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Author(s): Guo-pei Yu, Chung-cheng Hsieh, Li-yi Wang, Shun-zhang Yu, Xue-liang Li and Tie-hua Jin

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Green-tea consumption and risk of stomach cancer: a population-based case-control study in Shanghai, China

Guo-pei Yu, Chung-cheng Hsieh, Li-yi Wang, Shun-zhang Yu, Xue-liang Li, and Tie-hua Jin

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The effect of drinking Chinese green tea on the risk of stomach cancer was evaluated in a population-based case-control study conducted in Shanghai, China, from October 1991 to December 1993. Eligible cases were incident cases of primary stomach cancer diagnosed during the study period among residents of Hongkou district and Nanhui county aged under 80 years. Controls were selected from the same street or commune where the case resided and were matched to the cases on age (within three years) and gender. A total of 711 cases and 711 matched controls, more than 90 percent of the eligible subjects, completed the interview. Information was obtained on the types of tea used, age when habitual tea drinking started, frequency of new batches of tea leaves used per day, number of cups brewed from each batch, total duration of drinking for each batch, strength and temperature of the tea consumed. Statistical analysis was based on modelling through conditional logistic regression. After adjusting for age, gender, place of residence, education, birthplace, alcohol consumption, and cigarette smoking, the odds ratio (OR) comparing drinkers of green tea with nondrinkers was 0.71 (95 percent confidence interval = 0.54-0.93). The adjusted OR decreased with increasing number of new batches of the green tea consumed each day (P value trend = 0.006). With the largest series of stomach cancer cases to date, this study found green-tea consumption associated with lower risk of stomach cancer. Among drinkers of green tea, the risk of stomach cancer did not depend on the age when habitual green-tea drinking started. Green tea may disrupt gastric carcinogenesis at both the intermediate and the late stages. *Cancer Causes and Control* 1995, 6, 532-538

Key words: China, stomach cancer, tea.

Introduction

Consumption of green tea recently has been found to be associated with a reduced risk of esophageal cancer.¹ The finding is consistent with the inhibitory effect of green tea on tumor induction found in experimental studies using laboratory animals.² Epidemiologic studies

on tea drinking and gastric cancer have examined mostly the effect of black tea,³⁻¹³ with the majority finding no association.³⁻¹¹ On the other hand, the few studies which examined green-tea drinking¹⁴⁻¹⁶ have reported an inverse association with the risk of stomach

Drs G-p Yu, S-z Yu, and Li are with the Department of Epidemiology, School of Public Health, Shanghai Medical University, Shanghai, P.R. China. Drs G-p Yu and Hsieh are with the Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA. Dr Wang is with Hongkou Anti-epidemic Station, Shanghai, P.R. China. Dr Jin is with Nanhui Anti-epidemic Station, Shanghai, P.R. China. Address correspondence to Dr Hsieh, Cancer Center, University of Massachusetts Medical Center, Two Biotech, 373 Plantation St., Suite 202, Worcester, MA 01605, USA. This work was supported by US Public Health Service grant CA52560 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

Table 1. The distribution of age, gender, method of diagnosis, and location of tumor for the 711 stomach cases by study areas, China

Characteristics	Hongkou (n = 411)		Nanhui (n = 300)		Total (n = 711)	
	No.	(%)	No.	(%)	No.	(%)
Age						
< 50	58	(14.1)	42	(14.0)	100	(14.1)
50-59	61	(14.8)	62	(20.7)	123	(17.3)
60-69	160	(38.9)	110	(36.7)	270	(38.0)
70-79	132	(32.1)	86	(28.7)	218	(30.6)
Gender						
Male	271	(65.9)	182	(60.7)	453	(63.7)
Female	140	(34.1)	118	(39.3)	258	(36.3)
Diagnostic method						
Pathology	350	(85.2)	173	(57.7)	523	(73.6)
Surgery	17	(4.1)	25	(8.3)	42	(5.9)
Endoscopy	17	(4.1)	22	(7.3)	39	(5.5)
Computed tomography and ultrasound	3	(0.7)	3	(1.0)	6	(0.8)
Radiography	21	(5.1)	15	(5.0)	36	(5.1)
Clinical symptoms	3	(0.7)	0	(0.0)	3	(0.4)
Not available	0	(0.0)	62	(20.7)	62	(8.7)
Tumor site						
Cardia	106	(25.8)	22	(7.3)	128	(18.0)
Pylori	139	(33.8)	77	(25.7)	216	(30.4)
Antrum	84	(20.4)	69	(23.0)	153	(21.5)
Other sites	63	(15.3)	61	(20.3)	124	(17.4)
Unknown	19	(4.6)	71	(23.7)	90	(12.7)

cancer. These studies either were not designed specifically to study the effect of green tea or had small numbers of cases. We investigated the effect of drinking Chinese green tea on the risk of stomach cancer in a large population-based case-control study conducted in Shanghai, China.

