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Green Tea and Lung Cancer: A Systematic Review

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Abstract

Background: Green tea is a beverage widely used by lung cancer patients and the public for its purported anticancer properties. The authors conducted a systematic review of green tea for the treatment and prevention of lung cancer. *Methodology:* Six electronic databases were searched from inception until November 2011 for human interventional and preclinical evidence pertaining to the safety and efficacy of green tea for lung cancer. *Results:* A total of 84 articles met inclusion criteria: two Phase I trials, three reports of one surrogate study, and 79 preclinical studies. There is a lack of controlled trials investigating green tea for lung cancer. Two Phase I studies showed no objective tumor responses at the maximum tolerated dose, ranging from 3 to 4.2 g/m^2 green tea extract (GTE) per day. Four cups of green tea daily decreased DNA damage (8OH-dG) in smokers. Human studies indicate that 800mg of green tea catechins daily does not alter activity of the CYP2D6, CYP1A2, CYP3A4 and CYP2C9 enzymes, however *in vitro* evidence suggests that green tea may bind to and reduce the effectiveness of bortezomib. Green tea applied topically may improve the healing time of radiation burns. *Conclusions:* Although some evidence suggests that chemopreventative benefits can be accrued from green tea, there is currently insufficient evidence to support green tea as a treatment or preventative agent for lung cancer. Green tea should not be used by patients on bortezomib therapy. Further research is warranted to explore this natural agent for lung cancer treatment and prevention.

Keywords

Camellia sinensis, cancer, catechins, chemoprevention, complementary and alternative medicine, epigallocatechin gallate, green tea, herb-drug interactions, lung cancer, natural health products, systematic review

Introduction

Lung cancer is one of the most prevalent and fatal cancers, accounting for more than 150 000 deaths in 2010 for the United States alone.[1] Median survival for patients presenting with stage IIIB or IV disease is only 6 to 10 months.[2] In search of better outcomes, cancer patients frequently use natural health products. Up to 50% of cancer patients use some form of complementary and alternative medicine (CAM), and among lung cancer patients who do use CAM, up to 11.5% report taking medicinal teas specifically.[3,4] Green tea is popular among the public at large as a cancer prevention strategy; however, to date there has been no synthesis of current evidence regarding the safety and efficacy of green tea for use in the treatment and prevention of lung cancer.

Green tea is a beverage made from the leaves of *Camellia sinensis* that have undergone minimal oxidization and fermentation. Green tea has potent antioxidant activity, and green tea polyphenols (GTPs) are thought to be active in protecting against carcinogen-induced DNA damage as well as in promoting apoptosis of tumor cells and inhibiting angiogenesis.[5-8] Observational evidence has reproducibly documented an association between green tea consumption and reduced risk of cancer. Specifically, a recent meta-analysis of observational studies reported a trend toward reduced risk of lung cancer recurrence associated with higher intake of green tea.[9] No study, however, has comprehensively reviewed data from all levels of evidence, including intervention

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trials and preclinical evidence to assess the effects of green tea for lung cancer.

GTPs consist of the catechins: epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate, and epicatechin; EGCG is the major green tea catechin.[10] By dry weight, one 120-mL cup of green tea (~250-500 mg of dried green tea leaf[11,12]) typically contains 30% to 40% of total catechins and approximately 25 to 35 mg EGCG.[10-13] Green tea contains a variable amount of caffeine, ranging from 11 to 20 mg/g dry weight or approximately 2.5 to 10 mg per cup, depending on the method of preparation.[14] The relative amounts of green tea constituents also depend on geography, growth conditions, and method of preparation.

For therapeutic purposes, green tea is often administered as an encapsulated extract (green tea extract, GTE) and standardized to EGCG. In the products used for the studies reviewed here, concentrations ranged from 13.9% to 65% EGCG,[15,16] with composition up to 80% EGCG in other available products. Polyphenon E is a standardized GTP preparation containing 65% EGCG and has been extensively studied in lung cancer models as well as in preliminary human studies that are unrelated to lung cancer.[17]

To synthesize the evidence pertaining to the use of green tea/GTE in lung cancer, we conducted a systematic review of the safety and efficacy of green tea for the treatment and prevention of lung cancer, considering potential interactions with conventional chemotherapy and radiation therapy.

Methodology

We searched the following electronic databases for all levels of evidence pertaining to green tea and lung cancer from inception to February 2010: PubMed, EMBASE, CINAHL, Alt HealthWatch, Cochrane, and the National Library of Science and Technology. We used a broad-based MeSH and keyword approach combining clinical (lung cancer) and therapeutic (green tea) search terms, as listed in Table 1. An initial search was conducted in June 2008 (HF), and this was repeated by an independent researcher in June 2009 (DAK). An updated search was conducted in November 2011. Records from both searches were pooled and screened for inclusion. As the first search identified relatively few studies of interest in the databases CINAHL, Alt HealthWatch, Cochrane, and the National Library of Science and Technology, the updated search was conducted only in PubMed and EMBASE.

Screening of studies was initially conducted based on title review. In the event of uncertainty, abstracts and/or full texts were also reviewed. Only English language publications were included. Human trials had to assess the efficacy of green tea/GTE in people with lung cancer for the purposes of treatment or prevention of lung cancer, reduction of side effects and toxicities associated with chemotherapy or radiation therapy, or assessment of potential interactions with these therapies in patients with lung cancer. Biomarker studies were included if they examined end points directly related to lung cancer risk or pathogenesis. All types of lung cancers (small-cell lung cancer, non-small-cell lung cancer, and mesothelioma) were included.

