Prospective cohort study of tea consumption and risk of digestive system cancers: results from the Shanghai Women's Health Study[1–3]

Sarah Nechuta, Xiao-Ou Shu, Hong-Lan Li, Gong Yang, Bu-Tian Ji, Yong-Bing Xiang, Hui Cai, Wong-Ho Chow, Yu-Tang Gao, and Wei Zheng

ABSTRACT

Background: Data from in vitro and animal studies support a protective role for tea in the etiology of digestive system cancers; however, results from prospective cohort studies have been inconsistent. In addition, to our knowledge, no study has investigated the association of tea consumption with the incidence of all digestive system cancers in Chinese women.

Objective: We investigated the association of regular tea intake ($\geq$3 times/wk for >6 mo) with risk of digestive system cancers.

Design: We used the Shanghai Women's Health Study, a population-based prospective cohort study of middle-aged and older Chinese women who were recruited in 1996–2000. Adjusted HRs and associated 95% CIs were derived from Cox regression models.

Results: After a mean follow-up of 11 y, 1255 digestive system cancers occurred (stomach, esophagus, colorectal, liver, pancreas, and gallbladder/bile duct cancers) in 69,310 nonsmoking and non–alcohol-drinking women. In comparison with women who never drank tea, regular tea intake (mostly green tea) was associated with reduced risk of all digestive system cancers combined (HR: 0.86; 95% CI: 0.74, 0.98), and the reduction in risk increased as the amount and years of tea consumption increased (P-trend = 0.01 and P-trend < 0.01, respectively). For example, women who consumed $\geq$150 g tea/mo ($\sim$2–3 cups/d) had a 21% reduced risk of digestive system cancers combined (HR: 0.79; 95% CI: 0.63, 0.99). The inverse association was found primarily for colorectal and stomach/esophageal cancers.

Conclusion: In this large prospective cohort study, tea consumption was associated with reduced risk of colorectal and stomach/esophageal cancers in Chinese women. *Am J Clin Nutr* 2012;96:1056–63.

INTRODUCTION

In 2008, $\sim$1.5 million digestive system cancers were diagnosed in women throughout the world (1). Although digestive system cancers are less frequent than breast cancer, which is the most common cancer in women worldwide, digestive system cancers are associated with lower survival rates (2). Among the digestive system cancers, colorectal and stomach cancers rank as the third and fourth most common causes of cancer deaths in women in the world, respectively (1). In China, digestive system cancers combined accounted for 370,587 cancer deaths (50% of total cancer deaths) in women in 2008 (2).

Tea consumption is a modifiable factor that has been implicated in the prevention of cancers of the digestive system (3–7).

Tea as a protective factor for cancer has support from in vitro and in vivo studies (7–14). The major tea polyphenols include catechins, such as ($-$)-epigallocatechin-3-gallate (EGCG)[4], ($-$)-epigallocatechin (EGC), ($-$)-epicatechin-3-gallate, and ($-$)-epicatechin, which are antioxidants and also possess other cancer-inhibitory properties (7, 13–15). For example, EGCG is the most abundant catechin and may reduce DNA damage by reactive oxygen species (13, 16) and inhibit tumor cell growth, invasion, and angiogenesis (7, 8, 10, 11).

Despite strong experimental evidence from in vitro and animal studies to suggest a role of tea in the prevention of cancer, including cancers of the digestive system, epidemiologic studies of the association between tea intake and risk of digestive system cancers have been inconsistent (3–7, 17–20). In addition, few large prospective cohort studies have been conducted, particularly in Chinese populations (6, 21, 22). A recent meta-analysis by Kang et al (4) reported an inverse association for tea drinking and risk of stomach cancer in 11 case-control studies and no association in 7 cohort studies. However, all of the cohort studies were conducted in Japan (the case-control studies included studies from both Japan and China), where tea processing and drinking habits (eg, frequency and brewing) differ in comparison with other countries, including China (4, 23). In addition, there has been concern in past studies of potential residual confounding from lifestyle factors correlated with tea drinking, specifically smoking and alcohol consumption, because of the high prevalence of smoking and alcohol drinking in men in many Asian populations (20, 22, 24).

We used the Shanghai Women's Health Study (SWHS), a population-based prospective cohort study, to investigate the association of tea consumption with risk of digestive system cancers in middle-aged and older Chinese women. In this cohort, few women have ever smoked or drank alcohol regularly (<3%); hence, we had the opportunity to investigate the association of tea drinking with digestive system cancers in nonsmoking and non–alcohol-drinking women.

SUBJECTS AND METHODS

Study cohort

The SWHS is an ongoing population-based prospective cohort study in Chinese women. The study methods and rationale have been reported in detail elsewhere (25). Briefly, participants were recruited from 7 urban areas in Shanghai, China. A total of 74,941 women aged 40–70 y were recruited from December 1996 through May 2000 with a participation rate of 92.7%. The baseline survey included an in-person interview, self-administered questionnaire, and anthropometric measurements taken by trained interviewers using standardized protocols. Information was collected on demographics, diet, and lifestyle habits (eg, physical activity, alcohol, smoking, and tea consumption), menstrual and reproductive history, medical history, occupational history, and select information from each participant's spouse (eg, disease history and smoking and alcohol habits). The food-frequency questionnaire and physical activity assessment have been validated (26, 27). All participants provided written informed consent, and human subjects institutional review board approval was obtained by the appropriate institutional review boards in China and the United States.