Materials and methods

Study subjects

Eligible cases were individuals with incident primary stomach cancer who were under 80 years of age and were diagnosed between October 1991 and December 1993 among residents of Hongkou district, one of 12 urban districts of Shanghai, and Nanhui county, a suburban area of Shanghai. Case-finding was organized by the health station for disease control in each of the two study areas.

The case-reporting network in the Hongkou area was the same as that for the Shanghai Cancer Registry. The network identified the majority of cases through local and referral hospitals and ascertained the remainder from death certificates to ensure a complete collection of incident cases. A similar system which included

reporting from the area hospitals to the disease control station and searching of death certificates was set up for the Nanhui area. After reporting by a hospital of a subject with a diagnosis of stomach cancer to one of the disease control stations, the physicians at the station reviewed the medical records of the case to verify the diagnosis and eligibility. Interval between the diagnosis and case identification was typically two to three months. Records for some of the deceased cases could not be reviewed since they had been kept by the patients and were burned customarily, especially in rural areas, along with other personal belongings. For a deceased case, the interview was conducted with the spouse or a first-degree relative.

Community controls were selected from same street or commune where the respective cases resided and were matched to the cases on age (within three years) and gender. Among the eligible persons, the one living in the nearest residence to that of the case was selected as the control.

Data collection and analysis

Interviews with the study subjects were conducted by trained interviewers at the subjects' homes using a

Table 2. Birthplace, education level, alcohol drinking, cigarette smoking, and stomach cancer risk, China

Factors	Cases	Controls	OR ^a	(CI) ^b
Birthplace				
Shanghai	448	470	1.00	—
Jiangsu	152	100	1.84	(1.28-2.64)
Zhejiang	79	101	0.93	(0.63-1.38)
Other areas	32	40	0.94	(0.55-1.63)
Education level				
No schooling	228	197	1.00	—
Primary and middle school	388	396	0.72	(0.53-0.98)
High school and college	95	118	0.54	(0.35-0.83)
Alcohol drinking				
Never	438	452	1.00	—
Ever	273	259	1.14	(0.87-1.49)
Cigarettes smoked per day				
0	374	416	1.00	—
1-9	40	42	1.20	(0.75-1.92)
10-19	89	105	1.07	(0.75-1.54)
≥ 20	208	148	1.85	(1.35-2.52)

^a OR = odds ratios, adjusted for matched variables.

^b CI = 95% confidence interval.

structured, pilot-tested questionnaire. Information was sought on demographic characteristics, past medical history of the study subject and family members, tobacco use, alcohol consumption, and dietary intake. Information on tea drinking was obtained in terms of the types of tea (green, black, oolong, and others) used, age when habitual tea drinking started, frequency of new batches of tea leaves used per day, number of cups brewed from each batch, total duration of drinking for each batch, and the strength and temperature of the tea consumed.

The standard analytic method for a matched case-control study was applied.¹⁷ Analysis was based on modelling through conditional logistic regression which adjusts inherently for the matched variables and also can control for additional unmatched variables.

Results

During the study period, a total of 778 eligible subjects with stomach cancer who were under 80 years of age were identified in the study areas, with 478 from Hongkou and 300 from Nanhui. Among these, eight could not be located due to moving away or incorrect address; 59 could not be interviewed because the patients were dead and the relatives refused to be interviewed. A total of 711 cases completed the interview, with a participation rate of 91.4 percent. A total of 715 potential community controls were approached, and 711 completed the interview. The

interview took an average of one hour and 10 minutes for cases and one hour and 13 minutes for controls.

Table 1 shows the distribution of the 711 stomach cancer cases by age, gender, study area, diagnostic method, and location of the tumor. Median age was 65 years. There were more males (63.7 percent) than females. Most cases (73.6 percent) had a pathologic confirmation of the diagnosis. The diagnosis for 62 (8.7 percent) cases could not be confirmed by any method chiefly due to the death of the patient.

