Review Article

Preventive and therapeutic effects of green tea on lung cancer: a narrative review of evidence from clinical and basic research

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Background and Objective: Green tea is a popular beverage worldwide and has numerous health-promoting properties. Accumulating evidence indicates that green tea has preventive and therapeutic effects on lung cancer. This study aimed to investigate the association between green tea consumption and lung cancer.

Methods: We performed a narrative review to summarized the association between green tea consumption and lung cancer.

Key Content and Findings: Green tea consumption is known to decrease lung cancer risk in the general population, as indicated by meta-analyses of observational studies. Two active components of green tea, theabrownin and (–)-epigallocatechin gallate (EGCG), mediate the antitumor activity of green tea. Theabrownin promotes apoptosis, induces cell cycle arrest, and inhibits the migration, clone formation, and proliferation of lung cancer cell lines *in vitro* and *in vivo*. EGCG inhibits lung cancer cell proliferation and promotes apoptosis, agenesis, and epithelial-mesenchymal transition (EMT). In addition, EGCG sensitizes lung cancer cells to cisplatin and tyrosine kinase inhibitors (TKIs). The possible molecular mechanisms underlying the antitumor activity of EGCG and theabrownin were reviewed.

Conclusions: Observational studies have indicated that green tea has preventive effects on lung cancer. *In vitro* and animal studies have indicated that green tea has therapeutic effects on lung cancer. Further clinical trials are needed to illustrate the therapeutic effects of green tea or its active components (i.e., theabrownin, EGCG) on lung cancer.

Keywords: Green tea; lung cancer; theabrownin; (–)-epigallocatechin gallate (EGCG)

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Introduction

Tea is one of the most popular beverages worldwide (1). It is made from the leaves of *Camellia sinensis*. According to the handling methods after the leaves are picked, tea can be categorized into 3 types: green tea, black tea, and oolong tea (2). The handling methods for green tea involve steaming or pan-frying tea leaves, while black tea involves rolling and fermenting (3). The steaming and pan-frying prevent the oxidation of polyphenols, while rolling and fermenting do not. Therefore, green tea has a much higher amount of polyphenols than does black tea (4). Catechin is the primary type of polyphenol and has numerous health-

Table 1 The search strategy summary

Items	Specification
Date of search	August 1st, 2022
Databases and other sources searched	PubMed
Search terms used	("green tea" or polyphenol or "Epigallocatechin-3-gallate" or egcg or "epigallocatechin gallate"[nm] or "Catechin"[nm]) and ("lung cancer" or "Lung Neoplasms"[mesh])
Timeframe	From January 1st, 1980 to August 1st, 2022
Inclusion and exclusion criteria	Clinical trials, observational studies, animal studies and basic researches were included. Only articles published in English were included
Selection process	Three authors selected studies together

promoting properties (4). In addition, other chemical constituents of green tea, such as amino acids, vitamins, and trace elements, also have health-promoting properties. During the past year, numerous preclinical and clinical studies indicated that green tea exerts preventive effects on various types of cancer, including lung cancer, gastric cancer, and prostate cancer (5). Here, we reviewed the association between green tea consumption and lung cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1791/rc).

Methods

To perform this narrative review, we searched the PubMed database to screen scientific literature concerning lung cancer and green tea. All clinical trials, observational studies, animal studies and basic researches published between January 1st, 1980 to August 1st, 2022 were considered. The search was performed till August 1st, 2022. The following search terms were used: ("green tea" or polyphenol or "Epigallocatechin-3-gallate" or egcg or "epigallocatechin gallate"[nm] or "Catechin"[nm]) and ("lung cancer" or "Lung Neoplasms"[mesh]). We only considered research articles written in English. Three authors (ZD Hu, YJ Wang, L Zhang) read the potential studies and wrote the draft. The search strategy was summarized in *Table 1*.

