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OTTAWA INTEGRATIVE CANCER CENTRE

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CENTRE DE CANCÉROLOGIE INTÉGRATIVE D'OTTAWA

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Professional Resource: GREEN TEA

Green tea is made from fresh leaves of the plant *Camellia sinensis*, which are then dried or steamed. It contains caffeine and at least four green tea catechins—EGCG, (-)-epigallocatechin (EGC), (-)-epicatechin (EC) and (-)-epicatechin gallate (ECG). EGCG is the main constituent.

Common Name

Green tea, green tea extract, GTE, polyphenol E, EGCG, green tea catechins, GTC, green tea polyphenol, GTP

Common Uses in Cancer Care

Green tea is most commonly used:

- To prevent cancer or a recurrence of cancer
- To slow disease progression
- As an antioxidant

Route of Administration

Oral, as a brewed tea or in capsules.

Mechanism of Action

Recent studies focused on the mechanisms of action of green tea polyphenols (GTPs), such as epigallocatechin-3-gallate (EGCG), on cancer cells show a cumulative chemopreventive effect that appears to be attributed to a well-coordinated cascade of events rather than a single pathway (1). Animal and in vitro studies indicate that GTPs activate anti-growth signals (eg. p53, p73, p16) and pro-apoptotic factors (eg. Bax, FAS, DR5), and also regulate epigenetic changes including DNA methylation, histone modification, and microRNA expression. GTPs have been shown to inhibit oncogene modulation (eg. EGFR, HER2/neu), survival factors (eg. Bcl-2, Cox-2), angiogenesis pathways (eg. VEGF), replicative potential (eg. Telomerase activity) and tissue invasion and metastasis (eg. MMPs, uPA) in cancer cells (2).

In vitro studies demonstrate that EGCG causes cell cycle arrest through modulation of the levels and activity of cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors, and tumor suppressors, p53 and Rb in human breast, prostate, cervical, pancreatic, bladder, and head and neck cancer cells. EGCG inhibits protein synthesis, lipogenesis, and cell cycle progression through activation of AMP-activated protein kinase (AMPK) and inhibition of mammalian target of rapamycin (mTOR) in p53-positive and p53-negative human hepatoma cells (2). Also, EGCG has recently been shown to bind with high affinity to several "target" proteins, including: the 67-kDa laminin receptor, the Bcl-2 homology 3 (BH3) pocket of antiapoptotic Bcl-2 proteins, vimentin, IGF1-r (insulin-like growth factor I receptor), Fyn oncogene, GRP78 (glucose-regulated protein 78kDa), and Zap-70 (70 kDa zeta-associated protein) (3).

Lung cancer studies indicate that green tea acts as an antioxidant to reduce DNA damage and reduce the formation of DNA adducts, increases apoptosis and prevents the perpetual miscoding of DNA (possibly by inducing gene regulation). GTP also activates Phase II detoxifying enzymes and increases the secretion of carcinogens (also possibly by inducing gene regulation) (4).

Laboratory and clinical prostate cancer studies show that green tea catechins (GTCs), particularly epigallocatechin gallate (EGCG), exert chemopreventive effects largely driven through proteasome inhibition induced regulation of the nuclear factor kappa beta (NFκB) pathway. GTCs cause proteasome inhibition and subsequent cell cycle arrest, growth suppression, and ultimately apoptosis in prostate cancer cells. GTC-induced apoptosis results in the reduction of cancer cell dissemination, causing the inhibition of prostate cancer development, progression, and metastasis (1).

Clinical Evidence related to Effectiveness

Breast Cancer

A few systematic reviews, including one meta-analysis, have been conducted to explore the association between green tea consumption and risk of breast cancer or breast cancer recurrence (5-8). These reviews independently demonstrate a small potential for reduction in risk of breast cancer with green tea consumption, especially among heavy green tea drinkers. Authors of one systematic review conclude that green tea components, such as EGCG, may have antiproliferative effects on breast tumor cells (5). It is unclear whether there is a dose-response relationship between green tea consumption and risk reduction for both breast cancer development and recurrence. Some studies demonstrate a positive dose-response relationship, while others do not indicate any dose-response trend (8). In one study, a protective association was restricted to Chinese women with the ACE high-activity genotype, versus Chinese women with the ACE low-activity genotype (5).

