GREEN TEA
In the Fight Against Cancer
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“Green tea is healthy, yes. You are crazy if you don’t drink green tea.”
- Jonathan Reynolds

This is true provided:
• your tea comes straight from the plantation, or
• you drink High-Potency Green Tea!

Green tea leaf powder has been reported to be effective in reducing the risk of human cancers if it is swallowed or sprinkled on foods or ice cream. This is far from the truth. There is an urgent need to disseminate accurate information about drinking green tea for health promotion among the public consumers, who want to manage their own health by adopting a healthy lifestyle and a healthy diet.

Read to manage your health by asking
“What is in your Green Tea?”

A Note to the Reader: This review is written for the health professionals who are treating cancer patients and for those readers who are interested in obtaining reliable scientific information on the use of green tea as a dietary supplement in the combat against cancers. Recent molecular biology research has unveiled a secret in medical science that the ancient beverage of green tea helps humans to fight cancer, not only in preventing or in delaying its occurrence, but also playing a role in boosting the anticancer effects of chemotherapy. If you are not familiar with the terminology used in molecular biology, just skip that paragraph. If you have any questions, consult your local medical oncologist who may be able to help you.

For more information, visit www.teaforhealth.com.
Summary

This article summarizes the most recent scientific research data relevant to drinking green tea, a soothing herbal beverage, as a chemopreventive dietary supplement and as an adjunct to chemotherapy in the fight against cancer. There is ample scientific evidence to support the decision of drinking green tea to reduce the cancer risk of the breast, lung, esophagus, stomach, colon, rectum, prostate and pancreas, and to boost the anticancer effects of chemotherapy without any added toxicity, which in fact can be reduced by green tea. Since we are drinking green tea for its medicinal purposes, we must drink tea of high quality at an appropriate dosage in order to obtain the best health benefits of tea drinking. Readers are encouraged to consult their health care professionals for additional personal advice.
Introduction

In a routine medical practice, doctors only prescribe an FDA-approved drug listed in the Physicians’ Desk Reference® (PDR) for a specific condition listed in the PDR as an indication to be treated by the drug. Tea is a natural product. It is not under the jurisdiction of the FDA drug regulation. However, tea is a beverage with important medicinal functions. One of them is its chemopreventive effects in reducing cancer risk and its effects on enhancing the anticancer activities of many chemotherapeutic drugs, a potential health benefit only unveiled in the past few years. We are relating this information to the medical doctors, their cancer patients, and other educated consumers who are interested in the subject.

Carcinogenesis (how a cancer is formed)

At the cellular level, an original “cancerous” cell is nothing but an ordinary cell affected by genetic mutation, namely damage (alteration) to its DNA code usually caused by carcinogen if the damage is not repaired. The mutated cells remain latent for a long period of time until some new qualities become evident and the phenomenon can be diagnosed as cancer. This latency may average from 9 years for cancer induced by X-rays to 40 years for cancer caused by solar radiation. During this latent period a number of mutated genes may accumulate in the damaged cell, causing it to become a biologically active cancer cell. Most genetically damaged cells never become cancerous, or remain in the stage of pre-cancerous until the host dies of unrelated diseases.

Some cancers may be the result of inadequate DNA repair. For example, cigarette smokers with lung cancer have a DNA repair capacity five times lower than healthy controls, and patients with xeroderma pigmentosum have an inherited reduced capacity of DNA repair, a predisposition to skin cancer. Cigarette smoke as a toxin damages the DNA bases, resulting in large disruptive molecules called DNA adducts. When these adducts occur in cells that divide and reproduce throughout our lives (such as the cells that line our lungs), these cells can become cancerous.

The clinical history of cancer development may be divided into three stages, namely initiation, promotion and progression. It is not possible to avoid carcinogens in life. Carcinogens, or pro-carcinogens, are being introduced into our bodies, or formed in the body constantly. Cancer initiation happens frequently at the cellular level, as a result of carcinogenic damage to the DNA. But these genetically altered or mutated cells may remain dormant until a promoter comes along to encourage them to proliferate. However, to be potentially fatal to the host organism like a human body, the cancer cells must be able not only to divide, but also to invade the surrounding normal cells, i.e., to grow and to spread at the expense of their normal neighboring tissues – a process called metastasis. Numerous drugs have been developed in an attempt to interrupt this procession of cancer development, but all at a cost in terms of adverse side effects associated with the drugs. Green tea is almost like a “drug” with multiple actions, but with little toxicity.

Chemotherapy (using chemicals to control cancer growth)

Chemotherapy is the use of chemicals, namely approved drugs, to kill cancer cells, usually by preventing the formation of new DNA or by blocking some other essential function in the cell. Although not being comprehensive, the commonly used chemotherapeutic drugs fall into one of the following four categories:

Alkylating agents: They work by preventing DNA from uncoiling, thereby blocking DNA replication and cell division. Examples are nitrogen mustard and cyclophosphamide commonly known as Cytoxan [Mead Johnon].

Anti-metabolites: They masquerade as building blocks of DNA and other vital components of the cell, working as competitive inhibitors to prevent proper cell replication. Examples are 5-fluorouracil and methotrexate.

Plant alkaloids: They inhibit cell division by preventing formation of the microtubules critical to mitosis. Examples are vincristine, vinblastine, Paclitaxel (Taxol®) and colchicine.

Anti-tumor antibiotics: They block cell division by binding to DNA or by inhibiting the enzymes needed for proper unwinding, such as DNA topoisomerases, and replication of DNA. Examples are doxorubicin (a topoisomerase II inhibitor), camptothecin (a quinoline-based alkaloid found in the barks of the Chinese camptotheca tree, a topoisomerase I inhibitor), bleomycin, mitomycin and cisplatin.
All these drugs are often used in combination with one another. Being cancer cell killers, they also kill healthy dividing cells, such as those lining the gastrointestinal tract, in hair follicles and in the bone marrow. They are referred to as cytotoxic agents, and may be carcinogens themselves, capable of causing a secondary cancer in the patients. Some of them have organ-specific toxicities. For example, doxorubicin is more toxic to the heart and liver than to other organs. Therefore, doctors do not prescribe chemotherapy for their patients unless they have evidence to prove that the malignant tumor is spreading or has a high tendency to spread.

