Coffee, green tea, and caffeine consumption and subsequent risk of bladder cancer in relation to smoking status: a prospective study in Japan

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Coffee and caffeine consumption are thought to increase the risk of bladder cancer. However, few studies have stratified this risk by smoking status, which is a potential confounder. Here, we investigated the association between coffee, green tea (another major source of caffeine), and caffeine, and bladder cancer incidence in relation to smoking status. We conducted a population-based prospective study in a cohort of Japanese, comprising a total of 49 566 men and 54 874 women aged 40–69 years who reported their coffee and green tea consumption at baseline. During follow-up from 1990 through 2005, 164 men and 42 women were newly diagnosed with bladder cancer. Cigarette smoking was associated with an increased risk of bladder cancer, with a strong dose–response relationship. Coffee was positively associated with bladder cancer risk in men, without statistical significance. When stratified by smoking status, coffee and caffeine consumption were associated with an increased risk of bladder cancer in never- or former-smoking men, with hazard ratios (95% confidence interval) in the highest categories of coffee (one or more cups per day) and caffeine consumption compared with the lowest of 2.24 (95% CI = 1.21–4.16) and 2.05 (95% CI = 1.15–3.66), respectively. In conclusion, cigarette smoking was confirmed as a risk factor for bladder cancer. Coffee and caffeine may be associated with an increased bladder cancer risk in never or former smokers among Japanese men. (*Cancer Sci* 2009; 100: 284–291)

The incidence of bladder cancer is increasing slightly worldwide, particularly in industrial countries, including Japan.[1,2] Many epidemiological studies have suggested that bladder cancer is influenced by environmental factors, such as smoking, exposure to industrial chemicals, and several lifestyle factors.[3] While the International Agency for Research on Cancer (IARC) reported that coffee is a possible carcinogenic agent (group 2B) in bladder cancer, it could not exclude the possibility that this was due to bias or confounding.[4] In a recent meta-analysis, Zeegers *et al*. demonstrated a small elevated risk (20%) of bladder cancer for current coffee drinkers,[5] and a pooled analysis of 10 case-control studies in European countries found that heavy coffee consumption showed a positive association with bladder cancer among non-smokers.[6] However, most of these previous studies were conducted in Western countries; and of the five conducted in Asian populations, results have been inconsistent: a prospective study in Japanese-Americans reported that coffee consumption increased the risk of bladder cancer albeit without a dose–response,[7] two case-control[8,9] and a prospective study[10] among Japanese people found that the relative risk of coffee drinking was insignificant; while a case-control study in Japanese-American women showed an inverse association with coffee consumption.[11] These findings indicate that the relationship between coffee consumption and bladder cancer in Asian populations is largely unknown.

Caffeine, which is contained in coffee, has been suggested to contribute to the increased risk of bladder cancer, although its carcinogenicity or otherwise in humans has not been classified (group 3).[4] In Asian populations, green tea is a major source of caffeine, but only three studies have investigated the association between green tea and bladder cancer, and their results are inconsistent.[8–10]

Given that Asian populations have a low incidence of bladder cancer, and that their coffee and green tea consumption habits and amounts differ by geographic area, an understanding of the relationships between coffee, green tea or caffeine consumption and bladder cancer among Asian populations should be useful. Moreover, the distribution of phenotypes of N-acetyltransferase,[12,13] which metabolizes caffeine, differs between Asian and Caucasian populations.[14] The effect of coffee, green tea, or caffeine on bladder cancer in Asian populations may therefore differ from that in other populations.

Here, we analyzed the association between coffee, green tea, or caffeine consumption, and bladder cancer in a population-based prospective study in Japan. In addition, we explored these associations by smoking status, which is a known confounder between them.

