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Association between green tea/coffee consumption and biliary tract cancer: A population-based cohort study in Japan

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Key words

Biliary tract cancer, coffee, cohort, green tea, prospective study

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Green tea and coffee consumption may decrease the risk of some types of cancers. However, their effects on biliary tract cancer (BTC) have been poorly understood. In this population-based prospective cohort study in Japan, we investigated the association of green tea (total green tea, *Sencha*, and *Bancha/Genmaicha*) and coffee consumption with the risk for BTC and its subtypes, gallbladder cancer, and extrahepatic bile duct cancer. The hazard ratios and 95% confidence intervals were calculated using the Cox proportional hazard model. A total of 89 555 people aged 45–74 years were enrolled between 1995 and 1999 and followed up for 1 138 623 person-years until 2010, during which 284 cases of BTC were identified. Consumption of >720 mL/day green tea was significantly associated with decreased risk compared with consumption of ≤120 mL/day (hazard ratio = 0.67 [95% confidence interval, 0.46–0.97]), and a non-significant trend of decreased risk associated with increased consumption was observed (*P*-trend = 0.095). In the analysis according to the location of the primary tumor, consuming >120 mL green tea tended to be associated with decreased risk of gallbladder cancer and extrahepatic bile duct cancer. When *Sencha* and *Bancha/Genmaicha* were analyzed separately, we observed a non-significant trend of decreased risk of BTC associated with *Sencha* but no association with *Bancha/Genmaicha*. For coffee, there was no clear association with biliary tract, gallbladder, or extrahepatic bile duct cancer. Our findings suggest that high green tea consumption may lower the risk of BTC, and the effect may be attributable to *Sencha* consumption.

Biliary tract cancer, comprising GBC and EHBDC, is a highly fatal malignancy. Although the incidence is globally rare, it is relatively higher in East Asia, including Japan.[1] One of the causes of this disease is chronic inflammation in the biliary tract (e.g., stones, pancreaticobiliary maljunction, and primary sclerosing cholangitis),[2–4] but its etiology, especially any association with dietary factors, is poorly understood owing to its low incidence.

Many epidemiological studies have been carried out to investigate the effect of green tea against several types of cancers, including colorectal,[5] lung,[6] stomach,[7] esophageal,[8] breast,[9] and prostate cancer[10] in humans, in which the protective effect of green tea has been suggested, but not conclusively proven.[11] Epigallocatechin-3-gallate, a form of polyphenol, is abundant in tea, especially green tea, and may play a key role in its protective effect.[11–13] The effect of coffee consumption on cancer risk is more controversial and may differ depending on the type of cancer because both protective and promoting effects have been observed in epidemiological studies.[14,15]

In contrast, evidence of the effect of green tea and coffee on BTC was very limited. Although several epidemiological studies have been carried out, they were small-scale; most were retrospective case–control studies, and the results were inconsistent. Some showed decreased risk associated with tea[16–18] and coffee,[18–20] and others showed no effect of tea[21,22] or coffee.[16,23] Laboratory studies also indicated the possibility that green tea may have a protective effect on BTC. An inhibitory effect of EGCG on growth of gallbladder and bile duct cancer cells has been observed.[24–26] Furthermore, different effects of green tea consumption may be observed in Japan because the preferred type of tea and frequency of consumption varies in different countries. Japanese people frequently consume green tea, which is rich in catechin.[27]

Therefore, we investigated prospectively the association of green tea/coffee consumption with the risk of BTC, especially in Japanese people. We further investigated the association according to the location of the primary tumor (gallbladder or extrahepatic bile duct).

Materials and Methods

Study cohort and participants. The JPHC-based Prospective Study is a cohort study that mainly investigates non-communicable disease. This study comprises two cohorts, one (Cohort I) initiated in 1990 and the other (Cohort II) initiated in 1993. The participants were identified by population registries maintained by local municipalities. In total, 140 420 residents participated in this study, with 61 595 participants in Cohort I aged 40–59 years identified in the areas supervised by six PHCs and 78 825 participants in Cohort II aged 40–69 years identified in the areas supervised by five PHCs. The study design was reported in detail elsewhere.[28] The JPHC study was approved by the Institutional Review Board of the National Cancer Center (Tokyo, Japan). The present study was approved by the Ethical Review Board of Osaka University (Osaka, Japan).

