

Cancer prevention by green tea: evidence from epidemiologic studies^{1–4}

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ABSTRACT

In contrast to the consistent results of an inhibitory effect of green tea extracts and tea polyphenols on the development and growth of carcinogen-induced tumors in experimental animal models, results from human studies are mixed. Both observational and intervention studies have provided evidence in support of a protective role of green tea intake in the development of oral–digestive tract cancer or an inhibitory role of oral supplementation of green tea extract on a precancerous lesion of oral cavity. Evidence in support of green tea intake against the development of liver cancer risk is limited and inconsistent. An inverse association between green tea intake and lung cancer risk has been observed among never smokers but not among smokers. Although observational studies do not support a beneficial role of tea intake against the development of prostate cancer, several phase 2 clinical trials have shown an inhibitory effect of green tea extract against the progression of prostate pre-malignant lesions to malignant tumors. Prospective epidemiologic studies so far have not provided evidence for a protective effect of green tea consumption on breast cancer development. Current data neither confirm nor refute a definitive cancer-preventive role of green tea intake. Large randomized intervention trials on the efficacy of green tea polyphenols or extracts are required before a recommendation for green tea consumption for cancer prevention should be made. *Am J Clin Nutr* 2013;98(suppl):1676S–81S.

INTRODUCTION

All tea is produced from the leaves of *Camellia sinensis*, but differences in processing result in different types of tea. In the making 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. Black tea is produced by drying and crushing tea leaves on harvesting to encourage oxidation. The partially oxidized tea leaves yield oolong tea (1). Worldwide, ~78% of the tea production is black tea, which is the main tea beverage in the Americas, Europe, and the Middle East. Green tea, which is popular in Japan and parts of China, accounts for ~20% of total tea production. The remaining 2% of tea production is oolong tea, which is consumed mainly in southeast 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% (by dry weight) are catechins (2, 3). Epigallocatechin-3-gallate (EGCG)⁵, epigallocatechin, epicatechin-3-gallate, and epicatechin are the major catechins in green tea. EGCG is the most

abundant catechin in green tea, accounting for approximately two-thirds of the total catechins (1).

Extensive laboratory studies in multiple animal models have consistently shown the inhibitory activities of green tea extract and/or green tea polyphenols against tumorigenesis at different organ sites (2). Mechanisms of action of tea polyphenols, especially EGCG, have been extensively investigated (4). The results of green tea consumption on the protection/risk of various cancer sites in humans assessed here are extracted largely from the author's previously published work and updated with an additional literature review of newly published observational studies and clinical trials (5, 6).

ORAL CANCER

Epidemiologic studies on the association between green tea consumption and oral cancer risk are limited. The Japan Collaborative Cohort Study enrolled 50,221 Japanese men and women aged 40–79 y. After >10 y of follow-up, 37 oral cancer cases occurred among cohort participants. A borderline significant, inverse association between green tea intake and oral cancer risk was observed, with an HR of 0.44 (95% CI: 0.19, 1.04) for those consuming ≥ 5 cups green tea/d relative to <1 cup/d (P -trend = 0.07). The borderline significance in the inverse relation could be a result of the relatively small number of cancer cases.

Two randomized, placebo-controlled phase 2 clinical trials were conducted to examine the inhibitory effect of green tea

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² Presented at the conference “Fifth International Scientific Symposium on Tea and Human Health,” held at the US Department of Agriculture, Washington, DC, 19 September 2012. The conference was organized by Jeffrey Blumberg, Tufts University, Boston, MA, and a Steering Committee including representatives from each of the symposium cosponsors: the American Cancer Society, the American College of Nutrition, the American Institute for Cancer Research, the American Medical Women's Association, the American Society for Nutrition, and the Linus Pauling Institute. The symposium was underwritten by the Tea Council of the USA. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Tea Council of the USA or the cosponsoring organizations.

³ This work was partially supported by NIH grant R01CA144034.

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⁵ Abbreviations used: COMT, catechol-*O*-methyltransferase; EGCG, epigallocatechin-3-gallate; IGF, insulin-like growth factor; PSA, prostate-specific antigen.

