Green tea for the prevention of breast cancer: a meta-analysis

Frances Jing *

March 28, 2022

Abstract

The potential of polyphenols to prevent and treat cancer has been extensively studied in human cancer cells, where multiple polyphenols have been found to prevent, inhibit, and activate autophagy and apoptosis in human cells of various cancers. However, this relation between polyphenols and treating cancer has been studied substantially less in human patients. Although there are numerous observational, case-control, and cohort studies investigating anti-cancer polyphenol effects, few randomized controlled trials (RCTs) have been conducted to assess the true anticancer effect of polyphenols in preventing and treating cancer. In fact, some evidence suggests that polyphenols may interact negatively in human cancer patients by conflicting with their prescription cancer medication. Despite this, most US cancer patients still use dietary supplements to aid in their recovery, many of which include polyphenols. Therefore, the true anticancer effect of polyphenols must be identified. In this meta-analysis, we analyze eligible RCTs that demonstrate the effects of green tea, a popular dietary supplement, on risk factors of breast cancer (blood pressure, weight, IGF-1, and mammographic density). After thorough analysis, we find that green tea has a modest effect in preventing breast cancer by impacting these breast cancer risk factors.

1 Background

1.1 Polyphenols

Polyphenols are natural products abundantly found in plants. Besides being consumed in a normal diet, polyphenols, such as resveratrol, quercetin, and EGCG can be consumed through dietary supplements [Mar10].

Polyphenols are reported to provide benefits such as prevention against neurodegenerative diseases, inflammation, cardiovascular diseases, type 2 diabetes, and obesity [Cor18]. The anticancer effects of polyphenols have been extensively researched using human cancer cells and to a limited extent in human

*Advised by: Patrick Emedom-Nnamdi of Harvard University

patients and animals. Many experiments have found that green tea prevents and inhibits cancerous growth and activates autophagy and apoptosis in human breast cancer cells [Tha07]; [Lia99]; [Kim06]; [Zen14]; [Stu06]. Although these anticancer properties of polyphenols have yet to be confirmed in humans due to the lack of available clinical trial data, the majority of US adults and cancer patients already use dietary supplements [BR13]; [Lee06], the majority of which contain polyphenols, such as vitamin A, C, E, and fish oil [Lan13].

However, taken in large doses, these supplements can be detrimental. For example, there are some reports of hepatotoxicity due to heavy consumption of tea-based supplements (10-29 mg/kg/day) where people had elevated serum alanine aminotransferase (ALT) and bilirubin levels, both of which are signs of liver damage. Additionally, in an oral administration of Teavigo (a green tea polyphenol with 90% EGCG, but with no caffeine) to Beagle dogs, the study resulted in dose-dependent toxicity and death [Lam07].

Yet, even when taken at normal doses, polyphenol supplements may be detrimental when taken simultaneously with cancer medication. Although the percentage of US adults who use dietary supplements fluctuates at around 50%, the percentage of cancer patients rises to 60-70% [Lee06], mostly because their condition increases their desire to "do [something] to help themselves" and "boost their immune system." [Fer09] However, in a study of 200 cancer patients, it was found that the risk of potential negative interactions between their cancer medication and dietary supplement was 12% [Lee06]. Popular supplements such as multivitamins, iron, and calcium could interact with cancer medications to result in decreased anticoagulation, absorption of the cancer medication, and therapeutic effect. Given the fact that only 28% of the cancer patients told their doctors about any potential supplement usage, potential negative interactions could make their cancer harder to understand and treat.

However, it is important to recognize that polyphenols themselves may not be detrimental to cancer recovery. In a separate study of 827 cancer survivors, 69.3% of the survivors used dietary supplements after their cancer diagnosis [Fer09], suggesting that polyphenols may actually aid in cancer recovery. More intriguingly, 82.4% of the survivors informed their physician of their supplement usage, compared to the 28% in the Lee study. While many factors behind cancer recovery, this drastic percentage increase suggests that patients that inform their doctors of supplement usage may experience higher rates of recovery. In any case, because of the popular usage of polyphenols and their potential interactions with cancer treatment, there should be a larger focus on identifying if supplement usage aids in cancer prevention and cancer recovery.

1.2 Randomized Controlled Trials

Randomized controlled trials (RCTs) minimize the risk of confounding factors that affect the true result compared to other intervention methods [A.K05]. Thus, RCTs are considered the most reliable type of interventional study. For this reason, RCT studies are commonly analyzed in meta-analyses [Bas17]. Therefore, to summarize the true effect of green tea consumption in preventing

breast cancer, we only included RCTs in this meta-analysis.

2 Risk Factors of Breast Cancer

In this section, we investigate green tea's effects on various breast cancer risk factors: blood pressure, weight, IGF-1, and mammographic density. Other primary breast cancer risk factors such as age and number of children are not included due to their little to no relationship with green tea.