Materials and Methods

Study population. The Japan Public Health Center-based Prospective Study (JPHC study) started in 1990 for Cohort I and in 1993 for Cohort II. The study design has been described in detail previously.[15] Cohort I consisted of five Public Health Center (PHC) areas (Iwate, Akita, Nagano, Okinawa, and Tokyo), and Cohort II of six PHC areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka) across Japan. When analyzing the present data, we excluded all subjects in Tokyo, whose incidence data were not available. As a whole, this cohort consisted of 133 323 men and women aged 40–69 years at baseline who registered in the study areas. After excluding 239 subjects with non-Japanese nationality ($n = 51$), late report of emigration occurring before the start of the follow-up period ($n = 178$), incorrect birth date ($n = 6$), and duplicate enrollment ($n = 4$), a population-based cohort of 133 084 subjects (65 660 men and 67 424 women) was established. This study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Baseline survey. A self-administered questionnaire, which included information on coffee and green tea consumption, smoking history, medical history, and other lifestyle factors, was distributed to all registered residents at baseline. A total of

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106 326 subjects returned valid responses (response rate 80%). After excluding subjects with self-reported bladder cancer at baseline (11 persons) and incomplete data on coffee and green tea consumption, 104 440 subjects (49 566 men and 54 874 women) were included in analysis.

Information on coffee or green tea consumption was obtained in terms of frequency and amount of intake in six categories: almost none, 1–2 times/week, 3–4 times/week, 1–2 cups/day, 3–4 cups/day, and ≥5 cups/day. Based on the distribution in each category, we divided categories of coffee into the following four categories in men: almost none, 1–4 times/week, 1–2 cups/day, and ≥3 cups/day. The type of coffee consumed (decaffeinated or caffeinated) was not included in the questionnaire, because decaffeinated coffee is rarely consumed in Japan. Similarly, green tea consumption was divided into the following four categories in men: <1 cup/day, 1–2 cups/day, 3–4 cups/day, and ≥5 cups/day. For women, we classified coffee and green tea consumption by three categories because of the small numbers of cases. Caffeine consumption was summed as the total amount contained in coffee, green tea, black tea, and Chinese tea. Caffeine consumption from each was calculated by multiplying the amount per cup by the quantity of caffeine per cup for each beverage. Amount per cup for each beverage was determined as the median value in a validation study among subsamples using 28-day dietary records,[16] and found to be 150, 140, 150, and 120 mL in men, and 120, 130, 150, and 120 mL in women for coffee, green tea, black tea, and Chinese tea, respectively. Quantity of caffeine per cup for each beverage was taken from the fifth revised edition of the Standard Tables of Food Composition in Japan.[17]

The validity of coffee or green tea consumption was assessed among subsamples using 28-day dietary records. Spearman's correlation coefficients between coffee or green tea consumption from the questionnaire and from dietary records in men and women were 0.42 and 0.38 (Cohort I) and 0.59 and 0.51 (Cohort II) for coffee, respectively, and 0.57 and 0.63 (Cohort I) and 0.37 and 0.43 (Cohort II) for green tea, respectively.[16]

Follow-up. We followed subjects from the baseline survey until 31 December 2005. Changes in residence status including survival were identified annually through the residential registry in each area or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Generally, mortality data for residents included in the residential registry are forwarded to the Ministry of Health, Labour and Welfare and coded for inclusion in the National Vital Statistics. Residency and death registration are required by the Basic Residential Register Law and Family Registry Law, respectively, and the registries are believed to be complete. Among the study subjects, 8897 (8.5%) died, 5892 (5.6%) moved out of the study area, and 413 (0.4%) were lost to follow-up during the study period.

The occurrence of cancer was identified by active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries, with permission from the local governments responsible for the registries. Cases were coded using the International Classification of Diseases for Oncology, third edition (ICD-O-3). Death certificate information was used as a supplementary information source, with 4.4% of cases of bladder cancer first notified by death certificate (DCN). The proportion of case patients with bladder cancer ascertained by death certificate only (DCO) was 1.9%. The mortality/incidence ratios were 0.19 for bladder cancer and 0.36 for all cancer except skin. These results were considered to be of adequate quality for the present study based on the international standard.[18]

For the present analysis, the earliest date of diagnosis was used in cases with multiple primary cancers at different times. A total of 206 newly diagnosed bladder cancer cases (164 men, 42 women) were identified by 31 December 2005.