For the current study, we excluded participants who ever smoked and/or drank alcohol regularly (n = 3513), were lost to follow-up since enrollment (n = 7), or had missing or implausible covariate data [missing anthropometric measures (n = 59), missing food-frequency questionnaire items for main foods of interest (n = 11), extreme daily energy intake defined as <500 or ≥3500 kcal/d (n = 108), implausibly high amount of tea intake (>750 g/mo) (n = 2)], history of a gastrectomy at baseline (n = 204), cancer diagnosed before baseline (n = 1486), self-reported but unconfirmed cancer cases or cases waiting to be confirmed (n = 59), in situ cases (n = 58), and unknown type of cancer or diagnosis date (n = 124) for a final sample size of 69,310 women.

Tea consumption

At the baseline interview, women were asked if they ever drank tea regularly. Regular was defined as ≥3 times/wk for >6 mo continuously. Women who reported yes to ever drinking tea were queried about the age they started drinking tea and their current tea-drinking status. Former tea drinkers (only 1.1% of the cohort) were asked the age that they stopped drinking tea. Current tea drinkers were further queried about the type of tea they regularly consumed and the amount of tea (dry tea leaves) consumed per month over the past year. Updated information on regular tea consumption was obtained in the first follow-up survey, which occurred at a mean of 2.6 y (range: 0.8–4.9 y) after the baseline survey. In a validation study in 683 SWHS

participants, we examined the association between green tea leaves consumed (g/d) and urinary excretion of EGC (a specific tea polyphenol) (28). We found a statistically significant trend for increasing EGC and amount of tea leaves consumed. Specifically, the mean (25th, 75th percentiles) urinary excretion of EGC (nmol/mg creatinine) by amount of tea leaves consumed were as follows: 0.12 (0.08, 0.36) for nondrinkers, 0.12 (0.03, 0.61) for consumption of >0–1.7 g/d, 0.16 (0.12, 1.20) for consumption of 1.8–3.3 g/d, 0.25 (0.12, 1.85) for consumption of 3.4–5.0 g/d, and 0.96 (0.12, 5.16) for consumption of >5 g/d (P-trend < 0.01). These data provide support for the validity of our tea measurement.

Cohort follow-up and outcome ascertainment

Follow-up of the SWHS includes in-person interviews every 2 to 3 y. These surveys were conducted during 2000–2002, 2002–2004, and 2007–2010, with response rates of 99.8%, 98.7%, and 96.7%, respectively. Data on vital status and cancer diagnoses were also obtained by annual linkage to the population-based Shanghai cancer and vital statistics registries. Cancer cases were confirmed via home visits and medical chart review. Cancer-site information from the cancer registry was coded according to the International Classification of Diseases, Ninth Revision. Digestive system cancers included stomach [n = 293; 92% were distal cases (International Classification of Diseases for Oncology–2 codes C16.1–16.6, 16.8, 16.9) and 8% were cardia cases (International Classification of Diseases for Oncology–2 code C16.0)], esophageal (n = 27), colon (n = 360), rectal (n = 226), pancreas (n = 132), liver (n = 134), and gallbladder/bile duct (n = 83). Stomach and esophageal cancer cases were combined because of the small number of esophageal cases.

Statistical analysis

Adjusted HRs and corresponding 95% CIs were derived from Cox proportional hazards regression models with age (continuous variable) as the timescale. Entry time was defined as age at baseline, and exit time was defined age at cancer diagnosis, death, or last follow-up (31 December 2009), whichever occurred first. The reference group for all analyses was women who reported never drinking tea regularly (regular was defined as intake ≥3 times/wk for >6 mo). Potential confounders selected a priori (3, 6, 17) included education (elementary school or less, junior high school, high school, or more than high school), occupation (manual and agricultural workers or unknown, clerical, or professional), marital status (single, married, widowed, or divorced or separated), BMI (in kg/m^2) calculated as weight divided by height squared (continuous), waist-hip ratio (continuous), physical activity in standard metabolic equivalents (none, 1.0 to <2.0, or ≥2.0 metabolic equivalent task hours/wk), meat intake and fruit and vegetable intake (in g/d categorized into tertiles), first-degree family history of digestive system cancer, and history of diabetes. Final models included age at baseline, education, occupation, marital status, BMI, exercise participation, meat intake, fruit and vegetable intake, family history of digestive system cancer, and history of diabetes. We also considered additional adjustment for exposure to spousal smoking, which was available for 62,137 women with a husband at the baseline interview. Adjustment for spousal smoking did not

change associations (data not shown), and this factor was not included in final models.

Differences in sociodemographic and lifestyle factors by tea-drinking status were assessed by using the chi-square test. In current tea drinkers, the amount of tea was categorized on the basis of the 50th (100 g/mo) and 75th (150 g/mo) percentiles (<100, 100–149, or ≥150 g/mo) and years of consumption was categorized on the basis of a priori cutoffs (<10, 10–19, or ≥20 y). Joint categories for the amount of tea and years of consumption were created by using collapsed cutoffs because of smaller sample sizes (<15 y and <100 g/mo, <15 y and ≥100 g/mo, ≥15 y and <100 g/mo, or ≥15 y and ≥100 g/mo). Analyses that used the amount and duration of tea drinking were conducted only for specific cancers for which the number of cases was ≥100.

Tests for linear trend were conducted by using the Wald test, with scored variables for the amount and years of tea consumption treated as continuous variables. We examined the proportional hazards assumption, both graphically and by testing the significance of interaction terms for regular tea consumption at baseline and years of follow-up, and found no evidence of apparent departure from the assumption of proportional hazards. All analyses were conducted with SAS software (version 9.2; SAS Institute). Tests of statistical significance were based on 2-sided probability, and P values <0.05 were considered statistically significant.