Participants who responded to a 5-year follow-up survey were enrolled. Participants from one PHC area (Katsushika PHC, 7097 participants) in Cohort I were excluded because cancer incidence data was not collected. Participants were also excluded for the following reasons: non-Japanese nationality (n = 51); late report of relocation out of the study area before the start of follow-up (n = 187); ineligibility owing to an incorrect date of birth (n = 7); duplicate registration (n = 4); and death, moving out of a study area, or lost to follow-up before the starting point of the present study (n = 11 689). After excluding these ineligible participants, 98 636 participants aged 45–74 years responded from 1995 to 1999 (approximately 81.3% response rate).

Exposure assessment. The survey consisted of a self-administered questionnaire asking about a variety of lifestyle factors, including frequency of beverage consumption with the following choices: 0, 1–2, 3–4, or 5–6 times/week and 1, 2–3, 4–6, 7–9, or ≥10 cups/day. The survey asked about the two main types of green tea consumed in Japan, *Sencha* (first or second flush of green tea, which is the first seasonal picking) and *Bancha* (third or fourth flush of green tea, which is the late seasonal picking)/*Genmaicha* (blend of *Bancha* and roasted brown rice), and two forms of coffee, coffee (excluding canned coffee) and canned coffee.[29] The total amounts of green tea and coffee consumption were defined as the sum of both types of tea and coffee, respectively. The consumption of each beverage (mL/day) was calculated by multiplying the frequency by the portion size (120 mL/cup for *Sencha*, *Bancha/Genmaicha*, and coffee and 250 mL/can for canned coffee). The validity of the total green tea and coffee consumption reported by the cohort was assessed using dietary records for 28 or 14 days. Spearman's correlation coefficients between the dietary record data and the questionnaire were 0.44 in men and 0.53 in women for green tea and 0.75 in men and 0.80 in women for coffee.[30]

We categorized consumption as follows: ≤120, 120–360, 360–720, and >720 mL/day for total green tea; no consumption, 0–90, 90–240, and >240 mL/day for coffee so that each category could include as equal number of subjects as possible. For total green tea, we did not set the group of 0 mL/day as a reference because the number was relatively small (n = 4326, 4.8%). For *Sencha* and *Bancha/Genmaicha*, the following category was used to make this align with the category of total green tea; ≤1, 2–3, 4–6, ≥7 cups/day.

Follow-up and case identification. Follow-up was carried out using information about residential status and survival collected from the residential registers from each municipality in the study area. Death certificates were coded in accordance with the requirements of the Japanese Ministry of Health, Labor, and Welfare. Of the eligible participants, 5128 moved out of the study area, 198 were lost to follow-up, seven withdrew from the study, and 12 199 died during the at-risk period.

Cancer incidence was identified mainly from two data sources: active patient notification from major local hospitals in the study area, and population-based cancer registries. Death certificate information was used as a supplementary information source. The site of origin and histological cancer type were coded using the International Classification of Diseases for Oncology, Third Edition, with the gallbladder as C23.9, the extrahepatic bile duct as C24.0, overlapping lesions of the biliary tract as C24.8, and unspecified as C24.9; in the present analysis, BTC included all of these subtypes. If a participant was diagnosed with more than one of these BTC subtypes, that with the earliest diagnosis date was used for the analysis. The proportion of cases where incidence was ascertained by death certificate only was 15.1% for BTC and 6.4% for all types of cancer.

Statistical analyses. The number of person-years of follow-up was calculated from the date of the 5-year follow-up survey until the end of follow-up, which was the earliest date of any of the following events: moving out of the study area, lost to follow-up, withdrawal from the study, death, diagnosis of BTC, or the last date of the follow-up period (December 31, 2009 in Osaka PHC and December 31, 2010 in all other areas). The subjects diagnosed with BTC before follow-up start were excluded (n = 22). Follow-up did not end when the participants were diagnosed with cancer other than BTC. The subjects who were diagnosed with cancer other than BTC before follow-up start were not excluded. The incidence rate was calculated by number of cases divided by years of follow-up.

