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Camellia Sinensis Tea Consumption and Effect on Disease Progression and Remission Rates in Cancer Patients on Standard Therapy. A systematic Review and Meta-Analysis

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ABSTRACT

Background: Tea is an ancient and beloved beverage consumed by individuals worldwide. Camellia sinensis is an evergreen shrub used to make green, white, oolong and black tea. The leaves are known to contain significant amounts of polyphenols, a type of protective antioxidant. These polyphenols are linked to several health advantages, most notably as supplementary therapy for the treatment of cancer. Previous clinical research indicated that tea extracts may have cancer-preventing properties. However, its effectiveness remains uncertain.

Search Methods: A systematic review of clinical research on the effectiveness of consuming Camellia sinensis teas by patients diagnosed with various malignancies was conducted. This project comprehensively searched eligible studies from January 1, 1980, up to July 1, 2024, in all databases (Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, PubMed Central® (PMC), Scopus, and reference lists of previous reviews and included studies). Studies were searched and included in accordance with the PICOS criteria, as determined by the PRISMA standards, considering the inclusion and exclusion criteria. JBI SUMARI was utilized to conduct the risk of bias assessment and pool the data to carry out a meta-analysis. Findings were presented on an Excel spreadsheet, and statistics were summarized using a forest plot.

Main Results: 100 studies were included in this systematic review and meta-analysis. The systematic review revealed that green tea outperformed all other Camellia sinensis teas since the highest and lowest intakes of green tea (> 2 cups/day) were associated with a lower overall cancer incidence (summary RR 0.83, 95% CI = 0.65,1.07). As a result, a meta- analysis was carried out on similar studies of green tea yielding similar outcomes.14 meta- analyses were conducted on green tea and standard anti – cancer treatment versus standard anti – cancer treatment alone, including tests for cancer prevention, cancer risk reduction, and adverse events. All 14 effect sizes were statistically insignificant at $p > 0.001$ using random-effects model demonstrating an overall high methodological quality based on the JBI 'Risk of bias' assessment tool with no evidence of between-study heterogeneity ($I2 < 50$).

Conclusion: In addition to being safe and well-tolerated, green tea may have beneficial effects on cancer prevention. To obtain a definitive conclusion and identify the mechanisms behind this association, future research is necessary. Larger, longer-term prospective cohort and clinical studies on oolong, white, and black tea are also warranted.

Abbreviations: ALT: Alkaline Phosphate Enzyme; ASAP: Atypical Small Acinar Proliferation; BCG: Bacillus Calmette-Guerin; BT: Black Tea; BTE: Black Tea Extract; C Sinensis: Camellia sinensis; CA: Colorectal Adenomas; CAM: Complementary and Alternative Medicine; CENTRAL: Cochrane Central Register of Controlled Trials; CI: Confidence Interval; COMT: Catechol-O-Methyltransferase; CRC: Colorectal Cancer; CRPC: Castration-Resistant Prostate Cancer; DBGT: Double Brewed Green Tea; EGCG: Epigallocatechin-3-Gallate (Green Tea Catechin); ESCC: Oesophageal Squamous Cell Carcinoma; GSP: Green Select Phytosome; GT: Green Tea; GTE: Green Tea Extract; GTP: Green Tea Polyphenols; HCC: Hepatocellular Carcinoma; HGPIN: High-Grade Prostatic Intraepithelial Neoplasia; HuR: Human Antigen R ; JBI: Joanna Briggs Institute; MeSH: Medical Subject Headings; NHL: Non-Hodgkin's Lymphoma; OPL: Oral Leucoplakia; OR: Overall Risk; OR: Odds Ratio' ORR: Overall Response Rate; OS: Overall Survival; OT: Oolong Tea; OTE: Oolong Tea Extract; PC / PCa: Prostate Cancer; PFS:

Progression Free Survival; PICOS: Population, Intervention, Comparison, Outcomes and Study; PMC: PubMed Central ®;Poly EPolyphenon E (Green Tea Polyphenol);PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROSPERO: Prospective Register of Systematic Reviews; RCT: Randomized Control Trials; RR: Risk Ratio / Relative Risk; SCE: Sister Chromatid Exchange; SUMARI: System for the Unified Management, Assessment and Review of Information; VITRO: Outside the Living Body and in an Artificial Environment; VIVO: Inside the Living Body of a Plant or Animal; WHO: World Health Organization; WT: White Tea; WTE: White Tea Extract

Acknowledgement

At times our own light goes out and is rekindled by a spark from another person. Each of us has cause to think with deep gratitude to those who have rekindled the spark within us. Firstly, I would like to express my gratitude to my creator Allah (SWT), the most Beneficent, the most Merciful, for guiding me and granting me the strength and perseverance to complete this dissertation. I owe all of my success to him. His endless blessings have been a constant source of light throughout my academic journey. Thanks must go to the Faculty Research Committee (FRC) for funding. I would also like to thank the Division of pharmacology, Lelo and Professor Robyn Van Zyl for their assistance, funding and encouragement while I was completing this dissertation. Thanks must go to my secondary reviewer, Yumna Johnson, for appraising my articles and ensuring my research was of the highest quality. A special thanks to my supervisors Prof Schmollgruber and Prof Neil Butkow for their invaluable advice and feedback on my dissertation. My deepest gratitude goes out to my primary supervisor Dr Armorel Van Eyk, thank you for your unwavering faith in my ability to complete this dissertation. I could not imagine doing this under anyone else's guidance and I am so grateful for your encouragement, patience and warmth throughout the last two years. I would like to thank my mum, sister and grandparents for continuously supporting me throughout my journey at university. Thank you for believing in me even when I did not believe in myself. This achievement is as much theirs as it is mine. I dedicate this work to my beloved father who passed away from pancreatic cancer; I am forever grateful for his love, prayers, and guidance. I hope to always make him proud.

Chapter 1 - Introduction

After decades of research and development concerning cancer treatment, cancer is still at large and very much a threat to the global human population. Cancer remedies have been sought from all possible directions, including chemicals, irradiation, nanomaterials, natural compounds, and the like. Tea is yet another important source of innumerable natural compounds with chemo-preventative capacity (Oh, et al. [1]). *Camellia Sinensis* is an evergreen shrub belonging to the Theaceae family of flowering plants. Green, black, white and oolong can be made from its leaves, leaf buds, and stems. In Southeast Asia, where tea is a prevalent part of the culture and way of life, *Camellia Sinensis* tea has been associated with lower risks for bladder, stomach, and pancreatic cancers. A thorough literature search from 1980 up to 2024, revealed that among the various variants of teas, green tea is the best-studied system for its cancer chemo- preventative and chemotherapeutic effects.

Study findings demonstrated a high worldwide consumption of green tea, that contains polyphenols which have a powerful antioxidant activity that can prevent the formation of free radicals that may cause damage and cell death. Therefore, it has been suggested that green tea might reduce cancer risk, a theory that has been tested through a number of studies on human populations, which examined the link between green tea consumption and cancer (Filippini, et al. [2]). Additionally, C. Sinensis contains polyphenols, one subgroup being catechins. Catechins are powerful antioxidants, and laboratory studies have suggested that these compounds may inhibit cancer cell proliferation (Filippini, et al. [2]). Some experimental and non-experimental epidemiological studies have suggested that green tea may have cancer-preventative effects (Filippini, et al. [2]). However, the main underlying mechanisms of green teas potentially preventive effect against cancer is still unknown. Additionally, current research shows a lack of knowledge regarding the anticancer potential of black, white and oolong tea. More research in humans is needed before *Camellia Sinensis* tea can be recommended as a cancer fighter.

This systematic review protocol is registered on Prospero (CRD42024607504; see Appendix L, page 122) and a poster presentation was successfully presented at the 2024 SASBCP conference (Appendix M, page 123). Furthermore, this systematic review and meta-analysis evaluated the effectiveness of consuming C. sinensis teas by patients diagnosed with various malignancies. This project comprehensively searched eligible studies from January 1, 1980 up to July 1, 2024, in all databases. Numerous clinical research indicated that green, black, white and oolong tea may have cancer-preventing properties. Thus, the importance of this study was to further understand the beneficial role that C. sinensis teas consumed by cancer patients on standard anti-cancer therapy may play in cancer prevention and reduction in cancer risk. This study hopes to shed light on the importance of C. Sinensis tea's mechanisms as supplementary therapy in the treatment of cancer. The outlay of the dissertation is illustrated in Figure 1.

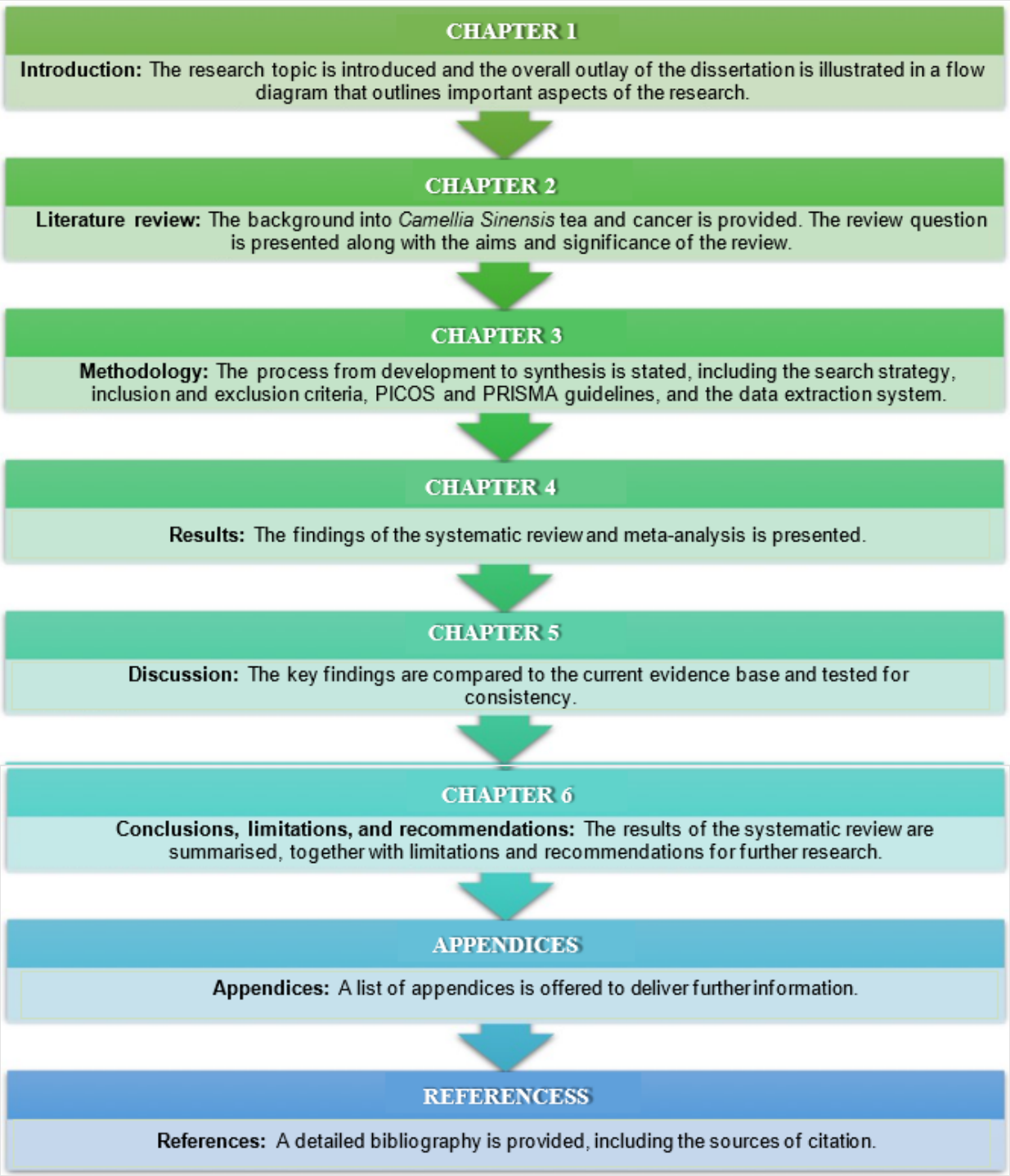

Figure 1: Flow diagram of the dissertation.

Chapter 2 - Literature Review

Background

Cancer is a fatal condition with poor prognosis and a growing global occurrence. In 2022, nearly 20 million new cancer cases were detected, with 9.7 million people dying from the disease globally. Africa's greatest cause of cancer-related mortality is breast cancer, followed by cervical cancer, with 85,787 and 76,745 deaths, respectively. Current standard cancer treatment options may include chemotherapy, radiotherapy, and/or surgery (Cheng, et al. [3]). However, chemotherapy had poor effectiveness and is associated with significant toxicity. As a result, viable therapies for cancer patients are still desperately required (Cheng, et al. [3]). Tea brewed from the leaves of the Camelia sinensis plant is one of the most ancient beverages consumed by individuals worldwide (Wang [4]). There are four main types of tea originating from the C. sinensis shrub; black, oolong, green and white tea. The majority of Camelia sinensis tea's health benefits are due to its main polyphenolic components having potent antioxidant properties which protect against diabetes, cancer, and cardiovascular disease (Bondarian [5]).

These polyphenols may also act as supplementary therapy for the treatment of cancer (Kopustinskiene [6]). Flavonoids, one of the polyphenols, has been discovered to have a variety of anticancer effects, including modulation of reactive oxygen species, programmed cell death, autophagy, participation in cell cycle arrest, and suppression of cancer cell proliferation (Kopustinskiene [6]). Preclinical investigations of green and black tea have shown promising efficacy for the inhibition of tumour growth, development and proliferation with fewer adverse events (Cheng, et al. [3]). A phase II randomised, double-blind, placebo-controlled clinical trial discovered that green tea may have a protective role against breast cancer that is comparable to tamoxifen's (Samavat [7]). Researchers believe that processing may play a role in the tea's cancer-fighting ability.

Cultivation of Camelia Sinensis Tea: The four main types of tea originating from the Camelia sinensis shrub are distinguished by the extent of fermentation and the methods of manufacturing. Oolong tea is only partially fermented, black tea is fully fermented, and green and white teas are unfermented. According to Manzocco, et al. [1998] black tea is produced by fermenting green tea to create oolong. The manufacturing process has an impact on the number of polyphenols in the tea Manzocco [1998].

Composition of Tea: Green tea contains polyphenols such as flavanols, flavandiols, flavonoids, and phenolic acids. The flavonoids are known as catechins, which are present in higher concentrations than black or oolong tea (Chacko, 2014). As mentioned before, due to the limited processing of white tea, there is a higher quantity of polyphenols present. There are four types of catechins found in green tea: epigallocatechin, epicatechin, epicatechin-3-gallate, and EGCG. Black tea is manufactured through fermentation, a process in which polyphenol oxidase converts catechins into theaflavin (oligomeric polyphenols) and thearubigins (polymeric polyphenols). In addition to the four main theaflavins, black tea also contains theaflavin stereoisomers, numerous theaflavin derivatives, thearubigins and flavonoids, which are important for preserving health (Kumar, 2013). Theobromine, theogallin, quercetin and numerous other polyphenols are also present (Kumar, 2013). Oolong tea leaves contain polyphenols categorized into several sub-groups: flavanol glycosides, catechins, quercetin, tannins, and other flavonoids (Wang [8]). In aged oolong tea leaves, three flavonols, including quercetin, kaempferol, and myricetin have been detected (Wang [8]). White tea is composed of phenolic compounds, theogallin (3-galloylquinic acid) and caffeine (Piyasena [9]).

Cancer and Treatment: The diverse group of diseases collectively referred to as cancer are categorized by the uncontrolled division of abnormal cells with the capacity to invade and harm healthy body tissue. Cancer is the second-leading cause of death worldwide. Cancer was the leading cause of disease burden in 2016, according to the World Health Organization (WHO), accounting for 244.6 million mortalities in both men and women (O'Neill [10]).

Breast Cancer: In 2020, 2.3 million women were diagnosed with breast cancer, and 685 000 died as a result [11]. Breast cancer, as defined by the World Health Organization (2023), is a condition in which abnormal breast cells develop out of control and create tumours. If left untreated, tumours can spread throughout the body and be deadly. Treatment is tailored to the individual, the kind of cancer, and its spread. Treatment includes Surgery, radiation, and chemotherapy such as doxorubicin, paclitaxel and docetaxel, 5-fluorouracil or capecitabine. Cyclophosphamide, and carboplatin are administered to treat inoperable malignancies (O'Shaughnessy [12]). The five-year survival rate is 91% (American Cancer Society [13]).

Prostate Cancer: Prostate cancer (PC) is the most frequent malignancy among males globally. Furthermore, it is one of the leading causes of cancer-related deaths. Hormonal treatment, particularly androgen deprivation therapy, is considered the standard treatment (Miyata [14]). First line chemotherapy using docetaxel and cabazitaxel are also utilized, however chemoresistance is developed in patients with castration-resistant prostate cancer (CRPC). This is because CRPC is thought to entail a variety of gene alterations and alternative signaling pathways.As a result, therapy techniques that target only a few pathways are ineffective. The five-year survival rate is 97% (American Cancer Society [15]).

Bladder Cancer: Bladder cancer is a complex disease associated with high morbidity and mortality rates if not treated optimally (Kamat [16]). The bladder-sparing Tri modality treatment of transurethral resection combined with chemotherapy and radiation is available to a select group of patients with muscle-invasive tumours. Systemic cisplatin-based chemotherapy is the best treatment for advanced cancer; immunotherapy is becoming a feasible salvage option for patients whose disease cannot be controlled with first-line che-

motherapy (Kamat [16]). The five-year survival rate is 78 % (American Cancer Society [17]).

Liver Cancer: Primary liver cancer, also known as hepatocellular carcinoma (HCC), is the third greatest cause of cancer-related deaths globally (Liu [18]). Surgery, local destructive therapy, and liver transplantation all have the potential to cure individuals with early HCC. However, HCC is typically identified at an advanced stage, and many patients at this stage are ineligible for curative therapy. Furthermore, standard systemic chemotherapy, namely single-agent Doxorubicin, has low effectiveness and limited survival advantages (Liu [18]). The approval of sorafenib, a multichines inhibitor, has demonstrated modest survival benefit in patients with advanced HCC and retained liver function (Liu [18]). The five-year survival rate is 22% [19].

Lung Cancer: Lung cancer is the second most common cancer among men and women. Smoking is the leading cause of lung cancer, accounting for 75-80% of all deaths from the disease (Cersosimo [20]). Treatment includes surgery, radiation, and chemotherapy such as cisplatin or carboplatin. Chemotherapy used synergistically with radiation may enhance survival (Cersosimo [20]). The five-year survival rate for non – small and small cell lung cancer is 28% and 7%, respectively [21].

Colorectal Cancer: Colorectal cancer is one of the deadliest and most common tumours in the world. Treatment includes surgery and Adjuvant chemotherapy. Novel target-oriented drugs, primarily used in combination with chemotherapy such as cetuximab and bevacizumab, have demonstrated strong efficacy (Labianca [22]). However, chemoresistance limits its efficacy (Zhao, et al. [23]). The five-year survival rate is 63% [24].

Ovarian Cancer: Ovarian cancer accounts for 4% of all cancers in women and is the greatest cause of mortality among gynaecologic malignancies. Treatment includes surgical staging, operative tumour debulking, and six cycles of carboplatin and paclitaxel intravenous chemotherapy (Hennessy [25]). The five year survival rate is 50% for invasive epithelial ovarian cancer [26].

Non-Hodgkin Lymphoma: Non-Hodgkin lymphomas are a diverse category of lymphoid-related cancers. These disorders are categorised as B-cell and T-cell neoplasms by the World Health Organisation based on their haematological and lymphoid tumour characteristics. Treatment includes radiation, chemotherapy (doxorubicin-based chemotherapy mixed with rituximab or rituximab alone in severe cases for stage III and IV), immunotherapy, or radioimmunotherapy (Ansell [27]). Disease relapse is an issue, and high-dose therapy with stem cell support is the preferred treatment for chemo-sensitive recurrent aggressive lymphomas (Ansell [27]). The five year survival rate for Diffuse large B-cell lymphoma and Follicular lymphoma is 65% and 90%, respectively [28].

Gastric Cancer: Gastric cancer is the fourth most frequent kind of cancer and the second major cause of cancer mortality globally. Surgery is still the sole curative treatment, however perioperative and adjuvant chemotherapy, as well as chemoradiation, can enhance the result of respectable gastric cancer with extensive lymph node dissection (Orditura [29]). Second-line chemotherapy such as ramucirumab combined with paclitaxel has proven efficacy (Orditura [29]). The five year survival rate is 36% (American Cancer Society [30].

Pancreatic Cancer: Pancreatic cancer, is the fourth highest cause of cancer mortality in both men and women. It is an aggressive malignancy with a dismal prognosis and patient survival rate of fewer than 5% after five years. Despite breakthroughs in surgery and radiation therapy, no substantial increase in overall survival was seen. Treatment for locally advanced, unresectable, and metastatic illness is palliative, albeit fluorouracil chemoradiation for locally advanced and gemcitabine chemotherapy for metastatic disease may give palliative advantages. Preoperative chemoradiation was being promoted with a broader role for gemcitabine (Li [30]). The five-year survival rate is 13% [31].

Tea as Supplementary Therapy During Cancer Treatment: Tea consumption ranks among the various options used to prevent cancer development and progression (O'Neill [11]). Previous studies on green tea have reported that the tea has cancer protective effects. Polyphenols in green tea exhibit increased antioxidant effects when compared to vitamin C and E. Green tea consumption is one of many modalities used in the prophylaxis of cancer development and progression. Green tea catechins were found to induce apoptosis of carcinogenic cells (Ahmad [32]). Proposed mechanisms of action by which green tea exerts cancer prevention and progression include:

1. Activation of tumor suppressor genes, inducing apoptosis and inhibiting angiogenesis and other transcription factors involved in the promotion and progression of aberrant cells to a malignant phase (Rahmani [33]).
2. Inhibiting enzymes and pathways, via the action of EGCG and other catechins, involved in cancer initiation, promotion, and progression such as interleukin, cyclooxygenase, lipoxygenases and tumor necrosis factor (Rahmani [33].
3. Scavenging free radicals and neutralizing the damage of macromolecules since green tea has high antioxidant activity (Rahmani [33]).
4. Modulating genes involved in tumorigenesis, promotion and progression (Rahmani [33]).

Tea polyphenols help to prevent the development of potential carcinogens in the body. Theaflavins are a class of polyphenol found exclusively in black tea. The administration of theaflavins found in black tea, either orally or topically, has been shown to protect against

the initiation, promotion, and progression of cancer (O'Neill [11]). Evidence suggest that theaflavins have potent anti-cancer properties that inhibit key signalling pathways linked to cancer's hallmarks. In vitro, theaflavins appear to promote cell cycle arrest and apoptosis while reducing cancer cell proliferation, survival, and migration. (O'Neill [11]). In vitro studies have also discovered a correlation between theaflavins' anti-proliferative effects and elevated pro-apoptotic protein Bax expression and decreased anti-apoptotic protein Bcl-2 expression, supporting theaflavins' pro-apoptotic potential. Oolong tea extracts have a great potential as a chemo-preventive agent against breast cancer (Wang [34]). Oolong tea polyphenols induce cell apoptosis in breast cancer cell lines (MDA-MB231) primarily via the death-receptor- mediated extrinsic apoptotic signalling pathway, as the extract not only downregulated intracellular reactive oxygen species (ROS) levels but also induced oxidative damage to mitochondria (Wang [34]).

