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Tea drinking and the risk of biliary tract cancers and biliary stones: A population-based case-control study in Shanghai, China

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Keywords

biliary tract cancers; gallstones; tea consumption; polyphenol; epidemiology

Biliary tract cancers, encompassing tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater, are rare but highly fatal malignancies. Apart from gallstones, etiologic factors of biliary tract cancer are not clearly defined. Several epidemiologic studies have suggested that consumption of tea, especially green tea, is protective against a variety of cancers, including gastrointestinal malignancies. As part of a large population-based case-control study of biliary tract disease in Shanghai, China, we evaluated the effects of tea consumption on the risk of biliary tract cancers and biliary stones. The study included 627 incident cases with biliary tract cancer, 1,037 cases with biliary stones, and 959 randomly selected controls. Study subjects were interviewed to ascertain data on demographic, medical, and dietary factors, including tea consumption. Forty one percent of the controls were ever tea drinkers, defined as those who consumed at least 1 cup of tea per day for at least 6 months. After adjustment for age, education, and body mass index, among women, ever tea drinkers had significantly reduced risks of biliary stones (OR=0.73, 95% CI=0.54-0.98) and gallbladder cancer (OR=0.56, 95% CI=0.38-0.83). The inverse relationship between tea consumption and gallbladder cancer risk was independent of gallstone disease. Among men, tea drinkers were more likely to be cigarette smokers, and the risk estimates were generally below 1.0, but were not statistically significant. Further studies are needed to confirm these results in other populations and clarify the hormonal and other mechanisms that may be involved.

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Biliary tract cancers, consisting of tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater, are rapidly fatal.[1,2] Although these cancers are uncommon in most parts of the world, incidence rates are elevated among native Americans and Hispanics living in the United States, and among populations in Central and South America, Eastern Europe, and Japan.[1,2] Due to the rarity and high fatality of biliary tract cancers, little is known about their etiology apart from a strong link with gallstones.[2]

A number of epidemiologic studies have suggested that consumption of tea, especially green tea, is protective against certain cancers, including tumors of the lung, stomach, pancreas, and esophagus.[3-6] The anti-tumor effects of green tea have been attributed to polyphenols, which in laboratory studies have demonstrated inhibitory effects on tumor growth.[7-10] Results of epidemiologic studies examining the association between tea consumption and biliary tract cancer have been mixed, perhaps related to the small number of cases, different types of tea consumed, and lack of data on potential confounding factors, such as gallstone disease, diet, and cigarette smoking.[11-14]

In this report, we evaluate the effect of tea consumption on the risk of biliary tract cancers and biliary stones as part of a large population-based case-control study conducted in Shanghai, China, where the incidence rates for these cancers have risen sharply in recent years.[1,15]

Materials and methods

Study subjects

Details of the study methods have been reported elsewhere.16[-18] Briefly, cancer cases were permanent residents of urban Shanghai, between 35-74 years of age, who were newly diagnosed with biliary tract cancer (ICD9 code 156) between June 1997 and May 2001. The rapid reporting system established in 42 collaborating hospitals in Shanghai captured more than 95% of the incident cases diagnosed during the study period. A total of 627 cancer cases, including 368 gallbladder, 191 extrahepatic bile duct, and 68 ampulla of Vater cases, were included in this study. In addition, 1,037 patients with biliary stones (774 gallbladder stones and 263 bile duct stones) without a history of cancer were selected from the same hospital as the index cancer case and were frequency-matched to the index cancer case on age (5-year groups) and gender. A total of 959 subjects who were permanent residents of Shanghai and had no history of any type of cancer were randomly selected from the Shanghai Resident Registry (~6 million residents) as population controls. Controls were frequency-matched to cancer cases in a 1 to 1 ratio by the age (5-year groups) and gender distributions of biliary tract cancer cases. All study subjects provided written informed consent. The Institutional Review Boards of the National Cancer Institute and Shanghai Cancer Institute approved the study protocol.

Clinical and pathologic review

Diagnoses of all biliary tract cancer cases were confirmed by a panel of clinicians, ultrasonographers and pathologists, using a combination of medical and surgical records, pathology slides, and radiological films. Due to the late-stage diagnosis of most biliary tract cancers, pathology materials were only available to confirm 70% of the cancer cases. Among cases without pathology materials, we reviewed imaging data, medical records, and surgical reports to confirm the diagnosis of cancer on clinical grounds. As part of the diagnostic workup, all cancer cases underwent magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), or computed tomography (CT). All biliary stone cases were confirmed clinically by review of abdominal ultrasound data or ERCP films, or pathologically for those who underwent cholecystectomy.