Overview of findings

Green tea consumption and lung cancer risk

The first study to investigate lung cancer risk and green tea consumption was published in 1988 (6). In that prospective cohort study, tea consumption was surprisingly associated with increased lung cancer risk (6). However, the subsequent cohort and case-control studies indicated that green tea consumption decreased lung cancer risk (7-9). A meta-analysis indicated that consumption of green tea, but not black tea, was associated with decreased lung cancer risk [risk ratio (RR) 0.78; 95% confidence interval (CI): 0.60–1.00] (10). However, subgroup analyses did not support the association between green tea consumption and lung cancer risk. Notably, the estimated RR of green tea is <1.00, but its 95% CI is 1.00, indicating that green tea's effect on lung cancer risk is not statistically significant. This may be because only 12 studies investigated green tea in this meta-analysis, and considerable heterogeneity was observed (I^2=78.5%). Therefore, further studies are needed to address the association between tea consumption and lung cancer risk.

In 2014, an updated meta-analysis was published (2). By pooling 26 case-control studies and 12 cohort controls, this meta-analysis revealed that tea consumption decreased lung cancer risk, with an RR of 0.78 (95% CI: 0.70–0.87). In subgroup analysis, both green tea and black tea were associated with decreased lung cancer risk. However, the study design (case-control or cohort) and the sex of the participants can affect the strength of the association between tea consumption and lung cancer risk. In a most recently published meta-analysis (11), tea consumption was proven to be associated with decreased lung cancer risk (odds ratio 0.80; 95% CI: 0.73–0.87). Consumption of 7.5 g of green tea a day can significantly decrease lung cancer risk, as demonstrated by both case-control studies and cohort studies. In 2020, a meta-analysis performed by Cochrane group analyzed the relationship between green tea and cancer (12). They concluded that green tea may have a small preventive effect for lung cancer, but there is possible risk of bias due to case-control studies (12).

The above-mentioned meta-analyses, which pooled the results of both case-control and cohort studies, indicate that green tea consumption can decrease lung cancer risk. These meta-analyses also revealed that great heterogeneity exists across the available studies. Indeed, the participants in available studies varied. For example, some studies included only nonsmokers (13) or heavy smokers (14). In addition, the confounding factors adjusted in each eligible study are variable. These design characteristics are possible sources of heterogeneity among available studies. The association between lung cancer risk and tea consumption may be affected by confounding factors, such as smoking status, gender, dietary habit, and economic status. For example, in a recently published cohort study with a large sample size (n=455,981) (15), green tea consumption was found to only decrease lung cancer risk in smokers and excessive alcohol consumers. Therefore, further studies with large sample sizes are needed to address the clinical factors affecting the association between tea consumption and lung cancer risk.

Notably, the majority of eligible studies categorize participants into several groups with a prespecified threshold. This design characteristic may complicate the clinical explanation of the pooled results of eligible studies with different categories. Under this condition, a dose-response meta-analysis is a good choice for pooling the findings of available studies. Indeed, one dose-response meta-analysis revealed a nonlinear relationship between green tea consumption and lung cancer risk (16), with individuals who consume 7 cups/day of green tea having a significantly decreased risk of lung cancer.

Theabrownin

Theabrownin is an active pigment of green tea that can determine the color and taste of green tea. *In vitro* studies indicated that it could promote apoptosis (17-19), induce cell cycle arrest (20), and inhibit migration (18), clone formation (19), and proliferation (17,19,20) of lung cancer cell lines in a dose-dependent manner. *In vivo* studies indicated that it could inhibit the growth of tumors in xenograft zebrafish (18) or mice (20). The expressions of several genes were dysregulated after theabrownin treatment, such as *p53* (17), *Bax* (17,18), *TOPO* 1/2 (17), and *Bcl-2* (17,18), suggesting that the antitumor effect of theabrownin is associated with these molecules. It is hypothesized that the apoptosis-inducing effect of theabrownins is mediated by the *p53*-mediated caspase-dependent pathway (17,18). Theabrownin-induced cell cycle arrest may be mediated by *C-myc* and its downstream molecules (20). Further studies are needed to validate this hypothesis.