First published online October 30, 2013; doi: 10.3945/ajcn.113.058271.

extract on the progression of oral precancerous lesions toward malignant tumor. Li et al (7) randomly assigned 59 patients with oral mucosa leukoplakia to either the green tea treatment (3 g of a mixed green tea product/d) or the placebo arm. After 6 mo, 37.9% of patients in the green tea treatment arm showed reduced size of oral lesions, whereas 3.4% of patients had increased lesion size. In contrast, 6.7% of patients in the placebo arm had decreased and 10% of patients had increased size of oral mucosa leukoplakia. These differences between the treatment and placebo arms were significant. Tsao et al (8) recruited 42 patients with one or more histologically confirmed, bidimensionally measurable, oral premalignant lesions with high-risk features of malignant transformation that could be sampled by biopsy and randomly assigned the 42 patients to 1 of the following 4 groups: 500, 750, or 1000 mg/m² green tea extract per day or placebo. At 12 wk after the initiation of the treatment, 39 patients who completed the trial were evaluated; 14 (50%) of the 28 patients in the 3 combined green tea arms had a favorable response, whereas only 2 (18.2%) of the 11 patients in the placebo arm showed a similar response (*P*-difference = 0.09). A dose-dependent effect was observed; the favorable response rates were 58% in patients given 750 or 1000 mg/m² green tea extract and 36.4% in those given 500 mg/m² but was only 18.2% in those assigned to the placebo arm (*P*-trend = 0.03).

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 2 clinical trials further support a protective role of green tea extract against the progression of precancerous lesions in the oral cavity toward malignant transformation. Phase 3 clinical trials with large numbers of patients are required to confirm the efficacy of green tea intake against the formation of oral cancer in humans.

ESOPHAGEAL CANCER

There have been numerous epidemiologic studies examining the association between green tea consumption and esophageal cancer risk. Virtually all studies were conducted in Chinese and Japanese populations in whom a high incidence of esophageal cancer and a high consumption of green tea have been recorded. In a recent review of 15 epidemiologic studies, 6 reported a significantly reduced risk of esophageal cancer associated with high amounts of tea consumption; 4 reported a lower, but nonsignificant risk with green tea consumption; 3 reported a significantly positive association between tea consumption and esophageal cancer risk; and the remaining 2 studies reported a null association (5). The inconsistent results across different studies may be explained by other factors associated with tea drinking.

Tea beverages, if consumed at a high temperature, could cause damage to the esophageal epithelia and result in increased risk of esophageal cancer. In the early 1970s, epidemiologic studies already suggested a link between tea consumed at a high temperature and increased risk of esophageal cancer (9). In a systemic review, Islami et al (10) examined the consumption of high-temperature beverages (coffee, tea, and *maté*, a traditional South American caffeine-rich infused drink) in relation to risk of esophageal cancer. The majority of these studies showed an increased risk of esophageal cancer with consumption of high-temperature beverages regardless of the type of beverage.

Cigarette smoking and alcohol drinking, the 2 established risk factors for esophageal cancer (11, 12), 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. In a large population-based case-control study of esophageal cancer in Shanghai, China, Gao et al (13) found a significantly reduced risk of esophageal cancer associated with green tea consumption only among people who did not smoke cigarettes or drink alcoholic beverages [ORs: 0.43 (95% CI: 0.22, 0.86) in men and 0.40 (95% CI: 0.20, 0.77) in women]. Similar results were found in another study in a Chinese population (14).

The inconsistent results of these studies could be due, at least partly, to the potential confounding effect of smoking and alcohol intake as well as the adverse effect of the high-temperature tea beverage on the green tea–esophageal cancer association. Further studies that are well controlled for these factors would clarify the association between green tea intake and esophageal cancer risk.

