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Green tea drinking and risk of pancreatic cancer: A large-scale, population-based case–control study in urban Shanghai

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ABSTRACT

Background: Little is known about the etiology of pancreatic cancer. Epidemiological studies on tea consumption and pancreatic cancer risk have been inconclusive. The purpose of the present study was to investigate the association between green tea drinking and the risk of pancreatic cancer in urban Shanghai, China. *Methods*: In this population-based case–control study conducted in urban Shanghai, 908 cases of pancreatic cancer and 1067 healthy controls were recruited. Information on tea drinking, including type of tea, amount of tea consumption, temperature of tea, and the duration of regular tea drinking, were collected via interview questionnaire. *Results*: We examined the association of multiple tea drinking habits with the risk of pancreatic cancer. In women, regular green tea drinking was associated with 32% reduction of pancreatic cancer risk (OR 0.68, 95% CI 0.48–0.96), compared to those who did not drink tea regularly. Increased consumption and longer duration of tea drinking were both associated with reduced pancreatic cancer risk in women. Among regular tea drinkers, lower temperature of tea was associated with reduced risk of pancreatic cancer in both men and women, independent of amount or duration of tea drinking. *Conclusions*: Habits of green tea drinking, including regular drinking, amount of consumption, persistence of the habit, and tea temperature, may lower pancreatic cancer risk.

1. Introduction

Pancreatic cancer is one of the most aggressive cancers. In China, the incidence of the disease has been increasing dramatically over the last 30 years. The annual incidence rate of pancreatic cancer in urban Shanghai increased from 3.66 per 10^5 in 1973 to 11.22 per 10^5 in 2000, and 3.20 to 10.93 per 10^5 in men and women, respectively [1]. There is no screening test for early diagnosis, and no effective treatment to prolong survival. Because of the late onset of disease-specific symptoms, most patients are diagnosed at late stage. The prognosis of this cancer is extremely poor, with an overall 5-year survival of less than 5%; the median survival time is less than 6 months [2]. Cigarette smoking and family history are known risk factors for the disease but do not explain much of it [3].

Tea is the most commonly consumed beverage worldwide, and has been studied extensively as a potential cancer chemopreventive agent. Animal and cellular studies have shown that tea polyphenols, in particular (−)-epigallocatechin-3-gallate (EGCG) which is found only in green tea, can inhibit carcinogenesis in a spectrum of cancers [4]. However, the effects of tea consumption against human cancers have been inconclusive. Among nine epidemiological studies regarding tea intake and risk of pancreatic cancer, four reported inverse associations [5–8], another four showed no associations [9–12], and one study even found a positive association [13].

The purpose of the present analysis was to investigate the relationship between tea drinking and risk of pancreatic cancer in a large-scale population-based case–control study in urban Shanghai. An "instant case reporting" system was established to maximize the accession of cases and therefore the generalizability of the study, and multiple aspects of tea drinking habits were ascertained.

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2. Materials and methods

2.1. Study population

A population-based case–control study of pancreatic cancer was conducted in urban Shanghai, from Dec 2006 through January 2011. All participants were Shanghai residents aged 35–79 years. Cases were identified in urban Shanghai through an "instant case reporting" system in 37 major hospitals, in which the overwhelming majority of such cases are diagnosed and receive care. In total, 1241 patients newly diagnosed with pancreatic cancer were reported to the Shanghai Cancer Institute. Of these patients, 149 were unable to be contacted or refused to participate, and the remaining 1092 were recruited into the study (88% participation fraction). All relevant hospital records, pathology reports, pathological slides, and/or imaging material (CT, Pet CT and/or MRI) were collected for review of case eligibility by a panel of pathology and clinical experts. Among the 1092 patients, 184 were excluded because of diagnoses of benign tumors or non-pancreatic primaries, leaving 908 confirmed pancreatic cancer patients as the cases for analysis. In total, 350 cases (39%) were microscopically confirmed and the remaining cases were confirmed by imaging and other clinical materials. During the same period of patient accrual, normal control individuals were randomly selected from files of the Shanghai Residents Registry using frequency matching by age group and gender. In total, 1653 individuals were contacted, among whom 462 refused to participate, 94 were diagnosed with malignant or other severe diseases, 30 had died before the day of interview, and the remaining 1067 subjects were recruited as controls (65% participation fraction). The study was approved by IRBs of both the Shanghai Cancer Institute and Yale University, and all participants gave written informed consent.