In one RCT, investigators explored the effects of green tea (decaffeinated Polyphenon E, 400mg or 800mg for 2 months) on circulating hormone levels, as breast cancer risk factors, in addition to the effects on lipoprotein cholesterol and glucose. The authors report that green tea supplementation did not produce consistent patterns of changes in estradiol, estrone, or testosterone levels. Low-density lipoprotein (LDL)-cholesterol decreased significantly in people taking green tea supplements as compared to those taking a placebo. Statistically significant differences in changes in glucose and insulin concentrations were found between the placebo and green tea groups (9).

In a separate cross-over RCT, investigators evaluated the effect of green tea (400mg green tea extract for 3 weeks) on oxidative stress and antioxidant reserve level in patients treated with tamoxifen. The levels of oxidative stress and antioxidant reserve did not change significantly in the subgroup who took

green tea extract for 3 weeks followed by 3 weeks washout, while there was a statistically significant reduction in the levels of oxidative stress and an increase in the antioxidant reserve in the subgroup when 3 weeks of no treatment were followed by 3 weeks of green tea extract supplementation (10).

In another RCT, investigators explored the effect of green tea consumption (960mL decaffeinated green tea daily for 6 months) on select metabolic parameters and lipid profiles in overweight breast cancer survivors (11). Green tea intake was associated with elevated high-density lipoprotein (HDL) levels, resulting in positive shifts in the HDL/LDL ratio, in addition to a decrease in mean fasting insulin concentrations.

Prostate Cancer

Several observational studies, in addition to a meta-analysis of data from observational studies, have been conducted to explore the relationship between green tea consumption and prostate cancer risk. Further intervention studies, including randomized controlled trials, have explored the effects of green tea consumption on biomarkers of prostate cancer carcinogenesis.

The meta-analysis included data from a total of 7 cohort and case-control studies (12). Accounting for heterogeneity across studies, the meta-analysis indicates a statistically significant decreased risk of prostate cancer incidence for the highest consumers of green tea compared to those with low or no green tea consumption (OR = 0.52; 95% CI: 0.35, 0.79). A dose response analysis conducted as part of the meta-analysis suggests an inverse but not statistically significant association for 2 cups/day increment of green tea consumption against prostate cancer risk (OR = 0.83; 95% CI: 0.64, 1.06). For Asian populations, high green tea consumption had a borderline significant decrease of 38% in prostate cancer risk.

Intervention research has focused on the effects of green tea consumption on cancer diagnoses, as well as biological markers of cancer development and progression. In one randomized, placebo controlled proof of principle study, 60 men with high-grade prostate intraepithelial neoplasia (the primary premalignant lesion for prostate cancer) took green tea catechins (200 mg, 3x per day) or placebo for 1 year (13, 14). After 1 year of treatment, only one cancer was diagnosed among the 30 men that received green tea daily (3%), while nine cancers were found among the 30 men treated with placebo (30%). Further, quality of life improved among men in the green tea group, but not in the placebo group. PSA values did not differ significantly between groups throughout the study. Other intervention studies have shown mixed results concerning the effects of green tea consumption on PSA levels. In a randomized controlled trial, 50 men with prostate cancer were randomized to take 800 mg of EGCG or placebo for 3-6 weeks before surgery. Men in the EGCG group demonstrated favorable but not statistically significant changes in their PSA levels (15). In this study, tissue biomarkers of cell proliferation, apoptosis, and angiogenesis in the prostatectomy tissue did not differ between the two arms. A separate randomized controlled trial using a similar protocol included 33 men with a recent diagnosis of prostate cancer and demonstrated decreases in several tissue biomarkers (16). In this study, a significant decrease was observed in PSA in addition to serum levels of hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF)-I, and IGF binding protein-3 (IGFBP-3) in men who took EGCG as opposed to men who took placebo ($p < 0.03$ for all comparisons). One Phase II uncontrolled trial explored the effect of consumption of 6 grams of green tea per day taken orally in 6 divided doses, on PSA levels in 42 men diagnosed with androgen independent prostate cancer (17). After one month, PSA levels increased by 43% (median change). Only one man sustained a 50% decrease in PSA levels, from 229 ng/dL to 105 ng/dL, which did not continue after 2 months. A separate