2.1 Blood Pressure

Blood pressure has been established as a potential risk factor for breast cancer, especially for hypertensive post-menopausal women, in which an association between high blood pressure and increased risk of breast cancer has been found [Han17]. There are two types of blood pressure: systolic blood pressure (SBP) and diabolic blood pressure (DBP). The effects of green tea on both types of blood pressure are included in this meta-analysis.

2.2 Weight

Weight is an established risk factor for breast cancer. The idea among popular culture that green tea aids in weight loss has merit; evidence shows that green tea consumption not only leads to a modest decrease in weight, but also helps in maintaining weight after initial weight loss [Hur09]. In an RCT consisting of 42 obese post-menopausal women and 18 obese men aged between 40 and 60 years old, green tea was found to significantly reduce weight by increasing energy expenditure and fat oxidation [PA08]. All 60 subjects in the study consumed identical diets prepared by the Nutritional Unit at Srinagarind Hospital and had normalized levels of physical activity. The mass differences between the placebo and green tea groups after 4, 8, and 12 weeks were 2.70, 5.10, and 3.3 kg, respectively. Importantly, the mass differences at 8 and 12 weeks were significant ($p < 0.05$), suggesting that green tea lowers the risk of breast cancer by encouraging weight loss. However, weight is not included in this meta-analysis due to its very strong relationship with blood pressure [Sta88], which is already included.

2.3 IGF-1

Insulin-like growth factor (IGF-1) is a growth hormone that promotes tissue growth and maturation [Wri17]. Not only is IGF-1 a risk factor of breast cancer, but it is also hypothesized to cause proliferate and anti-apoptotic effects, which may increase the severity of the disease by increasing risk of cancer development, progression, and metastasis [Chr15]; [Sha16]. Therefore, because the relationship between IGF-1 and breast cancer risk is positive and strong, the effect of green tea on IGF-1 is included in this meta-analysis.

2.4 Mammographic Density

Mammographic density is a risk factor of breast cancer and is measured with percent mammographic density (PMD), the percentage of the breast that is radiologically dense. Women with a PMD of 75% or higher have a 4 to 6-fold gradient in breast cancer risk than women with 10% or lower [F.13]. In an RCT of green tea's effect on PMD, green tea significantly reduced PMD by 4.40%, while the placebo group had a 1.02% PMD increase in postmenopausal women aged 50-55 years. However, green tea had no effect on PMD of the two older age groups, women aged between 56-60 and 61-70 years old [Sam17]. Thus, the study suggests that green tea aids in breast cancer prevention for younger postmenopausal women. To our knowledge, this trial is the only published RCT to have investigated the effect of green tea supplementation on PMD. Given the lack of additional data, PMD could not be included in this meta-analysis.

3 Methods

3.1 Keywords

RCTs were found using Google Scholar and PubMed.

PubMed search terms:

Advanced search "breast cancer" AND "green tea" with filter "randomized controlled trial." Advanced search "green tea" AND "hypertension" with filter "randomized controlled trial."

Google Scholar search terms:

Advanced search for articles that contain the words "green tea blood pressure," with the exact phrase "randomized controlled trial," and with at least one of the words "postmenopausal women weight." Advanced search for articles that contain the words "insulin growth factor green tea," with the exact phrase "randomized controlled trial." Advanced search for articles that contain the words "mammographic density green tea," with the exact phrase "randomized controlled trial."

3.2 Eligibility Criteria

To be included in this meta-analysis, only RCTs of humans orally taking green tea (either in capsule or liquid form) from the year 2000 and more recently were included.

3.3 Meta-Analysis

Data was uploaded from Excel into the programming language, R, to conduct the meta-analysis. Data for each risk factor is visualized with a forest plot.

4 Results

4.1 Blood Pressure

Six RCTs [McK10]; [Bog12]; [NT07]; [Bas10]; [Nan09]; [Hil07] with a cumulative total of 545 participants were used to analyze green tea's effect on blood pressure. Each of these trials included data on both markers of blood pressure: SBP and DBP. Participants were adult men or women (who were pre-menopausal or post-menopausal) and were either healthy or hypertensive and obese.

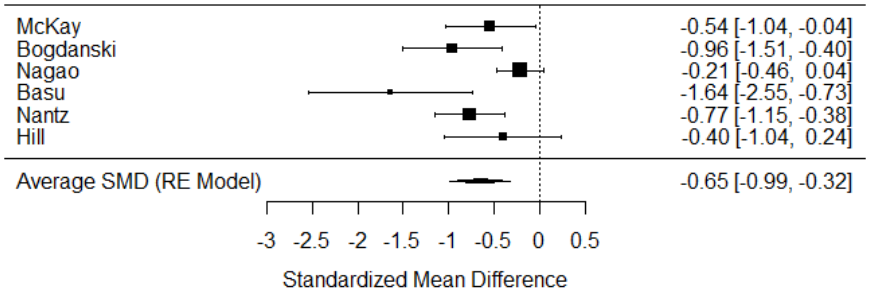

Figure 1: Change in SBP from baseline.