Table 1. Search Terms

Search Strings	AND
Green tea	Lung neoplasm[a]
Epigallocatechin gallate	Lung neoplasm
Catechins	Lung neoplasm
Camellia sinensis	Lung neoplasm
Green tea	Chemoprevention
Peracetylated epigallocatechin-3-gallate OR Epigallocatechin-3-(3′′-O-methyl)gallate OR theasinensin A (PubMed only)	Lung neoplasm

[a]*Lung neoplasm* was the MESH term used in PubMed; in other databases, *lung cancer* was used.

We did not include observational studies because of the fact that 2 systematic reviews on green tea consumption and risk of lung cancer have recently been published; however, we discuss the findings from these studies in brief here to ensure full comprehensiveness of the evidence as presented by our review.

For inclusion, preclinical studies had to be conducted using lung cancer models and examine either anticancer effects of orally administered green tea and/or GTE or their interaction with conventional chemotherapy or radiation therapy. Studies that examined synthetic catechins or black tea were excluded. Preclinical studies were categorized as positive, negative, neutral, or mixed. The term *positive* designates studies that found significant anticancer effects from at least 1 of the forms/extracts of green tea tested in models of lung cancer, alone or additively with other agents; *negative* designates studies that found significant procarcinogenic effects alone or in combination with other agents; and *neutral* designates studies that found no significant beneficial effect nor any evidence of harm. In the absence of reported levels of significance, the authors' interpretation was used to guide classification.

We piloted data extraction sheets and conducted the extractions in duplicate to assess interresearcher reliability. On completion of data extraction for more than 50% of human-level studies, there were no major inconsistencies, and further duplication of data extraction was deemed unnecessary. Data on quality and efficacy were extracted. Extraction sheets were prepared based on the Consolidated Standards of Reporting Trials (CONSORT) statement for

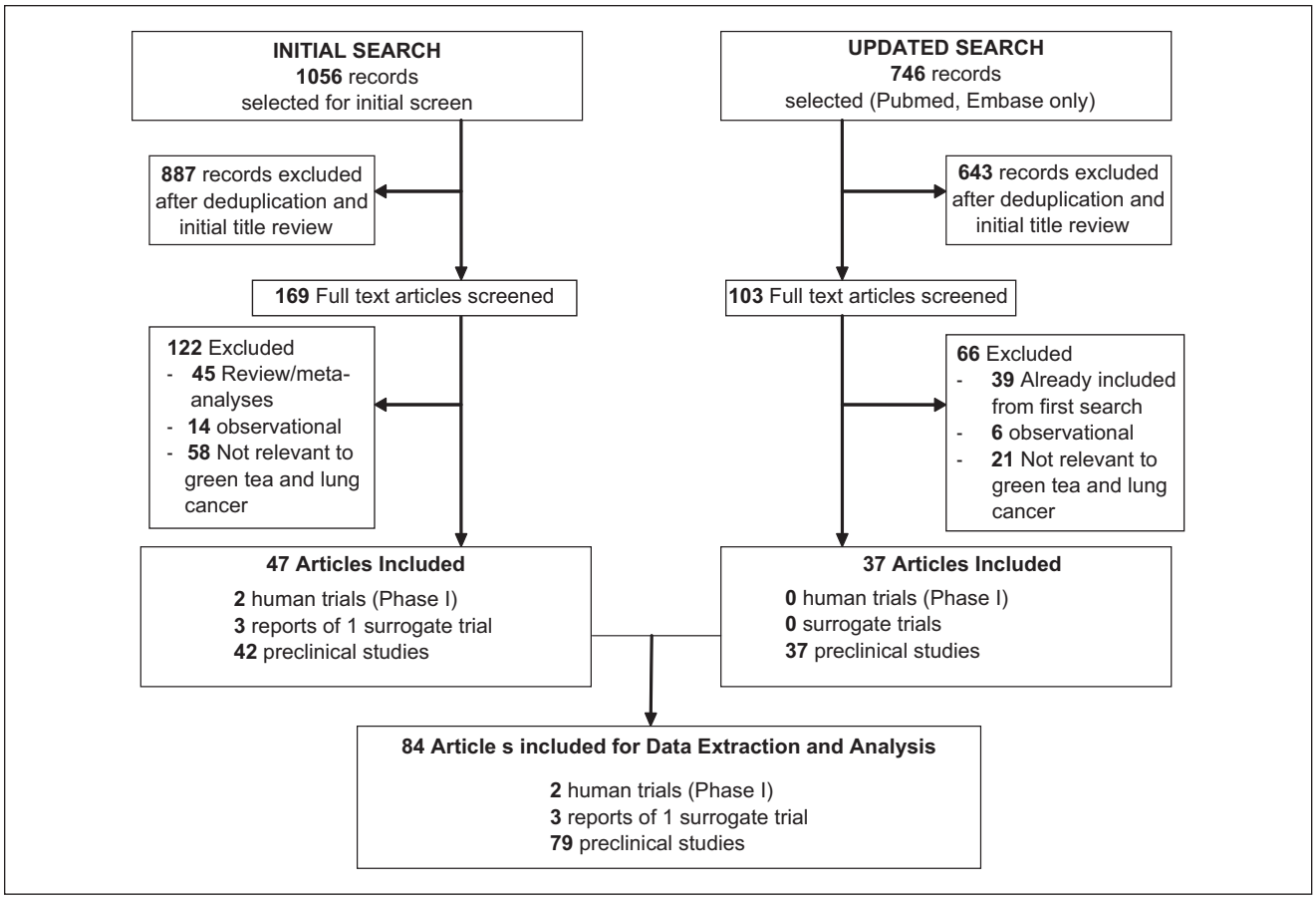

Figure 1. Literature flow chart

human trials[18,19] and the Score for Assessment of Physical Experiments on Homeopathy[20] for preclinical studies, respectively. Randomized trials were assessed for quality using the Jadad score.[21]

Results

A total of 84 studies were included for full analysis. Of these, 2 were phase I studies conducted in lung cancer patients, 3 reports were of a single clinical surrogate trial in smokers, and 79 were preclinical studies. No randomized controlled trials (RCTs) were identified that assessed green tea for the treatment or prevention of lung cancer. Figure 1 shows the literature flowchart.

