

Review

# Green Tea and Its Extracts in Cancer Prevention and Treatment

Johannes Schulze <sup>1,\*</sup>, Lena Melzer <sup>1</sup>, Lisa Smith <sup>1</sup> and Rolf Teschke <sup>2</sup>

<sup>1</sup> Institute of Occupational, Social and Environmental Medicine, Goethe-University Frankfurt/Main, Theodor-Stern-Kai 7, D-60590 Frankfurt/Main, Germany; melzerlena@gmail.com (L.M.); smithlisa89@gmail.com (L.S.)

<sup>2</sup> Department of Internal Medicine II, Division of Gastroenterology and Hepatology, Klinikum Hanau, Teaching Hospital of the Goethe-University, Leimenstrasse 20, D-63450 Hanau, Germany; rolf.teschke@gmx.de

\* Correspondence: j.schulze@em.uni-frankfurt.de; Tel.: +49-69-6301-4239; Fax: +49-69-6301-6621

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**Abstract:** Green tea (GT) and green tea extracts (GTE) have been postulated to decrease cancer incidence. In vitro results indicate a possible effect; however, epidemiological data do not support cancer chemoprevention. We have performed a PubMed literature search for green tea consumption and the correlation to the common tumor types lung, colorectal, breast, prostate, esophageal and gastric cancer, with cohorts from both Western and Asian countries. We additionally included selected mechanistical studies for a possible mode of action. The comparability between studies was limited due to major differences in study outlines; a meta analysis was thus not possible and studies were evaluated individually. Only for breast cancer could a possible small protective effect be seen in Asian and Western cohorts, whereas for esophagus and stomach cancer, green tea increased the cancer incidence, possibly due to heat stress. No effect was found for colonic/colorectal and prostatic cancer in any country, for lung cancer Chinese studies found a protective effect, but not studies from outside China. Epidemiological studies thus do not support a cancer protective effect. GT as an indicator of as yet undefined parameters in lifestyle, environment and/or ethnicity may explain some of the observed differences between China and other countries.

**Keywords:** chemoprevention; epidemiology; breast cancer; colorectal cancer; esophageal cancer; gastric cancer; lung cancer; prostatic cancer

## 1. Introduction

The long recognized connection between dietary factors and diseases has resulted in “healthy lifestyles” [1,2]. Primary prevention, e.g., exercise, has reduced cardiovascular mortality; similarly, smoking reduction is successful in the “fight against cancer” [3]. Other health claims, e.g., for herbal extracts, are less well founded. Among these claims for dietary supplements or “health food”, cancer prevention ranks high; different cancer types supposedly are prevented by eating (or avoiding) specific foods [2,4] as suggested by advertisements and publications. A popular book by Miller [5] is entitled “We can win the war against cancer by aggressively pursuing prevention”. Consequently, herbal extracts are marketed as teas (<http://www.canceractive.com>) or tea extracts [6,7] as “health food” or dietary supplements for the prevention and treatment of cancer. Claims extend to green tea (GT) [4,7,8], black tea (BT) [9] and extracts from green tea (GTE) [10]. Whereas green and black tea contain all water soluble components of tea leaves in differing amounts, green tea extract mostly contains catechins and gallic acid, with low amounts of methylxanthines [11–13].

Evidence for the protective role of GT and GTE is often claimed based on data from animal experiments and cell culture data; epidemiological correlation of GT with a variety of different tumor types has been published. All reviews of epidemiological data about the connection between green tea intake and cancer prevention have judged the epidemiological evidence as ambiguous at best, whereas in vitro studies and their reviews usually emphasize the positive green tea effects (e.g., [14]).

### 1.1. Cancer Initiation and Development

Our understanding of cancer development and growth still is limited. Some tumors are clearly induced by exogenous factors (e.g., lung and bladder cancer caused by smoking). Activation of carcinogenic compounds to reactive intermediates by CYP450 has been investigated for some decades. Beginning as early as 1973 [15] modulation of CYP450 activity was studied to explain chemical carcinogenesis and chemoprevention [16–20]. Xenobiotic metabolism is mainly catalyzed by CYP450 isoenzymes, its modulation by tea extracts has been summarized previously [21–25]. However, no direct link between changes in carcinogen metabolism by GT and cancer incidence has been found. Other mechanisms drive tumor promotion, i.e., the accumulation of additional genetic changes necessary for invasion, metastasis or drug resistance [26]. A variety of intracellular signaling factors have been described, with no dominant pathway determined for any cancer type. Modulation of cell signaling by GT and GTE has been published [26–28]; however, no consistent mechanism has been postulated to explain the multitude of results.

### 1.2. Current Concepts of Chemoprevention

Cancer chemopreventive compounds from foods and beverages, dietary supplements, vitamins, micronutrients and/or synthetic chemicals decrease the cancer incidence in general or for specific cancer types. For all of the above groups, examples are known for both carcinogenic and preventive effects, like carcinogenic (e.g., red meat, [29]) or anticarcinogenic food (tea extracts, [30]); carcinogenic (e.g., vitamin A and  $\beta$  carotene, [31]) or preventive food supplements (e.g., herbal preparations, [32]), or chemopreventive chemicals (e.g., NSAIDs and colon cancer, [33]); the number of proven or putative carcinogens among chemicals is very high.

In early studies catechins were investigated as potential carcinogens; Pignatelli [34] reported in 1982 the increased nitrosation of proline to the carcinogenic N-nitrosoproline, but soon antioxidant properties of catechins, interpreted as chemopreventive effects, became apparent. The first case control study of green tea extracts and cancer incidence was published in 1984 [35]. This study correlated local food consumption patterns and cancer incidences and was intended to detect cancer increases, it did not consider cancer prevention as a possible outcome. In 1985, Ohno et al. [36] published a case control study in Japan on the connection between bladder cancer and GTE; this study suggested a lower bladder cancer incidence in women taking GTE powder (matcha). Later studies also included drinking green tea, the study design was changed to investigate the decrease in overall cancer incidence [37] or in specific cancer types.

### 1.3. Green Tea and Cancer

Since tea is the most consumed beverage worldwide, with 3,362,000 tonnes black tea and 884,000 tonnes green tea production in 2006 [38], health effects of tea and tea extracts have attracted considerable interest; since 1991, PubMed lists 187 reviews summarizing the literature about cancer and GT (PubMed search “green tea” AND catechin\* AND cancer). Most dealt with cancer in general or mechanistic aspects of carcinogenesis, only a few reviews focused on the prevention of specific cancer types like lung cancer [39–41], breast cancer [42,43], colon cancer [44], prostate cancer [14,45–47] and gastric cancer [48]. Epidemiological evidence for the protective effects of GTE for cancer of all types has been reviewed in 2009 by Boehm et al. [37], using the Cochrane collaboration criteria for randomized prospective studies. This review included 51 randomized clinical studies, it found “highly contradictory evidence” for a protective effect of green tea or its extracts.

Analyzing green and black tea leaves and their extracts has identified catechin and flavone compounds as major antioxidant agents, and identified four catechins with probable anticarcinogenic effects, i.e., epigallocatechin-3-gallate (EGCG) being the most abundant compound, epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epicatechin (EC) [49]. In tea leaves these compounds are present in high concentrations, they are extracted from green tea (green tea extract, GTE [13]) and marketed as nutraceuticals such as Polyphenon E [11,12]. EGCG has also been investigated as a defined chemical compound in both in vitro experiments and interventional patient studies [50]. Until now, no consistent mechanism has been forwarded explaining the multitude of published GT and GTE effects.

Since 2009, additional epidemiological analysis has been published for cancer prevention by GT. Cancer prevention has not been proven for a specific cancer type but is suggested for cancers caused mainly by exogenous carcinogens like tobacco smoke. Therefore, a preventive effect should be expected for (at least some) common cancer types which this review is focused upon. Lung cancer is the leading cancer type worldwide, the majority is smoking related [51]; similarly, colon cancer—another common cancer type—is associated with certain food types [29,52,53]. Breast cancer [54–56] and prostate cancer [51,57] are both hormonally promoted; they represent the major sex specific cancer forms [58,59]. Additionally, we included the organs with direct food contact, i.e., esophagus and stomach. If GT/GTE prevents cancer types caused by exogenous carcinogens, like lung or colon cancer, these cancer types should be affected by GT intake. Similarly, if GT/GTE modifies hormonally driven cell growth as is relevant for breast and prostate cancer, a similar effect should be seen in these cancer types.

Study protocols—if available—indicate a wide variation of criteria for the quantification of green tea exposure; most studies used questionnaires or interviews, only a few studies used serum flavonoid levels as exposure criteria. Only two studies for esophageal cancer tried to estimate tea temperature as a relevant confounder; many studies—especially from Western countries—did not differentiate between green and black tea consumption and only listed “tea consumption”.

If epidemiological studies rule out a correlation between tea extracts and cancer prevention, nonhuman evidence cannot change the negative epidemiological results, as has been shown for saccharin [60]; only if epidemiological data are lacking or are inconclusive, other evidence may be used for hypothesis generation and/or study design. Thus we have focused on epidemiological evidence; recent in vitro experiments and animal studies have been included to indicate the width of experimental data; their results are discussed only as ancillary evidence.

GT and GTE effects have increasingly been investigated for intracellular signaling in tumor cell cultures and for changes in aberrant cell growth and function; these studies do not prove chemoprevention. A PubMed search identified 432 articles for “green tea” and “signal\*” and “pathway”, focusing on cancer as well as other relevant diseases like diabetes mellitus (e.g., [61]), neurodegenerative diseases (e.g., [62]) or osteoporosis (e.g., [63]), with all publications on intracellular signaling published after 1997. An even newer development is “omics”-based methods in GT effects, with genomic research dating back to 2001, proteomics to 2004 and metabolomic studies not earlier than 2008. Again, positive effects for GT and GTE have been found for a variety of parameters by all three methods.

In this review, GT chemoprevention is first assessed by evidence from prospective cohort studies and case control studies. Additional data on confounders are included focusing on genetic polymorphisms or tumor markers. Ideally, prospective studies consider all relevant confounders and have a sufficiently long follow up period since tumor latencies are estimated to be 5 to 20 years [64], since only those parameters can be evaluated that were included at the beginning of the study. In case control studies, dietary protocols and other data are obtained after a cancer is diagnosed; these data may be influenced by the Rosenthal effect (data collection and interpretation is affected by the patient status). Case control studies are more suitable for the identification of possible factors for tumor initiation and promotion; they are less well suited for confirmation studies.

## 2. Methods

In order to identify relevant studies for the connection between green tea intake and cancer development, we searched the PubMed database to identify publications for the following terms:

- Lung cancer: (“green tea” OR GT) AND (lung OR bronchial) AND cancer (98 results);
- Colorectal cancer: (“green tea” OR GT) AND (colon OR colorectal) AND cancer (369 results);
- Breast cancer (“green tea” OR GT) AND (breast OR mammary) AND cancer (174 results);
- Prostate cancer (“green tea” OR GT) AND prostat\* AND cancer (198 results);
- Esophageal cancer: (“green tea” OR GT) AND esophag\* AND cancer (109 results);
- Gastric cancer: (“green tea” OR GT) AND gastric AND cancer (229 results).

All publications published before 31 March 2016 were included; the abstracts were searched manually for relevance. All English language publications of epidemiological studies were retrieved as full text versions; for studies in other languages the English abstract was evaluated. Literature cited in these articles was screened for studies not retrieved by the PubMed search and relevant studies were also included. For non-English language publications the publication language is given in the tables.

Additionally, epidemiological studies of risk factors were included if green tea intake or tea flavone intake was analyzed as a possible modifier of the primary study parameter. Non-epidemiological studies were included only to exemplify mechanisms for tumor initiation or promotion; for these parameters only exemplary studies are cited.

Primary data (study population, identification of cases, calculation of GT or GTE intake, confounder, odds ratios (OR) and confidence intervals (CI), other relevant data like type of tea, tea temperature) were extracted and summarized in the Tables 1, 2, 4, 6 and 8. Since the variability in methodical details and outcome parameters was very high among the epidemiological studies, we analyzed the study outcome only qualitatively.

