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Potential Benefits of Green Tea on Cancer-Related Outcomes: The Impact of Dosage and BMI as Effect Modifiers

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Abstract

Introduction: *Green tea (GT), catechins, epigallocatechin-3-gallate (EGCG), and its polyphenol extract, Polyphenon E have been studied as potential anticancer agents. This systematic review evaluates the effect of GT exposure on cancer outcomes while focusing on the influence of green tea dosage and body mass index (BMI) as effect modifiers.*

Methods: *A systematic review of studies among PubMed, Scopus, and Embase until June 2024, evaluating green tea or Polyphenon E among cancer patients was performed. Of 150 publications, five studies were included, comprising four RCTs and one single-center prospective cohort study. We evaluated the effects of green tea interventions on cancer biomarkers and survival outcomes and the possible modifying role of BMI on such endpoints.*

Results: *The included studies have different types of cancers, green tea dosages, and intervention durations. High-dose green tea (≥800 mg EGCG) was associated with reduced specific biomarkers; for example, insulin-like growth factor-1 (IGF-1) and proliferating cell nuclear antigen (PCNA); however, results were consistent across biomarkers and cancer types. Only one of the observational studies reported a statistically significant dose-response association between green tea consumption and improved survival among ovarian cancer patients. BMI data varied little between the intervention and placebo arms across the studies; this certainly limits the ability to assess BMI as an effect modifier.*

Conclusion: *While there was a trend towards a reduction of specific cancer biomarkers associated with green tea consumption, due to limitations in the data, it is not possible to conclusively determine effect modification by dosage or BMI. Variability in study designs, dosages, and cancers limits generalizability. Future studies are warranted that are well-designed regarding dosage standardization, long-term effects, and identification of an interaction between green tea and standard cancer therapies.*

Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide. According to the American Cancer Society (ACS), there will be an estimated 2

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million new cancer cases and 611,720 cancer deaths in the U.S. in 2024. These statistics have significant implications for individuals, families, and the healthcare system. Surgery, chemotherapy, immunotherapy, and radiation remain the standard treatments for cancer with proven efficacy; however, these treatments have considerable side effects and limitations. Nowadays, there is increased interest in complementary therapies, which could enhance treatment effects and alleviate adverse effects.

One of the many potential adjunctive therapies that have been studied over the years is green tea (GT) due to its potential chemopreventive properties. The group of green tea catechin derivatives includes epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate (EGCG). The last of these presents the most potent anti-inflammatory and anticancer potential (Musial et al., 2020).

Several mechanisms are responsible for GT's effects. The main bioactive compound, epigallocatechin-3-gallate (EGCG), is known for inhibiting cancer cell proliferation by inducing apoptosis and interfering with various signaling pathways that represent an important route in cancer progression and development. Additional GT polyphenols, including catechin, have been described as potential agents in alleviating oxidative stress, preventing angiogenesis in tumors, and helping to modulate immune responses. Crew et al. (2015) investigated Polyphenon E, a GT extract, and suggested a possible reduction in systemic biomarkers related to growth factor signaling in women with hormone receptor-negative breast cancer. These findings highlight one of GT's many roles in cancer therapy.

However, the effect of GT on cancer survival, systemic biomarkers, and carcinoma progression remains inconclusive. Challenges include the absence of population-based cohorts of significant size, difficulty determining GT's effect as a single compound, and limited discussion of effect modifiers such as genetic variation, lifestyle factors, and cancer subtypes (Filippini et al., 2020). Various factors influence outcomes related to green tea and its role in cancer, including dosage and BMI. It is essential to define an optimal green tea dosage to maximize therapeutic benefits while minimizing potential toxicity. In vitro studies have shown that higher amounts of green tea polyphenols have a stronger effect against cancer. However, the relationship appears to be highly individualistic (Zhang et al., 2004), raising the hypothesis that the bioavailability of green tea compounds may be influenced by individual BMI, thereby affecting its efficacy.

The primary aim of this review is to investigate the effects of green tea on cancer-related outcomes such as recurrence, survival, disease progression, and changes in biomarkers. We also examine the potential modifying effect of BMI and green tea dosage on these outcomes.

Materials and Methods

Information Sources and Search Strategy

This systematic review was conducted following the Cochrane Handbook recommendations (Higgins et al., 2023) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant studies were selected after a comprehensive search conducted across PubMed, Scopus, and Embase databases from 2020 to 2024. The search strategy encompassed a combination of terms related to cancer and green tea, including but not limited to "cancer," "neoplasms," "malignancy," "green tea," "Camellia sinensis," and "randomized controlled trial." A detailed search strategy is available in the supplementary materials (Table 3).