Statistical analysis. Person-years of follow-up were calculated for each person from the date of completion of the baseline questionnaire to the date of bladder cancer diagnosis, the date of emigration from the study area, or the date of death, whichever came first; or if none of these occurred, follow-up was through to the end of the study period (31 December 2005). Subjects who were lost to follow-up were censored at the last confirmed date of presence in the study area. The hazard ratios (HRs) of bladder cancer were calculated in four categories for coffee and green tea or in quartiles for the categories of caffeine consumption, with the lowest consumption category as the reference. HRs and 95% confidence intervals (CIs) were calculated by the Cox proportional hazards model according to the SAS PHREG procedure (Version 9.1; SAS Institute, Cary, NC, USA). Covariates used in the model were age at enrollment, study area (10 PHC areas), smoking status (never, former [<10, 10–19, and ≥20 years since cessation of smoking], current [1–19, 20–29, 30–39, 40–49, and ≥50 pack-years, defined by multiplying the years of smoking by the average number of cigarettes divided by 20] in men and never, former, current [<25 and ≥25 pack-years] in women), alcohol consumption (non- or occasional drinkers, 1–150, ≥150 g/week), green tea, and coffee consumption. Moreover, we also calculated the HRs of bladder cancer for combined categories of coffee, green tea, or caffeine consumption and smoking status, and tested statistical interactions using the differences between two likelihood ratios of the models with and without the interaction terms between coffee, green tea, and caffeine consumption and smoking status. Interaction terms were generated by multiplying the ordinal of these consumption categories by ordinal smoking categories (never, former, or current smokers).

P-values for trends for coffee, green tea, and caffeine consumption were calculated by treatment as ordinal variables in the proportional-hazards model. All *P*-values are two-sided, and statistical significance was determined at the $P < 0.05$ level.

Results

During 1314 586 person-years of follow-up (average 12.6 years) of 104 440 subjects (49 566 men and 54 874 women), 164 men and 42 women were newly diagnosed with bladder cancer.

Baseline characteristics of subjects according to coffee and green tea consumption are shown in Table 1. Both men and women with high coffee consumption were younger than those who hardly drank. The proportion of current smokers increased as coffee consumption increased in both men and women. As coffee consumption increased, alcohol intake decreased in men and increased in women. Subjects with higher green tea consumption tended to be older, drink less alcohol, and consume less coffee in both men and women. The proportion of current smokers increased as green tea consumption increased in men, whereas that in women was high in both the lowest and highest categories of green tea consumption. As expected, caffeine consumption increased as coffee and green tea intake increased.

Results for smoking status at baseline in relation to bladder cancer risk are showed in Table 2. Cigarette smoking was associated with an increased risk of bladder cancer, with a strong dose–response relationship in both men and women. Moreover, no increased risk was observed in men who had given up smoking for 10 or more years.

Table 3 shows hazard ratios of bladder cancer in relation to coffee, green tea, and caffeine consumption among men. Most daily caffeine intake was derived from coffee (53%) and green tea (40%) in men. Although coffee drinking was associated with a marginally statistically significant increase in bladder cancer risk (age- and area-adjusted HR for men who drank ≥ 3 cups/day *vs* men who hardly drank was 1.71, 95% CI = 0.99–2.96; $P_{trend} = 0.01$), the results were attenuated after further adjustment

Table 1. Baseline characteristics of study subjects according to coffee and green tea intake category

	Coffee intake				Green tea intake			
	Almost none	1–4 times/week	1–2 cups/day	≥3 cups/day	<1 cup/week	1–2 cups/day	3–4 cups/day	≥5 cups/day
Men								
Number of subjects	14 929	14 600	12 966	7071	12 868	11 679	13 092	11 927
Proportion (%)	30.1	29.5	26.1	14.3	26.0	23.6	26.4	24.0
Age (years, mean) ± SD	53.7 ± 7.8	52.1 ± 7.8	50.6 ± 7.9	48.3 ± 7.3	49.7 ± 7.4	50.7 ± 7.9	52.3 ± 8.1	53.9 ± 7.8
Current smokers (%)	43.3	49.7	55.9	71.3	51.4	52.9	51.7	54.1
Regular drinkers (%)	68.7	68.5	68.8	62.3	66.4	71.6	69.1	63.8
Coffee intake (%), daily	–	–	–	–	42.9	47.6	40.4	30.8
Green tea intake (%), daily	75.3	74.9	74.5	68.7	–	–	–	–
Caffeine intake (g, mean) ± SD	0.09 ± 0.06	0.12 ± 0.06	0.21 ± 0.06	0.43 ± 0.09	0.13 ± 0.13	0.16 ± 0.12	0.20 ± 0.12	0.23 ± 0.12
Women								
Number of subjects	17 509	15 968	15 994	5403	13 441	11 492	15 316	14 625
Proportion (%)	31.9	29.1	29.1	9.9	24.5	20.9	27.9	26.7
Age (years, mean) ± SD	55.0 ± 7.7	52.2 ± 7.8	49.8 ± 7.5	47.3 ± 6.7	49.8 ± 7.4	50.8 ± 7.9	52.7 ± 8.2	53.9 ± 7.9
Current smokers (%)	4.4	4.4	7.6	18.0	7.8	6.5	5.4	7.1
Regular drinkers (%)	8.6	10.5	15.8	19.6	12.7	13.6	12.1	11.3
Coffee intake (%), daily	–	–	–	–	43.3	48.8	38.4	27.9
Green tea intake (%), daily	76.8	77.7	75.0	66.2	–	–	–	–
Caffeine intake (g, mean) ± SD	0.09 ± 0.06	0.11 ± 0.06	0.19 ± 0.05	0.35 ± 0.08	0.10 ± 0.10	0.13 ± 0.09	0.17 ± 0.08	0.19 ± 0.09