A protective effect of GT or GTE for a given cancer type was assumed if

- Inclusion criteria and outcome parameters were plausible;
- The majority of the studies reported at least qualitatively identical results;
- No major study with a comparable study layout reported a conflicting outcome;
- Alternatively, the results were supported by additional evidence.

Similar criteria were used in causality assessments [23,65] and have been used in prior reviews [65,66]; they allow the comparison of evidence from variable sources, different diagnostic and outcome criteria or different study layouts.

## 3. Results

### 3.1. Lung Cancer

Lung cancer is the most common cancer worldwide, its occurrence is strongly correlated with cigarette smoking. Prevention of lung cancer by other means than a smoking stop has attracted a lot of attention; only a few studies have delved into a connection between lung cancer and diet, mostly focusing on micronutrients and vitamins. Intervention studies trying to prevent cancer with vitamin A and  $\beta$  carotene (reviewed by [31]) have yielded disappointing results with higher cancer incidences in the treatment groups.

#### 3.1.1. Cohort Studies

Boehm et al. [37] published a Cochrane review and could locate only three observational studies. Our comparison additionally includes a Chinese study [67], the Japan Collaborative Cohort Study using a complete dietary survey [68] and the only European study [69]. Wang [70] included a review based on publications from Chinese databases and summarized 26 case control studies and 12 cohort

studies, all of them published in Chinese. Among the four cohort studies included in Table 1, only Jin et al. [67] in a Chinese study found a protective effect; no data are available about the number of patients included, the confidence interval ranged from 0.68 to 0.95. Two Japanese studies [68,71] and a Dutch cohort study [69] found “no effect for lung cancer”, the raw data from Li et al. [71] reported OR ratios of 1.14 to 1.18 indicating a slightly increased lung cancer risk (Table 1). This conclusion concurs with the Cochrane review [37] and the review by Yuan [72], which also could not confirm a protective effect in cohort studies.

In contrast, other reviews [70] postulated a decreased lung cancer risk, especially in women. For lung cancer “both Western and East Asian cohort studies reported a protective effect, which also may extend to black tea” [70]. Wang et al. [73] pooled the results from six cohort studies with 1675 cases, among them prospective studies in Chinese workers exposed to lung carcinogens [74,75] and retrospective case control studies [76,77] and calculated a decreased risk in the high GT intake group. However, in 12 Chinese studies evaluated by Yuan [72,78], significance was only obtained for one group of tea drinkers in each study, which was not necessarily the group with the highest intake [71,74,79,80], or only in a trend analysis. A significantly increased lung cancer incidence was seen by Tewes et al. [77] in Hong Kong Chinese, as was seen for some subgroups in other studies [71,72].

### 3.1.2. Case-Control Studies

We were able to identify three well documented case control studies [77,81,82], and two studies with scant data [74,83]. Xu and Cai [82] and Zhong et al. [77] found a decrease in lung cancer by GT in Chinese patients. Lin et al. [84], studying genotype variations in lung cancer patients, reported a significantly higher tumor incidence in “never tea drinkers”; since their study had very low case numbers in many subgroups, these results are preliminary at best (Table 1). Taken together, neither cohort studies nor case control studies support a protective effect of GT drinking on lung cancer incidence.

### 3.1.3. Additional Evidence

A plethora of studies has been published using cell culture systems for the effects of catechins, GTE, GT or Polyphenon E on intracellular signaling factors or DNA repair systems. Among recent publications, EGCG inhibits HDGF (hepatocyte derived growth factor) in lung cancer cells, enhances platinum-induced apoptosis [85] and inhibits cell migration and tumor cell invasion [86]. Polyphenon E reverted AP-1 activation in lung tumor cell cultures [87], reduced NNK-induced A/J mouse lung tumors and inhibited the growth of H1299 and H460 lung cancer cells [88].

Greenberg et al. [89] reviewed *in vitro* evidence for the possibility of GT or GTE protection against lung cancers and concluded that *in vitro* evidence for chemoprevention also is weak. The lack of epidemiological evidence for a protective effect of GT catechins likely shows that animal and cell culture experiments with GT and GTE have no relevance to human lung carcinogenesis; the single clinical study [90] did not suggest clinical efficiency.

**Table 1.** Evidence for green tea (GT) or green tea extracts (GTE) protection against lung cancer.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Evaluation
<b>Cohort studies</b>					
Jin et al. 2013 ([67], in Chinese)	Ganyu county in Jiangsu, China	Interview with QST	GT drinking: OR 0.78 (CI 0.65–0.95)	Garlic intake, smoking, cooking oil, fried food	Scant information about cohort, no absolute numbers
Li et al. 2008 [71]	41,440 Japanese, 7 year follow up; 302 lung cancer cases; Ohsaki NHI cohort	QST based dietary panel	OR 1.14–1.18, “no protective effect”	Multiple confounders including smoking	Thorough adjustment, crude data calculation for men: $p_{\text{trend}} < 0.01$ , adjusted $p = 0.32$
Iso and Kubota, 2007 [68]	Japan Collaborative Cohort study, 40,000–60,000 participants	Structured interviews for dietary habits	Lung cancer: n.s.	Food surveys, multiple food items calculated	Well documented study, no significant effects.
Arts et al. 2001 [69]	728 elderly men from Zutphen, Netherlands. 10 year follow up, 42 lung cancer cases	QST based dietary panel; calculation by tertiles	Total catechins: no effect, non tea catechins—borderline significance	low case number	For non-tea catechins: OR 0.66 (0.42–1.05); interpreted as “borderline significance”.
<b>Case control studies</b>					
Zablocka-Slowinska et al. 2015 ([83], in Polish)	92 lung cancer cases, 157 controls; Lower Silesia, Poland	Dietary pattern evaluated by QST	Increased risk with low cereals, vegetables, fruits, GT	No separation of GT effects from confounders possible	No numbers given in abstract
Xu and Cai, 2013 ([82], in Chi-nese)	1225 cases, 1234 controls, China	Interview, QST	OR 0.495 (0.345–0.625) for nonsmokers, in smokers decrease for <3 cups/day.	Separate analysis for GT, black tea, oolong tea, other tea.	Largest effect for “other teas”. For smokers significant increase with >3 cups/day; no case numbers given.
Bonner et al. 2005 [74]	122 cases, 122 controls, Xuan Wei, China	OGG1-, GSTM1, AKR1C3 polymorphism subgroups	Daily GT—nonsignificant reduction	no effect of genetic polymorphism	$p_{\text{trend}} = 0.20$ for dose
Zhong et al. 2001 [77]	649 lung cancer cases, 675 controls in Shanghai Cancer Registry; women only	Structured interview; tea intake in gram/year (1–500, 501–1500, >1500)	GT lowers lung cancer in nonsmoker significantly, in smokers n.s.	Confounder: education, occupation, smoking, alcohol, dietary habits	Nonsmokers, >1500 g/year: 13 cases, OR 0.46 (0.22–0.96); smokers, >1500 g/day: 23 cases, OR 0.62 (0.21–1.82); all tea drinkers: 70 cases, OR 0.65 (CI 0.45–0.93).
Tewes et al. 1990 [81]	200 female lung cancer patients, 200 controls, Hong Kong Chinese	Structured interviews for dietary habits	GT increases risk of lung cancer significantly	Confounder: smoking, alcohol, fruit.	Adjusted OR 2.7 (1.16–6.80).
<b>Additional studies</b>					
Lin et al. 2012 [84]	170 cases, 340 controls; Changwa county, Taiwan	QST for dietary habits, genotyping	OR 13.16 (2.96–58.51) for no tea vs. >1 cup/day; OR 3.34 (1.41–7.93) for >10 year tea drinking	GT modulates smoking induced lung cancer; interaction between smoking and IGF1, GT intake	For GT 3 cases in reference group for >1 cup/day, 7 cases for >10 year drinking.
Laurie et al. 2005 [90]	Phase I clinical trial, 17 patients with advanced cancer; USA	3 g/m <sup>2</sup> GTE	No improvement; no drug toxicity		

AKR1 C3—aldoketo-reductase family 1, member C3; GSTM1—glutathione-S-transferase, subtype M1; IGF1 = insulin like growth factor 1; OGG1 = 8-oxyguanin-glycosylase; PAH—polycyclic aromatic hydrocarbons; QST = questionnaire-based survey of dietary habits.



### 3.2. Colorectal Cancer

Colon and rectum carcinomas (colorectal carcinoma, CRC), often considered together as colorectal cancer, are among the most prevalent cancers worldwide. For CRC, specific mutations are well known causing genetic cancer syndromes; mutations in other genes like APC or MutL (for an exhaustive list see [www.omim.org](http://www.omim.org)) are major risk factors [91]; on the other hand, the association of colon carcinoma with red meat is well established [29]. A possible connection between GT/GTE and CRC has been intensively investigated resulting in numerous cohort and case control studies (Table 2). Some additional studies on genetic polymorphisms as risk factors for CRC and lifestyle factors were included in this analysis; data are summarized in Table 2 (cohort studies and case control studies) and Table 3 (studies with GT and flavonoles as modifiers).

For CRC and tea intake, cohort and case controls studies from Europe [92–97] and the USA [98–103] often did not specify the type of tea; since in these countries black tea is prevalent, it can safely be assumed that these studies cover black tea. Other studies calculated and quantified the amount of flavonoids from all food sources. These studies took into account other flavonoid sources as well, e.g., genistein from soy beans [104].

#### 3.2.1. Cohort Studies

Studies from Europe, USA and Australia often failed to find a protective effect of tea or tea flavonoids; only one Swedish cohort study found a slight increase for colon cancer in GT-drinking women [96]. A Spanish cohort [97] and an Italian cohort [95] found a protective effect of flavonoids. One American study found a decrease in colon adenoma recurrence correlating with flavonols [98] suggesting a secondary preventive effect rather than primary prevention. In contrast to these studies, Hartman et al. [93] in the earliest (European) cohort study in Finland, and Sun et al. [105] in the only Singaporean case control study reported a significant increase of CRC with GT.

Results from the 7 cohort studies in Japanese or Chinese populations (Table 2) are inconclusive. Of note, some prospective studies focused on patients after adenoma removal [106,107], with colon adenoma or carcinoma recurrence as criterion (secondary prevention), both studies found a protective effect. These likely documented a protective effect on cancer promotion rather than initiation. In other large cohort studies with CRC occurrence as end point, two studies from China reported a positive effect, with one study [108] focusing on Shanghai men only. Although no general effect of GT on CRC incidence was calculated, an analysis for a dose dependent effect indicated a significant protection. The other study [109] complemented the Shanghai Mens Health study and followed 69,710 Shanghai women for 6 years; this study also reported a significant protection including a dose response curve. In contrast to these Shanghai based studies, the only study with Singaporean Chinese reported an increased CRC incidence [105]. Three cohort studies from Japan could not find a protective effect of GT [106,110,111]. Taken together, a CRC protection by GT or GTE is not supported by epidemiological data.