RESULTS

After a mean of 11 y of follow-up (761,611 person-years), 1255 incident cases of digestive system cancers were identified. Approximately 28.0% ($n = 19,382$) of the cohort reported currently drinking tea regularly (regular was defined as intake ≥3 times/wk for >6 mo) at baseline, and 1.1% ($n = 788$) were former tea drinkers. Most tea drinkers reported drinking green tea only (88.2%) or green tea in combination with black or scented tea (5.1%); 3.5% of tea drinkers reported drinking only scented tea [ie, jasmine tea (white or green tea plus jasmine flowers) or green, black, or oolong tea in combination with herbs, other flowers, or fruit], 1.1% drank black tea alone or in combination with scented tea, 0.7% drank only oolong tea, and 1.4% of tea drinkers drank other types of tea. The median amount of tea consumed monthly was 100 g (25th, 75th percentiles: 50, 150 g). The median years of tea consumption was 15.4 y (25th, 75th percentiles: 7.0, 24.0 y).

Age-adjusted distributions for sociodemographic and lifestyle factors by tea-drinking status and for the entire cohort are shown in **Table 1**. Compared with women who reported never drinking tea regularly, current tea drinkers were younger, had a higher educational level, were more likely to have a professional occupation, and were more likely to report a family history of digestive system cancer and history of diabetes at baseline. Also, tea drinkers, compared with women who reported never drinking tea regularly, reported higher levels of daily physical activity and higher daily fruit and vegetable intake, and a slightly higher percentage were classified as overweight or obese.

Age-adjusted and fully adjusted HRs for current tea consumption of any type in association with all digestive system cancers combined and specific digestive system cancer types are shown in **Table 2**. The reference group for all multivariable

analyses was never regular drinkers of tea (regular was defined as ≥3 times/wk for >6 mo). In age-adjusted analyses, regular tea consumption was associated with a 17% reduced risk of all digestive system cancers combined (HR: 0.83; 95% CI: 0.72, 0.95). This association was not appreciably altered after adjustment for potential confounders. In age-adjusted analyses, regular tea intake was associated with a statistically significant 27% reduced risk of stomach and esophageal cancers combined; however, after adjustment for potential confounders, this association became marginally significant (HR: 0.79; 95% CI: 0.59, 1.05; $P = 0.097$). In both age-adjusted and fully adjusted analyses, although all HRs were <1.0, results were not statistically significant for the associations of regular tea intake and other specific types of digestive system cancers, including stomach, colon, rectal, colorectal, liver, and gallbladder/bile duct cancers. Fully adjusted HRs for current green tea consumption alone or in combination with one other type of tea (93% of tea drinkers) in association with digestive system cancers are also shown in Table 2; results were similar to those for any type of tea consumption.

Results for the association of tea consumption and risk of digestive system cancers were similar to findings in Table 2 after the exclusion of the first 2 y of follow-up (HR: 0.86; 95% CI: 0.74, 1.00; $P = 0.047$). Results were also similar after the exclusion of women with diabetes (data not shown). The association of tea consumption and incidence of distal stomach cancer was similar to overall findings (data not shown).

The amount of tea consumed per month in association with risk of digestive system cancers (93% of subjects consumed mainly green tea) is shown in **Table 3**. We found a significant trend for increasing amount of tea consumed monthly and reduced risk of cancers of the digestive system combined (P-trend = 0.01). Women who consumed ≥150 g tea/mo (∼2–3 cups/d) had a 21% reduced risk of digestive system cancers (HR: 0.79; 95% CI: 0.63, 0.99) compared with women who never drank tea regularly. However, for specific types of digestive system cancers, none of the HRs or tests for trend reached statistical significance.

Years of tea consumption in association with risk of digestive system cancers (93% of subjects consumed mainly green tea) are shown in **Table 4**. We found a significant trend for increasing years of tea consumption for all digestive system cancers combined (P-trend < 0.01) and a trend of borderline significance for colorectal cancer (P-trend = 0.05). Women who consumed tea for ≥20 y had a 27% reduced risk of digestive system cancers (HR: 0.73; 95% CI: 0.59, 0.90) and a 29% reduced risk of colorectal cancer (HR: 0.71; 95% CI: 0.52, 0.97) compared with women who never drank tea regularly.

We jointly examined tea amount (<100 and ≥100 g/mo) and duration (<15 and ≥15 y) (*see* Table S1 under "Supplemental data" in the online issue). We did not find evidence to suggest that women with both the longest duration of tea drinking and highest monthly consumption had lowest risk of digestive system cancers. For example, compared with women who never drank tea regularly, women who consumed <100 g tea/mo and who drank tea for ≥15 y had a 23% nonsignificant reduced risk of digestive system cancers, women who consumed ≥100 g of tea/mo and who drank tea for <15 y had a 17% nonsignificant reduced risk, and women who consumed ≥100 g tea/mo and drank tea for ≥15 y had significantly reduced risk of 19%.