Preclinical Evidence

Of the 79 included studies reviewed, 72 showed anticancer effects for green tea (Table 2).[6-8,22-97] In vivo, 28 of these studies supported a chemopreventive effect for green tea against lung cancer when given following exposure to environmental tobacco smoke[22,28] and tobacco-specific carcinogens,[6,17,23,25,27,29,30,33,34,37,39,41,45-47,53,54,57-60] or in models testing for spontaneous tumorigenesis (eg, decreased lung tumor incidence, size, or multiplicity).[51] Five studies found green tea to increase animal survival in vivo,[29,44,50,54,55] and 3 studies showed growth inhibitory effects on in vivo tumors.[30,40,41] In vitro, the most supported mechanisms were: growth inhibition and/or antiproliferative activity in tumor cells (n = 24),[23,24,31,34,44,64-69,71,75,80,84-86,90-93,95] pro-apoptotic activity in tumor cells (n = 17),[8,23,30,34,44,69,71-74,77,79,80,83,86,90,91,97] and anti-invasive, antimetastatic activity (n = 14).[8,26,36,38,44,50,55,56,61,69,72,76,81,94,97] Green tea and/or green tea catechins have also been found to protect against DNA damage (n = 5)[6,7,60,89,93] and inhibit the NF-κB signaling pathway, activation of which promotes proinflammatory cell changes and proliferation (n = 4),[25,81,84,87] and may induce apoptosis in lung tumor cell lines via modulation of various transcription factors and cytokines, such as NF-κB, the extracellular signal-regulated kinases pathway, TNF-α (tumor necrosis factor-α), and vascular endothelial growth factor,[8,74,77,84] and through upregulation of p53 expression

Table 2. Preclinical Evidence

	Design					Outcomes									
						In Vivo			In Vitro		In Vitro or In Vivo				
Reference	In Vivo	In Vitro	n	Form	Chemotherapy	Anticancer Effect[a]	↑Survival/↓Mortality/↑Time to Tumor Development	Antiproliferative Effect/Growth Inhibition	Antiproliferative Effect/Growth Inhibition	Proapoptotic Effect	Antimetastatic/ Angiogenic/ Invasive Effect[b]	Procarcinogenic/ Proangiogenic	Impact on Drug Effect (↑ or ↓)	Other	Overall +/−/n/m
Badari et al (2011)[22]	y	—	NR	GTE + selenite	n	y	—	—	—	—	—	—	—	—	+
Amin et al (2010)[23]	y	y	32	EGCG w/wo Luteolin	n	Alone, n; combination, y	—	—	y	y	—	—	—	—	+
Li et al (2010)[24]	y	y	50	EGCG	n	y	—	—	y	—	—	—	—	↑Oxidative DNA damage in tumor	+
Roy et al (2010)[25]	y	—	120	GTP	n	y	—	—	—	—	—	—	—	↓Cox-2 expression; ↓activation NF-κB	+
Shimizu et al (2010)[26]	y	—	NR	Polyphenon 70S	n	—	—	—	—	—	y	—	—	Improved NK cell activity	+
Zhang et al (2010)[27]	y	—	40	Poly.E EGCG	n	Poly.E only	—	—	—	—	—	—	—	—	+
Chan et al (2009)[28]	y	—	—	GT	n	y	—	—	—	—	—	—	—	antioxidant effect	+
Gu et al (2009)[29]	y	—	60	GT	n	y	y	—	—	—	—	—	—	—	+
Manna et al (2009)[30]	y	—	NR	EGCG ECG	n	—	—	y	—	y	—	—	—	↑expression of p53 25%, ↓Bcl-2	+
Milligan et al (2009)[31]	y	y	—	EGCG EC	Erlotinib	Alone, n; combination, y	—	—	y	—	—	—	Additive	—	+
Roomi et al (2009)[32]	y	—	25	NM including GTE	n	y	—	—	—	—	—	—	—	—	+
Anderson (2008)[33]	y	—	—	Poly. E	n	y	—	—	—	—	—	—	—	—	+
Lu et al (2008)[34]	y	y	NR	Poly E w/wo atorvastatin	n	y, Only in combination	—	—	y	y	—	—	—	Synergy with atorvastatin	+
Lu et al (2006)[35]	y	—	—	Poly E	n	y	—	—	—	—	—	—	—	—	+
Roomi et al (2006)[36]	y	—	36	NM including GTE	n	—	—	—	—	—	y	—	—	—	+
Manna et al (2006)[37]	y	—	NR	EGCG ECG	n	y	—	—	—	—	—	—	—	—	+
Roomi et al (2006)[38]	y	y	12	NM including GTE	n	y	—	—	—	—	y	—	—	—	+
Yan et al (2006)[39]	y	—	30	Poly E	n	y	—	—	—	—	—	—	—	—	+
Banerjee et al (2005)[40]	y	—	—	EGCG	n	—	—	y	—	—	—	—	—	Prevention of lung hyperplasia, dysplasia, and carcinoma in situ	+

(continued)

Table 2. (continued)