Table 2. GT and GTE extracts and colorectal carcinoma.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Evaluation
<b>Cohort studies</b>					
Dominianni et al. 2013 [100]	NCI study, 57,398 participants. 11.4 year follow up, 681 CRC cases; New York, USA	Food QST; 0, <1, 1, >1 cup tea per day	No effect by coffee or tea	Only “tea” is mentioned, likely black tea consumption	10–48 cases per subgroup; $p = 0.175$ for multivariate analysis
Yang et al. 2011 [108]	60,567 Chinese men, 40–74 year age, 5 year follow up, 243 CRC cases; Shanghai Mens Health Study	QST for beverage intake, type of tea; 0, <250, >250 g/month; 0, <25, >25 years	In nonsmokers $p_{\text{trend}} = 0.009$ with amount of tea, $p_{\text{trend}} = 0.02$ for duration. 2 g/day dry leaves—12% reduction	No association of GT in smokers	Small case numbers in nonsmokers (<250 g/month: 19 cases; >250 g/month, 10–<25 years, 18–>25 years: 10 cases each)
Sinha et al. 2012 [103]	489,706 participants, 10.5 year follow up, 2863 cases prox. colon, 1993 distal colon, 1874 rectum ca.; NIH-AARP study, USA	QST for beverage intake 0, <1 cups/month tea, 1–3/month, 1–6/week, >1/day	coffee—protective effect, tea—no association	Confounder: age, race, BMI, D.m., smoking, alcohol, activity, red meat, NSAID use	For green and black tea: $p_{\text{trend}} > 0.5$ ; OR for decaffeinated tea lower than for caffeinated
Lee et al. 2007 [110]	96,162 subjects, 1163 CRC cases (400 rectal ca., 763 colon ca.), JPHC study, Japan	QST for beverage intake; 0, <1, 1–2, 3–4, 5+ cups/day	Green tea—no effect in any group	Separate analysis for black and green tea. Confounder: smoking, alcohol, activity, red meat.	All $p_{\text{trend}}$ values >0.50 for green tea
Sun et al. 2007 [105]	Chinese Health Study, >60,000 pat.; 8.9 year follow up, 845 CRC cases; Singapore	In person interviews; black, green tea; none, monthly, weekly, daily tea drinking	GT increases risk in men OR 1.31 (CI 1.08–1.58), $p_{\text{trend}} = 0.009$ ; in women OR 0.89 (0.71–1.12), $p_{\text{trend}} = 0.52$ ; all OR 1.12 (0.97–1.29), $p_{\text{trend}} = 0.08$	Black tea—no effect; stronger effect for Duke C and D CRC. Confounder: D.m., alcohol, smoking, coffee	No dose response for green and black tea; no GT effect for localized ca., significant increase for colon, colorectal ca. For duration: both increases and decreases
Yang et al. 2007 [109]	Shanghai Womens Health Study, 69,710 Chinese women 40–74 year old, 6 year follow up, 256 CRC cases	Interviews at 0 and 3 years after begin of observation; 0, 1–4, 5+ g/day, 1–23 years, 24 year consumption	OR 0.63 (0.45–0.88) for tea drinker, positive dose response for amount and duration	No difference between colon and rectal cancer. Confounder: BMI, red meat, activity, vegetable/fruit intake	Small case numbers for high amount or long duration (10 cases each). Only significant data are presented
Suzuki et al. 2005 [111]	26,311 Japanese, ~8 year follow up, 305 colon ca., 211 rectum ca. cases. Miyagi prefecture, Japan	QST for GT consumption; 0, rare, 1–2, 3+ cups/day	No association between colon or rectum Ca and GT	Confounder: alcohol, smoking, age, BMI	GT and rectum ca., cohort 1: $p_{\text{trend}} = 0.4$ ; cohort 2: 0.02
Terry and Wolk, 2001 [96]	61,463 Swedish women, 9.6 year follow up; 460 CRC (291 colon, 159 rectal, 10 both); Sweden	Cohort study	No association with GT for total cancers, slight positive correlation for rectum cancer in women		
Nakamura et al. 2015 [106]	307 patients with endoscopic CR adenoma, 4 year follow up, Japan	Diet survey for beverages; 0, 1–3, 4× cups/day	>3 Cups of coffee—reduced risk, tea—no effect. Decrease in proximal tumors, increase in distal tumors	Older patients; no general population	
Shimizu et al. 2008 [107]	136 patients with colon adenoma removal, 1 year follow up, Japan. Intervention study	71 pat. with 1.5 g/day GTE intake, 65 controls; no change in tea drinking	Less, and smaller metachronous polyps with GTE. OR 0.49 (0.24–0.99)	Follow up in 65 and 60 patients; loss to follow up in 8 patients	



Table 2. Cont.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Evaluation
Case control studies					
Budhathoki et al. 2015 [112]	738 patients with colorectal adenoma, 697 controls, Japan	QST for coffee and GT intake	No effect of GT intake on adenoma recurrence, CRC development	Confounder: coffee (significant reduction), BMI, activity, smoking, alcohol, D.m., NSAID, red meat	For GT, 1st vs. 4th quartile: OR 1.50 (0.97–2.31), $p_{\text{trend}} = 0.20$ ; for coffee: OR 0.67 (CI 0.48–0.93), $p_{\text{trend}} = 0.02$ .
Green et al. 2014 [113]	Western Australia Bowel Health Study; 854 histologically confirmed cases, 948 controls	QST for beverages; hot black tea, hot green tea, hot herbal tea; 0, <1, 1+ cups/day	$p_{\text{trend}}$ for green tea 0.920, for black tea 0.196 (increase), herbal tea 0.149 (decrease)	Confounder: age, alcohol, activity, smoking, D.m., socioeconomic status, race, BMI	For tea variants: OR varying between 0.69 and 1.34; 7 OR values >1.0, 4 OR values <1.0
Li et al. 2011 [114]	540 CRC cases, 540 hospital controls, population controls; China	QST interviews; never, <6 times/week, more; 0, <10, >10 years	OR for >1 kg tea/year: 0.52 (0.29–0.94; hospital controls), 0.45 (0.25–0.82, population controls)	no difference between hospital and population controls	Low number of cases (10–13 cases per group)
Ilyasova et al. 2003 [101]	630 colon cancer cases, 1040 controls, North Carolina, USA	Case control study; 0, <2, 2+ cups/day	No race dependent, no GT-dependent change in colon cancer incidence	African-Americans, White Americans	<2 cups/day: OR 0.9 (0.7–1.2); 2+ cups/d: OR 1.3 (0.9–1.8)
Cerhan et al. 2001 [99]	685 colon ca., 635 rectum ca. cancers, 2434 controls, 40–85 years; Iowa USA.	Case control study in cancer registry; mailed QST for food and beverages	No effect for either colon or rectum cancer from tea intake	Confounder: age, sex, education, physical activity, smoking history, coffee, fiber, fruits, vegetables	No significant differences, lowest $p_{\text{trend}}$ value for current smokers
Zhang et al. 2002 [115]	102 CRC patients, 99 controls, Hebei, China	Interviews, 20 year food intake inventory; groups: never, 1–3, 4–6/week, daily, 2+ daily	Milk is protective (OR 0.38); in women tea is protective (OR 0.11–0.25)	Analysis for different duration of tea drinking, no effect for men	Men, current drinker: OR 0.98 (0.44–2.19); women: OR 0.11 (0.04–0.30)
Hartman et al. 1998 [93]	111 colon ca., 83 rectal ca. cases, 9.0 y follow up; Finland	<1, >1 cup GT/day, colon ca., rectal ca.; increase in rectal ca.	For colon ca., <1 cup/day: OR 1.40 (0.84–2.33); 1+ cups/d: 2.09 (1.34–3.26)	Confounder: coffee	
Ji et al. 1997 [116]	931 colon ca. cases, 884 rectum ca. cases, 1552 controls, from 1990–1993. Shanghai, China	Consumption categories 200 (women) or 300 (men) g/month GT	Men and women: protective for rectal ca., not for colon ca.	In women larger effects than in men. Confounder: alcohol, smoking, BMI, activity	Men, rectal ca.: OR 0.72 (0.46–1.13), $p_{\text{trend}} 0.04$ ; women, rectal ca.: OR 0.57 (0.34–0.97), $p_{\text{trend}} = 0.001$
Kono et al. 1991 [117]	80 patients with adenomas, 1148 controls, Japanese army members		Green tea—tendency to lesser adeno-mas	Confounder: activity, coffee, rice, smoking, alcohol, military rank	GT: $p_{\text{trend}} 0.22$ ; highest intake group, adenomas: OR 0.69

QST—questionnaire-based estimate of GT intake.

### 3.2.2. Case-Control Studies

In case-control studies a protective effect was reported in three Chinese studies [114–116]. On the other hand, in Japanese, Australian and US cohorts (one study each) no protective effect was found [101, 112,113]. As an exception, Hartman et al. [93] in a Finnish case control study found an increase of CRC with GT intake. Beside the fact that Chinese studies found a protective effect against CRC comparable to the protection against lung cancer, no evidence exists for CRC chemoprevention by green tea.

It is possible that GT consumption is an indicator of other nutritional, environmental and/or genetic factors for the individual risk for CRC rather than an independent protective compound; it is also possible that GT catechins and phenols prevent CRC only in people with a Chinese genetic background. In a meta analysis of six prospective cohort studies from China by Wang et al. [118] with 352,275 participants, 1675 patients with colorectal cancer were identified. Whereas the combined analysis only found a nonsignificant trend toward lower cancer rates, with an OR of 0.90 (0.72–1.08), one study with a large Shanghai cohort had a significant lower CRC incidence (OR 0.70, CI 0.55–0.85); because of the large patient number the results of this study also dominated the outcome of the meta analysis. In another meta analysis by Sun et al. [119] a protective effect of green tea for colon cancer was calculated in three case control studies (OR 0.74, CI 0.60–0.93), whereas for other sites (rectal cancer) or other study types (cohort studies) no significant protective effect was seen. Wang et al. [120] reanalyzed 13 case control studies with 12,636 cases. This analysis calculated an OR of 0.95 (CI 0.81–1.11) for studies from China whereas in subgroups a trend toward a protection against CRC was observed; in studies from Europe the OR was 1.00 or larger [120].

All reviews emphasize the large heterogeneity between the studies, irrespective of the study layout, as was also seen in this review [119]. This heterogeneity does not allow a simple addition of individual studies and complicates meta analyses. The difference in studies from China (showing a preventive effect of GT) and other countries which do not find a correlation is not explained. Possible explanations include genetic differences—to date, no polymorphism study has found a likely candidate gene, differing environmental and lifestyle factors, which are indicated by GT intake, or different compositions of GT/GTE. In order to clarify this topic, controlled prospective intervention studies are necessary. One possible study layout has been published in 2011 [121]. Although the study design called for a 3 year follow up of all persons included, no outcome data have yet been published. Current available data do not support a protective effect of GT/GTE on colon or colorectal cancer.

### 3.2.3. CRC—Association Studies

Studies about an association of CRC with genetic polymorphisms in the CAS9 and CAS10 genes—CRISPR associated—reported a protection against mobile genetic elements [122], against PLA2G4A—phospholipase A group IVA—gene associated inflammation [123], and increased XPC – xeroderma pigmentosum associated mutation repair ([124], see Table 3); all three studies included GT drinking as a modifying factor for the association of CRC with the genotypes; neither study confirmed effects of the polymorphisms studied. In a similar venue Jing et al. [125] studied single nucleotide polymorphisms. The association between the rs11202607 polymorphism in the phosphatase and tensin homolog (PTEN) gene, and CRC was stronger in never tea drinkers suggesting cooperative interactions between tea, PTEN and CRC development [125], but the overall GT effect on cancer incidence was weak. No correlation was found for the GT modulation of NAT and CYP4501A2 expression in Caucasians [92]. Despite the negative in vitro studies some authors claimed an independent protective effect of GT on CRC incidence ([117,123–125], Table 3), they assume that GT drinking may be a cofactor rather than the causal prevention agent for CRC. Since no mechanistic hypothesis has been forwarded these assumptions must be seen as speculative.