According to a 2015 in vitro study, white tea suppresses proliferation of the colon cancer cell line HT-29, activates caspases, and protects normal cell DNA from oxidative damage (Hajiaghaalipour [35]). White tea exhibited a strong antioxidant activity which correlated significantly to their phenolic content. White tea also displayed strong anti-proliferative action against HT-29 cells while being non-toxic to normal fibroblasts. Furthermore, white tea suppressed HT-29 colon cancer cells via the death receptor and mitochondrial apoptosis pathways, as evidenced by elevated caspase-3/7, -8, and -9 expression levels (Hajiaghaalipour [35]).

Numerous studies have been conducted on various types of therapeutic interventions for cancer (Al-Mahdi [36]). At present, the use of *Camellia Sinensis* as a supplemental therapy for cancer is the subject of considerable research. Furthermore, there have been many studies and trials on the use of *Camellia Sinensis*, but the results are equivocal (Al-Mahdi [36]). Although black, green, and oolong tea extracts are used as supplementary therapy after initial cancer treatment or to alleviate cancer and/or chemotherapy-induced side effects, it is unclear whether they are beneficial, detrimental, or have no effect (Al-Mahdi [36]). In addition, the extent of knowledge of any beneficial effects of *Camellia Sinensis* tea consumption while on or after cancer treatment by cancer patients, is not fully known (Al-Mahdi [36]). Taking the evidence into account thus far, an updated systematic review and meta-analysis will be performed to examine the latest findings on the topic at an evidence-based level. Findings of this study will further our knowledge whether the consumption of Camelia sinensis tea during or after standard cancer treatment has any effect on the progression of the disease.

Problem Statement

Is *Camellia Sinensis* tea consumption by cancer patients effective in reducing disease progression and increase in remission rate while on standard cancer treatment, compared to treatment alone?

Aims and Objectives

The study aims to assess the effect of *Camellia Sinensis* teas consumed by cancer patients on standard anti-cancer therapy, on cancer disease progression and remission rates as well as on quality of life and safety, by performing a systematic review of the literature. Additionally, a meta-analysis of the results extracted from sufficiently homogenous studies was performed.

Objectives:

1. To perform a systematic review of the literature as specified by the PICOS framework, inclusion and exclusion criteria and the PRISMA guidelines.
2. To evaluate the primary outcomes based on overall survival (OS), overall response rate (ORR), progression-free survival (PFS), risk of cancer incidence, morbidity, safety and quality of life and five-year mortality rate.
3. To employ JBI SUMARI to pool the data and conduct a meta-analysis of the results extracted from sufficiently homogenous studies.

The next chapter will focus on Methodology. An overview regarding study selection, search strategy, data extraction, outcome measures and data analysis is provided. Additionally, the inclusion and exclusion criteria is outlined taking into account the PICOS framework (Table 1, page 22) framework and Prisma guidelines (Table 2, page 23). A flow diagram of the next chapter is provided below (Figure 2).

Table 1: Table showing the search strategy for the database search.

Terms connected by OR	and	Terms connected by OR
"Tea" [MeSH terms] Or "*Camellia sinensis*" Or "green tea" Or "black tea" Or "oolong tea" Or "white tea" Or "polyphenols" Or "plant antioxidants"		"carcinoma " Or "tumour" Or "metastasis" "breast cancer", Or "lung cancer" Or "prostate cancer" Or "colorectal cancer" Or "ovarian cancer" Or "liver cancer" Or "non – Hodgkin's lymphoma" Or "gastric cancer" Or "pancreatic cancer" Or "cancer" Or "neoplasm"

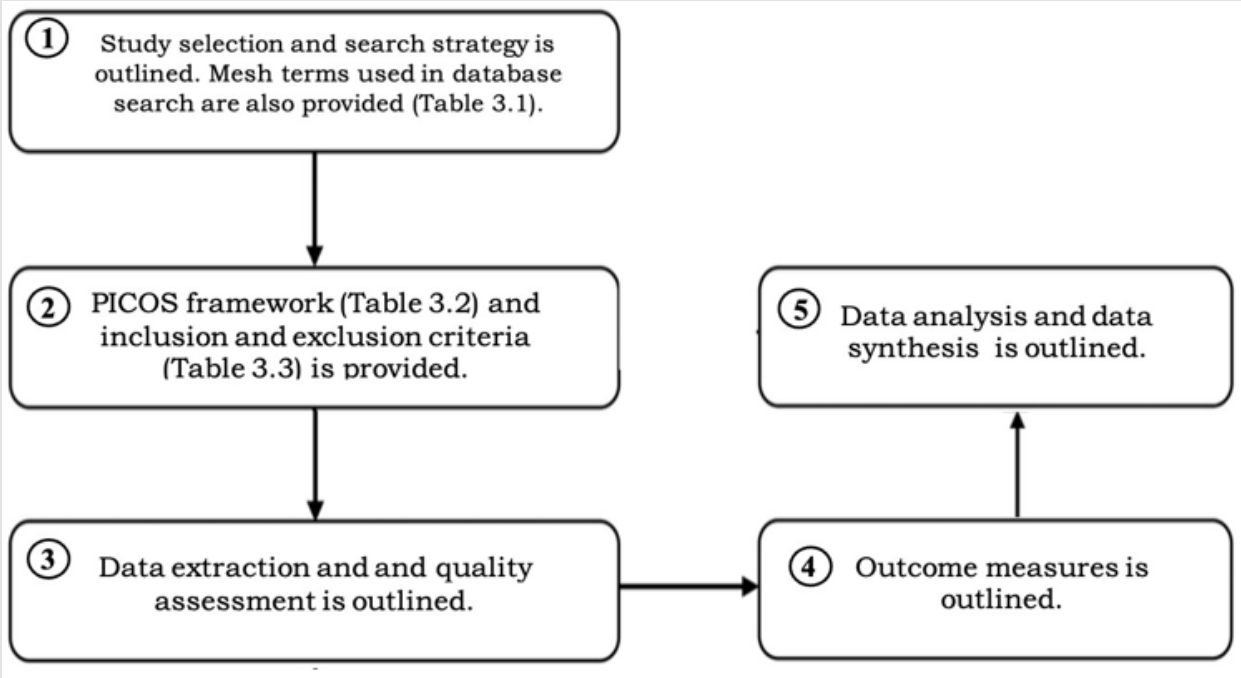

Figure 2: Flow diagram of the Methodology section.

Table 2: PICOS statement framework to determine the eligibility criteria for articles to be included in the research study.

Criteria	Description
P-Participants	Cancer patients (breast, prostate, bladder, lung, colorectal, ovarian, liver, non- Hodgkin lymphoma, gastric and pancreatic) over the age of 18, all genders and races.
I-Interventions	Various *Camellia sinensis* teas (Green, black, white and oolong) as
	supplementary therapy together with or after standard cancer therapy.
C-Comparators	Standard cancer therapy only without supplementary therapy.
O-Outcomes	The primary outcomes - evaluated based on overall survival (OS), overall response rate (ORR), progression-free survival (PFS), risk of cancer
	incidence, morbidity, safety and quality of life and five year mortality rate.
S-study Design	Randomized control trials; cohort studies; case – control studies; combined case - control and cohort studies, as well as combined case control and prospective studies; prospective studies; epidemiology studies and observational studies.

Chapter 4- Methodology

Study Selection and Search Strategy

An extensive search of the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, PubMed Central® (PMC), and Scopus databases was carried out from January 1, 1980 up to July 1, 2024, using a comprehensive strategy. The databases mentioned above were utilized as they offer a broad overview of existing literature on the research topic at hand. A reference list of relevant research was reviewed to determine if any other publications can be included. This project searched all databases and included any appropriate randomized control trials; cohort studies; case – control studies; combined case - control and cohort studies, as well as combined case control and prospective studies; prospective studies; epidemiology studies and observational studies. Moreover, studies were also obtained from systematic reviews regarding the current available literature on tea (*Camellia Sinensis*) consumed as supplementary therapy for cancer. For additional studies, meta-analyses on the subject were assessed and a recursive search was carried out on the references of the selected articles. The search strategy was conducted using certain key words (Table 3).

Table 3: Inclusion and exclusion criteria for articles in the research study.

Inclusion Criteria	Exclusion criteria
Studies with data from randomized control trials; cohort studies; case – control studies; combined case - control and cohort studies, as well as combined case control and prospective studies; prospective studies; epidemiology studies and observational studies.	*In vitro* studies, animal studies, and case studies
Various cancer patients consuming different types of tea from *Camellia sinensis* as supplementary in conjunction with or after standard cancer therapy	Patients under the age of 18 years
Studies reporting data on at least one of the primary outcomes	Patients with additional severe diseases that might alter the outcome measurements, such as cardiovascular disease or a major stroke
Any language and publication from January 1, 1980 up to July 1, 2024, in all databases.	Patients on additional medication for treatment of co-morbidities that can interfere with study results
	Herbal teas

This study incorporated all eligible randomized control trials; cohort studies; case-control studies; combined case - control and cohort studies, as well as combined case control and prospective studies; prospective studies; epidemiology studies and observational studies without any limits on language or publication. Sources with various languages were translated using a free online translation service. The author of the dissertation (Raeesah Laher) and a secondary reviewer (Yumna Johnson), independently reviewed the titles and abstracts of all selected studies for eligibility. Yumna Johnson is a GEMP VI student who has successfully completed several systematic reviews and meta-analysis over the course of her degree. The full texts were then reviewed for further selection using the stated eligibility criteria.

Any differences between the primary author and secondary reviewer were resolved by consulting a third reviewer (Supervisor; Dr AD Van Eyk). For example, disagreements occurred during full text screening whereby a decision made by a single reviewer was inconsistent with the final included list of studies. These disagreements were reconciled via consensus or arbitration by a third reviewer.

The systemic review and meta-analysis were conducted according to the eligibility criteria set by PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) guidelines (Appendix A, page 112). The study selection was organized according to the PICOS framework (Table 2): Participants, Intervention, Comparators, Outcomes, Study Design (Hutton, et al. [37]). The PRISMA flow diagram (Appendix A, page 112) was used for screening the literature. Articles were screened by title first and then the remaining articles underwent further screening by abstract according to the exclusion and inclusion criteria (Table 1). The articles meeting the inclusion criteria were then screened by full text and those that did not meet the inclusion criteria were removed. Additionally, Zotero 7.0 (Computer software, Roy Rosenzweig centre for History and New media (2016)) was utilized as a reference manger.

Data Extraction and Quality Assessment

On selected articles, data was extracted into a standard extraction tool (Excel form) based on the following information: age, race, gender and type of cancer of participants, sample sizes, risk (n/N), mean ± SD, intervention applied, comparator if any, outcome measures and adverse effects. The systematic review and meta-analysis utilised the methodology set out by the JBI Reviewer's Manual for JBI Systematic Reviews of Effectiveness (Tufanaru, et al. 2020). A modified data extraction tool from the JBI-SUMARI software was utilized for further data extraction and analysis. The data was extracted utilizing the JBI System for the Unified Management, Assessment and Review of Information (SUMARI) to produce several meta- analyses. The included studies' citations were imported into SUMARI software (Joanna Briggs Institute, Adelaide, Australia) for processing (Munn, et al. [38]). To elaborate, elements of data extraction were undertaken through JBI SUMARI modified data extraction tool. Data extraction began with recording the type of text. Once data extraction of the background details was complete, the extraction become highly specific to the nature of the data of interest and the question being asked in this systematic review. Additionally, a meta-analysis of the results extracted from sufficiently homogenous studies was performed. JBI SUMARI was utilized to pool the data and carry out the meta-analysis The JBI Risk of Bias Tool was used to assess the risk of bias in each included study. If the primary author and secondary reviewer disagreed on assessing the danger of bias, a tertiary reviewer was consulted for consensus. The quality of selected studies was evaluated using the same tool which assessed characteristics such as selection bias, performance bias (blinding of participants), detection bias (outcome assessment), attrition bias (incomplete outcome data) and selective reporting bias (Higgins et al. 2011).

This tool assesses the risk of bias in 7 domains, identifying high, ambiguous, or low risk. Each characteristic was judged according to the following criteria: low risk bias, uncertain risk of bias and high risk of bias (Higgins et al. 2011). Sensitivity analysis was performed to ensure the stability of the pooled results by excluding poor-quality research. If more than ten qualifying papers were included, the Egger linear regression test and a funnel plot were used to uncover potential publishing biases (Afonso [39]). Additionally, to assure the study's internal validity and reliability, the following measure was taken; selection bias was reduced with the use of inclusion and exclusion criteria and the exclusion of studies with patients on additional med-

ication for treatment of co-morbidities that can interfere with study results. Limitations arose when the studies presented with clinical heterogeneity due to variations in patient populations or demographics. For example, the population may not always be representative of a general target population or Observational studies may have greater heterogeneity in the target population because treatment is not randomly assigned.

Outcome Measures

The primary outcomes of this review were evaluated based on overall survival (OS), overall response rate (ORR), progression-free survival (PFS), risk of cancer incidence, morbidity, safety and quality of life as well as the five year mortality rate. For studies reporting multiple follow-up periods within an individual time point category, data at the latest follow-up time was extracted in each study. The final mean±*SD* values were extracted at the end of the follow- up. When unavailable the mean±*SD* changes from baseline were used. The primary outcome safety was measured based on the number of patients reporting any adverse events for each intervention (*Camellia Sinensis* tea) and comparator (standard anti-cancer therapy), withdrawal due to adverse events and serious adverse events. In cases where relevant data was not reported, the authors were contacted for details. When authors were unavailable data was estimated according to the Cochrane Handbook.

Data analysis and Data synthesis

The effect of *Camellia Sinensis* teas consumed by cancer patients on standard anti-cancer therapy, on cancer disease progression and remission rates as well as on quality of life and safety, was assessed as mentioned prior by performing a systematic review of the literature as specified by the PICOS framework, inclusion and exclusion criteria and the PRISMA guidelines. In this study, JBI SUMARI was employed to pool the data and conduct a meta- analysis of the results extracted from sufficiently homogenous studies. The meta-analysis analyzed the following: risk, relative risk (ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group), odds ratio (measure of association between an exposure and an outcome) , p value (sig $p < 0.05$; a number describing how likely it is that your data would have occurred under the null hypothesis of your statistical test), Confidence interval (mean of your estimate plus and minus the variation in that estimate), I2 statistic (test of heterogeneity), weighted average, standard mean difference, random effects model and fixed effects model. Dichotomous data was presented as a risk ratio with 95% confidence intervals (CIs). Continuous data was presented as mean difference, standardized mean difference, and 95% confidence intervals.

The Cochrane I2 test was used to examine heterogeneity. If the value of I2 >50%, significant heterogeneity was considered. Alternatively, if the value of I2 ≤ 50%, acceptable heterogeneity was considered. If appropriate heterogeneity was discovered, a fixed-effect model was employed to pool the data, and meta-analysis will be carried out. If considerable heterogeneity was detected, a random effect model will be used, followed by subgroup analysis. Meta- analysis was undertaken based on subgroup results. If there was still considerable heterogeneity after the subgroup analysis, no meta-analysis was undertaken. A narrative description was provided to elaborate findings of the study.

Methodology For Conduction the Meta-Analysis

Data Extraction and Data Combination: Fourteen of the original 100 studies were retrieved and assessed in more detail. The 14 studies that met the eligibility criteria consisted of 5 randomized control trials, 4 cohort studies 2 epidemiology studies and 3 observational studies (consisting of case-control and cohort studies) that met the eligibility criteria were included. For all 14 studies, the following characteristics were collected: author, publication year, country of origin, study design, sex of subjects, sample size, treatment exposure dosage and duration, the risk ratios or overall response and 95% CIs that reflected the greatest degree of control for potential confounders, and variables accounted for in the analysis. Study selection and data were carried out independently by two authors.

Statistical Analysis: Overall response with 95% CI was the common measure of the association in this meta- analysis, and risk ratio in the cohort studies were considered approximately as ORs and RRs.

The results that were reported by sex separately were combined with a fixed-effects model, and the combined results were used in the meta-analysis. The random-effects model accounting for between-study variation was assigned to compute the summary risk estimates. Statistical heterogeneity was assessed I2 statistics. For the I2 statistic the following cut-off points were set: <25% (low heterogeneity), 25%–50% (moderate heterogeneity) and >75% (severe heterogeneity). Potential publication bias was evaluated using Egger's test and Begg's funnel plot. All statistical analyses were performed using JBI SUMARI software (Joanna Briggs Institute, Adelaide, Australia) for processing (Munn, et al. [23]).

The next chapter will focus on results. An overview of study selection and characteristics (see Figure 3; page 28, PRISMA flow diagram of the review), publication bias (see Figure 4, page 29; JBI Risk of bias graph), characteristics of eligible studies (see Table 4, page 30 - 46), and subgroup analyses (see Table 5, page 47) is illustrated in table format, included studies illustrated in a Pie chart (see Figure 5 and 4.4, page 50), diagnosis, exposure, effects of interventions, primary outcomes (see Table 6, page 64) are provided. The results section includes a Meta analysis (see Figure 6; page 66, Flow diagram of the meta-analysis) of similar studies on green tea with similar outcomes (see Table 7, page 68 - 69). Forest plots illustrating associations between reduction in cancer risk, cancer prevention and adverse events and green tea exposure (see Figure 7, 4.7 and 4.8, page 71-73, respectively) are also provided. A flow diagram of the next chapter is provided below (Figure 8).

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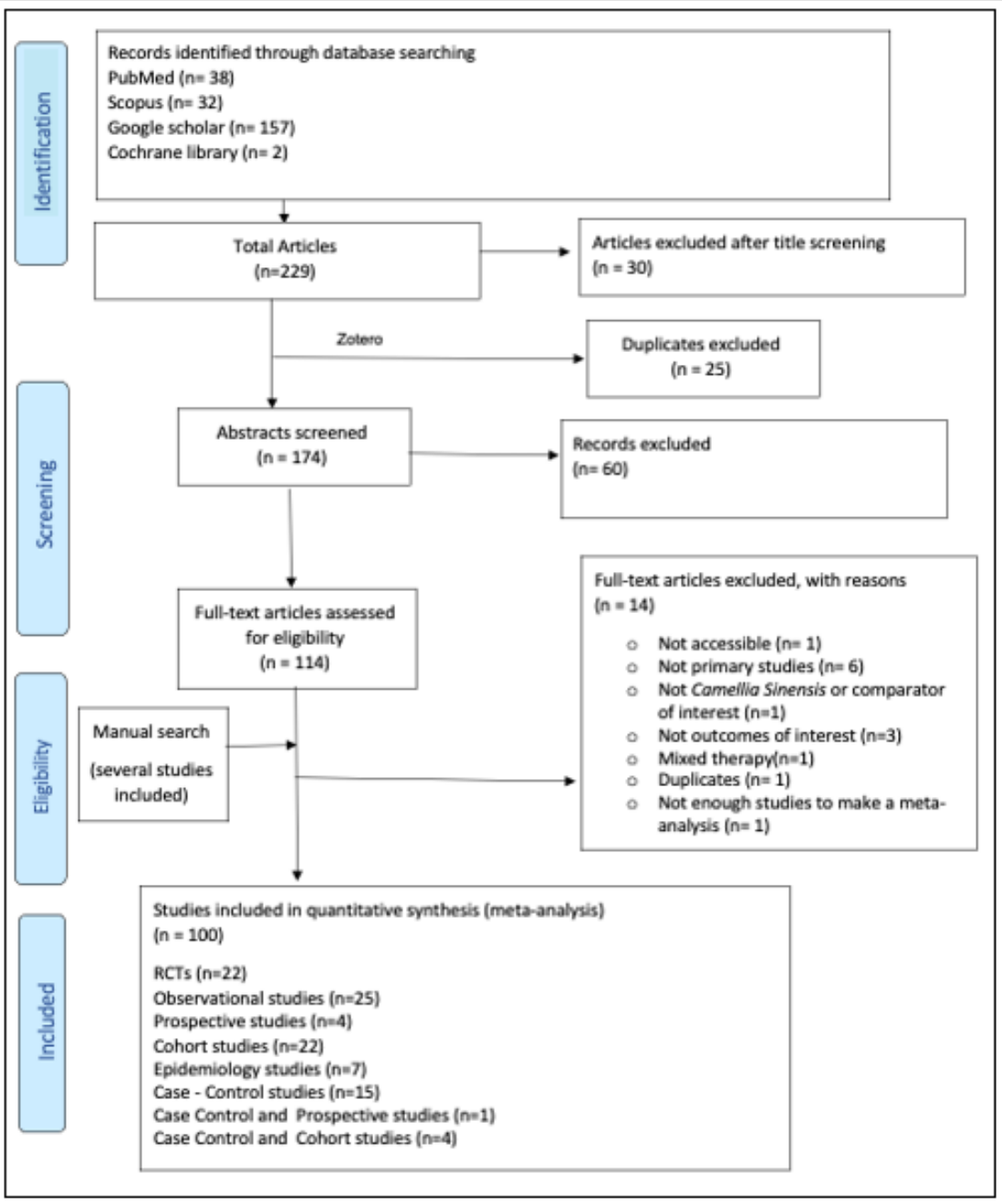

Figure 3: PRISMA flow diagram of the review (Page, et al. 2017).

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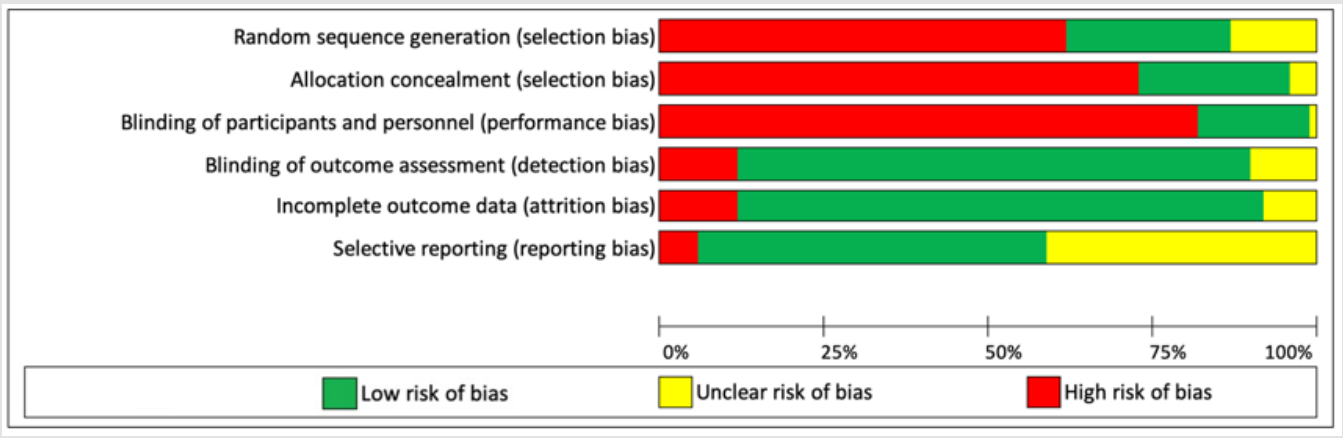

Figure 4: Risk of bias graph for all included studies.