TABLE 1
Baseline characteristics of study participants overall and by baseline tea-consumption status in nonsmokers and non–alcohol drinkers (n = 69,310) in the SWHS, 1996–2009[1]

Baseline characteristics	Entire cohort (n = 69,310)	Regular tea drinker (n = 19,382)[2]	Non–tea drinker (n = 49,140)	P
	n (%)	%	%	
Age at baseline				<0.01
40–49 y	34,560 (49.9)	57.6	46.9	
50–59 y	16,977 (24.5)	25.7	23.9	
60–70 y	17,773 (25.6)	16.7	29.3	
Education				<0.01
Elementary school or less	13,997 (20.2)	14.2	22.0	
Junior high school	26,031 (37.6)	33.9	39.6	
High school	19,664 (28.4)	31.9	27.0	
More than high school	9618 (13.9)	20.1	11.4	
Occupation				<0.01
Manual and agricultural workers/unknown	34,832 (50.3)	43.1	53.0	
Clerical	14,311 (20.7)	20.0	21.0	
Professional	20,167 (29.1)	36.9	26.0	
Marital status				<0.01
Single	617 (0.9)	0.89	0.88	
Married	61,853 (89.2)	90.6	88.8	
Widowed	4894 (7.1)	5.9	7.4	
Divorced or separated	1946 (2.8)	2.7	2.9	
Menopausal status[3]				<0.01
Premenopausal	35,996 (51.9)	52.8	51.6	
Postmenopausal	33,301 (48.1)	47.2	48.4	
BMI				<0.01
<18.5 kg/m^2	2296 (3.3)	2.3	3.7	
18.5–24.99 kg/m^2	42,872 (61.9)	60.4	62.4	
25.0–29.99 kg/m^2	20,704 (29.9)	31.8	29.1	
≥30.0 kg/m^2	3438 (5.0)	5.5	4.8	
Exercise participation				<0.01
None	45,198 (65.2)	62.4	66.4	
1.0 to <2.0 MET-h/d	16,686 (24.1)	25.6	23.3	
≥2.0 MET-h/d	7426 (10.7)	12.0	10.3	
Fruit and vegetable intake tertiles				<0.01
<404.2 g/d	23,103 (33.3)	28.2	35.4	
404.2–<626.1 g/d	23,104 (33.3)	34.1	33.0	
≥626.1 g/d	23,103 (33.3)	37.7	31.6	
Family history of digestive system cancer				0.032
No	59,635 (86.0)	85.5	86.2	
Yes	9675 (14.0)	14.5	13.8	
Diabetes				<0.01
No	66,385 (95.8)	95.2	96.0	
Yes	2925 (4.2)	4.8	4.0	

[1] All values (except age) were directly standardized to the age distribution of the cohort. P values were determined by using the chi-square test for general association. MET-h, metabolic equivalent task hours; SWHS, Shanghai Women's Health Study.
[2] Regular tea intake was defined as tea consumption ≥3 times/wk for >6 mo.
[3] Thirteen women were missing menopausal status information at baseline.

With the use of data from both the baseline and follow-up survey, we investigated the association of change in tea-drinking habits and risk of digestive system cancers (**Table 5**). This analysis was limited to women with both baseline and follow-up surveys who were cancer free at the follow-up survey (n = 63,049). Regular (≥3 times/wk for >6 mo) tea consumption was defined by using the following categories: 1) never drank tea as reported at both the baseline and follow-up surveys, 2) currently drinking tea at the baseline survey only; 3) currently drinking tea at the follow-up survey only; and 4) drinking tea at both baseline and the first follow-up. Women who drank tea at both the baseline and follow-up surveys had reduced risk of all digestive system cancers combined (HR: 0.74; 95% CI: 0.61, 0.91), cancers of the stomach and esophagus combined (HR: 0.68; 95% CI: 0.45, 1.02; P = 0.062), and colorectal cancer (HR: 0.69; 95% CI: 0.52, 0.92) compared with women who did not drink tea regularly at either the baseline or follow-up survey. For women who drank tea at baseline only or follow-up only (compared with women who did not drink tea regularly at either the baseline or follow-up), there appeared to be little evidence for an association of tea consumption with all digestive system cancers combined or specific digestive system cancers, although

TABLE 2
HRs (95% CIs) for the association of regular tea consumption and risk of digestive system cancers in nonsmokers and non–alcohol drinkers (n = 69,310) in the SWHS, 1996–2009[1]

Cancer sites	Any tea consumption				Green tea consumption[2]	
	Never	Current	Age adjusted	Fully adjusted[3]	Current	Fully adjusted[3]
	No. of cases	*No. of cases*			*No. of cases*	
All cancers combined	992	263	0.83 (0.72, 0.95)	0.86 (0.74, 0.98)	247	0.86 (0.75, 1.00)
Stomach	233	60	0.77 (0.58, 1.03)	0.82 (0.61, 1.09)	54	0.79 (0.58, 1.07)
Stomach and esophageal	258	62	0.73 (0.56, 0.97)	0.79 (0.59, 1.05)	56	0.77 (0.57, 1.03)
Colon	277	83	0.95 (0.74, 1.22)	0.95 (0.74, 1.22)	78	0.96 (0.74, 1.24)
Rectal	177	49	0.80 (0.58, 1.10)	0.82 (0.59, 1.13)	47	0.84 (0.60, 1.17)
Colorectal	454	132	0.89 (0.73, 1.08)	0.89 (0.73, 1.09)	125	0.91 (0.74, 1.12)
Liver	106	28	0.85 (0.56, 1.29)	0.86 (0.56, 1.32)	27	0.89 (0.58, 1.38)
Pancreas	105	27	0.88 (0.57, 1.34)	0.93 (0.60, 1.44)	26	0.96 (0.62, 1.49)
Gallbladder and bile duct	69	14	0.67 (0.38, 1.20)	0.74 (0.41, 1.34)	13	0.73 (0.40, 1.35)

[1] Regular tea intake was defined as ≥3 times/wk for >6 mo. Former drinkers (n = 788) were excluded from the analysis. SWHS, Shanghai Women's Health Study.

[2] In women who reported drinking green tea alone or in combination with other types of tea (n = 67,230).

[3] HRs were estimated by using Cox proportional hazards regression models with age as the timescale and were adjusted for age, marital status, education, occupation, BMI, exercise, fruit and vegetable intake, meat intake, diabetes, and family history of digestive system cancer. The reference group was never regular tea drinkers.

sample sizes were small for some specific cancer types. No evidence was found for an association between tea consumption and liver or pancreatic cancer.