Data collection

Study subjects were interviewed by trained interviewers, using a structured questionnaire to obtain information on demographic characteristics, medical and occupational histories, lifestyle behaviors, and diet. Information was collected on tea drinking, including age of first use, duration of consumption (years), and monthly intake (weight of tea leaves in grams). Ever tea drinkers were defined as subjects who consumed at least one cup of tea per day for more than six months. Current drinkers were a subset of ever tea drinkers who consumed tea at the time of interview. Lifetime tea consumption was calculated as monthly intake (grams) multiplied by 12 (months) and duration of consumption (years). The response rate for interview was over 95% among cases and 85% among controls. All interviews were recorded and reviewed to ensure adherence to the study protocol. Five percent of the subjects were randomly re-interviewed within three months of the first interview to assess reproducibility. Concordance between the two interviews on responses to key questions was greater than 90%.

Assessment of gallstones

Gallstone status among cancer cases was assessed both by self-reported history and clinical data from MRI, ERCP, and CT tests. Among population controls, gallstone status was assessed by self-reported history and by abdominal ultrasound among those who gave consent for the procedure (85% of all population controls).

Statistical analysis

Associations of tea consumption with biliary tract cancers and biliary stones were assessed by calculating odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. To make the appropriate case-control comparisons, only those controls at risk of developing each disease outcome were considered. Specifically, controls without a history of cholecystectomy were compared to gallbladder cancer cases, whereas controls without biliary stones were compared to biliary stone cases, and all population controls were compared to bile duct and ampulla of Vater cancer cases.

The Fisher's exact test was used to detect differences between cases and controls for selected characteristics. Those characteristics with statistically significant differences ($p < 0.05$) were considered potential confounders for biliary tract cancers or stones, and their associations with tea drinking were subsequently evaluated. Factors associated with both tea drinking and biliary tract cancer or stones were adjusted for in the logistic regression models.

The risk estimates for gallbladder cancer, bile duct cancer, and biliary stones (gallstones and bile duct stones combined) were evaluated by tea drinking status (never, ever, and current tea drinker). The risk of ampulla of Vater cancer associated with tea drinking was not estimated due to the small number of cases (n = 68). Among ever tea drinkers, biliary tract cancer and stone risks were assessed further by age of first tea consumption (years), duration of tea consumption (years), monthly tea intake (grams), and lifetime tea consumption (grams). Median values for these tea drinking characteristics were determined among population controls and were used as categorical cutoffs for risk estimate calculations. Gender-specific risk estimates were calculated because median values of tea drinking characteristics differed substantially between men and women. Initially, a full model was fit that included all potential confounding variables: age at interview, education, body mass index [BMI, weight (kg)/height $(m)^2$], smoking, alcohol use, hypertension, diabetes, allium vegetable intake, family history of gallstones, and gallstone status (for cancer cases only). We subsequently fitted a parsimonious model including only the variables associated with both tea consumption and biliary disease, i.e., age at interview, education, and BMI (for biliary stone cases only). Tests of linear trend were conducted categorically for all tea drinking characteristics, including age of first use, duration, monthly intake, and lifetime consumption.

Results

The frequency distributions of selected characteristics among cases and controls are shown in Table I. The majority of gallbladder cancers (73.1%) and biliary stones (62.4%) occurred among women, whereas slightly more cancers of the bile duct (51.8%) and ampulla of Vater (54.4%) occurred among men. The prevalence of gallstones was significantly higher among cancer cases at all three subsites than controls. Gallbladder cancer and biliary stone cases had a significantly higher prevalence of diabetes and obesity (BMI $\geq$ 23 kg/m^2, cutoff for obesity suggested for Asians),[19] but a lower prevalence of alcohol consumption. Bile duct cancer, ampulla of Vater cancer, and biliary stone cases were less likely to have hypertension than controls. Ampulla of Vater cancer and biliary stone cases had significantly greater intake of preserved foods. There was no difference in allium vegetable or total caloric intake between cases and controls, except for gallbladder cancer cases who consumed significantly fewer calories per day compared to controls.

Among the 959 controls, 394 (41%) were ever tea drinkers who consumed at least 1 cup of tea per day for at least 6 months. Most ever tea drinkers were also current tea drinkers at the time of interview, with 363 (92%) of the 394 ever tea drinkers being current tea drinkers. Ninety two percent of the ever tea drinkers reported drinking green tea, the most commonly consumed type of tea in China.[20] Since risk estimates for current and ever tea drinkers were similar, in Table II we present the risk of biliary tract cancers and stones in relation to tea consumption among ever tea drinkers by gender. Compared to women, men started drinking tea at an earlier age (median: 30 vs. 35 years), drank for a longer duration (median: 30 vs. 20 years), consumed a greater quantity (median: 250 vs. 150 grams per month), and had a higher lifetime consumption (median: 81,600 vs. 24,600 grams).