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of bladder cancer in relation to smoking

	Number of cases	Person-years of follow up	HR† (95% CI)	HR‡ (95% CI)
Men				
Never smoker	26	147 111	1.0 (reference)	1.0 (reference)
Former smoker	42	143 910	1.32 (0.80–2.16)	1.28 (0.78–2.11)
Current smoker	92	316 526	1.69 (1.09–2.63)	1.46 (0.92–2.31)
P_{trend}			0.01	0.10
Never smoker	26	147 111	1.0 (reference)	1.0 (reference)
Years since cessation of smoking in former smokers				
<10	29	72 905	1.88 (1.10–3.21)	1.82 (1.06–3.13)
10–19	7	48 324	0.71 (0.31–1.63)	0.69 (0.30–1.60)
≥20	6	22 682	0.98 (0.40–2.40)	0.98 (0.40–2.38)
Pack-years in current smokers				
<20	9	55 910	1.14 (0.53–2.44)	0.85 (0.37–1.98)
20–29	16	83 959	1.39 (0.74–2.61)	1.32 (0.70–2.49)
30–39	20	77 819	1.39 (0.77–2.50)	1.23 (0.67–2.26)
40–49	22	45 221	2.24 (1.26–3.99)	1.94 (1.06–3.56)
≥50	24	46 178	2.61 (1.49–4.56)	2.24 (1.24–4.04)
P_{trend}			<0.01	0.04
Women				
Never smoker	26	147 111	1.0 (reference)	1.0 (reference)
Former smoker	0	10 764	–	–
Current smoker	9	43 315	5.45 (2.56–11.61)	6.53 (3.02–14.11)
Pack-years in current smokers				
<25	7	28 118	6.91 (3.00–15.93)	8.30 (3.55–19.43)
≥25	2	12 433	4.06 (0.96–17.17)	5.27 (1.23–22.64)
P_{trend}			<0.01	<0.01

†Adjusted for age (continuous) and area (10 public health center areas).
‡Adjusted for age (continuous), area (10 public health center areas), alcohol drinking (non- or occasional drinkers, 1–150, ≥150 g/week), green tea (<1, 1–2, 3–4, ≥5 cups/day), and coffee (almost none, 1–4 times/week, 1–2, ≥3 cups/day).

for smoking status, alcohol drinking, and green tea consumption (multivariate HR = 1.37, 95% CI = 0.75–2.51; $P_{trend} = 0.09$). In contrast, green tea and caffeine consumption were not associated with bladder cancer, and HRs did not change substantially after adjustment for all potential confounding factors.

