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Original article

Tea consumption and risk of bladder cancer in the Bladder Cancer Epidemiology and Nutritional Determinants (BLEND) Study: Pooled analysis of 12 international cohort studies

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SUMMARY

Background & aims: Tea has been shown to be associated with reduced risk of several diseases including cardiovascular diseases, stroke, metabolic syndrome, and obesity. However, the results on the relationship between tea consumption and bladder cancer are conflicting. This research aimed to assess the association between tea consumption and risk of bladder cancer using a pooled analysis of prospective cohort data.

Methods: Individual data from 532,949 participants in 12 cohort studies, were pooled for analyses. Cox regression models stratified by study centre was used to estimate hazard ratios (HR) and corresponding 95% CIs. Fractional polynomial regression models were used to examine the dose–response relationship.

Results: A higher level of tea consumption was associated with lower risk of bladder cancer incidence (compared with no tea consumption: HR = 0.87, 95% C.I. = 0.77–0.98 for low consumption; HR = 0.86, 95% C.I. = 0.77–0.96 for moderate consumption; HR = 0.84, 95% C.I. = 0.75–0.95 for high consumption). When stratified by sex and smoking status, this reduced risk was statistically significant among men and current and former smokers. In addition, dose–response analyses showed a lower bladder cancer risk with increment of 100 ml of tea consumption per day (HR-increment = 0.97; 95% CI = 0.96–0.98). A similar inverse association was found among males, current and former smokers while never smokers and females showed non-significant results, suggesting potential sex-dependent effect.

Conclusions: Higher consumption of tea is associated with reduced risk of bladder cancer with potential interaction with sex and smoking status. Further studies are needed to clarify the mechanisms for a

Abbreviations: BLEND, BLadder cancer Epidemiology and Nutritional Determinants study; EGCG, epigallocatechin-3-gallate; EPIC, Cancer and Nutrition cohort study; HR, hazard ratio; MIBC, muscle-invasive bladder cancer; NLCS, NetherLands Cohort Study on diet and cancer; NMIBC, non-muscle invasive bladder cancer; RERF, Radiation Effects Research Foundation; VITAL, VITamins And Lifestyle cohort study; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

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protective effect of tea (e.g. inhibition of the survival and proliferation of cancer cells and anti-inflammatory mechanisms) and its interaction with smoking and sex.

1. Introduction

Bladder cancer is a common cancer worldwide accounting for an estimated 550,000 new cases and 200,000 deaths each year [1]. The disease has a wide variation between geographical regions and is more common in men where the lifetime risk of bladder cancer is 1.1% compared to 0.27% among women [1]. The highest incidence rate of bladder cancer is observed in Europe and North America (age-standardized incidence rate per 100,000 [ASR] is around 20 and 4.6 for males and females, respectively) in addition to some other countries like Egypt (ASR 22.5 and 5.2 for males and females, respectively) and Turkey (ASR 22.9 and 3.1 for males and females, respectively) [2]. In contrast, geographical regions like South-East and Central Asia, Latin America and Africa have much lower rates (ASR ranges from 3.2 to 7.2 for males and 0.73 to 2.3 for females) [2]. In addition to the differences in the access to care and diagnostic facilities, the large worldwide variation in the incidence of bladder cancer is mainly due to differences in population exposure to the disease risk factors. Various risk factors are associated with the risk of bladder cancer including genetic and environmental exposures (estimated to explain 7% and 81% of bladder cancer cases, respectively) [3] with tobacco smoking being by far the most important risk factor [4]. Other important risk factors identified in the Continuous Update Project (CUP) of the World Cancer Research Fund (WCRF) include older age, male sex, exposure to benzene and aromatic amines, arsenic in drinking water, and chronic infections such as schistosomiasis [5,6]. Consumption of fruits and vegetables may reduce the risk according to pooled analyses [6–8]. Gene-environment interaction also plays a role in the risk of bladder cancer [9]. Therefore, for the prevention of bladder cancer, it is of paramount importance to identify modifiable risk factors especially those factors with high prevalence of exposure among populations.

Tea (*Camellia sinensis*) is one of the most widely consumed beverages worldwide. Several studies showed that tea consumption was associated with reduced risk of cardiovascular disease events and mortality [10], stroke, metabolic syndrome [11], and obesity [12]. An umbrella review by Kim et al. [13] concluded there is convincing evidence that tea consumption is associated with reduced risk of oral cancer. Various substances in the tea were hypothesized to be responsible for its healthy effects [14]. The most suggested component is polyphenols such as catechins [15] which are at least partially responsible for the anti-inflammatory and antioxidant activities that tea exhibits. These characteristics may also be responsible for an anticancer effects of tea [15].

Numerous studies have been conducted to assess the relationship between tea consumption and bladder cancer [16–18]. However, the results of epidemiological studies are conflicting, and no definite conclusion could be established. For example, an analysis of prospective cohort data in Finland found a marginally statistically significant inverse association between tea and bladder cancer [16], while another cohort study in the United States found no association [18]. In their 2018 report, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that there is limited evidence that tea reduces bladder cancer, and more research is needed [19].

