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REVIEW

Green tea and prevention of esophageal and lung cancers

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Green tea contains high concentrations of tea polyphenols that have shown inhibitory effects against the development, progress, and growth of carcinogen-induced tumors in animal models at different organ sites, including the esophagus and lung. Green tea polyphenols also have shown to suppress cell proliferation and induce apoptosis. Besides antioxidative property, green tea polyphenols have pro-oxidative activities under certain conditions and modulate phase II metabolic enzymes that can enhance the detoxification pathway of environmental toxicants and carcinogens. Although epidemiological studies have provided inconclusive results on the effect of green tea consumption against the development of esophageal and lung cancers in humans overall, the inverse association between green tea intake and risk of esophageal cancer risk is more consistently observed in studies with adequate control for potential confounders. Epidemiological studies also have demonstrated an inverse, albeit moderate, association between green tea consumption and lung cancer, especially in non-smokers. This article reviews data on the cancer-preventive activities of green tea extract and green tea polyphenols and possible mechanisms against the esophageal and lung carcinogenesis in experimental animals, and summarizes the current knowledge from epidemiological studies on the relationship between green tea consumption and esophageal and lung cancer risk in humans.

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1 Introduction

Tea is the second most consumed beverage after water in the world. All tea is produced from the leaves of *Camellia sinensis*, but the differences in processing result in different types of tea. In the processing of green tea, fresh tea leaves are steamed or heated immediately after harvest, resulting in minimal oxidation of the naturally occurring polyphenols in the tea leaves. On the other hand, in the processing of black tea, the tea leaves are dried and crushed upon harvesting to encourage oxidation, which converts the indigenous tea polyphenols (primarily catechins and gallocatechins) into other polyphenols (mainly theaflavins and thearubigens). The partially oxidized tea leaves yield Oolong tea [1]. Worldwide, about 78% of the tea production is black tea, which is the main tea beverage in America, Europe, and Middle East. Green tea, which is popular in Japan and parts of China, accounts for about 20% of the total tea production. The remaining 2% of tea production is Oolong tea, which is mainly consumed in southeastern China and Taiwan.

Tea, from a biological standpoint, is a mixture of a large number of bioactive compounds including catechins, flavonols, lignans, and phenolic acids. A typical cup of green tea, brewed with 2.5 g of dry tea leaves in 250 mL of hot water

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Abbreviations: CI, confidence interval; **DGT,** decaffeinated green tea; **EC,** (−)-epicatechin; **ECG,** (−)-epicatechin-3-gallate; **EGCG,** (−)-epigallocatechin-3-gallate; **GST,** glutathione-*S*-transferase; **8-OH-dG,** 8-hydroxy-2′-deoxyguanosine; **NNK,** 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-1butanone; **NMBA,** *N*-nitrosomethylbenzylamine; **PPE,** polyphenon E; **RR,** relative risk

(called a 1% tea infusion) contains 620–880 mg water-extractable materials, of which 30–40% (by dry weight) are catechins [2, 3]. (−)-Epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epicatechin (EC) are the major catechins in green tea. EGCG is the most abundant catechin in green tea, accounting for approximately two-third of the total catechins [1].

Extensive laboratory studies in multiple animal models have consistently shown the inhibitory activities of green tea extract and green tea polyphenols against tumorigenesis at different organ sites including the esophagus and lung. The protective effects of green tea consumption against the development of esophageal and lung cancers in humans, however, remain inconclusive [2]. Mechanisms of action of tea polyphenols, especially EGCG, have been extensively investigated. Given the data based on cell culture systems are less relevant to cancer prevention in humans, this review will focus on the in vivo experimental studies in animals and epidemiological studies in humans. Most recent findings of laboratory studies in animals are used to illustrate the chemopreventive mechanisms. The results of green tea consumption on risk of esophageal and lung cancer in humans are critically assessed through a literature review on published epidemiological studies.

2 Materials and methods

A comprehensive search was carried out in the PubMed Database in February 2011 to retrieve all case–control or cohort studies or clinical trials published in English language, or in Chinese or Japanese language with an abstract in English on the association of tea, tea polyphenols or tea catechins and risk of esophageal or lung cancer. The following terms were used in the search for esophageal cancer: (esophag* or oesophag*) and (cancer or carcinoma or adenocarcinoma or neoplasm or neoplasia or neoplastic) and (tea or polyphenol* or catechin*). The same terms were used in the PubMed Database search for lung cancer with the replacement of (esophag* or oesophag*) with (lung). The selection criteria were reports of all prospective, case–-control observational studies, and controlled interventional studies, which either assessed the associations between green consumption and risk of esophageal or lung cancer incidence or mortality.

Using the aforementioned search approach, a total of 112 articles were retrieved for esophageal cancer. After reading the abstracts of the retrieved articles, 98 articles were excluded because they were not case–control or cohort studies or clinical trials of green tea and esophageal cancer; the excluded articles were reviews, animal studies, in vitro studies, case series, studies that did not report the level of tea consumption, and relative risk measure of the disease. In the case of any doubt, I reviewed the full texts of these articles to determine their eligibility. Some articles, although the type of tea was not specified, were included if they were carried out in Japan or China where green tea was the main tea type consumed. The present review included 18 articles of green tea intake and risk of esophageal cancer in humans. Similarly, a total of 255 articles related to tea and lung cancer were retrieved. After excluding 243 articles, the present review included 12 articles derived from epidemiological studies of green tea intake and risk of lung cancer in humans.

Owing to the nature of included studies, which were mainly epidemiological, results were summarized descriptively, and for esophageal and lung cancer separately.

3 Green tea and esophageal cancer prevention

The incidence rates for esophageal cancer vary internationally more than any other cancer, with more than 50-fold difference between high- and low-rate areas over the world. In most parts of the world, esophageal cancer is relatively uncommon, with the annual incidence rates below 5 cases per 100 000 persons-year. In the United States, esophageal cancer ranked at 15th in the number of cases in 2010 [4] whereas in parts of north China it was the most common cancer with its incidence and mortality rates exceeding 100 cases per 100 000 persons-year [5]. Esophageal cancer typically occurs in one of the two forms, squamous cell carcinoma, and adenocarcinoma. The natural histories of and risk factors for squamous cell carcinoma and adenocarinoma of the esophagus appear to differ substantially. Squamous cell carcinoma develops as the result of a sequence of histopathological changes that typically involves esophagitis, atrophy, dysplasia, carcinoma in situ and finally, invasive cancer [6]. Alcohol consumption, tobacco use, and deficiencies in certain nutrients present in fresh fruits or vegetables have been identified as the main risk factors for esophageal squamous cell carcinoma, especially in high-risk populations [7, 8]. Most adenocarcinomas, however, arise from glandular cells that are present at the junction of the esophagus and stomach. The gastro-esophageal reflux disease causes chronic inflammation, resulting in Barrett's esophagus, a condition that occurs when the esophagus is damaged and its inner lining replaced by the glandular cells because of the continued exposure to stomach acid [9]. Patients with Barrett's esophagus have esophageal cancer incidence rate of 7 per 1000 per year [10], which is more than 100-fold that for the rate in the general population in the United States [11]. Since treatment successes have been limited and esophageal cancers still are usually fatal, regardless of cell type, modifiable factors, if identified having chemopreventive effect, can be applied for the prevention and control of this malignancy. Tea drinking has been studied for its potential for anticarcinogenesis in the esophagus in experimental animals as well as humans.