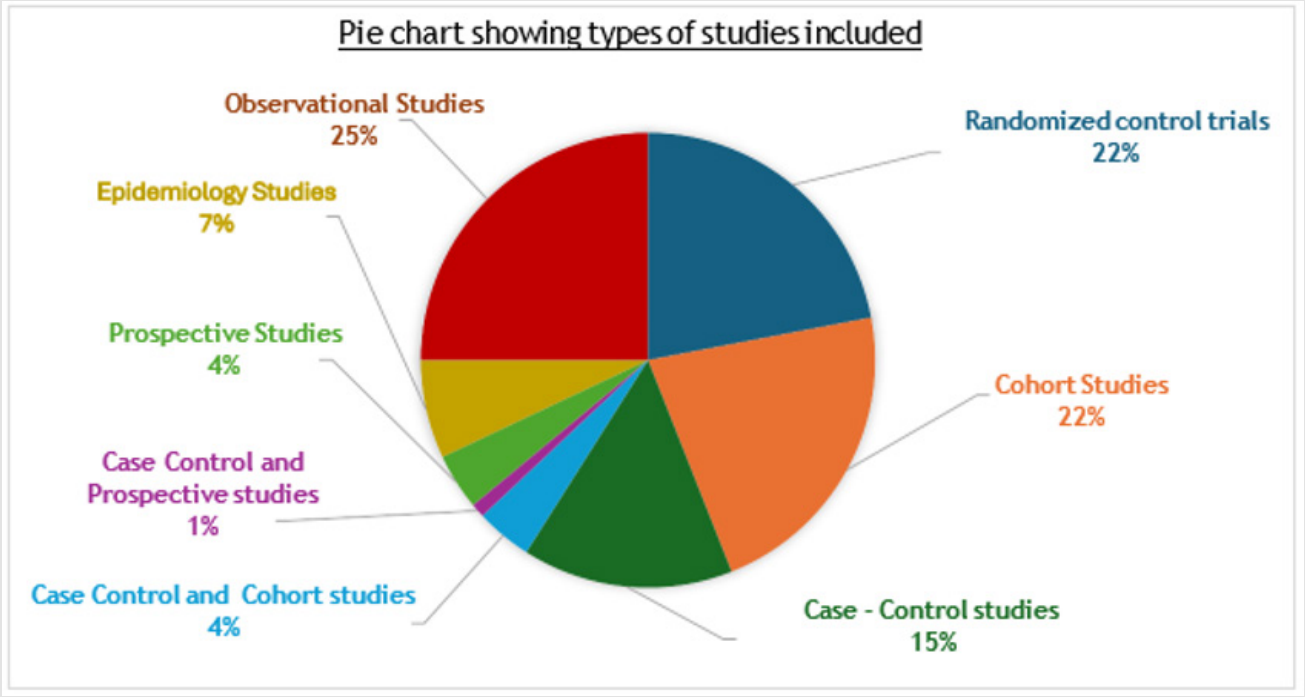

Figure 5: Pie Chart showing different types of studies included in the systematic review and meta-analysis.

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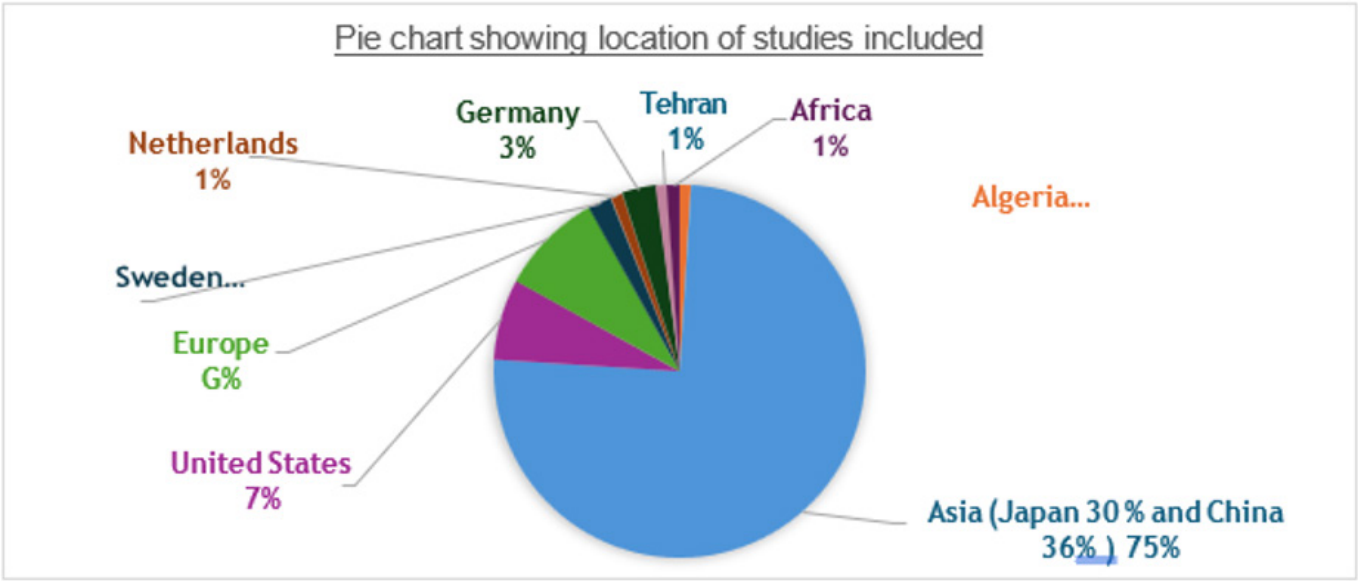

Figure 6: Pie Chart showing locations of the different types of studies included in the systematic review and meta-analysis.

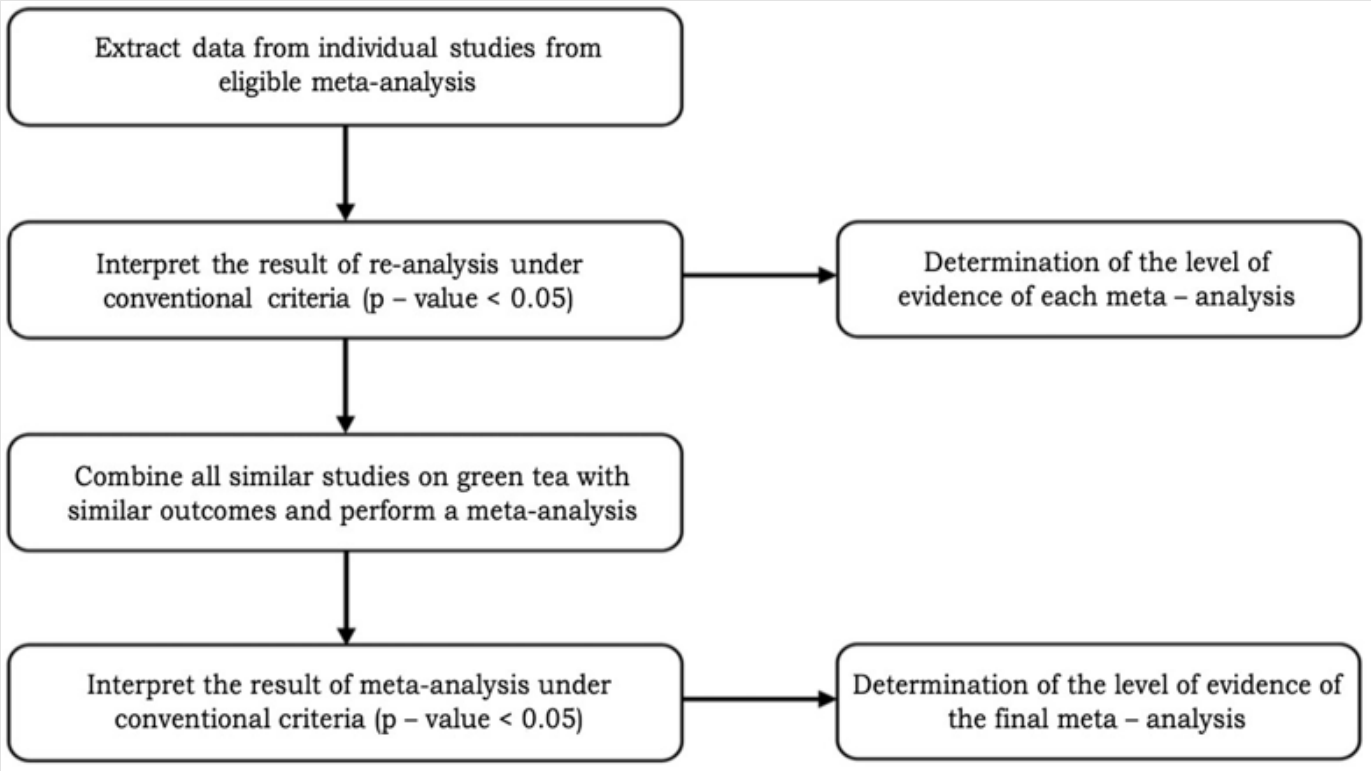

Figure 7: Flow diagram of the meta-analysis (Seung Kim, et al. 2020).

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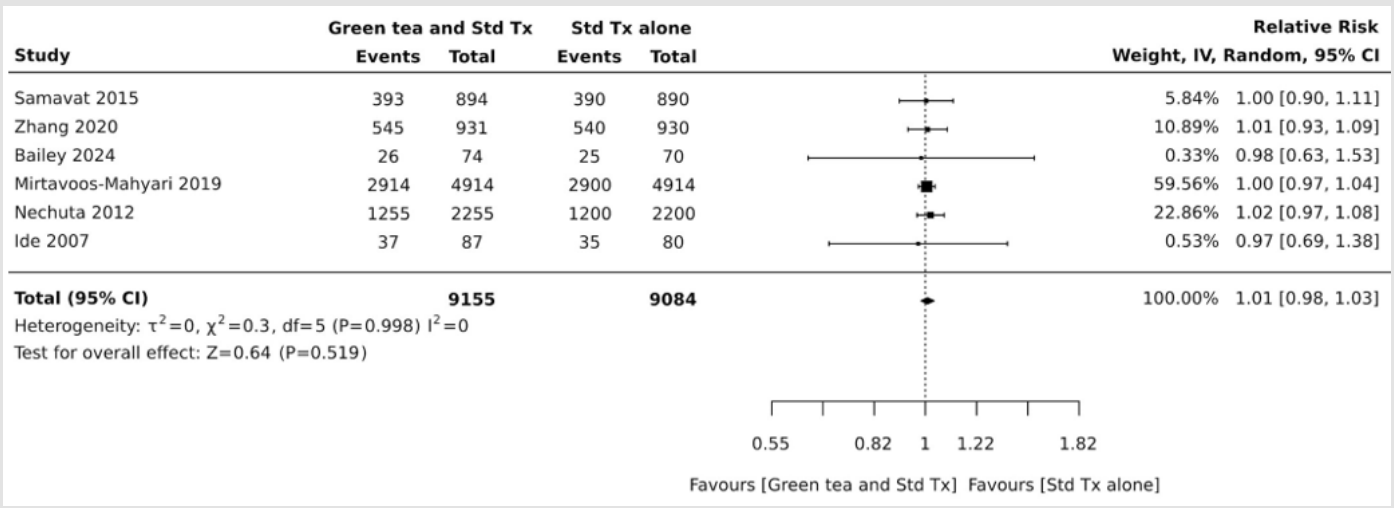

Figure 8: Forest plot illustrating associations between reduction in cancer risk and green tea exposure from systematic review and meta- analysis outlined by study design. The definition of each category of outcomes is presented in Supplemental Table 4.3 (page 64) and 4.4 (page 68 - 69).

Table 4: Characteristics of eligible studies included in this systematic review and meta-analysis.

Authors, year	Location	Study type	Number of participants	Age range	Sex	Standard treatment	OR (95 % CI)	Tea exposure level and period	Outcome	Authors, year	Location
All types of cancer											
1	Naveed, et al. [40]	China and Japan	Observational studies; (consisting of case-control studies and cohort studies)	1335	74 - 45	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy		OR for protection against cancer = 0.79; 95% CI: (0.65,0.97)	≥2 cups BT/day for ± 6 – 12 months	BT intake had a protective effect.
2	Zhao, et al. [41]	China	Observational studies; (consisting of case-control studies and cohort studies)	153,598	20 - 70	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy		OR for cancer risk = 0.67; 95% CI: (0.46,0.97), $p < 0.05$	≥ 1 cup BT or GT /day for ± 6 – 12 months	No association between BT band GT intake and cancer risk.
3	Yu, et al. [42]	China	Prospective studies	27,702	20 - 70	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy		OR for protection against cancer = CI 1.18; 95% CI: (1.05,1.32), $P >$ 0.05	≥ 3 cup BT or GT /day for ± 6 – 12 months	BT and GT intake did not have a protective effect.
4	Tang, et al. [43]	Japan	Cohort studies	240, 637	20 - 70	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy		OR for all-cause mortality = 0.93; 95% CI: (0.82,1.06), P<0. 001	≥ 1-2 cup BT or GT /day for ± 6 – 12 months	GT was inversely associated with all-cause mortality, whereas BT was inversely associated with all cancer and all-cause mortality.

5	Pisters, et al. [44]	Japan	Cohort studies	49	27 - 77	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for green tea safety/ adverse events = 1.06; 95% CI: (0.98,1.15)	1.0 g/m^2 GTE for ± 6 – 12 months (≡ 7 to 8 cups of GTE /day)	Oral GTE at the doses studied was taken safely for at 6 months.
6	Imai, et al. [45]	Japan	Cohort studies	8,552	≥ 40	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for cancer prevention = 0.63; 95% CI: (0.36,1.05)	≥ 10 cups GT /day for ± 6 – 12 months	GT intake had a preventative effect.
7	Schulze, et al. [46]	Western (Europe and USA) and Asian countries	Observational studies; (consisting of case-control studies and cohort studies)	59, 311	≥ 25	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for protection against cancer = 0.74; 95% CI: (0.6,0.93)	≥ 5 cups GT /day for ± 6 – 12 months	GT intake did not have a protective effect.
8	Johnson, et al. [47]	Ireland	Observational studies; (consisting of case-control studies and cohort studies)	216	20 - 70	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for cancer risk = 0.7; 95% CI: (0.55,0.85)	3 - 5 cups GT /day for ± 6 – 12 months (≡ 250 mg /day of catechins)	The evidence for GT and cancer risk is inadequate and inconclusive.
9	Liu, et al. 48]	Japan	Epidemiology studies	547,204	20 - 70	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for protection against cancer = 0.51; 95% CI: (0.3,0.86)	3 - 9 cups GT /day for ± 6 – 12 months	Studies showed protective effects of GT on GIT breast, lung and prostate cancer. However, these findings have not been confirmed by other studies covered in this review.
10	Naka,chi, et al. [49]	Japan	Cohort studies	8552	20 - 70	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for cancer prevention = 0.72; 95% CI: (0.6,1.04)	≥ 10 cups GT /day for ± 6 – 12 months	A significant delay in cancer onset was associated with increased consumption of GT.
11	Nagano, et al. [50]	Japan	Prospective studies	38,540	52 - 56	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for cancer risk = 1; 95% CI: (0.91,1.1)	2 - 4 cups GT /day for ± 6 – 12 months	GT intake was not related to reduced cancer risk.
12	Kuriyama, et al. [51]	Japan	Cohort studies	40,530	40 - 79	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for all-cause mortality = 0.93; 95% CI: (0.83,1.05)	1 - 2 cups GT /day for ± 6 – 12 months	GT intake was not associated with reduced cancer mortality.

13	Filippini, et al. [2]	Western and Asian countries	Case Control + Cohort studies	1795	20 - 70	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for cancer risk = 0.5; 95% CI: (0.18,1.36)	4 - 7 cups GT /day for ± 6 – 12 months	Limited evidence for the beneficial effect of green tea consumption on the overall risk of cancer.
14	Le, et al. [52]	United states	Epidemiology studies	410,309	30	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for cancer prevention = 0.83; 95% CI: (0.65,1.07)	≥ 5 cups of EGCG /day for ± 6 – 12 months	Intake of a green tea catechin (GTC) called Epigallocatechin-3- gallate (EGCG),was discovered to be a suitable adjuvant to potentiate anti-glioma therapies.
15	Yuan, et al. [53]	China and Taiwan.	Epidemiology studies	119	51 - 57	Male and female with cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy	OR for protection against cancer = 0.37; 95% CI: (0.2,0.7)	≥ 1 BT or GT cups/ day for ± 6 – 12 months	BT and GT intake did not have a protective effect.
Breast cancer										
16	Samavat, et al. [54]	Minnesota	RCT	937	59 - 60	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR for breast cancer risk = 0.91; 95% CI: (0.84,0.98)	843.0 ± 44.0 mg/day EGCG or placebo for 12 months.	GT may reduce breast cancer risk. GT extract / EGCG was safe and well tolerated.
17	Yu, et al. [55]	Baltimore	Observational studies	14,058	32 - 71	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR risk of breast cancer incidence= 0.57; 95% CI: (0.33,0.98), P<.00001, I^2=84%	≤ 5 GT cups/day for ± 6 – 12 months	GT consumption may have a decreased incidence of breast cancer despite significant heterogeneity.
18	Sun, et al. [56]	China and Japan	Cohort studies	152,731	20 - 71	Female with breast cancer and a BMI < 25 kg/m^2.	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR for breast cancer risk = 0.83; 95% CI: (0.72,0.96), P<.00001	≥ 2 GT cups/ day and ≥ 6 BT cups/day for ± 6 – 12 months	GT consumption yielded a lower risk for breast cancer in individuals with a BMI less than 25 kg/m^2. A modest increase in risk associated with BT intake.

19	Seely, et al. [57]	China and Japan	Cohort studies	163,810	20 - 87	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR for breast cancer prevention = 0.91; 95% CI: (0.84,0.98), p-trend = 0.08	3 - 8 cups GT /day for ± 6 – 12 months	GT intake had a protective effect.
20	Wu, et al. [58]	United sates	Case control Studies	501	40 - 64	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR for protection against breast cancer = 0.89; 95% CI: (0.71,1.1)	≤ 5 GT cups/day for ± 6 – 12 months	GT intake had a protective effect.
21	Samavat, et al. [7]	China and Japan	RCT	1,075	50 - 55	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR for breast cancer prevention = 0.95; 95% CI: (0.29,3.1)	4 GTE capsules containing 1,315 mg total catechins, including 843 mg EGCG for 12 months	GT intake might have a chemo-preventive effect. However, further investigation of the potential chemo preventive effect of green tea intake on breast cancer risk in younger women is warranted.
22	Lazzeroni, et al. [58]	Europe	RCT	12	50	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR for breast cancer prevention = 0.68; 95% CI: (0.39,1.21)	Greenselect Phytosome (GSP) 300 mg, equivalent to 44.9 mg of EGCG, daily for 4 weeks prior to surgery.	Oral GSP increases bioavailability of EGCG, which is detectable in breast tumor tissue and is associated with preventative effects on breast cancer tissue.
23	Dostal, et al. [59]	Minnesota	RCT	1075	59 - 60	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR for green tea safety/ adverse events = 0.66; 95% CI: (0.3,1.44)	843.0 ± 44.0 mg/day EGCG or placebo for 12 months.	GT intake had mild and transient adverse events. However, 6.7% of GTE consumers experienced ALT elevations, with 1.3% experiencing ALT-related serious adverse effects

24	Crew, et al. (2015)	Columbia University, New York	RCT	40	39 - 65	Female with stage I–III HR- negative breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. ⇒ Cyclophosphamide, and carboplatin.	OR for breast cancer prevention = 0.61; 95% CI: (0.36,1.06)	400, 600 or 800 mg of oral green tea extract, Polyphenon E (Poly E) for 6 months. (≡ 8 to 24 cups of GT/ day)	Poly E showed potential preventative mechanistic actions in growth factor signalling, angiogenesis and lipid metabolism in stage I–III HR-negative breast cancer.
25	Inoue, et al. [60]	Japan	Epidemiology studies	1160	20 - 87	Female with stage I breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR for breast cancer prevention = 0.69; 95% CI: (0.47,1)	≥ 3 GT cups/ day for ± 6 – 12 months	GT intake may be preventive against recurrence of breast cancer in early stage cases
26	Nakachi, et al. [61]	Japan	RCT	472	20 - 87	Female with stage I - II breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	OR for breast cancer prevention = 0.43; 95% CI: (0.22,0.84), p < 0.05 for crude disease-free survival	≤ 4 GT cups/day or ≥ 5 GT cups/ day for ± 6 – 12 months	Increased GT intake prior to clinical cancer onset was significantly associated with improved prognosis of stage I - II breast cancer. Additionally, increased consumption of green tea was correlated with decreased recurrence of stage I and II breast cancer ($p < 0.05$ for crude disease-free survival); the recurrence rate was 16.7 or 24.3%.
27	Suzuki, et al. [62]	Japan	Prospective studies	24 769	40 - 64	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin	OR for breast cancer risk =0.56; 95% CI: (0.35,0.91)	≤ 4 or ≥ 5 GT cups/ day for ± 6 – 12 months	GT intake was not associated with a lower risk of breast cancer.
28	Li, et al. [63]	Hong Kong	Case control studies	756	20 – 50	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin	OR for breast cancer risk = 0.33; 95% CI: (0.11,1.03)	≥ 1 GT cups/ day for ± 6 months	GT intake was not associated with overall breast cancer risk, which may be masked by the differential effect in pre- and post-menopausal women.

29	Zhang, et al. [64]	United states and Puerto Rico	Cohort studies	50,884	20 – 50	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin	OR for breast cancer risk = 0.62; 95% CI: (0.4,0.97), p-trend <0.01	≥ 5 GT or BT cups/ day for ± 6 – 12 months	GT and BT intake was associated with reduced breast cancer risk
30	Braal, et al. [65]	Europe	RCT	14	22 – 78	Female with breast cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; tamoxifen	OR for breast cancer prevention = 0.88; 95% CI: (0.78,1)	Tamoxifen monotherapy in combination with GT supplements (1 g twice daily; containing 300 mg EGCG) for 14 days (or vice versa).	This study demonstrated the absence of a pharmacokinetic interaction between green tea supplements and tamoxifen. Therefore, the use of green tea by patients with tamoxifen could be encouraged.
Prostate cancer										
31	Henning, et al. [66]	UCLA, Los Angeles	RCT	93	61 – 62	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for protection against prostate cancer = 1.2; 95% CI: (7.31,0.5)	6 GT or BT cups/ day for ± 6 – 12 months	GT-induced protective changes in NFκB and systemic oxidation, and uptake of GT polyphenols in prostate tissue
32	Guo, et al. [67]	Europe, North America, Africa and Asia	Observational Studies; (consisting of case-control studies and cohort studies)	96,332	≥ 35	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for prostate cancer prevention = 1.17; 95% CI: (0.67,2.05), *P* =0.02	≥ 7 GT or BT cups/ day for ± 6 – 12 months	GT intake linearly reduced PCa risk and green tea catechins were effective for preventing PCa.
33	Kumar, et al. [68]	University of South Florida, FL (USF)	Observational studies; (consisting of case-control studies and cohort studies)	34	61- 62	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for chemoprevention/ protection ageist prostate cancer = 0.75; 95% CI: (0.53,1.07)	843 mg of EGCG ± 3 weeks – 36 months	EGCG intake had chemoprevention and chemoprotective effects.
34	Bailey, et al. [69]	Japan and China	Epidemiology studies	90,000	≥ 35	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for prostate cancer risk = 0.977; 95% CI: (0.8,1.19)	< 1 GT cup/day, 1 to 2 GT cups/day, up to > 5 GT cups/ day for ± 6 – 12 months	GT intake had a reduced risk of prostate cancer.

