Coffee consumption and risk of bladder cancer

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META-ANALYSIS

Coffee consumption and risk of bladder cancer: a pooled analysis of 501,604 participants from 12 cohort studies in the BLadder Cancer Epidemiology and Nutritional Determinants (BLEND) international study

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Abstract

Recent epidemiological studies have shown varying associations between coffee consumption and bladder cancer (BC). This research aims to elucidate the association between coffee consumption and BC risk by bringing together worldwide cohort studies on this topic. Coffee consumption in relation to BC risk was examined by pooling individual data from 12 cohort studies, comprising of 2601 cases out of 501,604 participants. Pooled multivariate hazard ratios (HRs), with corresponding 95% confidence intervals (CIs), were obtained using multilevel Weibull regression models. Furthermore, dose–response relationships were examined using generalized least squares regression models. The association between coffee consumption and BC risk showed interaction with sex (P-interaction < 0.001) and smoking (P-interaction = 0.001). Therefore, analyses were stratified by sex and smoking. After adjustment for potential confounders, an increased BC risk was shown for high (> 500 ml/day, equivalent to > 4 cups/day) coffee consumption compared to never consumers among male smokers (current smokers: HR = 1.75, 95% CI 1.27–2.42, P-trend = 0.002; former smokers: HR = 1.44, 95% CI 1.12–1.85, P-trend = 0.001). In addition, dose–response analyses, in male smokers also showed an increased BC risk for coffee consumption of more than 500 ml/day (4 cups/day), with the risk of one cup (125 ml) increment as 1.07 (95% CI 1.06–1.08). This research suggests that positive associations between coffee consumption and BC among male smokers but not never smokers and females. The inconsistent results between sexes and the absence of an association in never smokers indicate that the associations found among male smokers is unlikely to be causal and is possibly caused by residual confounding of smoking.

Keywords Bladder cancer · Coffee consumption · Smoking · Dose–response analyses · Cohort study

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Abbreviations

BLEND	BLadder Cancer Epidemiology and Nutritional Determinants
BC	Bladder cancer
GLS	Generalized least squares
IARC	International Agency for Research on Cancer
EPIC	European Prospective Investigation into Cancer and Nutrition Cohort Studies
NLCS	NetherLands Cohort Study
VITAL	VITamins And Lifestyle cohort study
RERF-LSS	Radiation Effects Research Foundation-Life Span Study
FFQ	Food frequency questionnaires
ICD-O	International classification of diseases for oncology

NMIBC	Non-muscle invasive bladder cancer
MIBC	Muscle invasive bladder cancer
HR	Hazard ratio
CI	Confidence interval
CYP1A2	Cytochrome P450 1A2
PAHs	Polycyclic aromatic hydrocarbons
ATM	Ataxia-telangiectasia mutated
BMI	Body Mass Index
SES	Socioeconomic status
ml	Millilitre
kcal	Kilocalorie
g	Gram
mg	Microgram

Introduction

Bladder cancer (BC) is the 10th most common form of cancer worldwide, with an estimated 549,000 new cases and 200,000 deaths according to the latest global cancer statistics [1, 2]. Incidence rates of BC are highest in Europe and North America, with a strong predominance in males and the elderly [2–7]. BC is reported to be the most expensive of all cancer in terms of life-time treatment due to its high rate of recurrence [8]. The strongest risk factors for BC occurrence, such as certain occupational exposures to chemical, water contaminants, and smoking [9, 10] have long been identified. However, as the bladder is an excretory organ, the role of fluid consumption could also be important in the development of BC.

Coffee is one of the most consumed beverages around the world. Since early 1970s [11], many studies have been conducted to detect the association between coffee consumption and BC risk; however, inconsistent findings have ranged from null associations [12–16], inverse associations [17, 18] to positive associations [19–25]. A Monographs Programme by International Agency for Research on Cancer (IARC) in 2016 reviewed the accumulated evidence of the coffee carcinogenicity focusing on BC risk and concluded: "no consistent evidence of an association between drinking coffee and BC risk" [26]. Therefore, they highlighted the need for large prospective studies with sufficient case numbers and detailed information on coffee consumption to better understand the association of this beverage and BC risk, especially properly controlling for smoking which is shown to be strongly associated with coffee consumption [27–32]. Furthermore, it is unclear and worthwhile to detect the threshold of coffee consumption above which a negative effect on BC risk might occur.

Our previous study, based on 13 case–control studies with 5900 cases, yielded positive associations between heavy coffee consumption and BC among never smokers but not smokers [33]. Although this previous study had enough statistical power to provide definitive answers, it is commonly believed that results from case–control studies are unreliable due to a frequently occurring form of bias, namely; recall bias and selection bias. The present study, therefore, aims to replicate our previous findings based on BLEND data originated from 12 cohort studies from around the world and give definitive answers on the influence of coffee consumption on BC risk.

Methods

Study population

Data were derived from the BLadder Cancer Epidemiology and Nutritional Determinants Study (BLEND). BLEND is a large international epidemiology consortium that currently consists of 19 case–control studies and 16 cohort studies, which aims to pool data from available epidemiological studies on diet and BC. For the present study, 12 cohort studies (including 2601 cases/499,003 non-cases), originated from 11 different countries in 3 continents [i.e. Europe: European Prospective Investigation into Cancer and Nutrition cohort studies (EPIC) [34] [France [35], Germany [36], Greece [37], Italy [38], The Netherlands [39], Norway [40], Spain [37], Sweden [41, 42], United Kingdom [43, 44]], NetherLands Cohort Study (NLCS) [45]; North America: VITamins And Lifestyle cohort study (VITAL) [46]]; and Asia: Radiation Effects Research Foundation-Life Span Study (RERF-LSS) [47], had sufficient information on coffee consumption to be eligible for inclusion and each study was ethically approved [34, 45, 46, 48] (Supplementary Table 1).