Table 2 summarizes the results of the analyses of subject characteristics on birthplace, education level, alcohol drinking, and cigarette smoking. Subjects born in Jiangsu province had a higher rate of stomach cancer than those born in Shanghai. The risk of stomach cancer decreased with increasing level of education. Ever-users of alcohol had a marginally elevated odds ratio (OR) than never-users. Those who smoked more than 20 cigarettes per day had a significantly higher OR compared with never-smokers (OR = 1.85, 95 percent confidence interval (CI) = 1.35-2.52). These characteristics, as well as the matched variables, were adjusted in the analyses of the effect of tea consumption.

A total of 67.5 percent of cases and 64.4 percent controls were nondrinkers of any type of tea (boiled water being the main beverage consumed). Among those who drank tea, the majority (92.6 percent of cases and 93.3 percent of controls) drank only green tea. Eight cases and 11 controls also consumed black or oolong tea as well as green tea. Since very few subjects (nine cases

Table 3 Green-tea drinking and the risk of stomach cancer, China

Status	Cases/controls	OR	(CI) ^b
Nondrinkers	489/464	1.00	—
Drinkers of green tea	222/247	0.71	(0.54-0.93)
Number of new batches of green tea used per day			
1-3	177/187	0.76	(0.57-1.03)
≥ 4	45/60	0.54	(0.33-0.88)
Number of cups brewed from each new batch of green tea leaves			
1-3 new batches			
1-3 c batch	90/94	0.81	(0.57-1.16)
≥ 4 c batch	87/93	0.71	(0.48-1.05)
≥ 4 new batches			
1-3 c batch	6/7	0.60	(0.19-1.89)
≥ 4 c batch	39/53	0.52	(0.31-0.89)
Total duration of drinking each new batch of tea (hours)			
1	23/21	0.89	(0.46-1.72)
2-3	92/101	0.75	(0.52-1.07)
4-6	107/125	0.64	(0.44-0.92)
Age started habitual green tea drinking (yrs.)			
< 40	182/196	0.72	(0.54-0.97)
≥ 40	40/51	0.67	(0.42-1.07)
Strength of tea preferred			
Light	29/39	0.59	(0.34-1.02)
Medium	118/138	0.71	(0.51-0.98)
Strong	75/70	0.79	(0.52-1.20)
Temperature of tea preferred			
Boiling hot	69/45	1.18	(0.75-1.86)
Hot	128/167	0.63	(0.46-0.87)
Warm or cold	25/35	0.51	(0.29-0.91)
Interval between brewing and drinking			
≤ 10 m	167/161	0.86	(0.63-1.19)
> 10 m	55/86	0.50	(0.32-0.76)
Drinking tea before breakfast			
No	161/190	0.69	(0.51-0.92)
Yes	61/57	0.79	(0.50-1.25)
Drinking tea brewed from the previous day			
No	188/215	0.69	(0.51-0.92)
Yes	34/32	0.83	(0.49-1.38)

^a OR = Odds ratios adjusted for education, birthplace, alcohol drinking, cigarette smoking, and matched variables.

^b CI = 95% confidence interval.

and six controls) drank other types of tea exclusively, our study could only address the effect of green-tea drinking. In the analyses, a green-tea drinker was defined as a person who drank at least one cup of freshly brewed green tea per week for six months or longer for five years before the interview. The few subjects who drank other types of tea exclusively were classified as nondrinkers of green tea.

The adjusted OR comparing drinkers of green tea with nondrinkers was 0.71 (CI = 0.54-0.93) (Table 3). The

Table 4. Green-tea drinking and the risk of site-specific stomach cancer, China

Tumor site	Cases/controls	OR ^a	(CI) ^b
Cardia			
Nondrinkers	76/78	1.00	—
Drinkers	52/50	0.95	(0.51-1.77)
1-3 new batches	39/38	0.94	(0.47-1.87)
≥ 4 new batches	13/12	0.98	(0.34-2.89)
Pylori			
Nondrinkers	94/82	1.00	—
Drinkers	30/42	0.29	(0.13-0.68)
1-3 new batches	22/30	0.30	(0.13-0.73)
≥ 4 new batches	8/12	0.24	(0.05-1.17)
Antrum			
Nondrinkers	137/125	1.00	—
Drinkers	79/91	0.67	(0.41-1.08)
1-3 new batches	66/64	0.79	(0.48-1.31)
≥ 4 new batches	13/27	0.29	(0.12-0.71)
Other			
Nondrinkers	111/108	1.00	—
Drinkers	42/45	0.82	(0.41-1.65)
1-3 new batches	36/40	0.83	(0.40-1.73)
≥ 4 new batches	6/5	0.76	(0.15-3.87)
Site unknown			
Nondrinkers	71/71	1.00	—
Drinkers	19/19	0.69	(0.23-2.06)
1-3 new batches	14/15	0.62	(0.17-2.18)
≥ 4 new batches	5/4	0.87	(0.15-5.00)

^a OR = odds ratios adjusted for education, birthplace, alcohol drinking, cigarette smoking, and matched variables.

