Prospective Cohort Study of Green Tea Consumption and Colorectal Cancer Risk in Women

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Abstract

Tea and its constituents have shown anticarcinogenic activities in *in vitro* and animal studies. Epidemiologic studies, however, have been inconsistent. We prospectively evaluated the association between green tea consumption and colorectal cancer (CRC) risk in a cohort of 69,710 Chinese women aged 40 to 70 years. 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 6 years of follow-up, 256 incident cases of CRC were identified. The multivariate relative risk of CRC was 0.63 (95% confidence interval, 0.45-0.88) for women who reported drinking green tea regularly at baseline compared with nonregular tea drinkers. A significant dose-response relationship was found for both the amount of tea consumed (P_{trend} = 0.01) and duration in years of lifetime tea consumption (P_{trend} = 0.006). The reduction in risk was most evident among those who consistently reported to drink tea regularly at both the baseline and follow-up surveys (relative risk, 0.43; 95% confidence interval, 0.24-0.77). The inverse association with regular tea drinking was observed for both colon and rectal cancers. This study suggests that regular consumption of green tea may reduce CRC risk in women. (Cancer Epidemiol Biomarkers Prev 2007;16(6):1219–23)

Introduction

Tea and its constituents have shown antioxidative, anti-inflammatory, and anticarcinogenic activities in numerous *in vitro* and animal studies (1, 2). Organ sites that are accessible directly to orally administered tea, such as digestive tract, are thought to represent good targets for potential chemoprevention by tea because of the high bioavailability (2). A number of epidemiologic studies, mostly with case-control study design, have evaluated this hypothesis in various populations and yielded inconsistent results (3, 4). Differences in tea-drinking habits, types of tea consumed, and consumption levels may have contributed to some of the inconsistency (3, 5). Failure to control for potential confounding factors and inadequate assessment of tea consumption may also be important contributors (3).

Tea is the most popular beverage consumed in China. We have previously reported inverse associations between green tea consumption and risks of certain digestive tract cancers (6-9), including colorectal cancer (CRC), in case-control studies conducted in urban Shanghai. In this report, we analyzed the data from a large prospective cohort study in urban Shanghai with detailed and repeated assessment of tea consumption to test the hypothesis that green tea consumption may reduce the risk of CRC.

Materials and Methods

Study Population. The Shanghai Women's Health Study is a population-based prospective cohort study of women aged 40 to 70 years at baseline. The study was approved by the relevant Institutional Review Boards for human research in China and the United States. A written informed consent was obtained from all study participants. The details of the study design and methods have been published elsewhere (10). Briefly, the study recruited 74,942 women between 1996 and 2000 from seven urban communities of Shanghai, with a participation rate of 92.7%. All women completed a detailed baseline survey that was conducted in person by trained interviewers using structured questionnaires. The questionnaires covered information on demographic characteristics, lifestyle and dietary habits, medical history, and family history of cancer, among others. Anthropometric measurements, including current weight, height, and circumferences of the waist and hips, were also taken.

This study excluded subjects who reported a history of cancer (n = 1,490), diabetes (n = 3,302), or familial adenomatous polyposis (n = 86) at baseline, subjects with an extreme total energy intake (<500 or >3,500 kcal/d; n = 132), subjects lost to follow-up since enrollment (n = 10), or subjects who drank black or oolong tea regularly and exclusively (n = 381; 0.5%). After these exclusions (not mutually exclusive), a total of 69,710 women remained for the present study.

Outcome Ascertainment. This cohort was followed for occurrence of cancer and other chronic diseases by home visits biennially with all surviving cohort members or next of kin (typically their spouse or children) if the cohort members were deceased. The biennial active follow-up for the cohort was virtually complete, with a response rate of 99.8% for the first follow-up survey between 2000 and 2002 and 98.7% for the second follow-up survey between 2002 and 2004. In addition to the in-person active follow-up, we searched the records from the population-based Shanghai Cancer Registry on a monthly basis to assure a timely and complete ascertainment of new cancer cases in this study cohort. The death certificate data from the Shanghai Vital Statistics were used to update vital status of the cohort members and identify causes of death. Medical charts from hospitals were reviewed and the pathologic characteristics of the tumor were recorded. The majority of the cases (n = 246; 96.1%) were pathologically confirmed, with the remainder (n = 10; 3.9%) diagnosed with

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endoscopy, radiography (barium-air double contrast radiography and/or computed tomographic scans), or ultrasound.

