the presence of genetic polymorphisms [23]. Perhaps a controlled clinical trial using a defined amount of a standardized tea extract will clarify the chemopreventive activity of tea against lung cancer.

3 Tea preparations

As mentioned, study results on the chemopreventive effects of teas have been inconsistent and sometimes contradictory. An explanation for some of the disparity may lay with the tea itself. Since no standard tea preparation was used across the studies, particularly the epidemiological studies, variance in the teas may have led to significantly different chemopreventive effects. Technology needs to be utilized to ensure reproducible preparations. Tea variety, growth conditions, extraction conditions, and spectrophotometric characteristics of the preparation might be significant [28]. Also, the effects of any potentially carcinogenic pesticides and insecticides used in producing the plants should be con-

Table 1. Epidemiological studies on the chemoprevention of lung cancer by tea

Agent	Population	Results	Reference
Black tea	Males and females in the Netherlands (120 852)	No effect	[11]
Black tea	Japanese males	No effect	[12]
Any tea	Females in Hong Kong, never smoked (225)	No effect	[13]
Any tea	Postmenopausal females in Iowa (35 369)	No effect	[14]
Any tea	Males and females in New York (1138)	No effect	[15]
Black tea	Males and females in Hawaii (Caucasians, Japanese, Hawaiians) (582)	No effect	[16]
Green tea	Males and females in Hawaii (Caucasians, Japanese, Hawaiians) (582)	No effect	[16]
Green tea	Males in London, England	Increased risk	[17]
Green tea	Females in Hong Kong (400)	Increased risk	[18]
Black tea	Females in Hong Kong (400)	No effect	[18]
Okinawa tea[a)]	Males and females in Okinawa, Japan (999)	Decreased risk	[19]
Black tea	Male smokers in Uruguay (855)	Decreased risk	[20]
Green tea	Japanese males and females, smokers and nonsmokers (8552)		[21, 26]
	Males: 0	No effect	
	Females: +	Decreased risk	
	Males and females over 80: –	Increased risk	
Black tea	Czech females, both smokers and nonsmokers (2145)		[22]
	Nonsmokers: +	No effect	
	smokers: 0	Decreased risk	
Green tea	Males and Females in China		[23]
	OGG1 Cys^{326}: +	Decreased risk	
	OGG1 Ser^{326}: 0	No effect	
	GSTM1 null homozygotes: +	Decreased risk	
	GSTM1 present: 0	No effect	
	AKR1C3: 0	No effect	

a) Okinawa tea, similar to green tea but partially fermented.

sidered. Perhaps organic teas should be considered for use in some future studies. Other contaminants found in tea should also be closely examined. Three of these are fluoride, aluminum, and lead.

Fluoride may contribute to cancer by causing DNA damage. Although several studies have concluded that fluoride does not damage DNA [29], other studies have detected the mutagenic potential of fluoride in *Drosophila melanogaster* [30] as well as observing synergetic and antagonistic effects with known mutagens [31]. In a US study, ten brand-name instant tea samples were tested for fluoride levels [32]. Mean concentrations of fluoride in the solutions ranged from 1.0 to 6.5 ppm. The environmental protection agency (EPA) safety limit for fluoride in drinking water is 4.0 ppm [33] (http://www.epa.gov/safewater/mcl.html, accessed January 20, 2004). The food and drug administration (FDA) limit for bottled beverages is 1.4–2.4 ppm [34]. Caffeine might increase the absorption of fluoride [35].

Metals, including aluminum, contribute to oxidative stress by playing a major catalytic role in the production of free radicals [36]. Tea catechins have been shown to complex with aluminum, and may repress aluminum absorption during tea intake [37]. In this case, tea would have a protective effect by reducing the intake of aluminum and the resulting oxidative stress. However, some teas have high levels of aluminum [38], making it highly unlikely that the catechin content could counteract the majority of the aluminum. Also, if the catechins reduce the absorption of aluminum by complexing with it, this means that the aluminum content would reduce the amount of bioavailable catechins. Thus, aluminum in tea may raise cancer risk by increasing oxidative stress, and decrease the chemopreventive activity of the tea by binding the catechins.

Tea plants also take up lead, and high levels of lead have been detected in certain commercial brands of tea leaves [39]. Some preparations made from tea leaves have lead levels high enough to cause lead poisoning if consumed in sufficient quantity [40, 41]. High lead intake increases the risk of cancer, as well as stroke and high blood pressure [41]. Tea catechins have been demonstrated to provide some protection against lead toxicity [42]. This may be through binding to lead as they have been shown to bind to aluminum. If this is the case, like aluminum, lead may increase cancer risk while decreasing the chemopreventive activity of the tea by binding the catechins.