Table 4 presents the association between coffee, green tea, and caffeine consumption and bladder cancer in women. The proportions of coffee and green tea in caffeine were similar in women (43.3% for coffee and 46% for green tea). Coffee consumption tended to decrease the risk of bladder cancer in women who drank one or more cups of coffee per day (multivariate HR = 0.55, 95% CI = 0.23–1.33). In contrast, green tea dose-dependently increased the risk of bladder cancer in women. Multivariate HR for women who drank 5 or more cups

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Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) of bladder cancer in relation to consumption of coffee, green tea, and caffeine in men

Category of intake	Coffee				
	Almost none	1–4 times/week	1–2 cups/day	≥3 cups/day	P_{trend}
Number of cases	50	52	43	19	
Person-years of follow up	185 405	183 367	157 544	83 713	
HR† (95% CI)	1.0 (reference)	1.23 (0.83–1.82)	1.60 (1.05–2.43)	1.71 (0.99–2.96)	0.01
HR‡ (95% CI)	1.0 (reference)	1.26 (0.84–1.88)	1.53 (0.98–2.37)	1.37 (0.75–2.51)	0.09
	Green tea				
	<1 cup/day	1–2 cups/day	3–4 cups/day	≥5 cups/day	P_{trend}
Number of cases	33	39	39	53	
Person-years of follow up	161 557	140 218	158 952	149 301	
HR† (95% CI)	1.0 (reference)	1.13 (0.70–1.82)	0.83 (0.51–1.33)	0.99 (0.63–1.56)	0.67
HR§ (95% CI)	1.0 (reference)	1.18 (0.73–1.91)	0.71 (0.43–1.18)	0.90 (0.56–1.45)	0.31
	Caffeine (median, mg/day)				
	Lowest (0.04)	Second (0.13)	Third (0.18)	Highest (0.32)	P_{trend}
Number of cases	47	34	43	40	
Person-years of follow up	177 874	142 138	132 876	157 140	
HR† (95% CI)	1.0 (reference)	0.72 (0.46–1.13)	1.24 (0.82–1.89)	1.26 (0.82–1.94)	0.10
HR¶ (95% CI)	1.0 (reference)	0.67 (0.42–1.08)	1.23 (0.80–1.89)	1.05 (0.66–1.67)	0.36

†Adjusted for age (continuous) and area (10 public health center areas).
‡Adjusted for age (continuous), area (10 public health center areas), smoking status (never, former [<10, 10–19, ≥20 years since cessation of smoking], current [<20, 20–29, 30–39, 40–49, ≥50 pack-years]), alcohol drinking (non- or occasional drinkers, 1–150, ≥150 g/week), and green tea (<1, 1–2, 3–4, ≥5 cups/day).
§Adjusted for age (continuous), area (10 public health center areas), smoking status (never, former [<10, 10–19, ≥20 years since cessation of smoking], current [<20, 20–29, 30–39, 40–49, ≥50 pack-years]), alcohol drinking (non- or occasional drinkers, 1–150, ≥150 g/week), and coffee (almost none, 1–4 times/week, 1–2, ≥3 cups/day).
¶Adjusted for age (continuous), area (10 public health center areas), smoking status (never, former [<10, 10–19, ≥20 years since cessation of smoking], current [<20, 20–29, 30–39, 40–49, ≥50 pack-years]), and alcohol drinking (non- or occasional drinkers, 1–150, ≥150 g/week).

Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) of bladder cancer in relation to consumption of coffee, green tea, and caffeine in women

Category of intake	Coffee			
	Almost none	1–4 times/week	≥1 cups/day	P_{trend}
Number of cases	19	15	8	
Person-years of follow up	226 689	207 355	270 514	
HR† (95% CI)	1.0 (reference)	1.09 (0.55–2.16)	0.63 (0.26–1.52)	0.38
HR‡ (95% CI)	1.0 (reference)	1.03 (0.51–2.07)	0.55 (0.23–1.33)	0.23
	Green tea			
	<3 cups/day	3–4 cups/day	≥5 cups/day	P_{trend}
Number of cases	12	9	21	
Person-years of follow up	324 123	193 066	187 369	
HR† (95% CI)	1.0 (reference)	1.10 (0.45–2.68)	2.21 (1.05–4.66)	0.03
HR§ (95% CI)	1.0 (reference)	1.22 (0.49–3.00)	2.29 (1.06–4.92)	0.03
	Caffeine (median, mg/day)			
	Lowest (0.05)	Middle (0.13)	Highest (0.24)	P_{trend}
Number of cases	18	12	12	
Person-years of follow up	260 765	227 409	216 383	
HR† (95% CI)	1.0 (reference)	0.84 (0.40–1.76)	1.23 (0.58–2.61)	0.68
HR¶ (95% CI)	1.0 (reference)	0.88 (0.42–1.86)	1.13 (0.52–2.46)	0.81