Autophagy is a crucial physiological procedure that enhances cell survival. It is involved in the emergence and development of cancer (21). The formation of double-membrane vesicles (termed autophagosomes) is an initial step of autophagy. The autophagosome captures the cytosolic cargo and transports it to the lysosomes, where the cargo is degraded. The degradation product is subsequently recycled back to the cytoplasm. This procedure is known as autophagic flux (22). In vitro studies indicated that theabrownin can suppress PI3K/Akt/mTOR pathway and thus promote autophagic flux, leading to the accumulation of autophagosomes in lung cancer cells (19). Inhibition of autophagy partially impairs the antiproliferative and proapoptotic activities of theabrownin (19), indicating that the antitumor effect of theabrownin is partially mediated by autophagy.

(–)-Epigallocatechin gallate (EGCG)

Proliferation and apoptosis

As mentioned above, catechin is the primary type of polyphenol and has anticancer properties. Green tea has 4 types of catechin including EGCG, (–)-epigallocatechin (EGC), (–)-epicatechin gallate (ECG), and (–)-epicatechin (EC) (23-25). *In vitro* studies indicated that EGCG could inhibit proliferation (24,26-28) and promote the apoptosis (26,29) of lung cancer cells, indicating its antitumor activity. *In vivo* studies also found that EGCG could inhibit the growth of lung cancer (26,30-32). With long noncoding RNA (lncRNA) microarray or next-generation sequencing (NGS), 960 differentially expressed lncRNAs, 1,434 mRNAs, and >100 microRNAs were identified in EGCG-treated lung cancer cells (28,33). Bioinformatic analysis indicates that many pathways are involved in the antitumor activity of EGCG (28), especially MAPK pathway (33).

There are many mechanisms involved in the antitumor activity of EGCG. First, EGCG suppresses the activity of lung cancer stem cells (LCSCs). LCSCs represent a minor but significant population of lung cancer cells that have the ability of multipotent differentiation and self-renewal. LCSCs are thus important for lung cancer metastasis and chemotherapy resistance (34). The activation of the canonical Wnt/β-catenin pathway is critically involved in the maintenance of LCSCs (35). EGCG inactivates the canonical Wnt/β-catenin pathway by decreasing GSK-

3β phosphorylation, expression of β-catenin, and its downstream target gene *C-Myc* (36). These effects may be partially mediated by clock circadian regulator (CLOCK), a protein that regulates circadian rhythm (31). In addition, EGCG demethylates the promoter of Wnt inhibitory factor-1 (WIF-1) and increases its expression (37). Because WIF-1 is an inhibitor of Wnt signaling through direct binding to Wnt (38), increased WIF-1 expression can inactivate the Wnt/β-catenin pathway. However, it remains unknown whether WIF-1 mediates the stemness inhibitive effect of EGCG. In addition to the Wnt/β-catenin pathway, some other molecules can also mediate the inhibitive effective activity of EGCG on stemness, such as AXL receptor tyrosine kinase (AXL) (39) and miR-485-5p (30). EGCG upregulates the expression of miR-485-5p in lung cancer cells and inhibits the stemness by targeting retinoid X receptor-α (RXRα) (30) or CD44 (26).

Second, EGCG regulates the function of lung cancer cells through microRNAs (40). The expression of some microRNAs in lung cancer cells can be altered by EGCG (40), such as miR-210 (41) let-7a-1 (42), and let-7g (42). Green tea catechins upregulate the expression and let-7a-1 and let-7g, resulting in the decreased expression of 2 oncogenes, *C-MYC* and *LIN-28* (42). In addition, EGCG directly binds to hypoxia-inducible factors alpha (HIFα), preventing HIFα from degradation and thus increasing its activity (41). HIFα upregulates the expression of miR-210 by binding to the hypoxia-response element (HRE) in the miR-210 promoter (41). Increased miR-210 promotes apoptosis and inhibits the proliferation of lung cancer cells (41). However, the target of miR-210 that mediates this procedure remains unknown. In addition, EGCG has been found to decrease the expression of miR-98 and thus increase the sensitivity of lung cancer cells to cisplatin (43,44).