Data collection and coding

Details on the methodology of the BLEND consortium have been described elsewhere [49]. All included studies used a self-administered or trained interviewer administered food frequency questionnaire (FFQ) that was validated on either food groups [34, 46, 50–52], and/or energy intake [51, 53]. For each study, participants were asked to report on their usual coffee consumption during the preceding year before study enrolment. The collected coffee consumption were harmonized and categorized by using the hierarchal Eurocode 2 food coding system developed by the European Union [54], besides, weekly, monthly or yearly coffee consumption were converted to daily millilitres (ml) of coffee consumption. Person-years of follow-up for each participant was calculated from date of study enrolment until date of BC diagnosis, or date of ending follow up (e.g. date of death, lost to follow-up, or study exit), whichever came first. For the NLCS study, a nested case-cohort approach was applied,

in which the number of person-years at risk was estimated based on a sub-cohort that was randomly sampled [45].

Each study ascertained incident BC with International Classification of Diseases for Oncology (ICD-O-3 code C67) using population-based cancer registries, health insurance records, or medical records. The term 'bladder cancer' (BC) is used for all urinary bladder neoplasms. BCs were classified into non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). NMIBC included non-invasive papillary carcinomas confined to the urothelium (stage Ta), and carcinomas that invaded the lamina propria of the bladder wall (stage T1). High grade flat non-invasive carcinomas confined to the urothelium (carcinoma in situ; CIS) without other concomitant tumour stages [i.e. T1/Ta (classified to non-muscle invasive prior) or MIBC] were also classified as NMIBC. MIBC included carcinomas that invaded into the detrusor muscle (stage T2), carcinomas that invaded into the peri vesical tissue (stage T3), and carcinomas that invaded adjacent tissues and organs (most often the prostate or uterus, stage T4). Studies (e.g. EPIC-Greece, EPIC-Sweden, EPIC-Norway and RERF-LSS) without information on NMIBC or MIBC were excluded from the stratified analyses of BC subtypes.

In addition to information on coffee and other dietary intake data, the BLEND dataset also included data on study characteristics (design, method of dietary assessment, geographical region), participant demographics (age, sex and ethnicity), smoking status and smoking pack-years (i.e. the number of cigarettes smoked per day multiplying the years of smoking), which were measured at baseline.

Statistical analyses

The differences between cases and non-cases were examined by Chi square test for categorical variables and *t* test for continuous variables. To assess the influence of coffee consumption on the BC risk, multilevel (2-level) Weibull regression analyses were used to estimate the pooled hazard ratios (HRs) and 95% confidence intervals (CIs), which nested the individuals within study centres to adjust for cross-cohort heterogeneity. We found no violation for the appropriateness of the lognormal and Weibull model by using Wald test. Coffee consumption was divided into a never consumption group and 3 ever consumption groups based on a tertile ordered distribution: low consumption (0–180 ml/day), medium consumption (180–500 ml/day) and high consumption (> 500 ml/day). The Weibull regression models used never coffee consumers as the reference group and associations were computed as model 1: adjusted for age (years) and sex (male or female), model 2: adjusted for mode 1 and smoking (status-pack-years, smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e. smoking less than 20 pack-years)]; 2 [current heavy smokers (i.e. smoking more than 20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e. smokers who ceased smoking over 1 year prior and smoked less than 20 pack-years)]; 5 [former heavy smokers (i.e. smokers who ceased smoking over 1 year prior and smoked more than 20 pack-years)]; 6 [former smokers (smokers who ceased smoking over 1 year prior and no information on pack-years)]), or model 3: adjusted for model 2 and total energy intake [kilocalorie (kcal)/day, continuous]), and other potential confounders that showed to be different between BC cases and non-BC cases; which included tea consumption (ml/day, continuous; another popular and main caffeine-source beverage), other caffeine intake [gram (g)/day, continuous; residual caffeine content from other foods and beverages], and sweeteners intake (g/day, continuous; popular additive accompanied with coffee consumption). The effects of caffeinated or decaffeinated coffee on BC risk were assessed by comparing to never coffee consumers based on multilevel Weibull regression (model 3). To understand the relevance of the effect modification, the main interaction terms between coffee consumption and age, sex and smoking were added to the model 2. *P*-interaction < 0.05 was considered statistically significant where upon all analyses were stratified for the covariate of interest. Stratification analyses were assessed regarding BC subtypes (i.e. NMIBC and MIBC), sex and smoking. Several sensitivity analyses were performed: (a) participants who are neither smokers nor coffee consumers were used as a reference group to investigate the BC risk with coffee consumption in different smoking status; (b) BC cases diagnosed within the first 2 years after recruitment were excluded. Missing variables (e.g. total energy intake and tea consumption) were imputed separately in each participating cohort by multiple imputation method considering different study protocols and characteristics of participants across cohorts. Only participants with complete information on BC status (i.e. cases or non-cases), age, sex and smoking were included in building of the imputation models. Linear regression models were fitted for those two continuous variables (total energy intake and tea consumption) respectively. After imputation, one single complete dataset was created and used to estimate results based on model 3.

In our secondary analysis, a potential dose–response relationship between coffee consumption and BC was assessed by using generalized least squares (GLS) regression models [55]. Restricted cubic splines, which set knots at the 5th, 35th, 65th and 95th percentile, were used to investigate statistical linearity or non-linearity for all curves [56]. The results of the dose–response analyses were presented for each regular European cup (125 ml) of coffee increment up to 10 cups of coffee per day (1250 ml/day) compared to never coffee consumers. Adjustments were made for age, sex, smoking, total energy intake, tea consumption, other caffeine intake, and sweeteners intake.