†Adjusted for age (continuous) and area (10 public health center areas).
‡Adjusted for age (continuous), area (10 public health centers), smoking status [never, former, current smokers (<25, ≥25 pack-years)], alcohol drinking (non- or occasional drinkers, 1–150, ≥150 g/week), and green tea (<1, 1–2, 3–4, ≥5 cups/day).
§Adjusted for age (continuous), area (10 public health centers), smoking status [never, former, current smokers (<25, ≥25 pack-years)], alcohol drinking (non- or occasional drinkers, 1–150, ≥150 g/week), and coffee (almost none, 1–4 times/week, 1–2, ≥3 cups/day).
¶Adjusted for age (continuous), area (10 public health centers), smoking status [never, former, current smokers (<25, ≥25 pack-years)], and alcohol drinking (non- or occasional drinkers, 1–150, ≥150 g/week).

Table 5. Hazard ratios (HRs) and 95% confidence intervals (CIs) of bladder cancer in relation to consumption of coffee, green tea, and caffeine in men by smoking status

Category of intake	Coffee				
	Almost none	1–4 times/week	≥1 cups/day	P_{trend}	$P_{interaction}$
Never smoker					
Number of cases	6	9	11		
HR[†] (95% CI)	1.00 (reference)	1.89 (0.67–5.32)	2.48 (0.88–7.05)	0.09	0.25
Former smoker					
Number of cases	13	13	16		
HR[†] (95% CI)	1.00 (reference)	1.25 (0.58–2.71)	2.09 (0.96–4.54)	0.07	
Never/Former smoker					
Number of cases	19	22	27		
HR[†] (95% CI)	1.00 (reference)	1.47 (0.79–2.72)	2.24 (1.21–4.16)	0.01	
Current smoker					
Number of cases	29	30	33		
HR[†] (95% CI)	1.00 (reference)	1.11 (0.65–1.90)	1.13 (0.65–1.97)	0.67	
	Green tea				
Category of intake	<3 cups/day	3–4 cups/day	≥5 cups/day	P_{trend}	$P_{interaction}$
Never smoker					
Number of cases	13	6	7		
HR[‡] (95% CI)	1.00 (reference)	0.81 (0.30–2.19)	0.85 (0.31–2.32)	0.72	0.42
Former smoker					
Number of cases	14	12	16		
HR[‡] (95% CI)	1.00 (reference)	1.17 (0.53–2.56)	1.40 (0.67–2.95)	0.38	
Never/Former smoker					
Number of cases	27	18	23		
HR[‡] (95% CI)	1.00 (reference)	0.98 (0.53–1.79)	1.14 (0.63–2.04)	0.68	
Current smoker					
Number of cases	14	18	30		
HR[‡] (95% CI)	1.00 (reference)	0.44 (0.24–0.80)	0.62 (0.37–1.04)	0.05	
	Caffeine (median, mg/day)				
Category of intake	Lowest (0.06)	Middle (0.15)	Highest (0.28)	P_{trend}	$P_{interaction}$
Never smoker					
Number of cases	12	6	8		
HR[§] (95% CI)	1.00 (reference)	0.95 (0.35–2.58)	1.66 (0.66–4.20)	0.33	0.04
Former smoker					
Number of cases	13	13	16		
HR[§] (95% CI)	1.00 (reference)	1.19 (0.55–2.59)	2.30 (1.08–4.87)	0.03	
Never/Former smoker					
Number of cases	25	29	24		
HR[§] (95% CI)	1.00 (reference)	1.09 (0.59–2.00)	2.05 (1.15–3.66)	0.02	
Current smoker					
Number of cases	38	30	24		
HR[§] (95% CI)	1.00 (reference)	0.87 (0.53–1.44)	0.72 (0.41–1.27)	0.25	