GASTRIC CANCER

Numerous epidemiologic studies have examined and shown an inverse, albeit moderate, association between green tea consumption and gastric cancer risk. Myung et al (15) recently conducted a meta-analysis investigating the quantitative association between the consumption of green tea and the risk of gastric cancer. The analysis included 13 studies, which were all conducted in Japanese or Chinese populations. The summary adjusted RR of gastric cancer for the highest compared with the lowest amount of green tea consumption was 0.82 (95% CI: 0.70, 0.96). The inverse association was primarily seen in case-control studies rather than cohort studies. However, a more recent pooled analysis of 6 cohort studies with >3500 incident gastric cancer cases found a significant, inverse association between green tea consumption and gastric cancer risk in women (16). Compared with those drinking <1 cup/d, women who consumed ≥5 cups green tea/d had an ~20% decreased risk of gastric cancer (*P*-trend = 0.04). No protective effect was seen in all men or female nonsmokers (16).

Similar to esophageal cancer, the high temperature of tea beverages may have some harmful effects on the stomach. A case-control study of gastric cancer in northeast China did not find an overall association between green tea intake and gastric cancer. When data were analyzed by tea temperature, a dose-dependent relation was observed between consumption of green tea at lukewarm temperatures and decreased gastric cancer risk. Compared with nondrinkers, the ORs of gastric cancer were 0.61 (95% CI: 0.45, 0.82) for consumption of 500 g dry tea leaves/y and 0.19 (95% CI: 0.07, 0.49) for ≥750 g dry tea leaves/y. In contrast, there was no association between green tea consumed at a hot temperature and gastric cancer risk (17).

Data on specific green tea catechins and risk of gastric cancer are limited. Sun et al (18) conducted a case-control study of gastric cancer nested within a prospective cohort of Chinese men in Shanghai. Specific tea catechins and their metabolites were determined in urine samples that were collected from subjects before they developed gastric cancer. Urinary concentrations of tea catechins were significantly associated with a reduced risk of gastric cancer. Compared with the absence of epigallocatechin in

urine, the OR of gastric cancer for the presence of urinary epigallocatechin was 0.52 (95% CI: 0.28, 0.97) after adjustment for confounding factors (18). These findings support a protective role of epigallocatechin present in green tea on gastric cancer development in humans. Both case-control and cohort studies showed an inverse association between green tea consumption and risk of gastric cancer. The protection may be stronger for women than men or in nonsmokers.

COLORECTAL CANCER

Numerous epidemiologic studies have examined the association between green tea consumption and colorectal cancer. Sun et al (19) conducted a meta-analysis that included 25 epidemiologic studies evaluating the consumption of both green tea and black tea and risk of colorectal cancer in 11 countries. The inverse association between green tea intake and colon cancer risk was mainly observed in case-control studies (summary OR: 0.74; 95% CI: 0.60, 0.93) but not in prospective cohort studies (summary RR: 0.99; 95% CI: 0.79, 1.24). There was no relation between green tea intake and rectal cancer risk.

Several studies examined and reported the association between green tea consumption and colorectal cancer risk after that meta-analysis. After analyzing the database of the Singapore Chinese Health Study, a prospective cohort study of diet and cancer involving >60,000 Chinese men and women aged 45–74 y, Sun et al (20) found that subjects who drank green tea daily had a nonsignificant increased risk of 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). These data suggest that substances in green tea may exert an adverse, late-stage effect on the development of colorectal cancer. In a similar cohort of Chinese women, Yang et al (21) reported a reduced risk of colorectal cancer for women consuming ≥ 5 g dry green tea leaves/d compared with non-tea drinkers (HR: 0.56; 95% CI: 0.32, 0.98), especially among women with long-term tea drinking. On the other hand, 2 prospective studies in Japan failed to detect a significant, inverse association between green tea consumption and colorectal cancer risk (22, 23). By using validated biomarkers of specific tea polyphenols, Yuan et al (24) prospectively examined the urinary concentrations of specific tea catechins and their metabolites and the risk of developing colorectal cancer in the Shanghai Cohort Study as described above. Individuals with higher urinary catechin concentrations had a lower risk of colon cancer. Compared with the lowest quartile of epigallocatechin plus 4'-methyl-epigallocatechin, the ORs of colon cancer for the second, third, and fourth quartiles 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 -trend = 0.007). This study provides direct evidence for the specific tea catechins against the development of colon cancer in humans (24).