Among women, tea drinking was associated with lower risks of gallbladder and bile duct cancers and of biliary stones. Female ever tea drinkers had a 44%, 35%, and 27% reduced risk of gallbladder cancer (OR = 0.56; 95% CI = 0.38-0.83), bile duct cancer (OR = 0.65; 95% CI = 0.37-1.14), and biliary stones (OR = 0.73; 95% CI = 0.54-0.98), respectively. In addition, several tea drinking characteristics, including age of first use, duration, monthly intake, and lifetime consumption were also significantly and inversely associated with gallbladder cancer risk. Among women, the protective effect of tea on biliary tract cancer persisted after further adjustment for gallstones and other covariates.

Among men, risk estimates for biliary tract cancers and stones associated with tea drinking were generally below 1.0, but were not statistically significant. Smoking and tea drinking are strongly correlated among Chinese men ($r_{Spearman}$ for tea and smoking = 0.23, $p < 0.0001$). Further adjustment for smoking did not change the risk estimates of biliary tract cancers or stones among men. However, when the effect of tea drinking was evaluated by smoking status, the protective effect was evident among male non-smokers, but not male smokers, in particular for bile duct cancer (non-smokers: OR = 0.63; 95% CI = 0.28-1.43; smokers: OR = 1.17; 95% CI = 0.63-2.19). Due to the small number of male non-smokers, we had limited power to detect a significant interaction between smoking and tea drinking among men (Interaction *p* for bile duct cancer = 0.25).

Discussion

In this population-based study, tea drinking was associated with reduced risks of gallbladder and bile duct cancers, as well as biliary stones, especially among women. These findings add to the accumulating epidemiologic evidence linking tea consumption with a lower risk of various cancers, particularly of the digestive tract.

The exact mechanisms by which tea can protect against biliary tract cancer are unclear but may involve anti-proliferative and anti-inflammatory properties of tea polyphenols, in particular epigallocatechin-3-gallate (EGCG).21 Laboratory studies have shown that EGCG can inhibit inflammatory processes that are involved in the pathogenesis of epithelial cancers.22-24 Specifically, it has been shown that EGCG can inhibit 1) the expression of cyclooxygenase-2 (COX-2),25,26 a pro-inflammatory mediator that has been shown to be over-expressed in biliary tract cancer tissue,27-29 2) the expression of other key inflammatory mediators, such as cytokines and tumor necrosis factor-alpha,22-24 and 3) tumor growth through modulation of regulatory enzymes, such as cyclin-dependent kinases.[30] Data specific to biliary tissue are limited, but a laboratory study of biliary tract carcinoma showed that EGCG can suppress cell growth and the invasive ability of the carcinoma cells.[10]

Despite the longer duration and higher quantity of tea consumption among men, the statistically significant inverse relationship between tea drinking and risk of biliary tract cancers and stones was largely limited to women. Previous studies of other gastrointestinal cancers conducted in Asia have also reported a stronger protective effect of tea drinking in women than in men.[4,6,31-34] The less evident effect of tea drinking on biliary tract cancer in men may be related in part to the strong correlation between tea drinking and cigarette smoking among Chinese men, making it difficult to assess an independent effect of tea drinking. Among controls, 62% of men versus 9% of women were ever smokers. Among male tea drinkers, 70% smoked ($r_{Spearman}$ for tea and smoking = 0.23, $p < 0.0001$), whereas only 12% of the women who drank tea also smoked ($r_{Spearman} = 0.06$, $p = 0.18$). In addition, among men, smokers consumed more tea than non-smokers (median lifetime tea consumption: smokers 91,200 g, non-smokers 60,000 g), and heavy smokers were also heavy tea drinkers. In our study, smoking was not associated with an increased risk of gallbladder or ampulla of Vater cancers, but was associated with a 37% non-significant increased risk of bile duct cancer among men. Results from previous studies were mixed, with two reporting positive associations between smoking and bile duct cancer.[35,36] Hence, we cannot rule out the possibility that smoking may be related to bile duct cancer, and thus, may attenuate the protective effects of tea drinking among men. The fact that the protective effect of tea drinking was evident among male non-smokers and not male smokers further suggests a complex interplay of tea drinking and smoking for bile duct cancer among men. However, because there are few non-smoking men in this population, the interaction between tea drinking and smoking on the risk of biliary tract cancer was not statistically significant.

