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Chapter 8. Tea and Cancer Prevention: Epidemiological Studies

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Abstract

Experimental studies have consistently shown the inhibitory activities of tea extracts on tumorigenesis in multiple model systems. Epidemiologic studies, however, have produced inconclusive results in humans. A comprehensive review was conducted to assess the current knowledge on tea consumption and risk of cancers in humans. In general, consumption of black tea was not associated with lower risk of cancer. High intake of green tea was consistently associated with reduced risk of upper gastrointestinal tract cancers after sufficient control for confounders. Limited data support a protective effect of green tea on lung and hepatocellular carcinogenesis. Although observational studies do not support a beneficial role of tea intake on prostate cancer risk, phase II clinical trials have demonstrated an inhibitory effect of green tea extract against the progression of prostate pre-malignant lesions. Green tea may exert beneficial effects against mammary carcinogenesis in premenopausal women and recurrence of breast cancer. There is no sufficient evidence that supports a protective role of tea intake on the development of cancers of the colorectum, pancreas, urinary tract, glioma, lymphoma, and leukemia. Future prospective observational studies with biomarkers of exposure and phase III clinical trials are required to provide definitive evidence for the hypothesized beneficial effect of tea consumption on cancer formation in humans.

Keywords

cancer prevention; catechins; black tea; epidemiology; green tea; polypehnols

1. Introduction

Tea is the second most consumed beverage worldwide after water. All tea is produced from the leaves of *Camellia sinensis*, but differences in processing result in different types of tea. In the processing of green tea, fresh tea leaves are steamed or heated immediately after harvest, resulting in minimal oxidation of the naturally occurring polyphenols in the tea leaves. On the other hand, in the processing of black tea, the tea leaves are dried and crushed

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upon harvesting to encourage oxidation, which converts the indigenous tea polyphenols (primarily catechins and gallocatechins) to other polyphenols (mainly theaflavins and thearubigens). Finally, partially oxidized tea leaves yield Oolong tea [1]. Worldwide about 78% of the tea production is black tea, which is the main tea beverage in the United States, Europe, and Western Asia [2]. Green tea, which is popular in Japan and parts of China, accounts for about 20% of total tea production. The remaining 2% of tea production is Oolong tea, which is mainly consumed in southeastern China and Taiwan.

Tea, from a biological standpoint, is a mixture of a large number of bioactive compounds including catechins, flavonols, lignans, and phenolic acids. A typical cup of green tea, brewed with 2.5 g of dry tea leaves in 250 ml of hot water (called a 1% tea infusion) contains 620-880 mg water-extractable materials, of which 30-40% are catechins and 3-6% caffeine. A similarly prepared cup of black tea contains 3-10% catechins, 3-10% caffeine, 2-6% theaflavins and 15-20% thearubigins of the dry weight of black tea extract [3,4]. Epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epicatechin (EC) are the major catechins in green tea [1].

The widespread consumption of tea throughout the world evoked the interest of the scientific community in assessing tea's beneficial potentials on health including cancer preventive activities. Extensive laboratory studies in multiple animal models have consistently shown the inhibitory activities of green and black tea extracts and green tea polyphenols against tumorigenesis at different organ sites. Epidemiologic studies suggest that drinking tea offers some protection against the development of cancer at several organ sites in humans. However, the results are inconsistent. This chapter provides a general overview of the pertinent epidemiological studies on tea consumption and the risk of cancer at different organ sites in humans.

2. Tea and cancer by organ site

2.1 Oral cavity and pharynx

Although numerous epidemiologic studies examined the association between dietary factors and risk of oral and pharyngeal cancers [5], there are limited data on the effect of tea consumption on these malignancies. Combining a series of case-control studies in Italy with a total of 119 patients with cancer of the oral cavity and 6147 hospital controls, La Vecchia et al. reported a reduced, but statistically non-significant, risk of oral cancer with black tea consumption; odds ratio (OR) was 0.6 [95% confidence interval (CI) = 0.3, 1.1] for subjects who consumed ≥1 cups/day of black tea relative to nondrinkers [6]. Using a similar approach, Tavani et al. combined datasets of two hospital-based case-control studies conducted in Italy and Switzerland, respectively, and reported no association between black tea consumption and oral cancer risk (OR = 0.9; 95% CI = 0.7, 1.1 for ≥1 cups/day versus occasional or nondrinkers) [7]. Recently, Ren et al. examined the association between black tea consumption and the risk of developing oral and pharyngeal cancers in the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) Diet and Health Study [8]. The NIH-AARP cohort study enrolled 481,563 AARP members aged 51-71 years who resided in eight states of the United States in 1995-1996. After up to 8 years of follow-up, 392 study participants developed oral cancer and 178 developed pharyngeal cancer. The study demonstrated a statistically significant inverse relationship between consumption of hot tea and risk of pharyngeal cancer (P for trend = 0.0003). Compared with non-drinking, the hazard ratio (HR) of pharyngeal cancer for ≥1 cups/day of hot tea was 0.37 (95% CI = 0.20, 0.70). There was a suggestive inverse relationship between hot tea intake and risk of oral cancer (HR=0.75; 95% CI = 0.53, 1.06) [8]. Consumption of iced tea was not associated with risk of oral or pharyngeal cancer.

There was one prospective cohort study that examined the association between green tea consumption and risk of oral cancer in the Japan Collaborative Cohort Study. The cohort consisted of 50,221 Japanese men and women aged 40-79 years at baseline and identified 37 incident oral cancer cases after 10.3 years of follow-up. HRs of oral cancer for the consumption of 1-2, 3-4, and ≥5 cups/day of green tea were 0.65 (95% CI = 0.22-1.94), 0.69 (95% CI = 0.28-1.71), and 0.44 (95% CI = 0.19-1.04), respectively, compared to <1 cup/day (*P* for trend = 0.07). The inverse association was slightly stronger for women than for men [9]. The inverse relation did not reach statistical significance due to the relatively small number of cancer cases included in the analysis.

A randomized, placebo-controlled, phase II clinical trial was conducted to examine the effect of green tea extract on the oral mucosa leukoplakia, a well established precancerous lesion of oral cancer [10]. Fifty-nine patients were randomly assigned to either the treatment group, who were given 3 g/day of a mixed green tea product composed of dried water extract, polyphenols and pigments, or the placebo group. After 6 months, 37.9% patients in the green tea treatment arm showed reduced size of oral lesions whereas 3.4% patients had increased lesion size. In contrast, 6.7% patients in the placebo group had decreased and 10% patients had increased size of oral mucosa leukoplakia. The differences in the changes of lesion sizes between the treatment and placebo arms are statistically significant ($P = 0.03$) [10]. Recently, Tsao et al. completed another randomized, placebo-controlled phase II trial to evaluate the oral cancer prevention potential of green tea extract [11]. Forty-two patients with one or more histologically confirmed, bidimentionally measurable oral premalignant lesions with high-risk features of malignant transformation that could be sampled by biopsy were randomly assigned to receive 500, 750, or 1000 mg/m^2 of green tea extract per day or placebo orally. The efficacy was determined by the disappearance of all lesions (a complete response) or 50% or greater decrease in the sum of products of diameters of all measured lesions (a partial response). At 12 weeks after the initiation of the treatment, 39 patients who completed the trial were evaluated; 14 (50%) of the 28 patients in the three combined green tea extract arms had a favorable response whereas only 2 (18.2%) of the 11 patients in the placebo arm showed the similar response (*P* for the difference = 0.09). A dose-dependent effect was observed; the favorable response rates were 58% in patients given 750 or 1000 mg/m^2 green tea extract and 36.4% in those given 500 mg/m^2, but only 18.2% in those assigned to the placebo arm (*P* for trend = 0.03) [11].