Inclusion and Exclusion Criteria

The inclusion criteria for this systematic review involved studies performed on human participants diagnosed with cancer. Article eligibility focused on green tea and its extracts as an intervention and the report of its effects on cancer-related outcomes, such as recurrence, disease progression, or changes in biomarkers.

Contrarily, studies performed on non-cancer patients, animal models, or those with an intervention other than green tea consumption or with a comparator other than green tea or its extracts were excluded. Further exclusions were applied to studies that did not report cancer-related outcomes or biomarkers or focused solely on risk or incidence.

Systematic reviews, meta-analyses, narrative reviews, conference abstracts, multiple publications from the same article, and those not published in English were also excluded.

Inclusion Criteria

- Adult patients
- Cancer diagnosis of any stage
- Studies that report patients' Body Mass Index (BMI)
- Green tea or green tea extract as intervention
- Placebo-controlled studies
- Reported cancer-related outcomes, such as mortal-

ity, recurrence, or biomarker response
•Studies conducted in any geographic region
•Studies published in peer-reviewed journals

Exclusion Criteria

•Pediatric or adolescent patients (under 18 years of age)
•Non-cancerous or precancerous conditions
•Studies comparing green tea with other comparators, such as black tea, herbal treatments, or pharmacological therapies
•Non-human studies or animal models
•Studies that did not report clear cancer-related outcomes

Selection of Studies and Data Extraction

Selected studies for this systematic review were uploaded to Covidence, a platform utilized to manage abstract screening, full-text review, and data extraction. All duplicates were automatically removed. Initially, all abstracts were screened for relevance to the main aim of this review, followed by a full-text review to confirm eligibility based on predetermined inclusion and exclusion criteria. Articles were independently reviewed by two authors to ensure adequacy and minimize bias. A third review author was consulted to resolve conflict and reach consensus when discrepancies were found.

A standardized data extraction form was developed in Covidence by two review authors to collect all relevant information from selected studies. The form was elaborated to gather information regarding study design, participants' baseline characteristics, intervention specifics, comparator, and cancer-related outcomes. Once extraction was completed, data was double-checked by an independent reviewer to increase accuracy; the extracted data was consolidated in Covidence and downloaded for further data analysis to guarantee accurate capture of all selected study details.

Measurement of Effect Modification

In these studies, we assessed body mass index (BMI) as a potential effect modifier by analyzing BMI measurements on both genders and comparing them with the green tea dosage they received to evaluate any dose-response patterns. This is because the relationship between a patient's BMI and the dosage of green tea necessary to influence cancer outcomes may vary proportionally depending on BMI. In this scenario, cancer patients with a higher BMI may require higher doses of green tea to achieve a similar therapeutic effect as patients with a lower BMI. This effect modification could be due to adipose tissue distribution or metabolic rate.

Data Synthesis

We used descriptive analysis to summarize categorical variables (e.g., BMI, gender, race/ethnicity) and expressed continuous variables (e.g., green tea dosage, biomarker changes) as mean with standard deviation or frequency.

A systematic approach was used to ensure transparency and reliability of the data synthesis from all the selected studies. For synthesis, the eligibility of each study was determined by a structured process involving authors working independently on article review. Additionally, key characteristics were tabulated and coded, including baseline participant characteristics, dosage of GT or its compounds intervention details (e.g., dose, duration, frequency), and cancer-related outcomes (e.g., mortality, recurrence, biomarkers). This synthesis structure aimed to provide insight into the relationship between green tea use, dosage, and patients' BMI on cancer outcomes across the reviewed literature.

Risk of Bias Assessment

Three review authors independently assessed the risk of bias in the included studies. Two different standardized tools were used to assess the risk of bias in this systematic review: the Cochrane Risk of Bias 2 (ROB-2) tool (Sterne et al., 2019) for randomized control trials (RCTs) and the Newcastle-Ottawa Scale (NOS) for observational studies (Wells et al., 2019). ROB-2 evaluated the risk of bias in RCTs measuring five specific domains. Each study in this systematic review was rated as "low risk," "some concern," or "high risk" of bias according to the findings.

Observational studies quality was assessed following three specific criteria: 1) selection of the study group, 2) ascertainment of exposure or outcome, and 3) comparability of the groups. Studies were assigned stars based on the quality of the information in each category, with a maximum of nine stars corresponding to a low risk of bias.

Results

Description of the Studies

We retrieved 150 publications after removing 14 duplicates. After the initial screening by title and abstract, 91 studies were excluded, and the remaining 59 studies were assessed for eligibility criteria. Five studies that met the inclusion crite-

ria were included in this systematic review (Figure 1).