3.1 Inhibition of esophageal tumorigenesis in experimental animals

The cancer-inhibitory activities of green tea extract and green tea polyphenols have been studied in different models of oral-digestive tract carcinogenesis. Morse et al. [12] compared the inhibitory effects of the polyphenol fractions of green tea, EGCG, and the polyphenol fraction of black tea, theaflavins. The tea fractions were administered in the drinking water at concentrations of 360 and 1200 ppm for 2 wk before administration of the esophageal carcinogen *N*-nitrosomethylbenzylamine (NMBA). NMBA was administered subcutaneously in 10% dimethyl sulfoxide three times weekly for 5 wk. Twenty-five weeks after NMBA administration began, rats treated with NMBA only had an esophageal tumor incidence of 100% and a multiplicity of 3.3 ± 0.4 tumors per rat. The proportion of rats developing tumors was not significantly reduced by any of the four tea fractions at the concentrations tested. However, the 1200 ppm concentrations of each tea fractions in the drinking water produced some reduction in esophageal tumor multiplicity. The rates of esophageal tumor formation were significantly reduced at 360 and 1200 ppm by EGCG and theaflavins [12].

Wang et al. [13] carried out a similar experiment to investigate the effects of green tea and black tea, when given either during or after carcinogen treatment, on esophageal tumorigenesis in male Sprague–Dawley rats. Rats were treated with NMBA (2.5 mg/kg, s.c., twice weekly) for 5 wk; 39 wk after the initial dose of NMBA, 65% of the rats had esophageal tumors with an average of 1.4 ± 0.3 tumors per rat. In the groups of rats receiving 0.6% decaffeinated green tea or decaffeinated black tea (6 mg tea solids per mL) as the sole source of drinking fluid during the NMBA-treatment period, esophageal tumor incidence, and multiplicity were reduced by approximately 70%. When the tea preparations were given after the NMBA treatment period, the esophageal papilloma incidence and multiplicity were reduced by approximately 50%. In a second experiment, NMBA was given to rats at a dose of 3.5 mg/kg (s.c., twice weekly) for 5 wk; after 16 wk, the tumor incidence was 82% and tumor multiplicity was 6.7 ± 1.2 tumors per rat. In the groups of rats receiving 0.9% regular green tea or decaffeinated green tea after the NMBA treatment period, tumor multiplicity was decreased by more than 55%. The volume per tumor was reduced by approximately 60% in the rats receiving 0.9% regular green tea. Histological analysis indicated that both the incidence and multiplicity of esophageal carcinoma was decreased by both regular and decaffeinated green tea by approximately 20% and 60–70%, respectively [13]. The above results indicate that both green tea and black tea can inhibit the tumorigenic action of NMBA during the period of carcinogen treatment and the subsequent molecular events important for esophageal tumorigenesis.

The cancer-inhibitory activities of tea can be offset by the high temperature of fluid. Li et al. [14] arried out an experimental study to determine the effect of hot water on NMBA-induced rat esophageal tumorigenesis in rats that was given hot water (65°C) alone, NMBA injections alone, a combination NMBA and hot water, and with or without added EGCG for each of the three treatment. At week 20, the incidence and the number of tumors per rat were significantly increased in rats given hot water as compared with rats received NMBA injections only. EGCG treatment did not significantly reduce the number or the size of tumors as the temperature of added hot water increased, but slightly decreased the elevated prostaglandin E2 induced by NMBA. These data confirmed that the drinking of hot beverages increased the risk of esophageal carcinogenesis, and may abolish the inhibitory effects of EGCG on esophageal tumorigenesis [14].

3.2 Green tea consumption and risk of esophageal cancer in humans

Given the thermal irritation of hot fluid including tea beverage to the esophagus, tea drinking, if consumed at high temperature, could cause damage to the esophageal epithelia and result in increased risk of esophageal cancer. In early 1970 s, epidemiological studies already suggested a link between tea consumed at high temperature and increased risk of esophageal cancer in humans [15]. In 1974, De Jong et al. reported that subjects who drank burning tea had statistically significant almost three times the risk of esophageal cancer that of non-drinkers [16]. Results on tea drinking and esophageal cancer risk from epidemiological studies with vigor in study design became available since 1990 s. In a case–control study in Shanghai, China, Gao et al. found that the consumption of burning-hot fluid (including green tea) was associated with statistically significantly fourfold increased risk of esophageal cancer compared with green tea drinkers who did not consumed burning-hot fluid [17]. In a similar study, Wu et al. examined the effect of green tea temperature on risk of esophageal cancer in Jiangsu Province, China, a high incidence area of esophageal cancer. Compared with non-drinkers, high tea temperature was associated with statistically significant two to threefold increased risk of esophageal cancer [18]. In a prospective cohort of more than 220 000 Japanese men and women with 15 y of follow-up, individuals who usually drank green tea at high temperature had a statistically significant 60% higher mortality of esophageal cancer than those who consumed green tea at moderate temperature [19]. In a systemic review, Islami et al. examined the consumption of high-temperature beverages (coffee, tea, and maté) in relation to risk of esophageal cancer [20]. Majority of the studies included showed an increased risk of esophageal cancer with high temperature of beverages consumed regardless of the type of beverages.

Of the 12 studies included in the systemic review, 8 reported a statistically significantly elevated risk and one reported non-significant increase in risk of esophageal cancer associated with very hot tea intake. Two studies reported a decreased risk with hot tea drinking, but both were not statistically significant. The remaining one reported a null association between high-temperature tea intake and risk of esophageal cancer. These findings have clearly demonstrated the thermal effect of tea beverage on esophageal carcinogenesis.

Despite the thermal carcinogenic effect of tea beverage, a number of epidemiologic studies have examined the potential protective effect of green tea consumption on risk of esophageal cancer. In most of those studies, the tea temperature was not assessed, thus was not adjusted for. Table 1 lists 15 epidemiological studies that examined the association between green tea intake. Thirteen studies were carried out in Chinese populations (10 in mainland China, 2 in Taiwan, and 1 in Singapore) and two in Japanese (both in Japan). Among the 15 studies, six reported a statistically significantly reduced risk of esophageal cancer associated with high level of tea consumption [17, 21–25]. Four studies reported a lower risk with green tea consumption for drinkers than non-drinkers, but the risk reduction was not statistically significant [26–29]. Three studies reported a statistically significantly positive association between tea consumption and esophageal cancer risk [18, 30, 31]. The remaining two studies reported a relative risk that was close to one [16, 32]. The inconsistent results of those studies could be, at least partly, due to the potential confounding effect of tea temperature. For example, a recent report from a population-based, large case–control study of esophageal cancer in Jiangsu Province, China, demonstrated that the elevated risk of esophageal cancer associated with green tea consumption was reduced considerably and some of the ORs became statistically non-significant after tea temperature was adjusted for, especially among current tea drinkers [18].

Cigarette smoking and alcohol drinking, the two established risk factors for esophageal cancer, might further complicate the association between green tea consumption and esophageal cancer risk because green tea consumers are more likely to smoke cigarettes and drink alcoholic beverages. For example, in a prospective study of more than 18 000 middle-aged or older Chinese men in Shanghai, China [33], 77% of men who smoked cigarettes and drank alcoholic beverages consumed green tea on a daily basis. In contrast, only 44% of men who neither smoked cigarettes nor drank alcoholic beverages consumed the similar amount of green tea (unpublished data). Gao et al. carried out a large, population-based case–control study of esophageal cancer in Shanghai, China [17]. The study included more than 900 patients with recently diagnosed esophageal cancer and more than 1500 healthy control subjects. A statistically significantly reduced risk of esophageal cancer associated with green tea consumption was observed for women (odds ratio (OR) = 0.50; 95% confidence interval (CI) = 0.30–0.83), and the inverse green tea-risk association was dose dependent. However, the same study did not demonstrate a statistically significant inverse association between green tea intake and esophageal cancer risk for men (OR = 0.80; 95% CI = 0.58–1.09). This gender difference in green tea–esophageal cancer association could be due to the residual confounding effect of smoking and alcohol drinking because Chinese men consumed greater amounts of tobacco and alcohol than their female counterparts. When data were analyzed separately for those who neither smoked cigarettes nor drank alcoholic beverages, a statistically significant decreased risk of esophageal cancer for green tea consumption was observed in both men (OR = 0.43; 95% CI = 0.22–0.86) and women (OR = 0.40; 95% CI = 0.20–0.77). Similarly, the study by Wu et al. demonstrated a statistically significantly inverse association between green tea consumption and the risk of esophageal cancer among never smokers (OR = 0.7, 95% CI = 0.5–0.9) or non-drinkers of alcoholic beverages (OR = 0.8, 95% CI = 0.6–1.1), but not in smokers or alcohol drinkers [18]. These findings suggested that the residual confounding of cigarette smoking and alcohol intake might exist and mask the potential protective effect of green tea consumption against the risk of developing esophageal cancer even after they were adjusted for in the statistical regression models. It also is possible that the moderate protective effect of green tea consumption on esophageal cancer could be cancelled out by the strong adverse effects of cigarette smoking and alcohol consumption on the esophagus.