Other explanations for the inconsistencies between studies of tea chemoprevention need to be identified and thoroughly examined. Reports of increased cancer risk associated with tea consumption need to be carefully examined before a recommendation of significant consumption of tea is advised to those at risk for lung cancer. The populations and subpopulations most likely to benefit from the tea need to be identified, as well as elucidation of the factors that determine these differences.

4 Animal models

Green tea is a potent inhibitor of carcinogenesis in many rodent models including skin, lung, forestomach, esophagus, liver, colon, and mammary glands [43, 44]. Green tea contains flavanols or catechins including EGCG. These polyphenols have various biological activities including antioxidation, modulation of enzyme systems for metabolizing chemical carcinogens, inhibition of nitrosation reactions, scavenging of activated metabolites of chemical carcinogens, and inhibition of tumor promotion. Green tea and one of its components, EGCG, has been shown to inhibit 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced mouse lung tumorigenesis by 63 and 28%, respectively [45] (Table 2). Similarly, green tea significantly inhibited benzo(a)pyrene (BP)-induced lung tumorigenesis in A/J mice [46]. Green tea and decaffeinated green tea reduced lung tumor incidence and multiplicity in *N*-nitrosodiethylamine (NDEA)-treated A/J mice [43]. Green tea decreased tumor multiplicity in both p53 mutant mice and wild-type mice that were treated with NNK, indicating that its chemopreventive effects are p53 independent. p53 mutations have been identified in 50–80% of sporadic human lung cancers, and they are thought to play a vital role in the predisposition and development of lung cancer [47]. It was reported that oolong and green tea administered to Kumming mice inhibited urethane-induced lung neoplasia [48]. Green tea greatly reduced tumor incidence and multiplicity in *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG)-induced lung cancers and precancerous lesions in LACA mice [49].

Green tea has also been found to inhibit the growth and cause the regression of established benign tumors, suggesting that it may be preventative at all stages of carcinogenesis [44]. Gupta *et al*. [50] have shown, using transgenic adenocarcinoma of the mouse prostate (TRAMP), that green tea caused a significant delay in primary tumor incidence and tumor burden and almost complete inhibition of distant site metastases. Furthermore, the green tea resulted in a significant inhibition of angiogenesis and vascular endothelial growth factor (VEGF). Also, significantly higher levels of apoptosis were observed [51]. However, studies indicate that green tea does not protect A/J mice against tumorigenesis induced by tobacco smoke [52, 53].

In addition to the effect of green tea, black tea, EGCG, and caffeine have also been demonstrated to be protective against lung tumorigenesis in A/J mice treated with the tobacco-related carcinogens [1, 45, 51]. When administered during the NNK treatment period, green and black teas appeared to have the same effectiveness. When adminis-

Table 2. Animal studies on the chemoprevention of lung cancer by tea

Agent	Carcinogen	Animal model	Results	Reference
Green tea	NDEA	A/J mice	Decreased risk	[43]
Decaffeinated green tea	NDEA	A/J mice	Decreased risk	[43]
Decaffeinated black tea	NDEA	A/J mice	Decreased risk	[43]
Green tea	NNK	A/J mice	Decreased risk	[45]
EGCG	NNK	A/J mice	Decreased risk	[45]
Green tea	Tobacco smoke	A/J mice	No effect	[52]
Green tea	Tobacco smoke	A/J mice	No effect	[53]
Black tea	Sporadic	A/J mice	Decreased risk	[54]
Green tea	NNK	FAF_1 wt mice	Decreased risk	[47]
Green tea	NNK	FAF_1 p53 mutant mice	Decreased risk	[47]
Green tea	Urethane	Kumming mice	Decreased risk	[48]
Oolong tea	Urethane	Kumming mice	Decreased risk	[48]
Green tea	MNNG	LACA mice	Decreased risk	[49]
Decaffeinated green tea	DMN	C3H mice	Decreased risk	[55]
Decaffeinated black tea	DMN	C3H mice	Decreased risk	[55]
EGCG	BP	A/J mice	Decreased risk	[56]
Theaflavin	BP	A/J mice	Decreased risk	[56]
Green tea	BP	A/J mice	Decreased risk	[46]
EGCG	Cisplatin	A/J mice	Decreased risk	[58]
Black tea	NNK	F344 rats	Decreased risk	[60]
Caffeine	NNK	F344 rats	Decreased risk	[60]
Green tea	Crocidolite +BP	Wistar rats	Decreased risk	[61]
Green tea	NNK	Hamsters		[64]
		Neuroendocrine tumors	Decreased risk	
		Adenocarcinomas	Increased risk	
Theophylline	NNK	Hamsters		[64]
		Neuroendocrine tumors	Decreased risk	
		Adenocarcinomas	Increased risk	