In the past few years, medical research has shown that green tea or its components can work independently or synergistically with the standard chemotherapeutic drugs to control spreading cancers. Drinking green tea as a dietary supplement to standard chemotherapy may offer a greater chance of saving life, re-establishing health or alleviating suffering to the cancer patients.

**Multi-focal anticancer mechanisms of green tea**

The exact mechanism of chemoprevention and anticancer activity of green tea is still poorly understood. However, its anticancer activities at multiple steps of the cancer development and its synergistic anticancer effects when combined with certain chemotherapeutic agents have been extensively studied worldwide. A brief summary of some of these publications, which may be useful for the evidence-based counseling between doctor and patient to support an informed decision to use green tea as a dietary supplement for reducing cancer risk and to boost the effects of chemotherapy in the fight against cancer, is presented as follows.

**Cancer prevention**

I. **Green tea inhibits formation of N-Nitroso-compounds (carcinogens) in stomach.**

Some food products, for example, salt-preserved fish and preserved meats containing nitrite, are nitrosated in the stomach, resulting in release of potent elastogenic and mutagenic compounds which are carcinogenic. Green tea inhibits this chemical reaction. Simultaneous intake of green tea with these food products has been shown to reduce the formation of mutagenic nitrosamine products in the stomach (1).

II. **Green tea modulates gene expression of enzymes responsible for carcinogen metabolism.**

Certain environmental substances require an endogenous enzyme or enzymatic system in the body to convert them into active carcinogen. For example, when sodium nitrite and methylbenzylamine are administered in rats, in vivo nitrosation will take place to form N-nitrosomethylbenzylamine, a carcinogen through enzymatic activities in the body. Green tea blocks the in vivo formation of the N-nitroso compounds and inhibits carcinogenesis (2).

In another example, green tea inhibits the gene expression of the hepatic cytochrome P450-dependent mixed-function oxidase system, which is closely associated with bioactivation of chemical carcinogens. It is well known that aryl hydrocarbon induces cancers in animals and its action can be blocked by green tea. The aryl hydrocarbon receptor (AhR) mediates the transcriptional activation of CYP1A1 and CYP1A2. Green tea inhibits the transcription of a human CYP1A promoter-driven reporter gene induced by the AhR ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in a concentration-dependent manner and inhibits the induced accumulation of both CYP1A1 and CYP1A2 mRNAs. Green tea extract and (-)-epigallocatechin gallate (EGCG), the most abundant active catechin antioxidant in tea leaves, were able to inhibit TCDD-induced binding of the AhR to DNA and subsequent CYP1A transcription (3). The effects of green tea polyphenols against skin-tumor-initiating activity induced by polycyclic aromatic hydrocarbons (PAHs), the “pro-carcinogens” present in smoke from cigarettes, automobile emissions and grilled foods have been known since 1989 (4).

On the other hand, green tea may activate numerous other detoxifying enzymes, such as quinone reductase, glutathione/glutathione-S-transferases, epoxide hydrolase, and UDP-glucuronosyltransferases, enhancing the activity of these so-called phase II enzymes, to metabolize the carcinogens (5, 6).

III. **Green tea inhibits tumor promoters (e.g. TPA, enhancer of the effects of many carcinogens).**
Topical application of a green tea polyphenol fraction on the mouse skin can inhibit the effects of the tumor promoter, 12-O-tetradecanoyphorbol-13-acetate (TPA), on the initiation of tumor induced by benzo[a]pyrene- and 7,12-dimethylbenz[a]anthracene (DMBA). Topical application of the green tea polyphenol fraction also inhibits TPA-induced inflammation, ornithine decarboxylase activity, hyperplasia and hydrogen peroxide formation (7).

IV. Green tea inhibits inducible NO-synthase (thus endogenous carcinogens).

Chronic inflammation is associated with excessive release of nitric oxide (NO) and superoxide anion, which can react together to yield peroxynitrite. The latter compound can eventually cause damage to the DNA, inducing cancer formation. Green tea polyphenols are potent inhibitors of nitric oxide synthase gene expression, thus performing an important function of cancer prevention (8,9)

Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are important enzymes that mediate inflammatory processes. Green tea suppresses improper up-regulation of COX-2 and/or iNOS, which is associated with pathophysiology of certain types of human cancers as well as inflammatory disorders. Green tea EGCG may inhibit COX-2 and iNOS expression by blocking improper activation of a transcription factor, nuclear factor-kappa B [NF-kappa B] (10).

V. Green tea catechins are antioxidants to free radicals, thus reducing DNA damage by carcinogens, e.g., ultraviolet (UV) radiation.

The most remarkable cancer chemopreventive effect of green tea (or its components) is due to its antioxidative activity. In the skin, oxidative stress induced by ultraviolet irradiation can be readily observed. The pathological changes may be in the form of erythema, edema, epithelial hyperplasia, dysplasia, or skin cancer. Topical application of EGCG to human skin before UV irradiation decreases the UV-induced erythema, UV-induced production of hydrogen peroxide and nitric oxide in both epidermis and dermis. The degree of UV-induced infiltration of inflammatory leukocytes into the skin, which are considered to be the major producers of reactive oxygen species, is markedly reduced by EGCG pretreatment. The latter treatment also restores the UV-induced decrease in glutathione level and protects the antioxidant enzyme glutathione peroxidase (11). At high concentration, EGCG, which is an antioxidant, may have pro-oxidative activities causing generation of hydrogen peroxide, functioning as a mediator to apoptosis (12).

VI. Green tea inhibits telomerase that co-determines the division capacity of a cell.

More than 85% of all cancers express telomerase activity whereas most somatic cells appear to lack detectable levels of telomerase. Germ line cells also express telomerase activity, but they have longer telomeres than cancer cells. A group of researchers discovered that EGCG is a strong inhibitor of telomerase, and suggested that telomerase inhibition may be one of the major mechanisms underlying the anticancer effects of tea (13).