Data on green tea consumption and risk of specific histological types of esophageal cancer are scarce. Three epidemiological studies have examined the effect of green tea consumption on the risk of esophageal squamous carcinoma, the dominant histological type of esophageal cancer in high-risk area. A population-based case–control study involved 107 patients with esophageal squamous cell carcinoma and an equal number of sex- and age-matched control subjects in Jiangsu Province, China, reported that regular green intake was associated with a statistically significantly reduced risk of esophageal carcinoma (multivariate-adjusted OR = 0.13, 95% CI = 0.03–0.62, $p = 0.01$) compared with no consumption of green tea [24]. A similar study involved 355 patients with esophageal squamous cell cancer and 408 healthy control subjects living in a different county of Jiangsu Province from those of the previous study found a similar protection (OR = 0.26, 95% CI = 0.07–0.94) for women, but not for men [29]. As a matter of fact, the slightly increased risk of esophageal squamous cell carcinoma among men who consumed green tea regularly was due to the confounding effect of cigarette smoking and alcohol intake that were not adjusted for. A more recent study in Taiwan confirmed these findings; OR of esophageal squamous cell carcinoma for the consumption of ≥ 7 cups per week was 0.4 (95% CI = 0.2–0.6) compared with < 1 cup per week after adjustment for smoking and alcohol intake

Table 1. A summary of studies on the association between green tea consumption and risk of esophageal cancer

Author [reference] (country, years of study period)	Type of study design (no. of cases/controls or cases/cohort participants or person-years)	Green tea drinking: status, frequency, duration or amount by tea temperature, if available	Estimates of RR[a] (95% CI)	Comments
De Long et al. [16] (Singapore Chinese, 1970–1972)	Hospital-based case–control (total 131/665, ♂95/465, ♀36/200)	♂Drinking frequency		(i) Green tea was not explicitly stated
		Not daily	1.00	(ii) Controls were individually matched for age and sex
		Daily	0.99 (NS/NR)	(iii) Nearly, 82% of cases were histologically confirmed EC; all were ESCC
		Burning hot		(iv) Results were adjusted for dialect group
		No	1.00	
		Yes	2.96 ($p<0.01$)	
		♀Drinking frequency		
		Not daily	1.00	
		Daily	0.82 (NS/NR)	
		Burning hot		
		No	1.00	
		Yes	2.28 (NS/NR)	
Tao et al. [26] (China, 1984–1988)	Population-based case–control within a cohort (♂71/1122)	Drinking frequency		(i) Controls were 1% of total non-cancer all male cohort members
		<1 cup/day	1.00	(ii) EC diagnosis method was not reported
		≥1 cup/day	0.70 (0.39–1.25)	(iii) Results were adjusted for age, education, medical history, occupational history, pesticide exposure, lifestyle factors, dietary habits, and monthly food expenses
Hu et al. [30] (China, 1985–1989)	Hospital-based case–control (total 196/392, ♂170/340, ♀26/52)	Amount of tea		(i) Controls were individually matched for age, sex, and area of residence
		Non-drinker	1.0	(ii) All cases were histologically confirmed EC; % of ESCC was not reported
		50–1500 g/y	1.2 (0.7–2.1)	
		1501–3000 g/y	1.8 (1.04–3.3)	(iii) The matched results were adjusted for tobacco and alcohol use, income, and occupation
		3000+ g/y	3.9 (1.7–9.1)	
			($p_{trend}<0.001$)	
		Strength of tea		
		Non-drinker	1.0	
		Weak	0.8 (0.3–2.0)	
		Medium	1.1 (0.6–1.9)	
		Strong	2.5 (1.4–4.3)	
			($p_{trend}=0.005$)	
Gao et al. [17] (China, 1986–1993)	Population-based case–control (total 902/1552, ♂417/654, ♀242/658, ♂never smokers and never alcohol drinkers 69/192, ♀never smokers and never alcohol drinkers 184/564)	♂Amount of tea		(i) Controls were frequency matched to cases of gastrointestinal cancer cases
		Non-tea drinker	1.00	(ii) 81% of cases were histologically confirmed EC; 83% of confirmed EC cases were ESCC
		Tea drinker	0.80 (0.58–1.09)	(iii) Results were adjusted for age, education, birthplace and tobacco and alcohol use
		1–199 g/month	0.79 (0.53–1.17)	
		200+ g/month	0.79 (0.56–1.13)	
			($p_{trend}=0.20$)	
		♂Burning hot fluid and tea intake		
		No and non-tea drinker	1.00	
		Yes and non-tea drinker	4.80 (2.85–8.08)	
		No and tea drinker	0.88 (0.61–1.29)	
		Yes and tea drinker	3.09 (1.94–4.93)	

Table 1. Continued

Author [reference] (country, years of study period)	Type of study design (no. of cases/controls or cases/cohort participants or person-years)	Green tea drinking: status, frequency, duration or amount by tea temperature, if available	Estimates of RR[a] (95% CI)	Comments
		♀Amount of tea		
		Non-tea drinker	1.00	
		Tea drinker	0.50 (0.30–0.83)	
		1–149 g/month	0.77 (0.48–1.11)	
		≥150 g/month	0.34 (0.17–0.69)	
		♀Burning hot fluid and tea intake	(p_{trend} < 0.01)	
		No and non-tea drinker	1.00	
		Yes and non-tea drinker	4.78 (2.89–7.90)	
		No and tea drinker	0.50 (0.27–0.91)	
		Yes and tea drinker	2.00 (0.75–5.07)	
		Never smokers and never drinkers		
		♂Amount of tea		
		Non-tea drinker	1.00	
		Tea drinker	0.43 (0.22–0.86)	
		1–199 g/month	0.33 (0.14–0.80)	
		≥200 g/month	0.62 (0.25–1.54)	
		♀Amount of tea	(p_{trend} = 0.05)	
		Non-tea drinker	1.00	
		Tea drinker	0.40 (0.20–0.77)	
		1–149 g/month	0.70 (0.31–1.58)	
		≥150 g/month	0.17 (0.05–0.58)	
			(p_{trend} < 0.001)	
Inoue et al. [32] (Japan, 1990–1995)	Hospital-based case–control (total 185/21 128, ♂161/6307 ♀24/14 821)	Drinking frequency		(i) Controls were outpatients of 40 y or older without a history of cancer and were not matched for any factors
		Rarely	1.00	
		Occasionally	1.02 (0.50–2.10)	
		1–3 cups/day	1.07 (0.58–2.00)	(ii) All cases were histologically confirmed EC; % of ESCC was not reported
		4–6 cups/day	0.96 (0.50–1.83)	
		≥7 cups/day	1.14 (0.55–2.34)	(iii) Results were adjusted for age, sex, year, and season at first hospital visit, tobacco and alcohol use, regular physical exercise, and intakes of coffee, black tea, fruit, rice and beef
			(p_{trend} = NS/NR)	
Gao et al. [21] (China, 1995)	Population-based case–control (total 81/234, ♂44/154, ♀ 37/80)	Amount of tea		(i) Controls were individually matched for age, sex, and neighborhood of residence
		Non-drinker	1.00	
		1–199 g/month	0.63 (0.28–1.42)	(ii) All cases were histologically confirmed EC.
		≥200 g/month	0.42 (0.19–0.95)	(iii) Results were adjusted for age and sex
			(p_{trend} = NR)	
Ishikawa et al. [31] (Japan, 1984–1997)	Prospective cohort (♂78/196 686 person-years)	Drinking frequency		(i) Controls were all non-cancer members of the two cohorts
		Never/occasionally	1.00	
		1–2 cups/day	1.03 (0.46–2.28)	(ii) EC diagnosis method was not reported
		3–4 cups/day	1.13 (0.53–2.42)	(iii) Results were adjusted for age, tobacco and alcohol use, and coffee and black tea intake
		5+cups/day	1.67 (0.89–3.16)	
			(p_{trend} = 0.04)	
Takezaki et al. [27] (China, 1995–2000)	Hospital-based case–control (total 199/333, ♂150/235, ♀49/98)	Amount of tea		(i) Controls were not matched to cases and were chosen from neighborhood of cases
		Non-drinker	1.00	