tered after the carcinogen treatment period, green tea seemed to be more effective than black tea [43]. One study reported that groups that received caffeine (as part of the green tea or alone) had consistently lower body weights than the noncaffeine groups. The inhibitory activity of caffeine is likely to be partially due to its effect on body weight [45]. Black tea significantly reduced sporadically acquired lung tumors in A/J mice [54]. Decaffeinated black tea decreased lung tumor multiplicity but did not significantly decrease tumor incidence [43]. Decaffeinated green and black tea showed a dose-dependent chemoprevention of lung tumors in dimethylnitrosamine-treated C3H mice [55]. Theaflavin and EGCG exhibited a protective effect against BP-induced lung tumorigenesis in strain A mice [56].

Cisplatin is a chemotherapy drug that can enhance carcinogenicity in experimental animals [57]. In A/J mice, EGCG reduced tumor multiplicity but not tumor incidence in cisplatin-treated mice [58]. This indicates the potential of EGCG to be used in conjunction with cisplatin to counteract its toxicity. Green tea was shown to heighten the tumor-inhibitory effect of doxorubicin by increasing its concentration in tumor tissue, but not normal tissue in CDF_1 and BDF_1 mice [59]. It is also possible that green tea may increase doxorubicin toxicity. If green tea has the same effect in humans, it could potentially be used to increase the efficacy of this cancer therapy.

A study of the effects of black tea and caffeine on lung tumorigenesis in NNK-treated F344 rats showed decreases in tumor incidence for both agents. Remarkably, caffeine at a concentration found in 2% black tea reduced tumor incidence more than 2% black tea did. The rats receiving the caffeine showed no differences in body weight from the controls, so the effect of the caffeine, in this case, could not be due to changes in weight [60]. Rats drinking 2% green tea for life showed decreased incidence of lung carcinoma induced by Crocidolite plus BP, as well as delayed onset of carcinoma and increased mean survival time of rats with carcinoma [61]. Repeated, subcutaneous injection of black tea tannin given to NIH black rats resulted in tumor formation at the injection site; however, this effect was not observed in rats treated with the total aqueous extract from black tea [62, 63].

Green tea and theophylline (a green tea component) inhibited neuroendocrine lung carcinogenesis but promoted the development of adenocarcinomas in NNK-treated hamsters [64]. The theophylline and caffeine (both methylxanthines) in tea inhibit the enzyme adenosine 3′, 5′-cyclic monophosphate phosphodiesterase (cAMP), resulting in the intracel-

lular accumulation of cAMP [65]. cAMP can block Raf-1 [66]; thus inhibiting hamster neuroendocrine lung tumors (which resemble human small cell lung carcinoma) [67–69]. However, accumulation of cAMP can stimulate the β-adrenergic growth-regulating pathway, promoting the development in adenomas and adenocarcinomas in hamsters. *In vitro* growth of cell lines from human pulmonary adenocarcinomas of bronchiolar Clara cell lineage is controlled by the same pathway [70, 71], indicating that green tea may promote this type of cancer in humans. Growth of cells derived from human small cell lung cancer (SCLC) is partially dependent on signaling by Raf-1 [72–74], thus, inhibition of Raf-1 in humans by green tea is likely to result in inhibition of SCLC. NNK-induced adenomas and adenocarcinomas in mice and rats are derived from alveolar type II cells [75, 76], while in hamsters, NNK-induced adenocarcinomas are derived from bronchial and bronchiolar Clara cells [77]. In human patients, pulmonary adenocarcinomas of both cell lineages are found. Research suggests that human and hamster adenocarcinomas of Clara cell lineage are regulated *via* activation of cAMP [70, 71, 78, 79], and may be promoted by consumption of green tea. In contrast, human and murine pulmonary adenocarcinomas of alveolar type II cell lineage may be inhibited by the blocking of Raf-1 by cAMP accumulation [80–85] caused by green tea.

5 Mechanisms

The mechanisms for chemopreventive activity of green tea are antioxidation, induction of phase II enzymes, inhibition of TNFα expression and release, induction of apoptosis, and inhibition of cell proliferation [86]. For example, green tea polyphenols inhibited 12-0-tetradecanoylphorbot-13-acetate (TPA)-induced hydrogen peroxide formation and 8-hydroxydeoxyguanosine (8-OHdG) formation, supporting their antioxidation role. The antioxidant activity of catechins is reported to be 25 times more potent than vitamin E and 100 times more potent than vitamin C, and green tea or EGCG inhibited the formation of 8-OHdG, a biomarker for oxidative damage in lung DNA of NNK-treated mice [87–91].

