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Does Green Tea Aid in Cancer Prevention?

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A review of the published scientific literature indicates that green tea has a strong protective effect against cancer and other diseases. One study, however, failed to demonstrate that green tea drinkers have a lower risk of stomach cancer. The media used this study to attack the value of green tea. In this article, we discuss the one negative report and point to numerous positive studies that document green tea's anti-cancer properties. We also reveal findings showing that stomach cancer is a preventable disease.

By Ivy Greenwell

The anti-cancer benefits of green tea against a variety of cancers appeared to be well-established. However, a Japanese study published in the March 1, 2001 issue of the *New England Journal of Medicine* casts doubt upon the efficacy of green tea in lowering the risk of stomach

cancer. Because this was a prospective epidemiological study using a fairly large sample over an eight-year period, its findings and conclusions deserve to be seriously examined. After an adjustment for sex and age (male sex and older age are risk factors), history of peptic ulcer (a rough indication of *Helicobacter pylori* infection), smoking status, alcohol consumption and certain dietary components, persons who drank less than one cup of green tea a day were found to have approximately the same risk of gastric cancer as those who drank more than five cups a day (Tsubono 2001). The media publicized these negative findings, making some consumers wonder whether green tea offered any protection against any kind of cancer.



However, it is unwise to draw firm conclusions on the basis of only one study, especially if several other studies disagree. Before we review studies that found a protective effect of green tea against gastric cancer, let's take a look at the various risk factors for this type of cancer.

Gastric cancer risk factors

Although the rates of gastritis and stomach cancer have declined in this century, stomach cancer is the second most common cancer in the world, after lung cancer. It remains the most common cause of cancer death in Japan and Korea. Stomach cancer is also the most common cancer in China, among both men and women.

Interestingly, the geographic distribution of stomach cancer shows that it is very rare in the Western world, with rates of less than 1 per 100,000, as opposed to Eastern Europe, China, Korea and Japan, with rates of over 40 per 100,000 in some areas. What is even more revealing is the fact that stomach cancer used to be a lot more common in both the Western world and Japan, but there has been a dramatic decline in its incidence that appears to parallel the introduction of refrigeration. Even though gastric cancer is still the leading cause of cancer-related mortality in Japan, between 1970 and 1995 its mortality rate declined from 88.9 to 45.4 per 100,000 among Japanese men, and from 46.5 to 18.5 per 100,000 among Japanese women (note the wide gender difference).

A great deal of epidemiological evidence points to certain components of a traditional diet that appear to be causally involved in carcinogenesis: very salty foods, smoked foods and pickled foods. Many Japanese enjoy salty treats such as salt-cured *dikon* with every meal. Contrary to the sentimental view, not all traditional ethnic foods are good for health. The pre-refrigeration practice of preserving foods by smoking and/or heavily salting them has a great potential for harm. A diet high in sodium and smoked and pickled foods, especially if combined with heavy smoking and drinking, has been repeatedly associated with increased risk of stomach cancer. High sodium intake alone is estimated to increase the risk of stomach cancer up to six times (Lam 1999). Thus, reducing salt intake is the cornerstone of gastric cancer prevention.

There is a parallel in the incidence of stroke and gastric cancer: both decline as the intake of sodium goes down. As one reviewer put it, "High salt intake is associated with high blood pressure and with stomach cancer, especially with inadequate intake of potassium from fruits and vegetables, and of calcium from certain vegetables and low-fat dairy products" (Weisburger 2000). Inadequate intake of potassium generally goes hand in hand with inadequate intake of antioxidants.

Food preserved with nitrites is also under suspicion as a carcinogen that could lead to stomach cancer. Nitrites can be converted to nitrosamines, known to be carcinogenic. In some rural regions, drinking water is contaminated with nitrogen compounds due to infiltration of nitrogen fertilizers. A Spanish study showed that gastric cancer mortality correlated with increasing exposure to nitrates (under some conditions, nitrates may be converted to nitrites).