All statistical analyses were performed with STATA version 14 SE (Stata Corporation, Texas, USA). Two-tailed probabilities (*P* values) < 0.05 were considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the study population are shown in Table 1. Altogether, 2601 incident cases of BC (1940 males, 661 females) and 499,003 non-cases were included in our analyses, with a total of 5,373,352 person-years of follow-up (median follow-up: 12 years). Of the cases, only 1617 (62%) were recorded diagnoses by NMIBC (38%) and MIBC (24%). The median age at baseline was 61 years for cases and 52 years for non-cases. The majority (97.94%) of participants were Caucasian, with only 2.06% non-Caucasian (i.e. Asian, Indian and Black). Approximately 23% of participants reported drinking coffee more than 500 ml per day, with an average consumption of 789 ml/day. Among those heavy consumers, most of them (64%) reported a smoking history, with 35% being former smokers. At baseline, a higher coffee consumption was observed among smokers (446 ml/day) compared to never smokers (326 ml/day), as well as among males (430 ml/day) compared to females (369 ml/day).

Association between coffee consumption and BC risk

Amount of coffee consumption with BC risk

The results of multilevel Weibull regressions for the association between coffee consumption and BC risk are shown in Table 2. Overall, compared to never coffee consumers, an increased BC risk was observed for coffee consumption of more than 500 ml/day ($HR_{model3} = 1.56$, 95% CI 1.38–1.77, *P*-trend < 0.001) and of 180–500 ml/day ($HR_{model3} = 1.39$, 95% CI 1.23–1.58, *P*-trend < 0.001). In addition, both NMIBC and MIBC showed similar results; an increased BC risk was observed for coffee consumption of more than 500 ml/day ($HR_{model3} = 1.39$, 95% CI 1.11–1.74, *P*-trend < 0.001; $HR_{model3} = 2.05$, 95% CI 1.41–2.96, *P*-trend = 0.21, respectively).

Coffee consumption with BC risk stratified by sex and smoking

Since coffee consumption showed interaction with sex (*P*-interaction < 0.001) and smoking (*P*-interaction = 0.001), analyses were stratified by sex and smoking and compared to never coffee consumers (Table 3). For males, according to model 3, a significant increased BC risk was observed in high (> 500 ml/day) coffee consumption for both current and former smokers (current smokers: $HR_{model3} = 1.75$, 95% CI 1.27–2.42, *P*-trend = 0.002; former smokers: $HR_{model3} = 1.44$, 95% CI 1.12–1.85, *P*-trend = 0.001), while no association was found among male never smokers. Similar increased BC risks were observed for heavy (more than 20 pack-years) male smokers and light (less than 20 pack-years) male smokers when comparing high (> 500 ml/day) coffee consumers to never consumers (heavy smokers: $HR_{model3} = 1.72$, 95% CI 1.13–2.62, *P*-trend = 0.02; light smokers: $HR_{model3} = 1.93$, 95% CI 1.07–3.47, *P*-trend = 0.03). In addition, the moderate (180–500 ml/day) coffee consumption of male current smokers and male heavy smokers also showed increased risks of BC ($HR_{model3} = 1.69$, 95% CI 1.23–2.34, *P*-trend = 0.002; $HR_{model3} = 1.60$, 95% CI 1.05–2.43, *P*-trend = 0.02, respectively). For females, no significant association or increased BC risk could be observed for neither smokers nor never smokers.

Caffeinated and decaffeinated coffee with BC risk

Results for the comparison of caffeinated and decaffeinated coffee are shown in Table 4. Nine cohort studies [35–44], with a total of 310,116 participants (1040 BC cases, 182,716 caffeinated coffee consumers, 18,058 decaffeinate coffee consumers, and 109,342 neither caffeinated or decaffeinated coffee consumers), were included in the analyses. For the analysis on caffeinated coffee, the consumption over 500 ml/day showed an increased BC risk compared to never coffee consumers based on model 3 ($HR_{model3} = 1.12$, 95% CI 1.01–1.23, *P*-trend = 0.46); here the significant association maintained in smokers ($HR_{model3} = 1.22$, 95% CI 1.06–1.42, *P*-trend = 0.10) while not in never smokers. Consumers of decaffeinated coffee suggested similar BC risks compared to consumers of caffeinated coffee. However, since the sample size for decaffeinated coffee decreased significantly, results should be interpreted with caution.

Dose–response analyses

Dose–response relationships between coffee consumption and the risk of BC are displayed in Fig. 1. The curves for the overall population showed slightly increased BC risks with significant increment for consuming over 500 ml/day (4 cups/day), even though the tendency went down marginally after 1000 ml/day (8 cups/day). Similar results were found among male smokers with significant increased risks for consuming over 400 ml/day (3.2 cups/day). No significant dose–response relationships were observed for never smokers (Fig. 1) and females (Supplementary Fig. 1). Adjusted HRs (model 3) and 95% CIs for 125 ml/day (1 cup/day)

Table 1 Characteristics of the study population (2601 cases and 499,003 non-cases) and coffee consumption amount of included studies in BLEND