Another possible explanation for the significant protective effect of tea drinking in women may be related to the effects of EGCG on estrogen biosynthesis and other hormonal processes. Obesity and parity have been consistently linked to higher risks of gallstones[16,37] and gallbladder cancer,[16,38] probably due to higher levels of circulating estrogens among obese women and during pregnancy.[39-41] Both animal and human data suggest that tea polyoneols, in particular EGCG, can affect estrogen metabolism, although the precise mechanisms are unclear.41-44 In humans, a recent cross-sectional study showed that women who drank tea had lower levels of circulating estrogens than non-drinkers41 In laboratory studies, it has been shown that EGCG inhibits the methylation of catechol estrogens in the human liver by catechol-O-methyltransferase[44] and binds to estrogen receptors (ER-alpha and ER-beta), thereby influencing ER-mediated gene expression to exert an anti-estrogenic effect.[42,43] In animal studies, tea catechins reduce serum levels of testosterone, leptin, insulin, and insulin-like growth factor-1,45 which may also play a role in the development of gallbladder cancer and/or gallstones.

Several strengths and limitations of this study should be noted. Given the high case ascertainment (>95%) and response rates (>80%), selection and survival biases were minimal. Also, rigorous pathology and clinical review minimized misclassification of outcome and

gallstone status. Any misclassification of tea drinking characteristics, such as amount and duration, due to the difficulty in recall, is likely to be non-differential between cases and controls. Despite the relatively large size of this study, there was limited statistical power to accurately evaluate risks of bile duct and ampullary cancers associated with tea drinking, and to formally test for interactions among covariates. Although we cannot rule out the possibility that our findings resulted from chance, given the abundant animal and laboratory data on tea drinking, and our consistent findings for lower risks of cancers of the gallbladder and bile duct, and biliary stones, it is likely that tea drinking can reduce the risk of biliary tract diseases, at least among non-smoking women.

In summary, this population-based case-control study in Shanghai, China, revealed a protective effect of tea consumption on biliary tract cancer and biliary stones among women. Future studies are needed to replicate these results in other populations and clarify the hormonal and other mechanisms that may be involved.

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References

1. Hsing AW, Gao YT, Devesa SS, Jin F, Fraumeni JF Jr. Rising incidence of biliary tract cancers in Shanghai, China. Int J Cancer 1998;75:368–70. [PubMed: 9455795]
2. Hsing, AW.; Rashid, A.; Devesa, SS.; Fraumeni, JF. Biliary Tract Cancer. In: Schottenfeld, D.; Fraumeni, JF., Jr, editors. Cancer Epidemiology and Prevention. 3rd. New York: Oxford University Press; 2005. In press
3. 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. [PubMed: 8640692]
4. 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. [PubMed: 9033623]
5. Bushman JL. Green tea and cancer in humans: a review of the literature. Nutr Cancer 1998;31:151–9. [PubMed: 9795966]
6. Setiawan VW, Zhang ZF, Yu GP, Lu QY, Li YL, Lu ML, Wang MR, Guo CH, Yu SZ, Kurtz RC, Hsieh CC. Protective effect of green tea on the risks of chronic gastritis and stomach cancer. Int J Cancer 2001;92:600–4. [PubMed: 11304697]
7. Graham HN. Green tea composition, consumption, and polyphenol chemistry. Prev Med 1992;21:334–50. [PubMed: 1614995]
8. Katiyar SK, Agarwal R, Mukhtar H. Protective effects of green tea polyphenols administered by oral intubation against chemical carcinogen-induced forestomach and pulmonary neoplasia in A/J mice. Cancer Lett 1993;73:167–72. [PubMed: 8221629]
9. Pandey M, Shukla VK. Diet and gallbladder cancer: a case-control study. Eur J Cancer Prev 2002;11:365–8. [PubMed: 12195163]
10. Takada M, Ku Y, Habara K, Ajiki T, Suzuki Y, Kuroda Y. Inhibitory effect of epigallocatechin-3-gallate on growth and invasion in human biliary tract carcinoma cells. World J Surg 2002;26:683–6. [PubMed: 12053219]
11. Yen S, Hsieh CC, MacMahon B. Extrahepatic bile duct cancer and smoking, beverage consumption, past medical history, and oral-contraceptive use. Cancer 1987;59:2112–6. [PubMed: 3567872]
12. Kato K, Akai S, Tominaga S, Kato I. A case-control study of biliary tract cancer in Niigata Prefecture, Japan. Jpn J Cancer Res 1989;80:932–8. [PubMed: 2515177]

