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Green Tea as a Functional Food Against Breast Cancer: A Review

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Abstract: Green tea has been purported to have a protective effect against cardiovascular disease, hypertension, inflammatory disease and cancer. Recently, there has been considerable scientific interest in "functional foods", or conventional foods that are demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions. This article examines green tea as a possible "functional food" for breast cancer. It is believed that the bioactive compound in green tea with purported anticancer potential is the catechin, (-)-epigallocatechin-3-gallate (EGCG). EGCG has been demonstrated to have antioxidant, anti-angiogenic and apoptotic effects using *in vitro* models. The results from epidemiological studies conducted in human populations are not statistically significant to warrant inclusion of green tea as a functional food against breast cancer. Nevertheless, certain trends observed in these studies and results from preclinical models necessitates further research into employing green tea as a functional food for breast cancer.

Key words: Green tea, functional food, conventional foods

INTRODUCTION

Tea is the second most consumed beverage in the world after water. Its global consumption far outstrips that of coffee, beer, wine and carbonated drinks (Cabrera *et al*., 2006). Tea is made from the bud and leaves of the plant *Camellia Sinensis* and is classified as green, oolong or black tea depending on the manufacturing process. Approximately 20-22% of tea produced and consumed is in the form of green tea which is produced by drying and steaming fresh leaves to inactivate the polyphenol oxidase (Cabrera *et al*., 2006). Green tea is produced primarily in China and Japan and has been purported throughout history to have several health benefits. However scientific investigation of these health benefits has only begun in the past 30 years (McKay and Blumberg, 2002). Recent studies suggest that green tea may contribute to cardiovascular health, oral health and that it may help promote anti-hypertensive effects, body weight control and serve as a neuroprotective agent (Cabrera *et al*., 2006). Finally, green tea has also been elucidated as a possible protective agent against cancer (Bushman, 1998).

Breast carcinomas are one of the most common cancers and are prevalent in the western world. One in ten of the neoplasms diagnosed worldwide are cancers of the female breast (Bray *et al*., 2004). Therefore, this review will examine the use of green tea as a potential functional food against breast cancer. According to Health Canada, a conventional food such as green tea may be defined as a functional food if it is demonstrated to have physiological health benefits and/or reduce risk of disease beyond basic nutritional functions (Health Canada, 2002). This paper will thus encompass a review of the potential beneficial components of green tea, their possible role in preventing breast cancer, and of current scientific literature that may warrant further study of green tea as a functional food in reducing the severity and incidence of this crucial pathology.

Breast cancer: According to the World Health Organization (WHO), Noncommunicable Diseases (NCDs) are the leading causes of death worldwide (WHO, 2010). These NCDs comprise cardiovascular diseases, diabetes, chronic respiratory diseases and cancers (WHO, 2010). Breast cancer is the most prevalent cancer in women globally, with an estimated 1.2 million new diagnoses each year (Kamangar *et al*., 2006). Breast cancers caused nearly 400,000 deaths worldwide in 2008 and have a global economic impact of approximately $88 billion (American Cancer Society, 2010).

The exact etiology of breast carcinogenesis has yet to be fully understood (Veronesi *et al*., 2005). The molecular mechanisms that induce cancer formation and metastasis are topics of current research and debate. Nonetheless, the pathophysiology of breast cancer is well described. Most types of breast cancers are tumours of the epithelial cells found in the breast ductal or lobule linings. Less common, are the sarcomas that develop from the supporting stromal tissue (Merck Manual, 2008). The carcinomas are classified as invasive cancers and carcinomas *in situ*, in which the cancer cells proliferate within ducts or lobules without invading the stromal tissue. After local invasion the breast cancer can spread through the blood and lymph to afflict any part of the body but most commonly the lungs, liver, brain and skin (Merck Manual, 2008). Ductal

carcinomas *in situ* are usually treated with mastectomies, whereas early and advanced stage cancers of the breast are treated with surgery followed by radiation therapy and chemotherapy (Merck Manual, 2008). Special therapeutic drugs are currently being developed that target some of the functional hallmarks of carcinogenesis such as angiogenesis (growth of new blood vessels for tumour growth and metastasis), the EMT (epithelial mesenchymal transition) and cell proliferation (through apoptotic drugs). Monoclonal antibodies are being engineered as drugs, to target specific receptors involved in cancer development such as the drug trastuzumab for the HER-2 receptor and other antibodies are being designed to target tyrosine kinase receptors and steroid hormone receptors that are implicated in signalling cascades associated with cancer (Veronesi *et al*., 2005).