uncontrolled trial enrolled 19 men to take green tea extract capsules at a dose level of 250 mg twice daily, and assessed the effects on PSA levels and disease progression (18). The study was closed early after an interim analysis revealed only a remote probability of positive outcomes. Of the 15 patients who consumed green tea for at least 2 months, nine patients had progressive disease within 2 months of starting therapy and the other six patients had progressive disease within 3-5 months. None of the participants met the standard definition of a "responder", indicating a PSA drop of greater 50% from baseline. In summary, further rigorous controlled intervention trials are needed to understand the effect of green tea on PSA levels.

Lung Cancer

Several systematic reviews and meta-analyses have been conducted to assess clinical effectiveness of green tea on lung cancer. In one systematic review exploring the association between green tea consumption and lung cancer risk (20 published studies, including 6 cohort studies), overall results demonstrate a slight protective effect with green tea consumption (19). A dose–response analysis of observational data from 6 publications including 2,381 lung cancer cases suggests a favorable effect of green tea consumption on lung cancer, especially for consumers of more than 7 cups per day. In this meta-analysis, the combined risk ratio (RR) for consumers of 7, 8, 9 and 10 cups per day were 0.82 (0.68–0.99), 0.77 (0.62–0.94), 0.72 (0.56–0.87), and 0.67 (0.48–0.79), respectively. Notably, no significant association was found for black tea consumption with lung cancer (20). Further, four of seven studies that reported associations among nonsmokers showed a significant protective association for a high intake of tea. With respect to smokers, there is limited evidence that green tea has a protective effect. A systematic review of 78 studies suggests that regular intake of green tea at high levels (>3 cups per day) may offer protection against tobacco carcinogens for smokers, provided that the duration of green tea consumption covers the smoking period (9). It is possible that consuming high levels of green tea over a long period may reduce DNA damage caused by tobacco smoking. A systematic review of clinical trials and preclinical studies explored the safety and efficacy of green tea for the treatment and prevention of lung cancer and considered potential interactions with conventional chemotherapy and radiation therapy (21).Three intervention trials were reviewed, in addition to 79 preclinical studies. One included randomized controlled trial documented a decrease in a biomarker of DNA damage (8-OHdG) following daily consumption of four 8oz cups of green tea for 4 months. Neither of the two Phase I studies that were included documented an objective tumour response; however, disease stabilization was observed for up to 4-6 months. A separate meta-analysis on green tea consumption and the risk of lung cancer included data from 12 studies (five prospective studies and seven case-control studies). This meta-analysis showed a borderline significant 22% decreased risk of developing lung cancer for highest green tea consumption compared with non/lowest green tea consumption (RR = 0.78, 95% CI = 0.61–1.00), although statistically significant heterogeneity was observed among the study results ($P < 0.001$, $I^2 = 78.5\%$). Given the wide array of measurement categories reported among studies, a dose–response analysis of green tea consumption for lung cancer risk was also conducted and indicated that an increase in green tea consumption of two cups/day was associated with an 18% decreased risk of developing lung cancer (RR = 0.82, 95% CI = 0.71–0.96) (22). Within individual studies, there is a need to improve measurement of green tea intake in order to confirm the chemopreventive effect of green tea observed from *in vivo* animal and human trials (4).

One prospective clinical trial aimed to determine the maximum tolerated dose of green tea extract in patients with advanced lung cancer. In this Phase I study, 17 patients with advanced lung cancer received daily oral green tea extract, starting at a dose of 0.5 g/ m^2, with an accelerated dose-escalation scheme. The maximum tolerated dose was 3 g/m^2 (equivalent to 20 cups of tea), with no grade 3 or 4

toxicities observed at this dose. No treatment effect was observed, however, and there was consistent development of progressive disease regardless of dosing level. Despite a very small sample size per dose, the authors concluded that green tea is unlikely to be an effective cytotoxic agent against existing tumors (23).