Assessment of Tea Consumption. Tea consumption was assessed at the baseline survey for all participants and reassessed 2 to 3 years later for more than 91.4% of the participants at the first follow-up survey. Each participant was asked whether she drank tea regularly (at least thrice per week lasting at least 6 months) and at what age she started such habit, followed by questions on the type and amount (dry weight) of tea (tea leaves) consumed during the past year, as well as current status of tea consumption. Those who were former tea drinkers were further asked about the age when they last drank tea regularly.

Statistical Analysis. Person-years of follow-up were calculated for each participant from the date of the baseline interview to the date of cancer diagnosis, death, or date of last follow-up (June 30, 2004), whichever came first. The Cox proportional hazards model was used to compute relative risks (RR) of developing CRC associated with green tea consumption and their 95% confidence intervals (95% CI) after adjusting for potential confounding variables. Potential confounding variables that were chosen based on *a priori* considerations included age at baseline, education, household income, cigarette smoking, alcohol drinking, regular leisure time exercise, body mass index (kg/m^2; calculated as weight in kilograms divided by the square of height in meters), postmenopausal status, and intakes of calories, red meat, total vegetables, and fruits. We also included following covariates of medical history in the multivariate model, including family history of CRC, regular vitamin supplement use (defined as using vitamins C, E, or multivitamins at least thrice per week for more than 2 consecutive months in the past 12 months), regular aspirin or other nonsteroidal anti-inflammatory drug use (defined as using nonsteroidal anti-inflammatory drugs at least thrice per week for more than 2 consecutive months in the past 12 months), as well as histories of colorectal polyps and chronic ulcerative colitis, to account for their potential confounding effects on the tea-CRC association. Among tea drinkers, the amount and years of tea consumption were dichotomized at the 75th percentile of intake or years of consumption. Tests for linear trend were done by scoring the amount and the duration of tea consumption and modeling them as continuous variables. Stratified analyses were also conducted to assess further the independent effect of tea and possible effect modification by age, body mass index, waist-to-hip ratio, physical activity, as well as intakes of red meat, vegetables, and fruits. Log-likelihood tests were used to evaluate potential multiplicative interaction between tea consumption and lifestyle and dietary covariates. We also conducted sensitivity analyses by either excluding the observations of early follow-up or stratifying by tumor stage to evaluate the potential effect of prediagnosed disease on the association between tea consumption and CRC risk. Graphic evaluation of Schoenfeld's residual plot suggested no evidence of violation of the proportional hazards assumption that underlies the Cox model. Statistical analyses were carried out using SAS version 9.1 (SAS Institute). All tests for statistical significance were two sided.

Results

Approximately 30% of the cohort members reported drinking green tea regularly at baseline. Among green tea drinkers, the median monthly consumption was 100 g dry weight of tea leaves, ranging from 50 g (the 25th percentile) to 150 g (the 75th percentile). The median duration of lifetime green tea consumption was 16 years, ranging from 8 years (the 25th percentile) to 24 years (the 75th percentile). Compared with those who never or occasionally drank tea, regular tea drinkers were slightly younger, had higher household income and educational attainment, and tended to exercise regularly and consume a little more vegetables and fruits (Table 1). There were no appreciable or only slight differences in body mass index, waist-to-hip ratio, intakes of total energy and red meat, and family history of CRC between tea drinkers and nondrinkers. Few women in this cohort ever smoked cigarettes (2.7%), drank alcoholic beverages (2.3%), or used aspirin and other nonsteroidal anti-inflammatory drugs (1.8%) or postmenopausal hormones regularly (2.2%).

During 397,840 person-years of follow-up, 256 incident cases of CRC (150 colon and 106 rectal cancer cases) were documented. Table 2 presents RRs of CRC associated with green tea consumption at baseline. After adjustment for age, women who reported drinking green tea regularly had a RR for CRC of 0.63 (95% CI, 0.45-0.88) compared with nonregular tea drinkers. This inverse association persisted after further adjustment for known risk factors for CRC, as well as other demographic, lifestyle, and dietary factors. The inverse association was found for both colon and rectal cancers, with multivariate RRs being 0.66 (95% CI, 0.43-1.01) and 0.58 (95% CI, 0.35-0.98) for colon and rectal cancers, respectively (data not shown in tables). Exclusion of nonpathology confirmed cases ($n = 10$) did not alter the result (RR for CRC, 0.64; 95% CI, 0.46-0.90); therefore, we decided to include all cases in subsequent analyses.