Research has also yielded a list of important risk factors for developing breast cancer. Some genetic factors that are associated with poor prognosis are over expression of the HER2 gene (Human epidermal growth factor receptor 2) and the BRCA gene (Veronesi *et al*., 2005). Relative risk for breast cancer is observed to be higher in women with early menarche, occurring before the age of 15, compared to women in whom it occurs after the age of 15 (Helmrich *et al*., 1983). Other risk factors are increased age at first birth and risk is observed to decrease with increasing parity (Helmrich *et al*., 1983). The absence or short duration of breast-feeding, especially in developed countries is found to be associated with higher risk and other risk factors may include but are not limited to; alcohol consumption, breast cancer in a first degree relative, genetic predisposition, inherited high mammary density, advanced age, use of exogenous hormones and environmental exposure to ionizing radiation (Veronesi *et al*., 2005).

Studies have also shown that risk of developing breast cancer can be attributed to the diet, with increased consumption of vegetables and to a lesser extent, fruits, shown to marginally reduce the risk of developing breast cancer (Gandini *et al*., 2000). Recent studies have attempted to study the substitution of carbohydrates with certain types of dietary fats but no strong association is found to exist (Smith-Warner *et al*., 2001). It is observed however that increased intake of animal fats from red meat and dairy products prior to menopause heightens the risk of breast cancer (Veronesi *et al*., 2005). It can be stated hence, that evidence exists to suggest that dietary factors and nutritional agents may have a role in inhibiting the incidence and/or severity of breast cancer.

Composition of green tea: In order to elucidate and characterize possible anti-carcinogenic agent(s) found within green tea, a brief classification of the chemical components of green tea is essential. Green tea composition is complex. Proteins constitute nearly 15-20% of the dry weight of green tea. Amino acids such as tryptophan, glycine, serine and arginine make up about 1-4% of the dry weight (Cabrera *et al*., 2006). Carbohydrates, such as cellulose, glucose, fructose and pectins make up about 5-7% of the dry weight. Other compounds found in green tea include xanthic bases such as caffeine and theophylline, sterols, alcohols, vitamins (B, C, E) and trace minerals such as calcium, magnesium, copper and zinc (Cabrera *et al*., 2006).

Another class of compounds found in green tea, constituting roughly 30% to 42% of the dry weight are polyphenols, especially flavonoids (Cabrera *et al*., 2006). Flavonoids are phenol derivatives synthesized and widely distributed in plants. The major flavonoids found in green tea are catechins (McKay and Blumberg, 2002). Catechins are characterized by di- or tri-hydroxy substitution of the B ring and the meta-5,7-dihydroxy substitution of the A ring. The four major catechins in green tea are as follows (-)-epigallocatechin gallate (EGCG), that accounts for approximately 50-80% of all catechins found in green tea, (-)-epigallocatechin (EGC), (-)- epicatechin-3-gallate (ECG) and (-)-epicatechin (EC) (Yang *et al*., 2002). It is these catechins that are of most interest to researchers studying the potential anti-carcinogenic potential of green tea (Chung *et al*., 2003). In particular, (-)-epigallocatechin-3-gallate (EGCG), has been observed to have potent antioxidant effects and a plethora of *in vitro* studies have outlined its anti-angiogenic and anti-tumor potential in cancer therapy (Singh *et al*., 2011).