**Table 3.** Evidence for GT flavonoids, contribution of genetic factors and colorectal carcinoma risk.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Evaluation
Jing et al. 2014 [125]	545 CRC cases, 522 controls, Jiashan county, China	Histologically confirmed CRC, PTEN SNPs, food QST	Variable correlation of CRC with SNPs, decreased risk in tea drinkers	Decreased risk in married participants, non-farmers	For tea drinkers: $p = 0.038$ ; non-farmers: 0.042; married; 0.009
Dik et al. 2014 [92]	EPIC, 477,071 participants, 11 year follow up, 1252 cases of CRC, 2175 controls; Europe	Cohort study, beverage consumption by QST	Coffee or tea—no effect, CYP1A2, NAT—no effect	No specification of tea, likely black tea	No significant effects
Liu et al. 2013 [122]	Case control study, 506 CRC cases, 1141 controls, China		never tea drinking: OR 1.755, CI 1.319–2.334	Designed to investigate CAS9 and CAS10 polymorphisms	No significant correlations
Yu et al. 2012 [123]	300 CRC patients, 296 controls, Hangzhou China	SNP in PLA2G4A gene, tea drinking as modifier	Tea reduces CRC—OR 0.61 (0.39–0.97)	Similar effects on colon and rectal cancer	Some SNP modify GT effects
Wu et al. 2011 [124]	421 CRC patients, 845 controls; China	XPC complementation analysis, GT as modifier	OR 2.3 (1.7–3.3) for never tea drinker	Stratified for risk alleles, no specific information on other subgroups	No effect of XPC complementation
<b>Flavonoid studies</b>					
Zamora-Ros et al. 2013 [97]	424 incidental colon ca. cases, 401 controls; Spain	Food QST from interviews, flavonoid content from database; quartile evaluation	Tea or coffee: no independent parameters for CRC, colon and rectal cancer	In separate calculation for cancer sites—result unchanged	For total flavonoids, 1st vs. 4th quartile: OR 0.59 (0.34–0.99), $p_{\text{trend}} = 0.03$
Kyle et al. 2010 [94]	264 cases, 408 controls; UK	QST, flavonoids calculated from database	CRC decreased with non-tea flavonols, increased with total flavonols	For quercetin reduced colon ca., not rectum ca. after stratification	For colon ca. and non-tea flavonol intake: OR 0.5 (0.3–0.8), $p_{\text{trend}} 0.01$ ; increase for total flavonols: OR 1.3 (0.7–2.4), $p_{\text{trend}} = 0.01$
Wang et al. 2009 [120]	Womens Health study, China, 38,408 women >45 years, 3234 CRC cases	Prospective cohort study; flavonoid containing food from QST and database	No correlation of flavonoids with CRC: OR 1.01	No association for breast, lung, endometrial, ovarian cancer. Sources: tea, apples, broccoli, onion, tofu	Total flavonoids: $p_{\text{trend}}$ (multivariate adjusted) = 0.47, with increased risk for flavonoids (most OR > 1)
Bobé et al. 2008 [98]	Polyp prevention trial, adenoma recurrence, 8 centers in USA	Food intake, flavonoid intake calculated by databases; cohort study	Flavonols reduced recurrence of large adenomas	Similar effects for isoflavonoids, kaempferol, genistein, formononetin	For flavonols and advanced recurrence: OR 0.24 (0.11–0.53), $p_{\text{trend}} = 0.0006$ , $n = 13$ ; linear increase with quartiles
Yuan et al. 2007 [126]	18,244 Chinese men, 16 y follow up. 162 CRC cases, 806 controls; Shanghai, China	Cohort study with nested case control study	Protective effect for colon ca. by high urinary EGC amount	Identical results for 4-Me-EGC as metabolite, no association with EC	1st vs. 4th quartile, for EGC: OR 0.40 (0.19–0.83), $p_{\text{trend}} 0.02$ ; for 4-Me-EGC: OR 0.41 (0.20–0.84), $p_{\text{trend}} 0.00$
Rossi et al. 2006 [95]	1225 colon cancers, 728 rectal cancers, 4154 hospital controls; Italy	QST, flavonoid calculation from food databases	Significant reduction for isoflavones, flavones, flavonols, anthocyanidins	No differences between colon and rectum, male and female participants	$p_{\text{trend}} < 0.01$ for flavonoids
Michels et al. 2005 [102]	USA, Nurses Health Study, Health Professional Follow up Study, 1,438 CRC cases	QST for tea and coffee intake, other factors	No effect of tea on CRC incidence	2 Mio patient years total follow up; coffee—no effect; decaffeinated coffee—significant reduction (OR 0.48)	CRC, men: $p_{\text{trend}} 0.32$ (increase); women: 0.43 (decrease); colon ca. in men: 0.40 (increase); women: 0.18 (increase); rectal ca., men; 0.59 (mixed); women: 0.27 (decrease)
Wang et al. 2013 [127]	816 cases, 815 controls, Fukuoka CRC Study, Japan	Interview, polyphenol assessment for 148 food items by food algorithm; quintile analysis	No correlation between polyphenols and CRC in subgroups and location analysis	Confounder: smoking, alcohol, activity, “others”. Suggestion of decrease with coffee intake	For tea polyphenols and CRC: $p_{\text{trend}} 0.08$ (increase), coffee polyphenols: $p_{\text{trend}} 0.07$ (decrease); other polyphenols: $p_{\text{trend}} 0.19$ (increase)

CAS9, CAS10—CRISPR associated protein 9, 10; CRC = colorectal carcinoma; EPIC—European Prospective Investigation into Cancer and Nutrition; NAT—N-acetyl transferase; PLA2G4A—phospholipase 2 group 4A; QST = questionnaire; SNP single nucleotide polymorphism; XPC—xeroderma pigmentosum complementation factor.

### 3.2.4. CRC—Nonhuman Studies

The discrepancy between Chinese and non Chinese epidemiological studies has sparked investigations into possible protective pathways for GT and GTE in models. Animal and cell culture experiments suggest specific effects of GT compounds on intracellular signaling and cell cycle control, for these studies usually the potent gallic acid EGCG has been used. In a rat dimethylhydrazine model of colon carcinogenesis, 1% green tea as the sole drinking source lowered inflammatory cytokines like TNF- $\alpha$ , iNOS or COX-2 [128]; similarly, preneoplastic lesions in an azoxymethane-induced rat colon carcinoma model were suppressed [129], as were cell proliferation and angiogenesis in a SCID mouse model [130]. EGCG modulated multiple intracellular signaling pathways like ERK1/2, JNK1/2, p38 $\alpha$ , p38 and AKT signaling inducing apoptosis [131], Wnt/ $\beta$ -catenin pathway stimulating cell growth [28] and vascular epidermal growth factor receptor 2 [132,133]. These effects have been reported in multiple colorectal carcinoma cell cultures [134] and provide in vitro evidence for apoptosis induction, inhibition of cell growth, vascularisation and connective tissue synthesis at very high EGCG concentrations [28,130–135].

Effective concentrations in cell culture experiments are  $\geq 50$   $\mu\text{mol/L}$  [130,136],  $\geq 20$   $\mu\text{mol/L}$  [28] or  $\geq 25$   $\mu\text{mol/L}$  [134]. In bioavailability studies, EGCG serum concentrations rarely exceeded 1  $\mu\text{mol/L}$  [136,137], making in vivo effects of EGCG extremely unlikely. Although these in vitro experiments show that GT catechins and flavonols modulate intracellular pathways and cell cycle control factors, the relevance of these criteria for tumor development is unknown. Considering the lack of evidence from cohort and case control studies it must be concluded that in vitro GT effects are likely not relevant in humans.

### 3.2.5. CRC—Flavonoid-Based Studies

The assumption that GT may be an indicator for as yet unknown protective factors rather than a modulator by itself is also borne out by studies using flavonoid content as variable instead of green tea amount. These studies focussed on the flavonoids as presumed active ingredients rather than GT; this approach has been validated by urinary phenolic metabolites as biomarkers in GT drinkers which increase with increasing flavonoid intake [138].

Studies calculating flavonoid intake from food and beverages are included in Table 3. Multiple human studies in China [126], Italy [95], Spain [97], the UK [94] and USA [98] found a decrease in CRC with increasing flavonol levels; a consistent pattern of CRC reduction was observed in these studies which was independent of ethnicity and flavonol source. These data emphasize the association of flavonoids with CRC reduction irrespective of the specific flavonoid source.

Only one clinical study has focused specifically on secondary CRC prevention by GT [139,140]. Prevention by GT, but also by folic acid, unspecified antioxidants, prebiotic fibers and phytoestrogens were not seen [140]; this lack of effects agrees with other reviews [106,107,112,117].

## 3.3. Breast Cancer

For women breast cancer is the most common cancer diagnosis worldwide and the leading cause of cancer mortality [141]; breast cancer is associated with alcohol, smoking, diabetes mellitus and dietary factors like fat or “processed products” [142]; in contrast to lung cancer and CRC, breast cancer growth is strongly stimulated by estrogen. Its worldwide distribution is uneven [141], thus prevention by dietary factors like tea has attracted considerable interest. GT was proposed as a protective agent as early as 1986 [143,144].

Previous reviews of epidemiological evidence for the protective effect of GT or GTE against breast cancer are not consistent. Epidemiological data have been interpreted as supporting a protective effect of green, but not of black tea (OR for GT 0.78, CI 0.61–0.98 [145]); another review found evidence for the prevention of cancer recurrence, but not its primary prevention [146,147], or significant reduction only in case control studies but not in prospective cohort studies. A Cochrane review judged the evidence as very weak, also with positive results only in case control studies, but not in cohort studies [37]. This review also summarized the evidence as inconclusive.

Wu et al. [43,148] reanalyzed the data from 9 epidemiological studies with green tea and found a nonsignificant reduction (OR 0.82, CI 0.64–1.04) for green tea, and a similar OR value (0.98, CI 0.93–1.03) for black tea; subgroup analysis did not change these negative findings. Michels et al. [149] also considered the effects from 3 studies in the general population, one study in atomic bomb survivors and one pooled analysis as nonsupporting, and concluded from epidemiological studies: “The apparent lack of association between diet and breast cancer may reflect a true absence of association between diet and breast cancer incidence, or may be due to measurement errors exceeding the variation in the diet studied, lack of sufficient follow-up, and focus on an age range of low susceptibility.” [149].

### 3.3.1. Epidemiological Evidence

Only three large cohort studies investigated the connection between breast cancer and GT in the general population (Table 4); two of these are based on the large “Japanese Public Health Study”, a prospective cohort study [150]. This study included 45,000 participants with a median follow up of 13.6 years; for participants drinking more than 5 cups/day tea the OR for breast cancer was higher than 1.0 (not significant) indicating—if anything—a tumor promoting effect of high doses of GT. In the Miyagi prefecture subgroup an OR of 0.84 (CI 0.57–1.24) was calculated for high green tea consumers [151]. In the Shanghai Womens Health study GT effects on breast cancer were also studied in the general population, with emphasis on the age of breast cancer development [152]; a delay in cancer development related to drinking tea since an age of 25 was postulated [152]. From the raw data, premenopausal breast cancer prevention was only significantly reduced if the age at diagnosis was used as stratifier. The incidence of postmenopausal breast cancer was significantly increased in the patient group with the longest intake, if years of GT consumption was used as stratifier. Data from other prospective cohort studies do not support a beneficial effect of green tea (Table 4).

In contrast, from 13 case control studies 10 studies (Table 4) reported protective effects of GT; 7 of these studies were conducted in China, one study in Japan. This protection was restricted to a high activity ACE genotype in Singapore Chinese women [153], or in women with low soy intake [154]. Other cofactors are a low COMT activity [154] or specific SNP genotypes associated with breast cancer [155]. Since these studies were aimed to elucidate effects of patient subgroups, they cannot be taken as evidence for a general protective GT effect against breast cancer.

No protection from GT intake was found in a Japanese study from Nagano county [156]; when the authors based their calculation on serum catechin concentrations, they found a nonsignificant decrease of breast cancers with EGC and EC, but also a nonsignificant increase with EGCG and ECG [157] (Table 4).

Since the connection between estrogenic activity and breast cancer incidence is well supported [142], the modulation of estrogenic activity may act as a chemopreventive effect. This activity, as well as known estrogenic effects in cells have extensively been studied, selected recent publications are compiled in Table 5. In accordance with the growth stimulation of breast cancer cells by estrogens, drinking green tea lowered serum estrogenic activity in premenopausal Japanese women [158], in Singaporean women it lowered serum estrone only, but not estrogen values [159]. In Singaporean women serum estradiol was also lower when drinking black tea [159]; strangely, in this study for black tea the effects were stronger with daily versus weekly tea drinkers, whereas for green tea the effects were reversed, i.e., stronger in weekly versus daily drinkers. Urinary estrogen metabolites are decreased by GT in both premenopausal and postmenopausal women, independent

from ethnicity [160], supporting an effect of GT catechins in estrogenic activity. The relevance of these observations remain to be seen because of the inconsistencies in different study cohorts [158,159]. Clinically, mammography is used as a screening method for breast cancer. In a Singaporean cohort, mammographic density was reduced in patients with high GT consumption (which is considered protective), whereas black tea had no effect [161]; this effect was only significant when comparing the highest consumption quartile in postmenopausal participants with the combined other quartiles, but not in other comparisons. The results of this study have to be repeated independently before they can be accepted as valid.