Study Characteristics

Of the selected studies, four were randomized controlled trials, including two phase II trials. Three of these trials were multicenter studies, while one was conducted at a single center. The fifth study was a single-center prospective cohort study (Table 1).

Population

Participants' characteristics varied among the studies, and differences and similarities were considered. Each study investigated the impact of dietary or supplementary interventions with GT or Polyphenon E. The population varied across the studies, with differences in the proportion of males and females as well as the total number of participants in each study.

Ovarian cancer (Zhang et al., 2004) had the largest sample size of 254 female participants. Breast cancer (Crew et al., 2015) had 34 female participants, and bladder cancer (Gee et al., 2017) had a similar number of male and female participants (n=31). One prostate cancer study (Henning et al., 2015) involved 93 male participants, and the other enrolled 50 male participants (Nguyuen et al., 2012). Ovarian and prostate cancer studies noted large sample sizes compared to the other studies. All study participants were adults aged 18 to 70 years across the studies. The mean age reporter in three studies was 44.1 years in the ovarian cancer study (Zhang et al., 2004), 54.5 years in the breast cancer study (Crew et al., 2015), bladder cancer patients had a mean age of 67.2 years (Gee et al., 2017) and prostate cancer patients had a mean age of 62 years (Henning et al., 2015).

Gender distribution varied according to the type of cancer and the study. Ovarian and breast represented the female population with 254 and 34 participants, respectively. Bladder study had a majority male population (84%). Race and ethnicity were reported to be inconsistent between the studies. White participants were the majority in all studies, with Hispanic/Latino participants having a greater representation in breast and bladder studies.

Cancer types were specific to each study. The studies which analyzed ovarian cancer included various histological subtypes: serous cystadenocarcinoma (41.8%), mucinous cystadenocarcinoma (13.9%), endometrioid cystadenocarcinoma (8.6%), mixed epithelial cystadenocarcinoma (2.9%), undifferentiated carcinoma (14.3%), borderline malignancy (15.2%), clear cell carcinoma (2.0%), transitional cell carcinoma (0.4%), and malignant Brenner's tumor (0.8%). Breast studies focused on estrogen and progesterone-negative cancer. The bladder cancer study included patients with primary or recurrent tumors at any clinical stage. The prostate cancer study reported biopsy Gleason scores. .

Intervention Characteristics and Effects/Exposure/Control

The interventions in the included studies varied in type, dosage, frequency, and duration of GT. Gee et al. (2017), Nguyen et al. (2012), and Crew et al. (2015) used the green tea extract Polyphenon E (enriched green tea polyphenol extract). Dosage levels ranged from 400 mg to 1.200 mg daily or twice daily, administered orally in capsules containing 200 mg of EGCG each. The duration of the intervention also varied, with one study implementing a 14-day treatment period while the other extended up to six months. In all three RCTs, the control groups received matching placebos that did not contain green tea extracts, and for one of the RCTs, the control group intervention was water.

Henning et al. (2015) evaluated the consumption of six cups per day of brewed green tea (equivalent to 1,010 mg of polyphenols and 562 mg of EGCG). At the same time, another group received black tea and the control group water. The duration of the intervention was three to eight weeks.

Zhang et al. 's (2004) prospective cohort study, with a minimum three-year follow-up, evaluated green tea consumption by measuring the frequency in the number of cups drunk, the frequency of new batches of tea brewed, and the number of dried tea leaves consumed.

Outcomes

In this study, the primary outcomes measured were dosage and frequency of green tea consumption, as well as body mass index (BMI). Secondary outcomes included survival, tissue and systemic biomarkers of carcinoma progression, and bioavailability of green tea polyphenols in tissue, plasma, and urine.

Prostate cancer proliferation biomarkers (Ki67), nuclear and cytoplasmic NF-kB were measured through immunostaining; 8OHdG oxidation and serum prostate-specific antigen (PSA) levels were measured through blood samples and urine samples. Ovarian cancer survival time was calculated from the date of ovarian cancer diagnosis to the date of death, for participants who passed away or to the date of the follow-up interview for survivors.

