

**UCLA**  
**Nutrition Bytes**

**Title**

Reviewing the Evidence: Is There a Role for Green Teas in Cancer Prevention?

**Permalink**

<https://escholarship.org/uc/item/1hw7d6t8>

**Journal**

Nutrition Bytes, 6(1)

**ISSN**

1548-4327

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**Publication Date**

2000

Peer reviewed

## Introduction

Tea is the second most commonly consumed beverage worldwide. Among Asian cultures, it has long been believed that tea, particularly green tea, can have some health-promoting effects (1). In more recent times, epidemiological studies conducted primarily in Asia seemed to support the notion that tea may have some preventive effects against many forms of cancer. The potential of using a cheap and common food source such as tea as a chemopreventive agent has since aroused a considerable amount of interest.

Most common teas derive from the plant species *Camellia Sinensis*, which is part of the Theaceae family of evergreens. The three major forms of tea consumed worldwide (oolong, green and black) are all produced by the differential treatment of leaves from this plant. In their natural state, the leaves contain both polyphenol compounds and an enzyme polyphenol oxidase. Once the leaves are cut, polyphenol oxidase is activated and the polyphenols become oxidized. In the case of black tea, the oxidation results in the formation of new polyphenol compounds known as theaflavine gallate and thearubigins. In the case of green tea, however, the leaves are traditionally steamed following clipping, which prevents enzyme activity thus preserving the naturally occurring polyphenols known as catechins. More specifically, the active ingredients in green tea appear to be epicatechin (EC), epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate (EGCG) (2). It is these catechins and their anti-oxidant effects that are believed to be primarily involved in the anti-carcinogenic effects of green tea. In simplest terms, it is believed that this class of molecules exerts its effect by inhibiting the damage to DNA that normally occurs upon exposure to oxidants.

## Proposed Mechanisms of Action of Green Tea Polyphenols

The potential inverse relationship between green tea consumption and cancer that was shown in early epidemiological studies prompted researchers to attempt to study the effects of green tea extracts more directly both in cell culture experiments and animal studies. A logical and important first step was to attempt to understand in more detail how these green tea polyphenols (GTPs) exerted their action. As such, many studies have been performed in an effort to elucidate the precise biochemical mechanisms. Early studies focused on assessing the antioxidant and free-radical scavenging activity, stimulation of detoxification enzymes, prevention of mutagenicity and the reduction in biochemical markers of tumor initiation and promotion (3). More recent studies have been successful in identifying more specifically the possible sites of action. Several of these proposed mechanisms are described below.

It is known that Phase II detoxification enzymes (which can metabolize carcinogens) often have an Antioxidant Responsive Element (ARE) located upstream from the genes themselves. By constructing a clone linking an ARE to a reporter gene and stimulating with green tea extract, Yu et al. were able to show that GTPs can induce transcription. Furthermore, increased levels of Mitogen Activated Protein Kinases (MAPKs) were found in cells induced by GTP. These two observations in combination suggest that GTPs may prevent cancer by upregulating the transcription of detoxification enzymes through the activation of MAPKs (4).

Studies have also been done suggesting that EGCG can prevent cancer by inhibiting growth cascades. The Epidermal Growth Factor Receptor (EGFR) cascade is a particularly well-studied system involved in cellular proliferation. Hyperactivation of a growth cascade such as this one can cause cancer. Recent studies done in human epidermoid carcinoma cells have shown that EGCG inhibits autophosphorylation of the EGFR receptor (a key step in the initiation of the cascade) in addition to directly blocking EGF binding to the receptor thus indicating another possible way that green tea mediates anti-cancer effects (5).

A third important mechanism by which GTPs are currently thought to promote their action is by causing selective apoptosis of cancer cells. One study by Ahmad et al. showed that EGCG caused apoptosis in a variety of cancer cell lines including human epidermoid carcinoma, human carcinoma keratinocytes, human prostate carcinoma cells and mouse lymphoma cells, but not in normal human epidermal keratinocytes (2). This selective induction of cell death might also be responsible for cancer prevention.

## The Bioavailability of Tea Catechins in Humans

While the results of many of these cell culture studies seem promising, the data is irrelevant without human studies that test the amount of absorption and uptake of these compounds in vivo. Two recent studies seem to indicate a positive relationship between green tea intake and antioxidant levels in plasma, thus confirming the bioavailability of these compounds in humans. Benzie et al. studied plasma and urine "antioxidant power" in humans after the consumption of 400 ml of green tea. (Antioxidant power refers to a compound's strength as a reducing agent). Blood and urine samples were measured before and at various time points after consumption of tea using the FRAP method which measures the total reductive ability of a solution using a colorimetric method. The results of this study indicated that consumption did in fact mediate a rapid (20-40 minutes post-consumption), albeit small rise in antioxidative power in blood plasma and a corresponding rise in urinary levels (6). In a similar study, Yang et al. looked more directly at blood and urine levels of the catechins EGCG, EGC and EC following ingestion of varying amounts of green tea. This study similarly showed increased levels of these catechins in both plasma and urine further suggesting that these compounds are indeed absorbed by humans and therefore may be "available" to exhibit the anti-cancer effects studied in vitro (7).

### Localizing GTP Activity to Specific Cancers

It seems likely, then, that GTPs can promote some degree of anti-cancer effects at the cellular level. However, studies have still been inconclusive in determining the specific localization of these effects to the various human organs. Nevertheless, there is some clinical evidence that GTPs may play a role in decreasing the incidence of breast, prostate, gastrointestinal and even lung cancers (3).