Although limited, data from the prospective cohort study suggest a moderate protective effect of green tea consumption against the development of oral cancer. Both phase II clinical trials further support a protective role of green tea extract against the progression of precancerous lesions in the oral cavity towards malignant transformation. Phase III clinical trials with large number of patients are required to confirm the efficacy of green tea extract against the formation of oral cancer in humans. Data on the effect of black tea consumption against the development of oral cancer are too limited to draw any conclusion. One prospective study showed a statistically significant inverse association between black tea consumption and risk of pharyngeal cancer, more epidemiologic studies are warranted to evaluate the potential protective effect of either green tea or black tea on the development of pharyngeal cancer in humans.

2.2 Esophagus

Given the physiologic irritation of hot beverages to the esophagus, tea drinking, if consumed at high temperature, could cause damage to the esophageal epithelia and result in increased risk of esophageal cancer. In early 1970s, epidemiological studies already suggested a link between tea consumed at high temperature and increased risk of esophageal cancer in humans [12]. Results on tea drinking and esophageal cancer risk from epidemiological studies with rigorous study designs became available since 1990s. In a case-control study in

Shanghai, China, Gao et al. found that the consumption of “burning-hot” fluid (including green tea) was associated with statistically significantly 4-fold increased risk of esophageal cancer compared with green tea drinkers who did not consumed “burning-hot” fluid [13]. In a similar study, Wu et al. examined the effect of green tea temperature on risk of esophageal cancer in Jiangsu Province, China, a high incidence area of esophageal cancer. Compared with nondrinkers, high-temperature tea was associated with statistically significant 2- to 3-fold increased risk of esophageal cancer [14]. In a prospective cohort of more than 220,000 Japanese men and women with 15 years of follow-up, individuals who usually drank green tea at high temperature had a statistically significant 60% higher mortality of esophageal cancer than those who consumed green tea at moderate temperature [15]. In a systemic review, Islami et al. examined the consumption of high-temperature beverages (coffee, tea and maté) in relation to risk of esophageal cancer [16]. Majority of the studies included showed an increased risk of esophageal cancer with high-temperature beverages consumed regardless of the beverage type. Of the 12 studies included in the systemic review, 8 reported a statistically significantly elevated risk and one reported non-significant increased risk of esophageal cancer associated with very hot tea intake (see details in [16]). Two studies reported a decreased risk with hot tea drinking, but neither was statistically significant. The remaining study reported no association between high-temperature tea intake and risk of esophageal cancer. These findings have clearly demonstrated the adverse thermal effect of tea beverage on esophageal carcinogenesis.

Despite the thermal carcinogenic effect of tea beverage, a number of epidemiologic studies have examined the potential protective effect of tea consumption on risk of esophageal cancer. In most of those studies, the tea temperature was not assessed, and thus was not adjusted for in the analyses. In a systemic review on tea consumption and esophageal cancer risk, the majority of the studies included did not report on the type of tea [16]. However, green tea is mostly consumed in East and South Asia whereas black tea represents the predominant type of tea that was traditionally consumed in Western countries. Among 12 studies conducted in China and Japan, where green tea was mainly consumed, 8 reported a reduced risk of esophageal cancer associated with high level of tea consumption (5 of them reached statistical significance level) whereas 2 reported a positive association between tea consumption and esophageal cancer risk (one reached statistical significance level). The remaining two studies reported a relative risk that was close to one [16]. Since then, there have been 2 reports on green tea intake and esophageal cancer risk. One study in Taiwan enrolled 343 patients with squamous cell carcinoma of esophagus and 755 controls and reported an inverse association between tea consumption and risk of esophageal cancer; OR of esophageal squamous cell carcinoma for the consumption of ≥7 cups per week was 0.4 (95% CI = 0.2-0.6) compared with <1 cup per week after adjustment for smoking and alcohol intake [17]. The second study reported a statistically significantly increased risk of esophageal cancer associated with green tea consumption. However, the increased OR was attenuated to the null after adjustment for tea temperature [14]. Thus, the inconsistent results of those studies could be due in part to confounding by tea temperature.

Cigarette smoking and alcohol drinking, the two established risk factors for esophageal cancer [18,19], might further complicate the association between tea consumption and esophageal cancer risk because tea consumers, especially in Asia, are more likely to smoke cigarettes and drink alcoholic beverages. For example, in a prospective study of more than 18,000 middle-aged or older Chinese men in Shanghai, China [20], 77% of men who smoked cigarettes and drank alcoholic beverages consumed green tea on a daily basis. In contrast, only 44% of men who neither smoked cigarettes nor drank alcoholic beverages consumed the similar amount of green tea (unpublished data). As described above in a large population-based case-control study of esophageal cancer (902 cases and 1552 controls) in Shanghai, China [13], Gao et al. found a statistically significantly reduced risk of esophageal

cancer associated with green tea consumption in women (OR = 0.50; 95% CI = 0.30-0.83), but not in men (OR= 0.80; 95% CI = 0.58-1.09). This gender difference in green tea-esophageal cancer association could be due to the residual confounding effect of smoking and alcohol drinking because Chinese women rarely use tobacco or alcohol. When data were analyzed separately for those who neither smoked cigarettes nor drank alcoholic beverages, a statistically significant decreased risk of esophageal cancer for green tea consumption was observed in both men (OR = 0.43; 95% CI = 0.22-0.86) and women (OR = 0.40; 95% CI = 0.20-0.77) [13]. Similarly, the study by Wu et al. demonstrated a statistically significant or borderline significant inverse association between green tea consumption and risk of esophageal cancer among never smokers (OR = 0.7, 95% CI = 0.5-0.9) or alcohol nondrinkers (OR = 0.8, 95% CI = 0.6-1.1), but not in smokers or alcohol drinkers [14]. These findings suggested that the residual confounding of cigarette smoking and alcohol intake might exist and mask the potential protective effect of green tea consumption against the risk of developing esophageal cancer even after both smoking and alcohol intake were adjusted for in statistical regression models. It is also possible that the modest protective effect of green tea consumption on esophageal cancer could be cancelled out by the strong adverse effects of cigarette smoking and alcohol consumption on the esophagus.

The concentration of catechins in a given cup of tea varies according to several factors including tea type, the preparation method of tea leaves (e.g., blended or decaffeinated), the season of tea harvest, and preparation method of tea beverage (e.g. brewed or iced with or without milk). Thus, the use of biologic markers of tea catechins and their metabolites would be a better approach for the assessment of internal dose of exposure to tea polyphenols than self-reports. To our knowledge, there is only one epidemiologic study that examined specific tea catechins in relation to risk of esophageal cancer in humans. Sun et al. conducted a nested case-control study within the Shanghai Cohort Study, a prospective cohort of more than 18,000 men aged 45-64 years in 1986-1989 when subjects were recruited and information on dietary and lifestyle factors and blood and urine samples were collected. Using validated urinary biomarkers for tea polyphenol uptake and metabolism, the investigators demonstrated a decreased risk for both esophageal and gastric cancer for the presence of EGC in urine. The inverse association was stronger in nonsmokers or nondrinkers of alcohol or among those with lower serum level of carotenes (OR = 0.46, 95% CI = 0.26-0.84) [21]. Additional epidemiologic studies using validated biomarkers in pre-diagnostic specimens are warranted to confirm these findings.

In the review by Islami et al. described above [16], 14 epidemiological studies were included that examined the association between tea consumption and risk of esophageal cancer conducted in areas outside of East Asia, presumably where black tea was mainly consumed. Among these 14 studies, 6 reported a reduced risk (3 reached statistical significance level) whereas 4 reported an increased risk of esophageal cancer associated with high level of tea consumption (3 reached statistical significance level). The remaining 3 studies found a null association (see details in [16]). Two additional papers [8,22] were published after the review by Islami et al [16]. Ganesh et al. conducted a hospital-based case-control study in Mumbai, India, and found that consumption of black tea was associated with statistically significantly 4-fold increased risk (95% CI = 2.0, 8.3) of esophageal cancer [22]. However, the temperature of tea consumed was not controlled for in the analyses. Ren et al. analyzed database of the NIH-AARP Diet and Health Study described above and found a statistically non-significant inverse relation for risk of squamous cell carcinoma of the esophagus [8].