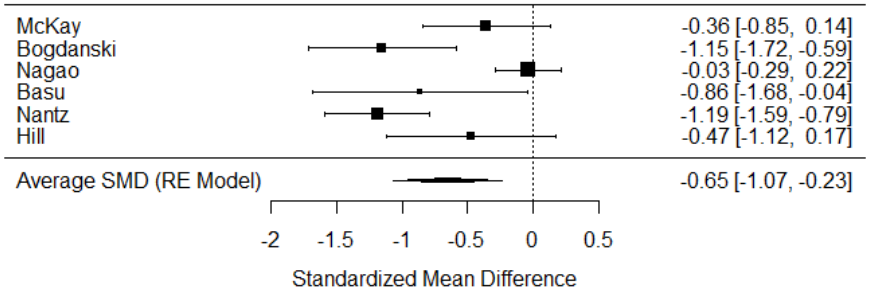

Figure 2: Change in DBP from baseline.

For both SBP and DBP, the average standardized mean difference (average

SMD) was -0.65 mm Hg. This negative value means that green tea supplementation decreased an adult's SBP and DBP by an average of 0.65 mm Hg each. Furthermore, because the confidence intervals are between -0.99 to -0.32 mm Hg and -1.07 to -0.23 mm Hg for SBP and DBP, respectively, where the greater ends of the intervals remain less than 0, it can be concluded that green tea significantly decreases blood pressure in the study population of healthy or obese and hypertensive adults. Because higher blood pressure is associated with higher breast cancer risk, this result indicates that green tea has a modest preventative effect against breast cancer by lowering blood pressure.

4.2 IGF-1

Two RCTs [Sam19]; [SH21] with a cumulative total of 1017 participants were used to analyze green tea's effect on IGF-1. Because most of these participants were healthy postmenopausal women with a mean age of 60 years old, which is the age that is the most susceptible to breast cancer [HN20], this analysis targets breast cancer's most common victims. However, the meta-analysis also includes participants who are healthy men aged 60 years and above to better represent the entire adult population.

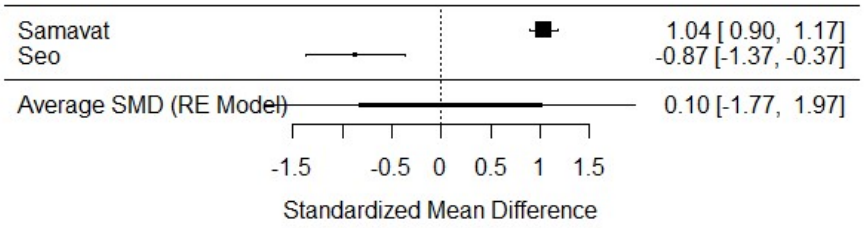

Figure 3: Change in IGF-1 from baseline.

The average SMD of green tea's effect on IGF-1 was 0.10 ng/mL. This positive difference indicates that green tea increased IGF-1 levels by an average of 0.10 ng/mL. However, due to the confidence interval ranging from -1.77 to 1.97 ng/mL, where the interval is neither wholly positive nor negative, the data is inconclusive. Thus, the data indicates that green tea is neutral against the occurrence of breast cancer due to its statistically insignificant impact on IGF-1.

5 Discussion

By definition, a risk factor is a variable that increases the risk of a disease. By lowering risk factors of breast cancer, it can be concluded that green tea lowers the risk of developing breast cancer. Although one factor, IGF-1, did not significantly change with green tea supplementation, green tea's effect on SBP, DBP, weight, and mammographic density suggests that overall, green tea has a preventative effect against breast cancer.

This result is supported with other evidence in the scientific community, where green tea has been shown to prevent illnesses such as various types of cancers, metabolic syndrome, and cardiovascular disease [Yan14].

Green tea's effect on disease prevention could have widespread implications not only for the potential applications of green tea in medicine, but also for the application of Traditional Chinese Medicine (TCM) in Western medicine. After Western medicine was first introduced to China in the 17th century, some people argued for the complete separation of the two systems of medicine, while others advocated for the integration of the two [Kej03]. Currently, the efficacy and safety of integrating TCM and Western medicine is being researched; for example, this integration of medicine has recently been shown to be safe and effective in treating rheumatoid arthritis in a meta-analysis consisting of 2269 patients [Xin20]. Ultimately, increased evidence supporting the positive medicinal effects of green tea and other TCM ingredients and treatment methods encourages TCM to be further integrated into Western medicine, which can produce more treatments in the future.

6 Conclusion

In conclusion, because of green tea's impact on risk factors of breast cancer, green tea may significantly, albeit modestly, decrease breast cancer risk. Four risk factors of breast cancer were discussed: blood pressure (both SBP and DBP), weight, IGF-1, and mammographic density. Green tea significantly decreases weight, mammographic density, and both markers of blood pressure, but does not change IGF-1. Thus, by decreasing three of four primary risk factors of breast cancer, green tea has a modest preventative effect against breast cancer.

7 Conflict of Interest

None declared.

8 Acknowledgements

Thank you to Horizon Academic for providing this research program and to my advisor, Patrick Emedom-Nnamdi of Harvard University, for guidance on this research project.

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