Therefore, the current study aims to investigate the association between tea consumption and bladder cancer using a pooled analysis of cohort studies. Secondary aims include stratified analysis by sex and smoking status, stratified analysis according to bladder cancer stage groups, and dose–response analysis.

2. Methods

2.1. Study population

The BLadder cancer Epidemiology and Nutritional Determinants study (BLEND) is an international consortium formed to investigate the effect of dietary factors on the risk of bladder cancer development by pooling and standardizing data from world-wide epidemiological studies [20]. In the present study, cohort studies from BLEND were included if they provided data on tea consumption and covariates of interest. Out of the 15 cohort studies in BLEND, 12 studies satisfied the inclusion criteria; the 12 included studies were conducted in Denmark [21], France [22], Germany [23], Italy [24], Spain [25], Sweden [25], the Netherlands [26,27], the United Kingdom [28,29], the United States [30], and Japan [31]. These studies represent the European Prospective Investigation into Cancer and Nutrition cohort study (EPIC) [25], the NetherLands Cohort Study on diet and cancer (NLCS) [27], the VITamins And Lifestyle cohort study (VITAL) [30], and the Radiation Effects Research Foundation (RERF) atomic bomb survivors Study [31]. Studies have been approved by their corresponding local research ethic committees.

2.2. Data collection and assessment

The methodology of the BLEND consortium has been described in detail elsewhere [20]. Briefly, the BLEND data involved study characteristics (geographical location, design, assessment method and subject status), participant characteristics (age, sex, and ethnicity), disease characteristics (stage and metastasis), smoking status including duration and intensity (duration of smoking and number of cigarettes), and dietary measurements. Dietary intake was assessed in each of the included studies using a validated food frequency questionnaire. Subsequently when included in BLEND, the consumption of dietary items was then standardised across studies by using the Eurocode 2 food coding system [32]. In the present study, tea consumption was defined as consuming drinks based on tea tree leaves and thus excluding herbal tea and other infusions. Ten studies reported tea consumption in millilitres while 2 studies reported consumption in cups. Tea consumption data were harmonized by converting reported cups consumption into millilitres using the appropriate cup size in each setting (1 cup = 237 ml in the United States and 1 cup = 150 ml in other countries) and the daily tea consumption in millilitres was computed for every participant.

Incident first bladder cancers in each study were ascertained based on the International Classification of Diseases (code C67) using population-based cancer registries, health insurance records, or medical records. The term bladder cancer is used for all urinary bladder neoplasms.

2.3. Statistical analyses

Baseline characteristics of cases and non-cases were compared between different levels of tea consumption using t-test for continuous variables and chi-square for categorical variables. Cox proportional hazard regression analysis, stratified by study centre, was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% C.I.) for the association between tea consumption and bladder cancer risk. Proportional hazard assumption was tested based on Schoenfeld residuals after fitting cox model [33]. We tested linearity by including linear and quadratic terms in the models followed by a likelihood ratio test. The daily tea consumption was divided based on tertile in the pooled data (i.e., across all studies) into four categories: never consumption group, low consumption group (tertile 1), medium consumption group (tertile 2), and high consumption group (tertile 3). Never consumption group was used as the reference group. Cox regression models was employed as model A (crude model); Model B adjusted for age at recruitment (continuous), sex, smoking and energy intake (kcal/d; continuous); and model C adjusted for age at recruitment (continuous), sex, ethnicity, smoking, energy intake, fruit (g/d; continuous), vegetables (g/d; continuous), coffee (mL/d; continuous), juice (mL/d; continuous), and alcohol (mL/d; continuous). Smoking was defined as follows: never smokers; current light smokers (i.e., smoking <20 pack-years); current heavy smokers (i.e., smoking >20 pack-years); former light smokers; former heavy smokers; current smokers (no information on pack-years); and former smokers (no information on pack-years). The Wald-test was used to test for the presence of interaction between tea consumption and sex and smoking, and p-interaction < 0.05 was considered statistically significant. Based on the knowledge that some risk factors may have different effect on different bladder cancer stage groups [34,35] (i.e., non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC)), additional subgroup analyses were performed on bladder cancer stage groups. Multiple imputation procedures using data augmentation algorithm, were utilized to accommodate variables with missing values. The convergence of imputation models was assessed visually using trace plots. Only subjects with complete data on the outcome, sex, age, smoking status, and tea intake were included in the analysis. The overall proportion of missing data was 0.03% for vegetables intake, 1.23% for juice and energy intake, and 4.76% for fruits intake.

In a secondary analysis, we analysed the dose–response relationship between hazard ratios of bladder cancer and tea consumption for every 100 ml increment (up to 1000 ml) using fractional polynomial regression. Based on the results of the main analysis, results for dose–response analyses were presented with stratification by sex and smoking status (current smokers, former smokers, and never smokers). P-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using Stata version 14 (Stata Corporation, Texas, USA).

We also conducted sensitivity analyses: a) we excluded cases of bladder cancer diagnosed within the first two years of follow-up; b) we separately assessed the association between tea and bladder cancer in each participating cohort and then combined estimates in a meta-analysis using a random-effect model.