Hazard ratios, 95% CIs, and P-trend for BTC in all participants and by sex (men *versus* women) were estimated using the Cox proportional hazards model with adjustment for potential confounders. Additionally, subanalysis by type of primary tumor (GBC *versus* EHBDC) was carried out. For the analysis of green tea, we further assessed the association of *Sencha* and *Bancha/Genmaicha* with BTC. This multivariate analysis model was adjusted for age (continuous), study area (10 PHC areas), sex (not applicable to the analysis stratified by sex), body mass index (<23, 23–25, 25–27, ≥27 kg/m^2), history of cholelithiasis (no/yes), history of diabetes mellitus (no/yes), history of chronic hepatitis or cirrhosis (no/yes), history of smoking (no, past or current, unknown), alcohol drinking frequency (never or almost never, 1–3 times/month, 1–2 times /week, 3–4 times/week, ≥5 times/week, unknown), physical activity by metabolic equivalents/day (quartiles, unknown), total energy consumption (quartiles), and energy-adjusted consumption of fish (quartiles), red meat (quartiles), and fruits and vegetables (quartiles). This was further adjusted by coffee consumption (no consumption, 0–90, 90–240, or >240 mL, unknown) when analyzed for green tea and by green tea consumption (≤120, 120–360, 360–720, or >720 mL, unknown) when analyzed for coffee. In the analysis of green tea by *Sencha* and *Bancha/Genmaicha*, the model was additionally adjusted by *Bancha/Genmaicha* (≤1, 2–3, 4–6, ≥7 cups/day) when analyzed for *Sencha* and adjusted by *Sencha* (≤1, 2–3, 4–6, ≥7 cups/day) when analyzed for *Bancha/Genmaicha*. We excluded participants for whom both green tea and coffee consumption were unknown (n = 5607). We used a residual method to carry out energy adjustment[31] for consumption of fish, red meat, and fruits and vegetables after excluding participants who consumed <800 or >4000 kcal total energy (n = 3259).

All P-values reported are two-sided, and the significance level was set at $P < 0.05$. All statistical analyses were carried out using Stata version 13 (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics of the participants are shown in Table 1. A total of 89 555 participants were included and followed up for 1 138 623 person-years. During the follow-up period, 284 cases of BTC (121 GBCs, 152 EHBDCs, 11 overlapped lesions, and no case of unknown location) were identified. Participants with a higher consumption of green tea tended to be older and to consume more energy, fish, and fruits and vegetables and less red meat and coffee; more were women, and fewer were current smokers or regular drinkers. Conversely, participants with a higher consumption of coffee tended to be younger and consumed more energy and red meat and less fish, fruits and vegetables, and green tea; fewer were women, fewer had a history of diabetes mellitus and hepatitis/cirrhosis, and more were current smokers and regular drinkers.

The HRs and 95% CIs of BTC incidence associated with green tea and coffee consumption in all participants and by sex are shown in Table 2. Consuming >720 mL/day of green tea was significantly associated with a decreased risk (HR = 0.67; 95% CI, 0.46–0.97), and a non-significant trend of decreased risk associated with increased consumption was observed (P-trend = 0.095). A similar trend of decreased risk was observed in both men and women when stratified by sex. For coffee, there was no clear association with consumption volume.

The HRs and 95% CIs of BTC incidence associated with green tea and coffee consumption by location of the primary tumor (GBC *versus* EHBDC) are shown in Table 3. For green tea, consumption of 120–360 mL/day was significantly associated with a decreased risk of GBC (HR = 0.56; 95% CI, 0.32–0.97), and the association between consumption of >720 mL/day and a decreased risk of GBC was marginally significant (HR = 0.57; 95% CI, 0.32–1.01); additionally, there was a non-significant trend of decreased EHBDC risk associated with increased volume of consumption (P-trend = 0.160). For coffee, there was no clear association between the volume of consumption and GBC or EHBDC.