Table 1. Continued

Author [reference] (country, years of study period)	Type of study design (no. of cases/controls or cases/cohort participants or person-years)	Green tea drinking: status, frequency, duration or amount by tea temperature, if available	Estimates of RR[a] (95% CI)	Comments
		1–149 g/month	0.73 (0.44–1.22)	(ii) All cases were histologically confirmed; % of ESCC was not reported
		≥150 g/month	0.64 (0.36–1.15)	(iii) Results were adjusted for age, sex, and tobacco, and alcohol use
			(p_{trend} = NR)	
Gao et al. [22] (China, 1998–2000)	Hospital-based case–control (total 141/223, ♂78/149, ♀ 63/74)	Amount of tea		(i) Controls were individually matched to cases of esophageal and stomach cancer for age, sex, and neighborhood
		Non-drinker	1.00	(ii) All cases were histologically confirmed EC; % of ESCC was not reported
		≥1 g/month	0.45 (0.26–0.78)	(iii) Results were adjusted for age, sex, smoking, alcohol drinking, raw vegetables, pickled vegetables, meat, soybean products, *GSTM1* genotype and *GSTT1* genotype
Hung et al. [23] (Taiwan, 1996–2002)	Hospital-based case–control (♂365/532)	Drinking frequency (age 20–40 yr)		(i) Only male participants; controls were individually matched for age and date of hospitalization
		<1 time/wk	1.0	(ii) All cases were histologically confirmed ESCC
		1–6 times/wk	1.0 (0.5–1.7)	(iii) Results were adjusted for age, level of education, ethnicity, hospital location, tobacco and alcohol use, and areca nut chewing
		≥7 times/wk	0.7 (0.4–1.1)	
		Drinking frequency (age 40+y)		
		<1 time/wk	1.0	
		1–6 times/wk	0.7 (0.4–1.2)	
		≥7 times/wk	0.5 (0.3–0.8)	
Wang et al. [24] (China, 2002–2003)	Population-based case–control (total 107/107, ♂60/60, ♀47/47)	Drinking status		(i) Controls were individually matched for age, sex, and residency
		Non-drinker	1.00	(ii) All cases were ESCC, confirmed by endoscopy, X-ray, or clinical pathology
		Drinker	0.13 (0.03–0.62)	(iii) Matched results were adjusted for family history of cancer, esophageal lesions, eating fast, regular cleanup of food storage utensils, and serology of *H. pylori* infection
Yang et al. [28] (China, 2003–2004)	Hospital-based case–control (total 185/185, ♂119/119, ♀66/66)	Drinking frequency	1.00	(i) Controls were individually matched for age and sex and were chosen from the same town where case patients resided
		≤1 time/wk	0.45 (0.15–1.36)	(ii) All cases were histologically confirmed EC; 97% were ESCC
		2–4 times/wk	0.57 (0.25–1.31)	(iii) Matched results were adjusted for family history of EC, occupation, tobacco and alcohol use, water supply, eating speed, and intakes of eggs, fruit and vegetables, pickled vegetables, fresh and processed meats
		≥5 times/wk	(p_{trend} = 0.20)	

Table 1. Continued

Author [reference] (country, years of study period)	Type of study design (no. of cases/controls or cases/cohort participants or person-years)	Green tea drinking: status, frequency, duration or amount by tea temperature, if available	Estimates of RR[a] (95% CI)	Comments
Wang et al. [29] (China, 2004–2006)	Population-based case–control (total 355/408, ♂223/252, ♀132/156)	♂Drinking years		(i) Controls were frequency matched for age and sex
		Non-drinker	1.00	(ii) All cases were histologically confirmed ESCC
		Drinker	1.37 (0.95–1.98)	(iii) Results were adjusted for age, marital status, and education
		<30 y	1.31 (0.85–2.03)	
		30+years	1.44 (0.91–2.27)	
		♀Drinking years		
		Non-drinker	1.00	
		Drinker	0.26 (0.07–0.94)	
		<30 y	0.33 (0.06–1.68)	
		30+years	0.18 (0.02–1.54)	
Chen et al. [25] (Taiwan, 1996–2005)	Hospital-based case–control (343/755)	Drinking frequency		(i) Among tea drinkers of controls, 70% drank unfermented tea only (i.e., green tea), 4% drank fermented tea only (black tea), and 26% drank both fermented and unfermented tea
		<1 time/wk	1.0	(ii) Controls were male patients of the same hospital and individually matched for age
		1–6 times/wk	0.5 (0.3–0.8)	(iii) All cases were histologically confirmed ESCC
		≥7 times/wk	0.4 (0.2–0.6)	(iv) Results were adjusted for age, level of education, ethnicity, source of hospital, tobacco and alcohol use, and areca nut chewing.
		Tea type	(p_{trend} = 0.005)	
		Non-drinker	1.0	
		Fermented tea only	1.2 (0.3–5.1)	
		Unfermented tea only	0.5 (0.3–0.8)	
		Mixed	0.5 (0.3–1.0)	
Wu et al. [18] (China, 2003–2007)	Population-based case–control (total 1520/3879, high-risk area 637/1938, low-risk area 883/1941, ♂1191/2916, ♀329/963; high-risk)	*High-risk area*		(i) Controls were frequency matched for age, sex, and county of residence
		Drinking status		(ii) Nearly, 61% of cases in high-risk area and 30% of cases in low-risk area were histologically confirmed EC; the remaining cases were diagnosed with endoscopy or X-ray
		Never drinker	1.0	
		Ever drinker	1.0 (0.7–1.3)	
		Former drinker	2.2 (1.6–5.3)	
		Current drinker	0.8 (0.6–1.1)	
		Tea temperature		(iii) Results were adjusted for age, gender, level of education, household income of 10 years before, family history of cancer, body mass index, tobacco and alcohol use, and tea temperature. The multivariate-adjusted association between age at starting to drink green tea regularly or number of years of tea drinking and risk of esophageal cancer was null
		Never drinker	1.0	
		Normal temperature	1.0 (0.7–1.3)	
		High temperature	1.9 (1.2–2.9)	
		Amount of tea		
		Never drinker	1.0	
		1–149 g/month	1.0 (0.7–1.3)	
		150–249 g/month	1.0 (0.6–1.8)	
		≥250 g/month	1.0 (0.6–2.0)	
		Low-risk area	(p_{trend} = 0.93)	
		Drinking status		
		Never drinker	1.0	
		Ever drinker	1.3 (0.9–1.7)	
		Former drinker	4.2 (2.3–7.6)	
		Current drinker	1.1 (0.8–1.5)	

Table 1. Continued

Author [reference] (country, years of study period)	Type of study design (no. of cases/controls or cases/cohort participants or person-years)	Green tea drinking: status, frequency, duration or amount by tea temperature, if available	Estimates of RR[a] (95% CI)	Comments
		Tea temperature		
		Never drinker	1.0	
		Normal temperature	1.3 (0.9–1.7)	
		High temperature	3.1 (2.2–4.3)	
		Amount of tea		
		Never drinker	1	
		1–149 g/month	1.1 (0.7–1.7)	
		150–249 g/month	1.0 (0.7–1.6)	
		≥ 250 g/month	1.6 (1.1–2.2) (p_{trend} = 0.014)	

a) Estimates of RR included odds ratio from case–control studies, or rate ratios and hazard ratios from cohort studies; ♂ Male; ♀ Female; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; NR, not reported.