Epidemiologic studies provide suggestive evidence to support a protective role of green tea consumption, especially in high amounts and over long durations, 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.

LIVER CANCER

A limited number of epidemiologic studies have examined the association between green tea consumption and liver cancer risk. Wang et al (25) conducted an analysis of green tea intake and liver cancer mortality in a cohort of 60,076 Chinese men and 29,713 Chinese women in a high-risk region for liver cancer. After an average 12.8 y of follow-up, 1803 cohort participants who were free of cancer at baseline died of liver cancer. Regular green tea drinkers had a lower mortality of liver cancer relative to nondrinkers among women (HR: 0.51; 95% CI: 0.27, 0.96), but there was no association in men. Similarly, Ui et al (26) prospectively examined the association between green tea intake and the incidence of liver cancer in a cohort of 41,761 Japanese men and women. After an average 9 y of follow-up, 247 participants developed liver cancer. Green tea intake was associated with a decreased risk of liver cancer; the HR was 0.58 (95% CI: 0.41, 0.83) for those consuming ≥ 5 cups green tea/d relative to <1 cup green tea/d after adjustment for confounding factors. Inoue et al (27) analyzed 18,000 men and women in the Japan Public Health Center-based Prospective Study Cohort II and found an increased risk of liver cancer in women who drank 3–4 cups or ≥ 5 cups of tea compared with women consuming <3 cups of tea per day. There was no association between green tea intake and liver cancer risk among men in this study. Thus, observational studies provide very limited support for green tea consumption in reducing the risk of liver cancer.

A recent randomized, placebo-controlled, phase 2 clinical trial supported a protective role of green tea polyphenols in liver damage by aflatoxin exposure and hepatitis B, which are established risk factors for liver cancer (28). Individuals carrying hepatitis B surface antigen and positive aflatoxin B₁-albumin adducts were randomly assigned to 1 of the 3 following groups: 500 or 1000 mg green tea polyphenols/d or placebo. At both 1- and 3-mo time points after the initial intervention, subjects in both the 500- and 1000-mg green tea polyphenol arms showed significant 7- to 14-fold increased concentrations of aflatoxin B₁ mecapturic acids in urine, a detoxification biomarker for aflatoxin exposure, compared with those in the placebo arm (29). The same study also showed 50% lower in urinary 8-hydroxydeoxyguanosine, a biomarker of oxidative DNA damage, in both green tea-treated groups compared with the placebo group (30). These results suggest that the oral administration of green tea polyphenols at 500–1000 mg/d is effective in enhancing the detoxification of aflatoxin and in reducing oxidative DNA damage.

LUNG CANCER

A dozen epidemiologic studies have examined the association between green tea consumption and lung cancer risk. A recent systemic review analyzed 12 reports on the intake of green tea or tea polyphenols in relation to lung cancer risk (5). Among them, 5 studies found a significant inverse association between green tea intake and lung cancer risk, 3 studies reported a nonsignificant lower risk of lung cancer in green tea drinkers than in nondrinkers, 1 study reported a significantly increased risk of lung cancer in green tea drinkers compared with nondrinkers, 1 study reported a positive but nonsignificant association between green tea intake and lung cancer risk, and the remaining 2 studies reported a null association. The inconsistent results of those studies could be partly a result of the potential confounding

effect of smoking. For example, Zhong et al (31) examined the association between consumption of green tea and the risk of lung cancer in Chinese women living in Shanghai. Among nonsmoking women, regular tea drinkers experienced a 35% reduction in lung cancer risk compared with their counterparts who did not drink tea regularly (OR: 0.65; 95% CI: 0.45, 0.93). On the other hand, there was no association between green tea intake and lung cancer risk among smokers.

In a recent meta-analysis, Tang et al (32) reported that the summary RR of lung cancer associated with green tea intake was 0.78 (95% CI: 0.61, 1.00). Each 2 cups of green tea per day was associated with an 18% decreased risk of lung cancer (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 for 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. These findings, along with those described above, further suggest that cigarette smoking may confound or cancel out the potential protective effect of green tea against the development of lung cancer.