35	Choan, et al. [70]	Japan and China	RCT	19	≤ 65	Male with hormone refractory prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for prostate cancer prevention = 0.7; 95% CI: (0.5,1)	GT extract capsules at 250 mg twice daily ± 2 months	GT as alternative complementary (CAM) therapy, was found to have minimal preventative clinical activity against hormone refractory prostate cancer.
36	Montague, et al. [71]	Singapore and China	Cohort studies	298	≥ 18	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for protection against prostate cancer = 0.87; 95% CI: (0.59,1.28)	≥ 1 GT or BT cups/ day for ± 6 – 12 months	GT intake does not protect against prostate cancer and BT intake may increase prostate cancer risk.
37	Kikuchi, et al. [72]	Japan	Cohort studies	9 561	≤ 65	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for prostate cancer risk =1.08; 95% CI: (0.79,1.47)	≥ 5 GT cups/ day for ± 6 – 12 months	GT intake was not associated with prostate cancer risk.
38	Berroukche, et al. [73]	Western Algeria	Case control studies	160	50 – 74	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for prostate cancer risk = 0.85; 95% CI: (0.5,1.43)	≥ 1 GT cups/ day for ± 6 – 12 months	GT intake was negatively associated with prostate cancer risk.
39	Jian, et al. [74]	Southeast China	Case control studies	130	≥ 40	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for protection against prostate cancer = 0.6; 95% CI: (0.3,1.1)	≥ 3 GT cups/ day for ± 6 – 12 months	GT intake had a protective effect
40	Kurahashi, et al. [75]	Japan	Prospective studies	49,920	40 – 69	Male with advanced stage prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for prostate cancer risk = 0.59; 95% CI: (0.4,0.87)	≥ 5 GT cups/ day for ± 6 – 12 months	GT intake was not associated with prostate cancer risk. However, GT consumption was associated with a dose-dependent decrease in the risk of advanced prostate cancer.
41	Bettuzzi, et al. [76]	Europe	RCT	60	≥ 40	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel	OR for prostate cancer chemoprevention = 0.52; 95% CI: (0.28,0.96)	600 mg/ day of GTC for ± 6 – 12 months (≡ 3 capsules of GTCs/ day)	Study data suggest that up to 90% of chemo-prevention efficacy can be obtained by green tea catechin (GTC) intake in men prone to develop CaP.

42	Kumar, et al. [77]	United states	RCT	97	≥ 40	Male with prostate cancer	⇒ Hormonal treatment; androgen deprivation therapy ⇒ Radiation ⇒ Chemotherapy; docetaxel and cabazitaxel		OR for prostate cancer prevention = 0.85; 95% CI: (0.43,1.66), P = 0.25.	400 mg EGCG per day for 12 months	GT intake was well tolerated but did not reduce the likelihood of prostate cancer in men with baseline HGPIN or ASAP.
Bladder cancer											
43	Wang, et al. [78]	Asia	Case Control + Cohort studies	532,949	≥ 40	Male and female with bladder cancer	⇒ Chemotherap; ⇒ cisplatin-based Immunotherapy	OR for bladder cancer protection = 0.87; 95% CI: (0.09,1.66), *P* = 0.014	100 ml/day of GT for ± 6 – 12 months	GT intake may have a protective effect on bladder cancer in Asian people.	
44	Yasuda, et al. [79]	Japan and China	RCT	360	≥ 40	Male and female with bladder cancer	⇒ Chemothrap; ⇒ cisplatin-based Immunotherapy	OR for bladder cancer prevention = 0.86; 95% CI: (0.77,0.97)	<1 GT cup/day or 1- 4 GT cup/day or >5 GT cup/day for ± 6 – 12 months	GT intake suppressed urinary tract recurrence and the risks of up- grading and up-staging by recurrence in never smokers.	
Liver cancer											
45	Luo, et al. [80]	Japan and China	RCT	124	≥ 40	Male and female with Liver cancer	⇒ Surgery ⇒ Chemotherapy; doxorubicin ⇒ Multikinase inhibitor; sorafenib		OR for liver cancer prevention = 0.33; 95% CI: (0.11,1.03)	500 mg GTP / day or 1000 mg GTP/day for 3 months	Green tea polyphenol (GTP) intake had a chemo preventative effect.
Lung Cancer											
46	Wang, et al. [81]	Japan and China	Observational studies; (consisting of case-control studies and cohort studies)	59,041	≥ 40	Male and female with Lung cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin or carboplatin.		OR for lung cancer risk = 0.84; 95% CI: (0.75,0.95), $p < 0.01$	≥ 3 GT or BT cups/day for ± 36 months	GT and BT intake were significantly associated with reduced lung cancer risk.
47	Garland, et al. [82]	University of Arizona, Tucson, Arizona	RCT	99	≥ 40	Male and female with Lung cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin or carboplatin		OR for green tea safety/adverse events = 0.78; 95% CI: (0.87,0.87)	Poly E capsule containing 200 mg /day of EGCG for 6 months	Poly E intake in former smokers with at least a moderate smoking history and FEV1 ≤70% is effective and safe.
48	Laurie, et al. [83]	University of Ottawa	RCT	17	≥ 40	Male and female with Lung cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin or carboplatin.		OR for lung cancer prevention = 0.86; 95% CI: (0.77,0.96)	3 g/m2 GTE per day for 4 – 16 weeks	GTE has limited activity as a cytotoxic agent, and further study of GTE as a single-agent in advanced malignancies is warranted.

49	Fritz, et al. [84]	Toronto, Canada	Observational studies; (consisting of case-control studies and cohort studies)	21	57 - 63	Male and female with Lung cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin or carboplatin.	OR for lung cancer prevention = 0.96; 95% CI: (0.5,1.86)	3-4.2 g/m^2 GTE per day for ± 4 – 6 months (≡ 7 to 8 cups (of GT / 3 times daily)	Insufficient evidence to support GT intake as a preventative agent for lung cancer. GT should not be used by patients on bortezomib therapy
50	Shim, et al. [85]	Shanghai, China	RCT	52	20 – 52	Male, smoker, with Lung cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin or carboplatin.	OR for chemoprotection against lung cancer = 0.95; 95% CI: (0.45,1.99)	2-3 GT cups/day for 6 months	Sister chromatid exchange (SCE) frequencies are elevated in patients receiving chemotherapy for lung cancer. GT intake had chemoprotective effects by blocking the increase in SCE frequency.
51	Zhong, et al. [86]	Shanghai, China	Case control studies	675	20 – 50	Female with Lung cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin or ⇒ carboplatin.	OR for lung cancer risk = 0.78; 95% CI: (0.44,1.37)	2 GT cups/day for ± 6 – 12 months	GT intake was associated with a reduced risk of lung cancer
52	Hakim, et al. [87]	North America	RCT	143	20 – 50	Male and female, smoker, with Lung cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin or carboplatin.	OR for lung cancer prevention = 0.65; 95% CI: (0.45,0.93)	4.1 – 4.9 GT cups/ day for 4 months	GT intake has been associated with decreased occurrence of cancer
53	Wang, et al. [88]	Western countries and Japan and China	Case Control + Cohort studies	59,041	20 – 50	Male and female, with Lung cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin or carboplatin.	OR for protection against lung cancer = 0.66; 95% CI: (0.31,.44), $p <$ 0. 01	≥ 1 GT or BT cups/ day for ± 6 – 12 months	GT but not BT intake may offer some protection against lung cancer.
Colorectal cancer										
54	Ettrich, et al. (2015)	Germany	RCT	918	50 – 80	Male and female with colorectal cancer	⇒ Surgery ⇒ FOLFOX chemotherapy; Folinic acid, fluorouracil and oxaliplatin ⇒ Novel target-oriented drugs; as cetuximab, bevacizumab	OR for colorectal cancer prevention = 0.78; 95% CI: (0.7,0.87)	300 mg EGCG/day for 36 months	EGCG intake was well tolerated and had a preventive effect on colorectal adenomas in the large bowel.

55	Fakhri, et al. [89]	Asia and the United States,	Observational studies; (consisting of case-control studies and cohort studies)	44,992	19 – 80	Male and female with colorectal cancer	⇒ Surgery ⇒ FOLFOX chemotherapy; Folinic acid, fluorouracil and oxaliplatin ⇒ Novel target-oriented drugs; as cetuximab, bevacizumab	OR for colorectal cancer risk = 0.87; 95% CI: (0.59,1.28), $p < 0.0001$	≥ 1 GT cup/ day ± 6 – 12 months	GT intake reduced colon cancer risk, while it had the minimum influence on CRC.
56	Guan, et al. [90]	Germany, Asia and the United States,	Observational studies; (consisting of case-control studies and cohort studies)	2864	19 – 85	Male and female with colorectal cancer	⇒ Surgery ⇒ FOLFOX chemotherapy; Folinic acid, fluorouracil and oxaliplatin ⇒ Novel target-oriented drugs; as cetuximab, bevacizumab	OR for colorectal cancer prevention = 0.82; 95% CI: (0.69,0.98), $P = 0.454$)	≥ 1 GT cup/ day ± 6 – 12 months	GT intake had a preventive effect on colorectal adenomas.
57	Suzuki , et al. (2005)	Japan	Cohort studies	65,915	50 – 57	Male and female with colorectal cancer	⇒ Surgery ⇒ FOLFOX chemotherapy; Folinic acid, fluorouracil and oxaliplatin ⇒ Novel target-oriented drugs; as cetuximab, bevacizumab	OR for colorectal cancer risk = 0.81; 95% CI: (0.66,0.98)	≥ 5 GT cup/ day ± 6 – 12 months	GT intake was not associated with a lower risk of colorectal cancer.

58	Sun, et al. [91]	China	Cohort studies	845	40 - 74	Male with colorectal cancer	⇒ Surgery ⇒ FOLFOX chemotherapy; Folinic acid, fluorouracil and oxaliplatin ⇒ Novel target-oriented drugs; as cetuximab, bevacizumab	OR for colorectal cancer risk = 1.06; 95% CI: (0.74,1.52), p-trend<0.01	250 g/day of GT or BT for ± 48 months	GT colorectal cancer association was mainly found in advanced disease while BT intake was not associated with risk of colorectal cancer.
59	Yang, et al. [92]	Nashville, Tennessee	Cohort studies	69,710	51	Female with colorectal cancer	⇒ Surgery ⇒ FOLFOX chemotherapy; Folinic acid, fluorouracil and oxaliplatin ⇒ Novel target-oriented drugs; as cetuximab, bevacizumab	OR for colorectal cancer risk = 0.76; 95% CI: (0.47,1.21)	50 - 150 g/day of GT for ± 6 months	Regular GT intake may reduce Colorectal cancer risk in women
Ovarian, endometrial and cervical cancer										
60	Baker, et al. [93]	United states	Observational studies	1282	30 - 55	Female with ovarian cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for ovarian cancer risk = 0.63; 95% CI: (0.45,0.88)	≥ 2 GT cup/day for ± 6 – 12 months	BT intake was associated with a 30% decline in ovarian cancer risk.
61	Zheng, et al. [94]	North America, Europe and Asia	Observational studies; (consisting of case-control studies and cohort studies)	20,980	30 - 55	Female with ovarian, endometrium, and cervical cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for morbidity= 0.7; 95% CI: (0.51,0.97), p = 0.109	1.40 to 3.12 GT or BT or WT cups/day for ± 6 – 12 months	GT, BT and WT had no significant correlation to morbidity of gynaecologic tumours in different sites (ovary, endometrium, and cervix)

62	Zheng, et al. [95]	Iowa	Cohort study	35, 369	40 - 76	Female, postmenopausal with ovarian, endometrium, and cervical cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for prevention/ protection against ovarian, endometrium, and cervical cancer = 1; 95% CI: (0.96,1.04)	≥ 2 WT cup/ day for ± 96 months	WT intake was related to a slight, but not statistically significant, reduced incidence of all cancers combined. WT may protect against ovarian, endometrium, and cervical cancer
63	Larsson, et al. [96]	Sweden	Observational study; (consisting of case-control studies and cohort studies)	61 057	40 - 76	Female with ovarian cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for ovarian cancer risk = 0.77; 95% CI: (0.64,0.91)	1- 2 BT cup/ day ± 18 months	BT intake was inversely associated with the risk of ovarian cancer. GT and BT consumption was associated with reduced mortality due to all causes but not with reduced mortality due to cancer.
64	Steevens, et al. [97]	Netherland s	Observational study; (consisting of case-control studies and cohort studies)	2589	46 - 55	Female with ovarian cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for ovarian cancer risk = 0.94; 95% CI: (0.88,1.01). p = 0.12	≥ 6 BT cup/ day for 12 months	BT intake was inversely, but not statistically significantly, associated with ovarian cancer risk.
65	Cassidy, et al. [98]	United states	Observational study; (consisting of case-control studies and cohort studies)	171 940	30 - 55	Female with ovarian cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for ovarian cancer risk = 0.94; 95% CI: (0.81,1)	>1 and ≤ 1 BT cup / day for 48 months	BT intake may be associated with a lower risk of ovarian cancer.
66	Shimazu, et al. [99]	Japan	Observational study; (consisting of case-control studies and cohort studies)	53,724	40 - 69	Female with endometrial cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for endometrial cancer risk = 0.76; 95% CI: (0.59,0.98)	1-2 or ≥ 3 GT cups/ day for ± 18 months	GT intake was not significantly associated with a reduced risk of endometrial cancer.

67	Uccella, et al. [100]	Iowa	Observational study; (consisting of case-control studies and cohort studies)	23,356	55 - 69	Female with stage II endometrial cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for endometrial cancer risk = 0.8; 95% CI: (0.74,0.86)	≥ 4 WT cup/ day for ± 12 months	WT was not associated with stage II endometrial cancer risk.
68	Weiderpass, et al. [101]	Sweden	Observational study; (consisting of case-control studies and cohort studies)	42,270	46 - 58	Female with endometrial cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for endometrial cancer risk = 0.65; 95% CI: (0.47,0.89)	1-2 BT cups/ day for ± 36 months	BT was not associated with endometrial cancer risk among middle-aged women.
69	Paul, et al. [102]	China	Observational study; (consisting of case-control studies and cohort studies)	30,744	20 - 50	Female with cervical cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for protection against cervical cancer = 1; 95% CI: (0.98,1.02)	≥ 1 GT or BT cup/day for ± 6 – 12 months	GT and BT intake contributed to a protective effect against cervical cancer development. BT intake was not associated with cervical cancer risk.
70	Gates, et al. [103]	Harvard Medical School, Boston	Observational study; (consisting of case-control studies and cohort studies)	66,940	30 - 55	Female with ovarian cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for ovarian cancer risk= 0.97; 95% CI: (0.76,1.22)	≥ 1 WT cup/ day for ± 60 months	WT flavonoids may reduce ovarian cancer risk, although additional prospective studies are needed to further evaluate this association.
71	Trudel, et al. [104]	Europe	RCT	16	≥ 30	Female with ovarian cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for ovarian cancer prevention = 0.75; 95% CI: (0.51,1.09)	500 mL/day of DBGT) for ± 18 months	Double-brewed green tea (DBGT) supplementation does not appear to be a promising maintenance intervention in women with advanced stage ovarian cancer.
72	Zhan, et al. [105]	China	Epidemiology studies	701,857	≥ 30	Female with ovarian cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for protection against ovarian cancer = 0.84; 95% CI: (0.57,1.24), p > 0.01	≥ 1 GT cup/ day for ± 60 months	GT intake had a significant protective effect against ovarian cancer

73	Gao, et al. [106]	Shanghai, China	Case control studies	995	30 - 69	Female with endometrial cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for endometrial cancer risk= 0.86; 95% CI: (0.76,0.96)	>7 and ≤ 7 BT cup / week for ± 60 months	GT intake had a weak but inverse association with endometrial cancer risk. This protective effect was limited to premenopausal women.
74	Zhang, et al. [107]	Hangzhou, China	Cohort studies	254	≥ 30	Female with ovarian cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for overall survival = 0.74; 95% CI: (0.54,1.01)	≥ 1 GT cup/ day for ± 36 months	Increased GT intake may enhance epithelial ovarian cancer survival.
75	Lee, et al. [108]	China	Case Control studies	254	≥ 30	Female with ovarian cancer	⇒ Surgical staging & operative tumour debulking ⇒ Six cycles of chemotherapy; carboplatin and paclitaxel	OR for ovarian cancer risk= 0.55; 95% CI: (0.34,0.9)	≥ 1 GT or OT cup/day for ± 12 months	Increased GT intake reduced the risk of ovarian cancer. However, the protective effects of OT need to be further investigated.
Non – Hodgkin lymphoma										
76	Mirtavoos – Mahyari, et al. [109]	Tehran	Observational studies; (consisting of case-control studies and cohort studies)	315,972	30 - 75	Male and female with ovarian cancer Non – Hodgkin's lymphoma	⇒ Radiation ⇒ Chemotherapy; doxorubicin-mixed with rituximab or rituximab alone ⇒ Immunotherapy, or radioimmunotherapy	OR for Non – Hodgkin's lymphoma cancer risk= 1.2; 95% CI: (0.65,2.22), $p < 0.05$	≥ 1 GT or BT cup/day for ± 12 months	GT intake may be associated with reduced risk of NHL
Gastric cancer										
77	Hoshiyama, et al. [110]	Japan	Cohort studies	73,851	≥ 40	Male and female with gastric cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer risk= 1.21; 95% CI: (0.97,1.5)	≥ 5 GT cup/ day for ± 36 months	GT intake had no association with the risk of gastric cancer.

78	Sasazuki, et al. [111]	Japan	Cohort studies	892	≥ 40	Male and female with gastric cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer risk= 1.6; 95% CI: (0.9,2.9)	≥ 5 GT cup/ day for ± 36 months	While no association between GT intake and gastric cancer was observed among men, a decreased risk of gastric cancer was observed among women.
79	Yoshitaka Tsubono, et al. [112]	Japan	Cohort studies	26 311	≥ 40	Male and female with gastric cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer risk= 0.51; 95% CI: (0.3,0.86)	≥ 5 GT cup/ day for ± 36 months	GT intake had no association with the risk of gastric cancer.
80	Yu, et al. [113]	Japan	Epidemiology studies	1231	20 - 75	Male and female with gastric and intestinal cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer prevention= 1.1; 95% CI: (0.8,1.6)	≥ 5 GT cup/ day for ± 60 months	GT intake did not play a role in the prevention of stomach and intestinal cancer.
81	Hoshiyama, et al. [114]	Japan	Case control studies	157	40 -79	Male and female with gastric cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer risk= 0.51; 95% CI: (0.29,0.91)	≥ 10 GT cup/ day for ± 60 months	GT intake had no association with the risk of gastric cancer.
82	Yu, et al. [115]	Shanghai, China	Case control studies	711	18 – 80	Male and female with gastric cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer risk= 1.3; 95% CI: (0.6,2.8)	≥ 1 GT cup/ day for ± 48 months	GT intake was associated with a lower risk of stomach cancer.

83	Huang, et al. [116]	China	Observational studies; (consisting of case-control studies and cohort studies)	6627	18 – 80	Male and female with gastric cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer risk= 0.71; 95% CI: (0.54,0.93), *P*=0 ·286	≥ 6 GT cup/ day for ± 60 months	GT intake had a preventive effect on reducing the risk of gastric cancer, particularly for long-term and high-dose consumption.
84	Wang, et al. [117]	China	Case control studies	160	18 – 80	Male and female with gastric cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer risk= 1.05; 95% CI: (0.9,1.21)	≥35 g/week of GT for ± 60 months	GT intake, including regular drinking, larger amount of consumption, lower temperature and longer interval were strongly associated with a lower risk of stomach cancer.
85	Nechuta, et al. [118]	Shanghai, China	Cohort studies	69,310	30 – 80	Male and female with gastric and oesophageal cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer risk= 0.72; 95% CI: (0.32,0.98)	2–3 GT cup/ day for ± 6 months	GT intake was associated with reduced risk of colorectal and stomach/oesophageal cancers in Chinese women.
86	Mao, et al. [119]	China	Case control studies	200	52 – 62	Male and female with gastric cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	OR for gastric cancer risk= 0.86; 95% CI: (0.74,0.98)	≥ 2 GT cup/ day for ± 12 months	Low temperature GT intake showed a protective effect on gastric cancer, while a heavy risk of gastric cancer was found in high temperature GT intake.
Pancreatic cancer										
87	Zeng, et al. [120]	China and Japan	Case Control + Prospective studies	288 209	18 - 80	Male and female with pancreatic cancer	⇒ Surgery ⇒ Chemoradiation with fluorouracil ⇒ Chemotherapy; gemcitabine	OR for pancreatic cancer risk= 1.82; 95% CI: (1.03,3.52), *P* = 0.04,	≥ 2 – 5 GT cup/day for ± 6 – 12 months	GT intake had no association with the risk of pancreatic cancer

88	Chen, et al. [121]	China	Case Control + Cohort studies	859, 783	60	Male and female with pancreatic cancer	⇒ Surgery ⇒ Chemoradiation with fluorouracil ⇒ Chemotherapy; gemcitabine	OR for pancreatic cancer risk= 0.95; 95% CI: (0.85,1.06), P=0.922	≥ 2 GT cup/day for ± 24 months	Increased GT intake can reduce the risk of pancreatic cancer.
89	Luo, et al. [122]	Japan	Cohort studies	233	35 - 79	Male and female with pancreatic cancer	⇒ Surgery ⇒ Chemoradiation with fluorouracil ⇒ Chemotherapy; gemcitabine	OR for pancreatic cancer risk= 0.99; 95% CI: (0.89,1.11)	≥ 3 GT cup/day for ± 132 months	GT intake did not have a substantial impact on pancreatic cancer risk.
90	Ji, et al. [123]	Shanghai, China	Cohort studies	2266	30 - 79	Male and female with pancreatic cancer	⇒ Surgery ⇒ Chemoradiation with fluorouracil ⇒ Chemotherapy; gemcitabine	OR for colorectal and pancreatic cancer risk= 0.99; 95% CI: (0.78,1.25)	≥ 300 g/month of GT ± 36 months	GT intake may lower the risk of colorectal and pancreatic cancers.
91	Wang, et al. [124]	Shanghai, China	Case control studies	908	35 - 79	Male and female with pancreatic cancer	⇒ Surgery ⇒ Chemoradiation with fluorouracil ⇒ Chemotherapy; gemcitabine	OR for pancreatic cancer risk= 0.77; 95% CI: (0.6,0.99)	225.2 ± 83.3 g/month of GT ± 60 months	GT intake, including regular drinking, amount of consumption, persistence of the habit, and tea temperature, may lower the risk of pancreatic cancers.
Various other types of cancer										
92	Chen, et al. [121]	China	Observational studies; (consisting of case-control studies and cohort studies)	2803	35 - 79	Male and female with laryngeal cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin ⇒ Novel target-oriented drugs; as cetuximab and bevacizumab	OR for laryngeal cancer risk= 0.68; 95% CI: (0.48,0.96), P<0.001	≥ 1 GT or BT cup/day for ± 60 months	GT and BT intake was not associated with risk of laryngeal carcinoma
93	Tsao, et al. [125]	United States	RCT	39	30 - 74	Male and female with oral cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin and fluorouracil	OR for oral cancer prevention= 1.03; 95% CI: (0.66,1.61)	GTE at 500, 750, or 1,000 mg/m for 12 weeks	Higher doses of GTE may improve short-term oral premalignant lesions outcome. The present results support longer-term clinical testing of GTE for oral cancer prevention
94	Ramshankar, et al. [126]	India	RCT	39	40 - 79	Male and female with oral cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin and fluorouracil	OR for oral cancer prevention= 0.65; 95% CI: (0.38,1.1)	Oral GTE dose of 1gm/m^2 thrice daily for 6 months	Study results support a potential role of GT intake for oral cancer prevention.

