Family history and risk of bladder cancer

Family History and Risk of Bladder Cancer: An Analysis Accounting for First- and Second-degree Relatives

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ABSTRACT

Although evidence suggests that a positive family history of bladder cancer in first-degree relatives is an important risk factor for bladder cancer occurrence, results remain unclear. The influence of family history of non-bladder cancers and more distant relatives on bladder cancer risk is inconsistent. This research, therefore, aims to increase the understanding of the association between family history and bladder cancer risk based on worldwide case–control studies. In total 4,327 cases and 8,948 non-cases were included. Pooled ORs, with corresponding 95% confidence intervals (CI), were obtained using multilevel logistic regression models, adjusted by age, sex, ethnicity, smoking status, and smoking pack-years. The results show bladder cancer risk increased by having a first- or second-degree relative affected with bladder cancer (OR, 2.72; 95% CI, 1.55–4.77 and OR, 1.71; 95% CI, 1.22–2.40, respectively), and nonurologic cancers (OR, 1.61; 95% CI, 1.19–2.18). Moreover, bladder cancer risk increased by number of cancers affected first-degree relatives (for 1 and >1 first-degree relatives: OR, 1.42; 95% CI, 1.02–2.04; OR, 2.67; 95% CI, 1.84–3.86, respectively). Our findings highlight an increased bladder cancer risk for a positive bladder cancer family history in first- and second-degree relatives, and indicate a possible greater effect for an increment of numbers of affected relatives.

Prevention Relevance: This study found a positive association between family history and bladder cancer in first- and second-degree relatives, with an added effect attributed to smoking. Given the detriments of bladder cancer, at-risk individuals should receive family history screening and tobacco cessation and avoidance counseling.

Introduction

Bladder cancer is the most common malignancy of the urinary tract and the seventh leading cause of death from cancer, with nearly 550,000 new diagnoses and 200,000 deaths per year worldwide (1, 2). Three-quarters of all bladder cancer cases occur in men (3), and the incidence rate of bladder cancer is higher in the United States, Canada, and the European Union (4–7). As with many solid tumors, bladder cancer incidence increases with age and it rarely occurs before the age of 40–50 years (8). Given its high frequency of recurrence, bladder cancer is reported to be among the most expensive lifetime treatment of all cancers which results in burden to the health care system (9).

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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Previous studies have revealed that genetic susceptibility might play an important role in the occurrence and development of bladder cancer (10). However, studies assessing the influence of genetics on bladder cancer risk, using family history as a surrogate marker for genetic susceptibility, showed inconsistent results. Some epidemiologic studies reported an increased bladder cancer risk for individuals with a positive family history of bladder and nonbladder cancer types (11–16), while an analysis within the Nordic Twin Study of Cancer including 203,691 twins from nationwide registries in Denmark, Finland, Norway, and Sweden suggested that hereditability is weaker for bladder cancer (30%) compared with other urologic cancer, such as renal cancer (38%) and prostate cancer (57%; ref. 17). Moreover, information on familial clustering of bladder cancer with other cancer types is still scanty. In addition, most of the studies only investigated the effect of first-degree relatives, thereby lacking evidence on the effects of more distant relatives on bladder cancer risk. Furthermore, the detailed information on smoking habits was not well considered when investigating the association of family history with bladder cancer risk in previous studies.

The current study, therefore, aims to examine the association between history of bladder and other cancer types among first- and second-degree relatives and bladder cancer risk, using data from Bladder Cancer Epidemiology and Nutrition Determinants (BLEND) study.

Material and Methods

Study participants and data collection

Data were derived from the BLEND, an international consortium that collected data on diet and bladder cancer, details of its methodology have been described elsewhere (18). For the current study, seven case–control and one case–cohort study (including 4,327 cases/8,948 non-cases) with information on family history of bladder cancer and nonbladder cancer in either first- or second-degree relatives were originated from five countries [i.e., United States (19–22), Italy (23, 24), Germany (25), the Netherlands (26), and China (27)] eligible for inclusion. Information on family history of bladder cancer and/or nonbladder cancer types (including urologic cancers: i.e., renal cancer and/or prostate cancer; nonurologic cancers: i.e., lip, oral cavity and pharynx cancer, oesophagus cancer, stomach cancer, intestinal cancer, colorectal cancer, liver cancer, gall bladder cancer, pancreas cancer, respiratory tract cancer, nasopharyngeal cancer, lung cancer, heart cancer, bone/cartilage cancer, breast cancer, other female genital organ cancer, cervical cancer, ovarian cancer, soft-tissue neoplasm, skin cancer, testicular cancer, penile cancer, central nervous system cancer, endocrine cancer, lymphoma cancer, leukemia cancer) was either self-reported or interviewed at the data collection phase, followed by harmonizing all of them according to the European coding system developed by European Union (28). Bladder cancer cases were diagnosed and histologically confirmed through the study centres of the participating individual studies, with International Classification of Diseases 9 or 10. Through this, a pooled dataset with standard input was built up for further analysis. In addition to information on family history, the BLEND study includes data on: study characteristics (design, method of dietary assessment, recall time of dietary consumption, and geographical region), participant demographics (age and sex), smoking status, passive smoking, and smoking pack-years. Family history was evaluated using dichotomous variables (yes/no) distinguishing for bladder cancer or nonbladder cancer types among first- and second-degree relatives. Also, we considered the number of first- or second-degree relatives with total cancer types. The detailed information for inclusion criteria, study design, ascertainment of case and control, exposure assessment were performed in Supplementary Materials and Methods, Supplementary Table S1, and Supplementary Fig. S1. Each participating study has been approved by the local ethic committee.