[†]Adjusted for age (continuous), area (10 public health center areas), smoking status (never, former [<10, 10–19, ≥20 years since cessation of smoking], current [<20, 20–29, 30–39, 40–49, ≥50 pack-years]), alcohol drinking (non- or occasional drinkers, 1–150, = 150 g/week), and green tea (<1, 1–2, 3–4, ≥5 cups/day).
[‡]Adjusted for age (continuous), area (10 public health center areas), smoking status (never, former [<10, 10–19, ≥20 years since cessation of smoking], current [<20, 20–29, 30–39, 40–49, ≥50 pack-years]), alcohol drinking (non- or occasional drinkers, 1–150, ≥150 g/week), and coffee (almost none, 1–4 times/week, 1–2, ≥3 cups/day).
[§]Adjusted for age (continuous), area (10 public health center areas), smoking status (never, former [<10, 10–19, ≥20 years since cessation of smoking], current [<20, 20–29, 30–39, 40–49, ≥50 pack-years]), and alcohol drinking (non- or occasional drinkers, 1–150, ≥150 g/week).

of green tea per day was 2.29 (95% CI = 1.06–4.92; $P_{trend} = 0.03$). We observed no association between caffeine consumption and bladder cancer risk in women.

We also assessed the effect of coffee, green tea, and caffeine consumption according to smoking status (Table 5). To avoid residual confounding by smoking, we first stratified smoking status to never, former, or current. Because the HRs of never and former smokers did not substantially differ, these were then combined. Coffee consumption was positively associated with bladder cancer risk in never or former smokers (for 1–4 times per week, multivariate HR = 1.47; for 1 cups or more per day, HR = 2.24, compared with men who hardly drank). For current smokers, coffee was not substantially associated with bladder cancer risk regardless of the amount of coffee consumption (HR = 1.13, 95% CI = 0.65–1.97 for men who drank 1 or more cups per day compared with men who hardly drank). In contrast, green tea was not statistically significant associated with bladder cancer in either never- or former-smoking men. Among current smokers, green tea appeared to be associated with a decreased risk of bladder cancer. We also found a positive association

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between caffeine intake and bladder cancer in never- or former-smoking men, with a HR (95% CI) in the highest category of caffeine consumption compared with the lowest of 2.05 (95% CI = 1.15–3.66). In addition, we observed that HRs slightly decreased as caffeine consumption increased among current smokers, and detected an interaction between caffeine consumption and smoking status ($P_{interaction} = 0.04$).

Discussion

In this study, coffee consumption was associated with an increased risk of bladder cancer, without statistical significance. In contrast, we found no association between green tea and caffeine consumption and bladder cancer risk in men. In never and former smokers, however, a positive association between coffee and caffeine and bladder cancer was observed. Additionally, significant interaction between caffeine and smoking was found ($P_{interaction} = 0.04$), suggesting that the effects of the caffeine might be modified by smoking status.

Cigarette smoking is an established risk factor for bladder cancer.[19] A meta-analysis of 43 published case-control and cohort studies reported that smoking amount and smoking duration were positively associated and that cessation of cigarette smoking was inversely associated with urinary tract cancer risk (most cases being bladder cancer).[20] Our study confirmed these previous results.

Many previous studies have reported a positive association between coffee drinking and bladder cancer in Western countries,[7,12,21–29] although many others have reported no association.[30–37] However, several studies have shown higher risks in coffee drinkers who were non-smokers,[12,27,31,32,34,36,38,39] suggesting the necessity of separate interpretation by smoking status due to the difference in association between coffee consumption and bladder cancer according to smoking status. Our study showed that HRs of subjects who drank 3 or more cups of coffee were attenuated by adjustment for smoking status. Moreover, when we stratified these results by smoking status, we found a positive association between coffee and bladder cancer only in never or former smokers. Thus, our results suggest that the effect of coffee on bladder cancer risk in Japanese may be similar to that in other populations, notwithstanding that the type, strength, and amount of coffee drinking differ among countries.