2.2. Assessment of tea drinking habits

Information on tea drinking habits and other factors was collected by trained interviewers using a validated questionnaire in face-to-face interviews with all subjects [14]. "Drinking tea regularly" was defined as "at least 3 times per week and lasting more than 6 months". Participants were asked "do you or did you drink tea regularly" and "are you currently drinking tea regularly"; then the age or year of the beginning and the end of regular tea drinking were asked, and the duration of tea drinking was calculated. Types of tea were identified: "green tea", "black tea", "jasmine tea", "oolong tea", "green and black tea", "green and jasmine tea", "black and jasmine tea", and "other tea". The amount of tea consumption was asked in terms of the weight of dry tea leaves in liang per month (1 liang equals 50 g), and converted to grams per month. The temperature of tea as consumed was ascertained in 4 categories: "hot", "warm", "lukewarm", and "cool". Very few individuals reported consumption of "cool" tea, thus this category was combined with "lukewarm".

2.3. Assessment of other factors

The study questionnaire included additional questions on demography, personal health conditions and family history of cancer, cigarette smoking, alcohol drinking, occupation, education, and use of various medications. Menstrual and reproductive history was recorded for women and women who had gone for 12 months or more without a menstrual period were classified as postmenopausal. Education level was coded as primary school or lower, middle school, college or higher. Smoking was coded as 0, 1–9, 10–19, 20–29, and $\geq$30 cigarettes per day. Alcohol drinking was coded as "Yes" (drink at least one kind of alcoholic drinks) or "No" (did not drink at all). Anthropometric information was also asked as "height at age 21" (in meters), "body weight at age 21", and "adult body weight last year" (both in kilograms), and BMI was calculated as adult body weight divided by the square of height.

2.4. Statistical analysis

Results were expressed as numbers and/or percentages for categorical variables, and for continuous variables as means and standard deviations (SDs). Differences between cases and controls in certain characteristic were tested using *t*-tests for continuous variables and by χ^2 tests for categorical variables.

Over 92% of tea drinkers were green tea drinkers, so all of the risk analyses have been carried out within green tea drinkers. Participants who drank other types of tea ($N = 71$) were excluded. The independent variables of tea drinking habits included regular tea drinking (yes/no), amount of green tea (0 g/month, 1–99 g/month, 100–149 g/month, or $\geq$150 g/month for women; 0 g/month, 1–149 g/month, 150–249 g/month, or $\geq$250 g/month for men), years of tea drinking (0 years, 1–14 years, 15–29 years, or $\geq$30 years for women; 0 years, 1–24 years, 25–34 years, or $\geq$35 years for men), and tea temperature (hot, warm, lukewarm or cool). Associations between tea drinking habits and risk of pancreatic cancer were examined using unconditional logistic regression models: the crude model was unadjusted; the adjusted model for men included variables of age, BMI, education level (primary school or lower, middle school, college or higher), family history of cancer (yes, no), smoking (0, 1–9, 10–19, 20–29, and $\geq$30 cigarettes per day), and history of type 2 diabetes (yes, no); the adjusted model for women further included menopausal status (yes, no), oral contraceptives use (yes, no), and menopausal hormone therapy (yes, no). All the analyses were repeated without endocrine tumors ($N = 15$), and the results stayed the same. All statistical analyses were performed using STATA statistical software (version 9.2; Statacorp, College Station, TX). All reported *p*-values are two-sided.

3. Results

In total, 908 cases and 1067 normal controls were recruited into the study. Basic characteristics of the cases and controls were similar (Table 1). Among the study subjects, 68.7% of men and 26.9% of women were regular tea drinkers, of whom 94.7% and

Table 1
Characteristics of case patients with pancreatic cancer and normal controls in urban Shanghai, 2006–2011. Values are numbers (percentages) of participants unless stated otherwise.

Characteristic	Cases ($n = 908$)	Controls ($n = 1067$)	*p* value
Age, years, mean (SD)	64.8 (9.7)	65.2 (10.0)	0.37
Gender			0.58
Men	526 (57.9)	605 (56.7)	
Women	382 (42.1)	462 (43.3)	
Ethnicity			0.63
Han	905 (99.7)	1060 (99.3)	
Education			0.38
Primary school or lower	174 (19.2)	208 (19.5)	
Middle school	534 (58.8)	651 (61.0)	
College and higher	200 (22.0)	208 (19.5)	
Alcohol use			0.12
Yes	404 (44.5)	512 (48.0)	
Tobacco use, number of cigarettes per day			0.06
0	505 (55.6)	626 (58.7)	
1–9	61 (6.7)	83 (7.8)	
10–19	110 (12.1)	145 (13.6)	
20–29	184 (20.3)	171 (16.0)	
$\geq$30	48 (5.3)	42 (3.9)	

Table 2
Tea drinking habits and risk of pancreatic cancer in women, urban Shanghai, 2006–2011. Values are numbers of participants unless stated otherwise.