The higher content of tea catechins present in green tea than in black tea may explain the more consistent inverse association between tea and esophageal cancer risk in studies conducted in China and Japan than European and American countries. This view is further

supported by the findings by Sun et al. [21] showing that high urinary EGC is inversely associated with risk of esophageal cancer. The putative protective effect of tea consumption, if any, on esophageal cancer development could be confounded and/or overshadowed by the thermal effect of tea beverages, if consumed at high temperature, as well as cigarette smoking or alcohol intake. Future prospective cohort studies are required to collect detailed information on tea temperature and histories of tobacco and alcohol use that can then be adjusted for when evaluating the protective effect of tea on esophageal cancer.

3.3 Stomach

Recently, Myung et al. conducted a meta-analysis investigating the quantitative association between the consumption of green tea and the risk of stomach cancer in humans [23]. The analysis included 13 (5 cohort and 8 case-control) studies, all conducted in Japanese or Chinese populations. The summary adjusted relative risk (RR) of stomach cancer for the highest versus lowest level of green tea consumption was 0.82 (95% CI= 0.70-0.96). An inverse association was seen in case-control studies only (summary OR = 0.73; 95% CI, 0.64-0.83), but not in cohort studies (summary RR = 1.04, 95% CI = 0.93-1.17). However, in a recent pooled analysis of 6 cohort studies that included more than 218,000 Japanese men and women aged 40 years or older and more than 3500 incident stomach cancer cases found a statistically significant, inverse association between green tea consumption and stomach cancer risk in women, but not in men [24]. Compared with those drinking <1 cup/day, women with the consumption of ≥5 cups/day green tea had an approximately 20% decreased risk of stomach cancer (multivariate-adjusted pooled HR = 0.79, 95% CI = 0.65-0.96) (P for trend = 0.04). This protective effect was primarily seen among female nonsmokers [24].

Similar to esophageal cancer, tea temperature may also confound the association between tea consumption and stomach cancer risk. A case-control study of stomach cancer in Northeast China did not find an overall association between green tea intake and gastric cancer. When tea consumption was classified according to the tea temperature, however, there was a dose-dependent relationship between green tea intake at the lukewarm temperature and decreased stomach cancer risk. Compared to nondrinkers, ORs of stomach cancer were 0.61 (95% CI =0.45-0.82) for consumption of 500 g dry tea leaves per year and 0.19 (95% CI =0.07-0.49) for ≥750 g per year [25]. In contrast, there was no association between green tea consumption and stomach cancer for those who consumed tea at hot temperature [25].

Data on specific green tea catechins and risk of stomach cancer are limited. Sun et al. conducted a case-control study of stomach cancer nested within a prospective cohort of Chinese men in Shanghai, China [21]. Specific tea catechins and their metabolites (EGC, EC, M4 and M6) were determined in urine samples that were collected from subjects before they developed stomach cancer. Urinary levels of tea catechins were significantly associated with the reduced risk of stomach cancer. Compared with the absence of EGC in urine, OR of stomach cancer for the presence of urinary EGC was 0.52 (95% CI=0.28-0.97) after adjustment for cigarette smoking, alcohol intake, and other confounding factors [21]. These findings directly support a protective role of the tea catechin EGC on stomach cancer development in humans. More studies using a biomarker approach would provide critical data to confirm the findings of this study.

Most epidemiological studies that examined the association between black tea consumption and stomach cancer risk produced mixed results. Of the 10 case–control studies [26-35], three demonstrated a statistically significantly reduced risk of stomach cancer with black tea consumption [27,32,33], one study found a significantly low risk in women only, but not in men [31], one study found a statistically significantly increased risk with drinking strong

and hot tea [35], and the remaining five studies reported a null association between black tea consumption and risk of stomach cancer [26,28-30,34]. Among the 7 cohort studies that examined black tea consumption and stomach cancer risk [36-42], five studies did not find a statistically significant association [36,38-40,42] and two studies reported an increased rate of mortality from stomach cancer among those who drank black tea [37,41]. In the study by Kinlen et al., the positive association between black tea consumption and stomach cancer death could be, at least partly, due to the effects of smoking and social class [37]. Whereas in the cohort analysis by Khan et al. that included approximately 3100 Japanese men and women, black tea consumption was associated with a statistically significantly increased risk of stomach cancer for women (RR=3.8, 95% CI = 1.1-13.6), but not for men [41]. Given the small sample size and low intake of black tea in a population that usually consumed green tea, this positive association could be a chance finding.

Both case-control and cohort studies demonstrated an inverse association between green tea consumption and risk of stomach cancer. The protection may be stronger for women than men since the former are less likely to smoke cigarettes or drink alcoholic beverages. There is lack of evidence in support of a protective role of black tea consumption against the development of stomach cancer.

2.4 Large bowel

Numerous epidemiological studies have examined the association between tea consumption and colorectal cancer. Sun et al. conducted a meta-analysis that included 25 epidemiologic studies evaluating tea consumption and risk of colorectal cancer in 11 countries [43]. The inverse association between green tea intake and colon cancer risk was mainly observed in 4 case-control studies (summary OR = 0.74, 95% CI= 0.60, 0.93), but not in 4 cohort studies (summary RR = 0.99, 95% CI = 0.79, 1.24). There was no relationship between green tea intake and rectal cancer risk in 6 case-control or cohort studies.

Following the meta-analysis, several studies examined and published the results on the green tea consumption and colorectal cancer risk. After analyzing the database of the Singapore Chinese Health Study, a prospective cohort study of diet and cancer involved over 60,000 Chinese men and women aged 45-74 years, Sun et al. found that subjects who drank green tea daily had a statistically non-significant increased risk for colorectal cancer (HR = 1.12, 95% CI = 0.97-1.29) relative to nondrinkers of green tea. This association was confined to men (HR = 1.31, 95% CI = 1.08-1.58), and was stronger for colon cancer (HR=1.75, 95% CI = 1.24-2.46) than rectal cancer, especially for the advanced stage of colon cancer (RR=2.26, 95% CI = 1.49 – 3.44) [44]. These data suggest that substances in green tea may exert an adverse, late-stage effect on the development of colorectal cancer.

Yang et al. prospectively evaluated the association between green tea consumption and colorectal cancer risk in a cohort of 69,710 Chinese women aged 40 to 70 years, most of which were lifelong nonsmokers (97.3%) or nondrinkers of alcoholic beverages (97.7%). Information on tea consumption was assessed through in-person interviews at baseline and reassessed 2 to 3 years later in a follow-up survey. During the first 6 years of follow-up, 256 incident cases of colorectal cancer were identified. Regular tea drinkers had significantly reduced risk of colorectal cancer compared with nondrinkers. HRs of colorectal cancer for 1-4 g/day and ≥5 g/day of dry green tea leaves were 0.70 (95% CI = 0.47-1.02) and 0.56 (95% CI = 0.32-0.98), respectively (*P* for trend = 0.01). The reduction in risk was most evident among those who consistently reported to drink tea regularly at both the baseline and follow-up surveys (HR = 0.43; 95% CI = 0.24-0.77) [45].

There were two recent prospective studies on green tea consumption and colorectal cancer incidence and mortality in Japan [46,47]. The first consisted of 96,162 Japanese men and

women, and 1,163 incident cases of colorectal cancer [46]. There was no statistically significant association between green tea consumption and incidence of colon and rectal cancers combined or separately in either men or women or both (all *P* values for trend ≥0.45). The second cohort consisted of 14,001 Japanese men and women. After up to 6 years of follow-up, 43 subjects died from colorectal cancer. Compared with <1 cup/day, subjects with consumption of ≥4 cups/day of green tea had a HR of 0.35 (95% CI = 0.08-1.55) for death from colorectal cancer [47]. Given the small number of cases, the results should be interpreted with caution.