[25]. There have been no studies that examined the association between green tea consumption and risk of esophageal adenocarcinoma. Data from studies that examine the association between green tea consumption and the risks of both esophageal squamous cell carcinoma and adenocarcinoma, respectively, are needed to show whether green tea consumption has differential effect on different histological type of esophageal cancer.

Epidemiologic studies of specific tea catechins in relation to the risk of esophageal cancer in humans are sparse. Sun et al. carried out a nested case–control study within the Shanghai Cohort Study, a prospective cohort of more than 18 000 men aged 45–64 y in 1986–1989 when subjects were recruited and information on dietary and lifestyle factors and blood and urine samples were collected. Using validated urinary biomarkers for tea polyphenol uptake and metabolism, the investigators demonstrated a decreased risk for both esophageal and gastric cancers for the presence of EGC in urine. The inverse association was stronger in non-smokers or non-drinkers of alcohol or among those with lower serum level of carotenes (OR = 0.46, 95% CI = 0.26–0.84) [34]. More population-based studies are warranted to confirm those findings.

There has been one report on an intervention study that examined the effect of decaffeinated green tea (DGT) on the inhibition of progression of esophageal precancerous lesions in a high-risk population in northern China [35]. Two hundred patients with different severities of esophageal precancerous lesions were randomly assigned with equal likelihood to the treatment (given 5 mg DGT per day for 12 months) or placebo arm (given a placebo pill). At the beginning and the end of the treatment, esophageal biopsy specimens were taken at the middle and the lower thirds of the esophagus of each subject. Sixteen (25%) of the 63 patients in the DGT group who completed the study with evaluable biopsy specimens showed improvement of disease lesions in the middle-third esophagus while only did 9 (13%) of 71 patients in the placebo group. However, the difference was not statistically significant ($p = 0.12$). The distributions of lesions by severity in the low-third esophagus were comparable in the DGT and placebo group at the end of the study. The conclusion of this intervention study was that treatment with DGT had no effect on the alleviation of esophageal precancerous lesions and abnormal cell proliferation [35].

4 Green tea and lung cancer prevention

Lung cancer is the most common cancer in terms of incidence and mortality among all cancers worldwide. Approximately, 1.35 million people develop lung cancer and 1.18 million people die from the malignancy very year [36]. Lung cancer also is the leading cancer in terms of incidence and mortality among all cancers in the United States [37]. Although tobacco smoking is the single most important risk

factor for lung cancer [38], only a fraction of lifelong smokers develop lung cancer over their lifetime [39]. Other lifestyle factors including tea drinking may contribute, at least partly, to this inter-individual variation in smoking-related lung cancer risk. Numerous experimental and epidemiological studies have been carried out to examine the potential lung cancer-preventive effect of green tea and tea polyphenols.

4.1 Inhibition of lung tumorigenesis in experimental animals

Several experimental studies have examined the cancer-inhibitory effect of green tea polyphenols or EGCG during the initiation and promotion stages of 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-1butanone (NNK) or benzo(a)pyrene (B[a]P) induced lung tumorigenesis in rodents. Treatment of female A/J mice with a single dose of NNK (103 mg/kg) resulted in the formation of pulmonary adenomas in almost all of the animals with an average of 9.3 tumors per mouse after 16 wk. When 0.6% decaffeinated green tea was given during the NNK-treatment period, tumor incidence and multiplicity were reduced by approximately 20 and 65%, respectively. When the green tea extract was given after the NNK-treatment period until the end of the experiment, green tea extract decreased the tumor incidence and multiplicity by approximately 30 and 85%, respectively [40]. This was the first study that demonstrated an inhibitory action of green tea extracts on nitrosamine-induced lung tumorigenesis during the initiation and promotion stage of tumorigenesis. In a similar study, mice were treated with a single dose of NNK and kept for 20 wk to allow lung adenomas to develop, and then given 0.5% polyphenon E (PPE), a standardized green tea polyphenol preparation that contains 65% EGCG, 7% ECG, 3% EGC, 9% EC, 3% gallocatechin gallate, and $>0.5\%$ caffeine, in their drinking fluid until week 52 when the experiment ended. The PPE treatment significantly reduced the progression of lung adenomas to adenocarcinomas; the incidence of lung adenocarcinoma was reduced by 52% and multiplicity by 63% [41].

Besides drinking fluid, aerosol inhalation can deliver chemopreventive agents directly to the respiratory tract to inhibit the tumorigenic process. In the study by Yan et al. [42], PPE and EGCG were administered by aerosol delivery to A/J mice beginning 2 wk after the treatment of carcinogen, B[a]P, and continuing daily by inhalation throughout the remainder of the total study period (20 wk). PPE decreased tumor load by approximately 59%. However, EGCG failed to inhibit lung carcinogenesis. In a follow-up experiment by the same group [43], regular PPE and PPE without EGCG were administered by aerosol delivery to mice. Regular PPE decreased tumor multiplicity by 53%, whereas PPE without EGCG at the same dose failed to inhibit lung carcinogenesis. These results indicate that both EGCG and other compounds present in PPE are essential for the inhibitory effect of green tea polyphenols against the B(a)P-induced lung tumorigenesis in mice [43].

Tea polyphenols, in combination with other agents, may enhance its cancer-preventive activity. In a recent study, for example, Lu et al. demonstrated a synergistic inhibitory action of a combination of PPE and the lipid-lowering agent atorvastatin (trade name Lipitor) against NNK-induced lung carcinogenesis in mice [44]. Female A/J mice were given NNK (150 mg/kg total dose) and 1 wk later, treated for 16 wk with PPE (0.25 or 0.5% in drinking fluid) alone, atorvastatin (200 or 400 ppm in diet) alone, or PPE (0.25%) plus atorvastatin (200 ppm). Either PPE alone or atorvastatin alone did not show inhibitory effect on lung tumorigenesis, whereas the combination of PPE and atorvastatin significantly reduced both the tumor multiplicity and tumor burden by 56 and 55%, respectively ($p<0.05$). The possible synergistic actions between PPE and atorvastatin in humans warrant future investigation.

4.2 Green tea consumption and risk of lung cancer in humans

Epidemiological studies that examined the association between green tea consumption and lung cancer risk are limited. Table 2 lists 12 epidemiological studies that examined the association between intake of green tea or tea polyphenols and the risk of lung cancer. Five studies were carried out in Japan, four in China, two in the United States, and one in Czech. Among the 12 studies, five studies found a statistically significant inverse association between green tea intake or dietary tea catechins and lung cancer risk in the entire study population or in the subset of the study subjects [45–49]. Three studies reported a lower risk of lung cancer in green tea drinkers than non-drinkers, but the risk reduction was not statistically significant [50–52]. One study reported a statistically significantly increased risk for lung cancer in green tea drinkers than non-drinkers [53]. One study reported a positive but statistically non-significant association between green tea intake and lung cancer risk [54]. The remaining two studies reported a relative risk that was close to one [55, 56]. The inconsistent results of those studies could be, at least partly, due to the potential confounding effect of smoking. For example, Zhong et al. examined the association between consumption of green tea and the risk of lung cancer in Chinese women living in Shanghai, China [47]. The study enrolled 649 incident lung cancer cases and 675 healthy controls. Among non-smoking women, regular tea drinkers experienced a statistically significant 35% risk reduction for lung cancer compared with their counterparts who did not drink tea regularly (OR = 0.65, 95% CI = 0.45–0.93), and the inverse relation was dose dependent. On the other hand, there was no association between green tea intake and lung cancer risk among smokers.