Variables	Cases (n = 369)	Controls (n = 445)	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Regular tea drinking				
Never	290	327	1.0	1.0
Ever	79	118	0.75 (0.54–1.05)	0.68 (0.48–0.96)
p value			0.09	0.03
Amount of green tea (g/month)				
0	290	327	1.0	1.0
1–99	29	36	0.91 (0.54–1.52)	0.85 (0.49–1.46)
100–149	24	40	0.68 (0.40–1.15)	0.64 (0.37–1.11)
≥150	26	42	0.70 (0.42–1.17)	0.56 (0.32–0.98)
P for trend			0.07	0.02
Years of tea drinking				
0	292	328	1.0	1.0
1–14	24	38	0.71 (0.42–1.21)	0.67 (0.38–1.17)
15–29	27	36	0.84 (0.50–1.42)	0.72 (0.41–1.25)
≥30	26	43	0.68 (0.41–1.13)	0.60 (0.35–1.04)
P for trend			0.09	0.03
Tea temperature				
Hot	21	17	1.0	1.0
Warm	30	38	0.64 (0.29–1.42)	0.58 (0.25–1.36)
Lukewarm and Cool	28	63	0.36 (0.17–0.78)	0.34 (0.15–0.76)
p value			0.007	0.007

[a] The crude model was unadjusted.
[b] The adjusted model for women included terms for age, BMI, education level (primary school or lower, middle school, college or higher), family history of cancer (yes, no), smoking (0, 1–9, 10–19, 20–29, and 30+ cigarettes per day), history of type 2 diabetes (yes, no), menopausal status (yes, no), oral contraceptives use (yes, no), and menopausal hormone therapy (yes, no).

86.8% were green tea drinkers, respectively. All subsequent analyses of tea drinking consider drinking of green tea only.

The proportion of current smokers was 47.7% in men and 4.3% in women. Since an adverse effect of cigarette smoking might mask the protective effect of tea drinking, we carried out analyses in men and women separately. Sex specific cut-off points were used for tea amount and duration categories, because men tended to drink more, for longer durations, and started drinking earlier than women. Average intake among tea drinkers was 225.2 ± 152.9 g per month in men and 128.3 ± 83.3 g per month in women; duration of tea drinking was 31.8 ± 12.9 years in men and 23.5 ± 15.4 years in women; age at start of tea drinking was 30.1 ± 11.6 years old in men and 39.5 ± 15.4 years old in women. Associations between green tea drinking habits and risk of pancreatic cancer are shown in Table 2 for women and Table 3 for men.

After adjustment for potential confounding factors, female regular tea drinkers had reduced pancreatic cancer risk (OR 0.68, 95% CI 0.48–0.96) compared to those who never regularly drank tea. Increasing tea intake was associated with reduced risk of pancreatic cancer, with risk 43% lower among women who consumed more than 150 g of dry tea leaves per month (OR 0.56, 95% CI 0.32–0.98), compared with those who did not drink tea

Table 3
Tea drinking habits and risk of pancreatic cancer in men, urban Shanghai, 2006–2011. Values are numbers of participants unless stated otherwise.

Variables	Cases (n = 508)	Controls (n = 582)	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Regular tea drinking				
Never	158	196	1.0	1.0
Ever	350	386	1.12 (0.87–1.45)	1.02 (0.78–1.35)
p value			0.37	0.88
Amount of green tea (g/month)				
0	158	196	1.0	1.0
1–149	111	131	1.05 (0.76–1.46)	0.99 (0.71–1.40)
150–249	68	57	1.48 (0.98–2.23)	1.38 (0.91–2.11)
≥250	171	198	1.07 (0.80–1.44)	0.91 (0.65–1.27)
P for trend			0.48	0.77
Years of tea drinking				
0	159	196	1.0	1.0
1–24	91	108	1.04 (0.73–1.47)	0.95 (0.65–1.39)
25–34	115	107	1.32 (0.95–1.85)	1.20 (0.83–1.74)
≥35	143	171	1.03 (0.76–1.40)	0.95 (0.68–1.31)
P for trend			0.57	1.00
Tea temperature				
Hot	96	65	1.0	1.0
Warm	113	146	0.52 (0.35–0.78)	0.54 (0.36–0.81)
Lukewarm and Cool	141	175	0.55 (0.37–0.80)	0.55 (0.37–0.82)
p value			0.007	0.009