Oral Cancer

In a large cohort study, 50,221 people were followed for approximately 10 years to assess the relationship between green tea consumption and oral cancer incidence (24). The calculated hazard ratios suggest no association between green tea consumption and oral cancer incidence. A tendency towards a reduced risk was found in women, and among people who drank 5 or more cups of green tea per day, although neither association was statistically significant.

In a randomized controlled trial, 41 people with oral premalignant lesions were randomly assigned to receive either 500 mg/m^2, 750 mg/m^2 or 1000 mg/m^2 green tea extract, or placebo, three times a day after meals for 12 weeks (25, 26). In this study, no significant clinical or histological response was documented. In a separate controlled trial, 64 people with a premalignant lesion (oral leukoplakia) took daily capsules containing 0.38 g of green tea extract, green tea polyphenols and black tea polyphenols (theaflavins and thearubigins), (approximately equal to 800 mL of brewed tea), or a placebo, for six months (27). Tea mixed in glycerin was also topically applied to the lesions. Oral lesions were significantly reduced in size in 38% of people in the green tea group as compared with 10% of patients in the placebo group. Further, the cell proliferative index in oral mucosal cell nuclei was lower in the treatment versus the control group.

Liver Cancer

One meta-analysis of observational studies quantitatively summarized the results of 8 studies exploring the relationship between green tea consumption and the risk of primary liver cancer (28). A separate systematic review explored the relationship among liver diseases, including liver cancer, based on data from 10 studies using interventional and observational designs (29). Authors of the meta-analysis report a moderate protective effect of green tea on primary liver cancer (RR=0.79; 95% CI=0.68– 0.93). The authors of this review suggest that green tea might be more effective in fatty liver disease and liver disorders than in liver cancer treatment, as the 2 studies included in their review that focused on liver cancer did not demonstrate a significant protective effect.

Stomach and Esophagus

One systematic review evaluated all studies reporting an association between green tea consumption and the risk of gastrointestinal cancers (30). The case control studies included in this review indicate a decreased risk of gastric cancer with green tea consumption; the cohort studies, however, suggest no association. Similarly, case control studies suggest a significantly decreased risk of stomach cancer with high green tea consumption ($\geq$ 7 cups/day); but, the cohort studies suggest no association. A separate systematic review included a meta-analysis of data describing the association between the consumption of green tea and the risk of stomach cancer (31). As with the other systematic review (89), in this meta-analysis case-control studies indicate a preventive effect of green tea consumption on stomach cancer risk (RR= 0.73; 95% CI: 0.64–0.83), while cohort studies indicate no association (RR=1.04; 95% CI, 0.93–1.17).

Chronic Lymphocytic Leukemia (CLL)

Two early phase human studies have been conducted on patients with chronic lymphocytic leukemia (CLL), and both are suggestive of potential biologic response with green tea therapy. The most recent Phase 1/2, uncontrolled, non-randomized trial was conducted to evaluate the clinical efficacy of green tea extract, Polyphenon E (EGCG), for patients with early stage CLL. A total of 42 patients received Polyphenon E at a dose of 2,000 mg twice daily for up to 6 months. Overall, 29 patients (69%) fulfilled the criteria for a biologic response with either a sustained decline ≥ 20% in the absolute lymphocyte count (ALC) for at least 2 months and/or a reduction ≥ 30% in the sum of the products of all lymph node areas at some point during the 6 months of active treatment. In this study, EGCG plasma levels after 1 month of therapy were found to be correlated with reductions in lymphadenopathy (correlation co-efficient, 0.44; $P < .02$) (32).

A separate case series including four female CLL patients who self-initiated green tea polyphenol therapy, similarly suggests biologic response following consumption of green tea. In this case series, three of the four patients met criteria for partial response (PR) by standard response criteria (NCI criteria for patients with CLL and International Working Group Criteria for patient with follicular lymphoma) and one having stable disease despite the reduction in absolute lymphocyte count. Three of the four patients had documented steady clinical, laboratory, and/or radiographic evidence of progression immediately prior to initiation of various over-the-counter green tea products; but, then developed objective responses shortly after initiating green tea polyphenol therapy. As of the date of publication of the study, none of the four subjects had required conventional therapy at 27, 44, 77 and 120 months (respectively) after diagnosis (33).