For breast cancer a secondary prevention potential, i.e., the prevention of cancer recurrence was intensively studied (Table 5). When in patients with breast cancer of stages I to III Polyphenon E (a commercial GT catechin extract) was given, hepatocyte derived growth factor (HDGF) was decreased after 2 month treatment, but not with longer treatment, other growth factors like vEGF were unchanged [162]. In breast cancer patients, lower cancer recurrence rates were found in patients with high GT consumption; this effect was especially large in stage I patients [163,164].

Case control studies show a positive result, i.e., breast cancer prevention by GT, if mainland Chinese patient cohorts are studied, most other case control studies from other countries do not report positive results. Samavat et al. [165] have proposed a clinical study called the Minnesota Green Tea Trial (MGTT) which is designed to detect GT effects on postmenopausal womens health including cancer prevention. The layout of this large study was published in 2015, only safety data have been published [166].

### 3.3.2. Additional Evidence for Breast Cancer Chemoprevention—Nonhuman Studies

In a mechanistic study investigating cell division markers in breast cancer patients prior to surgery, 940 mg GTE decreased ki-ras67 activity in benign, but not in malignant breast tissue; other proliferation parameters were unchanged both in benign and malignant cells [167]. GT catechins may reactivate ER activity in ER-deficient MDA-MB-231 cancer cell cultures [168], the ER- $\alpha$ 36 receptor subtype, assumed to be responsible for persistent autocrine stimulation and is inactivated by GT preferentially in estrogen receptor negative breast cancer cell lines [169]. EGCG inhibits xenobiotic-mediated cell proliferation [170]. Based on these in vitro effects, GTE or purified GT catechins have repeatedly been suggested for clinical use in cancer treatment [171,172]. As is evident from the epidemiological studies, these results have mostly been negative and do not support a relevant role for the effects found in vitro.



**Table 4.** Epidemiological studies for GT and breast cancer.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Analysis
<b>Cohort studies</b>					
Iwasaki et al. 2010 [150]	Japanese Public Health Study; 45,000 participants, 13.6 year follow up, 581 plus 350 cases	QST based beverage intake; 0, <1/week, 1–2/day, 5+/day	No effect of GT intake, no difference between tea types (Ban-cha/Genmaicha, Sencha, Oolong, black).	Confounder: hormones, BMI, smoking, alcohol, activity, coffee, fish, meat	Total GT intake: $p_{\text{trend}}$ 0.60 (increase), Sen-cha: 0.48 (mixed), Bancha: 0.41 (mixed); Oolong: 0.40 (increase), black tea: 0.80 (mixed)
Dai et al. 2010 [152]	Shanghais Womens Health Study; 74,942 women; 6–9 year follow up	QST based dietary inter-view; 0, <1.7, <3.3, <5.0, >5.0 g/day tea leaves	Decreased premenopausal, in-creased postmenopausal risk for breast cancer in tea drinker	Confounder smoking, alcohol, activity, BMI, ginseng, energy, red meat	Increase with dose: $p_{\text{trend}}$ 0.47; preme-nopausal breast cancer: with dose 0.33 (decrease), with age 0.12 (decrease), with duration 0.12 (decrease); postmenopausal: with dose 0.11 (increase), with age 0.01 (increase), with duration 0.02 (increase)
Suzuki et al. 2004 [151]	35,004 Japanese women, 222 cancer cases	Pooled analysis of 2 sub-groups; <1, 1–2, 3–4, 5+ cups/day	No effect of GT intake on breast cancer	Confounder: age, smoking, alcohol, BMI, coffee	In multivariate analysis: $p_{\text{trend}}$ 0.51 in cohort 1, 0.95 in cohort 2
<b>Case control studies</b>					
Li et al. 2016 [173]	756 cancer patients, 789 controls, China	Tea consumption, ER status, menopause stage	Protective effect of GT in premeno-pausal women, increased risk in postmenopausal women	Confounder: BMI, hormones, smoking, alcohol, ER status. Low case numbers in subgroups	Postmenopausal women—GT: OR 1.82 (1.00–1.96); postmenopausal all tea: OR 1.40 (1.00–1.96). For ER <sup>−</sup> cases higher OR than in ER <sup>+</sup> cases
Iwasaki et al. 2014 [157]	369 patient/control pairs, Nagano, Japan	Dietary QST, SNP genotyping	No correlation for GT and BrCa	No interaction between SNP and GT	>120 mL tea/day: OR 1.27 (CI 0.75–2.14)
Mizoo et al. 2013 [155]	472 patients, 464 controls, Japan	Dietary QST, SNP analysis	GT phenotype decreases BrCa risk	Confounder: BMI, smoking, meat, vegetables, coffee, exer-cise, education	No interaction between SNP and GT
Wang et al. 2013 [174]	157 cases, 314 controls, Taiwan	Stress and lifestyle QST	Interactive risk modification by stress and lifestyle factors	Confounder: stress, alcohol, smoking, exercise, meat, sea-food	For <100 mL/day GT: OR 2.47 (1.40–4.38)
Li et al. 2011 [175]	540 cases, hospital and outpatient controls, China	Demographics, lifestyle QST	GT intake reduces breast cancer risk	Similar reductions for CRC, leukemia	For > 1 kg/year GT OR 0.06 (0.01–0.61)
Iwasaki et al. 2010a [157]	144 cases, 288 controls, 10 year follow up; JPHS	Plasma catechin levels, nested case control study	No protective effect of flavonoids	Confounder: activity, smoking, alcohol, diet, BMI	OR: EGC 0.90 (0.42–1.96); EC 0.95 (0.43–2.08), EGCG 1.21 (0.52–2.80), ECG 1.75 (0.81–3.78)
Shrubsole et al. 2009 [176]	3454 cases, 3474 controls, Shanghai. Study performed for COMT genotype effect	QST based dietary inter-view; 0, <50, 50–100, 100–225, >225 g/month; 0, <6, 6–14, 14–23, >23 years	Protective in regular drinkers, not genotype dependent	Group differences in BMI, age at menarche, hormone use, passive smoking and GT intake	Regular tea drinkers: OR 0.88 (0.79–0.98); $p_{\text{trend}}$ with dose 0.09 (decrease), with duration 0.09 (decrease), with begin 0.04 (decrease). Protection mainly in pre-menopausal cases
Zhang et al. 2009 [177]	1009 cancer cases, 1009 controls, southeast China, 20–87 year old participants	QST based dietary inter-view, GT and mushroom intake (< or >7 g/day)	GT increased protective effect of mushrooms	Confounder: BMI, rural residency, activity, hormones, alcohol, smoking	For mushroom and breast cancer, GT plus mushroom intake and breast cancer all values are “significant”
Inoue et al. 2008 [178]	380 cases, 662 controls, Singapore Chinese Women Health; for genotype differences in folate deprived individuals	Interview for lifestyle habits; 2 MTHF genotypes, TYMS deletions	GT decreased breast cancer incidence at low folate, MTHRE, TYMS major genotypes (not significant)	Confounder: education, BMI, hormones, smoking, coffee, folate intake	Very low case numbers in some groups; for 0–1 variants OR 0.66 (0.45–0.98)

Table 4. Cont.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Analysis
<b>Case control studies</b>					
Zhang et al. 2007 [179]	1009 cancer cases, 1009 controls, southeast China, 20–87 years old participants (see [177])	QST based dietary inter-view, green tea variants, duration, amount of tea, many new batches	GT for a long period (>20 year), large amounts per day (2+ cups/day) and year (750 g/year), freshly brewed (2 new batches/day)	Tea drinkers are urban, educated, consume coffee, alcohol, soy, vegetables, fruit	>20 y GT: OR 0.66 (0.56–0.78); 2+ batches/day: 0.59 (0.41–0.84); 2+ cups/day 0.57 (0.47–0.69); >750 g/year 0.61 (0.48–0.78). For amount/year and batches/day positive dose response
Yuan et al. 2005 [153]	297 cases, 665 controls, Singapore Chinese Women Health	QST with categories for food survey; genotyping	All women: no effect; ACE ge-notype TT and/or DD: increased risk	Confounder: education, BMI, smoking, alcohol, nr of births, hormones	High ACE activity group and GT: OR 0.29 (0.10–0.79), 8 cases; ACE + black tea: OR 1.20 (0.40–3.59), 11 cases
Wu et al. 2003 [154]	589 cases, 563 controls, Chinese, Japanese, Filipino patients, LA county, USA	In person interviews for food assessment; COMT genotyping	GT and/or black tea plus low acti-vity COMT allele decreased risk; no effects for other groups	Confounder: race, coffee, smoking, alcohol, soy intake, BMI, activity	Low activity COMT plus black tea: OR 0.44 (0.25–0.78); plus green tea: OR 0.42 (0.22–0.80); both teas: OR 0.56 (0.32–0.98)
Wu et al. 2003 [180]	501 cases, 594 controls, Chinese, Japanese, Filipino patients, LA county USA (see also [154])	QST based interviews for dietary habits, gynecological history, others	Dose dependent protection, OR 0.53 for >85,7 mL/day GT (CI 0.35–0.78)	Confounder: race, coffee, smoking, alcohol, soy intake, BMI, activity	>86 mL/day GT: OR 0.61 (0.40–0.93), $p_{trend}$ 0.01. For black tea drinkers OR > 1, for all subgroups OR < 1

Table 5. Evidence for GT flavonoids, surrogate parameters and breast risk.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Analysis
<b>Additional studies</b>					
Wu et al. 2008 [161]	3315 women from Singapore	mammographic density (MD) as biomarker		Ca reduced with decreased MD ( $p = 0.002$ )	Black tea: no effect; soy intake: association only in very high intake, postmenopausal women
Wu et al. 2005 [159]	130 women from Singapore Chinese Women Health	Plasma estrone levels	GT drinkers had lower plasma es-trone ( $p = 0.03$ ), black tea drinkers higher estrone values	27 regular tea drinkers, 84 irregular drinkers	
Nagata et al. 1998 [158]	50 premenopausal Japanese women	QST for dietary habits, coffee, tea; estradiol on cycle days 11, 22	GT lowered estradiol on cycle day 11		
Crew et al. 2015 [27]	Breast cancer I–III received 400 mg (10), 600 mg (11) or 800 mg polyphenon E (3 pat.)	Ancillary study to phase IB polyphenon study	Polyphenon E reduced HDGF, not vEGF, compared to placebo	Biomarker study, no clinical effect measured	
Inoue et al. 2001 [164]	1160 patients with breast cancer treated, 133 cases of recurrence in 5264 person years	QST for lifestyle factors	Decrease in breast cancer recurrence with GT >3 cups/d, especially in early stages	Histological confirmation	All patients: OR 0.69 (0.47–1.00); stage I cancer at initial diagnosis: OR 0.43 (0.22–0.84)
Nakachi et al. 1998 [163]	117 cases stage I, 273 stage II, 82 stage III; no controls	QST for dietary habits, other factors	GT associated with decreased recurrence after 7 years		No improvement in prognosis in stage III
<b>Other studies</b>					
Crew et al. 2012 [162]	For details see [27]	Mammography, biopsy	MTD for Polyphenon E 2 × 600 mg/day	Toxicity observed at all concentrations	
Samavat et al. 2015 [165]	MGTT, healthy postmenopausal women; 12 month follow up	Prospective study, bio-marker assays: mammo-graphy, sex hormones, interleukins	No results yet, description of study rationale		

HDGF—hepatocyte derived growth factor; MGTT—Minnesota Green Tea Trial; QoL: quality of Life scale; QST—questionnaire; vEGF—vascular endothelial growth factor.

### 3.4. Prostate Cancer

Like breast cancer in women, prostate carcinoma is the most prevalent hormone dependent cancer in men [181,182]. An increased risk for prostatic cancer correlates with reduced physical activity [183], high BMI [184,185] and diabetes mellitus [186]; farming has been published as a risk factor (although pesticide use is reported as protective; [187]), and lycopene from tomatoes [181,188], catechins, isoflavons and curcumin [7] are probably protective.

Prostate cancer protection by green tea has been reviewed before; Boehm et al. [37] considered only the positive study of Jian et al. [188] as being of sufficient methodological quality, no valid conclusion is possible based on one study. A pooled analysis of 21 cohort and case control studies could not find a significant cancer reduction for Asian or non-Asian patients, nor for green or black tea [189], Yuan [72] summarized current evidence for Japanese and Chinese cohorts and found the studies inconclusive.