Table 4 shows the HRs and 95% CIs of BTC incidence associated with *Sencha* and *Bancha/Genmaicha* consumption in all participants and by sex. A non-significant trend of decreased risk associated with *Sencha* consumption was observed in all participants (P-trend = 0.054), and a similar trend of decreased risk was observed in both men and women after stratification by sex. For *Bancha/Genmaicha*, there was no clear association with BTC.

Discussion

In this large-scale population-based prospective cohort study covering more than 140 000 people in Japan, a significantly decreased risk of BTC was associated with high green tea consumption. However, the dose response was not statistically significant, although a trend of decreased risk associated with increased green tea consumption was observed. In the analysis according to the location of the primary tumor, green tea consumption tended to be associated with decreased risk of

Table 1. Characteristics of study participants at baseline

Range, mL	Green tea†				Coffee			
	≤120	>120 ≤360	>360 ≤720	>720	0	>0 ≤90	>90 ≤240	>240
Number of subjects	21 868	23 733	23 773	17 505	20 858	22 781	20 776	21 072
Person-years	281 864	301 134	300 858	222 371	264 093	291 871	263 824	266 739
Sex (women), %	48.4	51.2	56.4	59.3	57.2	56.7	54.8	44.6
Age, years (mean, SD)	55.1 (7.4)	56.4 (7.8)	57.5 (7.9)	58.9 (7.7)	59.5 (7.7)	57.9 (7.7)	56.4 (7.8)	53.6 (7.1)
≤49, %	29.0	24.0	19.8	14.0	12.4	17.4	23.6	36.2
50–59, %	42.2	41.1	39.8	37.9	35.7	39.9	41.9	43.4
60–69, %	24.3	27.6	31.6	37.1	39.7	34.0	27.1	16.9
≥70, %	4.5	7.3	8.8	11.0	12.1	8.8	7.4	3.5
BMI, kg/m^2 (mean, SD)	23.8 (3.1)	23.5 (3.0)	23.3 (3.0)	23.4 (3.0)	23.5 (3.1)	23.6 (3.1)	23.5 (3.0)	23.4 (3.0)
History of cholelithiasis (Yes), %	3.7	3.7	4.2	4.4	4.0	4.3	3.9	3.6
History of diabetes mellitus (Yes), %	6.7	6.3	6.3	6.8	9.3	6.4	5.5	4.6
History of chronic hepatitis or cirrhosis, %	2.0	2.5	2.3	2.1	2.8	2.5	1.8	1.8
Current smoker, %	26.5	23.7	21.2	21.2	15.9	17.5	21.9	38.2
Regular drinker (≥1/week), %	40.4	40.5	36.3	32.2	33.1	35.6	39.2	43.0
Physical activity, mean METs/day	32.8	32.5	32.6	32.9	32.3	32.7	32.7	32.9
Mean dietary consumption								
Total energy, kcal	1914.2	1985.2	2020.7	2110.8	1889.8	1972.5	2025.6	2142.7
Fish, g	79.3	86.7	90.2	89.7	92.3	89.4	84.8	79.4
Red meat, g	52.6	48.6	46.3	45.7	45.5	49.3	50.4	49.1
Vegetable and fruit, g	362.3	406.1	444.8	481.7	449.4	446.4	418.3	371.6
Coffee, mL	181.5	160.9	141.6	118.9	0.0	50.6	135.5	429.9
Green tea, mL	64.3	274.8	586.1	1422.4	600.6	596.9	496.6	439.8

†Green tea consumption was defined as the sum of *Sencha* and *Bancha/Genmaicha* consumption (mL/day). METs, metabolic equivalents.

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) of biliary tract cancer incidence according to volume of green tea and coffee consumption