Third, EGCG promotes lung cancer cell apoptosis by targeting the p53 pathway. P53 is a crucial tumor suppressor, and decreased p53 is frequently observed in the development of various cancers (45). Its activation is regulated by multiple posttranslational modifications, such as ubiquitination, phosphorylation, and acetylation (46). Phosphorylated p53 has increased activity and promotes the expression of its target genes (46). EGCG has been shown to induce the expression of *p53* (47,48), inhibit the interaction between p53 and mouse double minute 2 (MDM2), and thus inhibit the p53 ubiquitination mediated by MDM2 (49). Furthermore, EGCG increases the p53 Ser15 and Ser20 phosphorylation and enhances its transcriptional activity (47,49).

Fourth, EGCG can inhibit 2 receptor tyrosine kinases, the epidermal growth factor receptor (EGFR) and C-Met, by inhibiting the phosphorylation of mTOR, STAT3, EGFR (Y1068), C-Met, AKT, S6, ERK1/2, and p38 (29,50); the expression and nuclear localization of EGFR; and its downstream target, cyclin D (50).

In addition, several other pathways also mediate the antiproliferation and proapoptosis of lung cancer. For example, EGCG was found to upregulate Ku70 acetylation and downregulate the interaction of Bax-Ku70 (32,51). Because the interaction of Ku70 and Bax is essential for cell survival, the separation of Ku70 and Bax can lead to lung cancer cell apoptosis (52). EGCG can directly interact with Ras-GAP SH3 domain-binding protein 1 (G3BP1) and suppress the binding of G3BP1 and Ras-GAP (53). The interaction of EGCG and G3BP1 can lead to the inactivation of Ras downstream targets (e.g., MEK and ERK), decreasing the proliferation of cancer cells (53). Both *in vivo* and *in vitro* studies have found that treatment of EGCG causes the generation of intracellular reactive oxygen species (ROS) and mitochondrial ROS (54). EGCG-induced ROS causes DNA oxidative damage and apoptosis (54). EGCG also inhibits lung cancer cell metastasis by suppressing matrix metalloproteinase 2 (MMP2) expression via the JNK pathway (55). In addition, telomerase (56), Bcl-2 (48), and B-cell lymphoma-extra large (Bcl-xl) (24,32,51) also mediate the inhibitive effect of EGCG on lung cancer proliferation and apoptosis.

Epithelial-mesenchymal transition (EMT)

EMT is characterized by a loss of epithelial phenotype and a gain of mesenchymal fibroblastic phenotype in polarized epithelial cells (57). This process can increase the metastatic and invasive potential of a cancer cell. Some studies indicated that ECGC could inhibit the EMT process of lung cancer cell lines. Transforming growth factor-β (TGF-β) is the primary mediator of EMT in lung cancer cells. Several *in vitro* studies indicated that EGCG could inhibit the EMT induced by TGF-β in lung cancer cell lines (58,59). Specifically, EGCG inhibits the expression of mesenchymal markers such as vimentin (59-61) and N-cadherin (59) while increasing the expression of epithelial marker E-cadherin (58,59) at the transcriptional level. The inhibitive effect of EGCG on EMT decreases the migration and invasion of lung cancer cells (58-61). There are some molecular mechanisms underlying the EMT-inhibitive effect of EGCG. For example, EGCG inhibits the phosphorylation of Smad2 (58) and ERK1/2 (58) or the

expression of transcription factors including Snail (58,59), ZEB1 (58), Twist (58), and Slug (58,59,61). In addition, EGCG inhibits the expression of p300 and CBP, thus decreasing their ability to acetylate Smad2 and Smad3 (59). Because the nucleus translocation of acetylated Smad2 and Smad3 is a critical step in TGF-β-induced expression of EMT-related genes (62), the inhibitive effect of EGCG on Smad2 and Smad3 acetylation downregulates the expression of EMT target genes.