^b CI = 95% confidence interval.

OR decreased with increasing number of new batches of the green tea used each day (P trend = 0.006). Information on other details of tea drinking was sought in this study and the respective results also are shown in Table 3. In this population, many green tea drinkers would brew more than one cup of tea from each batch of dried leaves. However, the OR varied only slightly with the number of cups brewed. Decreased ORs were observed with increased duration of time to complete drinking all the tea brewed from each batch and with longer interval between brewing and drinking. Among drinkers of green tea, the risk of stomach cancer did not depend on the age when habitual green-tea drinking started, on the strength of tea preferred, on whether tea was drunk before breakfast with an empty stomach, or on whether tea brewed in the previous day was consumed. The only elevated OR observed among drinkers of green tea in any of the analyses was for those who preferred to drink tea at a boiling hot temperature: the OR was 1.18 (CI = 0.75-1.86) compared with nondrinkers and was 1.93 (CI = 1.21-3.08) compared with other drinkers.

Table 5. Green-tea drinking and the risk of stomach cancer by gender, study site, cigarette smoking, and intake of preserved food, China

Modifier	Stratum 1			Stratum 2		
	Cases/controls	OR ^a	(CI) ^b	Cases/controls	OR ^a	(CI) ^b
Gender		<i>Male</i>			<i>Female</i>	
Nondrinkers	253/238	1.00	—	236/226	1.00	—
Drinkers	200/215	0.57	0.34-0.95	22/32	0.57	(0.09-3.65)
1-3 new batches	158/158	0.82	0.59-1.15	19/29	0.60	(0.30-1.21)
≥ 4 new batches	42/57	0.53	0.31-0.90	3/3	0.44	(0.07-2.97)
Study site		<i>Hongkou District</i>			<i>Nanhui County</i>	
Nondrinkers	235/220	1.00	—	254/244	1.00	—
Drinkers	176/191	0.80	0.50-1.10	46/56	0.56	(0.31-1.02)
1-3 new batches	141/139	0.92	0.65-1.30	36/48	0.53	(0.28-0.99)
≥ 4 new batches	35/52	0.51	0.29-0.89	10/8	0.76	(0.23-2.47)
Diagnostic method		<i>Pathology</i>			<i>Other methods</i>	
Nondrinkers	350/333	1.00	—	139/131	1.00	—
Drinkers	173/190	0.72	0.53-1.00	49/57	0.68	(0.37-1.27)
1-3 new batches	137/144	0.77	0.55-1.08	40/43	0.83	(0.42-1.61)
≥ 4 new batches	36/46	0.58	0.33-1.00	9/14	0.34	(0.10-1.15)
Type of interview for the case		<i>Direct interview</i>			<i>Indirect interview</i>	
Nondrinkers	264/247	1.00	—	225/217	1.00	—
Drinkers	123/140	0.66	0.46-0.95	99/107	0.73	(0.48-1.13)
1-3 new batches	98/106	0.72	0.49-1.06	79/81	0.78	(0.49-1.24)
≥ 4 new batches	25/34	0.46	0.22-0.93	20/26	0.61	(0.29-1.25)
Cigarette smoking		<i>Nonsmokers</i>			<i>Smokers</i>	
Nondrinkers	318/329	1.00	—	171/135	1.00	—
Drinkers	56/87	0.61	0.36-1.01	166/160	0.85	(0.56-1.28)
1-3 new batches	47/69	0.62	0.36-1.06	130/118	0.90	(0.57-1.42)
≥ 4 new batches	9/18	0.56	0.18-1.72	36/42	0.71	(0.36-1.39)
Intake of preserved food		<i>Less than once per month</i>			<i>At least once per month</i>	
Nondrinkers	119/144	1.00	—	370/320	1.00	—
Drinkers	87/112	0.89	0.54-1.47	135/135	0.58	(0.39-0.84)
1-3 new batches	76/89	0.99	0.59-1.69	101/98	0.59	(0.38-0.89)
≥ 4 new batches	11/23	0.48	0.17-1.35	34/37	0.55	(0.29-1.04)

^a OR = odds ratios, adjusted for education, birthplace, alcohol drinking, cigarette smoking, and matched variables.

^b CI = 95% confidence interval.