At the time of the interview, it was reported that 81 (77.9%) of 104 tea drinkers survived, and only 67 (47.9%) of 140 non-drinkers were still alive. Provid-

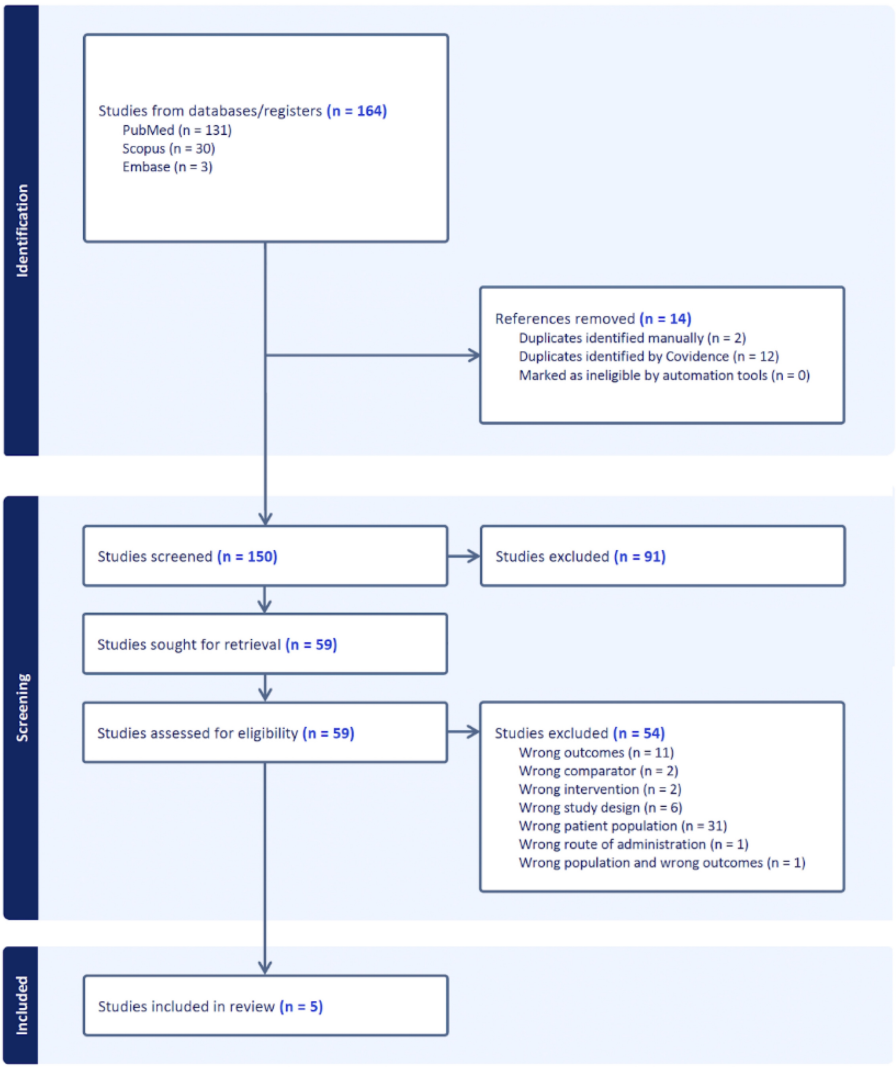

Figure 1: *PRISMA Flow diagram.*

Figure 2: *Risk of bias assessment.*

ing a statistically significant difference between Tea drinkers vs. non-drinkers: hazard ratio (HR) = 0.55 (95% CI: 0.34–0.90), $p < 0.05$ (Zhang et al., 2004).

The biomarkers PCNA, MMP2, Clusterin, VEGF, and p27 from the bladder tissue were assessed by IHC immunostaining and IHC scoring, while sandwich immunoassay was used to assess IGF-1 and IGFBP3.

Regarding breast cancer, serum HGF and VEGF levels were measured using an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA). The bioavailability of Polyphenon E in urine and plasma was assessed using established liquid chromatography-mass spectrometry techniques.

In the RCTs, the frequency and dosage of green tea were predetermined in each trial before the start of the study, and the intervention groups were randomly assigned to different dosages. BMI was described based on the data from the studies.

Main Results

Regarding the relationship between cancer and green tea, four studies discussed changes in various biomarkers, though only one study analyzed the survival rate as a clinical outcome; survival was described with HR. No statistical analysis was performed in this study.

This study addresses several types of cancer, each with distinct populations and primary outcomes. To ensure clarity, we stratified the findings by the specific cancer-related outcomes affected by green tea, such as biomarkers, survival, BMI, and dosage. Additionally, for a more detailed comparison, we've also organized each finding by cancer type in Table 3 to offer a better understanding of how the effects vary across different cancers.

Biomarkers

The changes in biomarkers reflect the progression of cancer and the potential therapeutic effects of green tea (GT). Reduction in prostate serum antigen (PSA) suggests a slower cancer progression and better response to treatment; lower hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1(IGF-1), and insulin growth factor 3 (IGF-3) imply slow tumor growth and DNA damage markers assess the integrity of the genetic material and may determine if green tea has a protective effect and reduces cancer progression.