13. Zatonski WA, Lowenfels AB, Boyle P, Maisonneuve P, Bueno de Mesquita HB, Ghadirian P, Jain M, Przewozniak K, Baghurst P, Moerman CJ, Simard A, Howe GR, McMichael AJ, Hsieh CC, Walker AM. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. J Natl Cancer Inst 1997;89:1132–8. [PubMed: 9262251]

14. Ishizuk H, Eguchi H, Oda T, Ogawa S, Nakagawa K, Honjo S, Kono S. Relation of coffee, green tea, and caffeine intake to gallstone disease in middle-aged Japanese men. Eur J Epidemiol 2003;18:401–5. [PubMed: 12889685]

15. Jin F, Devesa SS, Chow WH, Zheng W, Ji BT, Fraumeni JF Jr, Gao YT. Cancer incidence trends in urban shanghai, 1972-1994: an update. Int J Cancer 1999;83:435–40. [PubMed: 10508476]

16. Rashid A, Ueki T, Gao YT, Houlihan PS, Wallace C, Wang BS, Shen MC, Deng J, Hsing AW. K-ras mutation, p53 overexpression, and microsatellite instability in biliary tract cancers: a population-based study in China. Clin Cancer Res 2002;8:3156–63. [PubMed: 12374683]

17. Ueki T, Hsing AW, Gao YT, Wang BS, Shen MC, Cheng J, Deng J, Fraumeni JF Jr, Rashid A. Alterations of p16 and prognosis in biliary tract cancers from a population-based study in China. Clin Cancer Res 2004;10:1717–25. [PubMed: 15014024]

18. Liu E, Sakoda LC, Gao YT, Rashid A, Shen MC, Wang BS, Deng J, Han TQ, Zhang BH, Fraumeni JF Jr, Hsing AW. Aspirin use and risk of biliary tract cancer: a population-based study in Shanghai, China. Cancer Epidemiol Biomarkers Prev 2005;14:1315–8. [PubMed: 15894693]

19. World Health Organization. The Asia-Pacific perspective: redefining obesity and its treatment. 2005. http://www.iotf.org/asiapacific/)

20. Katiyar SK, Mukhtar H. Tea consumption and cancer. World Rev Nutr Diet 1996;79:154–84. [PubMed: 9111814]

21. Mukhtar H, Ahmad N. Tea polyphenols: prevention of cancer and optimizing health. Am J Clin Nutr 2000;71:1698S–702S. [PubMed: 10837321]

22. Chen PC, Wheeler DS, Malhotra V, Odoms K, Denenberg AG, Wong HR. A green tea-derived polyphenol, epigallocatechin-3-gallate, inhibits IkappaB kinase activation and IL-8 gene expression in respiratory epithelium. Inflammation 2002;26:233–41. [PubMed: 12238566]

23. Ahmed S, Wang N, Lalonde M, Goldberg VM, Haqqi TM. Green tea polyphenol epigallocatechin-3-gallate (EGCG) differentially inhibits interleukin-1 beta-induced expression of matrix metalloproteinase-1 and -13 in human chondrocytes. J Pharmacol Exp Ther 2004;308:767–73. [PubMed: 14600251]

24. Wheeler DS, Catravas JD, Odoms K, Denenberg A, Malhotra V, Wong HR. Epigallocatechin-3-gallate, a green tea-derived polyphenol, inhibits IL-1 beta-dependent proinflammatory signal transduction in cultured respiratory epithelial cells. J Nutr 2004;134:1039–44. [PubMed: 15113942]

25. Surh YJ, Chun KS, Cha HH, Han SS, Keum YS, Park KK, Lee SS. Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-kappa B activation. Mutat Res 2001;480-481:243–68. [PubMed: 11506818]

26. Hussain T, Gupta S, Adhami VM, Mukhtar H. Green tea constituent epigallocatechin-3-gallate selectively inhibits COX-2 without affecting COX-1 expression in human prostate carcinoma cells. Int J Cancer 2005;113:660–9. [PubMed: 15455372]

27. Ghosh M, Kawamoto T, Koike N, Fukao K, Yoshida S, Kashiwagi H, Kapoor VK, Agarwal S, Krishnani N, Uchida K, Miwa M, Todoroki T. Cyclooxygenase expression in the gallbladder. Int J Mol Med 2000;6:527–32. [PubMed: 11029518]

28. Hayashi N, Yamamoto H, Hiraoka N, Dono K, Ito Y, Okami J, Kondo M, Nagano H, Umeshita K, Sakon M, Matsuura N, Nakamori S, Monden M. Differential expression of cyclooxygenase-2 (COX-2) in human bile duct epithelial cells and bile duct neoplasm. Hepatology 2001;34:638–50. [PubMed: 11584358]