Female reproductive cancers (including ovarian, endometrial, vulva, cervical, vaginal)

One meta-analysis summarizes available evidence on the association between green tea consumption and the risk of ovarian and endometrial cancers (34). According to the authors, there are no published data from epidemiologic studies of green tea intake and risk of cervical, vaginal, or vulval cancers. Data from four case-control studies suggest an inverse association between green tea intake and risk of ovarian cancer (OR=0.66, 95% CI: 0.54, 0.80). Similarly, data from six case-control and cohort studies support a protective effect of green tea on endometrial cancer risk (OR=0.78; 95% CI: 0.62, 0.98).

In a separate systematic review, authors summarized available evidence from four case control studies concerning green tea and ovarian cancer (35). In their meta-analysis, it was shown that women who drink green tea (≥1 cup/green tea day) have a lower risk of ovarian cancer as compared to those women who never/seldom drink green tea (OR=0.58; 95% CI: 0.33–1.01).

A separate systematic review designed to evaluate the relationship between tea consumption and endometrial cancer risk, reports a subgroup analysis by tea type (green vs. black). In this subgroup analysis, green tea consumption was significantly associated with decreased risk for endometrial cancer (RR=0.79; 95% CI, 0.69–0.90), whereas no significant association was observed for black tea (RR=0.75; 95% CI, 0.45–1.27) (36). One population-based case-control study conducted in China demonstrates that the protective effect of green tea consumption on endometrial cancer is more pronounced among women with the *Asp/Asp* genotype, and in particular for post-menopausal women in this group.

Pancreatic

One large case-control study suggests that drinking 5 or more cups of green tea per day is positively associated with an increased risk of developing pancreatic cancer (37). A separate Japanese cohort study explored the relationship between green tea consumption and the risk of death from pancreatic cancer (38). From this study, no inverse association was observed between cups of green tea consumed per day and the risk of death from pancreatic cancer in men and women combined. The adjusted RR of mortality was 1.23 (95% CI 0.84-1.80) for people who consumed 7 or more cups of green tea per day as compared with those who consumed less than 1 cup per day.

Colorectal

One meta-analysis explored the relationship between green tea consumption and colorectal cancer risk (39). Overall, data from 4 cohort and 4 case-control studies support a moderate reduction in risk with high green tea intake (OR = 0.86; 95% CI = 0.73–1.00); however, this inverse association was significant only in case–control studies (OR = 0.74; 95% CI = 0.63–0.86), but not cohort studies (OR = 0.97; 95% CI = 0.82–1.16). The overall results in women show a non-significant 50% reduction in colorectal cancer risk with high intake of green tea (OR = 0.52; 95% CI = 0.25–1.05), but no such effect was observed in men (OR = 0.89; 95% CI = 0.73–1.08).

In a randomized controlled trial, 136 people newly diagnosed with colorectal polyps underwent surgery to remove their adenomas and 1 year later confirmed a clean colon (40). People were then randomized to 1.5g/day green tea extract or no supplementation for 1 year. After 1 year, at least one colorectal adenoma was diagnosed in 31% of the patients in the control group but in only 15% of those who took the green tea extract (RR= 0.49; 95% CI: 0.24-0.99). The size of the adenomas was also smaller in the supplementation versus control group.

Skin

Two randomized controlled trials have assessed whether topical application of green tea extracts could provide protection against solar radiation. In one RCT researchers investigated whether application of 3mg EGCG/100 µL acetone/2.5 cm^2 could inhibit UVB-induced infiltration of leukocytes (macrophage and neutrophils), a potential source of generation of both reactive oxygen species (ROS), and prostaglandin (PG) metabolites(41). In this study, green tea when applied topically before UVB exposure significantly blocked leucocyte infiltration, reduced myeloperoxidase activity and decreased UVB-induced erythema. Microscopic examination of skin revealed that green tea pretreated human skin contained fewer dead cells in the epidermis as compared to untreated skin. In the second RCT, researchers investigated whether topical application of green tea extract could prevent simulated solar radiation-induced oxidative damages to DNA and Langerhans cells, which could lead to immune suppression and carcinogenesis (42). They observed that green tea partially prevented UV-induced depletion of CD1a+ cells and UV-induced generation of 8-OHdG in irradiated healthy subjects; partially preserved the contact hypersensitivity response after solar exposure; and, contributed to a decreased number of Langerhans cells in a dose-dependent fashion.