Nguyen et al. (2012) showed a higher mean reduction of -0.66 ± 2.56 in the Polyphenon E group compared to -0.08 ± 1.28 ng/mL in the placebo group. However, this was not statistically significant (P=0.26). In addition, 58.3% of participants in the Polyphenon E group demonstrated a reduction in PSA levels compared to 36.4% in the placebo group, although this also was not statistically significant (P=0.15). This reduction in PSA levels can mean a potentially favorable effect of green tea consumption on the progression of prostate cancer. Although the reduction was clinically notable, it was not statistically significant. This study also found that IGF-1, associated with a higher risk for prostate cancer, was notably decreased in the Polyphenon E arm, -6.90 ± 20.97 compared to -1.20 ± 21.82 ng/mL in the placebo group. Still, it was not statistically significant (P = 0.53). A decrease in insulin-like growth factor binding protein-3 levels was also reported.

The ratio of urinary biomarker 8-hydroxy-2'-deoxyguanosine to deoxyguanosine, a biomarker for oxidative DNA damage, was slightly reduced in the Polyphenon E group -0.79 ± 6.75, compared to 1.81 ± 8.37 in the placebo group, although it was not statistically different between the groups, P = 0.17. The percentage with a reduction in oxidative DNA damage was higher in the Polyphenon E group versus placebo, 65.0% versus 35.3%, reaching a trend toward significance, P = 0.10. Green tea does seem able to reduce oxidative DNA damage; however, results cannot yet support clinical relevance.

Crew et al. (2015) studied biomarkers related to breast cancer, highlighting the involvement of the HGF-Hepatocyte Growth Factor in tumor cell growth, migration, and invasion. Low levels of HGF suggest green tea may inhibit these pathways. The mean serum HGF levels in the Poly E group decreased by 12.7% at 2 months, as opposed to an increase of 6.3% in the placebo group. However, although this result was statistically significant when evaluated at 4-6 months, this significance failed to be sustained, reducing confidence in any long-term clinical benefit.

Additionally, vascular endothelial growth factor (VEGF) is involved in angiogenesis. VEGF levels in the Polyphenon E group were reduced by 11.5% at 2 months (P = 0.02) and by 13.9% at 4 months, but when compared with placebo, these changes were not statistically significant.

The study by Henning et al. (2014) demonstrated that GT has statistically significant effects on prostate cancer biomarkers. Pointedly, GT consumption resulted in significantly lower nuclear NFkB staining in malignant prostate tissue, P=0.013, indicating reduced inflammation. This was later supported by the finding that urinary excretion of 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, was significantly lower in the GT group

Studies	Cancer	Intervention	Control	Study Design	BMI mean
Gee et al. (2017)	Bladder	EGCG (800 mg/day, 1200 mg/day)	Placebo	Double-blind RCT Multicenter	30.4
Crew et al. (2015)	Breast	EGCG (562 mg/day)	Placebo	Double-blind RCT Multicenter	28
Henning et al. -2015	Prostate	EGCG (562 mg/day)	Water	Phase II open-label RCT Multicenter	27.2
Nguyen et al. -2012	Prostate	Green tea (800 mg/daily)	Placebo	Double-blind RCT Single-center	26.9
Zhang et al. -2004	Ovarian	Green tea (1750 mg/batch)	None	Prospective cohort Single-center	< 25 87.2% > 25 12.8%

This table represents the characteristics of the included studies. Four randomized controlled trials (RCT) and one observational study were included. Of the RCTs 3 were conducted as a double-blind trial and one was open-label. The dosage of epigallocatechin gallate intake (EGCG) and body mass index (BMI) were reported in all studies.

Table 1: *Characteristics of the included studies.*

(-19.4 ± 13%) compared to controls (+23.6 ± 19%). Serum PSA levels also decreased significantly in the GT group, although an exact p-value was not provided. In addition, EGCG and further polyphenols had also been found in human prostate tissue and urine of GT drinkers, underlining the bioavailability and, thus, presumed effects of GT polyphenols.

Evidence by Gee et al. (2017) supports the possible anticancer role of green tea through its principal polyphenol, EGCG. In the statistically significant findings, there was a dose-dependent increase in the levels of EGCG in the bladder tissues, with high-dose Polyphenon E showing measurable levels in both normal and tumor tissues ($P < 0.05$). Moreover, the following biomarkers of cancer biology were significantly altered: PCNA (Proliferating Cell Nuclear Antigen), which is indicative of cellular proliferation, was substantially downregulated in a dose-dependent fashion (P=0.016); clustering associated with apoptosis also demonstrated significant downregulation (P=0.008). Although the decrease in the cell-cycle regulator p27 did not reach statistical significance (P=0.15), the trend does support its possible effect on cell-cycle regulation.