EGCG can thus be further studied as an important bioactive compound in green tea. In order to determine its effects, the bioavailability of EGCG must be properly elucidated. It was estimated by Wu and Wei (2002), that a cup of green tea (2.5 g of green tea leaves in 200 ml of water) may contain 90 mg of EGCG. Studies show that the bioavailability of EGCG varies according to species. In rats, oral administration of the four tea catechins (EC, ECG, EGC and EGCG) and subsequent identification of these catechins in the portal vein indicated that these were being absorbed intestinally (Cabrera *et al*., 2006). In humans, catechins reach peak plasma levels approximately 2 to 4 hrs after ingestion and EGCG is found to be less bioavailable but have a higher half-life than other tea catechins (Yang *et al*., 1998).

Anticancer potential of EGCG [H1]: EGCG is purported to affect several biological pathways that have a role in cancer development. Therefore, some of the key mechanisms through which EGCG mediates its anti-carcinogenic potential will be discussed followed by a review of current epidemiological studies conducted on the association of green tea with reduction in breast cancer incidence and/or severity in human populations. Even if EGCG can be demonstrated to have several anti-

carcinogenic effects *in vitro* and in animal models, statistically significant amounts of data will need to be collected from human studies to irrefutably prove an association between drinking green tea and protection against breast cancer in humans.

Antioxidant potential: Tea catechins and EGCG in particular, are known to have antioxidant potential, due in part, to their chemical structures (Singh *et al*., 2011). EGCG was observed to be a powerful scavenger of free radicals and have a protective antioxidant effect on neurons (Murakami *et al*., 2002). Furthermore, a 4-week ingestion of green tea extract capsules and green tea consumption was shown to reduce the biomarkers of oxidative stress (McKay and Blumberg, 2002). Human mammary cells treated with EGCG showed increased expression of SOD, super-oxide dismutase, suggesting that EGCG is able to induct endogenous antioxidative mechanisms in the cell (Lambert and Elias, 2010). The exact mechanism of green tea antioxidant potential and its effects in the human body are not well elucidated (Singh *et al*., 2011). Further study in humans is required to establish EGCG as an antioxidant of therapeutic or significant use.

Inhibition of angiogenesis: Angiogenesis is an important functional hallmark of cancer (Singh *et al*., 2011). Angiogenesis results in endothelial cell sprouting, tube and lumen formation and endothelial cell differentiation towards the formation of novel blood vessels (Shankar *et al*., 2008). This ability to generate novel vasculature is also exhibited during early development and it allows cancer cells to recruit their own blood supply. It has been shown that EGCG can inhibit angiogenesis through enhancing the activity of the FoXO transcription factors (Singh *et al*., 2011). Several transcription factors play an important role in de novo vessel formation during angiogenesis and FoxO transcription factors are important for maintaining tissue homeostasis in tissues such as the pancreas and the ovaries (Singh *et al*., 2011). FoxO which stands for forkhead box, class O, are proteins that are involved in regulation of stress response and in proliferation and apoptosis (Bartholome *et al*., 2010). It was found in a recent study that lower concentrations of EGCG caused nuclear accumulation and enhanced DNA binding activity of FoxO (Bartholome *et al*., 2010). The ability of EGCG to behave in an insulin-antagonistic fashion and affect several downstream pathways, at lower concentrations, highlights why green tea may have been purported to have cardioprotective and other health benefits. Further study in human mammary epithelial cell lines should be conducted to determine if angiogenesis inhibition can be achieved through EGCG at a dosage that does not have toxic effects on other cells in the body.

Induction of apoptosis: The induction of apoptosis or programmed cell death has been studied as an important therapy against cancer cells (Shankar *et al*., 2008). EGCG is found to affect several signalling pathways to induce apoptosis, cell cycle arrest and prevent cell proliferation (Singh *et al*., 2011). A recent study by Hastak *et al*. (2003) investigated the role of EGCG on the tumour suppressor gene p53 and NF-kB (nuclear factor kappa-light-chain-enhancer of B cells), which causes continuous cell proliferation if it is dysregulated. The study was conducted in human prostate carcinoma LNCaP cells. This carcinoma is analogous to breast carcinoma of the breast epithelial cells. EGCG treatment of these cells resulted in stabilization of p53 via phosphorylation of critical serine residues on p53. Concomitantly, EGCG was observed to inhibit the transcriptional activity of NF-kB, leading to down regulation of its downstream target Bcl-2, resulting in growth arrest and apoptosis in these cell lines (Hastak *et al*., 2003).