29. Asano T, Shoda J, Ueda T, Kawamoto T, Todoroki T, Shimonishi M, Tanabe T, Sugimoto Y, Ichikawa A, Mutoh M, Tanaka N, Miwa M. Expressions of cyclooxygenase-2 and prostaglandin E-receptors in carcinoma of the gallbladder: crucial role of arachidonate metabolism in tumor growth and progression. Clin Cancer Res 2002;8:1157–67. [PubMed: 11948128]

30. Liang YC, Lin-Shiau SY, Chen CF, Lin JK. Inhibition of cyclin-dependent kinases 2 and 4 activities as well as induction of Cdk inhibitors p21 and p27 during growth arrest of human breast carcinoma cells by (-)-epigallocatechin-3-gallate. J Cell Biochem 1999;75:1–12. [PubMed: 10462699]

31. Ohno Y, Aoki K, Obata K, Morrison AS. Case-control study of urinary bladder cancer in metropolitan Nagoya. Natl Cancer Inst Monogr 1985;69:229–34. [PubMed: 3834338]

32. Ohno Y, Wakai K, Genka K, Ohmine K, Kawamura T, Tamakoshi A, Aoki R, Senda M, Hayashi Y, Nagao K. Tea consumption and lung cancer risk: a case-control study in Okinawa, Japan. Jpn J Cancer Res 1995;86:1027–34. [PubMed: 8567392]

33. 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. [PubMed: 8182766]

34. Zhong L, Goldberg MS, Gao YT, Hanley JA, Parent ME, Jin F. A population-based case-control study of lung cancer and green tea consumption among women living in Shanghai, China. Epidemiology 2001;12:695–700. [PubMed: 11679799]

35. Ghadirian P, Simard A, Baillargeon J. A population-based case-control study of cancer of the bile ducts and gallbladder in Quebec, Canada. Rev Epidemiol Sante Publique 1993;41:107–12. [PubMed: 8493388]

36. Chow WH, McLaughlin JK, Menck HR, Mack TM. Risk factors for extrahepatic bile duct cancers: Los Angeles County, California (USA). Cancer Causes Control 1994;5:267–72. [PubMed: 8061176]

37. Ko CW, Beresford SA, Schulte SJ, Matsumoto AM, Lee SP. Incidence, natural history, and risk factors for biliary sludge and stones during pregnancy. Hepatology 2005;41:359–65. [PubMed: 15660385]

38. Pandey M, Shukla VK. Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. Eur J Cancer Prev 2003;12:269–72. [PubMed: 12883378]

39. Nakagaki M, Nakayama F. Effect of female sex hormones on lithogenicity of bile. Jpn J Surg 1982;12:13–8. [PubMed: 7069944]

40. Chen A, Huminer D. The role of estrogen receptors in the development of gallstones and gallbladder cancer. Med Hypotheses 1991;36:259–60. [PubMed: 1787822]

41. Wu AH, Arakawa K, Stanczyk FZ, Van Den BD, Koh WP, Yu MC. Tea and circulating estrogen levels in postmenopausal Chinese women in singapore. Carcinogenesis. 2005

42. Kuruto-Niwa R, Inoue S, Ogawa S, Muramatsu M, Nozawa R. Effects of tea catechins on the ERE-regulated estrogenic activity. J Agric Food Chem 2000;48:6355–61. [PubMed: 11312808]

43. Goodin MG, Fertuck KC, Zacharewski TR, Rosengren RJ. Estrogen receptor-mediated actions of polyphenolic catechins in vivo and in vitro. Toxicol Sci 2002;69:354–61. [PubMed: 12377984]

44. Nagai M, Conney AH, Zhu BT. Strong inhibitory effects of common tea catechins and bioflavonoids on the O-methylation of catechol estrogens catalyzed by human liver cytosolic catechol-O-methyltransferase. Drug Metab Dispos 2004;32:497–504. [PubMed: 15100171]

45. Kao YH, Hiipakka RA, Liao S. Modulation of obesity by a green tea catechin. Am J Clin Nutr 2000;72:1232–4. [PubMed: 11063454]