Survival

Zhang et al. (2004) found that green tea consumption post-diagnosis was related to improved survival in ovarian cancer patients. Green tea drinkers had higher survival as 77.9% of tea drinkers survived to the time of the interview, whereas only 47.9% of non-tea drinkers survived. Thus, the hazard ratios for tea drinkers compared with non-drinkers were 0.55 (95% CI: 0.34–0.90), indicating that tea drinking was associated with a significantly reduced risk of mortality. However, although more deceased patients than surviving patients were non-tea drinkers, there was no statistically significant difference.

BMI as an Effect Modifier

BMI data was analyzed across the five selected studies, focusing on the differences between male and female participants and evaluating the relationship between a patient's BMI and cancer outcomes.

The mean BMI ranged from 26.9 to 30.4 kg/m^2, except in one study that categorized it as <25 to ≥ 25 kg/m^2, and showed that 87.2% of patients had a BMI <25 kg/m^2. The wide range between the reported means indicates the variability in the study populations. The average BMI of female participants in all studies (n = 166) was 23.68, and the average BMI of male participants in all studies (n = 92) was 22.73 (Table 2).

TBMI values were similar between the intervention group (green tea) and the placebo group across all four RCTs included in this systematic review. Evaluating effect modification by BMI within those individual studies becomes challenging because there is not enough variation in BMI within the groups to observe any potential interaction effect. Unfortunately, the unavailability of additional data from these studies makes it difficult to perform subgroup analysis or meta-regression.

The only observational study included in this systematic review, by Zhang et al. (2004), on ovarian cancer survival, reported that all deceased patients

had a higher BMI pre-diagnosis compared to the survivors. BMI in this study was evaluated as a risk factor for mortality in ovarian cancer, not as an effect modifier of green tea.

Green Tea Dosage

This section summarizes the findings from five studies assessing the effects of different green tea dosages on cancer outcomes, including brewed green tea and tablet supplements.

Brewed green tea contains an average of 77.8 mg EGCG per 100 mL. Therefore, each 240 mL serving of brewed green tea may provide approximately 187 mg EGCG. Unfortunately, there is no universally agreed-upon cutoff value to differentiate between high-dose and low-dose green tea. Based on multiple published studies, four or more cups per day, which can provide 800-1,200 mg or more of catechins, is considered a high dose.

Based on the studies included in this systematic review, three studies (Nguyen et al., 2012; Gee et al., 2017; and Zhang et al., 2004) used a high dose of green tea (800 mg of EGCG or more) (Table 2).

Although we hypothesized that green tea has a dose-dependent effect, high-dose green tea consumption was not consistently associated with a reduction in all surrogate markers. There was a reduction in some surrogate markers, such as insulin-like growth factor-1, insulin-like growth factor binding protein-3 levels, tissue biomarkers (Proliferating Cell Nuclear Antigen and clusterin), but not in other markers, such as VEGF, lipid profile, oxidative damage, inflammatory biomarkers, and PSA.

Survival concerning green tea dosage was only evaluated in one study and showed an improved survival outcome with high-dose green tea intake.

Assessment of Risk of Bias in Individual Studies

Using the risk of bias tool (RoB2), we assessed the quality of the RCTs included in this review. In the absence of selection bias, handling missing data, maintaining participant personnel, and assessor blinding through the trial, all four studies were classified as low risk. The Newcastle-Ottawa scale (NOS) was used to assess the risk of bias in the cohort study (Zhang et al., 2004). This analysis also suggested that there was a low risk of bias as the study demonstrated a strong selection of cohorts, adequate control for confounding, and a robust assessment of outcomes.

Discussion

Effect modification is an important concept that needs to be considered when designing and analyzing data from clinical trials. It is also an essential concept to consider when performing meta-analyses that evaluate the effect of intervention.

The effect of intervention can be changed in either direction based on many factors such as age, gender, BMI, and genetic profile. Such assessment of effect modification may help in patients' selection for clinical trials as well as adjustment for specific confounders.

The potential effect modification of BMI is because fat accumulation in people with high BMI may alter the pharmacokinetics profile of drugs and nutritional supplements, especially their absorption, distribution, and elimination (Smit, 2018).

Additionally, obesity with high BMI is associated with a chronic inflammatory state characterized by higher levels of pro-inflammatory cytokines and chemokines expression. (Rodríguez-Hernández, 2013) These inflammatory mediators associated with obesity could alter the inflammatory effect and anticancer properties of green tea.