[a] The crude model was unadjusted.
[b] The adjusted model for men included terms for age, BMI, education level (primary school or lower, middle school, college or higher), family history of cancer (yes, no), smoking (0, 1–9, 10–19, 20–29, and 30+ cigarettes per day), and history of type 2 diabetes (yes, no).

regularly. Longer duration of tea drinking was also associated with reduced pancreatic cancer risk (P for trend 0.03). Drinking tea at lower temperatures also showed lower risk of pancreatic cancer (OR 0.34, 95% CI 0.15–0.76, lukewarm and cool tea combined compared to hot tea). We further included terms for amount and duration of tea drinking in the analyses of tea temperature and pancreatic cancer risk, though the results did not change appreciably (data not shown).

Among men, most tea drinking habits were not associated with reduced pancreatic cancer risk except for lower drinking temperatures. The risk was 0.54 (95% CI 0.36–0.81) for drinking warm tea compared to hot tea; and 0.55 (95% CI 0.37–0.82) for lukewarm and cool tea, and these results were also independent of intake amount and years of tea drinking. To exclude a possible adverse effect of smoking, we repeated the analyses among men who never smoked. Tea drinking habits had a similar trend of reducing pancreatic cancer risk as in women, but due to a smaller number of participants in the analysis ($n = 331$), the results did not reach customary statistical significance: OR 0.86, 95% CI 0.54–1.38 for the fact of regular tea drinking; OR 0.63, 95% CI 0.31–1.28 for tea amount, $\geq$250 vs. 0 g per month; OR 0.92, 95% CI 0.52–1.64 for duration of tea drinking, $\geq$35 vs. 0 years; OR 0.67, 95% CI 0.24–1.83 for tea temperature, lukewarm and cool combined vs. hot tea.

4. Discussion

In this population-based case–control study, we found protective effects of green tea drinking on risk of pancreatic cancer in women, adjusted for age, BMI, smoking, family history of cancer, history of type 2 diabetes, menopausal status, oral contraceptive use, and menopausal hormone therapy. Regular drinking of green tea, increased consumption, longer duration of tea drinking, and lower temperature of tea were associated with 30–40% reductions in pancreatic cancer risk in women. We did not find associations between most tea drinking habits and pancreatic cancer risk in men, except for lower drinking temperatures which were related with 40% reduction in pancreatic cancer risk. These findings, if validated, could be of potential importance in determining a protective role of tea drinking against pancreatic cancer and may have public health relevance in the prevention of this disease.

The present study adds new information regarding risk factors for pancreatic cancer. Pancreatic cancer is difficult to study because of its late diagnosis and short survival. In addition, the relatively low incidence in most populations compared to other cancers typically leads to rather small numbers of newly incident cases in cohort studies. Therefore, epidemiological studies have shown inconsistent results regarding the association between tea drinking and pancreatic cancer risk. Among studies from Europe and the US, where black tea is the major type consumed, three demonstrated a protective effect on pancreatic cancer. Shibata et al. found that pancreatic cancer risk decreased with increasing tea consumption in a large-scale cohort study [6]. Whittemore et al. and Zatonski et al. also showed inverse associations between tea consumption and pancreatic cancer risk in case–control studies [7,8]. However, Harnack et al. found that tea intake was not related to pancreatic cancer incidence in a large-scale prospective cohort study of American women [9]. Mack et al. did not find a link between pancreatic cancer and past consumption of tea in a case–control study [12]. Kinlen and McPherson revealed a positive association between tea drinking and pancreatic cancer risk in a case–control study in Liverpool, where tea drinking appears to be the dominant hot beverage rather than coffee, possibly reflecting insufficient adjustment for the effects of cigarette smoking [13]. Another three studies have been conducted in Asia, where it is mainly green tea that is consumed. Ji et al. showed that regular tea drinking was associated with lower risk of pancreatic cancer in an earlier population-based case–control study in Shanghai [5], whereas Lin et al. and Luo et al. found no link between green tea consumption and pancreatic cancer risk in two Japanese prospective cohort studies [10,11].