3. Results

3.1. Baseline characteristics

Our study population included pooled data from 12 cohorts with 532,949 participants and a total of 5,751,888 person years. During the follow up period (median 11.44 years), 2915 incident bladder cancer cases (1094 NMIBC and 656 MIBC) were detected. Among participants, 67.8% were females, 91.8% Caucasian, and the mean age was 52.5 years with a range of 19.3–98.5 years. The baseline characteristics of the study participants are presented in Table 1. Around one third of all subjects were never tea drinkers. Interestingly, 40.8% of the current smokers were never tea drinkers compared to former and never smokers (30.9% and 29.7% respectively).

3.2. Association between tea consumption and bladder cancer risk

A higher level of tea consumption was associated with lower risk of bladder cancer (Table 2). Compared with no tea consumption, all levels of tea consumption had statistically significant inverse association with bladder cancer (Model C: HR = 0.87, 95% C.I. = 0.77–0.98 for low consumption; HR = 0.86, 95% C.I. = 0.77–0.96 for moderate consumption; HR = 0.84, 95% C.I. = 0.75–0.95 for high consumption). A significant interaction was observed between tea consumption and smoking (p-interaction = 0.006). No other interaction terms showed to be relevant. When stratifying by sex, a similar inverse association for tea consumption was noted among males (Model C: HR = 0.84, 95% C.I. = 0.73–0.96 for low consumption; HR = 0.85, 95% C.I. = 0.75–0.96 for moderate consumption; HR = 0.86, 95% C.I. = 0.75–0.98 for high consumption), while the inverse association in the crude model among females became statistically non-significant in the fully adjusted model (Model C: HR = 0.96, 95% C.I. = 0.76–1.22 for low consumption; HR = 0.88, 95% C.I. = 0.70–1.11 for moderate consumption; HR = 0.79, 95% C.I. = 0.61–1.02 for high consumption). Interestingly, there was a statistically significant reduced bladder cancer risk with all levels of tea consumption among current (Model C: HR = 0.81, 95% C.I. = 0.67–0.98 for low consumption; HR = 0.82, 95% C.I. = 0.70–0.97 for moderate consumption; HR = 0.79, 95% C.I. = 0.65–0.96 for high consumption) and former smokers (Model C: HR = 0.83, 95% C.I. = 0.68–1.00 for low consumption; HR = 0.78, 95% C.I. = 0.66–0.93 for moderate consumption; HR = 0.81, 95% C.I. = 0.67–0.98 for high consumption) but not among never-smokers.

Stratified results for bladder cancer stage groups (i.e., NMIBC and MIBC) showed the high tea consumption was associated with a reduced overall MIBC risk, although it was not statistically significant in the fully adjusted model (HR = 0.80, 95% C.I. = 0.63–1.03). Similar results for MIBC risk were shown for males (HR = 0.81, 95% C.I. = 0.62–1.06), and former smokers (HR = 0.71, 95% C.I. = 0.48–1.05) in the fully adjusted model (Model C). Although the estimates of HRs showed the same pattern in patients with NMIBC, the associations were not statistically significant (Table 3).

3.3. Dose–response analysis

Results of our dose–response analyses are shown in Fig. 1. Overall, an increment of 100 ml of tea consumption per day was associated with a lower bladder cancer risk ($HR_{\text{-increment}}$ = 0.97; 95% CI = 0.96–0.98). A similar inverse association was found among males ($HR_{\text{-increment}}$ = 0.97; 95% CI = 0.95–0.98), and current- and former smokers ($HR_{\text{-increment}}$ = 0.96; 95% CI = 0.94–0.98; $HR_{\text{-increment}}$ = 0.95; 95% CI = 0.94–0.97, respectively), while females ($HR_{\text{-increment}}$ = 0.97; 95% CI = 0.95–1.00) and never smokers showed non-significant results ($HR_{\text{-increment}}$ = 1.00; 95% CI = 0.98–1.03).

In sensitivity analyses, similar estimates and trends were observed after excluding cases of bladder cancer diagnosed within the first two years of follow-up (Supplementary Table S1). A few categories such as low consumption category in the overall cohort becomes marginally statistically non-significant. Furthermore, the

Table 1
Baseline characteristics of individuals included in the pooled analysis by categories of tea consumption.[a]