PROSTATE CANCER

A number of epidemiologic studies have examined the association between green tea intake and the risk of prostate cancer. All studies were conducted in Japanese or Chinese populations. Two case-control studies examined and found an inverse relation between green tea intake and prostate cancer risk. One study that included 130 patients with prostate cancer and 274 hospital inpatients as controls in southeast China found an inverse relation between green tea intake and prostate cancer; the OR was 0.28 (95% CI: 0.17, 0.47) for drinkers relative to nondrinkers, with a dose-response relation (P -trend < 0.001) (33). The other study in 140 prostate cancer cases and an equal number of hospital patients as controls also found an inverse, but nonsignificant association (34). 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, examined the association between green tea consumption and the risk of prostate cancer (35–38). An early study in men of Japanese ancestry in Hawaii found that green tea consumption was associated with a nonsignificant increased risk of prostate cancer (HR: 1.47; 95% CI: 0.99, 1.13) (35). Three 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 (38). A dose-dependent inverse relation was observed for risk of advanced prostate cancer (P -trend = 0.01); the HR was 0.52 (95% CI: 0.28, 0.96) for men who consumed ≥ 5 cups green tea/d compared with <1 cup/d. 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.

There have been 5 intervention studies evaluating the effect of green tea intake on the change in risk markers for prostate cancer (39–43). Of these studies, 3 were single-arm, open-label phase 2 trials in prostate cancer patients. Among them, 2 did not find any inhibitory effect of green tea extract on the progression of prostate

lesion or risk biomarkers of prostate cancer (41, 42). The third single-arm phase 2 trial was conducted to evaluate the effect of 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 d significantly reduced the concentrations of several cancer-related risk biomarkers including prostate-specific antigen (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 values <0.05) (40). A more recent randomized, double-blind, placebo-controlled trial of polyphenon E in men with prostate cancer aimed to determine the bioavailability of green tea polyphenols in prostate tissue and to measure its effects on systemic and tissue biomarkers of prostate cancer carcinogenesis (43). After treatment of 3–6 wk, green tea polyphenol concentrations in the prostatectomy tissue were low to undetectable. Polyphenon E intervention resulted in favorable but nonsignificant changes in serum PSA, IGFs, and oxidative DNA damage in blood leukocytes. Tissue biomarkers of cell proliferation, apoptosis, and angiogenesis in the prostatectomy tissue did not differ between the polyphenon E and placebo arms.

There was only one randomized, double-blind, placebo-controlled trial to evaluate the efficacy of green tea supplementation on prostate cancer incidence. Sixty men with high-grade prostate intraepithelial neoplasia were randomly assigned to the green tea treatment (200 mg \times 3 times/d) or placebo arm. After 2 mo of treatment, total PSA concentrations were not significantly different between the treatment and placebo groups. However, only 1 (3.3%) of the 30 patients in the treatment arm compared with 9 (30%) of the 30 patients in the placebo arm developed prostate cancer (P < 0.01) (39). A 2-y follow-up study in a subset of the participants showed the lasting protective effect of green tea catechins against the development of prostate cancer (44). 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 intake against the development of prostate cancer. There is some suggestive evidence that green tea intake may reduce the risk of advanced prostate cancer. Phase 2 clinical trials have provided encouraging evidence for the development of green tea catechins as a chemopreventive agent against prostate carcinogenesis. However, the low bioavailability and/or bioaccumulation of green tea polyphenols in prostate tissue and the lack of significant changes in systemic and tissue-specific biomarkers after green tea administration suggest that the prostate cancer–preventive activity of green tea polyphenols, if occurring, may be through indirect means. Future studies are warranted to explore additional mechanisms of the cancer-preventive activity of green tea polyphenols against the development of advanced stages of prostate cancer.