Using validated biomarkers of specific tea polyphenols, Yuan et al. prospectively examined the urinary levels of specific tea catechins and their metabolites and the risk of developing colorectal cancer in the Shanghai Cohort Study as described above [48]. EGC, 4′-*O*-methyl-epigallocatechin (4′-MeEGC) and EC, and their metabolites in baseline urine samples were measured in 162 incident colorectal cancer cases (83 colon and 79 rectal cancer cases) and 806 matched controls. Individuals with high prediagnostic urinary catechin levels had a lower risk of colon cancer. Compared with the lowest quartile of EGC plus 4′-MeEGC, ORs of colon cancer for the 2nd, 3rd, and 4th quartile were 0.57 (95% CI = 0.29-1.11), 0.39 (95% CI = 0.19-0.80), and 0.43 (95% CI = 0.21-0.88), respectively (*P* for trend = 0.007). There was no association between urinary green tea catechins or their metabolites and risk of rectal cancer. This study provided a direct evidence for the chemopreventive effect of tea catechins against the development of colon cancer in humans [48].

In terms of black tea, the meta-analysis by Sun et al. [43] included 20 studies that examined black tea consumption and colorectal cancer risk and found no association. The summary ORs for the highest versus the lowest consumption levels of black tea were 0.99 (95% CI = 0.87, 1.13) for colorectal cancer combined, 1.02 (95% CI = 0.88-1.18) for colon cancer alone, and 0.91 (95% CI = 0.73-1.12) for rectal cancer alone. No association was found separately in case-control studies or prospective cohort studies. In our analysis of the Singapore Chinese Health Study, we did not find any association between black tea consumption and risk of colon cancer and rectal cancer combined or separately [44]. More recently, Zhang et al. conducted a pooled analysis for black tea intake and colon cancer risk on the combined dataset of 13 cohort studies conducted in North America or Western Europe. The analysis included 731,441 subjects and 5604 incident colon cancer cases [49]. Compared with nondrinkers, consumption of 900 g/day tea (approximately four 8-oz cups/day) was associated with a modest, but statistically significantly increased risk of colon cancer (pooled multivariable RR = 1.28; 95% CI = 1.02, 1.61; *P* for trend =0.01). This increased risk for colon cancer was only in women (pooled multivariable RR = 1.32, 95% CI = 1.02-1.71), but not in men (pooled multivariable RR = 1.17, 95% CI = 0.66-2.06).

Epidemiologic studies provided suggestive evidence to support a protective role of green tea consumption, especially in high amount and long-term duration of consumption, in reducing the risk of colon cancer. This effect of green tea on colon carcinogenesis may depend on the time of exposure, where late exposure may promote the growth of colon tumor cells. Current epidemiologic data suggest that black tea consumption may increase, instead of decrease, the risk of colorectal cancer.

2.5 Liver

Epidemiologic studies that examined the association between green tea consumption and liver cancer risk are limited. Ui et al. prospectively examined the green tea and the risk of developing liver cancer in a cohort of 41,761 Japanese men and women aged 40-79 years at baseline [50]. After an average 9 years of follow-up, 247 participants developed liver cancer. Green tea intake was associated with a statistically significant decreased risk of liver cancer; HR was 0.58 (95% 0.41-0.83) for those consuming ≥5 cups/day relative to <1 cup/

day of green tea (*P* for trend = 0.009) after adjustment for alcohol intake, cigarette smoking, coffee consumption and other potential confounders. The inverse association was stronger in women (*P* for trend = 0.04) than in men (*P* for trend = 0.11). Wang et al. conducted a similar analysis in a Chinese cohort of 60,076 men and 29,713 women [51]. At baseline 17% of men and 7% of women were regular tea drinkers. After an average 12.8 years of follow-up, 1803 cohort participants who were free of cancer at baseline died from liver cancer. Regular green tea drinkers had significantly lower mortality of liver cancer relative to nondrinkers among women (HR = 0.51, 95% CI=0.27-0.96). There was no association in men [51]. In contrast, a number of epidemiologic studies, including one of ours, did not find a statistically significant association between green tea consumption and liver cancer risk in men and women combined or separately [52-56].

There are a limited number of studies that examined black tea consumption and risk of liver cancer. Two studies (1 case-control and 1 cohort study) in Japanese populations and one cohort study in a Chinese population all failed to demonstrate either a protective or risk effect of black tea consumption on the development of liver [56-58].

A recent randomized, placebo-controlled, phase II clinic trial supported a protective role of green tea polyphenols in the protection of liver damage by aflatoxin exposure and hepatitis B, two established risk factors for liver cancer [59]. The trial was conducted in a high-risk population in southern China. Chinese persons carrying hepatitis B surface antigen (a marker for chronic infection with hepatitis B virus) and positive aflatoxin B_1-albumin adducts (a marker for dietary exposure to aflatoxin B_1) were randomly assigned to one of the three groups: 500 mg/day or 1000 mg/day green tea polyphenols or placebo. At both 1 and 3 months, subjects in both green tea polyphenol treatment arms showed statistically significant 7- to 14-fold increased levels of aflatoxin B_1 mecapturic acids in urine, a detoxification biomarker for aflatoxin, compared with those in the placebo arm [60]. At the end of the 3-months intervention, the levels of 8-hydroxydeoxyguanosine, an oxidative DNA damage biomarker, were statistically significant 50% lower in both green tea treated groups than in the placebo group ($P = 0.007$). There was no difference in urinary levels of aflatoxin B_1 mecapturic acids and 8-hydroxydeoxyguanosine between the 500-mg and 1000-mg green tea polyphenol groups [61]. These results suggest that the oral administration of green tea polyphenols at 500-1000 mg/day is effective in enhancing the detoxification of aflatoxin and reducing oxidative DNA damage.

Observational studies provided very limited support for green tea consumption in reducing risk of liver cancer, with a possible exception in women. There was no support for black tea consumption and liver cancer prevention. A phase II clinical trial demonstrated that oral administration of green tea polyphenols was effective in enhancing the detoxification of aflatoxin exposure and reducing oxidative DNA damage. These findings need to be confirmed by a similarly designed trial in a non-high risk population.

2.6 Pancreas

Similar to other gastrointestinal organs, epidemiologic studies have provided mixed results on the association between tea consumption and risk of pancreatic cancer. There are a limited number of studies that examined the association between green tea consumption and pancreatic cancer. From an early hospital-based case-control study in Japan (124 cases and 124 matched controls), no association was observed for pancreatic cancer risk with green tea drinking [62]. In contrast, analyses from a population-based case-control study conducted in Shanghai, China (451 cases and 1552 controls) demonstrated a statistically significant inverse association with increased green tea consumption and pancreatic cancer risk. ORs for highest green tea consumption relative to no consumption were 0.38 (95% CI=0.18-0.82) in women and 0.59 (95% CI = 0.34-1.17) in men [63]. A prospective cohort study in Japan

involved more than 100,000 Japanese adults with up to 11 years of follow-up and 233 incident pancreatic cancer cases did not find an association between green tea intake and pancreatic cancer risk [64]. In another prospective cohort study with up to 13 years of follow-up and 292 incident pancreatic cancer cases in Japan, Lin et al. reported an RR of 1.23 (95% CI = 0.84-1.80) of dying from pancreatic cancer for subjects who consumed ≥7 cups/day of green tea compared with those <1 cup/day [65].

Among the 11 case-control studies that examined black tea consumption and risk of pancreatic cancer, 10 were conducted in Western populations [28,66-74] and one in Japan [75]. Only one study showed an inverse association [73] while the other one demonstrated an increased risk [67]. The remaining 9 case-control studies reported a null association between black tea consumption and pancreatic cancer risk. In addition, 8 publications derived from 9 cohort studies evaluated associations between black tea consumption and pancreatic cancer risk [36,39,76-81]. Two of them demonstrated an inverse association [76,82] while five others did not find any association [39,57,77,79,80]. In a recent analysis based on the datasets of the Multiethnic Cohort (MEC) study (183,513 participants and 610 incident cases of pancreatic cancer) and the European Prospective Investigation into Cancer and Nutrition (EPIC) study (424,978 participants and 517 incident cases), Nothlings et al. evaluated black tea consumption and pancreatic risk. An inverse, dose-dependent association was found among current smokers of the MEC study. Compared with the lowest quintile, HRs of pancreatic cancer for the 2nd, 3rd, 4th, and 5th quintiles were 0.92 (95% CI = 0.55-1.53), 0.85 (95% CI = 0.49-1.46), 0.43 (95% CI = 0.20-0.91), and 0.62 (95% CI = 0.33-1.18), respectively (P for trend=0.026) among current smokers. However, no such inverse association was observed in never smokers or former smokers of the MEC. In the EPIC study, there was no association between black tea consumption and pancreatic cancer risk in total subjects, or in smokers or nonsmokers [83].