Biliary Tract

A large population-based case-control study (n=2,623) evaluated the effects of green tea consumption on the risk of biliary tract cancers and biliary stones (43). Among women in the study, green tea drinking was associated with lower risks of gallbladder (OR = 0.56; 95% CI = 0.38–0.83) and bile duct cancers (OR = 0.65; 95% CI = 0.37–1.14). Several green tea drinking characteristics, including age of first use,

duration, monthly intake and lifetime consumption were significantly and inversely associated with gallbladder cancer risk. Among men, risk estimates for biliary tract cancers were less than 1.0, but were not significant. When the effect of green tea drinking was evaluated according to smoking status, no significant difference could be discerned, however there appeared to a trend towards protection for male nonsmokers, but not for male smokers on the incidence of bile duct cancer (nonsmokers: OR = 0.63; 95% CI 5 0.28–1.43; smokers: OR = 1.17; 95% CI 5 0.63–2.19).

Cancer Prevention

Several studies have explored the effectiveness of green tea in preventing or slowing the progression of a range of cancer types. In one systematic review researchers analyzed 2 randomized controlled trials and 21 observational studies on green tea and cancer prevention related to gastric, esophageal, colon, rectal, pancreatic, oral, pharyngeal, prostate, breast, lung and "all" cancers (44). Across cancer types, individual study results support either an inverse association between green tea consumption and cancer risk, or no association, with some evidence to support a dose-response relationship. Importantly, none of the studies included in this review documented green tea consumption to be associated with increased cancer risk. In a separate literature review, researchers reviewed observational and interventional data on green tea, its extract or EGCG (45). They report that the systematic reviews assessed were generally inconclusive regarding the protective effect of green tea for most types of cancers; while cohort studies show that green tea consumption provides no protection against gastric and pancreatic cancers but perhaps some protective effect for lung, breast, ovarian and prostate cancer. The primarily observational research on the topic continues to be confounded by different preparations and doses of green tea, and various lengths of treatment, which makes drawing firm conclusions difficult.

Adverse Events and Side Effects

Side effects are predominantly mild and often related to caffeine content. Many people tolerate green tea consumption without experiencing any side effects (10, 13, 14, 17). Clinical evidence suggests that adverse effects include primarily gastrointestinal (GI) and central nervous system (CNS) disturbances (44). Common side effects include excess gas, upset stomach, nausea, vomiting, heartburn, abdominal pain, diarrhea, muscle pain, dizziness, headache, insomnia, anxiety, fatigue, agitation, restlessness and confusion (17, 18, 40, 46, 47). Chronic caffeine intake can lead to increased tolerance and psychological dependence.

Large doses may cause diarrhea, nausea and hypertension (23) and have been found to be associated with increased neurological toxicity, which might be related to higher caffeine plasma levels (25, 26).

Grade 3 and 4 side effects have been noted in various studies, including transaminitis, abdominal pain, insomnia, confusion, diarrhea, anorexia and fatigue (17, 18, 32).

Interactions with other Therapies, including Drugs and Natural Health Products

Green tea might interact positively with some chemotherapeutics but negatively with others. Preclinical evidence has demonstrated a synergistic effect with doxorubicin, gemcitabine (GEM), mitomycin C, paclitaxel, and 5-fluorouracil; however, green tea has been documented to inhibit the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors (2, 47, 48). Green tea should only be used in combination with chemotherapy under the guidance of a qualified health professional.

Other interactions associated with green tea are predominantly related to the caffeine content. Caution is therefore advised when taking other caffeinated agents concurrently with caffeinated green tea, for example coffee, colas, guarana, cola nut, and yerba mate. Concurrent use may increase the risk of stimulatory adverse effects. Other interactions are possible, for example with ACE inhibitors, antiypertensives and cardiovascular drugs, so caution is warranted when taking green tea in concentrated forms. Consultation with a naturopathic doctor and/or a pharmacologist with training in natural health products is recommended.