	Design					Outcomes									
						In Vivo			In Vitro		In Vitro or In Vivo				
Reference	In Vivo	In Vitro	n	Form	Chemotherapy	Anticancer Effect[a]	↑Survival/↓Mortality/ ↑Time to Tumor Development	Antiproliferative Effect/Growth Inhibition	Antiproliferative Effect/Growth Inhibition	Proapoptotic Effect	Antimetastatic/ Angiogenic/ Invasive Effect[b]	Procarcinogenic/ Proangiogenic	Impact on Drug Effect (↑ or ↓)	Other	Overall +/−/n/m
Saha et al (2005)[41]	y	—	—	EGCG	n	—	—	y	—	—	—	—	—	Prevention of dysplasia and carcinoma in situ; proapoptotic effect	+
Liao et al (2004)[8]	y	—	—	GTE	n	—	—	—	—	y	y	—	—	↓VEGF, microvessel density	+
Schuller et al (2004)[42]	y	—	—	GT	n	m	—	—	—	—	—	—	—	↓ Neuroendocrine tumors; ↑ adenocarcinomas	m
Hirose et al (2001)[43]	y	—	—	Poly. E (GTE)	n	no effect	—	—	—	—	—	—	—	—	n
Liu et al (2001)[44]	y	y	—	EGCG	Dacarbazine	—	y	—	y	—	y	—	↑	↓Adhesion, ↓metastasis	+
Zhang et al (2000)[45]	y	—	—	GT	n	y	—	—	—	—	—	—	—	—	+
Mimoto et al (2000)[46]	y	—	—	EGCG	CP	y	—	—	—	—	—	—	↑ in vivo; n, in vitro	EGCG + CP sign ↓ lung tumor multiplicity c/t CP alone; no effect on CP in vitro	+
Gunning et al (2000)[47]	y	—	—	GT	Dex, DFMO	w Dex only	—	—	—	—	—	—	↑	Combination w GT more effective than Dex or DFMO alone	+
Witschi (2000)[48]	y	—	—	GTE	n	No effect	—	—	—	—	—	—	—	—	n
Schut and Yao (2000)[49]	y	—	—	GT	n	—	—	—	—	—	—	—	—	No effect on formation of DNA adducts in lung tissue; ↓ in liver	n
Menon et al (1999)[50]	y	—	48	Catechin	n	y	y	—	—	—	y	—	—	—	+
Landau et al (1998)[51]	y	—	—	GT	n	y	—	—	—	—	—	—	—	—	+
Witschi et al (1998)[52]	y	—	—	GT	n	no effect	—		—	—	—	—	—	No effect on lung tumor induced by ETS smoke	n
Cao et al (1996)[53]	y	—	120	GT (decaf)	n	y	—	—	—	—	—	—	—	—	+

(continued)

Table 2. (continued)

	Design					Outcomes									
						In Vivo			In Vitro		In Vitro or In Vivo				
Reference	In Vivo	In Vitro	n	Form	Chemotherapy	Anticancer Effect[a]	↑Survival/↓Mortality/↑Time to Tumor Development	Antiproliferative Effect/Growth Inhibition	Antiproliferative Effect/Growth Inhibition	Proapoptotic Effect	Antimetastatic/ Angiogenic/ Invasive Effect[b]	Procarcinogenic/ Proangiogenic	Impact on Drug Effect (↑ or ↓)	Other	Overall +/−/n/m
Luo et al (1995)[54]	y	—	—	GT	n	y	y	—	—	—	—	—	—	—	+
Menon et al (1995)[55]	y	y	8/group	EC catechin	n	—	y	—	—	—	y	—	—	No direct cytotoxic activity	+
Sazuka et al (1995)[56]	y	—	15	GT	n	—	—	—	—	—	y	—	—	—	+
Shi et al (1994)[6]	y	—	152	GT, GTE, or isolated catechins	n	y	—	—	—	—	—	—	—	↓ DNA adduct formation in lung and liver	+
Katiyar et al (1993)[57]	y	—	140	GTP	n	y	—	—	—	—	—	—	—	—	+
Wang et al (1992)[58]	y	—	—	GTE	n	y	—	—	—	—	—	—	—	—	+
Wang et al (1992)[59]	y	—	—	GT	n	y	—	—	—	—	—	—	—	—	+
Xu et al (1992)[60]	y	—	—	GT, EGCG	n	y	—	—	—	—	—	—	—	↓ DNA adduct formation in the lung	+
Taniguchi et al (1992)[61]	y	—	—	EGCG	n	—	—	—	—	—	y	—	—	EGCG ↓ number of metastases to the lungs	+
Conney et al (1992)[62]	y	—	NR	GT	n	y	—	—	—	—	—	—	—	—	+
Khan et al (1992)[63]	y	—	20	GTP	n	—	—	—	—	—	—	—	—	Induction of phase 2 liver enzymes	+
Li et al (2010)[64]	—	y	—	EGCG	n	—	—	—	y	—	—	—	—	Additive cytotoxicity with AA	+
Saha et al (2010)[65]	—	y	—	EC w/wo curcumin	n	—	—	—	Alone, n; combination, y	—	—	—	—	EC may augment cell uptake of curcumin	+
Shim et al (2010)[66]	—	y	—	EGCG	n	—	—	—	y	—	—	—	—	↓Ras downstream signaling through G3BP1	+
Tan et al (2010)[67]	—	y	—	EGCG GTE	n	—	—	—	y	—	—	—	—	Induction of phase 2 enzymes	+
Gao et al (2009)[68]	—	y	—	EGCG	n	—	—	—	y	—	—	—	—	—	+
Lu et al (2009)[69]	—	y	—	GTE	n	—	—	—	y	y	y	—	—	—	+

(continued)

Table 2. (continued)