Available epidemiologic data are insufficient to conclude that either green tea or black tea may protect against the development of pancreatic cancer. Given the short survival and rapid progression of pancreatic cancer, the low participation rates of pancreatic cancer patients in retrospective case-control studies or the use of proxy respondents in interview for collection of information on tea consumption and other risk factors could bias the results of case-control studies. Prospective cohort studies offer methodological advantages over case-control studies. Additional data from well-designed and well-executed prospective cohort studies are required before any conclusion on the protective effect of green tea and/or black tea against the development of pancreatic cancer can be reached.

2.7 Lung

Numerous epidemiological studies examined the association between green tea or black tea consumption and risk of lung cancer. A systematic review was conducted to evaluate the association between the consumption of green tea or black tea and lung cancer risk among 19 studies (13 case-control, 6 prospective cohort) that were published prior to September 2007 [84]. Among the 8 studies examining green tea and lung cancer risk, 3 reported a significantly lower risk while one reported a significantly increased risk of lung cancer with high green tea consumption. The remaining 4 studies reported no association [84]. More recently, Tang et al. conducted a similar meta-analysis for green tea or black tea consumption with lung cancer risk [85]. This analysis included 22 studies published from 1966 to November 2008 and 12 of them also were included in the analysis by Arts [84]. Twelve studies examined the association between green tea and lung cancer risk, and yielded a summary RR of 0.78 (95% CI=0.61, 1.00). A statistically significant 18% decreased risk of lung cancer was associated with every 2 cups/day of green tea consumption (RR=0.82, 95% CI=0.71, 0.96). This inverse green tea-lung cancer association was slightly stronger for prospective cohort studies (RR = 0.68, 95% CI = 0.45-1.02) than

retrospective case-control studies (OR = 0.87, 95% CI = 0.65-1.17). The protective effect of green tea consumption on lung cancer risk was confined to nonsmokers [85].

In the same review by Arts [84], 11 of the 19 studies included examined the association between black tea consumption and lung cancer risk. Among them, two reported a statistically significantly reduced risk while one reported an increased risk for lung cancer associated with black tea intake. The remaining 8 studies reported a null association [84]. In a more recent meta-analysis by Tang et al., no statistically significant association was observed between black tea consumption and lung cancer risk based on 14 studies included (summary OR = 0.86, 95% CI = 0.70-1.05) [85]. Not included in the meta-analyses was a case-control study in Los Angeles, California with 558 cases and 837 controls. The results showed that high consumption of dietary epicatechin, mainly from black tea, was associated with significantly reduced risk of lung cancer, especially among smokers. OR for lung cancer was 0.64 (95% = 0.46-0.88) per 10 mg/day epicatechin intake and 0.49 (95% CI = 0.35-0.70) per 4 mg/day epicatechin intake [86].

Given that smoking is the most important risk factor for lung cancer and smokers are more likely to drink tea, especially in China, the association between tea consumption and lung cancer risk could be confounded by cigarette smoking. To account for the potential confounding effect of smoking, Zhong et al. examined the association between consumption of green tea and the risk of lung cancer in a case-control study living in Shanghai, China from 1992 through 1994 [87]. Regular tea drinkers experienced a statistically significant 35% risk reduction for lung cancer compared with their counterparts who did not drink tea regularly (OR = 0.65, 95% CI = 0.45-0.93), with a dose-dependent relationship, among nonsmokers (P for trend < 0.05). In the same study, there was no association between green tea intake and lung cancer risk among smokers [87]. Hu et al. conducted a similar case-control study of lung cancer among Canadian women who had never smoked cigarettes. Compared with nondrinkers, ORs of lung cancer for women with 1-7 cups/week and >7 cups/week of tea were 0.6 (95% CI = 0.3-0.9) and 0.4 (95% CI = 0.2-0.7) after adjustment for age, level of education and social class (P for trend = 0.0008) [88]. In another study in Czech Republic, Kubik et al. found that consumption of black tea was associated with significantly reduced risk of lung cancer among nonsmoking women (OR = 0.65, 95% CI = 0.43-0.99), but not among smokers [89].

One potential mechanism for the chemoprective effect of tea on carcinogenesis is the strong antioxidant effect of tea polyphenols. Hakim et al. conducted a phase II randomized controlled tea intervention trial to evaluate the efficacy of regular green tea drinking in reducing DNA damage as measured by urinary 8-hydroxydeoxyguanosine among heavy smokers [90]. After consuming 4 cups/day of decaffeinated green tea for 4 months, smokers showed a statistically significant 31% decrease in urinary 8-hydroxydeoxyguanosine compared with the baseline value. In the same study, no change in urinary 8-hydroxydeoxyguanosine was seen among smokers assigned to the black tea group [90]. These findings support that tea catechins, with highest levels in green tea, exert their antioxidative role in reducing the formation of 8-hydroxydeoxyguanosine. However, a lack of inverse association between green tea consumption and lung cancer risk in smokers suggest that the antioxidation mechanism plays a limited role in reducing the risk of lung cancer development. Furthermore, the protective effect of tea consumption on lung cancer development for nonsmokers, especially among women, indicates an alternative cancer-preventive mechanism of tea that is not driven by antioxidation. Additional experimental studies that utilize animal models to elucidate the cancer-preventive mechanisms of tea catechins on lung carcinogenesis are needed.

2.8 Breast

Three meta-analyses have been published on tea and breast cancer. Two included epidemiologic studies that evaluated green tea intake and breast cancer risk and recurrence [91,92], while the third reviewed results on green and black tea intake in relation to breast cancer risk [93]. All of the epidemiologic studies published to date have been observational in design.

The most recent meta-analysis included 7 (2 cohort, 1 nested case-control and 4 case-control) epidemiologic studies of green tea and breast cancer that were published as of December 2008 [92]. An inverse association between green tea and breast cancer risk was reported from case-control data (OR=0.81; 95% CI: 0.75-0.88), while no association was observed from cohort data [92]. The nested case-control study reported no association [94], so even if it had been included as a cohort study in the pooled analyses, the overall finding would have remained the same.

Following the meta-analyses, results were published from two prospective cohort studies [95,96]. In a cohort of 53,793 women in Japan, 581 incident cases of breast cancer were identified after a mean follow-up of 13.6 years. No association was observed for green tea intake in all women or in subgroups stratified by menopausal status or hormonal receptor status [97].

The second study evaluated green tea intake and breast cancer risk in a prospective cohort of 74,942 women in China with 614 incident cases of breast cancer identified after an average follow-up of 7.3 years [95]. No association was observed overall for ever or high intake of green tea, or number of years of green tea intake, compared to non-regular green tea intake [95]. In stratified analyses by menopausal status, a statistically significant positive association with breast cancer risk was observed among postmenopausal women who began drinking green tea at a young age (≤25 years) (HR=1.61; 95% CI: 1.18-2.20), and the risk increased with increasing number of years of green tea consumption (P for trend = 0.02). In contrast, a suggestive inverse relation between green tea intake and breast cancer risk among pre-menopausal women who began drinking tea at young age (HR=0.69; 95% CI: 0.41-1.17) or with increasing number of years of green tea intake (HR=0.63; 95% CI: 0.29-1.35; P for trend = 0.12), although the results did not reach statistical significance due to the small number of cases. These data suggest that green tea may have a dual, opposing role in breast carcinogenesis, based on menopausal status. Some research has shown that green tea can lower circulating estrogen levels [98,99], which could have more protective effects against the development of breast cancer in premenopausal women than in postmenopausal women. Additional studies on the effect of timing of green tea exposure on the development of breast cancer in both pre- and post-menopausal women may shed light on the understanding of tea on mammory carcinogenesis.