Characteristics	Tertiles of tea consumption								Overall		p-value	p-value for interaction
	No consumption		Low		Medium		High					
	No.	%	No.	%	No.	%	No.	%	No.	%		
Total	172677	32.4	121687	22.83	118510	22.24	120075	22.53	532949	100		
Non-case	171790	32.41	121216	22.87	117643	22.2	119385	22.52	530034	100	<0.001	
Case	887	30.43	471	16.16	867	29.74	690	23.67	2915	100		
Sex												0.235
Male												
Non-case	52029	30.68	45162	26.63	37746	22.26	34649	20.43	169586	100	<0.001	
Case	696	31.8	331	15.12	655	29.92	507	23.16	2189	100		
Total	52725	30.69	45493	26.48	38401	22.36	35156	20.47	171775	100		
Female												
Non-case	119761	33.23	76054	21.1	79897	22.17	84736	23.51	360448	100	<0.001	
Case	191	26.31	140	19.28	212	29.2	183	25.21	726	100		
Total	119952	33.21	76194	21.1	80109	22.18	84919	23.51	361174	100		
Smoking status												0.006
Current smokers												
Non-case	45584	40.86	26710	23.94	21747	19.49	17516	15.7	111557	100	<0.001	
Case	429	37.11	184	15.92	332	28.72	211	18.25	1156	100		
Total	46013	40.82	26894	23.86	22079	19.59	17727	15.73	112713	100		
Former smokers												
Non-case	48583	30.93	35144	22.37	34518	21.97	38845	24.73	157090	100	<0.001	
Case	345	28.73	177	14.74	354	29.48	325	27.06	1201	100		
Total	48928	30.91	35321	22.31	34872	22.03	39170	24.75	158291	100		
Never smokers												
Non-case	77623	29.7	59362	22.71	61378	23.48	63024	24.11	261387	100	<0.001	
Case	113	20.25	110	19.71	181	32.44	154	27.6	558	100		
Total	77736	29.68	59472	22.7	61559	23.5	63178	24.12	261945	100		
Ethnicity												0.816
Caucasian												
Non-case	170574	32.83	117983	22.71	112118	21.58	118819	22.87	519494	100	<0.001	
Case	881	30.81	448	15.67	841	29.42	689	24.1	2859	100		
Total	171455	32.82	118431	22.67	112959	21.63	119508	22.88	522353	100		
Non-Caucasian												
Non-case	1114	10.86	3156	30.75	5451	53.12	541	5.27	10262	100	0.214	
Case	4	7.41	23	42.59	26	48.15	1	1.85	54	100		
Total	1118	10.84	3179	30.82	5477	53.09	542	5.25	10316	100		
Age years (Mean [SD])												0.347
Non-case	52.79	8.44	51.48	10.56	52.69	10.55	52.7	11.53	52.45	10.17	<0.001	
Case	59.72	7.54	58.7	8.21	60.81	6.8	62.22	7.24	60.47	7.47		
Total	52.83	8.45	51.51	10.56	52.75	10.55	52.75	11.53	52.49	10.18		
Fruit g/day (Mean [SD])												
Non-case	114.99	115.83	113.08	114.35	110.24	99.21	115.11	100.88	113.5	108.6	0.448	
Case	105.09	107.67	85.18	92.1	126.73	110.43	120.19	102.58	111.96	105.89		
Total	114.93	115.79	112.97	114.29	110.36	99.3	115.14	100.89	113.49	108.58		
Vegetables g/day (Mean [SD])												
Non-case	178.57	126.71	164.95	125.68	165.63	119.61	223.77	140.83	182.77	130.31	<0.001	
Case	180.72	150.88	127.61	95.80	221.88	135.40	243.34	128.37	199.21	138.90		
Total	178.58	126.85	164.81	125.60	166.04	119.82	223.88	140.77	182.86	130.36		
Alcohol g/day (Mean [SD])												
Non-case	9.99	17.15	10.36	15.48	8.83	13.55	9.26	13.73	9.66	15.29	<0.001	
Case	15.47	21.07	13.4	18.89	12.83	17.62	10.97	15.17	13.29	18.49		
Total	10.02	17.17	10.38	15.5	8.86	13.59	9.27	13.74	9.68	15.31		

[a] The categories of tea consumption were based on tertiles; P-value was calculated using t-test for quantitative variables (cases vs non-cases) and Chi square test for categorical variables; p-value for interaction is from Wald test.

meta-analysis provided similar inverse association between tea consumption and bladder cancer ($HR_{\text{model c; high consumption}} = 0.83$, 95% CI = 0.73–0.95; $I^2 = 0.0\%$). In the meta-analysis, two studies had statistically significant estimates (RERF and NLCS studies) while EPIC-Sweden had marginally significant results (($HR_{\text{model c; high consumption}} = 0.63$, 95% CI = 0.40–0.998). All studies except three had reduced risk estimates (Supplementary Fig. 1).

4. Discussion

The present pooled analysis of 12 cohort studies showed a statistically significant reduced bladder cancer risk associated with tea consumption in the overall population. A similar inverse association was shown for males and current- and former smokers, while no evidence of association was observed for females and never smokers.

While our findings of a reduced bladder cancer risk with higher tea consumption are in line with some previous case–control [36] and cohort [17] studies (the cohort study included in the current pooled analysis), some meta-analyses failed to show a significant association between tea consumption and bladder cancer [13]. A recent meta-analysis by Zhao et al. [37] included five cohort studies and found a statistically significant 5% reduction in bladder cancer risk for each 1 cup increment of tea consumption, while no significant reduced risk could be observed by comparing the highest vs lowest tea consumption. One possible explanation for this observed null finding is the high variation in defining the categories of tea consumption between the included primary studies. For

Table 2
Pooled hazard ratios and 95% confidence intervals for the association between bladder cancer and tea consumption by sex and smoking status.