#### 3.4.1. Prostate Cancer—Epidemiological Evidence

Prostate cancer, like breast cancer, is much more prevalent in Western than in Asian societies [175,190]; possibly because of this geographical distribution no cohort study from mainland China was identified. Results from prospective studies are ambiguous, one Singaporean study [191] and three Japanese cohort studies [192–194] found no significant reduction (Table 6). Only in a multivariate risk analysis Kurahashi et al. [193] calculated a significantly lower odds ratio of 0.52 for advanced prostate cancer in GT drinkers (CI 0.28–0.96), but not for localized prostate cancer.

Li et al. [194] prospectively investigated the combined effects of citrus fruit and GT intake in the same Japanese cohort than Kikuchi [192], with a 9 year follow up. They reported an additive effect of both foods but did not provide specific data for GT intake. In this cohort, 110 prostate cancers developed after 5 years follow up, with no significant difference for GT [192], 206 cases after 9 years, also with no obvious GT effect [194].

Four case control studies (all from mainland China) were identified between 2004 and 2014 (Table 6) [175,188,195,196]. All four studies found significant protection by GT intake, two of these studies also included fruit (nutraceuticals [196]) and vegetable consumption (vegetables not specified [195]) in addition to GT. Two case control studies with GT alone [188,196] also found a protective effect; these studies, apparently from the same cohort, report identical case and control numbers, but different OR and CI.

**Table 6.** Epidemiological studies for GT and prostate cancer.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Evaluation
<b>Cohort studies</b>					
Montague et al. 2012 [191]	27,293 Singapore Chinese men, 11.2 year follow up, 298 cases	QST for dietary habits; none, monthly, weekly, daily 1 or 2+ cups	GT—no effect (increase not significant)	Confounder: education, activity, smoking, BMI, alcohol	GT: $p_{\text{trend}}$ 0.6 (increase); black tea: $p_{\text{trend}} < 0.01$ (increase)
Li et al. 2010 [194]	20,222 Japanese adult men, Ohsaki cohort. 9 year follow up, 206 cases	QST for dietary habits, green tea intake yes/no	Additive effect of GT and citrus fruit consumption, independent effect of citrus fruit intake	Confounder: smoking, alcohol, activity, occupation	
Kurahashi et al. 2008 [193]	49,920 Japanese men JPHC study group, 11 and 14 year follow up, 404 cases	QST at begin of study, GT categories <1, 1–2, 3–4, 5+ cups/day	GT no protection, tendency for decrease in advanced stages	Confounder: age, BMI, smoking, alcohol, marital state, coffee, soy food	For advanced prostate ca., comparison of >5 vs. <1 cup/day: OR 0.52 (0.28–0.96), $p = 0.01$
Kikuchi et al. 2006 [192]	19,561 Japanese men, Ohsaki study; 110 cases	QST for dietary habits, GT intake never, <1, 1–2, 3–4, 5+ cups/day	GT no effect on prostate cancer	Confounder: smoking, alcohol, BMI, calorie intake, physical activity, meat, fish, coffee, black tea consumption	For never vs. >5 cups/d: OR 0.85 (0.50–1.43), $p = 0.81$ . 18–32 cases per group
<b>Case control studies</b>					
Li et al. 2014 [175]	250 prostate ca. cases, 500 controls, Shanghai	QST for dietary habits, GT intake yes/no	Total tea consumption, GT intake are protective, black tea not	Confounder: education, occupation, BMI, smoking, alcohol, activity, red meat, fish, soy products, personality	Total tea consumption: OR 0.63 (0.45–0.87), $p = 0.005$ , 160 cases; green tea: OR 0.66 (0.48–0.90), $p = 0.008$ , 144 cases; black tea: OR 0.75 (0.33–1.73) $p = 0.50$ , 8 cases
Wu et al. 2009a [in Chinese] [195]	85 cases, 82 controls	Life style factors, dietary habits; blood samples for polymorphisms	GT, fruit intake are protective	Confounder: age, puberty, intercourse frequency, meat. Fruit intake also positive	GT: OR 0.52 (0.28–0.96); fruit intake: OR 0.25 (0.08–0.75). CYP17 A1/A1 and A2/A2 genotypes have increased risks
Jian et al. 2007 [188]	130 cases, 274 controls, Hangzhou, China	QST for dietary habits, esp. lycopene (<1609, <3081, <4917, >4917 $\mu\text{g}/\text{d}$ ), GT (0, <3, <5, 5+ g/d)	Significant protection in all tea dose groups, all lycopene group, all combination groups	Confounder: BMI, residency, education, marital status, fat intake, fruits	Highest dose GT: OR 0.13 (0.05–0.32), highest dose lycopene: OR 0.17 (0.08–0.39); combined: OR 0.03 (0.01–0.16); low case numbers in high intake groups (9, 13, 3 cases)
Jian et al. 2004 [196]	130 cases. 274 controls (see [188])	QST interviews for dietary habits, GT dose in cups/day (<1, 1–3, >3)	GT protects from prostate cancer	BMI, residency, education, marital status, vasectomy	GT drinker: OR 0.28 (0.17–0.47); increasing effect with tea amount and duration of drinking

### 3.4.2. Prostatic Cancer—Additional Evidence

Already in 2005, a “proof of principle” study tried to establish PSA as surrogate marker [197], but failed to show a protective effect in its 19 patients. A number of intervention studies in prostate cancer patients have been published using PSA or other surrogate endpoints (Table 7). A review of 44 clinical trials [198] describes large heterogeneity in clinical data presentation; only one trial using a combination of fruits and GT was judged as having sufficient data quality [199]. This study found a lower rise in PSA in the intervention group, as did another study supplementing Polyphenon E instead of GT [200]. In a similarly designed study comparing EGCG extract versus placebo, a significant decrease was obtained only for the combined endpoint “carcinoma plus atypical small acinar proliferations” but not for prostate cancer alone [201]. Contrary to these results, Gontero et al. [202] reported an increase in prostate cancer incidence in patients with high grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferations (ASAP), after supplementing the diet with selenium, lycopene and GTE.

Significant effects were seen in studies using other surrogate markers for tumor progression (Table 7); a mix of pomegranate, GT, broccoli and turmeric decreased NFkB expression in tumor tissue, 8-OH guanine excretion in the urine and PSA in the serum of older British prostate cancer patients, but failed to change the clinical outcome [199]. In a US study, freshly brewed GT decreased NFkB in tumor tissue and serum PSA; black tea had no effect on these parameters, apoptosis was not influenced by either tea [Henning 2015]. Taken together, these clinical studies indicate that GTE likely lacks any effect on prostate cancer growth or recurrence.

Kumar et al. [203] proposed a design for clinical trials. They argue that pharmacology data for nutraceuticals like Polyphenon E and food supplements like GT should be included in any study protocol, as well as for extending these studies to realistic clinical time scenarios relevant for tumor progression (i.e., 5 to 20 years observation). A preliminary evaluation for Polyphenon E versus placebo after one year follow up found no effect [201].

### 3.4.3. Prostatic Cancer—Nonhuman Evidence

Cell culture data and epigenetic changes [204] for surrogate parameters are contradictory. In analogy to studies with breast cancer cell lines, much effort has been put into hormonal studies; GT has been shown to inhibit testosterone glucuronidation (summarized by [205]) although the authors do not discuss the discrepancy between inhibition of testosterone hormone metabolism and testosterone stimulation of carcinoma growth. Inhibition of 5- $\alpha$ -reductase activation [206] or testosterone receptor inactivation [207] allude to hormonal effects, antagonism of bortezomib cytotoxicity by EGCG [208], or induction of Toll-like receptor 9-agonistic stimulating immune responses [209] have been forwarded as alternative mechanisms. All these studies postulate an effect for secondary prostate cancer prevention; based on these results in prostate tumor cell lines, Fujiki and Suganuma [210] proposed adding GT catechins to (traditional) chemotherapy.

Other studies do not support a primary or secondary preventive effect; EGCG addition decreased *in vitro* the effectivity of radiation [211] in tumor cell cultures. Thus, epidemiological data do not support GT effects in prostate cancer, only a minority of case control studies show significant reductions. Intervention studies with GT extracts or GT have been effective only for surrogate parameters, but not for clinical tumor recurrence.

**Table 7.** Green tea effects, surrogate parameters and intervention studies for prostate cancer.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Analysis
<b>Additional studies</b>					
Erdrich et al. 2015 [212]	20 men with prostate cancer. 3 month intervention with Mediterranean diet; New Zealand	PSA, CRP, DNA damage; QST for dietary habits	DNA damage is lower in patients with GT ( $p = 0.002$ )	Confounder: diet, folate, vitamin C intake, legumen	Significant reduction for adherence to diet, folate, vitamin C intake, legumen
Gontero et al. 2015 [202]	60 patients with PIN/ASAP; 6 month intervention study; Italy	35 mg lycopene + 55 µg selenium + 600 mg GTC	PCa increased in intervention group	No quantitative calculation	
Kumar et al. 2015 [201]	97 men, high grade PIN/ASAP; 1 year intervention; USA	Polyphenon E, 400 mg EGCG/d vs. placebo	Only for combined endpoints—ca. + ASAP growth reduction	No difference in adverse drug effects	Prostate ca.: no difference; combined endpoints prostate ca + ASAP: $p = 0.024$
Henning et al. 2015 [213]	Open label phase II trial, 93 cases, USA	6 cups GT, BT or water, prior to prostatectomy	GT decreased cell activation (NFkB), DNA damage (8OHG-excretion)	Black tea had no effect	NFkB decrease: $p = 0.013$ , urinary 8OHG-excretion: $p = 0.03$
Thomas et al. 2014 [199]	199 cases with localized prostate cancer	Mix of pomegranate, GT, broccoli, turmeric	Short term decrease in PSA	No data on clinical benefit	
Nguyen et al. 2012 [200]	50 prostate cancer cases, 3–6 weeks before surgery	800 mg/day Polyphenon E vs. placebo	PSA n.s. reduced		
Bettuzzi et al. 2006 [214]	60 PIN cases, 1 year follow up	600 mg GTC, proof of principle study	1 case in intervention group, 3 cases in control group		
Choan et al. 2005 [197]	19 patients with hormone refractory cancer	500 mg GTE	No effects observed	4 drop outs, all patients had progression after 4 month	

ASAP: atypical small acinar proliferations; PIN: prostate intraepithelial neoplasia.



### 3.5. Esophageal Cancer

The upper gastrointestinal tract is the first to come into contact with beverages, they are directly affected by temperature, and they are the only organs in contact with nonresorbable components. Among esophageal cancers, location (proximal and distal carcinoma) and histological subtype (adenocarcinoma and squamous cell carcinoma) can be separated [215–219], with differing etiology and prognosis. The upper gastrointestinal tract is most likely to show a specific response; this has been proven for viruses like human papilloma viruses [220] or hot and spicy food [221–223], cooking with wood and coal also are likely etiological agents [224,225]. In addition, genetic factors [226,227] contribute to the individual cancer risk, antibiotic treatment of *H. pylori* gastritis has caused a shift from squamous cell carcinoma to adenocarcinoma in esophageal cancers [218].

#### 3.5.1. Evidence from Epidemiological Studies

Boehm et al. [37] in their Cochrane review included one cohort study [228] and five case control studies; none of these studies was judged to have a sufficiently high methodological quality, so no conclusion was drawn. Reviews of Chinese studies [78,229] found conflicting evidence at best for a preventive effect of GT in esophageal cancer.

The only prospective cohort study in Miyagi prefecture, Japan, [228] found an increase in esophageal cancers in tea drinkers and attributed this increase to the heat rather than the type or amount of tea. Only one case control study [230] reports a decrease in esophageal cancer by green tea drinkers; since only scant details are available from the abstract, this study cannot be assessed.

Two other recent case control studies [231,232] confirm the lack of protective effects by GT, as well as the well known carcinogenic effect of hot tea [221,233]. Chen et al. [232] even used tempered tea to quantify the consumption temperature; their results do not find a protection by GT, but a cancer rate increased by temperature. Most older studies, i.e., before 2011, did not report GT temperature; even in 2014 a questionnaire was used without quantifying tea temperature [231]. Temperature as a confounder ought to be included in all studies on esophageal diseases.