One of the major mechanisms of induction of apoptosis is through modulation of pathways linked to the plasma membrane (Singh *et al*., 2011). A recent study was conducted to examine what membrane receptor associated signalling pathways are acted upon by EGCG to modulate apoptosis and cancer inhibition (Hsu and Liou, 2011). This *in vitro* study was conducted on the MCF-7 human breast cancer cell line. It was found that EGCG treatment resulted in decreased cell survival through modulation of the signalling pathways of laminin and epidermal growth factor receptors on the cell membrane, resulting in perturbed formation of adherens junctions and altered intracellular calcium (Ca^{2+}) concentration (Hsu and Liou, 2011). It was also observed to enhance apoptosis through upregulating expression of the apoptopic caspase-3 protein and down regulation of gelsolin, a regulator of actin filament assembly and breakdown (Hsu and Liou, 2011). EGCG therefore, is has promising potential against neoplastic cells through its ability to concomitantly decrease cancer cell survival and increase programmed cell death. However, further study of *in vivo* models is required to examine whether green tea consumption can actually inhibit or reverse cancer cell formation in human mammary tissue.

Green tea and breast cancer studies in human populations: It is imperative to review current epidemiological literature on green tea consumption and its effects on breast cancer incidence and development in humans. With the advent of novel computing technology, ample data on dietary consumption of green tea and breast cancer risk in the global population may be collected. These epidemiological studies can help provide the statistically

significant amounts of data that will prompt and necessitate further study into green tea as a potential therapeutic agent for breast cancer.

An epidemiological study was conducted by Wu *et al.* (2003) during 1995-1999, on the consumption of both black and green tea and risk of breast cancer in Asian American women. This population based, case-control study sampled women identified as Chinese, Japanese or Filipino, living in Los Angeles County. Using the resources of the Los Angeles County Cancer Surveillance Program, 501 breast cancer patients and 594 controls were interviewed (Wu *et al.*, 2003). Dietary intake prior to cancer development for cancer patients and dietary intake in the preceding year for control cases was analyzed using food frequency questionnaires. This 2-way analysis treated each type of tea as separate, so the baseline group consisted of individuals who were non-drinkers of that type of tea. Regression analysis was conducted using known risk factors (education level, age at menarche, parity etc.) as covariates. Risk of breast cancer was found to be not related to black tea consumption but significantly inversely linked to regular green tea consumption (Wu *et al.*, 2003). The odds ratio (OR) for cancer incidence for women who responded No, 0-85.7 ml/day and >85.7 ml/day respectively for green tea consumption were 1.00, 0.71 and 0.53 (95% CI), respectively, demonstrating a significant inverse association between green tea intake and risk of breast cancer (Wu *et al.*, 2003).

Another epidemiologically significant study was a prospective cohort study conducted in Japan over 9 years (Imai *et al.*, 1997). This study included an 8.522 strong sample of both men and women over the age of 40 living in a town in the Saitama prefecture, surveyed for daily green tea consumption for a period of 9 years. A negative association was found between cancer incidence and drinking more than 10 cups of green tea a day. The Relative Risk (RR) of cancer incidence in high consumption groups were 0.57 in women and 0.68 in men (95% CI) and despite the fact that these were lower than that for low consumption individuals, the protective effect against breast cancer incidence was not statistically significant (Imai *et al.*, 1997). Several possible factors can have an effect on how green tea interacts with the body. The amount of EGCG found in green tea can also vary considerably depending on how it is prepared (McKay and Blumberg, 2002). Since EGCG is our purported anti-carcinogenic agent of interest here, it can be posited that prospective longitudinal studies on consumption of encapsulated EGCG extract should also be conducted, controlling strictly for dietary and genetic predisposing factors for breast cancer.