		Cases/Total	Tertiles of tea consumption[a]				P-value for trend
			Never	Low	Medium	High	
Overall	Model A	2915/532949	Ref	**0.72 (0.64–0.81)**	**0.65 (0.59–0.72)**	**0.57 (0.51–0.64)**	
	Model B		Ref	**0.86 (0.76–0.97)**	**0.85 (0.76–0.94)**	**0.82 (0.73–0.93)**	
	Model C		Ref	**0.87 (0.77–0.98)**	**0.86 (0.77–0.96)**	**0.84 (0.75–0.95)**	0.004
Males	Model A	2189/171775	Ref	**0.75 (0.65–0.86)**	**0.74 (0.65–0.83)**	**0.71 (0.62–0.81)**	
	Model B		Ref	**0.83 (0.72–0.95)**	**0.84 (0.74–0.94)**	**0.84 (0.73–0.96)**	
	Model C		Ref	**0.84 (0.73–0.96)**	**0.85 (0.75–0.96)**	**0.86 (0.75–0.98)**	0.026
Females	Model A	726/361174	Ref	0.89 (0.70–1.13)	**0.77 (0.61–0.96)**	**0.66 (0.51–0.84)**	
	Model B		Ref	0.97 (0.76–1.22)	0.89 (0.71–1.11)	0.80 (0.62–1.02)	
	Model C		Ref	0.96 (0.76–1.22)	0.88 (0.70–1.11)	0.79 (0.61–1.02)	0.056
Current Smokers	Model A	1156/112713	Ref	**0.76 (0.63–0.91)**	**0.73 (0.63–0.86)**	**0.68 (0.56–0.81)**	
	Model B		Ref	**0.80 (0.66–0.96)**	**0.80 (0.68–0.94)**	**0.76 (0.63–0.92)**	
	Model C		Ref	**0.81 (0.67–0.98)**	**0.82 (0.70–0.97)**	**0.79 (0.65–0.96)**	0.011
Former Smokers	Model A	1201/158291	Ref	**0.75 (0.62–0.90)**	**0.68 (0.57–0.80)**	**0.67 (0.56–0.81)**	
	Model B		Ref	**0.81 (0.67–0.98)**	**0.76 (0.64–0.90)**	**0.78 (0.65–0.93)**	
	Model C		Ref	0.83 (0.68–1.00)	**0.78 (0.66–0.93)**	**0.81 (0.67–0.98)**	0.019
Never Smokers	Model A	558/261945	Ref	1.11 (0.84–1.47)	1.08 (0.83–1.41)	0.88 (0.66–1.18)	
	Model B		Ref	1.15 (0.87–1.52)	1.19 (0.91–1.55)	0.99 (0.74–1.33)	
	Model C		Ref	1.14 (0.86–1.51)	1.17 (0.90–1.52)	0.95 (0.71–1.28)	0.789

[a] Model A: crude model; Model B: adjusted for age at recruitment, sex, smoking and energy intake; Model C: adjusted for age at recruitment, sex, smoking, energy intake, ethnicity, fruit, vegetables, coffee, juice, and alcohol. Bold numbers indicate statistically significant results.

Table 3
Pooled hazard ratios and 95% confidence intervals for the association between stage groups of bladder cancer (NMIBC and MIBC) and tea consumption.