Design						Outcomes									
						In Vivo			In Vitro		In Vitro or In Vivo				Overall
Reference	In Vivo	In Vitro	n	Form	Chemotherapy	Anticancer Effect[a]	↑Survival/↓Mortality/↑Time to Tumor Development	Antiproliferative Effect/Growth Inhibition	Antiproliferative Effect/Growth Inhibition	Proapoptotic Effect	Antimetastatic/ Angiogenic/ Invasive Effect[b]	Procarcinogenic/ Proangiogenic	Impact on Drug Effect (↑ or ↓)	Other	+/−/n/m
Tomankova et al (2009)[70]	—	y	—	GTE	n	—	—	—	—	—	—	y	—	Moderate ↑viability of cancer cells exposed to oxidative therapy	+
Yamauchi et al (2009)[71]	—	y	—	EGCG ECG, EGC, EC	n	—	—	—	EGCG only	EGCG only	—	—	—	p53-Dependent apoptosis	+
Hazgui et al (2008)[72]	—	y	—	EGCG	n	—	—	—	—	y	y	—	—	—	+
Lambert et al (2008)[73]	—	y	—	EGCG	n	—	—	—	—	y	—	—	—	NAC ↑ uptake, proapoptotic effect of EGCG	+
Sadava et al (2007)[74]	—	y	—	EGCG	n	—	—	—	—	y	—	—	—	Cytotoxicity in MDR variant cells, IC50 70 μM	+
Kuzuhara et al (2007)[75]	—	y	—	EGCG	n	—	—	—	y	—	—	—	—	—	+
Lu et al (2007)[76]	—	y	—	GTE	n	—	—	—	—	—	y	—	—	—	+
Suganuma et al (2006)[77]	—	y	—	EGCG	Celecoxib, sulindac, fenretinide, aspirin	—	—	—	—	y	—	—	↑ Sulindac only	Synergy with sulindac but not other drugs	+
Kweon et al (2006)[78]	—	y	—	EGCG	n	—	—	—	—	—	—	—	—	One cell line was resistant to EGCG	n
Ganguly et al (2005)[79]	—	y	—	EGCG, ECG	n	—	—	—	y	y	—	—	—	Upregulation of p53, downregulation of Bcl-2	+
Kuo et al (2005)[80]	—	y	—	GT proanthocyanidin	n	—	—	—	y	y	—	—	—	—	+
Yang et al (2005)[81]	—	y	—	EGCG	n	—	—	—	—	—	y	—	—	Inhibition of NF-κB	+
Shigeoka et al (2004)[82]	—	y	—	Catechin	n	—	—	—	—	—	n	—	—	—	n
Vittal et al (2004)[83]	—	y	—	EGCG	n	—	—	—	y	y	—	—	—	Auto-oxidation of EGCG generated H_2O_2	+
Tichelaar et al (2004)[84]	—	y	—	EGCG	Budesonide, DFMO	—	—	—	y	—	—	—	↑	Inhibition of NF-κB	+

(continued)

Table 2. (continued)

Design						Outcomes									
						In Vivo			In Vitro		In Vitro or In Vivo				Overall
Reference	In Vivo	In Vitro	n	Form	Chemotherapy	Anticancer Effect[a]	↑Survival/↓Mortality/↑Time to Tumor Development	Antiproliferative Effect/Growth Inhibition	Antiproliferative Effect/Growth Inhibition	Proapoptotic Effect	Antimetastatic/ Angiogenic/ Invasive Effect[b]	Procarcinogenic/ Proangiogenic	Impact on Drug Effect (↑ or ↓)	Other	+/−/n/m
Seeram et al (2003)[85]	—	y	—	11 Catechins	Dox (comparator)	—	—	—	y	—	—	—	n/a	Cox-1, 2 inhibited; galloyl catechins ↓ proliferation approximately equal to Dox	+
Zhang et al (2002)[7]	—	y	—	GTE	n	—	—	—	—	—	—	—	—	↓DNA damage in cells from lung cancer patients	+
Fujimoto et al (2002)[86])	—	y	—	EGCG, ECG	n	—	—	—	y	y	—	—	—	—	+
Okabe et al (2001)[87]	—	y	—	EGCG	n	—	—	—	—	—	—	—	—	Inhibition of NF-κB in lung cancer cells	+
Steele et al (2000)[88]	—	y	—	GTE	n	—	—	—	y	—	—	—	—	↓Of transformation, increased GSH	+
Weitberg and Corvese (1999)[89]	—	y	—	EGCG	n	—	—	—	—	—	—	—	—	EGCG ↓NNK DNA damage	+
Suganuma et al (1999)[90]	—	y	—	EGCG and "tea polyphenols"	n	—	—	—	y	y	—	—	—	Synergy between EC and EGCG	+
Yang et al (1998)[91]	—	y	—	GTE, GTP, catechins	n	—	—	—	y	y	—	—	—	Mediated by induction of intracellular H_2O_2	+
Okabe et al (1997)[92]	—	y	—	EGCG, catechins	n	—	—	—	y	—	—	—	—	ECG may inhibit EGCG uptake	+
Leanderson et al (1997)[93]	—	y	—	GTP	n	—	—	—	y	—	—	—	—	↓ DNA damage; ↓ growth in H_2O_2 but not CS exposed cells	+
Sazuka et al (1997)[94]	—	y	—	EGCG	n	—	—	—	—	—	y	—	—	↓Type IV collagenase activity	+
Valcic et al (1996)[95]	—	y	—	6 Catechins	n	—	—	—	y	—	—	—	—	—	+
Ogata et al (1995)[96]	—	y	—	5 Catechins	n	—	—	—	—	—	—	—	—	Cytotoxicity	+
Isemura et al (1993)[97]	—	y	—	5 Catechins	n	—	—	—	—	y	y	—	—	—	+

(continued)

Table 2. (continued)