95	Am J, et al. (1997).	India	RCT	64	35 - 79	Male and female with head and neck cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin and carboplatin	OR for head and neck cancer prevention= 1.21; 95% CI: (0.94,1.54)	3.6 g and 5.4 g of GT per day for 6 months	GT intake had chemo preventative effects against head and neck cancer
96	Ide, et al. [127]	Japan	Cohort studies	50 221	40 - 79	Male and female with oral cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin and fluorouracil	OR for oral cancer risk= 0.84; 95% CI: (0.57,1.24)	≥ 5 GT cup/ day ± 120 months	No inverse association was found between GT intake and oral cancer, although there was a reduced risk in women.
97	Gao, et al. [128]	Shanghai, China	Case control studies	1016	30 – 74	Male and female with oesophageal cancer	⇒ Surgery ⇒ Chemo-radiation; paclitaxel and carboplatin	OR for protection against oesophageal cancer = 0.51; 95% CI: (0.1,2.68)	≥ 1 GT cup/ day ± 36 months	A protective effect of GT intake on oesophageal cancer was observed among women
98	Mu, et al. [129]	Taixing, Jiangsu province, China	Case control studies	628	40 - 80	Male and female gastric, oesophageal and liver cancer	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; cisplatin, doxorubicin, fluoropyrimidine based, ramucirumab combined with paclitaxel, carboplatin ⇒ Multikinase inhibitor; sorafenib	OR for protection against gastric, liver and oesophageal cancer = 0.5; 95% CI: (0.3,0.83)	≥ 1 GT cup/ day for ± 120 months	GT intake had significant protective effects on the development of gastric, oesophageal and liver cancer among alcohol drinkers
99	Zhang, et al. [130]	China	Case control studies	107	30 - 60	Male and female with leukaemia	⇒ Surgery ⇒ Radiation ⇒ Chemotherapy; Doxorubicin	OR for leukaemia risk= 0.23; 95% CI: (0.1,0.55)	≥ 4 GT cup/ day for 12 months	A reduced risk of leukaemia was found with longer duration, higher quantity, and frequency of GT intake
100	Zhang, et al. [131]	China	Observational studies; (consisting of case-control studies and cohort studies)	290	18 – 60	Male and female with oesophageal squamous cell carcinoma.	⇒ Surgery ⇒ Chemo-radiation; paclitaxel and carboplatin	OR for oesophageal cancer prevention = 0.2; 95% CI: (0.06,0.6)	≥ 5 GT cup/ week for ± 3 – 6 months	Postoperative GT intake had a positive effect on delay in clinical deterioration and improvements in multiple functions and symptoms associated with oesophageal squamous cell carcinoma.

Table 5: Subgroup analysis illustrating overall success of *Camellia Sinensis* tea exposure on several types of cancers included in this systematic review and meta-analysis.

Type of cancer	Number of studies	Region	Sample size	Cancer staging	5 year survival	Standard treatment	*Intervention*	Treatment exposure length	Overall success
Breast cancer	15	Japan, China, Hong Kong, Minnesota, Baltimore, USA, Europe, Porto Rico and Columbia University	387,525	Stage I - III	91% (American Cancer Society, 2023).	⇒Surgery ⇒Radiation ⇒Chemotherapy; doxorubicin, paclitaxel and docetaxel, 5- fluorouracil or capecitabine. Cyclophosphamide, and carboplatin.	GT, EGCG, Poly E, GSP and BT.	28 days ± 12 months	(1) GT and (2) BT had a protective effect with no association to breast cancer risk while (3) WT and (4) OT had a limited to no effect. Additionally, increased (1) GT intake was correlated with decreased recurrence of stage I and II breast cancer ($p < 0.05$ for crude disease-free survival).
Prostate cancer (PCa)	12	Europe, North America, UCLA, UCSF, Africa and Asia (Japan and China)	237,143	Stage I - IV	97% (American Cancer Society, 2024).	⇒Hormonal treatment; androgen deprivation therapy ⇒Radiation Chemotherapy; docetaxel and cabazitaxel	GT, EGCG, GTC and BT.	3 weeks ± 36 months	(1) GT intake reduced PCa risk, GTC were effective for preventing Pca and EGCG intake had chemoprevention and protective effects. (2) BT intake had an reduced risk of Pca while (3) WT and (4) OT had a limited to no effect.
Bladder cancer	2	Asia (Japan and China)	533,309	Stage I - V	78 % (American Cancer Society, 2022).	⇒Chemotherapy; cisplatin-based ⇒Immunotherapy	GT and GTP	6± 12 months	(1) GT intake may have a protective effect on bladder cancer in Asian people while (2) BT, (3) WT and (4) OT had a limited to no effect.
Liver cancer	1	Japan and China.	124	Stage I - III	22% (American Cancer Society, 2024).	⇒Surgery ⇒Chemotherapy; doxorubicin ⇒Multikinase inhibitor; sorafenib	GTP	± 3 months	(1) GTP intake had a chemo - preventative effect on liver cancer while (2) BT, (3) WT and (4) OT had a limited to no effect.
Lung cancer	8	University of Arizona, University of Ottawa, Toronto, Canada, Shanghai, China, Japan	119,089	Stage I - IV	NSCLC is 28% and SCLC is 7% (American Cancer Society, 2023).	⇒Surgery ⇒Radiation ⇒Chemotherapy; cisplatin or carboplatin.	GT,EGCG, Poly E, and BT	4 weeks ± 36 months	(1) GT and (2) BT intake were significantly associated with reduced lung cancer risk while (3) WT and (4) OT had a limited to no effect.

Colorectal cancer	6	Germany, Asia (Japan and China), United States, Nashville, Tennessee, Iowa, Sweden, Netherlands and Harvard medical school, Boston	185,244	Stage I - III	63% (American	⇒Surgery ⇒FOLFOX ⇒chemotherapy; Folinic acid, fluorouracil and oxaliplatin ⇒Novel target-oriented drugs; as cetuximab and bevacizumab	GT,EGCG,	6 ± 48 months	(1) GT intake had a preventive effect on colorectal adenomas while (2) BT intake was not associated with CRC risk. (3) WT and (4) OT had a limited to no effect.
Ovarian cancer	16	Boston, North America, Europe Sweden, Iowa, Netherlands, United Sates, Asia, Japan and China.	2,945,261	Stage I - III	50%(American Cancer Society, 2023).	⇒Surgical staging & operative tumour debulking ⇒Six cycles of chemotherapy; carboplatin and paclitaxel	GT, DBGT and BT	6 ± 96 months	(1) GT intake had a significant protective effect against ovarian cancer while (2) BT intake may be associated with a lower risk of ovarian cancer. (3) WT and (4) OT had a limited to no effect.
Non-Hodgkin	1	Tehran	315,972	Stage I - IV	Diffuse large B-cell lymphoma is 65% and Follicular lymphoma is 90%(American Cancer Society, 2023).	⇒Radiation ⇒Chemotherapy; doxorubicin-mixed with rituximab or rituximab alone ⇒Immunotherapy, or radioimmunotherapy	GT	± 12 months	Increased (1) GT intake reduced the risk of NHL while (2) BT, (3) WT and (4) OT had a limited to no effect.
Gastric cancer	10	Japan and Shanghai, China	85,084	Stage I - III	36% (American Cancer Society, 2024).	⇒Surgery ⇒Radiation ⇒Chemotherapy; cisplatin, fluoropyrimidine based, ramucirumab combined with paclitaxel	GT	6 ± 60 months	(1) GT intake had a preventive effect on reducing the risk of gastric cancer, particularly for long- term and high-dose consumption while (2) BT, (3) WT and (4) OT had a limited to no effect.
Pancreatic cancer	5	Japan and Shanghai, China	3407	Stage I - II	13% (American Cancer Society, 2024).	⇒Surgery ⇒Chemoradiation with fluorouracil ⇒Chemotherapy; gemcitabine	GT	6 ± 132 months	(1) GT intake may lower the risk of colorectal and pancreatic cancers while (2) BT, (3) WT and (4) OT had a limited to no effect.

Table 6: Characteristics of primary outcomes included in this systematic review and meta-analysis.

Outcome	Study characteristics
Overall survival (OS)	Overall survival (OS) was measured in 3 studies. Green and black tea consumption was associated with increased survival due to all causes but not with increased survival due to cancer [Kuriyama, et al. [51]. No inverse association between green tea consumption and the risk of stomach cancer death [Hoshiyama, et al. [110]. For all cancer survival, the summary RR for the highest v. lowest category of green tea and black tea consumption were 1.06 (95 % CI
	= 0.98, 1.15) and 0.79 (95 % CI = 0.65, 0.97), respectively [Tang, et al. [43)].
Overall response rate (ORR)	Overall response rate (ORR) was measured in 3 studies. ORR demonstrated protective effects of green tea consumption on gastrointestinal, breast, lung and prostate cancer. However, these findings have not been confirmed by other studies covered in this review [Liu, et al. [48]. Results from two Prospective studies did not show a protective role of green and black tea in five major cancers. However, subgroup analysis showed that increase in consumption of three cups of black tea per day was a significant risk factor for breast cancer (RR, 1.18; 95% CI = 1.05,1.32). Additionally, green tea consumption was virtually unrelated to incidence of cancers under study [Yu, et al. [42]; Nagano, et al. [50].
Progression-free survival (PFS)	Progression-free survival (PFS) was measured in 1 study. Result from the study showed that increased consumption of green tea was correlated with decreased recurrence of stage I and II breast cancer ($p < 0.05$ for crude disease-free survival); the recurrence rate was 16.7 or 24.3% among those consuming > or = 5 cups or < or = 4 cups per day, respectively [Nakachi, et al. [61].
Risk of cancer incidence	Risk of cancer incidence was measured in 33 studies. The evidence for green tea and cancer risk is inadequate and inconclusive as limited evidence for the beneficial effect of green tea consumption on the overall risk of cancer [Johnson, et al. [34]); Filippini, et al. [2]. No significant effect of green tea on breast cancer prevention. Green tea consumption, however, may be associated with a reduced risk of recurrence of stage I and II breast cancer. Some studies show lower risk and an important and protective role of green tea intake in relation to breast cancer risk for breast cancer with green tea consumption Seely, et al. [56-58,63], Further investigation of the potential chemo preventive effect of green tea intake on breast cancer risk in younger women is warranted [Samavat, et al. [7]. In conclusion, a 2020 study suggests drinking at least five cups of green or black tea per week may be associated with decreased breast cancer risk. [Zhang, et al. [64] Green tea was not associated with localized prostate cancer. However, consumption was associated with a dose-dependent decrease in the risk of advanced prostate cancer [Kurahashi, et al. [75]. High consumption of green tea suppressed urinary
	tract recurrence and the risks of up-grading and up-staging by recurrence in never smokers. Our results suggested that HuR expression played important roles in
	such mechanisms [Yasuda, et al. [79]). In a prospective study of 19,561 Japanese men, green-tea intake was not associated with a lower risk of prostate cancer (110 cases) [Kikuchi, et al. [51]. Both green tea (RR, 0.75; 95% CI = 0.62, 0.91) and black tea (RR 0.82; 95% CI = 0.71, 0.94) were significantly associated with reduced lung cancer risk. [Wang, et al. [81]. 11 Observational studies found that black tea consumption was associated with a linear decline in ovarian cancer risk , with individuals consuming two or more cups daily experiencing a 30% decline in risk (Baker, et al. [93-103]). Findings from 1 Observational study suggest that green tea intake may be associated with reduced risk of Non-Hodgkin lymphoma (NHL).
	The study found that a higher green tea intake was associated with a 39% reduced risk of NHL (pooled RR = 0.61; 95% CIs = 0.38, 0.99, I^2=60.4%, p- heterogeneity = 0.080) in high- versus low-intake meta-analysis (Mirtavoos, et al. [109]). 4 Cohort studies found no inverse association between green tea consumption and the risk of stomach cancer death [Hoshiyama et al. [110-112]) ;Nechuta, et al. [118]. 1 Prospective study [Zeng, et al. [120].and 3 Cohort studies found that GT intake had no association with the risk of pancreatic cancer and may even reduce the risk (Chen, et al. [121-123]). Additionally, 1 Case control study discovered that GT intake, including regular drinking, amount of consumption, persistence of the habit, and tea temperature, may lower the risk of pancreatic cancers [Wang, et al. [78].
Morbidity	Morbidity was measured in 1 study. No significant correlation between green, black and white tea intake and the morbidity of overall gynaecologic tumours in different sites (ovary, endometrium, and cervix), breast, liver, lung, prostate, colorectal blader and gastric tumours [Zheng, et al. [94].

Safety and Quality of life	Safety and Quality of life was measured in 5 studies. There were no safety issues and no major differences in adverse effects between green, oolong, white and black tea and placebo during the randomized phase (Ettrich, et al. 2015). Green and black tea were well tolerated and showed a trend towards a preventive effect on colorectal adenomas in the large bowel though not statistically significant (P = 0.058 and RR = 0.883). Oral GTE at the doses studied can be taken safely for at least 6 months (Pisters, et al. [44]). Adverse effects were mainly mild and transient. However, 6.7% of GTE consumers experienced ALT elevations, with 1.3% experiencing ALT-related serious adverse effects (Crew, et al. [131]). In a 2005 study, and at this dose of GTE 3 g/m2 per day was well tolerated with no grade 3 or 4 toxicity seen. Dose-limiting toxicities were diarrhea, nausea and hypertension. No objective responses were seen in this trial. Seven patients had stable disease ranging from 4 to 16 weeks; no patient remained on therapy longer than 16 weeks due to the development of progressive disease (Laurie, et al. [83].
	Regarding the safety of green tea. Green tea, a popular beverage, is largely nontoxic. A phase I trial of 17 patients with advanced lung cancer revealed that the maximal tolerable dose of green tea extract was 3 g/m2 per day. There have been no serious side effects documented in relation with the medical use of green tea. High dosages of green tea or green tea extract (about 5-6 litters per day) might produce nausea, vomiting, abdominal bloating/pain, dyspepsia, gas, and diarrhoea. Excessive use of caffeine from green tea may also produce central nervous system stimulation such as dizziness, sleeplessness, tremors, restlessness, disorientation, diuresis (increased urine output), heart rate abnormalities, and psychomotor agitation (Liu, et al. [48]. Human studies found no serious side effects in volunteers who consumed 15 pills of green tea per day (i.e. 2.25 g green tea extracts, 337.5 mg EGCG, and 135 mg caffeine) for 6 months. A randomised, placebo-controlled experiment (n = 40) demonstrated no negative effects in healthy people who took green tea polyphenols in amounts equivalent to
	the EGCG content in 8-16 cups of green tea once or twice a day in divided doses for four weeks (Liu, et al. [48].
Five year mortality rate	Five year mortality rate was measured in 3 studies. The present systematic review and meta-analysis indicated that green tea consumption not associated with all cancer mortality [Tang, et al. [43]. For all cancer mortality, the summary RR for the highest v. lowest category of green tea and black tea consumption were
	1.06 (95 % CI = 0.98, 1.15) and 0.79 (95 % CI = 0.65, 0.97), respectively. Green and black tea consumption was associated with reduced mortality due to all causes but not with reduced mortality due to cancer (Larsson, et al. [96]. In a seven-year follow-up of stage I and II breast cancer, and the relative risk of recurrence was 0.564 (95% CI = 0.35, 0.91) after adjustment for other lifestyle factors. [Nakachi, et al. [61].

Table 7: Characteristics of similar studies on green tea with similar outcomes included in this meta-analysis.

Author	Green tea and standard treatment		Standard treatment alone		Treatment dose and exposure length	Overall outcome
	Events	Total	Events	Total		
Samavat, et al. [7]	393	894	390	890	843.0 ± 44.0 mg/day EGCG for 12 months	GT may reduce breast cancer risk. (OR cancer risk reduction = 1.00; 95% CI: 0.90, 1.11; P =0.519; I^2 = 0; Egger p value < 0.10).
Zhang, et al. [64]	545	931	540	930	≥ 5 GT cups/ day for ± 6 – 12 months	GT intake was associated with reduced breast cancer risk. (OR cancer risk reduction = 1.01; 95% CI: 0.93, 1.09; P = 0.519; I^2 = 0; Egger p value <0.10).
Bailey, et al. 2024	26	74	25	70	< 1 - > 5 GT cups/day for ± 6 – 12 months	GT intake had a reduced risk of prostate cancer. (OR cancer risk reduction = 0.98; 95% CI: 0.63, 1.53; P = 0.519; I^2 = 0; Egger p value < 0.10).
Mirtavoos, et al. [109]	2914	4914	2900	4914	≥ 1 GT or BT cup/day for > 12 months	GT intake may be associated with reduced risk of NHL. (OR cancer risk reduction = 1.00; 95% CI: 0.97,1.08; P = 0.519; I^2 = 0; Egger p value <0.10).
Nechuta, et al. [118]	1255	2255	1200	2200	2–3 GT cup/day for ± 6 months	GT intake was associated with reduced risk of colorectal and gastric cancers in women. (OR cancer risk reduction = 1.02; 95% CI: 0.97, 1.08; P= 0.519; I^2 = 0; Egger p value < 0.10).
Ide, et al. [127]	37	87	35	80	≥ 5 GT cup/day for ± 120 months	No inverse association was found between GT intake and oral cancer, although there was a reduced risk in women. (OR cancer risk reduction = 0.97; 95% CI: 0.69, 1.38; p = 0.519; I^2 = 0; Egger p value < 0.10).

Imai, et al. [45]	384	768	380	760	≥ 10 cups GT /day for ± 6 – 12 months	GT intake had a preventative effect. (OR for cancer prevention = 1.00; 95% CI: 0.82, 1.22; p =0.677; I^2 = 0; Egger p value < 0.10)
Samavat, et al. [7]	462	932	460	931	4 GTE capsules containing 1,315 mg total catechins, including 843 mg EGCG for 12 months	GT intake might have a preventive effect in breast cancer. However, further investigation of the potential chemo-preventative effect of green tea intake on breast cancer risk in both pre and postmenopausal women is warranted. (OR for cancer prevention = 1.01; 95% CI: 0.84,1.21; p =0.677; I^2 = 0; Egger p value < 0.10)
Inoue, et al. [60]	113	230	100	228	≥ 3 GT cups/ day for ± 6 months	GT intake may be preventive against recurrence of breast cancer in early stage cases. OR for cancer prevention = 1.24; 95% CI: 0.86, 1.79; p =0.677; I^2= 0; Egger p value < 0.10)
Guan, et al. [90]	632	1300	630	1299	≥ 1 GT cup/day for ± 6 months	GT intake had a preventive effect on colorectal adenomas. (OR for cancer prevention = 1.00; 95% CI: 0.86,1.17; p = 0.677; I^2 = 0; Egger p value <0.10)
Huang, et al. [117]	480	960	475	958	≥ 6 GT cup/day ± 60 months	GT intake had a preventive effect on reducing the risk of gastric cancer, particularly for long-term and high-dose consumption. (OR for cancer prevention = 1.02; 95% CI: 0.85,1.22; p = 0.677; I^2 = 0; Egger p value < 0.10)
Crew, et al . 2015	24	40	20	39	400, 600 or 800 mg of green tea extract, Poly E for 6 months (≡ 8 to 24 cups of GT/day)	No adverse events, GT was safe and well tolerated. (OR for adverse events = 1.43; 95% CI: 0.58, 3.47; p= 0.462; I^2 = 0; Egger p value < 0.10)
Dostal, et al. [59]	717	937	700	930	843.0 ± 44.0 mg/day EGCG or placebo for 12 months.	GT intake had adverse events ranging from serious ALT elevations to diarrhea, nausea and migraines. (OR for adverse events = 1.07; 95% CI: 0.87, 1.32; p= 0.462; I^2 = 0; Egger p value <0.10)
Luo, et al. [80]	62	124	60	120	500 mg GTP / day or 1000 mg GTP/day for 3 months	No adverse events, GT was safe and well tolerated. (OR for adverse events = 1.00; 95% CI: 0.61,1.65; p = 0.462; I^2= 0; Egger p value < 0.10)

Chapter 5- Results

Study Selection and Characteristics

In the initial literature search, a total of 229 articles were found, 30 articles were removed after title screening and 174 articles were screened by abstract after the removal of duplicates (n = 25) from Zotero. A total of 60 articles were removed after abstract screening and the main reasons for exclusion included incorrect publication type, in vitro or vivo studies, not *Camellia Sinensis* related studies, case studies, not outcomes of interest and additional duplicates. This process resulted in 114 articles being selected for full-text screening. Of those, 13 articles were excluded for the following reasons: not accessible, not primary studies, not *Camellia Sinensis* or comparator (standardised anti-cancer treatment) of interest, not outcomes of interest, mixed therapies and duplicates.

A manual search was also conducted on the reference list of full-text articles and 101 studies met the inclusion criteria. However, 1 article was excluded from the analysis because there were not enough studies to make a meta-analysis group. Thus, this process resulted in a total of 100 articles describing 22 randomized control trials; 22 cohort studies; 15 case-control studies; 4 combined case control and cohort studies; 1 combined case - control and prospective study; 4 prospective studies; 7 epidemiology studies; and 25 observational studies that met the inclusion criteria and were included in the meta-analysis (see Figure 4, page 28). It is worth noting that studies on Oolong tea were partially included in this review because only one of the studies in the selection process met the inclusion criteria. Table 4 (page 30 – 46) summarizes the key characteristics of the included studies.