Angiogenesis

Angiogenesis is necessary for tumor cell growth, and suppressing angiogenesis is a treatment approach for various solid cancers. Hypoxia occurs in the growing tumor tissue and can promote the expression and release of hypoxia-inducible factors-1α (HIF-1α) and HIF-2α from cancer cells (63). HIF-1α and HIF-2α upregulate the expression of vascular endothelial growth factor (VEGF), which binds to the VEGF receptors (VEGFR) in endothelial cells and enhances angiogenesis (64). EGCG has been proven to inhibit the expression of HIF-1α in lung cancer *in vitro* (65) and *in vivo* (66). In *in vitro* studies, EGCG decreases the expression of HIF-1α induced by nicotine (60), human papillomavirus (HPV)-16 oncoprotein (66), or insulin-like growth factor 1 (IGF-1) (67). In addition, EGCG upregulates the expression of endostatin, a potent endogenous angiogenesis inhibitor (65). Decreased HIF-1α impairs the production of VEGF in the lung cancer cell and thus inhibits angiogenesis (65-67). In addition to HIF-1α/VEGF pathway, EGCG can rebalance angiopoietin-1 and angiopoietin-2 (68) and induce vascular normalization (69), thus relieving the hypoxia status of lung cancer cell and improving the efficacy of the chemotherapeutic agent (68,69).

Sensitizing lung cancer cells to cisplatin

Cisplatin is a conventional chemotherapy agent for patients with advanced non-small cell lung cancer (NSCLC), but cisplatin resistance occurs in some patients (70). The mechanisms underlying cisplatin resistance are complex, and many pathways or molecules are involved. Copper transporter 1 (CTR1, also known as SLC31A1) is a copper influx transporter that promotes cisplatin internalization in cancer cells. The decreased expression of CTR1 is associated with cisplatin resistance.

EGCG can upregulate the expression of CTR1 and thus enhance the cisplatin sensitivity *in vivo* and *in vitro* (44). Specifically, EGCG has been shown to increase the expression of NEAT1 by increasing ROS generation (71). NEAT1 decreases the expression of miR-98 (44). Because CTR1 is a target of miR-98 in lung cancer cells, decreased miR-98 downregulates the expression of CTR1 and sensitizes lung cancer cells to cisplatin (44). In addition, decreased miR-98 results in increased p53, which activates the p53-dependent apoptosis pathway and enhances the effect of cisplatin (43).

In addition to the ROS-NEAT1-CTR1 axis, an additional 3 pathways have been reported to be involved in the sensitizing of lung cancer cells to cisplatin. First, proteomic analysis revealed that hepatoma-derived growth factor (HDGF) mediates the anticancer effects of EGCG (72). EGCG enhances cisplatin-induced apoptosis by suppressing HDGF (72). Second, EGCG can downregulate the expression of 2 TAM receptors (Tyro3, Axl, and MerTK), Axl and Typo3 (73). Because the TAM receptors are critically involved in the progression of lung cancer (74), the decreased expression of Axl and Typo3 may cause cisplatin resistance. Third, by inhibiting the activity of DNA methyltransferase (DNMT) and histone deacetylase, EGCG upregulates the expression of some tumor suppressors (e.g., GAS1, TIMP4, ICAM1, and WISP2) and can partially reverse cisplatin resistance (75).