Green tea may have inhibitory effect of breast cancer recurrence. In two Japanese prospective cohorts [100,101], green tea intake was associated with a statistically significant decrease in risk of breast cancer recurrence (pooled RR=0.73; 95% CI: 0.56, 0.96) [92]. The association became stronger when the analyses were restricted to early stage of recurrent breast cancers (pooled RR=0.56; 95% CI: 0.38, 0.83) [91].

In the only meta-analysis published on black tea and breast cancer risk, Sun et al. included 13 studies (5 cohort and 8 case-control) that were published as of August 2004 [93]. A moderate positive association between high black tea consumption and risk of breast cancer was observed in cohort studies (summary OR = 1.15; 95% CI = 1.02-1.31) whereas no association was observed from the case-control data. Since the meta-analysis by Sun et al. [93], results have been published from 2 case-control studies [102,103] and 5 prospective

cohort studies [104-108]. No association between black tea intake and breast cancer risk were observed in either of the 2 case-control studies in all women or subgroups stratified by menopausal status or hormone receptor status [102,103]. Of the five cohort studies, three reported a null association [104-106], one reported a postive, but statistically non-significant, association (RR=1.44; 95% CI: 0.89, 2.34; *P* for trend=0.12) [108], and the remaining one found a statistically significant increased risk of breast cancer with high black tea intake (RR=1.22; 95% CI =1.05-1.42; *P* for trend=0.007) [107]. When the tumors were classified by estrogen receptor and progesterone receptor status, the positive association between black tea intake and breast cancer risk was confined to women with positive status of both receptors (RR=1.36; 95% CI: 1.09-1.69; *P* for trend=0.007) [107].

As described above, a biomarker approach would be better to assess the *in vivo* exposure to specific tea catechins than self-reports of tea consumption. Two studies have incorporated pre-diagnostic biomarkers of tea intake and metabolism on risk of breast cancer [109,110]. Urinary tea catechins including EGC, 4′-MeEGC and EC and their metabolites were measured in 353 cases and 701 controls nested within a prospective cohort in China [110]. There was no association between urinary levels of any biomarkers measured and risk of breast cancer [110]. In the second biomarker study, plasma concentrations of EGCG, EGC, ECG, and EC were determined on 144 breast cancer patients and 288 matched control women within a prospective cohort study in Japan [109]. Similarly, there was no association between plasma levels of tea catechins measured and the risk of developing breast cancer [109]. It should be pointed out that in both biomarker studies the detectable rates of some of the biomarkers were as low as 20-30% [109,110], which raised a concern about the sensitivity of the assays since approximately 50% of study participants reported drinking at least one cup of green tea on a daily basis.

Genetic polymorphisms in the enzymes that catalyze the metabolism of tea catechins may also introduce interindividual variability in the *in vivo* exposure to tea catechins [111]. For example, a single nucleotide polymorphism (SNP) in the catechol-O-methyltransferase (*COMT*) gene results in the valine to methionine amino acid change in codon 108/158 in the cytosolic/membrane-bound form of the protein. This amino acid change is believed to result in a 3- to 4-fold decrease in enzymatic activity [112], thus diminishing the elimination of tea catechins through urine and increasing the *in vivo* exposure to tea catechins. One study conducted in a Chinese population demonstrated that regular green tea drinkers with the homozygous low-activity AA *COMT* genotype had a 35% to 45% reduction in urinary levels of tea catechins as compared with green tea drinkers carrying at least one copy of high-activity *COMT* G allele [113]. These data support the hypothesis that *COMT* genotype has impact on the metabolic elimination of tea catechins through urine.

Two studies to date have incorporated genetic polymorphisms to account for inter-individual differences in tea polyphenol bioavailability. Using data from a population-based case-control study among Asians in Los Angeles County, California, Wu et al. reported that consumption of either black tea or green tea was associated with statistically significant reduced risk of breast cancer for women carrying at least one copy of the low-activity *COMT* allele (OR=0.48; 95% CI: 0.29, 0.77) relative to nondrinkers. On the other hand, there was no association between tea intake and breast cancer risk in women carrying both high-activity *COMT* alleles [114]. The effect modification by *COMT* genotype on the association between tea consumption and breast cancer risk, however, was not found in a recent case-control study in Shanghai, China [115]. Additional studies are required to resolve these inconsistent findings.

Green tea may also interact with other bioactive dietary components, such as those in soy, on breast cancer risk. The beneficial effects of green tea for the breast may only be apparent

when soy intake is low. For example, a study in Asian-American women demonstrated a statistically significant inverse association between green tea and breast cancer risk among women with low soy intake, but not among women with high soy intake [116]. A similar interaction between green tea and soy intake has also been observed for mammographic density, a risk predictor for breast cancer, in a Chinese population in Singapore [117].

A number of bioactive phytochemicals have been identified in many mushrooms species [118]. The inhibitory effect of those phytochemicals on aromatase activity [119] may protect against the development of breast cancer [120,121]. Using data from a case-control study in China, Zhang et al. found an inverse association between green tea consumption and breast cancer risk among women with no consumption of mushrooms only, but not among those with high consumption of mushrooms (P for interaction < 0.001). Although limited, these data suggest that tea constituents may act in concern with other dietary bioactive compounds or genetic determinants against the development of breast cancer. Additional studies are required to elucidate the potential mechanisms of action.

In summary, green tea may exert beneficial effects on breast carcinogenesis through inhibition of estrogen alone or in combination with other estrogen-inhibiting factors. Black tea does not appear to have protective effects on breast cancer incidence, and may increase risk of hormone-dependent tumors. Future research is needed to elucidate the interactive role of tea catechins and other dietary cancer-inhibitory compounds in mammary carcinogenesis in humans.

2.9 Prostate

Over the past two decades, the effects of green tea extract or green tea polyphenols against the prostate carcinogenesis in experimental models have been extensively studied. The findings of those studies, especially from cell lines and animal models, have been reviewed and summarized recently [122]. A number of epidemiological studies have examined the association between the consumption of green tea or black tea and risk of prostate cancer. Two case-control studies examined and found an inverse relation between green tea intake and prostate cancer risk. One case-control study including 130 patients with prostate cancer and 274 hospital inpatients as controls in southeast China found a statistically significant inverse relationship between green tea intake and prostate cancer (P for trend < 0.001). Compared with nondrinkers, regular green tea drinkers had an OR of 0.28 (95% CI = 0.17 - 0.47) and increasing amount of green tea leaves consumed with descreased risk of prostate cancer (P for trend < 0.001) [123]. The other case-control study involved 140 prostate cancer cases and an equal number of hospital patients as controls also found an inverse, but statistically non-significant association [124]. Compared with <1 cup/day of green tea, ORs for 1-2, 3-4, and ≥5 cups/day of green tea were 0.99 (95% = 0.48-2.03), 0.79 (95% CI = 0.38-1.63) and 0.67 (95% CI = 0.27-1.64) (P for trend = 0.30). Given the small sample size and hospital-based case-control study design, these results should be interpreted with caution.

Four prospective cohorts, all conducted in Japanese populations, have examined the association between green tea consumption and risk of prostate cancer [125-128]. An early study in men of Japanse ancenstry in Hawai found that green tea consumption was associated with a statistically non-significant increased risk of prostate cancer (HR = 1.47, 95% CI = 0.99-1.13)[125]. The other 3 more recent studies found no association between green tea intake and prostate cancer risk. Only one prospective cohort study examined the association between green tea consumption and risk of prostate cancer stratified by disease stage [128]. A dose-dependent inverse relation was observed for risk of advanced prostate cancer (P for trend = 0.01); HR was 0.52 (95% CI = 0.28 - 0.96) for men with ≥5 cups/day of green tea compared with <1 cup/day. On the other hand, there was no association between

green tea consumption and risk of localized prostate cancer. These results suggest that green tea constituents may reduce the growth of prostate tumors.