BREAST CANCER

Multiple meta-analyses have been published on green tea and breast cancer risk. The most recent meta-analysis included results from 8 epidemiologic studies on green tea intake and breast cancer risk (45). A summary RR of breast cancer based on 3 case-control

studies was 0.70 (95% CI: 0.61, 0.79) for the highest green tea intake compared with the lowest or no green tea intake. However, there was no risk reduction in breast cancer associated with green tea intake in 5 prospective cohort studies. The summary RR was 1.06 (95% CI: 0.93, 1.20) for the highest compared with the lowest or no green tea intake. Despite its chemopreventive potential and compelling evidence from animal studies, the role of green tea in breast cancer development remains unclear.

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 incorporated prediagnostic biomarkers of tea intake and metabolism on risk of breast cancer (46, 47). Urinary tea catechins including epigallocatechin, 4'-methyl-epigallocatechin, and epicatechin and their metabolites were measured in 353 cases and 701 controls nested within a prospective cohort in China. There was no association between urinary concentrations of any biomarkers measured and risk of breast cancer (46). In the second biomarker study, plasma concentrations of EGCG, epigallocatechin, epicatechin-3-gallate, and epicatechin were determined in 144 breast cancer patients and 288 matched control women within a prospective cohort study in Japan. Similarly, there was no association between plasma concentrations of tea catechins and the risk of developing breast cancer (47). It should be pointed out that in both biomarker studies the detectable rates of some of the biomarkers were as low as 20–30% (46, 47), which raises a concern about the sensitivity of the assays, because ~50% of study participants reported drinking at least one cup of green tea on a daily basis.

Mammographic density is a well-established breast cancer risk factor (48). Wu et al (45) conducted a cross-sectional study in 3315 Chinese women in Singapore. Daily green tea drinkers showed a significantly lower mammographic density percentage (19.5%) than did non-tea drinkers (21.7%; $P = 0.002$) after adjustment for multiple potential confounders. The difference in mammographic density was observed mainly among postmenopausal women. These results suggest that long-term exposure to green tea may be essential to exert its protective effect through the green tea's modulating effect on mammographic density.

The genetic polymorphism in the catechol-*O*-methyltransferase (*COMT*) gene has potential in modifying the association between tea consumption and breast cancer risk given the role of *COMT* in the metabolism and elimination of catechins (49). To date, 2 studies have incorporated the *COMT* genotype to account for interindividual differences in tea polyphenol bioavailability. With the use of data from a population-based case-control study in Asians in Los Angeles County, CA, Wu et al (50) reported that consumption of either black tea or green tea was associated with significant 50% reduced risk of breast cancer in women carrying at least one copy of the low-activity *COMT* allele relative to non-drinkers. On the other hand, no association between tea intake and breast cancer risk was seen in women carrying both high-activity *COMT* alleles. A more recent study in a Chinese population did not find any modifying effect of the *COMT* genotype on the association between tea consumption and breast cancer risk (51). Additional studies are required to resolve these inconsistent findings.

CONCLUSIONS AND FUTURE DIRECTIONS

During the past 3 decades, a large number of epidemiologic studies have examined the association between green tea con-

sumption and risk of cancers at various organ sites. These data neither confirm nor refute a definitive cancer-preventive role of green tea intake on cancer. This situation is in contrast to the strong, relatively consistent evidence from experimental studies. The inconsistent results from epidemiologic studies might be due, at least in part, to the following reasons. Human exposure to tea polyphenols is relatively low, in the range of 1 to 2 orders lower than those used in *in vitro* and *in vivo* experimental studies (52). The residual confounding effect of cigarette smoking and alcohol consumption may contribute to the varying results among different studies. The adverse effect of the high temperature of tea beverages would mask or complicate the tea-cancer risk association given the difference in tea-drinking habits across different populations. Furthermore, the heterogeneity of tea consumption amounts and nourishment across different populations also could contribute to the inconsistency in results on tea drinking and risk of cancer.

In addition to large prospective observational studies, randomized phase 3 intervention studies would ultimately provide definitive data to determine the beneficial or deleterious effects of green tea consumption on cancer development 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 a broad effect on all cancers in general populations. Thus, there is a need to define the population who 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.

J-MY received an honorarium and travel support from the Tea Council of the USA for speaking at the Fifth International Scientific Symposium on Tea and Human Health and for preparing this article for publication. The author declared no competing financial interests.

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