Stomach cancer also shows a strong male prevalence, which may be connected to estrogens being protective in women. Phytoestrogens, including the catechins found in green tea, very likely play a similar protective role. Soy also contains powerful phytoestrogens; the confounding factor here is that many Asian soy products are heavily salted. A couple of studies hint, however, that nonsalted soy products (e.g. plain tofu) help protect against gastric cancer. In addition, genistein and daidzein have been found to inhibit the growth of stomach cancer cells in vitro. Another phytoestrogen, kaempferol, has also been found to provide protection. Various other phenolic compounds, including anthocyanins (found in berries and dark grapes), have also been shown to be protective.

Yet another culprit is infection with *Helicobacter pylori*, often associated with gastric and duodenal ulcers (the infection is found in 80% of ulcer cases). *H. pylori* infection leads to an inflammation of the stomach lining, and can ultimately result in chronic gastritis (a precancerous stomach lesion), which may then progress to gastric cancer. *H. pylori* infection is seen significantly more frequently among gastric cancer patients than in healthy controls (Konturek 2000). According to most studies, *H. pylori* doubles or triples the risk of gastric cancer; one author estimates that *H. pylori* increases the risk of gastric cancer five times if the infection continues for 10 years (Lam 1999). Likewise, the presence of *H. pylori* infection was found to be associated with ten-times the risk of chronic atrophic gastritis. It is the moderately atrophied gastric mucosa that are most likely to become sites of malignancy. It is important to note that green tea has been found to be protective against chronic atrophic gastritis (Kuwahara 2000; Setiawan 2001).

In addition, *H. pylori* causes reduced bioavailability of vitamin C, and produces a cytotoxic protein known as CagA, which recruits immune cells that further destroy the stomach lining. While *H. pylori* infection is common also in the Western world, it appears to be kept at lower severity due to better nutrition, especially higher antioxidant status. Antioxidant deficiencies are suspected to favor the acquisition of *H. pylori* infection and increase its severity. Treatment with antioxidants, on the other hand, appears quite effective in reducing the bacterial load and the degree of gastric inflammation. Green tea polyphenols, especially epigallocatechin gallate, are known to be potent antioxidants. While Western populations may not be drinking much green tea, they obtain antioxidants from year-round fruit and vegetables, wine, coffee, black tea (also an excellent source of polyphenols, mainly the more complex type known as theaflavins), chocolate and nutritional supplements.

It should be pointed out that an infection with *H. pylori*, quite common around the world, including the Western world, does not mean that a person will go on to develop gastric cancer. It is estimated that half of the world population is infected to some degree with *H. pylori*. In Western countries, *H. pylori* infection is more likely to produce chronic early-stage gastritis or ulcers rather than gastric cancer. A diet low in sodium and rich in antioxidants appears to play a major role in arresting the infection at an early stage and limiting the damage it can do. Thus, even without eradicating *H. pylori* with antibiotics, it should be relatively easy to keep the infection from leading to precancerous chronic gastritis and cancer. A recent Chinese study put a special emphasis on smoking and vitamin C deficiency, in addition to *H. pylori*, as factors leading to progression from gastritis to gastric cancer. The risk of progression to cancer was only 20% in individuals in the highest tertile of baseline vitamin C level compared with the lowest tertile (You 2000).



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In general, both chronic gastritis (an inflammation of the stomach mucosa that often leads to gastric cancer) and gastric cancer are related to *H. pylori* infection, lower socioeconomic status, reliance on salt-preserved foods rather than refrigeration and dietary deficiencies of antioxidant vitamins and micronutrients such as selenium. *H. pylori* infection, high sodium intake and a diet poor in antioxidants appear to be the main risk factors for gastric cancer, as confirmed by numerous studies.