Sensitizing lung cancer cells to tyrosine kinase inhibitors (TKIs)

Activating EGFR pathway plays a critical role in the development and occurrence of lung cancer. EGFR is a member of the receptor tyrosine kinase (RTKs), and TKIs, such as gefitinib and erlotinib, have been recommended as the first-line treatment in NSCLC patients with the EGFR mutation. However, acquired resistance occurs after long-term exposure to gefitinib (76). EMT is a possible mechanism underlying TKI resistance. In gefitinib-resistant lung cancer cells, EMT can be caused by activation of the PI3K/Akt/mTOR pathway. An EGCG derivate can sensitize the chemosensitivity of gefitinib by inhibiting the phosphorylation of PI3K and Akt (77). In addition to EGFR, EGCG can also decrease the expression of C-MET, another type of RTK (78).

Conclusions

As shown in *Figure 1*, accumulating observational studies support that green tea consumption can decrease lung cancer risk. *In vitro* studies also demonstrated that EGCG and theabrownin can inhibit the growth, EMT, stemness, and angiogenesis of lung cancers and promote apoptosis. In

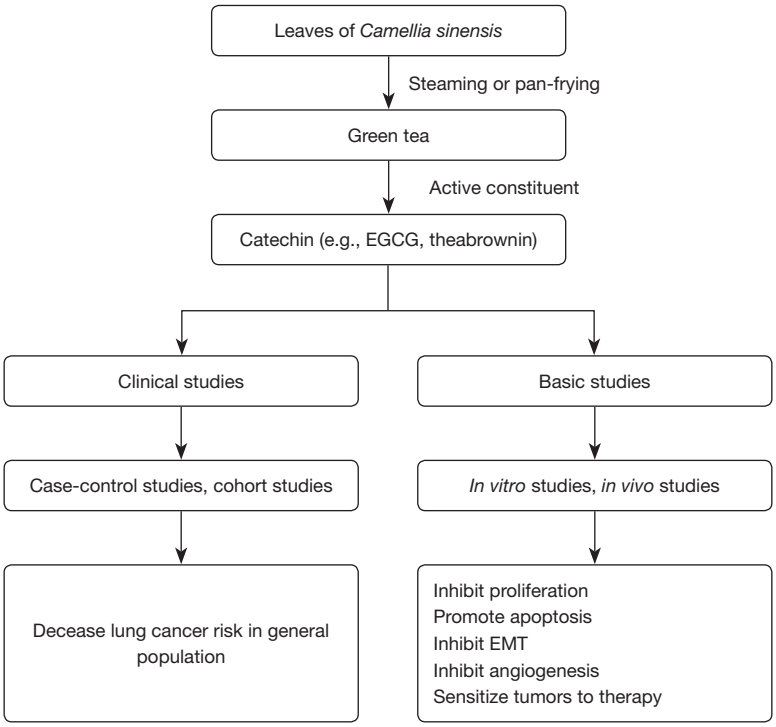

Figure 1 Green tea and lung cancer: findings from clinical and basic research. EGCG, (–)-epigallocatechin-3-gallate; EMT, epithelial-mesenchymal transition.

a lung cancer animal model, EGCG also showed anticancer activity. In a phase I trial of patients with locally advanced stage III NSCLC who received chemotherapy (cisplatin and etoposide) and radiation, oral administration of EGCG did not cause dose-limiting toxicities and could reduce the pain score of patients (79). Interestingly, dramatic regression of esophagitis to grade 0–1 was observed in >90% of the patients (79). These results indicate that EGCG is safe and effective in improving lung cancer patients' quality. Notably, most of the clinical evidence comes from observational studies, and little evidence based on randomized clinical trial. Further studies with high level of evidence are needed to investigate the long-term efficacy and safety of oral administration of EGCG in lung cancer patients. In addition, some studies also revealed that the derivates of EGCG also exert anti-lung cancer activity (25,80,81). The anti-lung cancer activity of these derivates needs to be investigated by further studies.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1791/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1791/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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