Variable	All						Men						Women					
	Person-years	Cases	IR per 100 000	HR	95% CI		Person-years	Cases	IR per 100 000	HR	95% CI		Person-years	Cases	IR per 100 000	HR	95% CI	
					Lower	Upper					Lower	Upper					Lower	Upper
Green tea†																		
≤120 mL	281 864	72	25.5	1.00‡			141 271	46	32.6	1.00§			140 593	26	18.5	1.00§		
120–360 mL	301 134	63	20.9	0.74	0.52	1.04	143 588	38	26.5	0.74	0.48	1.15	157 546	25	15.9	0.74	0.42	1.29
360–720 mL	300 858	82	27.3	0.86	0.62	1.21	128 002	47	36.7	0.89	0.58	1.37	172 856	35	20.2	0.84	0.49	1.44
>720 mL	222 371	54	24.3	0.67	0.46	0.97	88 829	29	32.6	0.66	0.40	1.08	133 542	25	18.7	0.66	0.37	1.20
P-trend					0.095						0.203						0.268	
Coffee																		
0 mL	264 093	91	34.5	1.00¶			109 224	50	45.8	1.00††			154 869	41	26.5	1.00††		
0–90 mL	291 871	78	26.7	0.90	0.66	1.22	122 577	41	33.4	0.83	0.55	1.26	169 294	37	21.9	1.01	0.64	1.60
90–240 mL	263 824	52	19.7	0.77	0.54	1.09	116 539	33	28.3	0.81	0.52	1.27	147 285	19	12.9	0.73	0.42	1.28
>240 mL	266 739	46	17.2	0.91	0.62	1.33	146 145	31	21.2	0.85	0.53	1.37	120 594	15	12.4	1.12	0.59	2.13
P-trend					0.341						0.446						0.761	

†Green tea consumption was defined as the sum of *Sencha* and *Bancha*/*Genmaicha* consumption (mL/day). ‡Adjusted for age, study area, sex, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by metabolic equivalents (METs)/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, and coffee. §Adjusted for age, study area, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by METs/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, and coffee. ¶Adjusted for age, study area, sex, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by METs/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, and green tea. ††Adjusted for age, study area, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by METs/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, and green tea. IR, incidence rate.

Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) of gallbladder cancer and extrahepatic bile duct cancer incidence according to volume of green tea and coffee consumption

Variable	Person-years	Gallbladder cancer					Extrahepatic bile duct cancer				
		Cases	IR per 100 000	HR	95% CI		Cases	IR per 100 000	HR	95% CI	
					Lower	Upper				Lower	Upper
Green tea†											
≤120 mL	281 864	31	11.0	1.00‡			40	14.2	1.00‡		
120–360 mL	301 134	22	7.3	0.56	0.32	0.97	38	12.6	0.83	0.53	1.31
360–720 mL	300 858	40	13.3	0.88	0.54	1.45	39	13.0	0.79	0.50	1.26
>720 mL	222 371	23	10.3	0.57	0.32	1.01	28	12.6	0.69	0.41	1.15
P-trend					0.213					0.160	
Coffee											
0 mL	264 093	38	14.4	1.00§			50	18.9	1.00§		
0–90 mL	291 871	36	12.3	0.98	0.62	1.56	40	13.7	0.85	0.56	1.30
90–240 mL	263 824	25	9.5	0.87	0.51	1.46	23	8.7	0.64	0.38	1.06
>240 mL	266 739	16	6.0	0.80	0.42	1.50	28	10.5	0.95	0.58	1.58
P-trend					0.431					0.452	

†Green tea consumption was defined as the sum of *Sencha* and *Bancha/Genmaicha* consumption (mL/day). ‡Adjusted for age, study area, sex, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by metabolic equivalents/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, and coffee. §Adjusted for age, study area, sex, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by metabolic equivalents/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, and green tea. IR, incidence rate.

both GBC and EHBDC. When the associations of *Sencha* and *Bancha/Genmaicha* consumption with BTC were analyzed separately, we observed a non-significant trend of decreased risk associated with *Sencha* consumption but no association with *Bancha/Genmaicha* consumption. No clear association with coffee was observed. This result suggests that high green tea consumption may lower the risk of BTC, and this effect may be attributable to *Sencha* consumption.

The strengths of our study include collecting information on a wide range of consumption frequency (from no consumption to ≥10 cups/day) and the large sample size, which enabled a detailed analysis of the effect by setting multiple consumption levels for green tea and coffee.