TABLE I

Selected Characteristics of Subjects by Case-Control Status

	Population Controls		Gallbladder Cancer[1]		Bile Duct Cancer[2]		Ampulla of Vater Cancer[2]		Biliary Stones[3]	
	N	%	N	%	N	%	N	%	N	%
Total	959	100.0	368	100.0	191	100.0	68	100.0	1,037	100.0
Gender										
Male	373	38.9	99	26.9*	99	51.8*	37	54.4*	390	37.6*
Female	586	61.1	269	73.1	92	48.2	31	45.6	647	62.4
Age (years)										
<50	71	7.4	29	7.9	18	9.4	4	5.9	200	19.3*
50-59	151	15.7	48	13.0	30	15.7	8	11.8	222	21.4
60-69	452	47.1	174	47.3	96	50.3	34	50.0	424	40.9
≥70	285	29.7	117	31.8	47	24.6	22	32.3	191	18.4
Education										
Illiterate and elementary	396	41.3	198	53.8*	86	45.0	29	42.6	317	30.6*
High school	423	44.1	129	35.1	74	38.8	31	45.6	537	51.8
College and above	140	14.6	41	11.1	31	16.2	8	11.8	183	17.6
Marital Status										
Married	751	78.3	284	77.2	161	84.3	55	80.9	884	85.3*
Widowed	175	18.2	77	20.9	27	14.1	12	17.6	134	12.9
Divorced, separated	33	3.4	7	1.9	3	1.6	1	1.5	19	1.8
Ever Drink Tea										
No	565	58.9	267	72.6*	110	57.6	39	57.4	625	60.3
Yes	394	41.1	101	27.4	81	42.4	29	42.6	412	39.7
Ever Drink Alcohol										
No	760	79.2	316	85.9*	141	73.8	53	77.9	870	83.9*
Yes	198	20.6	52	14.1	50	26.2	15	22.1	167	16.1
Ever Smoke										
No	674	70.3	279	75.8*	115	60.2*	38	55.9*	754	72.7
Yes	285	29.7	89	24.2	76	39.8	30	44.1	283	27.3

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	Population Controls		Gallbladder Cancer[1]		Bile Duct Cancer[2]		Ampulla of Vater Cancer[2]		Biliary Stones[3]	
	N	%	N	%	N	%	N	%	N	%
Body Mass Index[4] (kg/m^2)										
<23.0	484	50.5	150	40.8*	96	50.3	30	44.1	396	38.2*
23.0 - 24.9	197	20.5	73	19.8	49	25.7	15	22.1	259	25.0
≥25.0	278	29.0	145	39.4	46	24.1	23	33.8	382	36.8
Biliary Stones										
No	735	76.6	60	16.3*	64	33.5*	32	47.1*	0	0.0
Yes	224	23.4	308	83.7	127	66.5	36	52.9	1,037	100.0
Hypertension										
No	553	57.7	230	62.5	130	68.1*	48	70.6*	695	67.0*
Yes	406	42.3	138	37.5	61	31.9	20	29.4	342	33.0
Diabetes										
No	881	91.9	316	85.9*	171	89.5	63	92.6	926	89.3*
Yes	78	8.1	52	14.1	20	10.5	5	7.4	111	10.7
Preserved Food (g/month)										
Quartile 1 (<195.0)	259	27.0	89	24.2	41	21.5	15	22.1*	239	23.1*
Quartile 2 (195.0 - 426.5)	241	25.1	93	25.3	43	22.5	15	22.1	201	19.4
Quartile 3 (426.6 - 917.1)	244	25.4	96	26.1	52	27.2	11	16.2	271	26.1
Quartile 4 (>917.1)	215	22.4	90	24.4	55	28.8	27	39.7	326	31.4
Allium Vegetable (g/month)										
Quartile 1 (<165.5)	272	28.4	119	32.3	63	33.0	22	32.4	312	30.1
Quartile 2 (165.5 - 330.4)	267	27.8	109	29.6	43	22.5	21	30.9	292	28.1
Quartile 3 (330.5 - 706.0)	249	26.0	97	26.4	52	27.2	13	19.1	228	22.0
Quartile 4 (>706.0)	171	17.8	43	11.7	33	17.3	12	17.6	205	19.8
Total Calories (kcal/day)										
Quartile 1 (<1834)	239	24.9	113	30.7*	47	24.6	16	23.5	242	23.3
Quartile 2 (1834 - 2220)	242	25.2	109	29.6	47	24.6	12	17.6	244	23.5
Quartile 3 (2221 - 2698)	258	26.9	76	20.7	49	25.7	23	33.8	249	24.0
Quartile 4 (>2698)	220	22.9	70	19.0	48	25.1	17	25.0	302	29.1

[1] Compared to population controls without cholecystectomy

[2] Compared to population controls

[3] Compared to population controls without biliary stones

[4] Cutpoints for obesity among Asians and median BMI among population controls

* $p<0.05$ for Fisher's exact test for difference between cases and controls

TABLE II

Odds Ratios (ORs) and 95% Confidence Intervals (CI) for Biliary Tract Cancers and Stones in Relation to Tea Drinking by Gender