For black tea consumption, two of the six case-control studies [124,129-133] reported a statistically significant inverse association for prostate cancer risk [131,132]. In contrast, two others reported positive associations [124,133] and one reached statistical significance [133]. The remaining two found no association [129,130]. In addition, four prospective cohort studies examined the association between black tea intake and incidence or mortality of prostate cancer [36,127,134,135]. Three of them reported no association [36,127,134,135]. In the fourth cohort study among men of Japanese ancestry in Hawaii daily intake of black tea was associated with a 40% reduction in risk of prostate cancer (P for trend = 0.02) [36]. Given the low intake level of black tea in Japanese populations, these results should be interpreted with caution.

There have been 4 intervention studies evaluating the effect of green tea intake on the change of risk markers for prostate cancer [136-139]. Three were single arm open label phase II trials among prostate cancer patients. In the first phase II trial, 42 patients with androgen-independent prostate cancer took 1 g of green tea powder that consisted of pulverized green tea mixed with sugar, citric acid and flavoring in warm or cold water 6 times per day (total 6 g/day). Each dose of green tea powder contained 100 calories and 46 mg caffeine. Although the study was designed for a four-month intervention, the median intervention length was only one month. One of the 42 patients in the study showed a 50% decrease in prostate-specific antigen (PSA) level, but the PSA decrease was not sustained beyond two months. At the end of the first month of green tea powder supplementation, the median PSA level increased by 43% from baseline [138]. The second phase II trial was to evaluate the efficacy and toxicity of standardized green tea extract on prostate cancer [139]. Nineteen patients with hormone refractory prostate cancer were given green tea extract capsules at a dose level of 250 mg twice daily. Each capsule contained 75% polyphenols (of which greater than 30% was EGCG) and less than 2% caffeine. Of the 15 patients who completed at least 2 month of therapy, 9 (60%) had progressive disease within 2 months of starting therapy, and the other 6 patients developed progressive disease within 3 to 5 months of therapy. Among these 6 patients with delayed disease progression, the PSA levels remained unchanged for the first 1 to 4 months on treatment [139]. The most recent single arm open label phase II trial was conducted to evaluate the effect of standardized green tea polyphenols during the interval between prostate biopsy and radical prostatectomy. The supplementation of polyphenon E (containing 1300 mg tea polyphenols or 800 mg green tea catechins) for an average of 35 days significantly reduced the levels of several cancer-related risk biomarkers including PSA, human growth factor, vascular endothelial growth factor, and insulin-like growth factor (IGF)-1, and IGF-1:IGF binding protein-3 ratio (all $P < 0.05$) among 32 prostate cancer patients in the study [137].

The fourth phase II trial was a randomized, double blind, placebo controlled trial with the aim to assess the safety and efficacy of green tea catechins for the chemoprevention of prostate cancer in men with high-grade prostate intraepithelial neoplasia. Sixty patients were randomly assigned to the treatment or placebo arm. Patients in the treatment arm were given 600 mg green tea catechins (i.e., three 200 mg capsules) per day with each capsule containing 75.7% specified green tea catechins as follows: 51.9% EGCG, 12.4% EC,6.1% ECG, and 5.5% EGC; and <1% caffeine. After a 12-month treatment, total PSA levels were not significantly different between the treatment and placebo group. These data are consistent with the lack of clinic effect of green tea polyphenol supplementation on PSA level observed in the previous two studies. However, only one (3.3%) of the 30 patients in the treatment arm compared to 9 (30%) of the 30 patients in the placebo arm developed prostate cancer ($P < 0.01$) [136]. A 2-year follow-up study on a subset of the participants

showed the lasting protective effect of green tea catechins against the development of prostate cancer [140]. The critical difference between those single arm trials described above and this study by Bettuzzi et al. was that the former included patients with prostate cancer whereas the latter study included only patients with premalignant lesions. The lack of consistent clinical effect of green tea extract on reducing PSA levels or inhibiting the disease progression could be due to the short-term of green tea treatment, the timing of supplementation with respect to stage of the disease, and the lack of a comparison group in those earlier studies. Although by no means definitive, these data are encouraging for the development of green tea catechins as chemopreventive agents against the development of prostate cancer, especially for men at high risk of developing this malignancy.

In summary, observational studies do not provide strong evidence for a protective effect of green tea or black tea intake against the development of prostate cancer. There is some suggestive evidence that green tea intake may reduce the risk of advanced prostate cancer. The phase II clinical trials have provided encouraging evidence in the development of green tea catechins as a chemopreventive agent against prostate carcinogenesis.

2.10 Urinary bladder

Zeegers et al. conducted a meta-analysis of 20 studies that evaluated tea intake and risk of urinary tract cancer that were published before 1999 [141]. Except for two studies in Japanese populations, all were conducted in North America or Western Europe, where black tea was mainly consumed. Tea consumption was not associated with risk of bladder cancer. The smoking adjusted summary OR of bladder cancer for current tea consumers compared to nondrinkers was (OR = 1.09, 95% CI = 0.96-1.25) for both men and women combined.

After the publication of the meta-analysis by Zeegers et al. [141], 4 case-control studies examined and found an increased risk of bladder cancer for green tea or black tea consumption. Woolcott et al. conducted a case-control study involved 927 bladder cancer cases and 2118 controls in Canada [142]. Tea consumption was associated with a statistically borderline significant increase in bladder cancer risk. Compared with nondrinkers, those who consumed ≥5 cups of tea per day experienced approximately 30% increased risk of bladder cancer after adjustment for cigarette smoking and other potential confounders (*P* for trend = 0.07). Another case-control study of 255 bladder cancer and 501 control patients in Uruguay also found a positive association. Compared with nondrinkers, consumption of ≥7 cups/week of black tea was associated with a statistically significant 4-fold increased risk of bladder cancer [143]. Furthermore, 2 studies did not find any statistically significant association between green tea or black tea consumption and bladder cancer risk [144,145]. All of the studies described above, when examining the association between tea intake and bladder cancer risk, did not take into account for total fluid intake, a protective factor for bladder cancer found in some studies [146,147].

Using the database of the Netherlands Cohort Study, Zeegers et al. examined the association between tea consumption and bladder cancer risk. The analysis included 569 incident bladder cancer cases after 6 years of follow-up. Black tea consumption was inversely associated with bladder cancer risk in a dose-dependent manner (*P* for trend <0.01). Compared with nondrinkers, consumption of ≥5 cups/day of black tea had an approximately 30% decreased risk of bladder cancer [148]. These analyses were not adjusted for total fluid intake.

Bianchi et al. conducted a population-based case-control study of bladder cancer in Iowa [149]. In addition to tea, total fluid intake was assessed by in-person interview. The study included 1452 bladder cancer cases and 2434 control subjects. Overall, there was no association between tea consumption and bladder cancer risk. When subjects were stratified

by the amount of total fluid intake, the protective effect of black tea on bladder cancer was present in those who consumed lower amount (<2.6 liters/day) of total fluid (OR = 0.5, 95% CI = 0.3-0.9 for >2.6 cups of tea per day versus non-drinkers). These findings demonstrated the importance in controlling total fluid intake when examining the association between tea consumption and bladder cancer risk.