The effect of green-tea drinking was examined further for gastric cancers occurring at different locations of the stomach (Table 4). For each subgroup, the OR was lower for drinkers of green tea compared with nondrinkers. However, the effect estimate was near null for the cardia site (OR = 0.95, CI = 0.51-1.77) and more notable for the pyloric site (OR = 0.29, CI = 0.13-0.68).

Further adjustment for intake of fresh fruits and vegetables and intake of preserved food did not change appreciably the estimated effect of green tea: OR = 0.73 (CI = 0.55-0.97) for drinkers; OR = 0.79 (CI = 0.58-1.07), and OR = 0.54 (CI = 0.32-0.89) for those who drank, respectively, one to three and four or more new batches of green tea daily (*P* trend = 0.01). The inverse association between green-tea drinking and risk of

stomach cancer was not found to be modified by gender, study site, method of diagnosis, or interview for the case, cigarette smoking, or intake of preserved foods (Table 5).

Discussion

This population-based case-control study has the largest case series known to us for investigating the effect of Chinese green-tea drinking on the risk of gastric cancer. The study base consisted of all residents and all incident cases occurring over a 27-month period in two well-defined areas of Shanghai which has one of the highest incidence rates of this malignancy.¹⁸ More than 90 percent of the eligible cases and controls participated the study. Information on green-tea drinking was

obtained in detail. Potential confounding influences from other characteristics were addressed, as much as possible, in the analyses. Examinations within various subgroups did not reveal inconsistencies or heterogeneous effect estimates.

Green tea has been found in laboratory studies to have antioxidant activity and to inhibit nitrosation.² These functions have been proposed to be important in disrupting the gastric carcinogenesis at both the intermediate and the late stages.¹⁹ The nonvolatile compounds in green tea which might have inhibitory effects against tumorigenesis include polyphenols and ascorbic acid.²⁰ We have found that green-tea drinkers had a 30 percent lower risk of gastric cancer than nondrinkers and that the risk decreased with increased number of new batches of tea leaves consumed per day. The beneficial effect of tea drinking was not found in this study to be dependent on whether the habit was formed at an early or late age, supporting its blocking influence at multiple stages of carcinogenesis.¹⁹

From the analyses on the detailed aspects of the tea-drinking habit, only a small difference was found for the number of cups of tea brewed from each new batch. This observation does not support the hypothesis that the protective effect depends simply on the intake of liquid. We also found no evidence that auto-oxidation of polyphenols after brewing might affect the effect of green tea; the ORs were, if anything, slightly lower for longer duration of brewing and drinking.

The only elevated OR associated with green-tea drinking in this study was linked to the high temperature of tea consumed. This result supports the reported positive association between intake of very hot food and the increased risk of stomach cancer in Italy,²¹ and that between drinking hot mate and cancer of the upper gastrointestinal tract.²⁰ Other aspects of this drinking habit did not affect appreciably the effect estimates among drinkers of green tea.

Among the tumor sites within the stomach, the inverse association of green tea with risk was most pronounced for the pylori and antrum of the stomach; it was less clear for tumors of the gastric cardia. The observation on tumors of the gastric cardia needs further confirmation—not only because both a strong positive and a strong negative association between tea drinking and esophageal cancer have been reported by studies conducted in China,^{1,22} but also because stomach cancer of the cardia might have an etiology which is more similar to esophageal adenocarcinoma.²³ One also could speculate that this observation might be related to the more likely physical contact between the ingested tea and the pyloric and antral areas of the stomach than between the tea and the cardiac area. Also, in the light of the findings on the tea temperature, a

further analysis by tumor location has shown that the ORs associated with drinking tea at boiling hot, hot, and warm/cold temperatures were, respectively, 2.09, 0.65, and 0.69 for the cardia site; they were 0.56, 0.27, and 0.08 for the pylori site; and were 0.82, 0.63, 0.67 for the antrum site. Whether the anticarcinogenic compounds and the high temperature can have opposing effects on different areas of the stomach requires further investigation.

In this study, we did not evaluate infection with *Helicobacter pylori*, an established cause of stomach cancer.²⁴ It is not known whether infection with *H. pylori* is associated with consumption of green tea in this population. It is also unclear whether green tea drinking could affect the persistence of the infection or some of the consequences of that infection. It therefore would be desirable in future research to examine whether the effect of green tea could be confounded or modified by status of the *H. pylori* infection.

If green tea is confirmed to be protective against stomach cancer, it would add to the currently limited list of beneficial agents which could block carcinogenesis and it might be important to understand better the mechanism involved and to study whether the mechanism is relevant to other cancers.^{2,20}

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