Risk of CRC tended to decrease further with increasing amount of tea consumed ($P_{trend} = 0.01$) and with increasing duration of lifetime tea consumption ($P_{trend} = 0.006$; Table 2). Compared with nondrinkers, each 1.67-g increase (approximately equivalent to the amount of tea in a tea bag) in daily green tea consumption was associated with a 10% reduction in CRC risk (RR, 0.90; 95% CI, 0.80-1.00), and additional 5-year consumption of green tea was also associated with a 10% reduction in CRC risk (RR, 0.90; 95% CI, 0.83-0.97) after fully adjusting for potential confounding factors.

In sensitivity analyses, the results were not materially altered when the analysis was restricted to CRC cases that were diagnosed 1, 2, and 3 years after the baseline survey, with RRs (95% CI) for CRC being 0.57 (0.40-0.83), 0.56 (0.38-0.82), and 0.60 (0.39-0.92), respectively. Nor did the association vary by tumor stage, with RRs (95% CI) of 0.56 (0.35-0.88) for early stage (Dukes A or B) CRC and 0.63 (0.42-0.95) for late stage (Dukes C or D) CRC.

Table 3 shows baseline tea consumption in relation to CRC risk, stratified by age and known risk factors for CRC, including physical activity, body mass index, waist-to-hip ratio, red meat consumption, and vegetable and fruit intake. The inverse association between tea consumption and CRC risk was consistently seen across all strata. None of the statistical tests was significant for multiplicative interactions between tea and any of the stratifying factors. We also conducted analyses excluding those who had ever smoked cigarettes, consumed alcoholic beverages, or regularly used nonsteroidal anti-inflammatory drugs and found no material changes in risk estimates, with RRs ranging from 0.61 to 0.64.

Additional analysis among subjects with tea consumption assessed at baseline and reassessed 2 to 3 years later ($n = 63,737$; 91.4%) found that those who reported consistently to be a regular tea drinker had the most pronounced reduction in CRC risk (multivariate RR, 0.43; 95% CI, 0.24-0.77). The RRs were 0.91 (95% CI, 0.53-1.56) and 0.81 (95% CI, 0.50-1.30), respectively, for women who quitted tea drinking or started tea drinking after the baseline recruitment (data not shown in tables).

Discussion

In this large population-based prospective cohort study, we found that regular consumption of green tea was inversely

Table 1. Age-adjusted baseline characteristics by tea-drinking habit, the Shanghai Women's Health Study, 1996 to 2004

Characteristics	All subjects	Drinking green tea regularly	
		No	Yes
No. of participants	69,710	49,084	20,626
Age, y	51.7 (9.0)	52.4	50.0
Education, college and above (%)	13.7	11.3	19.5
Household income, >30,000 Yuan*/y (%)	17.7	16.1	21.6
Ever smoked regularly (%)	2.7	2.0	4.6
Ever drank alcohol regularly (%)	2.3	1.5	4.1
Exercised regularly (%)	34.4	33.2	37.3
Postmenopausal (%)	46.7	47.1	46.0
Family history of CRC (%)	2.2	2.1	2.4
Body mass index, kg/m^2	23.9 (3.4)	23.8	24.2
Waist-to-hip ratio	0.81 (0.05)	0.81	0.81
Total energy, kcal/d	1,688 (395)	1,684	1,695
Vegetables, g/d	296.4 (168.5)	290.1	311.2
Fruits, g/d	276.6 (181.3)	268.2	296.7
Red meat, g/d	51.2 (36.1)	50.6	52.6

NOTE: Age-adjusted mean values (SD) were given for variables unless otherwise indicated; all differences between tea drinkers and nondrinkers were statistically significant ($P < 0.05$).
*1 USD = ~7.8 Yuan (Chinese currency).

associated with the risk of CRC, particularly among women who maintained such habit over time. The longer the duration of lifetime tea consumption, the lower was the risk of CRC. CRC risk also decreased as the amount of tea consumption increased. This inverse association was independent of known risk factors for CRC and consistent with animal and *in vitro* experiments showing potential cancer-inhibitory effects of tea and its extracts.