In a recent meta-analysis, Tang et al. reported a summary relative risk of lung cancer associated with green tea intake

Table 2. A summary of studies on the association between green tea consumption and risk of lung cancer

Author [reference] (country, years of study period)	Type of study design (no. of cases/controls or cases/cohort participants or person-years)	Green tea drinking: status, frequency, duration or amount by tea temperature, if available	Estimates of RR[a] (95% CI)	Comments
Tewes et al. [53] (China, 1981–1983)	Hospital-based case–control (♀200/200)	Drinking status Non-daily drinker Daily drinker	 1.00 2.74 (1.10–6.80)	(i) Study subjects were women; controls were individually matched for age and residence (ii) The diagnosis method of cases was not reported (iii) Results were adjusted for age, number of live births, level of education, use of tobacco and alcohol, consumption frequency of fresh vegetables and fruit
Ohno et al. [45] (Japan, 1988–1991)	Hospital-based cases and community controls (total 333/666, ♂245/490, ♀88/176)	Drinking frequency of Okinawa tea ♂Drinking frequency Non-daily drinker 1–4 cups/day 5–9 cups/day ≥10 cups/day ♀Drinking frequency Non-daily drinker 1–4 cups/day 5–9 cups/day ≥10 cups/day	 1.00 0.85 (0.45–1.55) 0.85 (0.45–1.56) 0.57 (0.31–1.06) (p_{trend} = 0.053) 1.0 0.77 (0.28–2.13) 0.77 (0.26–2.25) 0.38 (0.12–1.18) (p_{trend} = 0.032)	(i) Okinawa tea is partially fermented tea (ii) Two controls were matched to one case for age, sex, and residence (iii) All cases were histologically confirmed, 40% squamous cell carcinoma, 50% adenocarcinoma, 8% small cell cancer, and 2% other types of lung cancer (iv) Matched results were adjusted for education, smoking, family history of lung cancer, medical history of lung disease, and intake frequency of green-yellow vegetables; the inverse association for tea intake was stronger for squamous cell carcinoma, daily tea drinkers had an OR of 0.50 (95% = 0.27–0.93) for men and an OR of 0.08 (95% CI = 0.01–0.68) for women, as compared with non-daily drinkers
Xu et al. [46] (China, 1987–1993)	Hospital-based cases and employee-based controls (♂610/959)	Drinking frequency Rarely Sometime Daily	 1.0 0.8 (0.5–1.1) 0.5 (0.4–0.6) (p_{trend} = NR)	(i) Study subjects were all male workers in an iron-steel company. Matching criteria were not reported (ii) The diagnosis method of cases was not reported (iii) Results were adjusted for year of birth, level of education, income, cigarette smoking, fruit consumption, pulmonary disease, and family history of cancer
Nagano et al. [50] (Japan, 1979–1994)	Prospective cohort (436/38540)	Drinking frequency 0–1 time/day 2–4 times/day ≥5 times/day	 1.00 0.78 (0.60–1.00) 0.79 (0.45–1.40) (p_{trend} = 0.21)	(i) Cases were identified from the cancer registry (ii) The diagnosis method of cases was not reported (iii) Results were adjusted for age, sex, city, level of education, calendar time, body mass index, radiation dose, smoking status, and drinking history
Zhong et al. [47] (China, 1992–1994)	Population-based case–control (♀649/675, non-smokers 504/601, smokers 145/74)	*Non-smokers* Amount of tea Non-drinker Regular drinkers 1–500 g/y 501–1500 g/y ≥1501 g/y *Smokers* Amount of tea Non-drinker Regular drinkers 1–1500 g/y ≥1501 g/y	 1.00 0.65 (0.45–0.93) 0.80 (0.45–1.42) 0.62 (0.36–1.08) 0.46 (0.22–0.96) 1.00 0.94 (0.40–2.22) 1.43 (0.47–4.35) 0.62 (0.21–1.82)	(i) All study subjects were women; controls were frequency matched for age (ii) Nearly, 72.9% of lung cancer cases were histologically or cytologically confirmed; 70% of histologically or cystologically confirmed cases were adenocarcinoma, 17.5% squamous cell carcinoma, and remaining 12.5% small cell carcinoma, large-cell carcinoma or mixed cell carcinoma (iii) Results were adjusted for age, income, number of years of exposure to environmental tobacco smoke at work, high-risk occupation, family history of lung cancer, intake of dietary vitamin C, cooking food at high temperature, and respondent status

Table 2. Continued

Author [reference] (country, years of study period)	Type of study design (no. of cases/ controls or cases/cohort participants or person-years)	Green tea drinking: status, frequency, duration or amount by tea temperature, if available	Estimates of RR[a] (95% CI)	Comments
Bonner et al. [48] (China, 1995–1996)	Population-based case–control (total 122/ 122, ♂79/78, ♀43/43)	*Total subjects* Drinking frequency Non-drinker 2–3 times/wk ≥1 time/day *OGG1 (Ser/Ser)* Drinking frequency Non-drinker 2–3 times/wk ≥1 time/day *OGG1 (Ser/Cys+Cys/Cys)* Drinking frequency Non-drinker 2–3 times/wk ≥1 time/day *GSTM1 carriers* Drinking frequency Non-drinker 2–3 times/wk ≥1 time/day *GSTM1 null* Drinking frequency Non-drinker 2–3 times/wk ≥1 time/day	 1.00 0.84 (0.38–1.85) 0.59 (0.26–1.37) (p_{trend} = 0.20) 1.00 1.18 (0.28–5.04) 1.53 (0.38–6.25) (p_{trend} = 0.53) 1.00 0.48 (0.15–1.54) 0.28 (0.09–0.94) (p_{trend} = 0.04) 1.00 1.46 (0.40–5.35) 1.67 (0.47–5.88) (p_{trend} = 0.45) 1.00 0.63 (0.21–1.87) 0.36 (0.12–1.13) (p_{trend} = 0.08)	(i) Controls were individually matched for age and sex, village of residence, and type of fuel for cooking and home heating (ii) Nearly, 86% of lung cancer cases were histologically or cytologically confirmed. The number of cases by histological type of lung cancer was not reported (iii) Matched results were adjusted for pack-years of smoking
Takezakie et al. [51] (Japan, 1988–1997)	Hospital-based case–control (total 1045/ 4153, ♂748/2964, ♀297/1189)	♂Drinking frequency <1 cup/day 1–3 cups/day 4–6 cups/day ≥7 cups/day ♀Drinking frequency <1 cup/day 1–3 cups/day 4–6 cups/day ≥7 cups/day ♂Drinking frequency <1 cup/day 1–3 cups/day 4–6 cups/day ≥7 cups/day ♀Drinking frequency	*Adenocarcinoma* 1.00 1.06 (0.72–1.57) 1.11 (0.74–1.66) 1.33 (0.83–2.18) (p_{trend} = 0.25) 1.00 0.98 (0.58–1.66) 1.14 (0.68–1.93) 1.14 (0.61–2.12) (p_{trend} = 0.46) *SCC* 1.00 0.99 (0.67–1.47) 1.17 (0.78–1.73) 1.08 (0.66–1.75) (p_{trend} = 0.44)	(i) Controls were outpatients with a history of cancer (ii) All cases were histologically confirmed; 58% adenocarcinoma and 42% squamous cell carcinoma (SCC) (iii) Results were adjusted for age, season and year of visit, occupation, prior lung diseases, cigarette smoking, and consumption of green vegetables and meat, and for women, exposure to environmental tobacco smoke from husband