VII. Green tea inhibits DNA topoisomerases I and II, which regulate DNA topology in cell division.

DNA topoisomerases I and II are essential for proper DNA rejoining and structural configuration during cell proliferation. DNA topoisomerases are the target of many anticancer drugs. Like doxorubicin, EGCG is a DNA topoisomerase inhibitor against cancer cells, but without its toxicity to normal tissues (14, 15). In addition, the special tea amino acid, theanine, is a biochemical modulator that has been shown to inhibit efflux of a DNA topoisomerase II inhibitor, doxorubicin, from the cancer cells, but not to reduce the outflow of the topoisomerase II inhibitor from the normal cells (16-19).

VIII. Green tea induces apoptosis via a mitochondrial pathway.

There are two distinct primary signaling pathways of apoptosis, one of which is the extrinsic or death receptor pathway controlled by caspase 8 and caspase 10 through a tumor necrosis factor receptor on surface of the cell membrane (TNF receptor).

The other is the intrinsic or mitochondrial pathway, which occurs within the cell through release of cytochrome C from the mitochondria and activation of caspase 9. Normal Bcl-2 and Bcl-XL proteins in the mitochondrial membranes prevent pore formation and leakage of cytochrome C from the mitochondria to the cytoplasm. Cytochrome C activates caspase 9, which in turn activates other caspases, a series of proteases that digest the structural proteins in the cytoplasm, damage the
DNA, and cause cell death. Bax protein is a Bcl-2 family member in the mitochondrial membranes, but is activated by this pathway to increase the permeability of the mitochondrial membrane, releasing cytochrome C to the cytoplasm.

EGCG decreases the Bcl-2 and Bcl-XL proteins, increases the Bax protein, and activates caspase 9 in the cancer cells. Therefore, its anticancer activity appears at least in part mediated by the mitochondrial pathway (20).

IX. Green tea exerts effects on signal transduction - to inhibit activation of transcription factors, e.g., nuclear factor-kappaB (NF-κB), Cyclin D1, tumor-associated protein kinases, epidermal growth factor (EGF) receptors, and the release of tumor necrosis factor-alpha (TNF-α), an endogenous promoter for cancer genes.

Molecular signals, such as hormones or growth factors, are received by interaction between the signaling molecule (ligand) and a receptor specific for that signal on the surface of the cell. Through a series of steps, the message from that signal gets transmitted and amplified within the receiving cell, often leading to activation or deactivation of specific transcription factors in the nucleus, thus regulating the events in cell proliferation, differentiation and apoptosis, for example by controlling the gene expression of endogenous promoters like a tumor necrosis factor (21). This process is referred to as signal transduction pathways, involving the products of several genes (for example, Ras) that are mutant in cancer cells.

One of the key pathways is the mitogenic signal transduction through the cascade of mitogen-activated protein (MAP) kinase that also includes other transducing molecules such as MAP kinase (MEK) and Raf-1. The MAP kinase signaling, for instance, enhances cyclin D1 for cell proliferation, but also arrests cell growth by increasing expression of the cyclin kinase inhibitor p21 (Cip-1/MDA6/WAF1). The level and duration of MAP kinase expression appears to control this differential effect.

Green tea has been shown to inhibit activation of many transcription factors. For example, it inhibits the tumor necrosis factor-α (TNF-α) gene expression (22, 23) as well as the okadaic acid-induced AP-1 and NF-kappa B activation (23).

Green tea EGCG inhibits both the autocrine activation of epidermal growth factor receptor (EGFR) signaling and the activation of the signal transducer by exogenous transforming growth factor-α (TGF-α). As a consequence, EGCG also inhibits signaling to the extracellular regulated kinase (ERK) proteins and activation of transcription 3 (Stat 3), which lies downstream of the TGF-α/EGFR signaling pathway and apparently protects cancer cells from apoptosis (20).

X. Green tea regulates faulty apoptosis independent of the p53 suppressor genes.

Green tea and its components significantly restore cancer cell apoptosis (24). They also affect p53 gene mutations. However, the cancer chemopreventive efficacy of green tea may be independent of p53 status of the cancer cells (25, 26).

XI. Green tea inhibits angiogenesis necessary for rapid tumor growth.

The components of green tea inhibit the process of forming new blood vessels (27) that are needed to support the fast growing rate of a malignant tumor. The anticancer effect of EGCG is at least in part due to its inhibition of angiogenesis through blocking the induction of vascular endothelial growth factor (VEGF) in human colon cancer cells. EGCG, not other catechins, inhibits ErK-1 and ErK-2 activation in a dose dependent manner (28). Physiological concentrations (0.01-1 µM) of EGCG induce a rapid and potent inhibition of VEGF-dependent tyrosine phosphorylation of VEGF receptor-2 (VEGFR-2). The inhibition of VEGFR-2 by EGCG is similar to that induced by Semaxanib (SU5416), a specific VEGFR-2 inhibitor (29).

XII. Green tea inhibits proteolytic enzymes, urokinase and collagenase, needed to establish cancer metastasis.

Human cancers need proteolytic enzymes to invade other neighboring normal cells and form metastases. One of these enzymes is urokinase (uPA). Inhibition of uPA can decrease tumor size or even cause complete remission of cancers in mice. The known uPA inhibitors, for example, amiloride, are unlikely to be used in anticancer therapy because of their weak inhibitory activity or high toxicity. EGCG binds to uPA, blocking the amino acids His 57 and Ser 195 of the uPA catalytic triad and extending towards Arg 35 from a positively charged loop. Such localization of EGCG would interfere with the ability of uPA to recognize its substrates and inhibits
its enzymatic activity. Based on laboratory studies, it has been recommended that drinking green tea containing 1,500 mg of EGCG per day may deliver more than adequate levels of EGCG to reduce the incidence of cancer in humans or the size of cancers already formed (30). A similar tea effect in suppressing cancer growth may be achieved by inhibition of type IV collagenase of the carcinoma cells by EGCG and some black tea components, such as theaflavin and theaflavin digallate (31).

Based on the scientific publications summarized above, drinking green tea helps to fight cancer at numerous steps, ranging from inhibiting the formation of carcinogens to hindering tumor metastases in the body after the cancer has been established.