Characteristics	Coffee consumption					Mean [ml/day (SD)]	*P* value[a]	*P*-interaction
	Total	Never	Low ≤ 180 ml/day	Medium 180–500 ml/day	High > 500 ml/day			
N (%)	501,604	126,875 (25.29)	125,621 (25.04)	132,731 (26.46)	116,377 (23.20)	388.41 (340.00)	< 0.001	
Case (%)	2601	405 (15.57)	394 (15.15)	887 (34.10)	915 (35.18)	505.55 (343.32)		
NMIBC (%)	994	140 (14.08)	135 (13.58)	321 (32.29)	398 (40.04)	527.20 (337.60)		
MIBC (%)	623	39 (6.26)	54 (8.67)	246 (39.49)	284 (45.58)	586.89 (342.55)		
Non-case (%)	499,003	126,470 (25.34)	125,227 (25.10)	131,844 (26.42)	115,462 (23.14)	387.72 (339.86)		
Person-years	5,373,352	1,376,399	1,409,850	1,402,186	1,184,917	388.41 (340.00)	< 0.001	
Sex								< 0.001
Male (%)								
Case	1940	283 (14.59)	281 (14.48)	652 (33.61)	724 (37.32)	521.19 (348.96)	< 0.001	
Non-case	153,204	42,484 (27.73)	36,512 (23.83)	34,167 (22.30)	40,041 (26.14)	430.51 (386.72)		
Female (%)								
Case	661	121 (18.31)	113 (17.10)	235 (35.55)	192 (29.04)	457.45 (320.93)	< 0.001	
Non-case	345,799	83,986 (24.29)	88,715 (25.66)	98,677 (28.54)	75,421 (21.81)	369.62 (316.24)		
Age [mean (SD)]								
Case	2601	58.35 (8.58)	58.92 (9.37)	62.54 (6.78)	60.92 (7.28)	505.55 (343.32)	< 0.001	0.281
Non-case	499,003	51.71 (10.25)	50.70 (11.17)	52.90 (10.84)	52.81 (10.15)	387.72 (339.86)		
Smoking								0.001
Smoking status								
Current (%)								
Case	981	141 (14.37)	142 (14.48)	274 (27.93)	424 (43.22)	572.54 (375.08)	< 0.001	
Non-case	99,029	23,443 (23.67)	21,436 (21.65)	21,722 (21.93)	32,428 (32.75)	482.68 (391.39)		
Former (%)								
Case	1094	142 (12.98)	152 (13.89)	414 (37.84)	386 (35.28)	498.67 (324.40)	< 0.001	
Non-case	144,232	27,689 (19.20)	32,705 (22.67)	43,076 (29.87)	40,762 (28.26)	421.85 (345.23)		
Never (%)								
Case	526	122 (23.19)	100 (19.01)	199 (37.83)	105 (19.96)	382.47 (275.87)	< 0.001	
Non-case	255,742	75,338 (29.46)	71,086 (27.80)	67,046 (26.22)	42,272 (16.53)	325.88 (298.32)		
Smoking pack-years [mean (SD)]	84,990	21.40 (17.62)	19.86 (17.13)	20.02 (15.81)	23.58 (15.87)	352.99 (372.15)	< 0.001	
Ethnicity (%)	501,324	126,800 (25.29)	125,572 (25.05)	132,678 (26.47)	116,274 (23.19)	388.33 (339.89)		
Caucasian	491,013	125,735 (25.61)	119,297 (24.30)	131,989 (26.88)	113,992 (23.22)	392.72 (339.49)	0.06	
Non-Caucasian	10,311	1065 (10.33)	6276 (60.87)	690 (6.69)	2280 (22.11)	215.21 (308.98)	0.35	
Total energy intake [kcal/day (SD)]	501,604	2087.70 (706.82)	2683.39 (866.49)	2039.71 (616.90)	2245.24 (1592.76)	388.41 (340.00)	< 0.001	
Tea consumption [ml/day (SD)]	501,604	161.17 (278.91)	242.83 (343.69)	283.47 (328.60)	214.56 (280.22)	388.41 (340.00)	< 0.001	
Other caffeine intake [g/day (SD)]	501,604	107.40 (279.88)	344.30 (104.07)	359.94 (122.84)	551.60 (174.57)	388.41 (340.00)	< 0.001	
Sweeteners intake [g/day (SD)]	501,604	44.81 (96.15)	37.15 (37.12)	36.90 (41.14)	33.26 (44.27)	388.41 (340.00)	0.02	

P value < 0.05 were considered statistically significant

P-interaction < 0.05 were considered statistically significant

BLEND = BLadder Cancer Epidemiology and Nutritional Determinants study; *N* = number; SD = standard deviation; ml = millilitre; kcal = kilocalorie; g = gram

[a]Calculated by Chi square (χ^2) test for categorical variables and *t* test for continuous variables between bladder cancer cases and non-cases

Table 2 Adjusted hazard ratios and 95% confidence intervals of bladder cancer according to coffee consumption amount stratified by NMIBC and MIBC

Study subgroup	Model adjustments	No. cases/total participants	Coffee consumption				*P*-trend
			Never	≤ 180 ml/day	180–500 ml/day	> 500 ml/day	
Overall	Model 1[a]	2601/501,604	Ref.	1.01 (0.88–1.16)	1.70 (1.51–1.92)	2.09 (1.85–2.35)	< 0.001
	Model 2[a, b]	2601/501,604	Ref.	1.01 (0.88–1.17)	1.38 (1.22–1.56)	1.55 (1.37–1.75)	0.01
	Model 3[a, b, c]	2601/501,604	Ref.	1.03 (0.89–1.19)	1.39 (1.23–1.58)	1.56 (1.38–1.77)	< 0.001
NMIBC	Model 1[a]	994/385,563	Ref.	0.75 (0.59–0.97)	1.05 (0.82–1.35)	1.30 (1.03–1.65)	0.001
	Model 2[a, b]	994/385,563	Ref.	0.77 (0.60–1.02)	1.36 (1.08–1.70)	1.38 (1.11–1.72)	< 0.001
	Model 3[a, b, c]	994/385,563	Ref.	0.75 (0.49–1.02)	1.34 (1.06–1.68)	1.39 (1.11–1.74)	< 0.001
MIBC	Model 1[a]	623/385,192	Ref.	1.15 (0.75–1.76)	1.26 (0.87–1.84)	1.62 (1.12–2.34)	0.001
	Model 2[a, b]	623/385,192	Ref.	1.37 (0.90–2.09)	2.28 (1.58–3.31)	2.00 (1.39–2.88)	0.27
	Model 3[a, b, c]	623/385,192	Ref.	1.47 (0.96–2.24)	2.44 (1.68–3.55)	2.05 (1.41–2.96)	0.21