The studies included were published in English and were randomized control trials; cohort studies; case – control studies; combined case - control and cohort studies, as well as combined case control and prospective studies; prospective studies; epidemiology studies and observational studies. Most of the trials included participants with breast, prostate, bladder, lung, colorectal, ovarian, liver, non-Hodgkin lymphoma, gastric and pancreatic cancer, 1 trial included participants with endometrial cancers and 2 other trials included participants with laryngeal cancer and pre-malignant oral legions, re-

spectively. The mean age and standard deviation of participants was 45.0 ± 55.0 years. The average proportion of women was higher in endometrial, breast and ovarian cancers while the average proportion of men was higher in prostate, bladder and lung cancers.

The treatment duration and follow-up period ranged between 3 months to 11 years. For studies in which the same intervention was investigated using different formulations (For example, green tea extract or Epigallocatechin gallate (EGCG) or different dosages, data was combined according to recommendations from the Cochrane handbook.

Publication Bias

The JBI risk of bias tool was used to assess the quality of the included studies in narrative form. The decisions about the scoring system and the cut-off for inclusion of a study in the review were made in advance and be agreed upon by all participating reviewers before critical appraisal commenced. The goal of critical appraisal (assessment of risk of bias) was to assess the methodological quality of a study and to determine the extent to which a study had excluded or minimized the possibility of bias in its design, conduct and analysis. The results of the risk of bias (methodological quality) assessment for each aspect of methodological quality (randomization; blinding; measurement; statistical analysis etc.) are illustrated in the risk of bias graph (Figure 5) below for each individual study and the overall risk of bias of the entire set of included studies.

For randomization 64.55% of studies were judged as high risk of bias whilst 27.27% were judged as low risk of bias. For allocation concealment, the risk of bias percentage in studies was judged as 25.89% (72.72 % high risk and 26.36% low risk). For blinding of the participants and personal, the risk of bias percentage in studies was judged as 17.85% (80.90 % high risk and 18.18% low risk). Blinding of outcome assessment and Incomplete outcome data were mostly judged as low risk of bias (83,63% and 87,27%, respectively). For selective reporting, about 4.55% were judged as high risk of bias, 70 % were judged as low risk of bias and 25.45% were judged unclear. The high-risk judgement was due to conflicts of interest. The rationale for the risk of bias ratings assigned to each study was assessed by looking for features of the design and conduct of the study that have been shown by empirical evidence to minimize the risk. Overall, the quality (risk of bias) of these studies were evaluated as low to moderate.

Characteristics of Included Studies

Characteristics of the 100 studies on Camelia sininsis tea consumption and cancer risk, as well as the 95 % confidence intervals for eligible studies included in this systematic review and meta-analysis is further elaborated in the table below (Table 4). The table below is color coded based on the different types of C. Sinensis tea; i.e. green tea (green), Black tea (peach), Green & black tea (pink), White tea (purple), Oolong tea (yellow), Green, black & white tea (blue) and Green & oolong tea (orange).

COLOUR KEY: Green tea (green), Black tea (peach), Green & black tea (pink), White tea (purple), Oolong tea (yellow), Green, black & white tea (blue) and Green & oolong tea (orange).

The overall success of *Camellia Sinensis* tea exposure on several types of cancers included in this systematic review and meta-analysis are further summarized in a subgroup analysis illustrated in the table below (Table 5, page 47).

Included Studies

Detailed Inclusion and Exclusion Criteria: Detailed inclusion and exclusion criteria for clarity and reproducibility, as follows:

a) Studies with data from randomized control trials; cohort studies; case – control studies; combined case - control and cohort studies, as well as combined case control and prospective studies; prospective studies; epidemiology studies and observational studies were included

b) Studies reporting data on various cancer patients consuming different types of tea from *Camellia Sinensis* as supplementary therapy in conjunction with or after standard cancer therapy were included

c) Studies reporting data on cancer patients (breast, prostate, bladder, lung, colorectal, ovarian, liver, non-Hodgkin lymphoma, gastric and pancreatic) over the age of 18, all genders, race; male and female were included

d) Studies reporting data on at least one of the primary outcomes were included, i.e. overall survival (OS), overall response rate (ORR), progression-free survival (PFS), risk of cancer incidence, morbidity, safety and quality of life and five-year mortality rate.

e) Studies reporting data on any language and publication from January 1, 1980 up to July 1, 2024, in all databases were included.

f) All in vitro studies, and animal studies, and case studies were excluded

g) Studies reporting data on patients with additional severe diseases that might alter the outcome measurements such as cardiovascular disease or a major stroke were excluded

100 studies were included in this systematic review and meta-analysis (see Table 4, page 30 - 46). The studies included 22 randomized control trials; 22 cohort studies; 15 case – control studies; 4 combined case control and cohort studies; 1 combined case - control and prospective study; 4 prospective studies; 7 epidemiology studies; and 25 observational studies. The Pie chart below (Figure 6) showcases the different types of studies included in the systematic review and meta-analysis. The locations of the different types of studies included in the systematic review and meta- analysis are showcased in the Pie chart below (Figure 7). The majority of research is conducted in Asia,

particularly in China and Japan. This is due to the fact that green tea consumption has been a fundamental aspect of both Chinese and Japanese culture for more than a millennium, with the Japanese creating their own special tea ceremony known as Chanoyu (Bree [132]).

Diagnosis

In the 100 studies (see Table 4, page 30 - 46), certain authors reported cancer risk by organ system (for example, lung cancer) whereas others by one or more categories (for example, Non- small and Small lung cancer).

Exposure

Some studies used a self-administered questionnaire in which participants were required to declare the frequency and amount of particular foods and beverages consumed, or they conducted structured interviews. Green, black, oolong, and white tea intake was assessed each day, week, month, or year, with values ranging from 3 to 9 cups or more per day. Some research determined the annual yield in grammes of *Camellia Sinensis* leaves.

Effects of Interventions

100 studies evaluated green, black, oolong or white tea consumption and effect on disease progression and remission rates in cancer patients on standard therapy. The key findings are summarized in Table 4 (page 30 - 46). The Subgroup analysis in Table 5 (page 47) provides a further summary of the overall success of *Camellia Sinensis* tea exposure on several types of cancers included in this systematic review and meta-analysis.

All Types of Cancer: Results on the 15 studies (see Table 4, page 30 - 32) are further explained below:

a) 5 Cohort studies indicated that green tea consumption was not associated with all cancer mortality and oral GTE at the doses studied can be taken safely for at least 6 months. For all cancer mortality, the summary RR for the highest v. lowest category of green tea and black tea consumption were 1·06 (95 % CI 0·98, 1·15) and 0·79 (95

b) % CI 0·65, 0·97), respectively. Additionally, the studies showed that showed that green tea has a potentially preventive effect against cancer among humans and a significant delay in cancer onset was associated with increased consumption of green tea. (Tang, et al. [43-45,49,51]).

c) 1 combined case - control and cohort study reported that there is limited evidence for the beneficial effect of green tea consumption on the overall risk of cancer. Additional large prospective cohort studies are needed to make a convincing case for associations (Filippini, et al. [2]).

d) Results from 2 Prospective studies did not show a protective role of green and black tea in five major cancers. However, subgroup analysis showed that increase in consumption of three cups of black tea per day was a significant risk factor for breast cancer (RR, 1.18; 95% CI, 1.05-1.32). Additionally, green tea consumption was virtually unrelated to incidence of cancers under study (Yu, et al. [42,50]).

e) 3 Epidemiology studies demonstrated protective effects of green tea consumption on gastrointestinal, breast, lung and prostate cancer. However, these findings have not been confirmed by other studies covered in this review. Future prospective studies are therefore warranted (Liu, et al. [48,52-53]).

f) 4 Observational studies showed black tea polyphenols can control cell proliferative pathways and induce apoptotic cell death so as to inhibit cellular proliferation, deregulated differentiation, and progression (Naveed, et al. [40-41,46-47]).

Breast Cancer: Results on the 15 studies (see Table 4, page 32 - 35) are further explained below:

a. 8 Randomized control trials findings suggest potential mechanistic actions of green and black tea polyphenols in growth factor signaling, angio- genesis and lipid metabolism. In one trial, Oral Green select Phytosome (GSP) increases bioavailability of EGCG, which is detectable in breast tumor tissue and is associated with antiproliferative effects on breast cancer tissue ($P = 0.02$). Adverse effects were mainly mild and transient. However, 6.7% of GTE consumers experienced ALT elevations, with 1.3% experiencing ALT-related serious adverse effects. In another trial, absence of a pharmacokinetic interaction between green tea supplements and tamoxifen was observed and thus the use of green tea by patients with tamoxifen could be encouraged. Additionally, a 1998 study results indicated that increased consumption of green tea prior to clinical cancer onset is significantly associated with improved prognosis of stage I and II breast cancer ($p < 0.05$ for crude disease-free survival), and this association may be related to a modifying effect of green tea on the clinical characteristics of the cancer. In a seven-year follow-up of stage I and II breast cancer, and the relative risk of recurrence was 0.564 (95% confidence interval, 0.350-0.911) after adjustment for other lifestyle factors. Further investigation of the potential chemo-preventive effect of green tea intake on breast cancer risk in younger women is warranted (Samavat, et al. [7,54,58-59, 61,65,133]).

b. In 3 Cohort studies, findings suggest a lower risk for breast cancer with green tea consumption. However, the overall evidence did not support black tea drinking as having a protective effect on breast cancer. There was no significant effect of green tea on breast cancer prevention. However, green tea consumption may be associated with a reduced risk of recurrence of stage I and II breast cancer. Additionally, a 2020 study, suggested that drinking at least five cups of green or black tea per week may be associated with decreased breast cancer risk. The multivariable model suggested an inverse association between black (≥5 vs. 0 cups/week: HR=0.88, 95% CI 0.78, 1.00, p-trend=0.08) and green tea

(≥5 vs. 0 cups/week: HR=0.82, 95% CI 0.70, 0.95, p-trend<0.01) consumption and breast cancer risk. (Sun, et al. [55-56,64]).

c. In the 2 Case - control study, one study pointed to an important and protective role of green tea intake in relation to breast cancer risk in Asian-American women. However, the alternate study reported that tea or green tea drinking was significantly associated with a lower risk for breast cancer in pre-menopausal women (OR=0.62, 95%CI: 0.40–0.97) but an increased risk in post-menopausal women (OR=1.40, 95%CI: 1.00–1.96). The positive association among postmenopausal women was strongest among ER-negative green tea drinkers (OR=2.99, 95% CI: 1.26–7.11). (Wu, et al. [57,63]).

d. 1 Prospective study was a pooled analysis of two prospective studies with 35004 Japanese women, green-tea intake was not associated with a lower risk of breast cancer (222 cases), the multivariate relative risk for women drinking ⩾5 cups compared with <1 cup per day being 0.84 (95% confidence interval 0.57–1.24, Trend P=0.69) (Suzuki, et al. [62]). Overall, green and black tea had a protective effect with no association to breast cancer risk (Table 5, page 47).

e. 1 Epidemiology study reported that although careful interpretation is needed, these results suggest the possibility that regular green tea consumption may be preventive against recurrence of breast cancer in early stage cases [Inoue, et al. [60]].

f. 1 Observational studies showed a lower risk (OR = 0.78, 95% CI = 0.61-0.98) for breast cancer with green tea consumption (Yu, et al. [134]).

Prostate cancer (Pca): Results on the 12 studies (see Table 4, page 35 – 37) are further explained below:

a. 4 Randomized control trials found that green tea-induced changes in NFκB and systemic oxidation, and uptake of green tea polyphenols in prostate tissue. Green tea, as complementary therapy was found to have minimal clinical activity against hormone refractory prostate cancer. Additionally, a 2015 study found that EGCG per day for 1 year accumulated in plasma and was well tolerated, but did not reduce the likelihood of a subsequent PCa diagnosis in men with baseline HGPIN or ASAP. Altogether, study data suggest that up to 90% of chemoprevention efficacy can be obtained by GTCs administration in men prone to develop CaP (Henning, et al. [66,70,76,77]).

b. 2 Cohort studies found that there was no association between daily green tea intake and prostate cancer risk, compared with no green tea intake [hazard ratio (HR) = 1.08; 95 % confidence interval (CI) 0.79, 1.47]. For black tea, a statistically significant positive association and trend were observed for daily intake compared with no black tea intake (HR = 1.41, 95 % CI 1.03, 1.92; p for trend <0.01. A 2012 study's findings support the notion that green tea intake does not protect against prostate cancer and that black tea intake may increase prostate cancer risk. [Montague, et al. [71-72]).

c. 2 Case - control studies found that green tea intakes showed no significant reduction in the risk of Pca. The dose response relationships were also significant, suggesting that green tea is protective against prostate cancer. Furthermore, the prostate cancer risk declined with increasing frequency, duration and quantity of green tea consumption. The adjusted odds ratio (OR), relative to non-tea drinkers, were 0.28 (95% CI = 0.17-0.47) for tea drinking, 0.12 (95% CI = 0.06-0.26) for drinking tea over 40 years, 0.09 (95% CI = 0.04-0.21) for those consuming more than 1.5 kg of tea leaves yearly, and 0.27 (95% CI = 0.15-0.48) for those drinking more than 3 cups (1 litre) daily. [Berroukche, et al. [73,74]).

d. 1 Prospective study of 49 920 Japanese men discovered that green-tea intake was not associated with a lower risk of prostate cancer. However, consumption was associated with a dose-dependent decrease in the risk of advanced prostate cancer. The multivariate relative risk was 0.52 (95% confidence interval: 0.28, 0.96) for men drinking 5 or more cups/day compared with less than 1 cup/day (p(trend) = 0.01) [Kurahashi, et al. [75]]. Overall, green tea intake reduced prostate cancer risk, GTC were effective for preventing prostate cancer and EGCG intake had chemo- prevention and protective effects. Black tea intake had an reduced risk of prostate cancer (Table 5, page 47).

e. 1 Epidemiology study showed that the majority of epidemiologic studies have observed a correlation between increased green tea consumption and reduced risk of prostate cancer. [Bailey, et al. [69]].

f. 2 Observational studies found that the gut microbiome has biologically plausible roles in PCa such as via its influence on hormone and inflammation regulation and production of metabolically active metabolite. Novel data demonstrated that higher green tea consumption was linearly reduced PCa risk with more than 7 cups/day and green tea catechins were effective for preventing PCa. However, further studies are required to substantiate these conclusions. (Guo, et al. [67,68]).

Bladder Cancer: Results on the 2 studies (see Table 4, page 37) are further explained below:

a. 1 Randomized control trial found that high consumption of green tea suppressed urinary tract recurrence and the risks of up-grading and up-staging by recurrence in non-smokers. In non-smokers, multivariate analysis showed that the frequency of green tea consumption was a significant predictor (middle: hazard ratio, HR, 0.36, p=0.002; high: HR, 0.20, p=0.003) of urinary tract recurrence. A high consumption of green tea was associated with low rates of urinary tract recurrence and up-grading in UC patients. In BC, high consumption was associated with a lower risk of up-grading (p=0.011) and up-staging (p=0.041) in recur-

rent cancer. HuR expression in the high- consumption group was lower (p=0.019) than that in other groups. These significant findings were not detected in ever smokers. Results suggested that HuR expression played important roles in such mechanisms (Yasuda, et al. [79]). Overall, green tea intake may have a protective effect on bladder cancer in Asian people (Table 5, page 47).

b. 1 combined Case - control and cohort study analysis indicated that green tea may have a protective effect on bladder cancer in Asian people. Further studies need to be conducted to better clarify the biological mechanisms (Filippini, et al. [2]).

Liver Cancer: Results on the 1 study (see Table 4, page 37) are further explained below:

- 1 Randomized control trial findings suggest that chemoprevention with GTP is effective in diminishing oxidative DNA damage. At the end of the 3 months' intervention, 8- OHdG levels decreased significantly in both GTP-treated groups, with medians of 2.02, 1.03 and 1.15 ng/mg-creatinine for placebo, 500 mg and 1000 mg group, respectively (P = 0.007). These results suggest that urinary excretions of EGC and EC can serve as practical biomarkers for green tea consumption in human populations. [Luo, et al. [77]]. Overall, GTP intake had a chemo - preventative effect (Table 5, page 47).

Lung Cancer: Results on the 8 studies (see Table 4, page 38) are further explained below:

a) 4 Randomized control trials data suggest that regular green tea drinking might protect smokers from oxidative damages and could reduce cancer risk or other diseases caused by free radicals associated with smoking. Green tea can block the cigarette-induced increase in sister chromatid exchange (SCE) frequency. SCE rates were elevated significantly in smokers (9.46 +/- 0.46) versus nonsmokers (7.03 +/- 0.33); however, the frequency of SCE in smokers who consumed green tea (7.94 +/- 0.31) was comparable to that of non-smokers, implying that green tea can block the cigarette-induced increase in SCE frequency. A 2005 study suggests that while relatively nontoxic at a dose of 3 g/m2 per day, GTE likely has limited activity as a cytotoxic agent, and further study of GTE as a single-agent in established malignancies may not be warranted. On this schedule, the dose of GTE was 3 g/m2 per day, and at this dose, GTE was well tolerated with no grade 3 or 4 toxicity seen. Dose-limiting toxicities were diarrhea, nausea and hypertension. No objective responses were seen in this trial. Seven patients had stable disease ranging from 4 to 16 weeks; no patient remained on therapy longer than 16 weeks due to the development of progressive disease. In a Phase III randomized, double blind controlled trial of chemoprevention of lung carcinogenesis using green tea beverage and tea polyphenols (Polyphenol E), no significant adverse events have been reported, including no liver toxicity [Garland, et al. [82,83,85,87])].

b) 1 Case - control study discovered that the inconsistency in the association between drinking tea and the risk of lung cancer reported in previous studies may in part be due to inadequate control of confounding of active smoking (Zhong, et al. [86]).

c) 1 combined Case - control and cohort study found that tea consumption may offer some protection against lung cancer. Both green tea (RR, 0.75; 95% CI, 0.62-0.91) and black tea (RR, 0.82; 95% CI, 0.71-0.94) were significantly associated with reduced lung cancer risk. (Wang, et al. [81]). Overall, green and black tea intake were significantly associated with reduced lung cancer risk (Table 5, page 47).

d) 2 Observational studies found that Both green tea and black tea were significantly associated with reduced lung cancer risk (RR, 0.78; 95% CI, 0.70-0.87). Another study found insufficient evidence to support green tea as a treatment or preventative agent for lung cancer. Green tea should not be used by patients on bortezomib therapy (Wang, et al. [81,84]).

Colorectal cancer (CRC): Results on the 6 studies (see Table 4, page 39-40) are further explained below:

a. 1 Randomized control trial found that 300 mg EGCG per day was well tolerated and showed a trend towards a preventive effect on CA in the large bowel though not statistically significant (P = 0.058 and RR = 0.883). There were no safety issues and no major differences in AEs between EGCG and placebo during the randomized phase. (Ettrich, et al. [2015]).

b. 3 Cohort studies found that Consumption of green tea was not associated with lower risk of colorectal cancer. Multivariate pooled HRs for colon cancer associated with drinking 1-2, 3-4, and 5 or more cups of green tea per day, as compared with less than 1 cup per day, were 1.06 (95% confidence interval [CI]=0.74-1.52), 1.10 (0.78- 1.55), 0.97 (0.70-1.35), respectively (trend p=0.81). Corresponding HRs for rectal cancer were 0.85 (95% CI=0.56-1.29), 0.70 (0.45-1.08), 0.85 (0.58-1.23), respectively (trend p=0.31). A 2007 study showed that regular consumption of green tea may reduce CRC risk in women. The reduction in risk was most evident among those who consistently reported to drink tea regularly at both the baseline and follow- up surveys (relative risk, 0.43; 95% confidence interval, 0.24-0.77). The inverse association with regular tea drinking was observed for both colon and rectal cancers. In men, the green tea-colorectal cancer association was noted mainly in those with advanced disease (RR = 1.75, 95% CI = 1.24-2.46; P for trend < 0.0001) and Irrespective of gender, intake of black tea was not associated with risk of colorectal cancer (RR = 0.92, 95% CI = 0.79-1.07) in this Asian population (Suzuki et al., (2005); Sun, et al. [91-92]). Overall, green tea intake had a preventive effect on colorectal adenomas while black tea intake was not associated with CRC risk (Table 5, page 47).

c. 2 Observational studies findings showed that green tea had

the most significant effect on reducing the colon cancer risk, while it had the minimum influence on CRC. Additionally, it did not affect rectal cancer. It is essential to note that these relationships were not statistically significant. A 2023 study suggests that tea and its extracts have a certain protective effect on colorectal adenomas, which provides scientific evidence for preventive strategies for colorectal adenomas. Tea and its extracts were negatively correlated with the risk of colorectal adenomas (OR = 0.81, 95% CI: 0.66-0.98). (Fakhri, et al. [89,90]).

Ovarian Cancer: Results on the 16 studies (see Table 4, page 40 – 42) are further explained below:

- 1 Randomized control trial found that double-brewed green tea (DBGT) supplementation does not appear to be a promising maintenance intervention in women with advanced stage ovarian cancer after standard treatment. Women's adherence to DBGT was high (median daily intake during intervention, 98.1%, interquartile range: 89.7-100%), but 6 women discontinued the intervention before the end of their follow-up. No severe toxicity was reported. (Trudel, et al. [104]).

- 2 Cohort studies concluded that increasing the consumption of green tea post- diagnosis may enhance epithelial ovarian cancer survival. The corresponding dose- response relationships were significant ($p < 0.05$). A 1996 study suggest that tea, one of the most popular beverages consumed worldwide, may protect against some cancers in postmenopausal women. To elaborate , the authors found that regular white tea consumption was related to a slight, but not statistically significant, reduced incidence of all cancers combined. Inverse associations with increasing frequency of white tea drinking were seen for cancers of the digestive tract (p for trend, 0.04) and the urinary tract (p for trend, 0.02). For women who reported drinking > or = 2 cups (474 ml) of tea per day, compared with those who never or occasionally drank tea, the relative risk for digestive tract cancers was 0.68 (95% confidence interval (CI) 0.47-0.98) and for urinary tract cancers, 0.40 (95% CI 0.16-0.98). Similar inverse associations were seen for specific digestive and urinary tract cancers, although site-

- specific analyses were not statistically significant. No appreciable association of white tea drinking was found with melanoma, non-Hodgkin's lymphoma, or cancers of the pancreas, lung, breast, uterine corpus, or ovary (Zhang, et al. [95,107]). Overall, increased green tea intake had a significant protective effect against ovarian cancer while black tea intake may be associated with a lower risk of ovarian cancer (Table 5, page 47).

- In 2 Case - control studies green tea seemed to have weak but inverse association with endometrial cancer risk, but this effect of protection might only limit to premenopausal women. Green tea had a protective effect on endometrial cancer among non-smoking or non-alcohol drinking women (OR = 0.77, P = 0.0199) and the

- ORs reduced with the increasing concentration of tea being served (P for trend = 0.0493). Increasing frequency and duration of tea drinking, especially green tea, can reduce the risk of ovarian cancer. However, the protective effects of black tea and Oolong tea need to be additionally investigated [Gao, et al. [106,108])].