Table 2. Continued

Author [reference] (country, years of study period)	Type of study design (no. of cases/ controls or cases/cohort participants or person-years)	Green tea drinking: status, frequency, duration or amount by tea temperature, if available	Estimates of RR[a] (95% CI)	Comments
		<1 cup/day	1.00	
		1–3 cups/day	0.36 (0.14–0.93)	
		4–6 cups/day	0.41 (0.16–1.04)	
		≥7 cups/day	0.49 (0.17–1.46)	
			(p_{trend} = 0.28)	
Le Marchand et al. [55] (USA, 1992–1997)	Population-based case–control (total 582/582, ♂375/375, ♀207/207)	Amount of tea beverage		(i) Controls were individually matched for sex, ethnicity and age
		1st quartile (0)	1.0	(ii) All cases were histologically confirmed; 43% adenocarcinoma, 23% squamous cell carcinoma, and 33% other cell type of lung cancer
		2nd quartile	1.0 (0.6–1.7)	
		3rd quartile	0.7 (0.4–1.3)	(iii) Matched results were adjusted for smoking status, cigarette smoking, and intakes of β-carotene and saturated fat
		4th quartile (>171.1 g/day)	0.9 (0.5–1.6)	
Li et al. [54] (Japan, 1995–2001)	Prospective cohort (total 302/257 276 person-years, ♂227/121 847 person-years, ♀75/135 429 person-years)	Drinking frequency		(i) Controls were all non-cancer cohort members
		<1 cup/day	1.00	(ii) The diagnosis method of cases was not reported
		1–2 cups/day	1.14 (0.80–1.62)	(iii) Results were adjusted for age, sex, level of education, marital status, passive smoking history, body mass index, number of hours of walking per day, family history of cancer, smoking status, number of cigarettes per day, years of smoking, alcohol drinking, total energy intake per day, and daily consumption of soybean products, total meat, total fish, dairy products, total fruits, and total vegetables, and coffee consumption
		3–4 cups/day	1.18 (083–1.66)	
		≥5 cups/day	1.17 (0.85–1.61)	
			(p_{trend} = 0.48)	
		♂Drinking frequency		
		<1 cup/day	1.00	
		1–2 cups/day	1.05 (0.70–1.57)	
		3–4 cups/day	1.21 (082–1.79)	
		≥5 cups/day	1.17 (0.82–1.68)	
			(p_{trend} = 0.32)	
		♀Drinking frequency		
		<1 cup/day	1.00	
		1–2 cups/day	1.48 (0.71–3.10)	
		3–4 cups/day	1.11 (052–2.37)	
		≥5 cups/day	1.30 (0.65–2.60)	
			(p_{trend} = 0.71)	
Khan et al. [52] (Japan, 1984–2002)	Prospective cohort (total 51/3158, ♂41/1524, ♀10/1634)	♂Drinking frequency		(i) Controls were all non-cancer cohort members
		Several times or less/month	1.0	(ii) Lung cancer death was the outcome measure
		Several times or more/wk	0.6 (0.3–1.2)	(iii) Results were adjusted for age and cigarette smoking; and for women, additional adjustment for health status, health education and health screening
		♀Drinking frequency		
		Several times or less/month	1.00	
		Several times or more/wk	0.7 (0.2–2.9)	
Cui et al. [49] (USA, 1999–2004)	Population-based case–control (total 558/837, smokers 462/447, non-smokers 96/390, ♂284/498, ♀274/339)	*Total subjects*		(i) Controls were frequency matched for age and sex
		Dietary epicatechin		(ii) All lung cancer cases were histologically confirmed
		<3 mg/day	1.00	(iii) Results were adjusted for age, sex, race/ethnicity, years of schooling, smoking status (for total subjects), pack-years of tobacco smoking (for total subjects and smokers), and daily energy intake.
		3–<6 mg/day	0.88 (0.63–1.20)	
		6–<9 mg/day	0.67 (0.45–0.99)	
		≥9 mg/day	0.66 (0.46–0.94)	
		Catechin	(p_{trend} = 0.007)	
		<1 mg/day	1.00	
		1–<2 mg/day	0.77 (0.54–1.11)	
		2–<3 mg/day	0.38 (0.25–0.57)	
		≥3 mg/day	0.54 (0.38–0.76)	
		Smokers	(p_{trend} = 0.0002)	

Table 2. Continued

Author [reference] (country, years of study period)	Type of study design (no. of cases/ controls or cases/cohort participants or person-years)	Green tea drinking: status, frequency, duration or amount by tea temperature, if available	Estimates of RR[a)] (95% CI)	Comments
		Dietary epicatechin		
		<3 mg/day	1.00	
		3–<6 mg/day	0.82 (0.54–1.20)	
		6–<9 mg/day	0.55 (0.34–0.89)	
		≥9 mg/day	0.61 (0.40–0.93)	
		Catechin	(p_{trend} = 0.007)	
		<1 mg/day	1.00	
		1–<2 mg/day	0.67 (0.43–1.00)	
		2–<3 mg/day	0.33 (0.20–0.55)	
		≥3 mg/day	0.44 (0.29–0.66)	
		Non-smokers	(p_{trend} < 0.0001)	
		Dietary epicatechin		
		<3 mg/day	1.00	
		3–<6 mg/day	1.10 (0.56–2.00)	
		6–<9 mg/day	1.10 (0.52–2.30)	
		≥9 mg/day	0.81 (0.40–1.60)	
		Catechin	(p_{trend} = 0.52)	
		<1 mg/day	1.00	
		1–<2 mg/day	1.10 (0.54–2.10)	
		2–<3 mg/day	0.44 (0.20–0.97)	
		≥3 mg/day	0.77 (0.39–1.50)	
			(p_{trend} = 0.41)	
Kubit et al. [56] (Czech, 1998–2006)	Hospital-based case–control (total 1096/ 2966, ♂509/788, ♀587/2178)	Drinking frequency		(i) Controls were spouses, relatives or friends of other patients admitted to the same hospital of the cases. Matching criteria were not reported
		♂Non-smokers		
		Non-drinker	1.00	(ii) All cases were histologically confirmed, 36% squamous cell carcinoma, 28% adenocarcinoma, 19% small cell cancer, and 17% other types of lung cancer
		Several times/wk or daily	1.08 (0.56–2.08)	
		♂Smokers		
		Non-drinker	1.00	(iii) Results were adjusted for age, residence, level of education and pack-years of smoking
		Several times/wk or daily	0.93 (0.63–1.38)	
		♀Non-smokers		
		Non-drinker	1.00	
		Several times/wk or daily	0.88 (0.61–1.27)	
		♀Smokers		
		Non-drinker	1.00	
		Several times/wk or daily	1.09 (0.80–1.49)	

a) Estimates of RR included odds ratio from case–control studies, rate ratios or hazard ratios from cohort studies; ♂Male; ♀ Female; NR, not reported; SCC, Sequence cell carcinoma.

was 0.78 (95% CI = 0.61–1.00). An increase in green tea consumption of two cups per day was associated with an 18% decreased risk of developing lung cancer (RR = 0.82, 95% CI = 0.71–0.96). This inverse green tea-lung cancer association was slightly stronger for prospective cohort studies (RR = 0.68, 95% CI = 0.45–1.02) than retrospective case–control studies (OR = 0.87, 95% CI = 0.65–1.17). The protective effect of green tea consumption on lung cancer risk was confined to non-smokers; the ORs for non-smokers and smokers were 0.77 (95% CI = 0.52–1.16) and 0.98 (95% CI = 0.75–1.29), respectively [57]. These findings, along with those described above, further suggest that cigarette smoking may confound or cancel out the potential protective effect of green tea against the development of lung cancer.