Reference group was never coffee consumers

P-trend < 0.05 were considered statistically significant

NMIBC = non-muscle invasive bladder cancer; MIBC = muscle invasive bladder cancer; ml = millilitre; kcal = kilocalorie; g = gram

[a]Model 1: Adjusted for age (years, continuous), sex (male or female)

[a, b]Model 2: Additionally, adjusted for smoking (smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e. smoking less than 20 pack-years)]; 2 [current heavy smokers (i.e. smoking more than 20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e. smokers who ceased smoking over 1 year prior and smoked less than 20 pack-years)]; 5 [former heavy smokers (i.e. smokers who ceased smoking over 1 year prior and smoked more than 20 pack-years)]; 6 [former smokers (smokers who ceased smoking over 1 year prior and no information on pack-years)])

[a, b, c]Model 3: Additionally, adjusted for total energy intake (kcal/day, continuous), tea consumption (ml/day, continuous), other caffeine intake (g/day, continuous), and sweeteners intake (g/day, continuous)

increment were 1.04 (95% CI 1.03–1.05) in overall study population, and 1.07 (95% CI 1.06–1.08) in male smokers.

Sensitivity analyses

Compared to participants who were neither smokers nor coffee consumers (Supplementary Table 2), both current and former smokers showed an increased BC risk with the every tertile ordered increment of coffee consumption [current smoker: $HR_{increase} = 1.72$, 95% CI 1.66–1.78; former smoker: $HR_{increase} = 1.40$, 95% CI 1.34–1.46, (model 3)]. Furthermore, the risk estimates for current smokers were higher than the estimates for former smokers. After removing BC cases diagnosed within the first 2 years after recruitment, similar BC risks were observed (Supplementary Table 3).

Discussion

This large multicentric cohort study found a consistently increased BC risk for high (> 500 ml/day) coffee consumption; however, the positive association was restricted to male smokers, while no evidence of an association or increased BC risk was observed among female and never smokers.

Coffee consumption is strongly associated with smoking due to the compound caffeine in coffee which increases subjective smoking reinforcement, and it appears that these two behaviours often occur at the same time [57–59]. It has been proposed that smoking increases caffeine metabolism, thereby requiring smokers to consume more caffeine to achieve desired stimulant effects [60, 61] and postpone experiencing symptoms of caffeine toxicity [33, 62, 63]. Moreover, this hypothesis is strengthened by experimental studies reporting that the cytochrome P450 1A2 (CYP1A2) metabolic pathway is upregulated by both caffeine and compounds in tobacco smoke, including nicotine and polycyclic aromatic hydrocarbons (PAHs) [64–66], so that the effect of caffeine is potentially weaker among smokers than among never smokers. Several previously conducted observational studies, including our BLEND study on data from case–control studies [67] and extensive meta-analysis [28] confirmed the clear experimental findings, in that a higher BC risks for coffee consumers was only observed among never smokers. In addition, a recent Finish study showed no association between coffee consumption and BC risk among male smokers [68]. The present study, however, showed opposite results; while among smokers an increased BC risk was observed, no such increased BC risk was observed among never smokers. One previously conducted prospective cohort study in United States showed a modest increased BC risk with 1 cup/day increment of coffee consumption among smokers but not never smokers, which is in line with the present study [25]. Since conflicting results were observed among both similar and different research designs, the

Table 3 Adjusted hazard ratios and 95% confidence intervals of bladder cancer according to coffee consumption amount stratified by sex and smoking