The clinical research in the realm of prostate cancer is still in the preliminary stages. One Canadian study, however, looked at approximately 600 newly diagnosed cases of prostate cancer and some 600 controls and questioned the subjects with regards to beverage intake during the previous year. The study showed reduced odds ratios for subjects that consumed tea (OR = 0.7), whereas cancer rates were not correlated with consumption of other beverages such as coffee and cola (8).

In the case of breast cancer, a retrospective study of surgical patients with disease in stage I, II and III showed that consumption of tea was inversely proportional to the number of axillary lymph node metastases. A prospective follow-up study with these patients also suggested that increasing the consumption of green tea post-surgery led to decreased recurrence (relative risk of 0.564 in those drinking 5 or more cups/day compared to those drinking 4 or less) of the early stage cancers, but not of those in stage III (9).

Several fairly large (N=1500) population studies have also been conducted in China which support green tea's role in prevention of esophageal, stomach, colon, rectal and pancreatic cancer. These retrospective studies showed statistically significant differences in rates of these types of cancers between habitual green tea consumers and their non-tea drinking counterparts (3).

Finally, a study comparing smokers who drank green tea and those who didn't also seemed to point towards a possible chemopreventive effect in smoking-related cancers. In this clinical trial, the end point used to measure the effect was the frequency of sister chromatid exchanges (SCE), a measure of mutagenic properties of the DNA. Over a six month period, it was shown that while the frequency of SCEs in smokers was significantly increased in comparison to non-smokers, the frequency found in smokers who drank 3 cups of tea/day was comparable to that of the non-smoker group. These results suggest that green tea may also play an inhibitory role in smoking related mutagenesis (10).

Verdict? Is it time to substitute our coffees and sodas with green tea?

With all of this seemingly promising data, the obvious question that we are left with is, is the data convincing enough to suggest that non-green tea drinkers change their habits? In order to objectively answer this question, it is necessary to take a step back. While it is true that there is a lot of data out there that suggests a relationship, it must also be noted that most of the definitive studies to date have been conducted in cell culture lines or in animal models (not explicitly described in this paper). The effects

observed in these model systems are not always reproducible in humans. One of the specific problems with these sorts of studies is that the levels of GTP which are used are often much higher than an amount that would be reasonable for human ingestion on a daily basis (11). The idea of taking green tea extract supplements in concentrated pill form seems to circumvent this problem. But what if the beneficial effects of green tea are a result of the synergistic effects of the natural components of the beverage? In such a case, in order to reap the benefits described in the animal studies, we would be forced to drink somewhere on the order of 10 cups of concentrated tea per day (3). At such high levels, the issue of toxicity then becomes a problem that must be studied.

Taking these points into account, proponents of green tea's effects may then argue that the results of the clinical and epidemiological studies alone are difficult to ignore. While the clinical trial results are encouraging, there simply isn't enough data yet to warrant too much excitement. In the case of epidemiological studies, the major problem is that they are retrospective and depend immensely upon accurate patient interviewing and responses (3). Both of these elements increase the risk of confounding factors entering into play, making it inherently more difficult to establish causal relationships. A study conducted by Tsubono et al. studied the relationship between green tea intake and one possible confounding factor, diet. This study of Japanese men and women showed that there were definite correlations between green tea intake and a variety of other potentially "beneficial" dietary choices. It was found that levels of green and yellow vegetable intake as well as that of soybean products, seaweed and certain fruits were also positively correlated with green tea intake (12). Since fruits and vegetables (also rich in antioxidants) and soy have also been implicated in chemopreventive anti-cancer roles, it is imperative that these factors be examined separately in order to establish causality. These results in and of themselves do not serve to specifically discredit any of the previously mentioned epidemiological studies, as many of them attempted to adjust for these factors. However, it does remind us of some of the limitations of these types of retrospective studies and further suggests the need for more controlled clinical trials in humans (such as those conducted for breast and smoking-related cancers) in order to allow us to establish more definitive conclusions.

A final point that should be considered when weighing the risks and benefits of green tea is that there have been some studies, although far fewer in number, that are in fact looking at potential harmful effects of the substance. At least one recent study conducted in Taiwan deserves some mention. In this particular study by Lu et al., the role of tea consumption in bladder cancer was examined. Patients diagnosed with bladder cancer were questioned concerning their beverage consumption patterns, as well as a host of other potentially confounding factors, and were then compared to control subjects. Using odds ratios, it was shown that drinking both oolong teas and black/non-oolong green teas were positively correlated with increased bladder cancer risk (OR ~3 and ~14 respectively) (13). According to the authors, a possible reason for the discrepancy between these observed effects in bladder cancer vs. those previously described in other tissues was that the level of tea catechins in urine are in fact very low in comparison to that of other tissues (such as gastric juices). Whatever the reason, this finding should at least raise some eyebrows amongst proponents of green tea for chemoprevention. Obviously, this is but one study and it is a study that is plagued by all of the previously mentioned limitations (size, possibility of confounding factors, retrospective nature, etc). Nevertheless, it is a reminder to us that there is still much to be learned and that much work is yet to be done.

## Conclusions

At least for now, then, it seems that the jury is still out on the issue of green tea as a cancer chemopreventive. While progress has been made in understanding the molecular mechanisms of action and the possible clinical localization of its effects, the fact remains that direct experimental human studies are still lacking, both in power and in number. Until more clinical trials are conducted and until they are shown to prove sufficiently significant causal relationships without significant side effects, physicians and dieticians should remain cautious in recommending green tea as a "miracle" cancer-preventive agent to their patients.

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