		Cases/Total	Tertiles of tea consumption[a]				P-value for trend
			Never	Low	Medium	High	
MIBC							
Overall	Model A	656/530690	Ref	**0.67 (0.49–0.92)**	**0.64 (0.52–0.78)**	**0.50 (0.40–0.63)**	
	Model B		Ref	0.81 (0.59–1.10)	0.86 (0.69–1.05)	**0.77 (0.60–0.97)**	
	Model C		Ref	0.81 (0.60–1.11)	0.88 (0.71–1.09)	0.80 (0.63–1.02)	0.089
Males	Model A	522/170108	Ref	**0.64 (0.45–0.91)**	**0.72 (0.57–0.90)**	**0.64 (0.49–0.83)**	
	Model B		Ref	0.70 (0.49–1.00)	0.82 (0.65–1.04)	**0.76 (0.58–0.99)**	
	Model C		Ref	0.70 (0.49–1.01)	0.86 (0.68–1.09)	0.81 (0.62–1.06)	0.127
Females	Model A	134/360582	Ref	1.30 (0.66–2.54)	0.91 (0.54–1.54)	0.68 (0.39–1.20)	
	Model B		Ref	1.42 (0.73–2.79)	1.12 (0.66–1.90)	0.93 (0.53–1.65)	
	Model C		Ref	1.38 (0.70–2.70)	1.07 (0.63–1.81)	0.86 (0.48–1.54)	0.481
Current Smokers	Model A	279/111836	Ref	0.67 (0.41–1.09)	**0.71 (0.52–0.95)**	**0.66 (0.47–0.92)**	
	Model B		Ref	0.70 (0.43–1.14)	0.75 (0.56–1.01)	0.72 (0.51–1.01)	
	Model C		Ref	0.70 (0.43–1.15)	0.79 (0.58–1.07)	0.77 (0.54–1.10)	0.120
Former Smokers	Model A	272/157362	Ref	0.73 (0.46–1.16)	**0.66 (0.48–0.92)**	**0.54 (0.37–0.79)**	
	Model B		Ref	0.80 (0.50–1.28)	0.76 (0.54–1.06)	**0.66 (0.45–0.96)**	
	Model C		Ref	0.82 (0.51–1.30)	0.79 (0.56–1.11)	0.71 (0.48–1.05)	0.083
Never Smokers	Model A	105/261492	Ref	1.17 (0.50–2.71)	1.58 (0.83–3.02)	1.17 (0.58–2.36)	
	Model B		Ref	1.26 (0.54–2.90)	1.81 (0.94–3.47)	1.33 (0.65–2.70)	
	Model C		Ref	1.28 (0.55–2.96)	1.81 (0.94–3.48)	1.29 (0.63–2.65)	0.520
NMIBC							
Overall	Model A	1094/531128	Ref	**0.75 (0.62–0.90)**	**0.63 (0.54–0.75)**	**0.54 (0.45–0.66)**	
	Model B		Ref	0.88 (0.73–1.06)	0.85 (0.72–1.00)	0.85 (0.70–1.03)	
	Model C		Ref	0.88 (0.73–1.07)	0.85 (0.72–1.01)	0.86 (0.71–1.05)	0.090
Males	Model A	817/170403	Ref	**0.78 (0.62–0.98)**	**0.78 (0.65–0.95)**	**0.75 (0.61–0.94)**	
	Model B		Ref	0.84 (0.67–1.05)	0.88 (0.73–1.07)	0.91 (0.73–1.14)	
	Model C		Ref	0.84 (0.67–1.06)	0.89 (0.73–1.08)	0.93 (0.74–1.17)	0.434
Females	Model A	277/360725	Ref	0.86 (0.61–1.21)	**0.61 (0.44–0.86)**	**0.54 (0.37–0.79)**	
	Model B		Ref	0.93 (0.66–1.31)	0.72 (0.51–1.02)	0.68 (0.46–1.00)	
	Model C		Ref	0.93 (0.66–1.31)	0.72 (0.51–1.02)	0.67 (0.45–1.00)	0.028
Current Smokers	Model A	422/111979	Ref	0.78 (0.58–1.06)	**0.68 (0.52–0.88)**	**0.63 (0.47–0.86)**	
	Model B		Ref	0.82 (0.60–1.11)	**0.74 (0.57–0.97)**	0.75 (0.55–1.02)	
	Model C		Ref	0.83 (0.61–1.12)	**0.76 (0.58–0.99)**	0.78 (0.57–1.07)	0.057
Former Smokers	Model A	472/157562	Ref	0.81 (0.61–1.09)	**0.67 (0.52–0.87)**	**0.68 (0.51–0.91)**	
	Model B		Ref	0.89 (0.67–1.19)	0.77 (0.59–1.00)	0.82 (0.61–1.10)	
	Model C		Ref	0.90 (0.68–1.20)	0.78 (0.60–1.02)	0.83 (0.62–1.12)	0.151
Never Smokers	Model A	200/261587	Ref	0.99 (0.63–1.54)	1.13 (0.75–1.70)	0.81 (0.50–1.31)	
	Model B		Ref	1.05 (0.67–1.65)	1.31 (0.87–1.97)	0.98 (0.61–1.59)	
	Model C		Ref	1.06 (0.68–1.66)	1.31 (0.87–1.97)	0.97 (0.60–1.58)	0.811

[a] Model A: crude model; Model B: adjusted for age at recruitment, sex, smoking and energy intake; Model C: adjusted for age at recruitment, sex, smoking, energy intake, ethnicity, fruit, vegetables, coffee, juice, and alcohol. Bold numbers indicate statistically significant results.