Design						Outcomes									
						In Vivo			In Vitro		In Vitro or In Vivo				Overall
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Total	44	42	—	—	—	28	5	3	24	17	15	1	—	↓ DNA damage, 5 ↓NF-κB, 4 ↓ Dysplasia/ Transformation, 3 cytotoxicity 3 ↑ p53 Expression, 3 Pro-oxidant to tumor, 2 ↑Phase 2 enzymes, 2	+, 72; n, 6; m, 1; −, 0

Abbreviations: 1,25 vitD, 1,25 dihydroxyvitamin D; ETS, environmental tobacco smoke; VEGF, vascular endothelial growth factor; CP, cisplatin; CS cigarette smoke; Dex, dexamethasone; DFMO, difluoromethylornithine; Dox, doxorubicin; ECG, epicatechin gallate; EGCG, epigallocatechin gallate; EC, epicatechin; Gem, gemcitabine; GT, green tea; GTE, green tea extract; GTP, green tea polyphenols; MDR, multidrug resistance; NM, nutrient mix, including amino acids; Poly E, Polyphenon E, a well-characterized pharmaceutical grade green tea polyphenol mixture, with 65% EGCG; Polyphenon 70S, a crude GTE that is 34% EGCG, with lesser amounts of the other catechins, vitamin C, selenium, copper, and manganese; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; Vin, vinorelbine; w/w/o with or without; +, results in favor of green tea; −, detrimental results found with green tea use; m, mixed effects, both positive and negative; n, no significant effect or neutral result; y, yes, effect demonstrated; —, not applicable/outcome not assessed.

[a]Includes ↓lung tumor incidence/multiplicity/volume in vivo following carcinogen administration or tumor xenograft.

[b]Includes effects on tumor growth observed in animal models of metastasis to the lungs, such as that induced by intravenous or subcutaneous injection of lung cancer cells as well as results from in vitro studies on markers such as VEGF or invasive capacity. Thus, results from animal models of metastasis are differentiated from effects on primary tumor growth induced by administration of carcinogen and are detailed under this column, whereas measures of (nonmetastatic) primary tumor growth are categorized under "Anticancer Effect."

(n = 3).[30,71,79] Two studies in mice and in vitro showed that green tea may induce phase II liver enzymes, possibly contributing to a chemopreventive effect and affecting drug metabolism; however, this has not been shown in human studies.[63,98-100] One in vitro study found that green tea reduced reactive oxygen species–induced apoptosis in lung cancer cells treated with photodynamic therapy.[70] Preclinical studies in lung cancer models have indicated an ability of green tea to potentiate the effects of certain drugs used as or with chemotherapy, including cisplatin,[46] dacarbazine,[44] erlotinib,[31] dexamethasone,[47] and sulindac.[77]

Human Trials

Surrogate trials. One RCT assessed for a shift in a biomarker of DNA damage and repair and found that green tea consumption at a dose of four 8-oz cups per day significantly reduced oxidative DNA damage in heavy smokers by 31% compared with baseline. The surrogate measured was urinary excretion of 8-hydroxydeoxyguanosine (8-OHdG),[101-103] which is elevated in current smokers compared with never smokers or those who have recently quit and is thought to represent DNA damage caused by smoking and repair.[104] The study found a decrease after 4 months from 8.7 to 6.0 ng/mg creatinine among patients taking green tea, a value similar to that in nonsmokers (7.36 ng/mg) according to Kanaya et al.[105]

Phase I trials. Two phase I trials assessed the use of GTE in lung cancer patients[15,16] (see Tables 3 and 4). Both dose-ranging trials were conducted in patients with late-stage disease; the study by Laurie et al,[15] was limited to lung cancer exclusively (small cell or non–small cell), whereas the study by Pisters et al,[16] was conducted in patients with various cancers, including 21 patients with non-small-cell lung cancer and 3 with mesothelioma. Both studies used a GTE of similar composition, with approximately 13% EGCG and 6.8% caffeine. No objective tumor responses were seen in either study; however, 10 of 17 (58.8%) patients and 10 of 49 (20.4%) patients, respectively, achieved disease stabilization for up to 4 to 6 months. In both these trials, a similar maximum tolerated dose (MTD) for GTE was found: 3.0 g/m^2 per day in 1 study[15] and either 1.0 g/m^2 3 times a day or 4.2 g/m^2 once daily in the other,[16] with the divided dosing (1.0 g/m^2) 3 times daily being better tolerated.[16] This daily dosing of GTE is approximately equivalent to 4.8 to 6.7 g GTE 3 times daily or 7 to 8 cups (120 mL/cup) of tea 3 times daily.[16]

In the study by Laurie et al,[15] mild side effects (grade 1 or 2) included fatigue, dyspepsia, diarrhea, headache, anxiety, and insomnia and were attributed in part to the caffeine content. Neurological symptoms (anxiety, insomnia, and headache) and fatigue occurred at the entry-level dose of 0.5 g/m^2, whereas digestive symptoms occurred at 1.0 to 2.0 g/m^2. Grade 3 side effects that were dose-limiting toxicities were diarrhea, nausea, and hypertension, which occurred at 4.0 g/m^2 per day; all symptoms improved through dose reduction.[15] In the study by Pisters et al,[16] GTE was well tolerated, with mild side effects, including nausea, restlessness, pain, polyuria, and polydipsia beginning at a dose of 1.0 g/m^2 per day, and this increased dramatically at a dose above 3.0 g/m^2. Dose-limiting toxicities included gastrointestinal upset and central nervous system stimulation (insomnia and agitation), attributed to the caffeine content. Pharmacokinetic analysis suggested that there was a dose-dependent accumulation of caffeine levels but not in levels of EGCG.[16] Investigators concluded that although GTE is unlikely to have a significant direct cytotoxic effect, it should be studied further for potential chemotherapy-enhancing and cytostatic properties.[15]