**Boosting chemotherapy**

1. **Green tea inhibits human high-grade non-Hodgkin's lymphoma transplanted in mice and is more effective than cyclophosphamide (also known as Cytoxan) at its maximum tolerable dose to prevent tumor occurrence at the tumor transplantation sites.**

   This work was performed by Bertolini and his colleagues at the IRCCS European Institute of Oncology, Milan, Italy and published in *Leukemia* 2000 (32).

   In this study, the malignant tumor cells were obtained from the bone marrow of a 61-year-old male patient who had a diagnosis of a T cell-rich B cell non-Hodgkin lymphoma. The tumor cells displayed a CD3-, CD10+, CD13-, CD19+, GlyA-, sm/cy kappa+, sm/cy lambda- phenotype and a t(14:18) karyotype after passage in the mouse.

   The concentration of green tea consumed by the mice in the experimental group contained 708 µg/ml EGCG. Remarkably, 50% of the mice transplanted with tumor cells and drinking green tea in place of water did not develop visible tumors at all and were found to be free of tumor by autopsy dissection. In comparison, all of the water-recipient control mice (100%) developed measurable tumors at the injection sites. In a third group of mice treated with a maximum tolerable dose of cyclophosphamide, all animals injected with tumor cells developed visible tumor (100%) although the growth of the tumor was delayed, compared to the water-recipient controls.

2. **The green tea component, EGCG, induces cancer cell apoptosis (a programmed death). It also inhibits various signaling pathways related to the activation of growth factor receptors and activities of certain gene expression promoters, which are essential for the cancer cell division cycle. In addition, EGCG even at a low concentration of 0.1 µg/ml is found to enhance the anticancer effects of 5-fluorouracil by 45-fold. As a result, it has been proposed to administer green tea or EGCG as an adjunct to supplement chemotherapy.**

   This work was performed by Masuda, Suzui and Weinstein (20). The authors used human head and neck cancer cell lines for the laboratory study. Over-expression of the epidermal growth factor receptor (EGFR) occurs frequently in these cancer cells, which is an adverse prognostic factor. The authors found that treatment with EGCG increased the proportion of cells in the G1 phase of the cell cycle and induced apoptosis.

   In the cells treated with EGCG, there was a decrease in the cyclin D1 promoter activity, an increase in the p21Cip1 and p27Kip1 proteins, and a reduction in the hyperphosphorylated form of pRB. Changes that may account for the arrest of the cancer cells in G1 phase of the cell cycle.

   EGCG also caused a decrease in the Bcl-2 and Bcl-XL proteins, an increase in the Bax protein, and activation of caspase 9, suggesting that EGCG induces apoptosis via a mitochondrial pathway.

   The authors suggested that EGCG inhibits both the autocrine activation of EGFR signaling and activation of the signal transducer by exogenous transforming growth factor-α (TGF-α). As a consequence, EGCG also inhibits signaling to the extracellular regulated kinase (ERK) proteins and activation of transcription 3 (Stat 3) which lies downstream of the TGF-α/EGFR signaling pathway and which apparently protects cancer cells from apoptosis.

   The authors hypothesize that in the aggressive cancer cells, the EGFR is activated by TGF-α, in an autocrine manner, thus leading to activation of the ras-ERK and Stat 3 pathways. The c-fos, cyclin D1, Bcl-XL, and Bcl-2 genes are targets of these signal transduction pathways; therefore, tumor growth is enhanced. EGCG inhibits these signal transduction pathways and thereby induces G1 arrest and
apoptosis and potentiates the cytotoxicity of 5-fluorouracil.

In conclusion, the authors stated that it is possible to administer green tea or EGCG instead of EGFR antibodies or selected tyrosine kinase inhibitors in combination with radiation and certain chemotherapy agents for the treatment of cancer because green tea or EGCG appears to be non-toxic and can be used for a relatively long period of time without adverse side effects.

More recently, Ahn et al. (33) used human papillomavirus (HPV)-16 associated uterine cervical squamous cancer cell lines to study the effects of green tea EGCG on the cancer cells. They also found that green tea EGCG induces G1 cell cycle arrest and apoptosis. The authors further demonstrated in human patients that green tea EGCG can be a potential effective therapy regimen for HPV infected cervical lesions (34).

(3) Like doxorubicin, EGCG is a DNA topoisomerase inhibitor against cancer cells, but without its toxicity on normal tissues. In addition, the special tea amino acid, theanine, is a biochemical modulator that has been shown to inhibit efflux of a DNA topoisomerase II inhibitor, doxorubicin, from the cancer cells, but not to reduce the outflow of the topoisomerase II inhibitor from the normal cells. The use of two topoisomerases of different classes may have synergistic effects against cancer cells. The tea amino acid, theanine, may further augment the synergistic anticancer cytotoxicity by directing the flow of the DNA topoisomerase inhibitors to the cancer cells. Thus the use of green tea during administration of doxorubicin for the treatment of a systemic malignancy may enhance the anticancer effects of the chemotherapeutic agent and reduce its adverse side effects on the heart and liver.

Several authors have published reports on these above subjects in the past few years. The major points of their articles are briefly summarized here.

Berger and colleagues of Case Western Reserve University, Cleveland, OH, found that EGCG inhibits DNA topoisomerase I in several human colon carcinoma cell lines in the laboratory and suggested that combination of EGCG with other conventional topoisomerase inhibitors would be an improved strategy for treatment of colon cancer (14).

Suzuki and colleagues of Faculty of Pharmaceutical Sciences, Kumamoto University, Japan, discovered that EGCG is an inhibitor of both DNA topoisomerases I and II from various sources and compared its activity with that of doxorubicin (15).

Kamat and colleagues of Department of Urology, West Virginia University, Morgantown, WV, first observed synergism of two classes of DNA topoisomerase inhibitors in the suppression of cancer cell growth when they used a low concentration of ciprofloxacin or ofloxacin, both inhibitors of topoisomerase type II, to enhance the cytotoxicity of doxorubicin on cancer cells. Based on their observation, they recommended quinolone antibiotics as a potential adjunct to intravesical chemotherapy for bladder cancer (35).