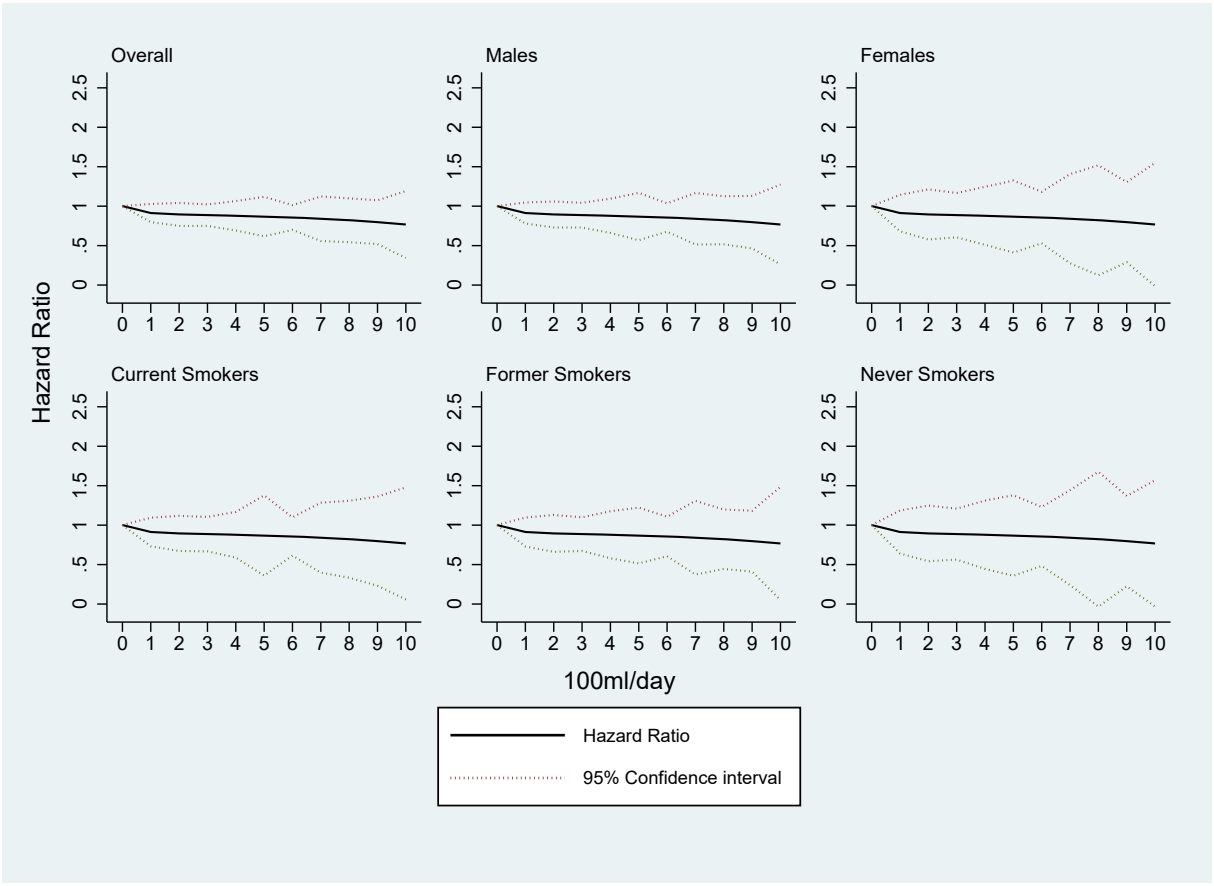

Fig. 1. Dose–response relationships between tea consumption and bladder cancer.

example, some primary studies compared ever vs never intake while other studies considered highest categories ranging from one to 14 cups per day. Another explanation might be that the included studies might have included different tea types (i.e., black- and green tea), and depending on the region, participants may consume tea in different concentrations. In addition, toxic contamination of tea products consumed in various regions in the world may also confound the relationship between tea consumption and bladder cancer. Several studies discussed tea contamination by fluoride [38], arsenic [39], and heavy metals [40] although the effect of such contamination on human health is debatable [39] when tea is consumed in reasonable amounts.

Several bioactive substances have been identified in tea and are believed to contribute in various degrees to its effects on health. These substances include polyphenols (such as catechins and its derivatives, gallic acid, chlorogenic acid, ellagic acid, and other flavonoids), pigments (such as theaflavins, thearubigins, and theabrownins), polysaccharides, alkaloids (such as caffeine, theobromine, and theophylline), free amino acids (such as aspartic acid, glutamic acid, arginine, alanine, tyrosine, and theanine), and saponins [14,41]. Among these compounds, the most important category in the anticancer effects is thought to be the polyphenols [15]. Experimental studies demonstrated that tea and its components contribute to cancer prevention through three main pathways: anti-inflammation properties like inhibiting genetic expression of inflammatory cytokines; inhibition of the growth of carcinogenesis-related pathogens; and inhibition of the survival and proliferation of cancer cells [42–44]. The latter pathway which is involved in cancer initiation, growth and metastasis is believed to be mediated through three mechanisms. First, it was shown that tea components such as epigallocatechin-3-gallate (EGCG) can inhibit cell proliferation specifically in cancer cells by inhibiting various pathways [15]. Second, EGCG and theaflavin suppress angiogenesis in cancer tissues by reducing the vascular endothelial growth factor A in addition to other mechanisms [15]. Third, in vitro and in vivo studies showed that tea components including EGCG and theaflavin can induce apoptosis in cancer cells via inhibitory effect on various enzymes and receptors [15].

The bioactive compounds in tea are available in different concentrations in different tea types and products and may have different biological effects. For example, the extensively studied compound Epigallocatechin gallate (EGCG) is the main component of green tea polyphenols which was demonstrated to have anticancer effects through various pathways [45]. In contrast, black tea has a lower concentration of EGCG and other flavonoids due to fermentation process which partially converts these flavonoids to other substances such as theaflavins and thearubigins [46].