DISCUSSION

In this large, population-based, prospective cohort study of middle-aged and older nonsmoking and non–alcohol-drinking women, we found that regular tea consumption was associated with reduced risk of cancers of the digestive system, particularly colorectal and stomach/esophageal cancers. Most tea drinkers (93%) consumed green tea alone or in combination with one other type of tea. Women who were consistent in their tea-drinking habits as assessed by intake at both the baseline and first follow-up surveys had the largest reductions in risk.

Although some previous studies, including population-based case-control studies conducted in Shanghai, China (24, 29), support our finding of an inverse association between tea and stomach/esophageal cancers, the literature overall is inconsistent. In addition, few prospective cohort studies have been conducted (3, 4, 19, 30, 31). A meta-analysis (2010) of 18 studies reported an inverse association for green tea with stomach cancer in 11 case-control studies (summary RR: 0.74; 95% CI: 0.63, 0.86) and no association in 7 cohort studies (RR: 1.03; 95% CI: 0.92, 1.16) (4). Results by country (all studies except for one were conducted in Japan or China) showed that the inverse association was present in Chinese studies (all case-control studies) and absent in Japanese studies (6 cohort or nested case-control and 4 case-control studies). Explanations suggested for the inconsistencies between studies conducted in Japan and China included *1*) the reference group in the Japanese studies included few

TABLE 3
Adjusted HRs (95% CIs) for the association of regular tea consumption (in g/mo) with risk of digestive system cancers in nonsmokers and non–alcohol drinkers (n = 69,310) in the SWHS, 1996–2009[1]

Cancer sites	Consumption								
	Never		<100 g/mo		100–150 g/mo		≥150 g/mo		P-trend
	No. of cases		*No. of cases*		*No. of cases*		*No. of cases*		
Digestive system[2]	992	1.00	85	0.95 (0.76, 1.18)	93	0.85 (0.68, 1.05)	85	0.79 (0.63, 0.99)	0.01
Stomach	233	1.00	19	0.88 (0.55, 1.41)	20	0.76 (0.48, 1.20)	21	0.82 (0.52, 1.29)	0.18
Stomach and esophagus	258	1.00	20	0.87 (0.55, 1.37)	21	0.74 (0.47, 1.17)	21	0.76 (0.48, 1.19)	0.10
Colon	277	1.00	26	1.01 (0.67, 1.52)	31	1.00 (0.68, 1.45)	26	0.85 (0.56, 1.27)	0.52
Rectal	177	1.00	14	0.81 (0.47, 1.41)	16	0.75 (0.45, 1.26)	19	0.89 (0.55, 1.43)	0.31
Colorectal	454	1.00	40	0.93 (0.67, 1.29)	47	0.89 (0.66, 1.21)	45	0.86 (0.63, 1.18)	0.26
Liver	106	1.00	11	1.17 (0.62, 2.20)	12	1.03 (0.56, 1.89)	5	0.44 (0.18, 1.08)	0.18
Pancreas	105	1.00	9	1.03 (0.52, 2.06)	10	0.95 (0.50, 1.84)	8	0.81 (0.39, 1.67)	0.61

[1] HRs were estimated by using Cox proportional hazards regression models with age as the timescale and were adjusted for age, marital status, education, occupation, BMI, exercise, fruit and vegetable intake, meat intake, diabetes, and family history of digestive system cancer. The reference group was never regular tea drinkers. Regular tea intake was defined as tea consumption ≥3 times/wk for >6 mo. Former drinkers (n = 788) were excluded from the analysis. SWHS, Shanghai Women's Health Study.

[2] Includes gallbladder and bile duct cases. Data are not presented separately for this type of digestive system cancer because of a limited sample size.

TABLE 4
Adjusted HRs (95% CIs) for the association of regular tea consumption in years of consumption with risk of digestive system cancers in nonsmokers and non–alcohol drinkers (*n* = 69,310) in the SWHS, 1996–2009[1]

Cancer sites	Consumption								P-trend
	Never		<10 y		10–19 y		≥20 y		
	No. of cases		No. of cases		No. of cases		No. of cases		
Digestive system[2]	992	1.00	100	1.02 (0.82, 1.25)	68	0.87 (0.68, 1.12)	95	0.73 (0.59, 0.90)	<0.01
Stomach	233	1.00	22	0.92 (0.59, 1.43)	15	0.76 (0.45, 1.29)	23	0.77 (0.50, 1.19)	0.14
Stomach and esophagus	258	1.00	22	0.85 (0.55, 1.32)	16	0.77 (0.46, 1.28)	24	0.74 (0.49, 1.14)	0.10
Colon	277	1.00	35	1.28 (0.90, 1.83)	21	0.98 (0.63, 1.54)	27	0.69 (0.46, 1.03)	0.16
Rectal	177	1.00	18	0.92 (0.56, 1.50)	13	0.80 (0.45, 1.41)	18	0.75 (0.46, 1.22)	0.18
Colorectal	454	1.00	53	1.13 (0.85, 1.51)	34	0.91 (0.64, 1.29)	45	0.71 (0.52, 0.97)	0.05
Liver	106	1.00	13	1.24 (0.69, 2.22)	6	0.73 (0.32, 1.67)	9	0.65 (0.33, 1.30)	0.22
Pancreas	105	1.00	7	0.78 (0.36, 1.69)	8	1.18 (0.57, 2.45)	12	0.91 (0.49, 1.66)	0.83

[1] HRs were estimated by using Cox proportional hazards regression models with age as the time scale and were adjusted for age, marital status, education, occupation, BMI, exercise, fruit and vegetable intake, meat intake, diabetes, and family history of digestive system cancer. The reference group was never regular tea drinkers. Regular tea intake was defined as tea consumption ≥3 times/wk for >6 mo. Former drinkers (*n* = 788) were excluded from the analysis. SWHS, Shanghai Women's Health Study.