Study subgroup	Model adjustments	No. cases/total participants	Coffee consumption				*P*-trend
			Never	≤ 180 ml/day	180–500 ml/day	> 500 ml/day	
Male							
Current smoker	Model 1[a]	786/38,526	Ref.	1.18 (0.88–1.59)	1.66 (1.21–2.30)	1.78 (1.30–2.44)	0.001
	Model 2[a, b1]	786/38,526	Ref.	1.09 (0.82–1.46)	1.59 (1.17–2.16)	1.69 (1.25–2.29)	0.001
	Model 3[a, b1, c]	786/38,526	Ref.	1.24 (0.92–1.67)	1.69 (1.23–2.34)	1.75 (1.27–2.42)	0.002
Former smoker	Model 1[a]	906/62,009	Ref.	1.12 (0.85–1.46)	2.39 (1.87–3.06)	1.87 (1.46–2.39)	< 0.001
	Model 2[a, b1]	906/62,009	Ref.	1.11 (0.84–1.45)	2.38 (1.86–3.04)	1.86 (1.45–2.38)	< 0.001
	Model 3[a, b1, c]	906/62,009	Ref.	1.08 (0.82–1.42)	1.29 (0.99–1.67)	1.44 (1.12–1.85)	0.001
Never smoker	Model 1[a]	248/54,609	Ref.	0.73 (0.48–1.12)	1.06 (0.73–1.54)	0.90 (0.60–1.34)	0.94
	Model 2[a, b1]	248/54,609	Ref.	0.77 (0.52–1.15)	1.00 (0.68–1.45)	0.85 (0.57–1.28)	0.70
	Model 3[a, b1, c]	248/54,609	Ref.	0.75 (0.49–1.15)	1.05 (0.72–1.55)	0.89 (0.60–1.35)	0.91
Heavy smoker[d]	Model 1[a]	706/17,778	Ref.	1.13 (0.77–1.66)	1.58 (1.04–2.38)	1.71 (1.13–2.58)	0.01
	Model 2[a, b2]	706/17,778	Ref.	1.12 (0.76–1.65)	1.55 (1.03–2.35)	1.73 (1.15–2.62)	0.02
	Model 3[a, b2, c]	706/17,778	Ref.	1.13 (0.77–1.67)	1.60 (1.05–2.43)	1.72 (1.13–2.62)	0.02
Light smoker[d]	Model 1[a]	241/11,774	Ref.	1.26 (0.72–2.21)	1.58 (0.90–2.77)	1.85 (1.05–3.27)	0.03
	Model 2[a, b2]	241/11,774	Ref.	1.28 (0.73–2.23)	1.55 (0.89–2.70)	1.88 (1.07–3.30)	0.02
	Model 3[a, b2, c]	241/11,774	Ref.	1.44 (0.82–2.53)	1.67 (0.94–2.98)	1.93 (1.07–3.47)	0.03
Female							
Current smoker	Model 1[a]	195/61,484	Ref.	0.79 (0.46–1.35)	0.75 (0.45–1.28)	0.95 (0.58–1.57)	0.85
	Model 2[a, b1]	195/61,484	Ref.	0.76 (0.45–1.30)	0.73 (0.43–1.23)	1.03 (0.62–1.69)	0.56
	Model 3[a, b1, c]	195/61,484	Ref.	0.81 (0.47–1.38)	0.76 (0.45–1.29)	0.94 (0.56–1.56)	0.94
Former smoker	Model 1[a]	188/83,317	Ref.	0.55 (0.32–0.93)	0.71 (0.46–1.10)	0.74 (0.47–1.16)	0.50
	Model 2[a, b1]	188/83,317	Ref.	0.57 (0.33–0.97)	0.71 (0.45–1.14)	0.73 (0.45–1.17)	0.51
	Model 3[a, b1, c]	188/83,317	Ref.	0.56 (0.33–0.95)	0.71 (0.46–1.10)	0.74 (0.47–1.16)	0.47
Never smoker	Model 1[a]	278/201,659	Ref.	0.92 (0.62–1.36)	0.95 (0.64–1.41)	0.90 (0.58–1.38)	0.67
	Model 2[a, b1]	278/201,659	Ref.	0.96 (0.66–1.41)	0.98 (0.66–1.44)	0.92 (0.60–1.41)	0.73
	Model 3[a, b1, c]	278/201,659	Ref.	0.95 (0.64–1.40)	0.97 (0.66–1.44)	0.93 (0.60–1.44)	0.79
Heavy smoker[d]	Model 1[a]	116/20,129	Ref.	0.88 (0.42–1.87)	0.93 (0.46–1.88)	0.92 (0.46–1.85)	0.87
	Model 2[a, b2]	116/20,129	Ref.	0.88 (0.42–1.87)	0.93 (0.46–1.88)	0.93 (0.46–1.85)	0.88
	Model 3[a, b2, c]	116/20,129	Ref.	0.89 (0.42–1.90)	0.90 (0.44–1.83)	0.86 (0.42–1.76)	0.68
Light smoker[d]	Model 1[a]	89/35,309	Ref.	0.60 (0.27–1.33)	0.51 (0.24–1.09)	0.80 (0.38–1.71)	0.91
	Model 2[a, b2]	89/35,309	Ref.	0.59 (0.27–1.31)	0.50 (0.23–1.08)	0.75 (0.35–1.62)	0.81
	Model 3[a, b2, c]	89/35,309	Ref.	0.60 (0.27–1.33)	0.48 (0.22–1.04)	0.73 (0.33–1.59)	0.73

Reference group was never coffee consumers

P-trend < 0.05 were considered statistically significant

ml = millilitre; kcal = kilocalorie; g = gram

[a]Model 1: Adjusted for age (years, continuous)

[a, b1]Model 2: Additionally, adjusted for smoking pack-years if applicable; [a, b2]Model 2: Additionally, adjusted for smoking status if applicable (smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e. smoking less than 20 pack-years)]; 2 [current heavy smokers (i.e. smoking more than 20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e. smokers who ceased smoking over 1 year prior and smoked less than 20 pack-years)]; 5 [former heavy smokers (i.e. smokers who ceased smoking over 1 year prior and smoked more than 20 pack-years)]; 6 [former smokers (smokers who ceased smoking over 1 year prior and no information on pack-years)])

[a, b1/b2, c]Model 3: Additionally, adjusted for total energy intake (kcal/day, continuous), tea consumption (ml/day, continuous), other caffeine intake (g/day, continuous), and sweeteners intake (g/day, continuous)

[d]Heavy Smoker: Pack-years > 20; Light Smoker: Pack-years ≤ 20; and both heavy and light smokers included current and former smokers

explanation for these contradictive results remain unclear. It underscores, however, the importance of assessing associations between coffee consumption and BC by smoking. Therefore, future experimental and large pooled observational study should further explore clear interaction between coffee consumption and smoking in relation to BC risk, in

Table 4 Hazard ratios and 95% confidence intervals of caffeinated and decaffeinated coffee consumption with bladder cancer risk based on model 3