Green tea contains many polyphenolic compounds, mainly catechins, comprising 30% to 40% of the extractable solids of dried green tea leaves (1). These compounds, especially epigallocatechin-3-gallate, the major catechin of green tea, are believed to mediate many of the cancer-protective effects of tea. Tea catechins have strong antioxidant activity, which is about 25 to 100 times more potent than vitamins E and C (11). Epigallocatechin-3-gallate has been shown to attenuate the inflammatory response in human colon adenocarcinoma cell lines by inhibiting the production of chemokines and prostaglandin E_2 (12). In addition to the antioxidant and anti-inflammatory activities, recent research has proposed many other possible mechanisms for the cancer-inhibitory effects of green tea, including modulation of signal transduction pathways, which leads to inhibition of cell proliferation and transformation, induction of apoptosis and cell cycle arrest, and inhibition of tumor invasion and angiogenesis (1, 13, 14). Because green tea catechins are not completely absorbed by the gut, catechins can be present as native forms at high concentrations in the intestinal lumen (15). In this respect, it has been postulated that digestive tract may represent good targets for potential chemoprevention with tea because of the high bioavailability (2).

Green tea is the most commonly consumed tea in Shanghai. The finding of an inverse association between green tea consumption and CRC risk in this prospective cohort study confirms results of our two previous case-control studies conducted in late 1980s and early 1990s (8, 9). In both case-control studies, involving 1,328 and 1,805 incident CRC cases, respectively, green tea consumption was found to be associated with a reduced risk of CRC in a dose-response manner. Other epidemiologic investigations of green tea and CRC were mainly from Japan (3, 4). Three cohort studies on this topic have thus far been published. One reported a reduced risk of CRC associated with green tea consumption (16), whereas the other two found null association (17, 18). The inconsistent findings may be partially explained by relatively crude assessment of green tea consumption in these studies, in

Table 2. RRs and 95% CIs of CRC associated with green tea consumption, the Shanghai Women's Health Study, 1996 to 2004

	All subjects				Analysis omitting the 1st year of observation	
	Person-years	Events, *n*	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)	Events, *n*	Multivariate RR* (95% CI)
Drinking green tea regularly						
No	278,529	212	1.0 (reference)	1.0 (reference)	189	1.0 (reference)
Yes	119,312	44	0.58 (0.42-0.81)	0.63 (0.45-0.88)	36	0.57 (0.40-0.83)
Amount of dry green tea consumed (g/d) †,‡						
1-4	73,604	30	0.64 (0.44-0.94)	0.70 (0.47-1.02)	25	0.64 (0.42-0.98)
≥5	41,260	13	0.51 (0.29-0.89)	0.56 (0.32-0.98)	10	0.48 (0.25-0.92)
P_{trend}			0.002	0.01		0.004
Years of green tea consumption ‡,§						
1-23	84,801	31	0.67 (0.46-0.98)	0.72 (0.49-1.06)	25	0.65 (0.42-1.00)
≥24	30,268	12	0.46 (0.26-0.82)	0.50 (0.27-0.89)	10	0.46 (0.24-0.87)
P_{trend}			0.001	0.006		0.003

*Adjusted for age; education; household income; cigarette smoking; alcohol drinking; physical activity; body mass index; menopausal status; nonsteroidal anti-inflammatory drug use; vitamin supplement use; prior histories of colorectal polyps and chronic ulcerative colitis; family history of colorectal cancer; and intakes of total energy, vegetables, fruits, and red meat.
†Data on the amount of tea consumed were missing for 798 participants.
‡Among tea drinkers, cutoff points for the amount and the years of tea consumption at the 75th percentiles.
§Data on years of tea consumption were missing for 720 participants.