Seven case control studies are included in Table 8, with one exception [231] all were located in China. The oldest study in Shanghai [234] found a lower cancer rate in female never-smoking GT drinkers, but not in male smokers. However, their study group was living in the Shanghai urban environment, and only 2/3 of the cases were histologically confirmed. An increase of esophageal cancers with hot food, but a protective effect of GT was described for women ever drinking GT in two other Chinese case control studies [230,235]. In contrast, Wu et al. [233] compared two areas in rural China with large differences in esophageal cancer incidence; they found no effect of GT and a significant increase in esophageal cancers with tea temperature, especially in the low incidence county. Also, the only non Chinese study in Japan [231] found increased upper gastrointestinal tract cancers in GT drinkers. All epidemiological studies with a putative protective effect are case control studies, whereas the cohort study and two case control studies calculated a procarcinogenic effect of hot beverages. GT does not prevent esophageal cancer, hot tea increases the cancer incidence.

Wang et al. [236] published the only prospective intervention study in 100 patients with precancerous esophageal lesions and compared the secondary protection of decaffeinated GT, calcium supplementation or placebo, given for one year. After 11 years follow up no GT effect was reported.

**Table 8.** Correlation of GTE consumption and chemoprevention of esophageal cancer.

Study	Cohort	Observation	Outcome	Comments	Statistical analysis
<b>Cohort studies</b>					
Ishikawa et al. 2006 [228]	9008 men (cohort 1), 17,715 men (cohort 2), Japan	QST for beverage consumption; GT (0, 1–2, 3–4, 5+ cups/day), black tea yes/no	No effect on esophageal cancer in either cohort, with tendency to higher incidence	Smoking, alcohol esophageal carcinogens	Green tea: OR 1.67 (0.89–3.16), $p_{\text{trend}} = 0.04$ . For non-smoking, non-alcohol GT drinker: OR 1.65 (0.29–9.19), $n = 4$ .
<b>Prospective interventional study</b>					
Wang et al. 2002 (in Chinese) [236]	100 histologically confirmed precancerous lesions in each study group; 578 precancerous lesions in total; China	Calcium, decaffeinated GT or placebo for 11 month; 11 year follow up	No effect of decaffeinated GT on tumor progression	No effect of treatment with Ca or DGT	No statistical calculation.
<b>Case-control studies</b>					
Wang et al. 1999 (in Chinese) [230]	209 UADT cases, 68 esophageal cancers, 69 cardia cancers, 72 gastric cancers; China	Observational study, no information about reference group	Increase with pickled vegetables	Scant data	Green tea: OR 0.20; fruit: OR 0.51
Oze et al. 2014 [231]	961 UADT, 2883 controls, Aichi, Japan	QST for coffee, green tea consumption, life style factors	Esophageal cancer—no effect; UADT, oral, pharyngeal, larynx ca.—increase	Confounder: age, smoking, alcohol, BMI, food, occupation, rice consumption	>3 cups GT and UADT cancer: OR 1.39 (1.13–1.70); esophageal cancer: OR 1.31 (0.95–1.814); oral, pharynx, larynx cancer: OR 1.47 (1.12–1.93)
Chen et al. 2011 [232]	150 cases with esophageal cancer, 300 controls, South China	QST for life style factors, low temp. vs. high temp. tea drinkers	GT has no effect, heat is carcinogenic	Additive effects effects with smoking, alcohol	For >250 g tea/month: <60 °C: OR 0.79 (0.29–0.97); >70 °C: OR 1.25 (0.61–1.69)
Wu et al. 2009 [233]	1520 cases, 3879 controls in high risk (Dafeng), low risk (Ganyu) area in China	QST for beverage intake, low temp. vs. high temp. tea drinkers	Hot tea is carcinogenic, for GT no consistent effect	Confounder: age, education, BMI, smoking, alcohol. No information on temperature estimate	Drinking hot tea: OR 1.9 (1.2–2.9) in high incidence area, and 3.1 (2.2–4.3) in low incidence area
Wang et al. 2007 [235]	355 histologically confirmed cases, 408 controls, Jiangsu, China	In person interviews, GT yes/no; duration 0, <30, >30 years	No effect of GT in men when controlled for confounders	Positive ass. for heat, smoking, alcohol, old stocked rice, chili, salty food	Men, GT drinker: OR 1.368 (0.948–1.975), $p = 0.094$ ; women: 3 cases
Mu et al. 2003 (in Chinese) [237,238]	628 cancer cases; Taixing and Jiangsu counties, China	No information given in abstracts	GT decreases esophageal cancer incidence in smokers, drinkers	Only scant details, no information on statistical evaluation	
Gao et al. 1994 [234]	1016 cancer cases, 902 in-terviews, 734 histologically confirmed; Shanghai, China	In person interviews for life style factors, incl. dietary habits. GT in 1–199; 200+ g/month tea	In women significant de-crease even in smokers, alcohol drinkers; in men effects n.s.	Confounder: alcohol, heat, smoking	All male groups: n.s.; women, GT: OR 0.34 (0.17–0.69), $p > 0.01$ ; women, nonsmoker: OR 0.17 (0.05–0.58), $p < 0.001$ ; for women low case numbers

QST—questionnaire-based assessment; UADT—upper aerodigestive tract.

### 3.5.2. Esophageal Cancer Prevention—Nonhuman Studies

For esophageal cancer, studies for possible mechanisms were published; hypermethylation of the repair gene O<sup>6</sup>-methylguanine-DNA-methyl transferase (MGMT) was found in tumor tissue from esophageal squamous cell cancers in Jiangsu province, China, a high incidence county [239]; GT drinking did not change the methylation status. In this county also, three case control studies [233,235,237] were performed. The catechin preparation Polyphenon E reduced growth and inhibited Bcl2 activity in Flo-1 esophageal cancer cells [240]. Numerous other effects have been investigated in vitro, usually in cell cultures from esophageal carcinoma; all studies used GT or catechin concentrations far in excess of concentrations usually obtained after GT drinking.

### 3.6. Gastric Cancer

The stomach is the organ with close contact to food and beverages for an extended time; additionally, gastric cancer is among the most common cancer forms with >600,000 cases annually. The incidence is especially high in Japan as compared to other countries [241]. Therefore, risk factors for gastric cancer and its association with GT or GTE have been investigated in six cohort studies from Japan [242–247], but no similar cohort study was published from other countries (Table 9). A variety of factors have been used to explain areas of high incidence, among them dietary nitrite and nitrosamines [248] or high salt food [249] as food specific carcinogens, and gastric inflammation in *H. pylori* infection [250]. As protective factors, fruit and vitamin C intake has been published [249].

A Cochrane review [37] included 27 studies for digestive tract cancers but found no evidence for gastric cancer protection by GT or GTE. Zhou et al. [251] included 4 cohort studies and 10 case control studies from Chinese language data bases. In contrast to other reviews they found a slight protective effect (OR 0.68, CI 0.49–0.92) in population based case control studies, whereas hospital based case control studies or cohort studies did not show significant effects [251]. A review by Hou et al. [252] included 17 studies, 11 of these in Japan and one in Hawaiians of Japanese descend. In 5 studies a significant cancer decrease was calculated for one subgroup, for one other subgroup a positive correlation was found. Of note, hot tea was found to be protective in one Chinese population-based case control study [253].

#### 3.6.1. Gastric Cancer—Epidemiological Evidence

Inoue [242] published the most recent meta analysis with 219,080 participants from six pooled Japanese studies and calculated a small protective effect by GT only for women with distal gastric carcinoma, with an OR of 0.79 (0.65–0.96); for men, no reduction was seen. When using plasma catechin concentrations, a significantly increased gastric cancer risk was found for men at high EGC levels (OR 2.06; 1.23–3.45) [245]. All studies included in these analyses originated from the same Japan Public Health Center (JPHC) study; therefore a confirmation from a different cohort is still lacking. Two other cohort studies from Japan with less participants did not find an effect of GT on gastric cancer incidence [243,247], nor did GT decrease the incidence of gastric cancer in the Hiroshima atomic bomb survivor cohort [246].

With one exception [254] published 11 years earlier, all case control studies were performed in China (Table 9); some Chinese areas also have a high gastric cancer incidence, but still lower than in Japan [241]. The results from these studies are ambiguous at best: the Japanese study found a decrease with high GT intake (set at >10 cups GT/day) [254]; two Chinese studies [230,237,238] found a similar protection with “high GT intake”, which here was set at >250 g tea/month. Another study in Fujian, a high incidence area [255,256], again reported an increase in gastric cancer incidence (OR 1.72, CI 1.26–2.36).

**Table 9.** Correlation of GTE consumption and chemoprevention of gastric cancer.

Source	Participants	Evaluation Criteria	Outcome	Comments	Statistical Analysis
Inoue et al. 2009 [242]	3577 gastric cancer cases, 219,080 subjects, cohort study. Reanalysis of study data from six pooled studies	Mostly QST based beverage intake, confounders; GT consumption 0, <1, 1–2, 3–4, 5+ cups/day	Proximal gastric cancer: no effect		Cancer in women: OR 0.79 (0.65–0.96); distal stomach in women: OR 0.70 (0.50–0.96); proximal stomach women: no cases
Sasazuki et al. 2008 [245]	494 cancer cases, 36,745 cohort size, 14 year observation; nested study	QST for beverage intake, lifestyle factors; plasma level of GT metabolites	Men EGC sign. increased gastric cancer; women: ECG decreased gastric cancer	Confounder: smoking, alcohol, salt intake, fish, vegetables, BMI	In men all flavonoids increased risk; EGC > 78 ng/mL: OR 2.06 (1.23–3.45), $p_{\text{trend}} = 0.003$ . In women all flavonoids decreased, ECG > 10 ng/mL: OR 0.25 (0.08–0.73), $p_{\text{trend}} 0.02$ (10 cases)
Sauvaget et al. 2005 [246]	Gastric cancer in 36,576 atomic bomb survivors	QST with mail survey; follow up study	No association with GT, soy products, fruit, vegetables	Significant cancer increase at 10 Gy	GT 5+ cups/day vs. <1: OR 1.06 (0.89–1.25), $p_{\text{trend}} > 0.50$
Sasasaki et al. 2004 [244]	Prospective cohort study, 892 gastric cancer cases, 72,943 participants	Registry study 1990 (cohort I), 1993 (cohort II); GT intake <1, 1–2, 3–4, 5+ cups/day	GT: no effect in men; women protected at high doses for distal tumors	Confounder: smoking, alcohol, dietary habits, salt, coffee	Women, distal: OR 0.51 (0.3–0.86), $p_{\text{trend}} = 0.01$ ; men, distal: OR 0.92 (0.69–1.22), $p_{\text{trend}} 0.37$
Koizumi et al. 2003 [243]	31,345 Subjects >40 years since 1984, 47,605 people >40 years since 1990.	QST for GT consumption (GT intake <1, 1–2, 3–4, 5+ cups/day)	No influence of tea on gastric cancer incidence, total and subgroups	Confounder: smoking, alcohol, di-etary habits, salt, coffee. Subgroups by histology and anatomy	Multivariate analysis; OR 1.06 (0.86–1.30), $p_{\text{trend}} 0.61$
Tsubono et al. 2001 [247]	26,311 residents, Miyagi, Japan, 1984–1992 419 gastric cancer cases	QST for GT consumption (GT intake <1, 1–2, 3–4, 5+ cups/day)	No association for men and women, tendency to cancer increase	Peptic ulcer, smoking, alcohol, dietary habits	Highest group: OR 1.4 (1.0–1.9), $p_{\text{trend}} 0.07$ ; men: OR 1.5 (1.0–2.3), $p_{\text{trend}} 0.05$ ; women: OR 1.1 (0.6–2.0), $p_{\text{trend}} 0.86$
<b>Case control studies</b>					
Mao et al. 2011 [257]	200 gastric cancer patients, 200 controls	In person interviews for beverages, hot or cold tea	Hot tea increases cancer risk, temperature, concentration dependent	Other factors smoking, drinking; protective SES	All patients: OR 2.59 (1.02–6.32), hot tea: OR 1.82 (1.03–3.52), very hot tea: 3.07 (1.78–7.36)
Deandrea et al. 2010 [258]	266 gastric cancer, 533 controls in Harbin, China	Tea temperature	Warm tea is protective, hot tea not.		Luke warm GT: OR 0.19 (0.07–0.46), hot tea: OR 1.27 (0.85–1.90)
Mu et al. 2003, (in Chinese) [237,238]	Population based study, 206 gastric cancer cases, 415 controls, Jiangsu China	Subgroups by amount of tea per month	Cancer incidence reduction of 60% at high amounts (>250 g/month)	See also esophageal cancer study, liver cancer study	In one paper (2003) 60% reduction, in the other paper 81% reduction for alcohol drinkers, 16% for smokers.
Ye et al.; 1998 [255,256]	272 cases, 544 controls in high risk area Fujian, China	Face to face interviews, tea consumption and lifestyle factors.	Gastric cancer risk decreases with GT	Alcohol, smoking, dietary habits, salt, fruit, fish.	GT <0.75 kg/year versus >0.75 kg/y: OR 1.72 (1.26–2.36)
Wang et al.; 1999 (in Chinese) [230]	131 gastric cancer cases, case control study, Jiangsu, China		GT reduces gastric cancer	Study included esophageal and gastric cancer	For GT intake: OR 0,28
Kono et al.; 1988 [254]	139 gastric cancer cases, 278 area controls, 2574 hospital controls, Kyushu	QST for tea intake, lifestyle factors	Protective effect of >10 cups of tea/day	Confounder other food types, smoking, alcohol	>10 cups/day: OR 0.6 (8 cases), $\chi^2 0.89$

QST—questionnaire-based data collection; SES = socioeconomic status.