Cautions and Contraindications

Contraindications: Green tea should not be taken in any form by people with atrial fibrillation, or with a known allergy or hypersensitivity to tea (Camellia sinensis), its constituents, caffeine, tannins, or members of the Theaceae family (47). Caffeinated green tea is best avoided by pregnant and lactating women, as well as children.

Cautions: while not absolute contraindication, caution and close monitoring is warranted in cases of either high or low blood pressure, where there is a risk of cardiovascular disease (other than atrial fibrillation in which case green tea should be avoided), with gastrointestinal disorders, with liver disorders, with or at risk of neurological or psychiatric conditions, with renal or electrolyte disorders, with or at risk of respiratory disorders, with diabetes, with or at risk of iron deficiency, with bleeding disorders, with hormone disorders or postmenopausal women and with or at risk of folic acid deficiency (47). Green tea should not be taken on an empty stomach.

Dosing

A range of green tea doses have been used across research studies, most commonly providing 400-800mg of green tea catechins (9, 10, 13). Positive effects of green tea on cancer risk have been documented with larger doses: more than 7 cups per day (20, 31, 37). One study documented the maximum tolerated dose to be 3 g/m^2, which is equivalent to 20 cups of tea (23, 44). Regular consumption is necessary for a sustained effect (4). Treatment recommendations at the OICC follow these guidelines.

Disclaimer

The OICC has prepared this monograph, as part of a series, to share results of a review of the scientific literature related to common therapies and products used within patient care at our centre. It therefore reflects therapies and products used within the defined scope of practice for our practitioners in Ontario, Canada. The information in this monograph should not be interpreted as medical advice nor should replace the advice of a qualified healthcare provider.

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Monograph Development Methodology

SEARCHING

Databases: Based on a systematic review of green tea for the treatment and prevention of lung cancer (Fritz et al., 2012), the search was limited to PubMed and EMBASE. For that systematic review, other databases were initially searched (e.g., CINAHL, Alt HealthWatch, Cochrane, and the National Library of Science and Technology) but relatively few studies of interest were identified.

Search terms: The following strategy was executed in PubMed and altered for EMBASE.

PubMed:
("Camellia sinensis"[Mesh] OR "green tea extract AR25" [Supplementary Concept] OR "epigallocatechin gallate" [Supplementary Concept) OR "Catechin"[Mesh] OR "peracetylated epigallocatechin-3-gallate" [Supplementary Concept] OR "epigallocatechin-3-O-(3''-O-methyl)-gallate" [Supplementary Concept] OR "theasinensin A" [Supplementary Concept] OR "polyphenon E" [Supplementary Concept])

(Green tea, camellia sinensis, egcg) Title/Abstract

"Chemoprevention"[Mesh] OR "Neoplasms"[Mesh] OR "Lymphoma"[Mesh] OR "Lymphoma, Non-Hodgkin"[Mesh]

(chemoprevention, cancer*, neoplasm*, carcino*, malignan*, lymphom*, tumor*, tumour*, oncolog*) Cancer,

Timeline: From inception to the most recent publication date of the database in question.

Language: Only English language studies will be included.

Reference list scan: Not done.

Contact experts: Not done.

SCREENING

All search results (titles and abstracts) were screened by one reviewer and decisions for inclusion (yes/no/maybe) were made based on predefined inclusion/exclusion criteria developed using the PICOD format. The full-text of articles passing through the title and abstract screening phase was obtained and a final decision regarding their inclusion was made based on the same inclusion/exclusion criteria by one reviewer. As needed, another reviewer helped resolve inclusion status for questionable items.

Inclusion

- Purposes of treatment or prevention of cancer, reduction of side effects and toxicities associated with chemotherapy or radiation therapy, or assessment of potential interactions with these therapies in patients with cancer.
- Human intervention study of any design
- Able to access full-text

Exclusion

- Studies that examined synthetic catechins derivatives or black tea were excluded.

DATA EXTRACTION

Data were extracted using a standardized and piloted form that includes fields within each monograph section. Data were extracted independently by one reviewer.

DATA ANALYSIS

Data analysis differed by monograph section, but was primarily be descriptive.

A quality assessment of all included articles was not conducted.