Interactions

Two studies investigating the impact of decaffeinated GTE for 2 to 4 weeks in healthy participants on CYP2D6, CYP1A2, CYP3A4, and CYP2C9 enzymes found no clinically significant impact on enzyme function.[99,100,106] Extracts used were (1) 800 mg/d mixed catechins,[99] approximately the amount found in ten 120-mL cups of tea[15,106] or in crude GTE at half the MTD, and (2) 800 mg EGCG,[100] approximately the amount found in 20 cups of tea,[106] close to the MTD. (Because extracts of differing composition possess differing biological activity, these estimates are given to provide a more concrete sense of volume involved, rather than to suggest substitutions in therapeutic administration.) A 2009 in vitro study found that EGCG may interact with bortezomib, binding with the cancer drug and blocking its therapeutic effect. The authors advised that patients undergoing treatment for multiple myeloma and mantle cell lymphoma or who are otherwise taking this medication avoid consumption of green tea or any products containing GTE.[107] More extensive investigations with green tea and other chemotherapeutic drugs have not been carried out in humans.

Patients undergoing radiation treatments often experience radiation-induced skin toxicity. Pajonk et al[108] studied the effectiveness of green tea applied to skin regions with grade 2+ toxicity. Green tea compresses applied to the affected skin regions 3 times per day for 10 minutes significantly reduced the duration of the skin reaction from 26 days to 16.5 days in participants receiving radiation for head and neck tumors and from 22 days to 16 days for those receiving chemoradiotherapy for cancers in the pelvic region.

Discussion

Dose-ranging trials have demonstrated the safety and tolerability of GTE in advanced lung cancer patients at

Table 3. Methods of Human Trials for Green Tea and Lung Cancer

	Population														
Reference	Population	Age	Gender	Smokers/ Asbestos Exposure	Staging	PS	Previous Chemotherapy or Surgery	Intervention	Control	Treatment Duration	Sample Size	Study Duration	Blinding	Random	Dropouts, Withdrawals, LTFU Reported	Jadad Score (RCTs)
Phase I trials																
Laurie et al (2005)[15]	American	Median, 63	M, 9; F, 8	NR	Advanced incurable lung cancer	KPS ≥70%	Previous chemotherapy (13) and radiation (9)	Escalating doses of green tea extract (13.9% EGCG, 7.7% EGC, 3.5% ECG, 2.6% EC, 6.8% caffeine); dose range 0.5 g/m^2 to 4 g/m^2 per day	None	Up to 16 weeks; median of 1 cycle (4 weeks) completed	17	2 years	n/a	n/a	y	n/a
Pisters et al (2001)[16]	American	Median, 57	M, 26; F, 23	NR	Incurable cancers: NSCLC, 21; head and neck, 19; mesothelioma, 3; other, 6	Zubrod PS 1 (n = 48), 2 (n = 1)	Previous chemotherapy (39), radiation (37), surgery (38), none (3)	Escalating doses of green tea extract (13.2% EGCG, 8.3% EGC, 3.3% ECG, 2.2% EC, 6.8% caffeine); Dose range 0.5 g/m^2 to 5.05 g/m^2 daily as a single dose or divided doses	None	Median, 2 months	49	2 years	n/a	n/a	y	n/a
Biomarker study																
Hakim et al (2003, 2004, 2008)[101-103]	American	Mean, 57	M, 33; F, 100	All current smokers	n/a	n/a	n/a	1. 4 Cups per day of commercially available decaffeinated green tea (brew bag ×3 minutes, each cup had ~36 mg EGCG, 73 mg total catechins, 145 mg total polyphenols, 2.9 mg caffeine) 2. 4 Cups black tea daily	Equal amounts of water	4 months	133	2 years	n	y	y	3

Abbreviations: PS, performance score; LTFU loss to follow up; n/a not applicable; NR, not reported; EC, epicatechin; ECG, epicatechin gallate; EGCG, epigallocatechin gallate; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; y, yes; n, no.

Table 4. Outcomes of Human Trials for Green Tea and Lung Cancer

Reference	Dose/Maximum Tolerated Dose (MTD)	Tumor Response	DNA damage	Adverse Effects	Dose-Limiting Toxicity
Phase I trials					
Laurie et al (2005)[15]	MTD: 3.0 g/m^2 given once daily with food	No objective tumor response CR/PR: 0 DS: 7 PD: 7	n/a		Grade 3 diarrhea (2), nausea (2), vomiting (1), hypertension (1)
Pisters et al (2001)[16]	MTD: 1.0 g/m^2 3 times/d, or 4.2 g/m^2/d as 1 dose	No major tumor response CR/PR: 0 DS: 10	n/a		Grade 3 constipation (1), tremor (1)
Biomarker study					
Hakim et al (2003, 2004, 2008)[101-103]	Four 8-oz cups green tea daily, decaffeinated	n/a	Green tea: 31% ↓ (mean 2.7, 95%CI = −9.6 to −2.2) c/t water (P = .002) Black tea: no change Water: no change		None

Abbreviations: CR, complete response; DS, disease stabilization; PD, progressive disease; PR, partial response; CI, confidence interval; c/t, compared to.

dosages from to 3.0 to 4.2 g/m^2/d with improved tolerability using divided doses.[15,16] There is at present a lack of evidence supporting direct cytotoxic effects for green tea as an anticancer therapy in lung cancer patients; however, existing evidence does suggest that green tea/GTE may be more useful instead as a cytostatic agent in conjunction with standard treatment, where it may prolong the period of disease stabilization.[15,16] Preclinical evidence suggests that GTE may potentiate the anticancer effects of chemotherapy drugs[44,46,84]; however, further investigation is required before green tea can be recommended for this purpose in humans.[74] Although there is no evidence from phase III or IV studies, green tea/GTE should not be used in conjunction with bortezomib at this time.[107] GTE appears to be better tolerated when given in divided doses, and common side effects include gastrointestinal upset and symptoms of central nervous system stimulations such as insomnia, anxiety, and headache.[15,16]