Study subgroup	No. cases/total participants	Coffee consumption					*P*-trend
		Never	Ever	≤ 180 ml/day	180–500 ml/day	> 500 ml/day	
Caffeinated coffee							
Overall population	968/292,058	Ref.	1.07 (0.92–1.23)	1.05 (0.88–1.25)	1.05 (0.88–1.25)	1.12 (1.01–1.23)	0.46
Ever smokers[a]	747/141,387	Ref.	1.15 (0.95–1.40)	1.10 (0.87–1.40)	1.17 (0.93–1.47)	1.22 (1.06–1.42)	0.10
Never smokers	221/150,671	Ref.	0.78 (0.57–1.07)	0.89 (0.60–1.32)	0.69 (0.46–1.03)	0.79 (0.48–1.29)	0.13
Decaffeinated coffee							
Overall population	389/127,400	Ref.	1.16 (0.87–1.55)	1.05 (0.75–1.47)	1.50 (0.90–2.50)	1.15 (0.49–2.73)	0.33
Ever smokers[a]	280/51,619	Ref.	1.30 (0.93–1.81)	1.17 (0.80–1.71)	1.43 (0.55–2.73)	1.78 (0.62–3.25)	0.08
Never smokers	109/75,781	Ref.	0.90 (0.49–1.66)	0.81 (0.39–1.67)	0.87 (0.12–1.50)	1.13 (0.45–2.90)	0.07

Model 3: Adjusted for age (years, continuous), sex (male or female), smoking (if applicable, smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e. smoking less than 20 pack-years)]; 2 [current heavy smokers (i.e. smoking more than 20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e. smokers who ceased smoking over 1 year prior and smoked less than 20 pack-years)]; 5 [former heavy smokers (i.e. smokers who ceased smoking over 1 year prior and smoked more than 20 pack-years)]; 6 [former smokers (smokers who ceased smoking over 1 year prior and no information on pack-years)]), total energy intake (kcal/day, continuous), tea consumption (ml/day, continuous), other caffeine intake (g/day, continuous), and sweeteners intake (g/day, continuous)

Reference group was never coffee consumers

P-trend < 0.05 were considered statistically significant

ml = millilitre; kcal = kilocalorie; g = gram

[a]Ever smokers included both current/former smokers and heavy/light smokers

order to provide definite answers on the influence of coffee consumption and BC risk. In addition, since BC is strongly smoking-related, residual confounding by smoking is a particular concern, and statistical adjustment for smoking might only partly separate the risk of BC due to smoking from a possible risk due to coffee consumption.

The present study and several previously conducted observational studies [25, 28, 69] did not observe an association between coffee consumption and BC among females. One possible explanation is that females are less likely to develop BC since the metabolic detoxification of carcinogens (e.g. from tobacco or coffee) is stronger in females than in males [70]. However, no mechanism for the influence of coffee consumption on BC risk in different sexes has been reported.

The mechanisms underlying the associations between coffee consumption and BC are likely mediated by any of the thousands of specific coffee chemicals present in the beans or produced during roasting [71]. However, in most epidemiological studies, assessment of coffee types is generally limited. Although caffeine showed to suppress the activation of the protein kinase ataxia-telangiectasia mutated (ATM) and the phosphorylation of the kinase Chk2, both important for the activation of the tumour suppressor gene P53 [72, 73], subsequent research studies have not confirmed this point. Recent studies based on observations and experiments have shown that coffee may play a role in antioxidant activity [74, 75] or enhance the anti-tumour immune response [76]. The present study, as well as our study based on data from case–control studies [67], observed increased effects on BC risk among caffeinated coffee consumers; again, the positive association observed in the present study was restricted to smokers. Notably, however, due to the limited available data on decaffeinated coffee consumption, no detailed analysis could be conducted on this coffee type. Therefore, no definitive conclusion can be made whether it is the caffeine in coffee that increases the BC risk.

Our dose–response analyses present slightly increasing curves in the overall population and among smokers and males up to 8 cups/day (1000 ml/day). After 8 cups/day a decrease in BC risk is observed. Although this observation was probably due to the scarcity of the sample size, it might be caused by the diuretic action of the bladder caused by a large dose of caffeine. A recent review suggests that coffee consumption of over at least 250–300 micrograms (mg), i.e. 2–3 cups of coffee with 200 ml cup size, have an obvious diuretic action. This profound tolerance to the diuretic effect of caffeine, however, is much diminished in individuals who regularly consume coffee, which might enhance the threshold of sensation of diuretic action to 8 cups [77]. Therefore, the contact time between coffee chemicals and bladder is shortened among those with a higher coffee consumption, thereby, decrease the penetration of coffee consumption into deep layer of bladder.

It is known that cancer might cause behaviour changes prior to diagnosis. It could, therefore, be argued that results obtained from cohort studies overestimate the true effect of coffee consumption on BC risk if a large proportion of cases