Our analysis showed an interaction between tea consumption and smoking. All levels of tea consumption were significantly associated with a reduced bladder cancer risk among current and former smokers, while never smokers showed a null association. A cohort study in Japan [47] showed a similar interaction pattern where current smokers consuming 3–4 cups of green tea per day had a reduced bladder cancer risk (HR = 0.44; 95% CI = 0.24–0.80), while never and ever smokers showed no such association. These results suggest that tea consumption in itself might modulate the carcinogenic effect of tobacco smoking, without considering the associated dilution of the tobacco carcinogens in the urine related

to tea intake, as total fluid intake is not associated with bladder cancer risk [48]. In fact, the protective effect of tea and its components against the toxic effects of smoking was previously demonstrated in cellular, animal, and human studies [49]. The tea catechins were demonstrated by in vivo studies to have antioxidant activity that is only observed when there is an oxidative stress [50]. In an animal study [51], tumorigenesis was induced in animal models using tobacco derived carcinogen. One group was administered black tea in drinking water and was demonstrated to be protected against tumorigenesis. Another animal study showed similar protection by green tea and EGCG against tumorigenesis and reduction in markers for oxidative DNA damage induced by tobacco carcinogen [52]. In a human study, smokers who were administered green tea extract for four weeks demonstrated reduction in DNA damage among smokers with no significant change in non-smokers [53]. These studies and several others [54–57] indicated that tea biological activities such as reducing inflammation, counteracting oxidation, changing gut microbiota, and inhibiting carcinogenesis at genetic and cellular levels may interfere with the cancer processes induced by tobacco smoking resulting in the observed protective effect.

The present study also showed an inverse association between tea consumption and bladder cancer in men but not women. This sex-differential protective effect has been observed in studies of other cancers. Seow et al. observed an inverse association between black tea consumption and lung cancer among men (HR = 0.67; 95% CI = 0.47–0.95) but not women [58]. Other cancers also showed sex-related associations although in different directions [59]. It was proposed that higher oxidative stress among men compared to women make them benefit more from the antioxidant effect of tea [58,60]. Moreover, previous studies found that male cells are more sensitive to oxidative stress leading to faster shortening of telomere length (which is related to various diseases including cancers) compared to women [61]. Therefore, men may benefit more from nutritional antioxidants to ameliorate the detrimental effect of antioxidants on telomeres. Lastly, residual confounding by unmeasured confounders is still an alternative explanation. More research is needed to explain this sex-related effect.

The present study has many strengths. The analyses included a large sample size which allowed for more precise estimates and thorough analyses including stratification by sex and smoking status. Moreover, the study pooled results from cohorts based in various regions and populations in the world which enhances the generalizability of results. The prospective design ensured that tea consumption was assessed before the diagnosis of bladder cancer which prevents recall bias and confirms temporal relationship. In addition, being a pooled analysis of individual data allowed for adjustment of various potential confounding factors which could not be accomplished in traditional meta-analyses.

The study has also some limitations: (a) Detailed characteristics of tea consumption such as number of years of tea consumption and concentration of tea consumed were not available for the analysis. Moreover, data on the type of tea consumed (green vs black tea) were not available for analysis and thus we were not able to conduct subgroup analysis to identify if the protective effect differs by the type of tea; (b) other factors potentially correlated to both bladder cancer and tea consumption such as physical activity, body weight, education, income, and occupational and environmental exposure to carcinogenic chemicals were not available for the analysis which poses the possibility of residual confounding. Nonetheless, these factors have been shown unlikely to play a major role in bladder cancer aetiology [6]; (c) only 2 cohort studies in BLEND reported the intake of plain water and therefore we could not adjust for fluid intake in the pooled analyses; (d) although we adjusted for smoking status, duration and intensity, residual confounding by smoking cannot be excluded due to self-reporting of smoking information and lack of data on passive smoking and other characteristics of smoking behaviour such as depth of inhalation; (e) many participants in the BLEND dataset have missing data on stage of bladder cancer (MIBC vs NMIBC) which might have led to low power reflected in the wide confidence intervals of various categories in the subgroup analyses by stage of bladder cancer; (f) information about personal history of cancer was not available. In the sensitivity analyses, we conducted an analysis after excluding subjects with outcome events in the first two years of follow-up; (g) due to lack of information on other outcomes, all events other than bladder cancer were treated as censored and thus we were unable to conduct competing risk analyses. In addition, we did not have enough details to conduct separate analysis for fatal and non-fatal events of bladder cancer.

5. Conclusion

In conclusion, there was an evidence of reduced risk of bladder cancer associated with consumption of tea. This reduced risk was statistically significant among men and current and former smokers but not among women and never smokers. The statistically significant association and dose response supports a causal relationship. However, inconsistency between males and females and the absence of association among never smokers weaken the evidence of causality and may indicate residual confounding. Further studies are needed to investigate more deeply the causality and mechanism of interaction between tea consumption and sex and smoking status.

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Author contributions

The authors' responsibilities were as follows— EYWY, AW and MPZ: conceived and designed the study; AHAZ: conducted data analyses and interpretation and drafted the manuscript; PvdB, EJG, EW, GS, FL, EW: provided the data; PvdB, EJG, EW, GS, FL, EW, EYWY, AW, and MPZ: revised the manuscript; and all authors: read and approved the final manuscript.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.03.020.

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