Green tea has also been shown to enhance the enzymatic activities of several phase II enzymes, such as glutathione peroxidase, catalase, glutathione S-transferase, NADPH-quinone oxidoreductase, UDP-glucuronosyl transferase, and methoxyresorufin-0-dealkylase. Green tea may have inhibitory activity against the synthesis and release of tumor necrosis factor alpha (TNF-α). The mechanism for this effect is not clear. EGCG was found to significantly inhibit EGFR's DNA synthesis and protein kinase activities [92]. More recently, EGCG was found to inhibit DNA methyltransferase (DNMT) activity, reverse hypermethylation, and cause re-expression of methylation-silenced genes, suggesting that EGCG may behave as a DNA demethylating agent under certain conditions [93].

Several lines of evidence suggest that green tea is a potent inducer of apoptosis in tumor cell lines and in mouse lung tissues [50, 86]. Green tea also inhibits cell proliferation and causes cell cycle arrest in most model systems tested. Green tea causes G1 arrest in both human breast and prostate cancer cell lines. p53 expression was induced by green tea in both human breast and mouse skin cells. The expression of cyclin-dependent kinase (CDK) inhibitors such p21WAF1, p27, and unphosphorylated Rb were elevated while CDK2/4 activities were inhibited upon treatment with green tea. Inhibition of ras gene-activated signal transduction pathway was suggested, since green tea was found to inhibit AP-1 activation. Also, EGCG has been shown to affect numerous events in the Ras-MAP kinase signaling pathway [94]. The inhibition of AP-1 activation by green tea may occur through the inhibition of a jun NH2-terminal kinase (JNK)-dependent pathway. EGCG, the major active component of Polyphenon E, has been shown to inhibit transcription of the AP-1 family member c-fos [95], as well as prevent the phosphorylation of c-jun *in vitro* [96]. In addition, EGCG has been shown to inhibit AP-1 activity in the skin of the AP1-Luc reporter mice [97].

One report from 2000 indicates that green tea could inhibit TPA-induced NFγB activity, suggesting that inhibition of NFγB activation also contribute to its chemopreventive effect [98]. Inhibition of NFγB by tea polyphenols has been reported *in vitro* and *in vivo* [98–101]. Nam *et al*. [101] demonstrated that EGCG inhibits proteasome function, a mechanism known to inhibit NFγB activity, at concentrations of EGCG that are seen in the serum of green tea drinkers, suggesting that this compound could be therapeutically useful. The study by Nomura and co-workers [98] showed that green tea extracts could inhibit TPA-induced NFγB, activity suggesting that inhibition of NFγB activation contributes to its chemoprevention effect in this skin model of carcinogenesis. Yang *et al*. [86] showed that tea polyphenol-induced production of oxidative species H_2O_2 may mediate apoptosis, which may serve as another pathway towards apoptosis. Abundant evidence indicates that the AP-1 and NFγB pathways are inhibited by green tea. Understanding the relative contributions of each pathway to lung tumor formation and progression is thus of great interest.

6 Future perspectives

Studies of tea tend to indicate a significant chemopreventive effect; however, some studies, mostly epidemiological, show no effect or harmful effects. Thus, a carefully con-

trolled clinical epidemiology study using a defined amount of a standardized tea extract is required to address this issue. Research reports indicate that many interesting mechanisms may be involved in the tea's chemopreventive effect. Among the suggested mechanisms, induction of apoptosis and cell cycle arrest by green tea are probably the most significant factors. However, the exact mechanisms for the action of green tea on apoptosis and cell cycle arrest are not clear. The current hypothesis is that green tea will induce apoptosis and cell cycle arrest through pathways involving AP-1 and NFγB. In these pathways, proteins regulating cell cycle and apoptosis may play a significant role to mediate these activities. Elucidation of which mechanisms are of critical importance remains to be determined. Further study needs to be done to establish the safety of large doses of tea and to identify target populations for clinical trials of tea chemoprevention.

Finally, clinical trials of green tea as a lung cancer chemopreventive agent are urgently needed. As part of a Program Project sponsored by the US National Institutes of Health (NIH 1P01-CA96964), a phase II chemoprevention trial is currently conducted by a consortium of cancer centers and universities in Canada and the United States in heavy smokers using a standardized decaffeinated preparation – Polyphenon E [102]. This trial will recruit former smokers between the age of 45 and 74 years of age [102]. Individuals harboring precancerous lesions are identified using image analysis of sputum cells. The design of the study includes double-blind, randomized, and placebo-control elements. The dose schedule will be Polyphenon E (800 mg of EGCG) orally twice a day for 6 month [102]. To our knowledge, this is the first phase IIb double-blind, randomized, placebo-control chemoprevention trial of green tea in former heavy smokers with precancerous bronchial lesions.

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7 References

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