[2] Includes gallbladder and bile duct cases. Data are not presented separately for this type of digestive system cancer because of a limited sample size.

nondrinkers [the prevalence of daily tea intake in Japan is high (>80%)] (4, 19) and *2*) differences in the preparation of tea (green tea is processed by using steam in Japan and mainly via dry roasting in China), which could impact the type and amount of bioactive compounds in tea (4).

Another possible reason for inconsistencies in studies of tea drinking and risk of stomach cancer may be residual confounding because of cigarette smoking or alcohol intake, which are both correlated with tea drinking, in particular in Asian men (20, 22, 24). Residual confounding because of these behaviors may also explain the observation in some studies of a significant inverse association in women and a null or suggested positive association in men (19, 20). For example, in a pooled analysis of 6 prospective cohort studies, a significant inverse association for tea and risk of stomach cancer was reported for women, but no association was shown in men, even when results were stratified by smoking status (19). However, all of the cohorts were from Japan. To our knowledge, our study is the first cohort study of tea drinking and stomach cancer in Chinese women. In addition, we excluded ever smokers or alcohol drinkers, minimizing the concern of residual confounding from these factors.

Some studies have suggested tea consumption, in particular green tea, may reduce risk of colorectal cancer; however, results have been inconsistent (6, 17, 20, 22). In 2006, a meta-analysis of 8 observational studies reported an inverse association for green tea and risk of colorectal cancer, which was shown to be limited to case-control studies in analyses by study design (17). After this meta-analysis, in 2007, we reported that green tea consumption was associated with reduced risk of colorectal cancer in the SWHS (6). In the current study, we had more than double the number of cases (*n* = 590) and 5 additional years of follow-up. The dose-response relation of colorectal cancer risk with years and amount of tea drinking remained, although the strength of the association was less apparent than previously reported. In the current study, the strongest reduction in risk of colorectal cancer in association with tea consumption was found for women with lifetime

TABLE 5
Adjusted HRs (95% CIs) for the association of digestive system cancers with regular tea consumption assessed at both baseline and follow-up surveys in nonsmokers and non–alcohol drinkers (*n* = 63,049) in the SWHS, 1996–2009[1]

Tea consumption	Cancers of the digestive system									
	Cancers combined[2]		Stomach and esophageal		Colorectal		Liver		Pancreas	
	n		n		n		n		n	
Never[3]	663	1.00 (reference)	165	1.00 (reference)	318	1.00 (reference)	65	1.00 (reference)	71	1.00 (reference)
Yes										
Baseline only	85	1.10 (0.88, 1.38)	18	0.92 (0.56, 1.51)	51	1.34 (0.99, 1.81)	6	0.78 (0.34, 1.82)	7	0.94 (0.43, 2.05)
Follow-up only	102	0.90 (0.73, 1.11)	26	0.90 (0.60, 1.37)	49	0.89 (0.66, 1.21)	8	0.73 (0.35, 1.52)	10	0.90 (0.46, 1.75)
Baseline and follow-up	122	0.74 (0.61, 0.91)	28	0.68 (0.45, 1.02)	57	0.69 (0.52, 0.92)	11	0.68 (0.36, 1.32)	16	1.00 (0.57, 1.74)

[1] HRs were estimated by using Cox proportional hazards regression models with age as the timescale and were adjusted for age, marital status, education, occupation, BMI, exercise, fruit and vegetable intake, meat intake, diabetes, and family history of digestive system cancer. Regular tea intake was defined as tea consumption ≥3 times/wk for >6 mo. Women (*n* = 6,261) for whom the follow-up survey was missing or who had a death or cancer diagnosed before the follow-up survey were excluded from the analysis. SWHS, Shanghai Women's Health Study.

[2] Includes gallbladder/bile duct cases. Data are not presented separately for this cancer type because of limited sample size.

[3] Reference group was never regular tea drinkers for all associations presented.

consumption of ≥20 y, supporting the potential importance of the role of long-term, cumulative exposure to tea in the risk and prevention of colorectal cancer.

Tea drinking has been suggested to reduce risk of both liver and pancreatic cancer, although results have been inconsistent (5, 32–42). Although we found a suggestion of an inverse association between liver cancer and tea drinking, results were not statistically significant. In addition, pancreatic cancer was not associated with tea intake in our study, which is consistent with the findings of some but not all previous cohort studies (37, 38, 40–42). The lack of associations in our study for liver and pancreatic cancer may have been due to the small number of cases. With additional follow-up, we will have a larger sample size for future studies of these cancers.

Although the exact mechanisms are unclear, a protective role of tea in digestive system cancer prevention is biologically plausible on the basis of in vivo and in vitro data. Tea is a major source of polyphenols, including EGCG, EGC, (−)-epicatechin-3-gallate, and (−)-epicatechin, which are the major polyphenols in green tea, and theaflavins and thearubigens, which are the major polyphenols in black tea (7). Tea polyphenols have antioxidant properties and play a role in several mechanisms that could inhibit the initiation and progression of cancer (7, 13–15, 43, 44). Specifically, data from in vitro studies have suggested that tea polyphenols may be scavengers of free radicals, reduce tumor cell proliferation and angiogenesis, and induce apoptosis (7, 13–15). In addition, evidence from animal studies for several organ sites, including the esophagus, stomach, liver, colon, and pancreas, have shown that tea polyphenols and tea constituents inhibit tumor formation and cancer-promotional cellular mechanisms such as cellular proliferation, invasion, and angiogenesis (7, 14, 15, 43, 44).