A group of researchers at the Canadian College of Naturopathic Medicine in Toronto, Ontario, conducted a comprehensive review and meta-analysis of observational studies of green tea consumption on breast cancer (Seely *et al.*, 2005). Such reviews, that employ advanced statistical testing and pooled analyses can help unify varying data from the literature to create a more lucid depiction of breast cancer incidence and recurrence risk and its association with green tea. Unfortunately all the studies analyzed were conducted in Asian and predominantly Japanese populations (Seely *et al.*, 2005). This is due green tea consumption being centred primarily in these Asian countries or among Asian women. Moreover, randomized controlled trials for green tea are virtually non-existent in the literature. Out of the 7 studies included in the analysis, only 3 demonstrated a dose-response relationship with green tea (Seely *et al.*, 2005). The pooled RR of cohort studies for breast cancer recurrence was 0.75 (95% CI; $p = 0.22$). The Odds Ratio (OR) for developing breast cancer in the highest consumption groups was 0.44 (95% CI; $p = 0.14$) (Seely *et al.*, 2005). Thus, the researchers concluded these results demonstrated that despite a general trend observed in prevention of breast cancer incidence and recurrence, the results were not statistically significant from human epidemiological studies to strongly warrant that green tea be used as a therapy for breast cancer (Seely *et al.*, 2005).

Conclusion: This review provides an interesting assessment of the association of green tea consumption and breast cancer. While animal models and *in vivo* studies have demonstrated several mechanisms whereby cancer inhibition is mediated through green tea, the results from epidemiological studies and *in vivo* studies conducted in humans are numerically few and statistically not significant enough to establish a clear causal link for green tea mediated cancer inhibition. However, the host of bioactive compounds in green tea and in particular EGCG, are continually being shown to have key roles in cell signalling and other important molecular pathways in human cells and animal models.

Possible confounding factors that must be considered is that very few studies are currently published that test for dosage dependent response of cancer cells to green tea or the bioactive compound, EGCG. Moreover, a standardized method of green tea preparation has not been used in the studies conducted to date. The steeping time, leaf content and potential re-use of the tea bags are all possible confounding factors for the amount of green tea being consumed by the individuals being observed. The genetic factors that may modulate an individual's response to green tea are also not well-researched (Seely *et al.*, 2005).

In the future the current literature provides several possible areas of research into green tea and EGCG use as a therapeutic agent. It is essential that both observational and longitudinal studies be conducted in Western populations to determine whether green tea

has at least a moderate, if not significant, association with reduction of breast cancer incidence. Studies such as these may also help determine for population based genetic differences in response of cancer cells to green tea. At the molecular level, novel pathways and mechanisms of EGCG mediated inhibition of cancer cell proliferation are continually being characterized. In addition to genetic changes, epigenetic modifications, which are heritable changes not encoded in the DNA and include mechanisms such as DNA methylation and histone modification and are known to be targeted by EGCG, represent a complex host of mechanisms which must be better characterized to understand carcinogenesis (Singh *et al*., 2011). In terms of the functional food and neutraceutical industry, the bioactive compound EGCG merits further research. Extracting this compound and marketing it in the North American context as capsules or other extracts, where green tea consumption is not as high as in Asian populations, can also be investigated. Lastly, the catechins represent simply one group of important compounds found in teas. Compounds such as caffeine and phenolic acids such as gallic acid may also be investigated as therapeutic agents for several of the afflictions green tea is purported to prevent or cure.

The potential beneficial effects of green tea have been claimed by its drinkers throughout history. Green tea is an important beverage that is consumed by a sizeable proportion of the world's population, centred in densely populated China and Japan. The drinking of tea has also taken on a strong cultural connotation for these cultures, symbolizing both relaxation and therapy. Despite the fact that evidence from the literature is not sufficient to validate the vastly therapeutic claims, the beneficial potential of green tea cannot be disregarded and necessitates further study and research. This intriguing move of West towards the East represents a host of exciting new frontiers and possible revelations that may arise from introducing these eastern dietary habits in the Canadian, and the larger Western,-population.

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