However, most of the studies mentioned above were relatively small. In cohort studies, Shibata et al. accumulated 65 incident cases after 9 years follow-up of 13 979 residents of a retirement community in US [6]; Harnack et al. reported 66 incident cases of pancreatic cancer after 8 years of follow-up of 33 976 postmenopausal women in the Iowa Women's Health Study [9]; Luo et al. documented 233 incident cases after 11 years of follow-up of 102 137 Japanese individuals [11]; Lin et al. found 292 pancreatic cancer deaths after 13 years of follow-up of 110 792 subjects in another study in Japan [10]. While in case–control studies, Ji et al. recruited 451 pancreatic cases in Shanghai [5]; Whittemore et al. recorded 126 pancreatic cancer deaths out of 50 000 male former students [7]; Mack et al. recruited 490 pancreas cancer patients from Los Angeles County residents [12]; Zatonski et al. recruited 110 cases of pancreatic cancer cases in Poland [8]; and Kinlen and McPherson had 216 cases of pancreas cancer eligible for study [13].

Our study is the largest population-based case–control study to-date, to our knowledge, to examine the association between tea drinking habits and pancreatic cancer risk. Our patients were recruited through an "instant case reporting" system in 37 major hospitals in urban Shanghai, and normal controls were randomly selected from the whole non-transient population of urban Shanghai, which greatly enhanced the representativeness of the study. Another study strength is that our case ascertainment was thorough, with clinical report as the first recruitment criterion and final review by a panel of pathology and clinical experts using hospital records, pathology reports, pathology slides, and/or imaging material. Finally a strength of our study was that multiple tea drinking habits were employed instead of single parameters of tea consumption. Different aspects of tea drinking, i.e. regular drinking, amount of consumption, duration of consumption, and tea temperature, may influence the association of tea drinking with disease risk.

Limitations of our study also merit consideration. Tea drinking habits were assessed by a retrospective questionnaire. All such questionnaire methods have attendant limitations. Our questionnaire, however, was designed to include different aspects of tea drinking habits to assist recall of details and thus to improve the accuracy of the factors assessed. Tea intake amounts were evaluated in grams per month because of typical tea purchasing habits in the study area, and reflect long-term tea consumption behaviors. Our population is predominantly of Han origin (>99%), thus our findings may not reflect associations in other ethnic or racial groups.

Tea drinking habits, except for tea temperature, did not show significant protective effects on pancreatic cancer risk in men in our study. This result might be attributed to the high co-linearity of tea drinking and smoking in Chinese men. (79.6% of male green tea drinkers were former or current smokers.) Smoking has been demonstrated to increase pancreatic cancer risk and to be an important confounding factor [15]. Gao et al. showed a protective effect of green tea consumption on oesophageal cancer in a subset of non-smoking men, while no protective effect was seen when examined in all men [16]. Similarly, reduced risk of colorectal cancer was seen for green tea drinking among nonsmoking men but not for men in general [17]. Therefore, the high prevalence of smoking in our study population might have masked the protective effect of green tea drinking. Among men who never smoked, in the present study a decreasing trend in risk was present but did not reach statistical significance, probably because of the relatively fewer participants included.

Mechanisms for an association between green tea drinking and reduced risk of pancreatic cancer are not fully understood. Tea polyphenols, in particular (−)-epigallocatechin-3-gallate (EGCG), most abundant in green tea extract, have been studied extensively in animal and molecular analyses and have been shown to suppress cell proliferation, enhance apoptosis, and inhibit cell invasion, angiogenesis and metastasis in a spectrum of cancers [4], but little is known regarding their effects on pancreatic cancer cells [18]. Moreover, the concentrations of tea polyphenols used in some of the cellular experiments are higher than the concentrations observed in human plasma and tissues after drinking green tea. It remains unclear whether the conclusions obtained from cell lines with high polyphenol concentrations can be extrapolated to cancer prevention in humans. Nevertheless, green tea extracts at physiological dietary doses have been found to reduce the incidence of and suppress growth of pancreatic cancers in the hamster *N*-nitrosamine model, thus supporting reduced risk with human consumption [19,20]. Studies have shown that thermal injury could increase risk of esophageal cancer [16], but the evidence on tea temperature and pancreatic cancer risk is scarce. We cannot explain our finding that high tea temperature is associated with increased pancreatic cancer risk, and this result warrants further investigation.

In summary, we have shown in a large-scale population-based case–control study that drinking green tea, i.e., increased consumption of tea, longer duration of regular tea drinking, and lower temperature of tea, were associated with lower risk of pancreatic cancer risk in women, independent of various confounding factors, and likely the same applies to non-smoking men. This finding has potential implications for preventing pancreatic cancer through a modifiable factor and merits further research.

Conflict of interest

The authors indicated no potential conflicts of interest.

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