Sadzuka and colleagues of School of Pharmaceutical Sciences, University of Shizuoka, Japan, reported that theanine inhibits the efflux of doxorubicin from the cancer cells selectively, thus raising its intracellular concentration in the malignant cells by 2.9-fold compared to the doxorubicin alone group. Theanine as a biochemical modulator enhances the antitumor activity of doxorubicin by inhibition of a cell membrane transporter system, which appears to be involved in glutamate uptake and export of topoisomerase inhibitors like doxorubicin. In the mice bearing P388 leukemia cells that were resistant to doxorubicin, administration of theanine rendered the leukemia cells sensitive to the cytotoxic effects of doxorubicin treatment again (16-19, 36).

(4) The growth-inhibitory effects of green tea EGCG are specific against cancer cells, and not against their normal counterparts. This property makes green tea a unique non-toxic natural substance for cancer control.

Z. P. Chen and colleagues at the Rutgers State University of New Jersey compared the effects of EGCG on the growth of SV40 virally transformed W138 human fibroblasts (W138VA) with that of normal W138 cells. They found that the IC50 value of EGCG was 120 µM and 10 µM for W138 (normal control) and W138VA (cancerous) respectively. This finding indicates that the cancerous cells were 12-fold more sensitive to the growth-inhibitory effects of the green tea EGCG than their normal counterpart. At a concentration of 40 µM, EGCG completely inhibited the growth of the cancerous cells, but had little or no inhibitory effect on the growth of the normal cells. Similar differential growth inhibition was also observed between a
human colorectal cancer cell line, a breast cancer cell line and their respective normal counterparts. The authors postulated that a differential modulation of certain genes, such as c-fos and c-myc, might cause these differential effects on the growth and death of cancer cells (37).

Using human leukemic cell lines for studies, Otsuka and colleagues in Kyushu University and Saitama Cancer Center Research Institute, Japan, demonstrated that the growth of four out of five (4/5) human leukemic cell lines was inhibited in the presence of 10 μM EGCG while the colony formation of normal hematopoietic progenitor cells was not suppressed at all. The authors suggested that EGCG appears to suppress growth factors' signaling as the molecular mechanism for the inhibition of the growth of leukemic cells in the laboratory (38).

### Drink green tea to reduce cancer risk

**Epidemiological human case-control studies**

Regular consumption of green tea has been observed in association with reduced human cancer rates of the breast (39-42), esophagus (43-46), stomach (41,44-54), colorectum (41,44, 49, 55-57), pancreas (55, 58), urinary bladder (59-61), prostate (62), lung (63, 64), liver (41, 45, 49), and ovary (65). These observations affirming a reduced cancer risk among heavy green tea drinkers were usually made in a population that has easy access to sources of quality green teas, for example, among those residents living in Saitama, Aichi, and Shizuoka, the prefectures known to produce green teas in Japan. On the average, the women who were high-volume green tea drinkers enjoyed 8.7 more cancer-free years in life than the low-volume tea-drinking women. Green tea consumption was apparently not associated with a reduction of cancer incidence in the northern rural Japan where no tea plantations exist (66).

It is not surprising that most of the epidemiological case-control studies providing evidence for green tea being a chemopreventive beverage to reduce human cancer risk have been conducted in Japan and China where there is a long tradition of drinking fresh green tea in the population. Population-based epidemiological data collected in the USA and Europe are difficult to analyze because 75-80% of the American and Western European tea drinkers consume black tea only. Most green tea drinkers in North America and Europe do not have the adequate daily intake of quality green tea to reach an effective level of bioactivity for cancer chemoprevention. Consequently, green tea experiments in the laboratory and clinical observations have yielded mixed results (67).

In order to maximize the health benefits of tea drinking for cancer chemoprevention, a daily consumption of at least 10 Japanese cups (about 1,200 to 1,500 ml) of quality green tea is required. Bioactivity of a cup of green tea obviously differs by the amount of green tea leaves used to brew it and the frequency of renewing a tea batch in the tea pot. In Shizuoka prefecture, which has the highest production of green tea leaves in Japan, residents of the towns with a low mortality from stomach cancer were found not only to drink green tea more frequently, but also to renew the tea leaves in the pot more frequently than those of a town with high mortality from stomach cancer (68).

Increased consumption of green tea was correlated with decreased recurrence of stage I and II breast cancer ($P < 0.05$ for crude disease-free survival); the recurrence rate was 16.7 or 24.3% among those consuming $> or = 5$ cups or $< or = 4$ cups per day, respectively, in a seven-year follow-up of stage I and II breast cancer patients, and the relative risk of recurrence was 0.564 (95% confidence interval, 0.350-0.911) after adjustment for other lifestyle factors. However, no improvement in prognosis was observed in stage III breast cancer (69). This observation indicates that green tea or a green tea product is not “a cure for all cancers” silver bullet, and should not be relied on for the treatment of any cancers in advanced disease stages (70).

**Educate yourself and consult your doctor**

Green tea and its components have been proven to be effective against cancer cell growth in the laboratory and in experimental animal model studies. The information on using green tea in the fight against human cancers still remains fragmented and has generally not been conveyed to the public. The scientific merit of green tea in the combat against cancer is evidenced by the publications quoted in the end of this review and in the other two documents presented in the website [www.teaforhealth.com](http://www.teaforhealth.com). If there were another chemical substance that had shown the promise as having such a low toxicity to humans and high anticancer activity in the research laboratories, the substance would have been a hotly pursued target of study as a potentially useful drug to fight human
cancer. However, green tea has not been recommended or endorsed by the medical profession as a “medicinal herbal beverage” to be used as a medication or a dietary supplement to fight cancer. This is due to a lack of human clinical trial data.

For the FDA to approve a drug, the active pharmaceutical ingredient must be a purified or synthesized substance with a defined chemical structure. It must be proven first in animals (at least in two species of rodents. Humans don’t count.) for its short-term and long-term safety in addition to numerous toxicity studies, then in human patients in a “randomized unbiased double-blind placebo-controlled” safety and efficacy three-phased clinical study. In such a study, neither the investigator nor the test subject, the patient, should know if the active pharmaceutical ingredient or the placebo is administered to the test subjects. It costs about $600-800 million to conduct all the regulatory studies for the FDA review in order to bring a new drug to the market. Since neither green tea nor its components can be patented, no pharmaceutical company would ever be interested being a sponsor to finance the clinical studies on green tea.