Observational evidence pertaining to the chemopreventive effects of green tea is conflicting. In a recent systematic review of observational data, Yuan[109] reported that of 12 included studies, 5 found a "statistically significant inverse association between green tea intake or dietary catechins and lung cancer risk," 1 study reported significantly increased risk associated with higher green tea intake, 4 studies showed no significant associations, and 2 studies "reported a relative risk that was close to one" (p. 895). A 2009 meta-analysis of 22 observational studies by Tang et al[9] found a "borderline significant association between highest green tea consumption and reduced risk of lung cancer (relative risk [RR] = 0.78; 95% confidence interval [CI] = 0.61-1.00)." In addition, Tang et al[9] found that intake of 2 cups of green tea per day was associated with an 18% decreased risk of developing lung cancer (RR = 0.82; 95% CI = 0.71-0.96). An observational study examining surrogates of DNA damage found that green tea consumption in smokers reduced the frequency of sister chromatid exchange to that found in nonsmoking individuals,[110] and similar findings were reported from an RCT of current smokers. Although there was no protective effect overall, among those individuals with the GSTM1 and GSTT1 genotypes, consumption of green tea significantly reduced the urinary marker of DNA damage, urinary 8-OHdG.[101-103] Other observational studies that conducted separate analyses in smoking individuals report mixed findings, with 1 study finding protective effects for higher amounts of green tea consumption in smokers[111] and 2 studies finding no such effects.[112,113] It should be noted that most of the observational studies were conducted solely in Asian populations. With the potential for differing effects in individuals of different genotypes, generalizing to a more heterogeneous North American population needs to be done with caution. Further investigation of green tea's potential chemoprotective effect is warranted.

Other Cancers

There is a lack of clinical evidence regarding green tea use in lung cancer. However, although evidence around green tea's effects in other cancer types cannot be directly extrapolated to lung cancer, clinical evidence showing beneficial effects from green tea/GTE administration on premalignant conditions does lend some support to the hypothesis that green tea may also be effective for the prevention of lung cancer. Doses of between 600 to 3000 mg GTE per day has been shown to (1) improve clinical response rates in patients with leukoplakia and oral premalignant lesions,[114,115] (2) reduce the incidence of metachronous adenomas in patients who underwent polypectomy for prevention of colorectal cancer,[116] (3) benefit cervical dysplasia,[117] and (4) reduce the incidence of prostate cancer by almost 80% in patients with high-grade prostate intraepithelial neoplasia.[118] Green tea has also been shown to reduce absolute lymphocyte count and lymphadenopathy in patients with chronic lymphocytic leukemia.[119]

Dose

At present there is insufficient evidence from clinical trials on which to base dose recommendations for lung cancer treatment or prevention. The MTD appears to range between 3.0 and 4.2 g/m^2 per day, equivalent to approximately 7 to 8 cups (150 mL) of tea 3 times daily.[15,16] No data are available indicating the therapeutic dose for use in lung cancer, if such is found; however, it is worth noting that this MTD exceeds the range of therapeutic doses used by the trials in other cancer types cited above. Observational evidence supporting the anticancer effects of green tea shows a variable level of therapeutic intake, with up to 10 cups per day or the equivalent of 1500 mL in 1 study[120] and intakes of 3 cups per day in another,[113] both showing benefit. A recent Cochrane review cited the "desirable green tea intake" for cancer prevention as 3 to 5 cups per day (up to 1200 mL/d), providing a minimum of 250 mg of catechins per day, and concluded that green tea appears to be "safe at moderate, regular and habitual use."[121] A recent meta-analysis by Tang et al[9] found a significant chemoprotective effect against lung cancer at an intake of 2 cups per day (300 mL) or more (RR = 0.82; 95% CI = 0.71-0.96).

Green tea's well-established antioxidant effects raise potential points of concern when used alongside chemotherapy.[122-126] It may be appropriate to schedule administration around chemotherapy as described by Seely et al[127] to minimize risk of interaction between interventions. In brief, antioxidants should be administered after 5 elimination half-lives ($t_{1/2}$) of the chemo drug have elapsed when given after chemotherapy and no sooner than 5 times the $t_{1/2}$ of green tea/catechins before chemotherapy. This minimizes the potential for pharmacodynamic interactions between the 2 agents because 5 × ($t_{1/2}$) is considered the time required for a substance to be cleared (>90%) from the body. Alternately, if the purpose of therapy is to obtain a positive interaction between the 2 agents, it would be important to administer them within a closer window of time. There is some preclinical evidence showing that green tea may reverse multidrug resistance in models of other cancer types[128-130]; however, at this time, there is insufficient clinical evidence to support a purposeful strategy of therapeutic combination with chemotherapy.

Conclusion

There is insufficient clinical evidence that green tea is effective at chemoprevention or treatment of lung cancer. GTE appears to be safe at dosages of up to 3.0 g/m^2/d in advanced lung cancer patients; however, caution should be applied for patients actively receiving chemotherapies, particularly bortezomib, because of unknown effects on drug metabolism and activity. Regular consumption of green tea as a beverage may exert a modest protective effect against lung cancer, but further clinical studies are needed to confirm this. The level of green tea consumption required to be chemopreventive is estimated by some as equivalent to 1500 mL of tea daily, although based on studies reviewed here, the range of the therapeutic dose varies considerably, starting from 1 cup daily to 10 or more per day.

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