The relationship between green tea and cancer was evaluated in this systematic review. The 4 RCT studies included in this systematic review evaluated the changes in different biomarkers before and after green tea consumption. The only observational study included in this systematic review examined the impact of green tea on decreasing cancer mortality.

Some of the surrogate biomarkers, such as PSA, are used extensively in clinical practice to screen for prostate cancer and monitor for treatment response and recurrence. Other surrogate biomarkers such as insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), proliferating cell nuclear antigen (PCNA), and Clusterin are currently used in various cancer research settings and are of limited clinical applicability.

In this review, we aimed to evaluate green tea dosage and BMI as potential effect modifiers of green tea's impact on cancer outcomes. However, we found that the BMI was similar between the intervention and placebo groups across all four included RCTs, limiting our ability to assess any potential interaction. Evaluating effect modification requires significant variation in the modifying factor- in this case, BMI - across the study population. Unfortunately, the homogeneity in BMI and the unavailability of individual-level data precluded further subgroup analysis or meta-regression.

Despite the marked heterogeneity of the included studies to the type of cancer, dosage of green tea and duration of consumption, and assessment of different

Studies	EGCG Dosage per day	Duration	Gender	N	BMI mean
Gee et al. (2017)	1,200 mg	2 – 4 weeks	Female	2	30.8
			Male	8	
	800 mg		Female	1	30.4
			Male	9	
Crew et al. (2015)	400 mg 600 mg 800 mg	6 months	Female	26	28
Henning et -2015	562 mg	2 – 8 weeks	Male	34 (GT group)	27.2
Nguyen et al. -2012	800 mg	3 – 6 weeks	Male	24	26.9
Zhang et al. -2004	1 cup 1 batch (1750 mg) 500 g per year	NR	Female	91 (71 alive 20 dead) 13 (10 alive 3 dead)	< 25 ≥ 25

Dosages of EGCG, Duration and Participant's BMI

This table illustrates the Dosages and Duration of Intervention of, respectively exposure to epigallocatechin gallate (EGCG) as well as the body mass index (BMI) and Sex of the participants. Only in the observational study by Zhang et al. (2004) the duration of exposure to EGCG was not reported (NR).

Table 2: *Dosages of EGCG, duration and participant's BMI.*

outcomes, the same tendency of reduction in specific prognostic biomarkers related to different types of cancers was seen across studies included in this meta-analysis.

Despite our attempt to classify green tea dosage into low and high doses based on previous studies, green tea effect modification by dosing or BMI cannot be concluded due to a lack of sufficient data.

The absence of a precise cut-off green tea dose that differentiates between high dose and low dose, as well as the duration of consumption required to show green tea's beneficial effects made it challenging to reach a clear conclusion. However, we believe assessing the effect modification is the key to finding the optimal use of green tea as a complementary treatment added to the conventional cancer standard of care.

The combined strength of this review lies in the inclusion of both RCTs and observational studies; while RCTs offer the benefits of a more controlled environment and randomization, which helps ensure internal validity, observational studies provide a comprehensive view of real-world outcomes. Collectively, these trials are subject to clinical implications where green tea shows a tendency to reduce PSA levels and DNA damage markers, with Henning et al. (2015) finding a statistically relevant result while Nguyen et al. (2012) showed a reduction in PSA levels without significance, but without an association with higher dosage or BMI. Besides that, higher doses of green tea were associated with a lower mortality ratio, although the study lacked sufficient statistical power (Zhang et al., 2004), and a greater reduction in tissue biomarkers associated with bladder cancer was described (Gee et al., 2017).

Conclusion

Despite heterogeneity among the included studies, a consistent trend in decreasing prognostic biomarkers was observed across various cancer types. However, due to limited data, we could not determine effect modification by BMI or green tea dosage. Evaluating effect modification remains essential to defining optimal green tea use as a complementary cancer therapy. At least one ongoing clinical trial may soon contribute further data on green tea's impact on cancer outcomes.

A well-designed, large-scale, prospective cohort study or pragmatic interventional trial may still be required.