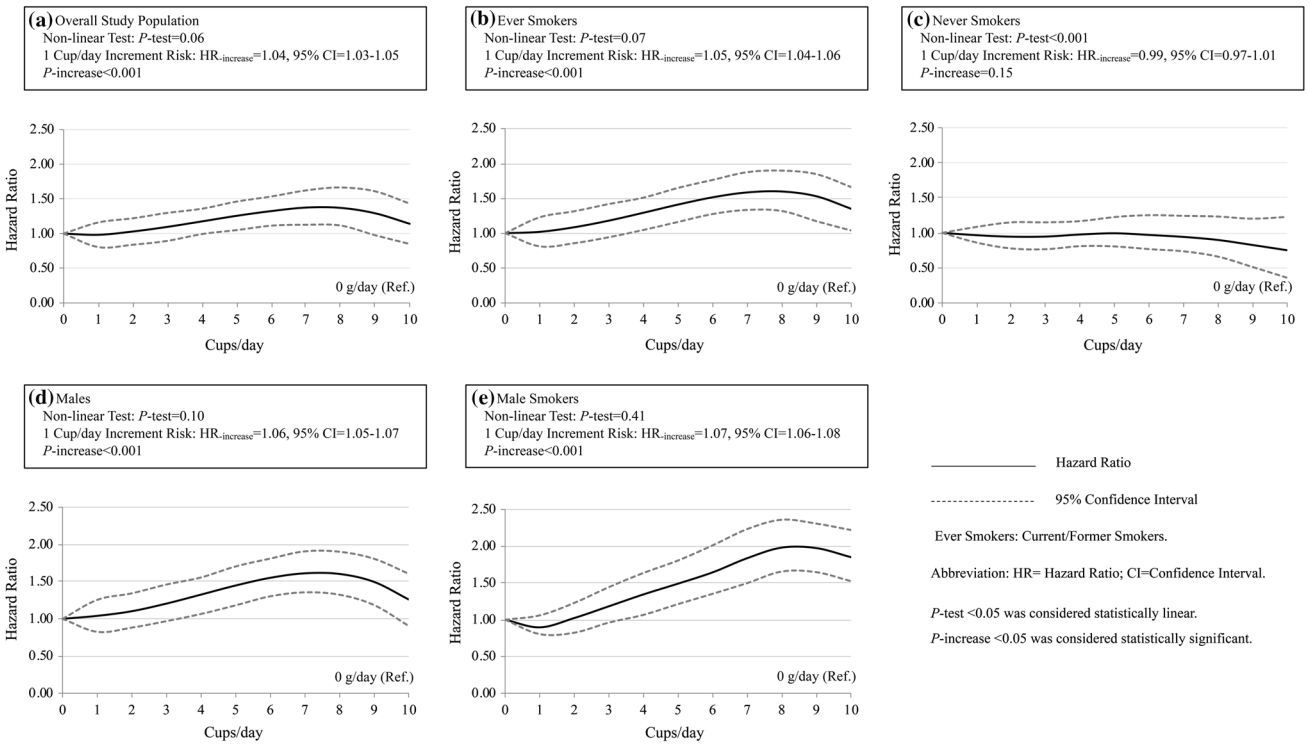

Fig. 1 Dose–response relationships between coffee consumption and the risk of bladder cancer among, **a** overall study population; **b** ever smokers; **c** never smokers; **d** males; **e** male smokers. The solid lines represent the hazard ratios (HRs); the dashed lines represent the 95% confidence intervals (CIs) for the trend; the 1 cup represents 125 ml. The HRs were adjusted for age (years, continuous), sex (male or female, if applicable), smoking (if applicable, smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e. smoking less than 20 pack-years)]; 2 [current heavy smokers (i.e. smoking more than 20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e. smokers who ceased smoking over 1 year prior and smoked less than 20 pack-years)]; 5 [former heavy smokers (i.e. smokers who ceased smoking over 1 year prior and smoked more than 20 pack-years)]; 6 [former smokers (smokers who ceased smoking over 1 year prior, and no information on pack-years)]), total energy intake (kcal/day, continuous), tea consumption (ml/day, continuous), other caffeine intake (g/day, continuous), and sweeteners intake (g/day, continuous) (model 3). Abbreviation: ml = millilitre; kcal = kilocalorie; g = gram. Reference group was never coffee consumers

are diagnosed within the first 2 years after recruitment. However, after exclusion of cases who were diagnosed within the first 2 years after recruitment, results remain similar.

For the present study, data was collected from 12 cohort studies, thereby yielding a large sample size, allowing to perform detailed and accurate analyses. However, the present study also has some limitations: (a) limited information was available on possible risk factors, other than age, sex and smoking, for the development of BC, such as body mass index (BMI), physical activity, socioeconomic status (SES), disinfection by-products, arsenic in the drinking water, and occupational exposures to potentially carcinogenic chemicals. Although, adjustments for these factors could have influenced the results, current literature shows that only a small proportion of BC cases can be attributed to these factors [72]; (b) all events other than BC were analysed as censored. This was done because of lack of specific information (e.g. death) on loss-to-follow-up subject. We were therefore, unable to perform competing risk analyses in addition to the survival analyses; (c) although status as well as duration and intensity of smoking were taken into account in our analysis, the adjustment for smoking might still be imperfect due to differences in smoking practices (e.g. depth of inhalation or amount of inhalation), or differences in types of smoke exposure [67]. In addition, since smoking is perceived as a socially undesirable behaviour, the use of self-reported questionnaires for smoking status, duration, and intensity might have led to underreporting of the actual smoking habits; (d) some additives accompanied with coffee consuming could not be adjusted for, such as non-dairy creamer which has been found to alter the biochemical activities of coffee by interacting with coffee components like polyphenol [78]; (e) for most included studies, the exposure variable was assessed by FFQs. Therefore, measurement error and misclassification of study participants in terms of the exposure are unavoidable.

Conclusion

In summary, the present study, with over 500,000 participants and 2600 BC cases, observed an increased risk between high (> 500 ml/day: around > 4 cups/day based on European standard cup size) coffee consumption and BC among male smokers, while no association between coffee consumption and BC risk was observed among females and never smokers. The inconsistent results between males and females and the absence of an association in never smokers indicate that no strong evidence for causal links between coffee consumption and the development of BC, and the positive associations among male smokers is possibly caused by residual confounding of smoking.

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Compliance with ethical standards

Conflict of interest All the authors declare no conflict of interest.

Ethics approval and consent to participate Each participating study has been approved by the local ethic committee. Informed consent was obtained from all individual participants included in each study.

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