Regarding green tea, the mechanism underlying the observed reduced risk of BTC is not clear, but EGCG, a polyphenol in green tea, is considered to play a key role because EGCG has antioxidative effects and is thought to suppress the inflammatory processes that lead to transformation, hyperproliferation, and initiation of carcinogenesis.[32,33] In addition, many mechanisms that support EGCG's cancer-preventive effect have been proposed, including cell cycle arrest, apoptosis induction, induction or inhibition of drug metabolism enzymes, modulation of cell signaling, inhibition of DNA methylation, and effects on micro-RNA expression, dihydrofolate reductase, proteases, and telomerases.[33] It is not clear which mechanisms are relevant to the cancer-preventive effect in BTC because of limited data specific to BTC, although some laboratory studies showed the protective effect *in vitro* and *in vivo*.[11–13] Another potential mechanism of EGCG specific to BTC is a potential protective effect against biliary stone formation, a major risk factor for BTC. Epigallocatechin-3-gallate was suggested to be protective against biliary stone formation in a laboratory study.[34] The effect of tea on biliary stone formation in humans is not clear, but one epidemiological study showed a protective effect in women.[17] Thus, part of the observed reduced risk of BTC may be attributable to protection against biliary stone formation by green tea.

It is possible that, in addition to EGCG, other nutrients in green tea like vitamin C and folate that potentially have a protective effect on cancer contributed to the observed protective effect. Protective effects of vitamin C and folate against cancer have been observed in epidemiological studies.[35,36] Furthermore, two case–control studies reported that vitamin C intake was associated with decreased risk of GBC.[16,37] *Sencha* has a higher vitamin C and folate, as well as catechin, content than *Bancha/Genmaicha*[29,38] and, in the present study, a non-significant trend of decreased risk associated with *Sencha* was observed whereas no clear association with *Bancha/Genmaicha* was observed. Therefore, these nutrients may contribute to the decreased risk of BTC, however, the magnitude would not be so large because the proportions of vitamin C and folate obtained from green tea were just 16.9% (13.9% from *Sencha*, 3.0% from *Bancha/Genmaicha*) and 15.9% (12.8% from *Sencha*, 3.1% from *Bancha/Genmaicha*) of total vitamin C and folate, respectively, in the present study.

Our results are not consistent with those of a previous cohort study that reported the association of tea consumption with BTC was not statistically significant,[21] although a trend of decreased risk was observed. This inconsistency may be explained by different sample sizes and consumption categories. The number of cases in the previous study was less than half that of the present study. Although consumption categories were never *versus* current drinker only in the previous study, a wide range of consumption levels was evaluated. Regarding the association of green tea consumption with subtypes of BTC, the finding of an association with GBC and EHBDC in the present study is consistent with the results of other studies.[17,18] For EHBDC, our study and a previous study[18] showed a trend of decreased risk, although it was not statistically significant. Also, a preventive effect of EGCG against cholangiocarcinoma was observed in a preclinical study.[26] Therefore, the non-significant finding may result from insufficient statistical power, and further study on a larger scale is needed to clarify the association with EHBDC.

Table 4. Hazard ratios (HR) and 95% confidence intervals (CI) of biliary tract cancer incidence according to frequency of *Sencha* and *Bancha/Genmaicha* consumption

Variable	All						Men						Women					
	Person-years	Cases	IR per 100 000	HR	95% CI		Person-years	Cases	IR per 100 000	HR	95% CI		Person-years	Cases	IR per 100 000	HR	95% CI	
					Lower	Upper					Lower	Upper					Lower	Upper
Sencha																		
≤1 cup/day	569 752	144	25.3	1.00†			269 984	89	33.0	1.00‡			299 768	55	18.3	1.00§		
2–3 cups/day	235 880	50	21.2	0.80	0.57	1.12	108 578	26	23.9	0.67	0.43	1.06	127 302	24	18.9	1.00	0.61	1.66
4–6 cups/day	179 647	46	25.6	0.87	0.61	1.23	72 838	29	39.8	1.00	0.64	1.56	106 809	17	15.9	0.72	0.40	1.27
≥7 cups/day	120 948	31	25.6	0.69	0.46	1.04	50 290	16	31.8	0.59	0.34	1.04	70 657	15	21.2	0.78	0.42	1.45
P-trend					0.054						0.134						0.183	
Bancha/Genmaicha																		
≤1 cup/day	736 594	178	24.2	1.00§			349 595	110	31.5	1.00¶			386 999	68	17.6	1.00¶		
2–3 cups/day	199 684	45	22.5	0.83	0.59	1.17	86 030	25	29.1	0.84	0.53	1.31	113 654	20	17.6	0.81	0.48	1.35
4–6 cups/day	112 202	24	21.4	0.72	0.47	1.12	43 778	12	27.4	0.66	0.36	1.21	68 424	12	17.5	0.79	0.42	1.49
≥7 cups/day	57 747	24	41.6	1.41	0.90	2.20	22 287	13	58.3	1.51	0.83	2.74	35 460	11	31.0	1.38	0.71	2.69
P-trend					0.721						0.761						0.756	