Most studies find smoking and heavy drinking to be additional risk factors. One study includes moldy cereals among high-risk foods; this is plausible since we know that mold toxins are carcinogenic. In addition, a degree of genetic susceptibility also appears to play a role. However, this risk is confounded by the finding of much higher prevalence of *H. pylori* infection among the offspring of parents with gastric cancer. It is also likely that the same carcinogenic dietary habits (heavily salted, smoked and pickled food, with low consumption of fresh fruits and vegetables) are being passed from one generation to the next. Nevertheless, even though diet and *H. pylori* infection play an extremely important part in the development of stomach cancer, genetic susceptibility should never be ignored. Anyone with a family history of this deadly disease should be considered at risk, and would be wise to observe the preventive protocol outlined in the sidebar.

The key to prevention

There is no question that green tea contains anti-carcinogenic compounds. In particular, catechins, the main group of polyphenols found in green tea, have been found in numerous in-vitro and in-vivo studies to show significant antiproliferative, anti-cancer activity. The most active catechin appears to be epigallocatechin gallate.

Chinese scientists recently discovered that epigallocatechin gallate inhibits angiogenesis (the production of new blood microvessels) in mice inoculated with human colon cancer. This blocking of new blood vessel growth may be an important part of the overall anti-cancer action of polyphenols, since it impedes tumor growth (Jung 2001).

Other anti-cancer mechanisms of green tea polyphenols involve irreversible cell-cycle arrest, decrease in the production of inflammatory prostaglandin E2, inhibition of TNF-alpha release, and of certain enzymes involved in tumor proliferation, such as ornithine decarboxylase, cyclooxygenase and lipoxygenase. Matrix metalloproteinases, a group of enzymes involved in tumor invasion and metastasis, can also be inhibited with the green tea polyphenols and theaflavins, polyphenols found in black tea (Isemura 2000). Finally, green tea polyphenols have also been found to interfere with the activation of the various carcinogens through enhancement of the detoxifying phase II enzymes.

Likewise, the ability of green tea polyphenols to reduce the damage of nitrites in the acidic environment of the stomach has been found to be much stronger than that of vitamin C. An early study showed that green tea extract significantly inhibits the development of gastrointestinal tumors in animals and humans by blocking the formation of carcinogenic compounds containing the nitroso- group, such as N-nitrosoproline (Yan 1993).

Powerful antioxidant properties of green tea polyphenols are an inextricable part of their overall anti-inflammatory and cancer-preventive benefits.

Stomach cancer prevention protocol

In view of the numerous positive findings that show the protective effects of high doses of green tea against stomach cancer, the consumption of green tea may be beneficial to individuals who may be at special risk, due to family history, for instance. At the same time, it should be clear that most likely, only a relatively high dose of green tea polyphenols is protective. In the light of the research findings, ten cups of green tea per day, or their equivalent in green tea extract, seems to be a reasonable recommendation.

At the same time, however, it would be unwise to rely on a single agent for cancer prevention. A combination of several supplements generally works best. Maintaining an adequate antioxidant status is critical for the prevention of stomach cancer. Based on many studies, the suggested stomach cancer prevention protocol is as follows:

- 2500 mg/day of vitamin C
- 400 IU of vitamin E
- 200 mcg of selenium
- 5,000 IU of beta carotene
- 1000 mg of citrus flavonoids
- 300 mg to 600 mg of green tea extract (or consumption of ten cups of green tea per day)
- Avoidance of salty foods. If processed foods are used, choose the low-sodium variety.
- Avoidance of smoked, pickled or nitrite-treated foods and leftovers (especially if they have not been properly refrigerated).
- Avoidance of smoking.
- Avoidance of excess alcohol.
- Adequate consumption of fresh fruits and vegetables, including berries and raw vegetables.

Thus, we already know a great deal about the mechanisms through which green tea polyphenols inhibit both the development and progression of cancer. However, a skeptic might point out that most of this knowledge has come out of in vitro and animal studies. Fortunately, we do have some human epidemiological studies that do indicate the anti-cancer effectiveness of green tea, including specifically protection against stomach cancer.