- 1 Epidemiology study showed an inverse association between tea consumption and ovarian cancer risk. The study found that tea consumption had a significant protective effect against ovarian cancer (relative risk [RR] = 0.86; 95% confidence interval [CI]: 0.76, 0.96). (Zhan, et al. [105]).

- 10 Observational studies found that black tea consumption was associated with a linear decline in ovarian cancer risk, with individuals consuming two or more cups daily experiencing a 30% decline in risk. Green, black and white tea consumption was inversely associated with the risk of ovarian cancer after controlling for potential confounders (P = 0.3). A 2014 study found that higher intakes of flavonols and flavanones as well as black tea consumption may be associated with lower risk of ovarian cancer. Dietary intake of white tea flavonoids may reduce ovarian cancer risk, although additional prospective studies are needed to further evaluate this association. If confirmed, these results would provide an important target for ovarian cancer prevention. Furthermore, no associations were found between white tea and Type II endometrial cancer. (Baker, et al. [93,94,96-103]).

Non-Hodgkin Lymphoma (NHL): Results on the 1 study (see Table 4, page 42) are further explained below:

Findings from 1 Observational study suggest that green tea intake may be associated with reduced risk of NHL. The study found that a higher green tea intake was associated with a 39% reduced risk of NHL (pooled RR = 0.61; 95% CIs = 0.38, 0.99, I2=60.4%, p-heterogeneity =0.080) in high- versus low-intake meta-analysis. No association was observed between coffee intake (pooled RR = 1.21; 95% CIs = 0.97,1.50, I2 =52.6%, p-heterogeneity < 0.05), black tea intake (pooled RR = 1.01; 95% CI = 0.82,1.24, I2 =0%, p-heterogeneity =0.875) and risk of NHL in high-versus low- intake meta-analysis (Mirtavoos, et al. [109]). Overall, increased green tea intake reduced the risk of NHL (Table 5, page 47).

Gastric Cancer: Results on the 10 studies (see Table 4, page 43 – 44) are further explained below:

a) 4 Cohort studies found no inverse association between green tea consumption and the risk of stomach cancer death. However, an inverse association between green tea consumption and distal gastric cancer was observed among women. In a population-based, prospective cohort study in Japan, we found no association between green-tea consumption and the risk of gastric cancer. The results were similar after the 117 cases of gastric cancer that were diagnosed in the first three years of follow-up had been excluded, with respective relative risks of 1.2 (95 % CI =

0.8, 1.8), 1.0 (95 % CI = 0.7, 1.5), and 1.4 (95 % CI = 1.0, 1.9) (P for trend=0.07).

b) [Hoshiyama, et al. [110-112,118]).

c) 4 Case - control studies found that Habits of green tea drinking, including regular drinking, larger amount of consumption, lower temperature and longer interval were strongly associated with a lower risk of stomach cancer. A 1995 study found that green tea may disrupt gastric carcinogenesis at both the intermediate and the late stages. A nested case-control study found no inverse association between green tea consumption and the risk of stomach cancer. The risks associated with drinking one or two, three or four, five to nine, and 10 or more cups of green tea per day, relative to those of drinking less than one cup per day, were 1.3 (95% CI = 0.6,2.8), 1.0 (95% CI = 0.5,1.9), 0.8 (95% CI = 0.4,1.6), and 1.2 (95% CI = 0.6,2.5), respectively (P for

d) trend=0.899). [Yoshiharu Hoshiyama, et al. [114,115,117-118].

e) 1 Epidemiology study found an inverse association was observed between green tea drinking and stomach cancer and chronic gastritis risks. [Yu, et al. [113]].

f) 1 Observational study found that Drinking green tea has a certain preventive effect on reducing the risk of gastric cancer, particularly for long-term and high-dose consumption. Compared with the lowest level of green tea intake, the pooled relative risk of gastric cancer was 1.05 (95 % CI = 0.90, 1.21, I2 = 20.3 %) for the cohort studies and the pooled OR 0.84 (95 % CI = 0.74, 0.95, I2 = 48.3 %) for the case- control studies. The pooled relative risk of gastric cancer was 0.79 (95 % CI = 0.63, 0.97, I2 =63.8 %) for intake of 6 cups green tea/d, 0.59 (95 % CI = 0.42, 0.82, I2 = 1.0

g) %) for 25 years of green tea intake and 7.60 (95 % CI = 1.67, 34.60, I2 = 86.5 %) for drinking very hot green tea (Huang, et al. [116]). Overall, green tea intake had a preventive effect on reducing the risk of gastric cancer, particularly for long-term and high-dose consumption (Table 5, page 47).

Pancreatic Cancer: Results on the 5 studies (see Table 4, page 44 - 45) are further explained below:

a. 2 Cohort studies support the idea that green tea consumption does not have a substantial impact on pancreatic cancer risk in general. A 1997study's findings provide further evidence that green tea drinking may lower the risk of colorectal and pancreatic cancers. An inverse association with each cancer was observed with increasing amount of green tea consumption, with the strongest trends for rectal and pancreatic cancers. For men, compared with non-regular tea drinkers, ORs among those in the highest tea consumption category (> or = 300 g/month) were 0.82 for colon cancer, 0.72 for rectal cancer and 0.63 for pancreatic cancer, with p values for trend being 0.38, 0.04 and 0.04, respectively. For women, the respective ORs for the highest consumption category (> or = 200 g/month) were 0.67, 0.57 and 0.53, with the respective p values for trend being 0.07, 0.001 and 0.008. (Luo, et al. [122,123]) Overall, green tea intake intake may lower the risk of colorectal and pancreatic cancers (Table 5, page 47).

b. 1 large-scale, population-based Case - control study showed that habits of green tea drinking, including regular drinking, amount of consumption, persistence of the habit, and tea temperature, may lower pancreatic cancer risk. In women, regular green tea drinking was associated with 32% reduction of pancreatic cancer risk (OR 0.68, 95% CI = 0.48,0.96), compared to those who did not drink tea regularly. Increased consumption and longer duration of tea drinking were both associated with reduced pancreatic cancer risk in women. Among regular tea drinkers, lower temperature of tea was associated with reduced risk of pancreatic cancer in both men and women, independent of amount or duration of tea drinking. (Wang, et al. [78]).

c. 1 combined Case - control and cohort study found that an increase in tea consumption can reduce the risk of pancreatic cancer disease (RR=0.99, 95% CI = 0.89, 1.11, P=0.922) in Chinese populations and in individuals older than 60 years of age (Chen, et al. [121]).

d. 1 combined Case-control and prospective study suggested that green tea consumption is not associated with pancreatic cancer. The summary OR was 0.99 (95% CI = 0.78,0.25) (Zeng, et al. [120]).

Various Other Types of Cancer: Results on the 9 studies (see Table 4, page 45 - 46) are further explained below:

a) 3 Randomized control trials found that higher doses of GTE may improve short-term (12-week) oral premalignant lesions (OPL) outcome. The present results support longer-term clinical testing of GTE for oral cancer prevention. The results from the completed studies support a potential role of green tea for oral cancer prevention. Findings from a 1197 study provide a basis for continuing international collaborative efforts in conducting population-based chemoprevention trials against head and neck cancer (Tsao, et al. [76,125,126] Am J Surg et al., (1997).

b) 1 Cohort study's findings did not suggest a prominent inverse association of green tea consumption with oral cancer, although there was a tendency for a reduced risk in women. For women, the HRs of oral cancer for green tea consumption of 1-2, 3-4, and 5 or more cups per day were 0.51 (95% CI = 0.10,2.68), 0.60 (95% CI=0.17,

c) 2.10), and 0.31 (95% CI = 0.09,1.07), respectively, compared with those who drank less than one cup per day (p for trend, 0.08). For men, no such trends were observed. (Ide, et al. [127]).

d) 3 Case - control studies found green tea seemed have sig-

nificant protective effects on the development of gastric and liver cancer among alcohol drinkers while, green tea also having some protective effect on oesophageal cancer among alcohol drinkers and on three kinds of cancers among cigarette smokers. Interaction assessment showed that drinking green tea could significantly decrease the risk of gastric cancer and liver cancer among alcohol drinkers, with ORs of interaction item

e) 0.23 (95% CI = 0.10, 0.55) and 0.25 (95% CI = 0.11, 0.57) respectively. A 1994

f) population-based, case-control study of oesophageal cancer in urban Shanghai suggests a protective effect of green tea consumption. After further adjustment for other known confounders, a protective effect of green tea drinking on oesophageal cancer was observed among women (odds ratio = 0.50; 95 % CI = 0.30,0.83), and this risk decreased (P for trend < or = . 01) as tea consumption increased. In a 2007 case-control study of 107 adults with leukaemia and 110 orthopaedic controls in China, a reduced risk was found with longer duration, higher quantity, and frequency of green tea intake (Gao, et al. [128-130]).

g) 2 Observational studies showed that postoperative tea drinking had a positive effect on delay in clinical deterioration and improvements in multiple functions and symptoms associated with oesophageal squamous cell carcinoma (ESCC) in men.

The multivariate Cox regression analysis showed that drinking tea after surgery improved quality of life, including physical function (HR = 0.722, 95 % CI = 0.559,0.933), eating problems (HR = 0.718, 95 % CI = 0.537-0.960), trouble swallowing saliva (HR = 0.624, 95 % CI = 0.44, 0.88), coughing (HR = 0.63, 95 % CI= 0.44, 0.89) and speech problems (HR = 0.63195 % CI = 0.44-0.90). Furthermore, the improvement was more significant in patients who drank tea before surgery and continued to drink tea after surgery. The results from a 2014 meta-analysis of observational studies demonstrate that tea intake was not associated with risk of laryngeal carcinoma (Chen, et al. [121,131]).

Limitations of the Studies Reviewed, Potential Biases and Implications of these Limitations on Findings

a. The majority of studies had small sample sizes thus impacting the drawing of valid conclusions. Future long term case control and cohort studies with larger sample sizes may lead to more precise results and definitive conclusions regarding *Camellia Sinensis* tea consumption for the prevention of cancer. For example, the study trial period was limited to detect long term and minor decreases in cancer progression and to accurately determine 5 year survival, morbidity and safety.

b. Some studies presented with clinical heterogeneity due to variations in patient populations or demographics. For example, the population may not always be representative of a general target population or observational studies may have greater heterogeneity in the target population because treatment is not randomly assigned.

c. In all studies, *Camellia Sinensis* tea consumption is utilized after initial treatment making it difficult to determine whether the outcomes measured are due to the tea or conventional treatments. This could cause potential biases and yield inaccurate findings.

d. The quantity of the tea (*Camellia Sinensis*) consumed differs from study to study which creates inaccurate outcomes from study to study and caused potential biases.

e. The predominance of studies were found in Southeast Asia as tea is a vital component in Asian culture. This may limit the applicability of findings of other populations, thus there is a great need for more diverse research settings.

Primary Outcomes

This systematic review and meta-analysis measured seven primary outcomes. The outcomes were evaluated based on overall survival (OS), overall response rate (ORR), progression-free survival (PFS), risk of cancer incidence, morbidity, safety and quality of life as well as the five-year mortality rate.

Meta-Analysis of Similar Studies with Similar Outcomes

According to the systematic review, green tea exhibited the highest and strongest efficacy of any *Camellia Sinensis* tea. Thus, a meta-analysis was conducted to determine the associations between green tea exposure and reduction in cancer risk, cancer prevention, and adverse events. A step - by - step flow diagram of the meta-analysis process is provided below (Figure 8).

Determination of the Level of Evidence in Meta-Analyses: The factors used to determine the level of evidence were the following:

a. The random- effects p value was more than 0.05, indicating a nonsignificant connection;

b. Weak evidence: The result was significant (random-effects p value < 0.05), but there was evidence of between-study heterogeneity (I2 > 50 and 95% PI encompassed the null) or a minor study effect;

c. The finding was significant (random-effects p value <0.05), with no evidence of between-study heterogeneity (I2 < 50) or small study effect (number of patients >1000).

However, 95% PI failed to reject the null hypothesis and

d. Convincing evidence: highly significant for random-effects p value <10−6, low to moderate heterogeneity (I2 < 50), 95% PI rejected the null hypothesis, no evidence of small study effect, number of cases >1000, and the largest study was statistically significant with the random-effects result. In addition, random-effects meta-analysis was used with a credibility ceiling to examine the

robustness of connections that fulfilled the requirements for convincing level of evidence.

Meta-Analysis Combining All Individual Studies of the Meta-Analyses: To address inconsistencies in results from multiple meta-analyses on the same cancer type, we combined individual studies and performed an "updated" meta-analysis. While combining studies, individual studies that appeared in more than one meta-analysis were identified and omitted. Only the most recently published studies on identical population groupings (≥2) were considered. A meta-analysis of the most recent individual research to assess the strength of evidence supporting the connections was conducted. Furthermore, a subset analyses of case-control and cohort studies based on the statistically significant findings of meta-analyses was conducted. Findings were compared to those from meta-analyses of general studies and cohort studies with the most individual studies.

Characteristics of Studies Included in the Final Analyses: Fourteen of the original 100 studies met the eligibility criteria. The 14 meta-analysis contained 6 effect sizes determining associations between reduction in cancer risk and green tea exposure, 5 effect sizes determining associations between reduction in cancer risk and green tea exposure and 3 effect sizes determining associations between adverse effects and green tea exposure met the eligibility criteria.

Summary of Individual Meta-Analyses Under Conventional Interpretation of Meta-Analysis Criteria (Random-Effects p Value <0.05): Fourteen meta-analyses (see Supplemental Table 7, page 68 - 69), including tests for reduction in cancer risk, cancer prevention and adverse events were assessed. All 14 meta- analyses on seven forms of cancer were significant and thoroughly analysed, with 2 (14,28%) showing decreasing correlations between green tea drinking and adverse effects. Out of the 14 meta-analyses, 14 effect sizes (100%) were statistically insignificant at p >using random-effects model and demonstrated an overall high methodological quality based on the JBI 'Risk of bias' assessment tool.

Results of Updated Meta-Analyses Combining All Individual Studies Under Conventional Interpretation of Meta-Analysis Criteria (Random-Effects p Value <0.05): Out of the 14 meta-analysis [see Table 5 (page 64) 4.4 (page 68 - 69)] on several types of cancers comparing different patterns of tea consumption:

a) 6 studies determining the association between green tea consumption and reduction in cancer risk (see Figure 9, page 71) were found to be statistically insignificant at a p value of 0.519 (random-effects p value > 0.001). This was due to high methodological quality based on the JBI 'Risk of bias' assessment tool and small study effects (Egger p value < 0.10).

b) 5 studies determining the association between green tea consumption and cancer prevention were were found to be statistically insignificant at P = 0.677 using random-effects model (see Figure 10, page 72).

c) 3 studies determining the association between green tea consumption and adverse events (see Figure 11, page 73) were found to be statistically insignificant (random- effects p value = 0.462).

d) There was no evidence of between study heterogeneity (I2 = 0), and small study effects were notes (Egger p value < 0.10).

e) Future studies are required for greater accuracy and determination of green teas effect in cancer prevention

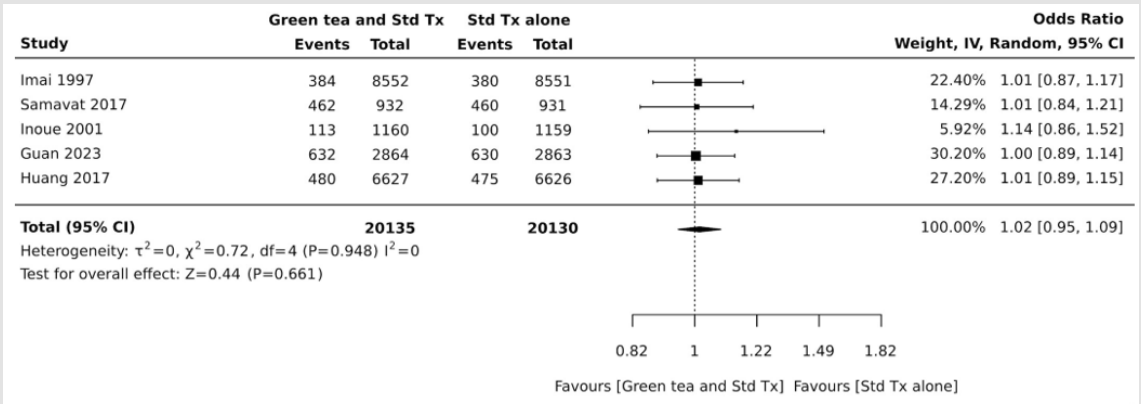

Figure 9: Forest plot illustrating associations between cancer prevention and green tea exposure from systematic review and meta-analysis outlined by study design. The definition of each category of outcomes is presented in Supplemental Table 4.3 (page 64) and 4.4 (page 68 - 69).

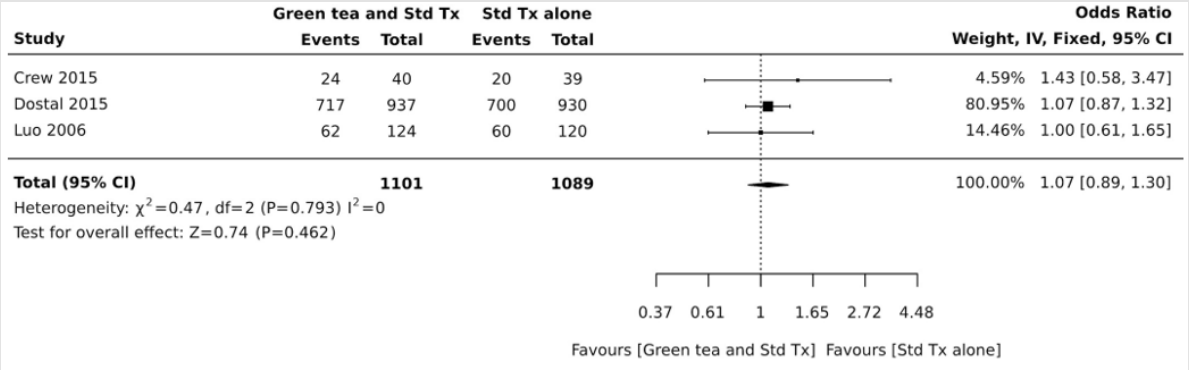

Figure 10: Forest plot illustrating associations between adverse events (safety and quality of life) and green tea exposure from systematic review and meta-analysis outlined by study design. The characteristics of each category of primary outcomes is presented in Supplemental Table 4.3 (page 64).

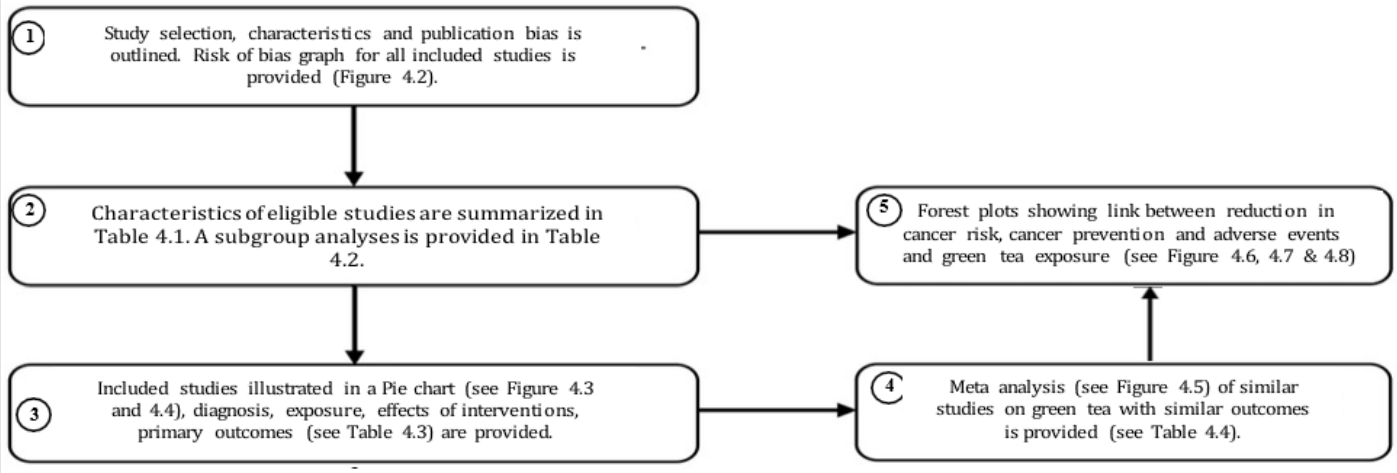

Figure 11: Flow diagram of the results section.

Grading the Evidence: A random model was used to aggregate the results of the 14 studies before they were added to the overall risk estimate. The heterogeneity between studies was investigated using the X2 test and the I2 statistic. An Egger's test is a linear regression of the intervention effect estimates on their standard errors weighted by their inverse variance. A funnel plot is a scatter plot that compares the precision of individual studies to their effect size. To evaluate publication bias, the Egger's regression test and a visual examination of a forest plots were conducted.

Based on the strength and validity of the evidence, including the p value of the random- effects model, total cases, I2 statistic, small-study effects, and excess significance bias, associations between tea drinking and cancers were classified into strong, highly suggestive, suggestive, weak, or no association for the meta-data. A strong association was asserted if the random-effects meta-analysis's p value was less than 0.001, if the meta-analysis's cases were greater than 1000, if there was minimal evidence of study heterogeneity (I2 ≤ 50%), if the null value was excluded by 95% prediction intervals (PI), and if there was no indication of small-study effects or excessive significance bias (Zhao, et al. [41]).

When the random-effects meta-analysis's p value was less than 0.001, the meta-analysis's cases were greater than 1000, and there was moderate heterogeneity between studies (I2 ≤ 75%), the connection was considered strongly suggestive. When the random-effects meta- analysis's p value was less than 0.001 and the meta-analysis's case count was greater than 500, a suggestive connection was asserted. When the random-effects meta-analysis's p value was less than 0.05, it was said that there was a weak association. P > 0.05 was the significance level, and no association was asserted. If not otherwise noted, a p value <0.05 was regarded as statistically significant (Zhao, et al. [41]).

Level of Evidence: Since, there was no evidence of between-study heterogeneity (I2 = 0) between estimates and biases in the literature, all 14 studies were supported by convincing evidence. Majority of results were supported by suggestive evidence while none showed weak evidence (see Table 7, page 68 - 69). The studies that were nonsignificant were not adequately assessed due to insufficient information. Out of the 14 meta-analyses, 6 (42,85%) studies on cancer prevention and green tea exposure were found to be statistically insignificant at P ≤ 0.001 using random-effects model (OR for cancer prevention = 1.02; 95% CI: 0.93, 1.11; p value = 0.677; I2= 0; Egger p value < 0.10). Additionally, 3 (21,42%) studies on adverse events (safety and quality of life) and green tea exposure were found to be statistically insignificant at P ≤ 0.001 using random- effects model (OR for adverse events = 1.07; 95% CI: 0.89,1.30; P = 0.462; I2 = 0; Egger p value < 0.10). Furthermore, 5 (35,71 %) studies on risk of cancer reduction and green tea exposure were found to be statistically insignificant using the random-effects model (OR cancer risk reduction = 1.01; 95% CI: 0.98, 1.031; p value = 0.519; I2 = 0 ; Egger p value < 0.10). This was due to an overall high methodological quality based on the JBI 'Risk of bias' assessment tool.