The strengths of this study include the population-based and prospective cohort design, high baseline response rate, and high follow-up rates (>97%). Few women drink alcohol or smoke cigarettes in China; hence, by excluding women who reported ever regularly smoking or drinking alcohol, we reduced the potential for residual confounding from these lifestyle factors, a concern of previous studies of tea consumption and digestive system cancers (7, 19, 24).

Several limitations should also be considered. First, we used self-reported data on tea drinking habits; hence, there is a possibility for measurement error in this exposure assessment. However, a validation study in 683 noncases of the SWHS, which measured one of the major specific catechins found in green tea (ie, EGC), showed a significant trend for increasing EGC and the amount of tea leaves consumed on the basis of self-reported data, suggesting our tea measurement was valid (28). Second, we did not have information on *Helicobacter pylori* status, which is an important potential confounding factor. However, in the SWHS, ≥95% of women are estimated to be infected with *H. pylori* (45); hence, lack of adjustment for this factor is not a major concern in our study. Third, tea drinkers were younger, had higher education, were more likely to have a professional occupation, exercised more, consumed more fruit and vegetables, and were more likely to have a family history of digestive system cancer and diabetes in the SWHS. Although we adjusted for these factors and other lifestyle factors, we cannot rule out residual confounding due to unmeasured or poorly measured factors.

In conclusion, we found that tea consumption was associated with reduced risk of cancers of the digestive system, particularly cancers of the stomach/esophagus and colorectum, in middle-aged and older Chinese women who mainly consumed green tea. Our results suggest that tea drinking may be a potential way to reduce risk of digestive system cancers in nonsmoking and non–alcohol-drinking women.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–917.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, cancer incidence and mortality worldwide. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr (cited 6 November 2011).
3. Myung SK, Bae WK, Oh SM, Kim Y, Ju W, Sung J, Lee YJ, Ko JA, Song JI, Choi HJ. Green tea consumption and risk of stomach cancer: A meta-analysis of epidemiologic studies. Int J Cancer 2009;124: 670–7.
4. Kang H, Rha SY, Oh KW, Nam CM. Green tea consumption and stomach cancer risk: a meta-analysis. Epidemiol Health 2010;32: e2010001.
5. Sing MF, Yang WS, Gao S, Gao J, Xiang YB. Epidemiological studies of the association between tea drinking and primary liver cancer: a meta-analysis. Eur J Cancer Prev 2011;20:157–65.
6. Yang G, Shu XO, Li H, Chow WH, Ji BT, Zhang X, Gao YT, Zheng W. Prospective cohort study of green tea consumption and colorectal cancer risk in women. Cancer Epidemiol Biomarkers Prev 2007;16: 1219–23.
7. Yang CS, Wang X, Lu G, Picinich SC. Cancer prevention by tea: animal studies, molecular mechanisms and human relevance. Nat Rev Cancer 2009;9:429–39.
8. Yamane T, Takahashi T, Kuwata K, Oya K, Inagake M, Kitao Y, Suganuma M, Fujiki H. Inhibition of N-methyl-N'-nitro-N-nitroso-guanidine-induced carcinogenesis by (-)-epigallocatechin gallate in the rat glandular stomach. Cancer Res 1995;55:2081–4.
9. Yang CS, Wang ZY. Tea and cancer. J Natl Cancer Inst 1993;85: 1038–49.
10. Ju J, Hong J, Zhou JN, Pan Z, Bose M, Liao J, Yang GY, Liu YY, Hou Z, Lin Y, et al. Inhibition of intestinal tumorigenesis in Apcmin/+ mice by (-)-epigallocatechin-3-gallate, the major catechin in green tea. Cancer Res 2005;65:10623–31.
11. Dashwood RH, Carter O, Wang R, Dashwood WM, Orner GA, Fischer KA, Lohr CV, Pereira CB, Bailey GS, Williams DE. Comparison of white tea, green tea, epigallocatechin-3-gallate, and caffeine as inhibitors of PhIP-Induced colonic aberrant crypts. Nutr Cancer 2007;58: 60–5.
12. Murugan RS, Mohan KV, Uchida K, Hara Y, Prathiba D, Nagini S. Modulatory effects of black tea polyphenols on oxidant-antioxidant profile and expression of proliferation, apoptosis, and angiogenesis-associated proteins in the rat forestomach carcinogenesis model. J Gastroenterol 2007;42:352–61.
13. Higdon JV, Frei B. Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. Crit Rev Food Sci Nutr 2003; 43:89–143.
14. Ju J, Lu G, Lambert JD, Yang CS. Inhibition of carcinogenesis by tea constituents. Semin Cancer Biol 2007;17:395–402.
15. Yang CS, Maliakal P, Meng X. Inhibition of carcinogenesis by tea. Annu Rev Pharmacol Toxicol 2002;42:25–54.
16. Hakim IA, Harris RB, Brown S, Chow HHS, Wiseman S, Agarwal S, Talbot W. Effect of increased tea consumption on oxidative DNA

damage among smokers: A randomized controlled study. J Nutr 2003; 133:3303S–9S.

17. Sun CL, Yuan JM, Koh WP, Yu MC. Green tea, black tea and colorectal cancer risk: a meta-analysis of epidemiologic studies. Carcinogenesis 2006;27:1301–9.

18. Zhang XH, Andreotti G, Gao YT, Deng J, Liu EJ, Rashid A, Wu K, Sun L, Sakoda LC, Cheng JR, et al. Tea drinking and the risk of biliary tract cancers and biliary stones: A population-based case-control study in Shanghai, China. Int J Cancer 2006;118:3089–94.