The most recent of these, published in the May 2001 issue of *The International Journal of Cancer*, is a case-control study conducted in Yangzhong, a region in China with a high incidence of chronic gastritis and gastric cancer. Over 600 subjects participated in the study: 133 stomach cancer patients, 166 chronic gastritis patients and 433 healthy persons. Those with stomach cancer or gastritis were less likely to be green tea drinkers than healthy individuals (Setiawan, Zhang 2001). After adjustment for factors such as age, gender, smoking and body-mass index, frequent long-term green tea drinkers had on the average only one half the risk for either gastric cancer or gastritis. The study strongly indicated that the more green tea people consumed, and the longer the period of time they consumed it, the lower their risk of gastric cancer.

Gastritis is a chronic inflammation of the stomach lining that may lead to cancer; thus, it is considered a precancerous condition. Preventing inflammation of the stomach lining may be a very important part of the mechanism through which green tea helps protect against stomach cancer.

It should be pointed out that in China green tea is a popular beverage and, unlike in the West, it is not necessarily associated with an overall healthy lifestyle. In fact, green tea is a folk cure for hangover, and green tea drinkers may also be smokers. Thus, the protection against gastritis and gastric cancer is most likely due to the anti-inflammatory and anticarcinogenic properties of green tea catechins.

This study confirms an earlier Japanese study that also found a significant drop in the risk of chronic atrophic gastritis with high consumption of green tea. Subjects who drank more than 10 cups of green tea a day had a 37% lower risk of gastritis (Shibata 2000).

Another large Japanese study found that the risk of stomach cancer decreased by 31% with the intake of seven or more cups of green tea per day (Inoue 1998). This finding closely parallels an early, large Shanghai study that found a 29% drop in risk for green tea drinkers as compared with non-drinkers, with the risk decreasing in proportion to the daily amount of newly brewed green tea being consumed. A smaller study in another Chinese province found that low consumers of green tea had a 72% greater risk of stomach cancer. Overall, the studies appear to be consistent: green tea and fresh fruits and vegetables are associated with lower risk of gastric cancer.

Note that these studies indicate that long-term consumption of high doses of green tea may be required for a significant degree of protection. Five cups a day may not be sufficient, especially in the presence of heavy salt consumption, smoking, *H. pylori* infection, multiple antioxidant deficiencies and other risk factors. In-vitro data also indicates that the induction of cell death in gastric tumor tissue by green tea polyphenols depends on concentration and length of exposure, suggesting that only habitual daily intake of large doses of green tea polyphenols may provide anti-cancer protection (Hibasami 1998). Ultimately, it will take an interventional study to provide more reliable answers.

- Overall healthy lifestyle, including regular exercise and stress reduction

In addition, if an infection with *H. pylori* is diagnosed, a treatment to eradicate it is recommended. Antibiotics such as clarithromycin are commonly used, in combination with Prilosec, a drug that lowers acid levels and curbs the growth of *H. pylori*. For best results, two different antibiotics are used in combination with Prilosec or a related drug; in most patients, this "triple therapy" can wipe out *H. pylori* after only a week's treatment. A holistic physician may try to eradicate *H. pylori* using natural antioxidants, possibly including such relatively novel agents as astaxanthin and mastic gum. —IG

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Antioxidants other than green tea polyphenols also play an important role in helping protect against gastric cancer, even in the presence of *H. pylori*. In fact, antioxidant deficiencies may be a crucial factor in susceptibility to the infection, while antioxidant supplements may be an effective means to diminish the bacterial load (Bennedson 1999). In fact, Tsubono, the same author who led the recent negative study on green tea and gastric cancer, earlier conducted an interesting comparison of gastric cancer mortality in various regions of Japan, and found a distinct relationship between gastric cancer mortality and plasma levels of various antioxidants, including especially alpha-tocopherol and beta carotene, as well as other carotenoids and ascorbic acid. Thus it comes as no surprise that a recent joint Chinese and U.S. National Cancer Institute interventional study showed that supplementation with vitamin E, beta-carotene and selenium significantly lowered gastric cancer mortality (Yang 2000).