Besides, it is difficult, if not impossible, to design an unbiased placebo-controlled study with an aqueous green tea extract as the active substance in treating any disease conditions because every human is quite familiar with the physical appearance and taste of water, the placebo. Any clinical trial using water as the placebo would be “unblinded” immediately by the test subjects. Thus, a psychosomatic result of tea drinking rather than the pharmacological efficacy of the tea can never be excluded even if a significant gain in the benefit against cancer was observed in the green tea drinkers over the non-tea drinkers. Some investigators attempted to overcome this placebo bias by putting the green tea powder and the placebo in capsules for the patients to swallow in the clinical trial study. It is highly questionable if all the active tea ingredients beneficial to human health which are traditionally extracted by boiling hot water in tea preparation, can be released from the plant cells of the dry tea leaves by the digestive enzymes of the human gastrointestinal tract.

Based on the above assessment, green tea will not become a government-approved medicine in the foreseeable future in spite of its known benefits in helping other mammals to fight cancer. We, the consumers, have to make the decision, for our own good.

What to drink – natural tea or purified chemicals

Most scientific research on the anticancer activity of tea has been conducted using green tea or its component, EGCG or theanine, as the active substance. Since much of the EGCG in black tea and oolong tea has been destroyed during the manufacturing process, green tea is the natural tea of choice as the dietary supplement to fight cancer. However, the anticancer activity of green tea cannot be attributed to the action of a single tea catechin, but rather is the combined effects of a complex mixture. It is inappropriate to assume that EGCG or any other purified ingredient of the green tea leaves can be used as a suitable substitute of the whole green tea extract for health promotion.

There are more than 300 ether-extractable volatile compounds in the dry leaves of green tea. Tea components other than EGCG and theanine may also contribute significantly to the anticancer activity of green tea. For example, Ohe and colleagues demonstrated that EGCG is not the major component responsible for the anti-genotoxic effects of tea extract against nitroarenes (71). Yang and colleagues reported that the oxidized products of EGCG, such as theaflavins in black tea, still have significant growth inhibitory activities against human cancer, inducing cancer cell apoptosis in the laboratory although the activities are lower than those of EGCG (24).

Williams and colleagues found that green tea extracts inhibit the transcription of a human CYP1A promoter-driven reporter gene induced by the aryl hydrocarbon receptor (AhR) ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in a concentration-dependent manner and inhibit the induced accumulation of both CYP1A1 and CYP1A2 mRNAs. Among the major catechins, only EGCG was able to inhibit TCDD-induced binding of the AhR to DNA and subsequent CYP1A transcription. However, EGCG alone was less effective than green tea extracts (3).

Oral administration of capsules of green tea leaf powders, commercial green tea concentrates, or commercially prepared green tea drinks in bottles or in cans is not a suitable substitute for drinking a mug of properly prepared green tea brewed in the traditional manner unless the tea in the ready-to-drink bottles contains the standard level of bioactive ingredients as the naturally brewed green tea. It is highly questionable that the active ingredients in the green tea leaf powders can be released from the cells
of the tea leaves by the digestive enzymes of the human gastrointestinal tract. An ethanolic extract product of green tea marketed in several European Union member states has been found to cause hepatotoxicity in women (WHO Pharmaceuticals Newsletter No. 3, 2003), indicating that deviation from the traditional methods of tea preparation with hot water extraction may be associated with unexpected adverse side-effects.

The catechins in commercially prepared green tea drinks have undergone various uncontrollable degrees of degradation during the manufacturing process, according to Chen and colleagues of the Chinese University of Hong Kong in a report published in 2001 (72). They found that bottled or canned green tea drinks had EGCG levels ranging from <0.01 mg/100 ml to 13 mg/100 ml, far below that in a typical green tea brewed in the traditional manner.

**Dosage of Green Tea**

Since drinking green tea for its medicinal value in the fight against cancer has only been seriously considered very recently and only in some parts of the world, and since the active ingredients responsible for its anticancer activity are still poorly defined, the basis for a scientific approach to study the bioavailability of the “active green tea ingredients” is still lacking. The following is an example of dosage calculation for green tea based on the scant published materials. It is subject to further revisions as new research data are made available, and should be a subject of discussion in the evidence-based counseling between doctor and patient.

According to a document published by the National Cancer Institute, DCPC, Chemoprevention Branch and Agent Development Committee (73), it is generally agreed that a typical cup of green tea contains about 710 µg/ml EGCG. If a daily intake of 1,200 ml green tea is needed for optimum chemoprevention against cancer as demonstrated in the Saitama experience, then the daily dosage of EGCG in the green tea consumed would be about 840 mg. This strength of green tea, using EGCG as a surrogate yardstick to measure, was used successfully to inhibit 50% of the tumor occurrences of a high-grade human lymphoma inoculated in experimental animals (32).

According to one clinical trial with permit from the FDA cited by Mukhtar and Ahmad (74), a daily dose equivalent to drinking at least 2.4 liters (10 cups) of green tea (EGCG 200 mg per a 240 ml cup) was given to each cancer patient. This therapeutic dose was at least a 2000 mg EGCG equivalent of green tea products per adult patient per day, i.e. about three times the above calculated chemopreventive dosage.

**High-Potency Green Tea**

In ancient China, the word “tea” always meant green tea in the Middle Kingdom. Tea was initially used for its medicinal purpose to maintain health in the mind and body, and was later used as an offering in place of liquor in funeral and other religious ceremonies. To make tea drinks, fresh tea leaves were plucked from the wild tea trees or from the tea gardens which belonged to the Taoist temples or were owned by the intellect elite class in southern China. Using fresh tea leaves to prepare tea drinks had been a common practice among the elite artists at least as late as in Ming Dynasty (1368-1644 A.D.). This traditional tea preparation is depicted in a poem written on a classic painting titled “Drinking Tea” by a famous artist, Tang Yin (1470-1523 A.D.), now on display in the Palace Museum, Beijing. If tea were prepared in this way, all tea drinks would have been high-potency green tea. However, it is not practical. Tea leaves must be dehydrated like any other dried natural produce or fruits for preservation to be a tradable commodity at distance. The basic technology of manufacturing commercial green teas is to use controlled heating to inactivate the intrinsic phenol oxidases of the tea leaf while preserving its catechin antioxidants as much as possible.