†Adjusted for age, study area, sex, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by metabolic equivalents (METs)/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, coffee, and *Bancha/Genmaicha*. ‡Adjusted for age, study area, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by METs/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, coffee, and *Bancha/Genmaicha*. §Adjusted for age, study area, sex, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by METs/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, coffee, and *Sencha*. ¶Adjusted for age, study area, body mass index, history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, drinking frequency, physical activity by METs/day score, total energy consumption, energy-adjusted consumption of fish, red meat, and vegetable and fruit, coffee, and *Sencha.* IR, incidence rate.

We found no clear association between coffee consumption and BTC or GBC or EHBDC. The effect of coffee on cancer risk is controversial because both inhibiting and promoting effects have been suggested. The antioxidative effect of chlorogenic acid and the inhibitory effect of DNA methylation are considered to contribute to coffee's protective effect.[14,39] A protective effect of coffee has been observed in humans for a variety of cancers including liver, kidney, premenopausal breast, and colorectal cancers.[14] However, the caffeine in coffee is known to modify the apoptotic response and perturb cell checkpoint integrity,[15,40,41] and a positive association between coffee consumption and bladder cancer has been observed in epidemiological studies.[15,42,43] Another potential effect of coffee related to BTC is contraction of the gallbladder. Coffee is considered to cause pain in gallstone patients, which may be attributable to gallbladder contraction caused by an increase in plasma cholecystokinin concentration induced by coffee.[44] Therefore, it may be that increased gallbladder stimulation caused by coffee consumption in gallstone patients leads to an increased GBC risk. It is not clear what accounts for our finding of no association, but it may be a complex combination of these inhibitory and promoting effects. Some of the previous epidemiological studies showed a statistically significant decreased risk of GBC and EHBDC.[18–20] This difference may be attributable to different study designs. The sample sizes of these previous studies were small, and the retrospective case–control design may be affected by recall bias. Furthermore, differences in ethnicity and frequency of coffee consumption may affect the results.

The present study has several limitations. First, despite the large-scale design with a long follow-up period, statistical power was limited because of the low incidence rates, and we cannot rule out the possibility that the observed association was by chance. Therefore, this result should be confirmed by further studies with a larger sample size. Second, there could have been some misclassification in the baseline survey because the data collected by self-administered questionnaires at only a single point were used as baseline data. Furthermore, the correlation coefficient of green tea for validity was moderate, which might attenuate the true association. Third, there could be some effect of unmeasured variables and residual confounding, although the statistical model was adjusted for as many variables as possible. Fourth, we did not obtain information about how tea was prepared, including brewing times. Concentration of extracted ingredients including EGCG might be decreased when hot water is added into a teapot without adding or exchanging tea leaf. Therefore, the effects of high amounts of green tea consumption may be underestimated in terms of extracted ingredients intake if this method of tea preparation was more observed in those who consumed more cups/day.

In conclusion, in a population-based cohort study in Japan, high green tea consumption was significantly associated with a decreased risk of BTC, and coffee did not show any clear association. This finding suggests that high green tea consumption may lower the risk of BTC in Japanese people, and the effect may be attributable to *Sencha* consumption.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

BTC	biliary tract cancer
CI	confidence interval
EGCG	epigallocatechin-3-gallate
EHBDC	extrahepatic bile duct cancer
GBC	gallbladder cancer
HR	hazard ratio
JPHC	Japan Public Health Center
PHC	Public Health Center

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