Several studies have found diminished risk of gastric cancer with higher plasma levels of antioxidants and selenium. An Italian study found increased survival in gastric cancer patients with a high intake of alpha-tocopherol. A Spanish case-control study found that those in the highest quartile of flavonoid intake had only 44% risk of gastric cancer compared to those in the lowest quartile (flavonoids are phenolic compounds found in vegetables and fruit). Synthetic antioxidants may also help somewhat: a Dutch study found a non-significant trend for decreased risk of gastric cancer with higher intake of BHA and BHT.

Thus, a variety of antioxidants appear to be effective in the prevention of gastric cancer: green tea polyphenols (based on the findings of studies other than Tsubono's), vitamin C, vitamin E, carotenes (including beta-carotene and astaxanthin, a carotenoid found in algae and seafood, also available as a supplement), flavonoids, selenium and possibly BHA and BHT.

Currently, stomach cancer kills one million people every year worldwide. This is especially tragic in view of our knowledge that stomach cancer is relatively easy to prevent. The great majority of stomach cancer cases could be eliminated.

Of special interest is an interventional study that compared the effectiveness of antioxidants and standard anti-*H. pylori* therapy in prevention of gastric dysplasia (a serious precancerous condition that is likely to progress to cancer). This study was conducted in a rural area in Colombia. Persons diagnosed with various types of precancerous gastric lesions were assigned to anti-*H. pylori* therapy, vitamin C therapy, beta-carotene therapy or placebo groups. Gastric biopsy specimens were collected at baseline and after 72 weeks. Those 74% of the subjects in the anti-*H. pylori* therapy in whom the treatment succeeded in eradicating the infection showed a marked regression in their lesions. However, subjects who received antioxidant therapy also showed excellent results, with vitamin C and beta-carotene being about equal in effectiveness. Combination of treatments did not produce a statistically significant increase in the rate of regressions (Correa 2000). Considering the low cost of vitamin C and beta carotene supplements, together with their safety, their effectiveness in regressing precancerous stomach lesions and preventing gastric cancer cannot be ignored.

Those who consider themselves at risk of stomach cancer may incorrectly assume that they shouldn't be using aspirin. Interestingly, aspirin, even though it can lead to damage to gastrointestinal mucosa, has been shown to lower the risk of gastric cancer (and colon cancer), most likely because of its anti-inflammatory action (Akre 2001). Chronic inflammation can lead to cell abnormalities and eventually to cancer. It is possible that selective COX-2 inhibitors will prove even better as NSAID-based cancer prevention, to be used in conjunction with other preventive measures. It should be remembered that green tea polyphenols also have anti-inflammatory activity, which is likely to be a very important part of their anti-cancer mechanism.

The fact that the incidence of stomach cancer has declined dramatically in the Western world leads to the conclusion that this type of cancer is largely preventable. It appears that the major factor associated with the drop in incidence of gastric cancer in the West has been the wide use of refrigeration, basically ending the demand for salt-preserved foods such as salted herring. At the same time, antioxidant-rich vegetables and fruit became available year-round, together with nutritional supplements.

Currently, stomach cancer kills one million people every year worldwide. This is especially tragic in view of our knowledge that stomach cancer is relatively easy to prevent. The great majority of stomach cancer cases could be eliminated. We can minimize the risk of stomach cancer by eradicating *H. pylori* infection, avoiding heavily salted foods, smoked foods, nitrite-containing and pickled foods, and by consuming an antioxidant-rich diet based on fresh rather than processed food, together with supplements

known to have anticarcinogenic benefits, including vitamins C, E and beta-carotene, selenium and green tea extract.

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