The tea leaf is like a natural factory of polyphenols which may account for 36% of its dry weight, including 16% to 30% in the form of tea catechins in which 7% to 13% is EGCG, depending on the growing conditions and the environments of the tea plantation.

A polyphenol is any natural product with more than one phenolic group in its chemical structure. Polyphenols are widely distributed in nature. They are responsible for the colors of many flowers and of all red berry fruits. They may be complex compounds as those present in the bark, roots and leaves of the plants that are used for tanning hides and skins to give leather, or in simpler form as in tea leaves.

EGCG was sometimes referred to as “green tea tannin” in the old chemistry textbooks because green
tea turns dark brown like any tanning materials, as in oolong tea and black tea, when the catechins in the tea leaf are oxidized and polymerized. The same brownish discoloration is observed when the fresh cut surface of a head of lettuce or of an apple is exposed to the air for a few minutes, only to a lesser degree.

When a fresh tea leaf is oxidized, it turns into oolong tea or black tea and loses its tea catechins, thus its antioxidants, depending on the degrees of oxidation (formerly mistaken as a process of fermentation) allowed to proceed before the oxidizing process is stopped by heat inactivation of its intrinsic phenol oxidases. As a result, oolong and black teas contain very low levels of catechin antioxidants, or none at all. They are produced for their special aroma, which is brought about by the chemicals newly formed during the tea oxidation process.

Historically, oolong and black teas were produced in ancient China as a salvage product when the fresh tea leaves were not processed fast enough for the production of high quality teas. Oolong and black tea leaves were heat-compressed into brick form for easy transportation in foreign trades since Tang dynasty. Only after the downfall of the once prosperous Ming Dynasty, oolong and black teas were produced in significant amounts in the mid 17th century for the peasants in southern China and for exports to the West. The southern Chinese farm laborers, deprived of an adequate calorie intake following the collapse of Ming dynasty, learned quickly that green tea depletes the body fat needed for survival in the famine years. To this date, most southern Chinese and their descendants in the USA still shun green tea as a beverage-an outdated wisdom passed from their ancestors. Green tea catechins, though as excellent antioxidants, are irritants to the gastric mucosa in an empty stomach. Oxidizing the fresh tea leaf, thus turning it into oolong tea or black tea, reduced the contents of its catechins which would have depleted the body fat reserve. Facing starvation, preservation of body fat and avoiding introduction of irritants to a stomach without food took priority over chemoprevention against cancer and aging.

Antioxidants serve to inactivate certain molecules called free radicals. In humans, free radicals usually come in the form of reactive oxygen species (ROS). They are formed as part of the normal living process, or are induced or introduced by exogenous factors. A highly reactive free radical would take an electron from another molecule, leaving the latter as an electron-deficient free radical. The latter newly formed free radical would then rob an electron from another molecule in a chain reaction. This chain of oxidation process can be damaging to the normal cells and subcellular structures, and can even be carcinogenic. Since the brain consumes the biggest share (20-25%) of the oxygen taken into the human body, more ROS molecules are generated in the brain than in other organs. Fortunately, the brain cells do not divide as frequently as the epithelial cells. Hence cancer rates of the brain are not as high as in the other epithelium-lining organs, like the colon. However, the ROS damages to the brain cells express in other forms, such as a loss of mental function, Parkinson’s disease, etc. as the individual ages.

Antioxidant molecules have loosely attached electrons, and can function as electron donors without becoming electron-deficient free radicals themselves. Therefore, antioxidants can quench the oxidative chain reaction caused by free radicals. Being excellent electron donors, tea catechins in the tea leaves can be oxidized when exposed to atmospheric oxygen or by donating their electrons to other electron-deficient molecules in the tea leaf during storage, leading to degradation of the tea.

Having adopted EGCG as the surrogate yardstick to measure the antioxidant bioavailability in tea leaves, in order to have a daily intake of 1,200 ml green tea liquid containing about 800 mg of EGCG for optimum chemoprevention against cancer, one must use a green tea leaf that contains at least 7% EGCG in dry weight if the customary 1:100 w/v tea leaf-to-water ratio is used to brew tea. If the EGCG contents in the dry tea leaves are below 7%, the bioactivity in the tea extract will not reach the level equivalent to 700 µg/ml EGCG, the desirable strength of a typical green tea.

A high quality green tea, if processed and packaged properly, should meet this standard. For lack of a more suitable label, we may refer to this tea as a “High-Potency Green Tea ” to be distinguished from other lower EGCG grade teas (not necessarily lower grades in taste and in aroma). Unfortunately, most green teas available on the market in the USA and in Europe are below this standard. For example, Khokhar and Magnusdottir reported that the green teas commonly consumed in the United Kingdom were all found to contain only 2.0-4.2% EGCG in dry weight (75). In another analysis, Chen et al. found three out of five (3/5) green teas purchased in Hong Kong contained an EGCG level below 7% (72). If a green tea leaf has a content of EGCG at...
3.5%, either the strength of the tea liquid or the volume of the tea to be consumed would have to be doubled to obtain the same dose equivalent with an inadvertently increased intake of caffeine since the latter, unlike EGCG, is not subject to oxidative degradation during improper processing and storage.

The need for standardization of green tea is self-evident if it is to be used as a dietary supplement in the combat against a disease like cancer. This is especially important in view of the reports that 50% or more of the green teas sampled on the markets in Europe [according to a February 1999 report of Stiftung Warentest, Berlin, Germany quoted by Bertram and Bartsch (76)] and in the USA [Frances Cerra Whittelsey (77)] were found to contain residues of pesticides, namely potential chemical carcinogens, in excess of government-regulated limits.

**Oxygen Exclusion in Tea Brewing**

Only very recently, after medical research had unveiled the anticancer activity of green tea polyphenols, especially EGCG, laboratory investigators began to study the methods of tea preparation for the maximum preservation of the antioxidants in the tea extracts. Green tea is usually extracted in hot water under pure nitrogen to avoid oxidation of the catechins for cancer research in the laboratory and in animal model studies (78).