The two most recent case control studies [257,258] confirmed a temperature dependent increase in gastric cancer (Yunnan province, southwest China, OR 3.07, CI 1.78–7.36 for very hot tea [257]; Heilongjian province, Northeast China: OR 1.27, CI 0.85–1.90 for hot tea [258]). Hot beverages are risk factors for gastric cancer (Linzhou, China, any beverage [259–261], as well as esophageal cancer [221–223,262]; however, hot food is not accepted as an independent factor [222,263]. Therefore, beverage temperature should be considered as a relevant confounder.

Whereas all studies indicated a larger protective effect in women, OR values were often not significantly different from 1 [264]; only when the 6 studies with the largest effect (from 11 studies included) were considered separately, the pooled OR change of 0.79 (CI 0.65–0.96) was significant [242,264]; this analysis was heavily influenced by studies from the same large JPHC cohort [242,264]. A slight protective effect for nonsmoking Japanese women may be present but appears unlikely; no protective effect has been published or suggested for other cohorts.

### 3.6.2. Gastric Carcinoma Prevention—Nonhuman Evidence

GTE inhibits *H. pylori* growth both in vitro and in animal models [265]; this effect may delay infection or reinfection after eradication therapy and reduce inflammation-mediated carcinogenesis. In animal studies both GTE and EGCG reduced gastric cancer incidence; apoptosis induction, cell cycle arrest and inhibition of metastasis are forwarded as possible mechanisms [26]. Multiple other cellular pathways and interleukin modulations involved in these mechanisms are altered by GT or GTE, including IL-8 and NFκB inhibition in gastric adenocarcinoma cells [266]. However, no convincing mechanism has been proven or suggested which could explain a postulated chemopreventive effect of GT against gastric cancers.

## 4. Risk—Benefit Analysis

Herbs and herbal extracts can harm the consumer [267,268]; for GTE the general safety of 843 mg EGCG has been described [166], with only minor adverse effects. Drinking green (or black) tea in itself likely does not carry a risk [37] since the amount of absorbed catechins remains low at or below 1 μmol/L [269]; herbal extracts including green tea extracts with much higher amounts of catechins and flavones can cause hepatotoxicity [268,270–272]. This compares to other plant extracts which are toxic in larger amounts if taken as tea (or in other preparations) [13,271,273], or in excessive doses as has been shown for caffeine [274,275].

Adverse effects were observed in Swiss Webster mice at 2000 mg/kg/day [276], approximately 200 fold higher than the toxic dose in humans; 1000 mg/kg/day Polyphenon E were well tolerated by C57Bl/6J mice [277]. Similarly, goitrogenic effects were observed in rats only in food concentrations in excess of 0.625%, equivalent to 600 mg/kg/day [278]. In fasted dogs, 150 mg/kg/day GT catechins have been lethal [279]; the relevance of this finding for humans is unclear but the dose still is much higher than the above estimate of 10 mg/kg/day for human toxicity.

Potential adverse effects of green tea extracts in humans have been tested for Polyphenone E containing approximately 50% EGCG and 30% other catechins [276]. 800 mg Polyphenon E catechins, equivalent to 8 cups green tea with 100 mL volume [269], did not cause detectable adverse effects in probands [280]. In neurological patients, however, 1 (of 10) participants developed hepatotoxicity, in a follow up safety protocol study 5 of 12 patients also developed liver dysfunctions [281]. Crew et al. [162] found one dose limiting liver toxicity with 800 mg/day Polyphenon E in breast cancer patients. Assuming 75 kg body weight, 800 mg catechins per day results in approx. 10 mg/kg bw/day which has been safe in all animal studies. GT and GTE are advertised and sold for primary prevention but will not only be taken by healthy people; in some people GT may cause adverse effects at even lower doses as has been demonstrated for hepatotoxic effects in cancer patients, e.g., patients with preexisting liver impairments.

Table 10 lists the number of cohort studies which found a protective effect of GT on cancer prevention (positive), no protective effect (no effect) or a procarcinogenic effect of GT on cancer (negative).

**Table 10.** Summary of studies and principal outcome, by country of origin.

Tumor type	China, Cohort	China, Case Control	East Asia, Cohort	East Asia, Case Control	Rest of World, Cohort	Rest of World, Case Control
Lung cancer	1; positive	3; 2 positive, 1 negative	2; no effect	0	1; no effect	2; 1 no effect, 1 negative
Colorectal cancer	2; 2 positive	3; 3 positive	5; 1 positive, 3 no effect, 1 negative	2; 1 positive, 1 no effect	3; 3 no effect	4; 3 no effect, 1 negative
Breast cancer	1; partially positive	6; 6 positive	2; no effect	5; 2 positive, 3 no effect	0	2; 2 positive
Prostate cancer	0	4; 4 positive	3; no effect	0	0	0
Esophageal cancer	2; 1 positive, 1 no effect <sup>a</sup>	5; 3 positive <sup>b</sup> , 2 negative	1; no effect	1; 1 negative	0	0
Gastric cancer	0	5; 4 positive <sup>d</sup> , 1 negative	5; 3 positive <sup>c</sup> , 2 no effect	1; 1 positive	0	0

China, cohort: cohort study from mainland China; <sup>a</sup>: prospective intervention study, 11 year follow up (Wang et al., 2002 [233]); <sup>b</sup>: 1 study positive, 1 study positive for women only, 1 study positive for cool tea, negative for hot tea; <sup>c</sup>: one study—positive only for distal gastric carcinoma in women, two studies—women decrease, men increase in OR; <sup>d</sup>: 2 studies decrease of OR for cool tea, increase for hot tea; 2 studies decrease of OR for all cases.

For the cancer types included in this review no benefit was seen in cohort studies. We selected lung and colorectal carcinoma as frequent cancer types with major exogenous factors (smoking, diet); breast and prostate cancer as cancer types with a strong hormonal control; and esophageal and gastric cancer from the organs of first contact with beverages and food. Published results vary strongly depending on the country of origin (see Table 10, with cohort and case control studies sorted by country). For lung, CRC, breast, prostate and gastric cancer, case control studies and even a few cohort studies report a protective effect. However, among these studies the comparability is very low, and methodological problems further complicate an interpretation. In case control studies the status of the participants as cancer cases usually is determined histologically, although not all studies have used this criterion [234]. Retracing food and beverage intake for decades is difficult and prone to recall bias [282]. Among the studies, no consistent quantification for GT consumption is used; some studies compare non-drinkers and GT-drinkers, others quantify the amount of GT in “cups per day” or in “grams tea per month or year”. These differences make a meta-analysis impossible. Some studies found drinking tea procarcinogenic (e.g., lung cancer: [71,81]); the publication of both positive and negative results nearly preclude the presence any protection by GT drinking.

Table 10 summarizes the studies according to positive (preventive), no effect, and negative findings. For lung cancer, 2 of 5 case control studies have found a positive association, for esophageal cancer 3 of 6 studies, for gastric cancer 1 of 6 studies, and for colorectal cancer 2 of 9 studies; for cohort studies one publication for colorectal cancer in Singaporean Chinese women [105] even found a procarcinogenic effect. A possibility for a protective effect of large amounts of GT appears to exist for breast cancer—four of nine case control studies outside China, and all six case control studies from China found a small protection—and for prostate cancer, where four case control studies were protective, but 3 cohort studies failed to find a protection. These cancer types are hormonally affected; in epidemiological studies, estrogen or testosterone activity has not been included, a consistent mechanism from other experiments has not yet been forwarded.

A surprising aspect is the large number of positive studies from mainland China cohorts, in contrast to cohort studies from other countries (including cohorts of ethnic Chinese); among the six cohort studies from China only one could not find a significant prevention, and one found a protection for a relevant subgroup. Among 22 cohort studies from other countries 17 could not find a protective effect, one study found an increase in CRC by green tea. For case control studies this phenomenon also existed, with only four from 26 studies from China reporting no significant protection, three of these studies for esophageal and gastric cancer, where temperature is a relevant confounder (Table 10). Similarly, in the 17 case control studies from other countries only 6 reported a



protection, four of these six studies for breast cancer. For prostate cancer, no case control study was published for cohorts from outside China.

This difference between mainland Chinese studies and other studies is not yet explained. Explanatory genetic variants have not been identified in Chinese (or other) populations, although this does not rule out genetic factors. Another explanation may be a specific lifestyle, or cultural differences. However, studies in cohorts of Chinese ancestry in Singapore, Australia or California could not confirm the results from Chinese studies. Another contributing factor may be the lack of standardization for green tea, with differences in the extract composition, or the fact that some studies were performed with EGCG extracts.

Drinking GT does not pose harm. However, GT or GTE does not influence cancer initiation or promotion, with a possible exception for breast cancer, and esophageal and gastric cancer increase. For these tumors the findings should be confirmed in well-designed and controlled cohort studies. For lung, CRC and prostate cancers, GT likely is ineffective, hot tea increases the esophageal and gastric cancer incidence.

## 5. Conclusions

The association of drinking green tea with longevity has long been known. Among the many possible explanations, cancer chemoprevention by GT catechins has ranked high. Possible protective effects have been published and are indicative for the hormone sensitive mammary and prostate cancer types, but not for lung, colorectal, esophageal or gastric cancer. Only a few positive prospective studies, and some retrospective case control studies have been published, mainly from China. Many other case control studies, and most prospective cohort studies could not find a chemopreventive effect. Thus the longevity of green tea drinkers likely is due to other (or additional) factors, which may include genetic and lifestyle factors, which could also explain the predominance of chemopreventive effects in Chinese studies. Other health benefits may contribute to the longevity, like the prevention or amelioration of major diseases like diabetes mellitus, hypertension, atherosclerosis or coronary heart disease.

## 6. Suggestions for Further Study

Further research in chemoprevention should emphasize in prospective studies the possible link between green tea and the hormonally affected cancer types; strict control for confounder variables will also identify possible susceptible subgroups. In vitro studies should use primary cell culture systems rather than tumor cell lines; the experimental design and outcome parameters should be closely linked to the initial steps in tumor development, i.e., cell growth, loss of contact inhibition, inhibition of apoptosis and DNA repair. Nonspecific parameters (e.g., reactive oxygen species formation) may be relevant if a causal connection to tumor development is likely. Tumor cell growth or resistance to cytostatic compounds, i.e., research in tumor cell lines, are relevant for cancer treatment but not for primary prevention, and do not contribute to the understanding of cancer chemoprevention. Outside the scope of this review, alternative mechanisms to explain the longevity of green tea drinkers should be investigated, including antiatherosclerotic or antiinflammatory mechanisms.

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