In our study, caffeine consumption also showed a positive association with bladder cancer among never or former smokers. Given that a similar association was seen in the Netherlands cohort study,[29] these findings suggest that caffeine contained in coffee might contribute to an increased risk of bladder cancer. Moreover, its ability to modify the apoptotic response and perturb cell checkpoint integrity[40,41] suggest that caffeine might be a causative agent of bladder cancer.[4] It is particularly noteworthy that the adverse effects of coffee and caffeine were observed among never or former smokers, and indeed plausible given a previous report that the clearance of caffeine in smokers is faster than that in non-smokers,[42] and that the urinary caffeine levels of smokers were approximately 70% lower than those of non-smokers.[43] In contrast, our study showed that the hazard ratio of current smokers who were in the highest tertile of caffeine consumption was lower than that of current smokers with lower caffeine consumption. Caffeine stimulates the production of cytochrome P450 (CYP) enzymes in the liver, such as CYP1A2 or NAT2, and these enzymes may increase the metabolic activation of carcinogens like polycyclic aromatic hydrocarbons in cigarette smoking.[44] Thus, the adverse effects of coffee and caffeine may be more clearly expressed among never or former smokers and caffeine may modify the increased bladder cancer risk caused by smoking. However, it should be noted that smoking is a major independent risk of bladder cancer. HRs among current smokers who hardly drank coffee were higher than those among never smokers who hardly drank coffee (HR = 4.17 [95% CI = 1.59–10.96], data not shown). Even though our study appears to show a negative tendency between caffeine and bladder cancer among current smokers, the HRs among current smokers was higher than those among never smokers irrespective of caffeine intake (never smokers in lowest category of caffeine intake: reference, current smokers in lowest category of caffeine intake: HR = 3.23 [95% CI = 1.47–7.08], current smokers in highest category of caffeine intake: HR = 2.13 [95% CI = 0.95–4.79]; data not shown).

Of the few papers which have investigated the association between green tea and bladder cancer, one prospective study showed no relation with bladder cancer,[10] a case-control study showed an elevated risk in heavy drinkers of green tea (5–9 cups/day),[9] while a third showed an inverse association with the consumption of matcha (powdered green tea) in women.[8] In our study, green tea was not associated with bladder cancer risk among men. This result is supported by a recent meta-analysis.[5] We speculate that several polyphenolic components of green tea with antioxidant properties might mask the adverse effects of caffeine on bladder cancer in men. In addition, green tea appeared negatively associated with bladder cancer risk among smoking men. Nevertheless, hazard ratios in current smokers were relatively high independently of green tea drinking, indicating that green tea was unable to cancel all the adverse effects of smoking (HR = 1.72 [95%CI = 0.80–3.70] for current smokers who drank five or more cups of green tea per day *versus* never smokers who drank less than three cups; data not shown). In contrast, a positive association between green tea intake and bladder cancer was observed in women. This sex difference might suggest that the contribution of green tea to total caffeine intake in women is higher than that in men. In any case, the negative tendency in bladder cancer risk with increasing coffee consumption in women is difficult to explain. At present, a biological mechanism that might explain this discrepancy between men and women remains unclear, and may have arisen by chance due to the small sample size in women.

This study was a large prospective study in a general Japanese population. Among its strengths were the high rate of participation (approximately 80%) and negligible proportion of loss to follow-up (0.4%), indicating that selection bias was unlikely. Another strength of the prospective design was that coffee and green tea intake were measured before the disease was diagnosed, thereby avoiding the probability of recall bias that is inherent to case-control studies. On the other hand, several limitations also warrant mention. First, we could not evaluate the validity of caffeine consumption. The amount of caffeine depends on the quantity of coffee beans and tea leaf and the length of time of extraction. Unfortunately, we were unable to obtain such information. Second, we could not evaluate the large number of substances other than caffeine contained in coffee. The risk of bladder cancer might be attributable to ingredients other than caffeine or metabolic substances. Third, the number of bladder cancer cases was small, and that therefore the results in women might have occurred by chance. Fourth, coffee and green tea were sources of total fluid intake, which might be inversely associated with the risk of bladder cancer.[35,45] However, we could not adjust for total fluid intake because we did not obtain such information. Finally, we were unable to determine exposure to chemical substances which might have increased the risk of bladder cancer. For example, coffee and green tea might be sources of potential exposure to drinking water contaminants such as chlorination by-products and nitrates.[28] However, any explanation of the different effects of coffee on bladder cancer in terms of smoking status by contaminants in drinking water would be difficult: if contaminants in coffee and green tea were a risk factor for bladder cancer,

coffee consumption would be associated with dose-related increase in risk even in current smokers.

In summary, we confirmed that cigarette smoking is major risk factor of bladder cancer and that coffee and caffeine are associated with an increased risk of bladder cancer in never- or former-smoking men. Considerable research effort is required to clarify the effects of caffeine on carcinogenic processes in the bladder.

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Appendix

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