	Zhang et al., 2007	**Nyguen et al., 2012**	**Crew et al., 2015**	**Henning et al.,2015**	**Gee et al., 2017**
Cancer type	Epithelial ovarian cancer	Prostate adenocarcinoma	Breast carcinoma (stage I-III)	Prostate adenocarcinoma	Bladder tumor
Population	Chinese women 40 years of age and older diagnosed with epithelial ovarian cancer	Patients with biopsy-confirmed prostate carcinoma electing prostatectomy as their primary treatment	Females aged 21– 65 years with a history of histologically-confirmed resected stage I–III estrogen receptor (ER)-negative and progesterone receptor (PR)-negative breast carcinoma	40 - 70 year old males that had a diagnosis of clinically localized prostate adenocarcinoma	Males and females 18 years of age and older with an office cystoscopy diagnostic of a bladder tumor
Intervention	Green tea consumption post diagnosis	Polyphenon E daily	Poly E capsules –decaffeinated oral green tea extract, containing 65% EGCG (200 mg equivalent to 3 cups of brewed green tea).	6 cups of green tea or black tea (daily)	Polyphenon E (mixture of catechins from green tea leaves) once daily
Dose	1 cup 1 batch (1750 mg) 500 g per year	Green tea (800 mg/daily)	400, 600 or 800 mg of EGCG (2–4 capsules) twice daily.	6 cups of GT provided a total of 1010 mg of GT polyphenols including 562 mg of EGCG and 6 cups of BT provided 80 mg of tea polyphenols including 28 mg of EGCG and 35 mg theaflavins in addition to 348 mg gallic acid	800 mg EGCG or 1,200 mg EGCG
Comparator	N/R	Placebo daily	Placebo twice daily for 6 months	Water control	Placebo once a daily
Time	N/R	3–6 weeks before surgery	6 months	The mean duration of the intervention in the GT, BT and the control group was 33, 31 and 29 days, respectively, prior to radical prostatectomy	14–28 days prior to transurethral resection of bladder tumor (TURBT) or cystectomy
Outcome	Survival time and the frequency and quantity of tea consumed post-diagnosis	GT polyphenols in prostate tissue Change in Systemic and tissue biomarkers (PSA, IGF-1, IGF-3) Oxidative DNA damage in blood	Evaluation of HGF, VEGF, oxidative damage (8-oxodG) and 15-F2t-IsoP, hsCRP, urine prostaglandin E2 metabolite biomarkers, and urinary tea	Evaluation of markers of cancer development and progression in malignant RP tissue by immunostaining. Assessment of polyphenols levels in tissue and urine + urinary 8OHdG and PSA levels.	Compare the post intervention EGCG tissue levels in patients receiving Polyphenon E vs placebo. Examine dose dependent modulation of biomarkers (PCNA, MMP2, clusterin, VEGF, p27, IGF-1, IGFBP-3); and levels of other catechins in tissue, plasma and urine.
Results	96 of 244 cases in the original cohort were deceased (all the deaths were due to ovarian).	PSA values demonstrated a greater decrease for those on Polyphenon E than those on placebo but this did not reach statistical significance (−0.66±2.56 and −0.08 ±1.28, ng/ml, p=0.26).	Increase of total urinary tea polyphenols in the Poly E-treated group.	Tea polyphenols were detected in prostate tissue from 32 of 34 men consuming GT but not in the other groups	Statistically significant dose–response relationship for EGCG levels was observed across study arms.
	There were 81 (77.9%) of 104 tea-drinkers who survived, compared to only 67 women (47.9%) still alive among the 140 non-drinkers.	The 8OHdG to dG ratio, a marker of oxidative DNA damage, (IGF-1, IGFBP-3) all showed reduction in the polyphenon group but not statistically significant.	Mean urinary tea polyphenol levels peaked at 2 months and decreased at 4 and 6 months in the Poly E group. Decrease of serum HGF and VEGF levels by 12.7% and 11.5% respectively.	Statistically significant reduction of urinary 8OHdG (p=0.03) and serum prostate-specific antigen (PSA) levels (p=0.04) only with GT consumption.	EGCG levels in plasma, urine, and bladder tissue followed a dose–response relationship, as did modulation of tissue biomarkers of proliferation and apoptosis. PCNA and Clusterin were downregulated.

This table provides a detailed summary of each study included in the review, outlining the population characteristics, intervention type, dosage, comparator, duration, outcomes measured, and key results.

Table 3: *Stratification by study.*

Limitations

This systematic review has limitations, including a small number of studies and participants, heterogeneity in cancer types, green tea dosing, and outcome measures. The diversity in biomarkers and their clinical relevance made comparison difficult.

Due to the limited number of studies, we did not include a funnel plot, limiting our ability to evaluate publication bias, which remains a concern. The inclusion of one observational study also introduces potential bias, reducing overall reliability.

There is room for future research exploring the standardized dosage gap, long-term effects, and potential interactions with current cancer standard therapies. Addressing these gaps could deepen insight into the mechanism behind green tea's effects and support broader integration into oncology.

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Conflicts of Interest

The authors declare no conflict of interest.

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