2.11 Kidney

Several epidemiologic studies examined the relationship between tea consumption and kidney cancer risk. Mellemgaard et al. conducted a population-based case-control study that enrolled 368 renal cell cancer cases and 396 matched controls living in Denmark [150]. The study did not find an association between black tea consumption and renal cell cancer risk. Bianchi et al. conducted a population-based case-control study of renal cell cancer in Iowa (406 cases and 2434 controls), and found no association [149]. Similarly, a more recent case-control study of renal cell cancer in Italy including 767 cases and 1534 controls did not find any association between tea consumption and risk of renal cell cancer [151]. Lee et al. analyzed datasets of the Nurses' Health Study and the Health Professionals Follow-up Study and found that consumption of ≥1 cup/day tea was associated with statistically non-significantly reduced risk of renal cell cancer relative to <1 cup/month (OR=0.78, 95% CI = 0.54-1.13) [152]. In a pooled analysis, Lee et al. combined data of 13 prospective cohorts including more than 774,000 men and women and 1478 incident renal cell cancer cases. Compared with nondrinkers, individuals who consumed ≥1 cups/day of tea had a statistically borderline significant 15% risk reduction (OR = 0.85, 95% CI = 0.71-1.02) in renal cell cancer after adjustment for body mass index, cigarette smoking, hypertension and other potential confounders (P for trend = 0.04) [153]. All these studies were conducted in North America and West Europe and examined the effect of presumably black tea on renal cell cancer risk. These findings do not support a protective role of black tea on kidney cancer. Additional prospective epidemiologic studies are warranted to examine the association between green tea consumption and kidney cancer risk.

2.12 Other organ sites

Glioma—Regular intake of tea was not associated with risk of adult glioma in a case-control study [154]. Recently Holick et al. examined the association between coffee, black tea and caffeine intake and risk of adult glioma in three prospective cohort studies in the United States. The analysis included 335 incident glioma cases. Compared with nondrinkers, there was a statistically non-significant, approximately 30% decreased risk of glioma incidence for those consuming 4 or cups/week of black tea [155]. More data are warranted to draw any conclusion on the association between tea consumption and adult glioma risk.

Lymphoma—Thompson et al. examined the association between black tea consumption and risk of non-Hodgkin's lymphoma in the Iowa Women's Health Study. The analysis included 415 incident lymphoma cases during the 20 years of follow-up following baseline interview. No association was found between black tea consumption and risk of non-Hodgkin's lymphoma [156].

Leukemia—A hospital-based case-control study involving 107 adults with leukemia and 110 orthopaedic controls in China found that green tea consumption was associated with a statistically significant 50% decreased risk of leukemia. The inverse association was dose-dependent with number of cups of tea per day, number of years of tea consumption, and the amount of dry tea leaves consumed (all P for trend < 0.01) [157]. A similar case-control study enrolled 252 leukemia patients aged 0-29 years and 637 sex- and age-matched control subjects in Taiwan. Compared with nondrinkers, high intake of total tea catechins was associated with approximately 50% reduced risk (OR = 0.49, 95% CI = 0.27-0.91). This

inverse association was stronger in older (16-29 years) than in younger (0-15 years) group [158]. Given the limitations of small study size and hospital-based study design, further studies are warranted to confirm these results.

3. Concluding Remarks

During the past 3 decades, a large number of epidemiologic studies have examined the association between tea consumption and risk of cancers at various organ sites. As described above, however, the epidemiologic data neither confirm or refute a definitive cancer-preventive role of tea intake. This is in contrast to the strong, relatively consistent evidence from experimental studies. The inconsistent results from epidemiologic studies might be due in part to the relatively low levels of tea or tea polyphenols consumed in some human populations compared to the high doses used in animal models.

The varying contents of tea catechins in different types of tea may contribute to the varying results of tea-cancer associations across different populations. Compared with black tea, green tea seems to be more consistently associated with reduced cancer risk, as least for gastrointestinal cancers and for lung cancer in nonsmokers. These results could be due to the relatively high concentrations of catechins in green tea than in black tea. It also could be due to the lower consumption level of black tea than green tea in the pertinent populations. For example, most of studies that examined the association between black tea consumption and cancer risk were conducted in North America and Western Europe, where the range of the tea consumption is narrow, resulting in risk estimates comparing subjects who consumed ≥1 cup/day of tea to nondrinkers [153]. On the other hand, studies conducted in Asia where a wide range of green tea intake is present, thus are able to compare those who consumed ≥5 cups/day of tea and those who consumed <1 cup/day [24]. A reduced risk of gastric cancer, for example, in the highest level of green tea consumption (i.e., ≥ 5 cups/day) suggests the requirement of both high consumption of green tea and a wide range of exposure in a study population to produce an effect that could be observed in epidemiological studies [24].

Biomarkers of the uptake and metabolism of tea polyphenols can overcome some of the limitations in measurement that are inherent in relying on self-report in epidemiological studies of tea and cancer risk. Available catechin biomarkers are specific, objective and have biological relevance. As a proof of principle experiment, we have demonstrated inverse associations between urinary levels of EGC and risk of esophageal, stomach and colorectal cancers in a prospective cohort study [21,48]. Additional prospective epidemiologic studies that use validated biomarkers to determine tea catechin levels in pre-diagnostic biospecimens are warranted to demonstrate whether a biomarker approach would provide more consistent results across populations.

Factors associated with tea drinking also may contribute to the inconsistent results observed in epidemiological studies of tea consumption and cancer risk. For example, the thermal carcinogenic effect of tea beverage could overshadow or eliminate the hypothesized protective effect of tea consumption on the development of esophageal cancer, if tea temperature was not be properly measured and controlled for. Another example is the protective effect of total fluid intake against bladder carcinogenesis that may confound the association between the association between tea and bladder cancer risk if it is not controlled for in statistical analysis. Early epidemiological studies were not designed to specifically test the hypothesis of tea consumption on the risk of cancer, thus information on potential confounders, such as tea temperature and total fluid intake, were not collected, and thus not accounted for in statistical analyses. Future studies need to take these potential confounders into consideration during data collection and statistical analysis.

Confounding effects of smoking and alcohol on the tea-cancer association may also play a role to the varying results across different populations. Tea drinking is associated with cigarette smoking and alcohol drinking, at least in Asian populations. More consistent findings of inverse associations between green tea consumption and risk of esophageal and lung cancers were observed among nonusers of tobacco and alcohol, suggesting the importance of eliminating their potential confounding effect when examining the tea-cancer association.

Epidemiologic studies and phase II clinical trials reviewed in this article demonstrated a protective role of tea, in particular green tea, against the development of cancers in the upper gastrointestinal tract including oral cavity, esophagus, and stomach. Green tea may also exert beneficial effect against mammary carcinogenesis among premenopausal women and the recurrence of breast cancer. An inverse association between green tea consumption and risk of advanced prostate cancer risk from a prospective cohort study seems consistent with the results from the inhibitory effect of green tea catechins on the progression of prostate pre-malignant lesions in a randomized phase II clinical trials. The contradictory results for colorectal cancer across different studies indicate the complexity of tea and/or its constituents in the colorectal carcinogenesis. Limited data support a protective effect of green tea, but not black tea, against the development of lung and liver cancer. There is lack of evidence in support of a protective effect of either green tea or black tea against the cancer development of the pancreas and urinary tract. More epidemiologic studies are required to assess the effect of both green tea and black tea on risk of other malignancies including glioma, lymphoma, and leukemia.

Results from large prospective observational studies with well-defined tea intake together with chemoprevention trials will provide the evidence for definite beneficial or deleterious effects of tea consumption on cancer formation in humans. Because the causative factors for cancers most likely differ across different populations, tea consumption may affect carcinogenesis only in selected situations rather than having an abroad effect on all cancers in general populations. Thus there is a need to define the population that could benefit from tea consumption. Such intervention studies in various populations may provide useful information on the protective effect of tea polyphenols on cancer of specific organs or in specific populations. Given that green tea is well tolerated at moderate doses, and can be safely administered without any serious side effects, it may be possible to recommend consumption of tea polyphenols by humans after careful evaluation of additional well designed epidemiologic studies and clinical trials.

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Abbreviations

4′-MeEGC	4′-*O*-methyl-epigallocatechin
M6	5-(3′,4′,-dihydroxyphenyl)-γ-valerolactone
M4	5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone
CI	confidence interval
EC	epicatechin
ECG	epicatechin-3-gallate
EGC	epigallocatechin

EGCG	epigallocatechin-3-gallate
HR	hazard ratio
OR	odd ratio
PSA	prostate-specific antigen
RR	relative risk

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