	MALE									FEMALE								
	Gallbladder Cancer			Bile Duct Cancer			Biliary Stones				Gallbladder Cancer			Bile Duct Cancer			Biliary Stones		
	Cases / Controls	OR[1]	95% CI	Cases / Controls	OR[1]	95% CI	Cases / Controls	OR[2]	95% CI		Cases / Controls	OR[1]	95% CI	Cases / Controls	OR[1]	95% CI	Cases / Controls	OR[2]	95% CI
Tea Drinking Status										Tea Drinking Status								
Never	39/126	1.00	-	35/133	1.00	-	130/110	1.00	-	Never	228/402	1.00	-	75/432	1.00	-	495/311	1.00	-
Ever[3]	60/231	0.82	0.52-1.30	64/240	1.03	0.64-1.64	260/203	0.98	0.70-1.35	Ever[3]	41/143	0.56	0.38-0.83	17/154	0.65	0.37-1.14	152/111	0.73	0.54-0.98
Age started drinking (years)										Age started drinking (years)									
<30	36/101	1.12	0.66-1.91	38/104	1.42	0.84-2.42	137/85	1.16	0.79-1.70	<35	18/66	0.55	0.32-0.95	3/68	0.26	0.08-0.85	87/51	0.87	0.59-1.30
≥30	24/130	0.59	0.33-1.04	26/136	0.73	0.42-1.29	123/118	0.84	0.58-1.22	≥35	23/77	0.57	0.35-0.94	14/86	0.94	0.51-1.75	65/60	0.61	0.41-0.90
			$P_{trend}=0.75$			$P_{trend}=0.22$			$P_{trend}=0.50$				$P_{trend}=0.01$			$P_{trend}=0.04$			$P_{trend}=0.15$
Duration of drinking (years)										Duration of drinking (years)									
<30	23/113	0.63	0.35-1.14	28/114	0.90	0.51-1.59	134/105	0.86	0.59-1.26	<20	19/63	0.58	0.33-0.99	11/69	0.93	0.47-1.86	75/46	0.76	0.50-1.16
≥30	37/118	0.99	0.59-1.69	36/126	1.15	0.67-1.96	126/98	1.11	0.76-1.64	≥20	22/80	0.55	0.33-0.91	6/85	0.41	0.17-0.98	77/65	0.70	0.48-1.02
			$P_{trend}=0.92$			$P_{trend}=0.63$			$P_{trend}=0.65$				$P_{trend}=0.01$			$P_{trend}=0.04$			$P_{trend}=0.04$
Monthly intake (grams)										Monthly intake (grams)									
<250	29/91	1.01	0.58-1.76	24/94	0.99	0.56-1.79	134/81	1.33	0.90-1.97	<150	20/81	0.51	0.33-0.86	7/86	0.48	0.21-1.08	77/65	0.60	0.41-0.88
≥250	28/140	0.63	0.37-1.09	40/146	1.04	0.62-1.75	126/122	0.75	0.52-1.09	≥150	21/60	0.64	0.38-1.08	10/66	0.88	0.43-1.78	72/44	0.91	0.60-1.38
			$P_{trend}=0.10$			$P_{trend}=0.87$			$P_{trend}=0.13$				$P_{trend}=0.01$			$P_{trend}=0.32$			$P_{trend}=0.17$
Lifetime consumption (grams)[4]										Lifetime consumption (grams)[4]									
<81,600	29/116	0.79	0.46-1.37	30/119	0.96	0.56-1.67	151/107	1.05	0.72-1.51	<24,600	19/72	0.52	0.30-0.89	7/76	0.54	0.24-1.22	69/56	0.62	0.42-0.94
≥81,600	28/115	0.77	0.44-1.33	34/121	1.09	0.64-1.86	109/96	0.89	0.61-1.32	≥24,600	22/69	0.62	0.37-1.03	10/76	0.77	0.38-1.55	80/53	0.83	0.56-1.23
			$P_{trend}=0.33$			$P_{trend}=0.76$			$P_{trend}=0.59$				$P_{trend}=0.01$			$P_{trend}=0.24$			$P_{trend}=0.12$

[1] Odds ratios for gallbladder and bile duct cancer were adjusted for age at interview and education status

[2] Odds ratios for biliary stones were adjusted for age at interview, education, and body mass index

[3] Drink at least one cup of tea per day for 6 months

[4] Lifetime consumption=monthly intake (grams) × 12 (months) × duration of drinking (years)