19. Inoue M, Sasazuki S, Wakai K, Suzuki T, Matsuo K, Shimazu T, Tsuji I, Tanaka K, Mizoue T, Nagata C, et al. Green tea consumption and gastric cancer in Japanese: a pooled analysis of six cohort studies. Gut 2009;58:1323–32.

20. Yuan JM, Sun C, Butler LM. Tea and cancer prevention: epidemiological studies. Pharmacol Res 2011;64:123–35.

21. Sun CL, Yuan JM, Koh WP, Lee HP, Yu MC. Green tea and black tea consumption in relation to colorectal cancer risk: the Singapore Chinese Health Study. Carcinogenesis 2007;28:2143–8.

22. Yang G, Zheng W, Xiang YB, Gao J, Li HL, Zhang X, Gao YT, Shu XO. Green tea consumption and colorectal cancer risk: a report from the Shanghai Men's Health Study. Carcinogenesis 2011;32: 1684–8.

23. Kim J. What should be taken into consideration for a meta-analysis of green tea consumption and stomach cancer risk? Epidemiol Health 2010;32:e2010012.

24. Gao YT, McLaughlin JK, Blot WJ, Ji BT, Dai Q, Fraumeni JF Jr. Reduced risk of esophageal cancer associated with green tea consumption. J Natl Cancer Inst 1994;86:855–8.

25. Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A, Li HL, Wen W, Ji BT, Li Q, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. Am J Epidemiol 2005;162: 1123–31.

26. Shu XO, Yang G, Jin F, Liu D, Kushi L, Wen W, Gao YT, Zheng W. Validity and reproducibility of the food frequency questionnaire used in the Shanghai Women's Health Study. Eur J Clin Nutr 2004;58: 17–23.

27. Matthews CE, Shu XO, Yang G, Jin F, Ainsworth BE, Liu D, Gao YT, Zheng W. Reproducibility and validity of the Shanghai Women's Health Study physical activity questionnaire. Am J Epidemiol 2003; 158:1114–22.

28. Dai Q, Shu XO, Li HL, Yang G, Shrubsole MJ, Cai H, Ji BT, Wen WQ, Franke A, Gao YT, et al. Is green tea drinking associated with a later onset of breast cancer? Ann Epidemiol 2010;20:74–81.

29. Ji BT, Chow WH, Yang G, McLaughlin JK, Gao RN, Zheng W, Shu XO, Jin F, Fraumeni JF Jr, Gao YT. The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. Cancer 1996;77: 2449–57.

30. Yuan JM. Green tea and prevention of esophageal and lung cancers. Mol Nutr Food Res 2011;55:886–904.

31. Ren JS, Freedman ND, Kamangar F, Dawsey SM, Hollenbeck AR, Schatzkin A, Abnet CC. Tea, coffee, carbonated soft drinks and upper gastrointestinal tract cancer risk in a large United States prospective cohort study. Eur J Cancer 2010;46:1873–81.

32. Nagano J, Kono S, Preston DL, Mabuchi K. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). Cancer Causes Control 2001;12:501–8.

33. La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P. Tea consumption and cancer risk. Nutr Cancer 1992;17:27–31.

34. Zatonski WA, Boyle P, Przewozniak K, Maisonneuve P, Drosik K, Walker AM. Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. Int J Cancer 1993;53:601–7.

35. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, Runia S, Boyle P. Lifetime consumption of alcoholic beverages, tea and coffee and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. Int J Cancer 1992;50:514–22.

36. Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, Ohyanagi H, Fujiki T, Motojima K. A multi-institute case-control study on the risk factors of developing pancreatic cancer. Jpn J Clin Oncol 1992;22:286–91.

37. Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly. Int J Cancer 1994; 58:46–9.

38. Zheng W, Doyle TJ, Kushi LH, Sellers TA, Hong CP, Folsom AR. Tea consumption and cancer incidence in a prospective cohort study of postmenopausal women. Am J Epidemiol 1996;144:175–82.

39. Ji BT, Chow WH, Hsing AW, McLaughlin JK, Dai Q, Gao YT, Blot WJ, Fraumeni JF Jr. Green tea consumption and the risk of pancreatic and colorectal cancers. Int J Cancer 1997;70:255–8.

40. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. Cancer Epidemiol Biomarkers Prev 2001;10:429–37.

41. Luo J, Inoue M, Iwasaki M, Sasazuki S, Otani T, Ye W, Tsugane S. Green tea and coffee intake and risk of pancreatic cancer in a large-scale, population-based cohort study in Japan (JPHC study). Eur J Cancer Prev 2007;16:542–8.

42. Lin Y, Kikuchi S, Tamakoshi A, Yagyu K, Obata Y, Kurosawa M, Inaba Y, Kawamura T, Motohashi Y, Ishibashi T. Green tea consumption and the risk of pancreatic cancer in Japanese adults. Pancreas 2008;37: 25–30.

43. Chung FL, Schwartz J, Herzog CR, Yang YM. Tea and cancer prevention: studies in animals and humans. J Nutr 2003;133:3268S–74S.

44. Frei B, Higdon JV. Antioxidant activity of tea polyphenols in vivo: evidence from animal studies. J Nutr 2003;133:3275S–84S.

45. Dong LM, Shu XO, Gao YT, Milne G, Ji BT, Yang G, Li HL, Rothman N, Zheng W, Chow WH, et al. Urinary prostaglandin E2 metabolite and gastric cancer risk in the Shanghai Women's Health Study. Cancer Epidemiol Biomarkers Prev 2009;18:3075–8.