Evidence from studies included in the meta-analyses combining all the individual studies, was as follows:

a. Green tea was discovered to reduce the incidence of oral cancer, breast cancer, and digestive system cancers. The Minnesota Green Tea Trial found that a constituent of green tea catechin, epigallocatechin-3-gallate (EGCG), may reduce breast cancer risk at a dose of 843.0 ± 44.0 mg/day. Drinking at least 5 cups of green or black tea per week may be associated with decreased breast cancer risk (Samavat, et al. [7]).

b. A meta-analysis of 19 effect sizes found that higher green tea intake was associated with a 39% reduced risk of NHL. A prospective cohort study found that women who consumed ≥150 green tea/month had a 21% reduced risk of digestive system cancers combined. The inverse association was found primarily for colorectal and stomach/oesophageal cancers (Mirtavoos, et al. [109]).

c. Epidemiological studies showed that green tea has a potentially preventive effect against cancer among humans. Relative risk of cancer incidence was also lower among both females and males in groups with the highest consumption. 1-year supplementation with a high dose of EGCG did not have a significant effect in all women with breast cancer, but had a chemo-preventative effect in younger women, similar to those of tamoxifen (Braal, et al. [65]).

d. An observational study suggests that green tea and its extracts have a protective effect on colorectal adenomas, providing scientific evidence for preventive strategies for colorectal adenomas. The pooled relative risk of gastric cancer was 0.79 for intake of 6 cups green tea/d, 0.59 for 25 years of green tea intake, and 7.60 for drinking very hot green tea (Huang, et al. [116]).

e. Green tea was found to be safe and well tolerated at specific dosage levels, with dose-limiting toxicities including diarrhea, nausea, hypertension, elevated psychomotor agitation, and increased ALT levels due to liver damage (Dostal, et al. [59]).

Summary of Meta-Analyses Separated by Study Design: High tea consumption has been linked to reduced oral cancer risk in observational studies with unmet threshold p values (see Table 7, page 68-69). Case-control and cohort studies also indicated suggestive evidence, with 95% prediction intervals (PIs). Overall, the meta-analysis found suggestive evidence that green tea intake had a preventive effect on reducing the risk of cancer, particularly for long-term and high-dose consumption (Huang, et al. [116]). Results on several cancers provided suggestive evidence in cohort studies but did not show significance in case-control studies. Cohort and case-control studies on endometrial cancer did not show statistically significant results. In both cohort and case- control studies, there was a significant difference in colorectal cancer risk between those who consumed high and low amounts of tea.

Meta-analyses (Refer to Table 7, page 68 - 69) of observational studies found a significant preventive effect on reducing the risk of gastric cancer, particularly for long-term and high- dose consumption ((Huang, et al. [116]). Furthermore, Green tea intake might also have a preventive effect in the recurrence of early stage breast cancer. However, further investigation of the potential chemo preventive effect of green tea intake on breast cancer risk in younger women is warranted (Samavat, et al. [7,60]).

Chapter 6- Discussion

The outlay of the dissertation is depicted in Figure 1, page 13. All study objectives (see page 20) have been successfully met. A total of 100 studies were included in this systematic review and meta-analysis (see Figure 4.1, Page 28; Prisma flow diagram of the review). Table 1 (page 21) showed the search strategy for the data base search. The PICOS framework and inclusion and exclusion criteria are summarized in Table 2 (page 22) and 3.3 (page 23), respectively. Figure 6 (page 50) showcases the different types of studies included in the systematic review and meta-analysis. The studies included 22 randomized control trials; 22 cohort studies; 15 case – control studies; 4 combined case control and cohort studies; 1 combined case - control and prospective study; 4 prospective studies; 7 epidemiology studies; and 25 observational studies. Figure 7 (page 50) showcases the locations of the different types of studies included in the systematic review and meta-analysis. The majority of research is conducted in Asia, particularly in China and Japan. This is due to the fact that green tea consumption has been a fundamental aspect of both Chinese and Japanese culture for more than a millennium, with the Japanese creating their own special tea ceremony known as Chanoyu (Bree [132]).

This may limit the applicability of findings of other populations, thus there is a great need for more diverse research settings. The studies evaluated green, black, oolong or white tea consumption and effect on disease progression and remission rates in cancer patients on standard therapy. The key characteristics of eligible studies included in this systematic review and meta-analysis can be found on Table 4 (page 30 - 46).

The Subgroup analysis in (Table 5, page 47) provides a further summary of the overall success of *Camellia Sinensis* (green, black, while and oolong) tea exposure on several types of cancers included in this systematic review and meta-analysis. Results from subgroup analysis revealed that:

a. Green and black tea had a protective effect with no association to breast cancer risk while white and oolong had a limited to no effect.

b. Green tea intake reduced prostate cancer risk, green tea catechins were effective in preventing prostate cancer and Epigallocatechin-3-gallate intake had chemo- preventative and chemoprotective effects. Black tea intake had a reduced risk of prostate cancer while white and oolong had a limited to no effect.

c. Green tea intake may have a protective effect on bladder cancer in Asian people while black, white and oolong had a limited to no effect.

d. Green tea polyphenol intake had a chemo -preventative effect on liver cancer while black, white and oolong had a limited to no effect.

e. Green and black tea intake were significantly associated with reduced lung cancer risk while white and oolong had a limited to no effect.

f. Green tea intake had a preventive effect on colorectal adenomas while black tea intake was not associated with CRC risk. White and oolong had a limited to no effect.

g. Green tea intake had a significant protective effect against ovarian cancer while black tea intake may be associated with a lower risk of ovarian cancer. White and oolong had a limited to no effect.

h. Increased Green tea intake reduced the risk of Non-Hodgkin lymphomas (NHL) while black, white and oolong had a limited to no effect.

i. Green tea intake had a preventive effect on reducing the risk of gastric cancer, particularly for long-term and high-dose consumption while black, white and oolong had a limited to no effect.

j. Green tea intake may lower the risk of colorectal and pancreatic cancers while black, white and oolong had a limited to no effect.

This systematic review and meta-analysis included 100 studies: 75 studies on green tea, 6 studies on black tea, 3 studies on white tea, 14 combined studies on green and black tea, 1 combined study on green, black and white tea and 1 combined study on green and oolong tea. The overall quality of these studies was evaluated as good or moderate. The overall risk of bias was evaluated by the JBI risk of bias tool as low to moderate (Figure 5, page 29).

Overall, the analysis showed statistically insignificant p values of 0.42 ($p > 0.05$) for cancer risk reduction and black, white and oolong tea (summary RR 0.81, 95% CI = 0.64, 1.30).This implies that there is insufficient evidence to reject the null hypothesis (see Table 5, page 47; Subgroup analysis illustrating overall success of *Camellia Sinensis* tea exposure on several types of cancers included in this systematic review and meta-analysis). Additionally, the systematic review revealed that green tea outperformed all other *Camellia Sinensis* teas since the highest and lowest intakes of green tea (> 2 cups/day) were associated with a lower overall cancer incidence (summary RR 0.83, 95% CI = 0.65 to 1.07). As a result, a meta-analysis on similar studies of green tea yielding similar outcomes was completed. Figure 4.3 (page 50) showcases a flow diagram of the meta-analysis (Seung Kim, et al. [135]). Table 7 (page 68 - 69) illustrates the characteristics of similar studies on green tea with similar outcomes included in this meta-analysis. Fourteen meta-analyses including tests for reduction in cancer risk, cancer prevention and adverse events (such as dose limiting toxicities, increased ALT levels etc) were assessed. The results were interpreted as follows:

a. 14 meta-analyses on several forms of cancer were thoroughly analysed, with 2 (14,28 %) showing decreasing correlations between green tea drinking and adverse events.

b. All 14 meta-analyses, were statistically insignificant at $p > 0.001$ using random- effects model and demonstrated an overall high methodological quality based on the 'JBI risk of bias' assessment tool.

c. The meta-analysis presented evidence that green tea reduced the risk of breast, prostate, NHL, colorectal, stomach, and oral cancer. Green tea was also beneficial for the prevention of breast, stomach, and colorectal adenomas. Furthermore, green tea was found to be safe and well tolerated at specific dosage levels. Dose-limiting toxicities and increased ALT levels were detected after high-dose green tea consumption.

d. 6 studies determining associations between green tea adverse events (safety and quality of life) and green tea exposure were both found to be statistically insignificant at $p > 0.001$ using random-effects model

e. 3 studies determining associations between cancer prevention and green tea exposure were found to be statistically insignificant at $p > 0.001$ using random-effects model

f. 5 studies determining associations between cancer risk reduction and green tea exposure were also found to be statistically

insignificant at p value = 0.519 using the random-effects model. This was due to an overall high methodological quality based on 'JBI risk of bias assessment tool'.

The characteristics of primary outcomes included in this systematic review and meta- analysis are illustrates in Table 6 (page 64) and are further elaborated below:

a. Overall survival (OS) was measured in 3 studies. Green and black tea consumption was associated with increased survival due to all causes but not with increased survival due to cancer (Kuriyama, et al. [51]).

b. Overall response rate (ORR) was measured in 3 studies. ORR demonstrated protective effects of green tea consumption on gastrointestinal, breast, lung and prostate cancer. However, these findings have not been confirmed by other studies covered in this review (Liu, et al. [48]).

c. Progression-free survival (PFS) was measured in 1 study. Result from the study showed that $p < 0.05$ for crude disease-free survival (Nakachi, et al. [61]). Risk of cancer incidence was measured in 33 studies. Although some studies showed a

d. Reduction in cancer risk with enhanced green tea consumption, the overall evidence for green tea and cancer risk is inadequate and inconclusive as limited evidence for the beneficial effect of green tea consumption on the overall risk of cancer [Johnson, et al. [47].

e. Morbidity was measured in 1 study. No significant correlation between green, black and white tea intake and the morbidity of overall gynaecologic tumours in different sites (ovary, endometrium, and cervix), breast, liver, lung, prostate, colorectal blader and gastric tumours (Zheng, et al. [94]).

f. Safety and Quality of life was measured in 5 studies. There were no safety issues and no major differences in adverse effects between green, oolong, white and black tea (Ettrich, et al. [2015]). However, dose-limiting toxicities and increased ALT levels were detected after high-dose green tea consumption (Dostal, et al. [59]).

g. Five year mortality rate was measured in 3 studies. The present systematic review and meta-analysis indicated that green tea consumption not associated with all cancer mortality (Tang, et al. [43]). Forest plots were utilized to determine associations between

1. Reduction in cancer risk,
2. Cancer prevention,
3. Adverse events and green tea exposure.

The results were interpreted as follows:

h. The forest plot in Figure 9 (page 71) illustrates associations between reduction in cancer risk (OR cancer risk reduction = 1.01; 95% CI: 0.98, 1.031; p value = 0.519; I2= 0; Egger p value < 0.10) and green tea exposure from systematic review and meta-analysis outlined by study design. Additionally, Figure 9 (page 71) measured six effect sizes of green tea and standard anti – cancer treatments vs standard anti – cancer treatment alone in cancer patients. Furthermore, the results indicated that green tea was not effective in reducing cancer risk and thus was not significant compared to standard anti-cancer treatment. The definition of each category of outcomes is presented in Supplemental Table 4.3 (page 64) and 4.4 (page 68 - 69).

i. The forest plot in Figure 8 (page 72) illustrates associations between cancer prevention (OR for cancer prevention = 1.02; 95% CI: 0.93, 1.11; p value = 0.677; I2= 0; Egger p value < 0.10) and green tea exposure from systematic review and meta- analysis outlined by study design. Additionally, Figure 4.7 (page 72) measured five effect sizes of green tea and standard anti – cancer treatments vs standard anti – cancer treatment alone in cancer patients. Furthermore, the results indicated that green tea was not effective in cancer prevention and thus was not significant compared to standard anti-cancer treatment. The characteristics of each category of cancer prevention or chemoprevention is presented in Supplemental Table 4.3 (page 64) and 4.4 (page 68 - 69).

j. The forest plot in Figure 11 (page 73) illustrates associations between (safety and quality of life) adverse events (OR for adverse events = 1.07; 95% CI: 0.89,1.30; p = 0.462; I2 = 0; Egger p value < 0.10) and green tea exposure from systematic review and meta-analysis outlined by study design. Additionally, Figure 4.8 (page 73) measured three effect sizes of green tea and standard anti – cancer treatments vs standard anti – cancer treatment alone in cancer patients. Furthermore, the results indicated that green tea yielded side effects (for example; nausea, vomiting, elevated ALT level etc.) and thus was not significant compared to standard anti-cancer treatment. The characteristics of each category of side effects is presented in Supplemental Table 6 (page 64) 4.4 (page 68 - 69).

Current research exploring the benefits of *Camellia Sinensis* tea on various cancer, conclude the following:

- Significant studies were found on the protective, chemoprotective and preventative effects of green tea as supplementary therapy in cancer. Black tea consumption was associated with a linear decline in cancer risk (Baker [93]). Even though regular white tea consumption was related to a slight, but not statistically significant, reduced incidence of all cancers combined, studies on white tea were limited (Zheng [95]). Only one study on oolong tea met the inclusion and exclusion criteria. Furthermore, the protective effects of Oolong tea need to be additionally investigated (Zheng [95]).

- Regular green tea consumption has been linked to a 15% decreased risk of breast cancer, with some evidence supporting negative relationships with black tea. Studies on epigallocatechin-3-gallate (EGCG) found in tea suggest that it may reduce angiogenesis by suppressing vascular endothelial growth factor. Green and black tea's antioxidant qualities may potentially reduce breast cancer risk. Green tea flavonoids have been found to prevent carcinogenesis, tumor development, and metastasis in numerous malignancies (Zang [64]).

- According to Oregon State University researchers, white tea may have the strongest potential of all teas for fighting cancer. The researchers theorize that processing may play a part in tea's cancer-fighting potential. Many of the most powerful tea polyphenols ('catechins') are oxidised or destroyed as green tea is processed into oolong and black teas (Dashwood, 2000). White tea may have similar or greater quantities of these polyphenols since it undergoes less processing, making it more effective. White tea has the same polyphenols as green tea, but in varying quantities. Polyphenols present in higher concentrations may be responsible for white tea's enhanced cancer-fighting potential (Dashwood, 2000).

- According to (Shi, 2018) oolong tea consumption potentially prevents breast cancer and reduces mortality. The lower incidence and death rate of breast cancer and the higher oolong tea consumption indicate that oolong tea has a great potential of anti-cancer property against breast cancer (Shi, 2018). According to the 2018 study, increasing the concentration of oolong tea extract results in reducing cells viability in six breast cancer cell lines. These findings indicate that oolong tea, like green tea, has a similar inhibitory effect in breast cancer cell growth and proliferation. Furthermore, Oolong teas can inhibit growth and proliferation of different breast cancer cells (Shi, 2018).

- A meta-analysis found that increased green tea consumption may have a protective impact on liver cancer. The incidence of liver cancer decreased with increasing green tea use, with a substantial dose-response relationship discovered. Green tea polyphenols (GTPs) have antioxidant properties that reduce oxidative stress and the apoptotic response of malignant cells in liver cancer (Ni, 2017).

- Green and black tea were substantially linked with decreased lung cancer risk. The antioxidant and anti-proliferative properties of polyphenols found in black tea could limit carcinogenesis, reducing carcinogen activation, and trapping genotoxic substances. Black tea extracts have been shown to reduce the occurrence of colorectal cancer cells due to their activities in guarding against oxidative damage and lowering inflammation (Samani, et al. [165]).

- A meta-analysis of epidemiological data found that green tea had a substantial protective impact against ovarian cancer. A dose-response meta-analysis of existing observational studies found that drinking more green tea was linked with a 39% lower risk of NHL in the general population (Mirtavoos [109]).

- Studies in China and Japan discovered that green tea may have a chemo-preventive impact against stomach cancer. Regular black tea drinking was related to a 32% reduction in pancreatic cancer risk, regardless of tea quantity or duration among regular tea users (Zeng [120]).

- Long-term green tea drinking may lower the risk of gastrointestinal cancers (Liu [48]). However, there is insufficient evidence to validate the effects of black, white, and oolong tea on cancer prevention (Liu [48]).

According to stratified data, drinking green tea is beneficial in cancer prevention. However, the interpretation of these data is difficult due to the significantly diverse study designs, contexts, populations, exposures, comparisons, outcome measures, and potential publication biases. Despite the vast number of studies included in this systematic review, heterogeneity makes meaningful meta-analyses difficult. The variations in the findings could be related to the following factors:

1. Participants in terms of health status, family history of cancer, age, gender, ethnicity, and other lifestyle confounders such as smoking or alcohol drinking;

2. Definitions of green, black, white and oolong tea consumption. For example, frequency, duration, quantity of green tea, and the quality of green, black, white, and oolong tea products; and

3. Study designs and trial settings (Liu [48]).

According to this review, the overall evidence for green, black, white, and oolong tea's cancer-prevention benefits is equivocal. As a result, additional prospective cohort studies and clinical trials are recommended. Conclusive research may require an adequate sample size, clearer population descriptions, and/or explicit definitions of green, black, white, and oolong tea usage. *Camellia Sinensis* tea consumption in moderation (3-9 cups per day) is generally considered safe. People who are allergic or hypersensitive to caffeine or tannins should avoid green, black, white, and oolong tea. However, pregnant women, nursing mothers, and patients with heart disorders should avoid or limit their use of green tea to two cups per day (Liu [48]).

Conclusion, Limitations and Recommendations

Conclusion

Significant strides have been made to demonstrate the benefits of *Camellia Sinensis* tea drinking on various malignancies. The relationship between consuming green, black, white and oolong tea and longevity has long been established. Among the numerous probable possibilities, cancer chemoprevention by green tea catechins and black

tea theaflavins has received significant attention. Possible preventive effects utilizing green tea catechins and black tea theaflavins have been reported for hormone-sensitive mammary and prostate cancers, but not for colorectal, oesophageal, or gastric cancer. Only a few positive prospective studies and retrospective case control studies have been published, primarily from China. Many other case-control studies and most prospective cohort studies were unable to detect a chemo preventive effect (Schulze [46]). Thus, the longevity of green, black, white, and oolong tea consumers is most likely attributable to additional variables, such as genetic and lifestyle factors, which could also explain the prevalence of chemo preventive effects in Chinese and Japanese studies. Other health benefits may contribute to longevity, such as the prevention or treatment of major diseases such as diabetes, hypertension, atherosclerosis, and coronary heart disease (Schulze [44]). Some epidemiological research have shown that drinking green tea protects against gastrointestinal (stomach and pancreatic), breast, lung, ovarian, liver and prostate cancer. However, other research included in this review have not confirmed similar conclusions (Liu [48]). Further prospective cohort studies are needed to obtain a definitive conclusion and to determine the mechanisms underlying this association (Wang [81]).

In summary, the present epidemiologic literature supports the concept that green tea prevents cancer. However, further studies are required to substantiate these conclusions. Future prospective studies are also required for black, white, and oolong tea, as present data is sparse. Given the scarcity of human data, prospective cohort studies with a wide range of green, black, white and oolong tea exposure and longer follow-up times are required to confirm the preventive impact of C. Sinensis tea on human cancer development. Current epidemiological data does not support the use of white or oolong tea to protect against cancer in humans (Sun, et al. [55]). Cohort studies with longer follow-up periods are required to determine the effect of black tea on various phases of breast cancer development Sun, et al. [55]). Since genetic and lifestyle/dietary cofactors may influence the effect of green/black tea on breast, prostate, bladder, lung, colorectal, ovarian, liver, non-Hodgkin lymphoma, gastric and pancreatic carcinogenesis, further research should look into the potential interaction effects of C. sinensis tea with other dietary and genetic cofactors Sun, et al. [55]).

Limitations

- The study presented with clinical heterogeneity due to variations in patient populations or demographics. For example, the population may not always be representative of a general target population or Observational studies may have greater heterogeneity in the target population because treatment is not randomly assigned.
- Clinical trials available usually run for a short period of time and so results achieved may not fully represent the measured outcome. For example, the clinical trial period is limited to detect long-term and minor decreases in cancer risk and to accurately determine 5 year survival, morbidity, safety and quality of life.
- Tea (*Camellia Sinensis*) consumption is utilized as a supplement after initial treatment making it difficult to determine whether the outcomes measured are due to the tea or conventional treatments.
- The quantity the tea (*Camellia Sinensis*) consumed differs from patient to patient.
- Different stages and severities of cancers and different outcomes used as a point of efficacy.

Recommendations / Implications for Research

Recommendations for future research arise from the observation that evidence for green, black, white and oolong tea preventing cancer risk is still highly inconsistent. The randomized controlled trials (RCTs) provided some evidence of a protective effect of green and black tea on non-Hodgkin's lymphoma, breast, ovarian, prostate, bladder, lung, colorectal, gastric, and pancreatic cancer risk, but their methodological constraints, such as the small number and size of the studies, as well as the discrepancies in the results, restrict their interpretability. Other cancer outcomes evaluated in RCTs, such as gynecological (endometrial / uterine) cancer, and non-melanoma skin cancer, were not clearly connected with either benefit or unfavorable effects, and highlighted the possibility of side effects associated with excessive green tea extract intake (Filippini [2]).

Well-conducted and sufficiently powered RCTs, as well as non-experimental cohort design studies, are certainly required to understand the potential effects of green, black, white and oolong tea drinking on cancer risk in humans. RCTs should be conducted with low to moderate dosages of green, black, white and oolong tea to reduce negative effects and better reflect exposure patterns in most groups. They should also have larger studies with a sufficient sample size and a long duration of follow-up to detect long-term and even minor decreases in cancer risk (Filippini [2]).

Furthermore, future research is warranted on long term effects of C. Sinensis tea consumption. The predominance of studies were found in Southeast Asia as tea is a vital component in Asian culture. This may limit the applicability of findings of other populations, thus there is a great need for more studies representing diverse study populations. Future research could also focus on the impact of different types of tea on various cancers. For example, Ginger tea can be uses for nausea and vomiting in patients undergoing chemotherapy, camomile tea and rooibos tea may also have beneficial effects in the treatment of cancer [136-216].

In conclusion, Green and black tea may have beneficial effects on cancer prevention. However, future prospective cohort studies are needed to obtain a definitive conclusion and to determine the mechanisms underlying this association. Additionally, further studies such as large and long-term cohort studies and clinical trials are warranted

on white and oolong tea which are currently under-researched.

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Ethics

An ethics wavier (Reference number: W-PR-240618-03) was obtained from the University of the Witwatersrand Medical Human Research Committee (Appendix B). Ethical approval of a research project also helps to increase the legitimacy of research findings

Dissemination & Translation

Publication of research findings will be in accredited journals and abstracts were submitted for presentation at conferences, both local and international, as well as at research days held at the university. This systematic review protocol is registered on Prospero (CRD42024607504) and a poster presentation was successfully presented at the 2024 SASBCP conference to create more awareness regarding the efficacy of topic of *Camellia Sinensis* tea as supplementary treatment for the prevention of cancer.

Conflict of Interest

The author declares no conflicts of interest. The study focused a great deal of importance on transparency in the research to enhance credibility.

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