Table 3. Multivariate RRs and 95% CIs of CRC associated with regular green tea consumption, stratified by selected covariates, the Shanghai Women's Health Study, 1996 to 2004

Covariates	Events, *n*	RR (95% CI) by green tea drinking		$P_{interaction}$
		No	Yes	
Age, y*				
<52	57	1.0	0.68 (0.37-1.25)	
≥52	168	1.0	0.54 (0.34-0.85)	0.46
Body mass index (kg/m^2)				
<25	137	1.0	0.62 (0.39-0.98)	
≥25	88	1.0	0.51 (0.28-0.93)	0.60
Waist-to-hip ratio*				
<0.81	98	1.0	0.77 (0.47-1.27)	
≥0.81	127	1.0	0.44 (0.25-0.76)	0.10
Physical activity				
No	103	1.0	0.52 (0.31-0.88)	
Yes	122	1.0	0.64 (0.38-1.07)	0.57
Red meat intake (g/d)*				
<51	142	1.0	0.58 (0.36-0.93)	
≥51	83	1.0	0.58 (0.33-1.03)	0.98
Total vegetable and fruit intake (g/d)*				
<568	130	1.0	0.52 (0.31-0.88)	
≥568	95	1.0	0.63 (0.38-1.05)	0.84

NOTE: Analyses omitted the 1st year of follow-up. Adjusted for age; education; household income; cigarette smoking; alcohol drinking; physical activity; body mass index; menopausal status; nonsteroidal anti-inflammatory drug use; vitamin supplement use; prior histories of colorectal polyps and chronic ulcerative colitis; family history of CRC; and intakes of total energy, total vegetables, fruits, and red meat. When variable was used for stratification, it was not included in the model.
*Stratified based on the mean values of the covariates.

which no distinction was made between individuals drinking modest and high amounts of green tea (17, 18). In addition, ~80% to 95% of study participants in Japan reported drinking tea everyday (19). The homogeneity in tea consumption may have hindered these studies from evaluating the association of CRC with green tea consumption.

Most tea consumed in Western societies is black tea. Frequent consumption of black tea was also found to be associated with reduced risks for digestive tract cancers (including CRC) in the Iowa Women's Health Study (20), colon cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up study (21), and rectal cancer in the Nurses Health Study (22). In contrast, several other studies reported no association (23, 24) or positive association of black tea consumption with CRC risk (25, 26). The reasons for these inconsistent findings are not clear. Most previous studies did not comprehensively assess tea intake. In our study, only 238 (0.32%) participants of the Shanghai Women's Health Study drank black tea regularly and exclusively, which limited our ability to assess the association of black tea with CRC risk.

Drinking practices of tea vary substantially in the types and amount of tea consumed among and between populations. The bioactivity of a cup of tea is affected by many factors, especially the amount of dry tea used for tea preparation (27). A recent case-control study found a significantly reduced risk of rectal cancer with increasing intake of black tea measured in grams of dry weight consumed per month (28). The observed association, however, was substantially diminished when the amount of tea consumption was measured in liters of tea drink. This observation suggests that difference in the assessment of tea consumption may have contributed to the conflicting results from previous epidemiologic studies. The common method of tea preparation in Shanghai is to brew dry tea leaves with hot water. Higher green tea consumption measured in dry weight has been consistently associated with reduced risks for cancers of the colorectum (8, 9), esophagus (6), stomach (29, 30), pancreas (8), and lung (31) in case-control studies conducted in Shanghai. In addition to the amount of tea consumed, our study also prospectively evaluated, for the first time, cumulative lifetime exposure to tea consumption in relation to CRC risk. Longer duration of green tea consumption was significantly associated with decreased risk; this inverse association persisted after further adjustment for the amount of tea consumed (data not shown).

The current study has several notable strengths. We comprehensively evaluated tea consumption and CRC risk by both the duration of lifetime tea consumption and the amount of tea leaves consumed. We also reassessed tea consumption during follow-up, allowing an evaluation of the effect of changing tea drinking over time on the association of tea and CRC risk. Other strengths of the study include a population-based prospective study design, high participation rates, and a virtually complete cohort follow-up, minimizing many sources of biases inherent to case-control studies.

As with any observational studies, the intake level of tea is likely to be measured with some errors in this study. However, because exposure assessment was conducted prospectively before cancer diagnosis, measurement errors are more likely to be nondifferential by case/control status, which tends to attenuate the true association between tea consumption and CRC risk. In addition, residual confounding may be a potential concern. However, we have carefully adjusted for a wide range of potential confounding factors, including socioeconomic status, and the results remained unchanged.

In conclusion, this prospective cohort study among women in Shanghai provides one of the strongest pieces of evidence in humans that regular consumption of green tea may confer a protection against CRC. These findings are consistent with data from *in vitro* and *in vivo* experiments, indicating that tea may serve as an effective chemopreventive agent. With prolonged follow-up, we should be able to provide a more precise risk estimate according to the duration and amount of tea consumption.

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