Chen and colleagues found that when pure longjing GTC (green tea catechins) was heated at 98ºC for 15 minutes in a closed test tube, a 10-15% loss of GTC was observed for the first half an hour. Further heating for another 6 hours led to only an additional 5% loss of GTC. In their opinion, the initial oxygen concentration was high in the tea solution so that oxidation of GTC was extensive. After the initial oxygen was exhausted, the rate of GTC oxidation decreased as heating continued.

This loss of GTC would have been higher during beverage preparation in an uncontrolled condition. If a person depends on the amount of green tea antioxidant intake for health protection, a 15-20% loss or gain in EGCG equivalent may make a difference in the end result. A more effective preservation of the active ingredients extracted from a High-Potency Green Tea makes it possible to use less dry tea leaves for tea preparation to reduce the bitter substances and caffeine co-extracted into the tea liquid to be consumed.

Therefore, it is advisable to brew High-Potency Green Tea leaves in boiling hot water (100ºC or 212ºF) under anaerobic conditions, or under substantially oxygen-excluded conditions, for 20 minutes for the maximum extraction and preservation of the antioxidants in the tea. The generally recommended method of brewing a dust-grade green tea in an infusion tea bag in hot water at 170 to 175ºF for less than two minutes is not good enough for preparation of the High-Potency Green Tea as a chemopreventive daily dietary supplement in the fight against cancer.
Concluding Remarks

This review has summarized the contributions of numerous scientists who have published their research on the anticancer effects of green tea in the past ten, but mostly in the last five, years. In their collective work, green tea, especially its major antioxidative component, EGCG, has been shown to interfere with or to interrupt the cancer development process at many steps. Green tea inhibits the formation of carcinogen from pro-carcinogens in the foodstuff ingested in the stomach, inhibits the hepatic enzymes which are responsible for converting pro-carcinogens into active carcinogens in the body, activates the phase II enzymes to detoxify the carcinogens, inhibits the formation of endogenous carcinogens, reduces the DNA damage caused by carcinogens, e.g. ultraviolet irradiation, through neutralization of free radicals, inhibits the telomerase activity, inhibits DNA topoisomerases, induces cancer cell apoptosis via the mitochondrial pathway, inhibits activation of transcription factors in the signal transduction pathway, inhibits angiogenesis needed for rapid tumor growth, and inhibits the proteolytic enzymes needed to establish cancer metastases. The anticancer activities of green tea are widely ranged starting at the formation of exogenous carcinogens in the stomach to the stage of tumor metastasis, the most dangerous phase that often ends the life of the patient.

The best of all is the fact that none of the laboratory studies has found any evidence of mutagenic or carcinogenic effects caused by green tea. These cellular and molecular anticancer effects have been confirmed by animal model studies, using human cancer cells or tissues transplanted into experimental animals. In a scientific case report accompanying this review and published on the website www.teaforhealth.com, green tea with at least 7% EGCG contents, designated as “High-Potency Green Tea ,” has been used to treat a multicentric canine lymphoma -- the first case of using green tea as a non-toxic drug regimen to treat a spontaneously occurring cancer in mammals, successfully. At this writing, the dog is in complete remission and lives like any normal dogs more than two years after the diagnosis of a multi-centric lymphoma, on a daily maintenance dosage of green tea only. The author, as a physician, has purposely refrained from making reference to personal observations on human patients in connection to this matter.

The purpose of this review is to pass the above scientific research information in an organized format to the educated consumers and their doctors for them to refer to when they are making an informed decision of using green tea as a supplementary beverage for chemoprevention and to boost the anticancer effects of chemotherapy. For the potential health benefits of the patient, the decision must be seriously considered now, not 20 years from now, when, and if ever, an authority from the government, the drug industry or a professional organization might endorse such application. Why would it take that long? Following is the answer.

In a classic case history of anticancer drug development, it usually involves a scientist who had found a natural product, for example, the bark of a tree that has anticancer activity. Then a group of chemists sponsored by a pharmaceutical company would isolate the active ingredient from the tree bark in the pure chemical form and characterize its molecular structure. The pharmaceutical company would patent the molecule and its applications, and probably its synthetic process as well. Then, with this potential monopoly of the drug market, the company would sponsor a series of toxicological and efficacy studies on animals and on human patients to collect the data for an investigational new drug application and then a new drug application to be submitted to the FDA, including three to four phases of clinical trial studies. The cost for each new drug approved is currently about $800 million.

Green tea may contain wonderful chemical ingredients for inhibiting cancer growth with little or no toxicity to humans. However, green tea and its major components as well as their potential health benefits have been known for a long time. In other words, they cannot be patented. In addition, green tea has traditionally been a popular beverage. It has been produced for centuries and it is relatively inexpensive. The most active ingredient, EGCG, in the green tea leaves constitutes up to 15% of its dry weight, a huge quantity compared to other drugs of plant origin. As a result, there is no incentive for any pharmaceutical company to isolate, to purify and to synthesize the green tea catechins although a few companies are in the process of synthesizing EGCG analogs that can be patented. Since there is no incentive to do any green tea clinical studies required for new drug application, the usual proceeding from discovery of an active extract of a plant to chemical isolation to laboratory study to animal toxicology study to human clinical trial study
to FDA application and finally FDA approval of a drug will not happen in the case of green tea.

Therefore, the consumers have to be on their own, making an informed decision to manage their own health. Fortunately, tea has been used for more than 5,000 years in humans as a beverage whose popularity is only second to water. As a result, its toxicity to humans has been proven to be negligible. Since it is no harm and probably will be effective in inhibiting cancer growth, there is little reason not to drink green tea to help in the fight against cancer.

The only thing we have to do is to make sure that the green tea leaves we are going to use must contain an adequate amount of the active ingredients and do not contain pesticide and heavy metal (lead and cadmium) residues in excess of the EPA limits. Dr. Lee’s TeaForHealth™ has provided the technology in the form of a High-Potency Green Tea and a proper method of tea brewing for an educated consumer to put him/herself in the driver’s seat to manage his/her own health in using green tea as a herbal beverage to fight cancer with the doctor acting as a consultant.
References


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