5 Mechanisms of anticarcinogenesis by green tea extracts and polyphenols

5.1 Antioxidation

One potential mechanism for the chemopreventive effect of green tea against carcinogenesis is its strong antioxidative property. Tea polyphenols are strong antioxidants and radical scavengers and metal chelators in model chemical systems. An increasing number of studies have demonstrated these antioxidative effects in vivo. For example, treatment of 24 month-old rats with EGCG decreased the hepatic levels of lipid peroxides by 50% and protein carbonyls by 39% [58]. EGCG treatment also increased the hepatic levels of both small molecule antioxidants and antioxidant enzymes compared to control rats. A second study by the same group found similar results in aged rats, but did not in young rats, suggesting that EGCG offered no improvement in antioxidant status in the absence of pre-existing oxidative stress [59]. In our biomarker study [34], a stronger protective effect of green tea catechins against the development of esophageal and gastric cancers for subjects deficient for other antioxidants (i.e. low serum carotenes) further supports the antioxidant hypothesis in the protective role of green tea polyphenols against the carcinogenesis.

In human experiments, both Schwartz et al. [60] and Hakim et al. [61] have shown that green tea treatment has antioxidant effects in smokers. In the former study, green tea total extract (400–500 mg per cup, five cups per day) was administered in drinking water to heavy smokers. Two oral cytology samples were taken weekly for measurements of tobacco carcinogen-induced DNA damage, including bulky adducts and oxidized bases, cell growth, DNA content, and apoptosis. The study showed that, during the course of green tea administration, smoking-induced DNA damage was decreased and cell growth was inhibited. Green tea extract reduced the levels of benzo[a]pyrene-7,8-dihydroxy-9,10-oxide-deoxyguanosine DNA adducts by 50% in oral cells collected from smokers at the end of the 4-wk study period compared to baseline. Tea treatment reduced the number of 8-hydroxy-2′-deoxyguanosine (8-OH-dG)-positive cells in smokers to a similar extent [60]. Hakim et al. carried out a phase II randomized controlled tea intervention trial to evaluate the efficacy of regular tea drinking in reducing DNA damage as measured by urinary 8-hydroxydeoxyguanosine among heavy smokers [61]. After consuming four cups of decaffeinated green tea per day for 4 months, smokers showed a statistically significant 31% decrease in urinary 8-OH-dG compared with the baseline value. In the same study, no change in urinary 8-OH-dG was seen among smokers assigned to the black tea group [61]. A more recent randomized phase II clinic trial demonstrated the similar results. Individuals with chronic hepatitis B and exposure to dietary aflatoxin given 500–1000 mg tea polyphenols per day for 3 months had 50% reduced urinary 8-OH-dG than those in the placebo arm [62]. These findings demonstrated the antioxidative property of green tea extract and green tea polyphenols in anticarcinogenesis.

5.2 Pro-oxidation

Although tea catechins are strong antioxidants, they can be oxidized to generate reactive oxidative species (ROS) and kill cells in certain conditions [63]. Pretreatment of esophageal squamous cell carcinoma KYSE 150 cells with EGCG before the addition of epidermal growth factor resulted in a decreased level of phosphorylated epidermal growth factor receptor (32–85% decrease) and epidermal growth factor receptor protein level (80% decrease). These effects of EGCG could be inhibited or diminished by the addition of superoxide dismutase to the cell culture medium. Under culture conditions for KYSE 150 cells, EGCG was unstable and the dimers and other oxidative products were formed. The presence of superoxide dismutase in the culture medium stabilized EGCG, and potentiated the activity of EGCG in inhibiting KYSE 150 cell growth [63]. These results suggest that in cell culture conditions, the auto-oxidation of EGCG exists and may lead to the inactivation of epidermal growth factor receptor-related signaling pathway.

5.3 Modulation of metabolic enzymes

Green tea treatment can increase the phase II enzymes in the detoxification pathway of environmental toxicants and carcinogenes. Treatment of female Wistar rats with 2% green tea solution for 4 wk was shown to increase cytosolic glutathione-*S*-transferase (GST) activity in the liver [64]. A later study with pure tea polyphenols, however, found no significant effect on hepatic GST activity in Wistar rats [65]. In humans, PPE treatment (800 mg/day for 4 wk) significantly enhanced the total GST activity and GST-pi level in blood lymphocytes. The enzyme induction effects of PPE were much stronger in individuals with low baseline

enzyme activity [66]. In the same randomized phase II clinic trial described above [62], PPE treatment increased urinary excretion of aflatoxin B mercapturic acid, a detoxification metabolite of dietary aflatoxin exposure (7–14-fold increase). These data from humans suggest the modulating effect of green tea polyphenols on metabolic enzymes.

5.4 Inhibition of cell proliferation and induction of angiogenesis

Vascular endothelial growth factor stimulates the initiation of angiogenesis, which provides nutrients for tumor growth. Several studies have shown the inhibitory activity of EGCG against angiogenesis. Treatment with green tea (0.6% green tea solid in drinking fluid) was shown to decrease vascular endothelial growth factor expression and suppression of angiogenesis in the NNK-induced lung tumorigenesis model [67]. In another experiment, Lu et al. [41] demonstrated that even after lung adenoma had formed, administration of PPE inhibited the progression of adenoma to adenocarcinoma. This inhibitory effect of PPE on tumor malignant transformation was closely associated with decreased cell proliferation (57% decrease) and enhanced apoptosis (fourfold increase). In humans, the administration of green tea extracts significantly reduced cell growth and increased markers of apoptosis in smokers [60].

6 Concluding remarks

The inhibitory activity of green tea extract and green tea polyphenols against the tumorigenesis has been demonstrated in different organ sites in animal models, but the active constitutes are not clearly understood. Many investigators believe EGCG is the active constituent, but recent data have suggested otherwise. EGCG alone was not shown the inhibitory effect on B(a)P-induced lung tumorigenesis in an animal model. Conversely, PPE without EGCG also lacks the antitumorigenic effect. These new findings have suggested the inter-dependence of green tea polyphenols present in PPE to exert their tumor-inhibitory effect. More studies are required to elucidate the mechanisms of cancer-preventive action of those tea polyphenols in PPE.

Although results from animal models support a protective effect of green tea extract and green tea polyphenols against tumorigenesis, the epidemiological studies have produced inconclusive results for green tea consumption in relation to risk of esophageal and lung cancers overall. Factors associated with green tea consumption may contribute to the inconsistent findings across different studies. The thermal carcinogenic effect of tea beverage certainly plays a role in confounding the association between green tea consumption and risk of esophageal cancers in studies that did not properly measure and controlled for the tea temperature. Cigarette smoking and alcohol intake also may contribute to the varying results across different populations. Biomarkers for the uptake and metabolism of tea polyphenols may overcome some of the limitations for the assessment of association between tea consumption and cancer risk since they are specific, objective and biologically relevant. More studies in different populations may help to demonstrate the usefulness of such biomarker approach in population-based studies.

Definite beneficial effects of green tea consumption against the development of esophageal and lung cancers in humans have to come from large intervention trials. Given the large cost and long time period required for a phase III clinical trial, phase II trial based on intermediate disease-risk markers may be feasible to provide critical data for us to understand the anticarcinogenic actions of green tea polyphenols in humans. Because the causative factors for cancers, in particular esophageal cancer, most likely differ across different populations, green tea consumption may affect carcinogenesis only in selected situations rather than having an abroad effect on the cancer in general populations. Thus, there is a need to define the population that could benefit from tea consumption. For example, previous clinical trials demonstrated a protective effect of vitamin–mineral supplementation on esophageal and gastric cancer in a Chinese population with marginally deficient antioxidant nutrients, but vitamin supplementation did not provide any cancer protection or even increased risk of certain cancer in Western populations with relatively high levels of antioxidant nutrients [68]. The protective effect of green tea consumption on esophageal and gastric cancer only in subjects with low background levels of other antioxidant nutrients [34] also support that green tea consumption may benefit to certain sub-populations at high risk for certain cancer. Such intervention studies in various populations may provide useful information on the protective effect of tea polyphenols on cancer of specific organs or in specific populations. Given that green tea is well tolerated and can be safely administered without any serious side effect, it may be possible to recommend consumption of tea polyphenols by humans after careful evaluation of additional well-designed epidemiologic studies and clinical trials.

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7 References

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