Statistical analysis

Descriptive statistics were utilized to determine frequencies, means, and SDs of all study variables, and the differences between cases and non-cases were assessed by χ^2 test for categorical variables and *t* test for continuous variables, respectively. For categorical variables, that is, ethnicity, missing data (9%) were replaced by an indicator (using 0 as unknown); for continuous variables, that is, smoking pack-years, missing data (11%) were replaced by the mean value of the smoking pack-years separated for sexes in each included individual study. No indicators were assigned for unknown information on family history in the current study.

To evaluate the associations between a positive family history of bladder cancer and nonbladder cancer types occurred in either first- or second-degree relatives and the risk of bladder cancer, multilevel logistic regression models were used to calculate ORs and their associated 95% confidence intervals (CI), which nested the individuals within study centres to adjust for cross-study heterogeneity. Models were adjusted: for (i) crude model without any adjustment; (ii) age (years, continuous), sex (male or female), and ethnicity (Caucasian or non-Caucasian); (iii) additionally adjusted for smoking status (never, current, or former smokers) and pack-years (cigarettes/day*years of smoking, continuous). To evaluate potential effect modification, the main interaction terms between family history (with or without any relative affected by cancer) and age, sex, and smoking status were added to the model 3. Given the important role of age and smoking as bladder cancer determinants, we also performed stratified analyses upon the sex and smoking status though there was no or borderline interaction. P_{trend} test was conducted by assigning the groups of number of family history as a continuous variable in the models. The combined effect of smoking and a positive family history was also assessed. In addition, the impact of the number of positive family history relatives on bladder cancer risk was analyzed, by comparing the family history of 1 and >1 affected relatives to non-family history.

Sensitivity analyses were performed by (i) additionally adjusting for passive smoking (unknown, non-passive smoking and passive smoking); (ii) removing the case–cohort study; and (iii) conducting a meta-analysis by combining each individual study using a random-effect model. All analyses were conducted using STATA version 14 SE (Stata Corporation). A significant two-tailed *P* value was set at 0.05.

Data availability

The data generated in this study are available upon request from the corresponding author. The data and code are not publicly available owing to their containing information that could compromise the privacy of research participants.

Results

The characteristics of the study participants are shown in **Table 1**. The mean age at recruitment among bladder cancer cases and non-cases were 60.49 and 61.41 years, respectively. Bladder cancer cases tended to be more frequently smokers (81.58%) compared with non-cases (62.92%), and to smoke more intensively with a longer duration (32.52 and 22.72 pack-years, respectively).

A positive family history of first-degree relatives was reported by 2.66% of all bladder cancer cases ($n = 115$) and 1.20% of all non-cases ($n = 107$). In addition, 2.60% of all bladder cancer cases reported a positive family history of second-degree relatives, while only 0.77% in non-cases. A similar significant pattern was observed for nonbladder cancer types (**Table 1**).

On the basis of the fully adjustment model (model 3), individuals with a first-degree relative affected by bladder cancer showed an increased bladder cancer risk compared with individuals without any affected relative (OR, 2.72; 95% CI, 1.55–4.77; **Table 2**). Similarly, there was a positive association between having positive first-degree relatives affected by nonurologic cancer types and bladder cancer risk (OR, 1.61; 95% CI, 1.19–2.18). A positive association of borderline statistical significance was observed for individuals with a first-degree affected relative for other urologic cancers. Family history in second-degree relatives only increased the bladder cancer risk when the second-degree relative was affected by bladder cancer (OR, 1.71; 95% CI, 1.22–2.40), while nonbladder cancer types in second-degree relatives showed weak or no evidence of association with bladder cancer risk (**Table 2**).

The association of family history and bladder cancer risk seemed to increase with 1 and >1 first-degree relative affected by any cancer type (OR, 1.42; 95% CI, 1.02–2.04; OR, 2.67; 95% CI, 1.84–3.86, respectively; $P_{trend} = 0.032$). In addition, we observed a positive association of family history and bladder cancer risk if >1 second-degree relative was affected by any cancers type, although the estimate was not greater than for just one affected relative (OR, 1.88; 95% CI, 1.35–2.56; **Table 3**).

Table 1. Characteristics of included participants and their family history by first- and second-degree relatives.

	Cases		Non-cases			
	No.	%	No.	%	P^a	$P_{interaction}{}^b$
Sex					<0.001	0.321
Male	3,506	81.03	5,494	61.40		
Female	821	18.97	3,454	38.60		
Age (mean (SD))[c]	60.49 (10.22)		61.41 (8.29)		<0.001	0.437
<55	909	21.01	1,198	13.39	<0.001	
55–65	1,925	44.49	4,784	53.46		
>65	1,493	34.50	2,966	33.15		
Smoking						
Smoking status						0.048
Never	797	18.42	3,318	37.08	<0.001	
Current	1,808	39.80	2,549	28.49		
Former	1,722	41.78	3,081	34.43		
Smoking pack-years (mean (SD))[d]	32.52 (29.05)		22.72 (24.83)		<0.001	
Ethnicity						
Caucasian	2,739	97.96	6,962	97.74	<0.001	
Non-Caucasian	57	2.04	161	2.26		
Bladder cancer (first-degree)						
Yes	115	2.66	107	1.20	<0.001	
No	4,210	97.34	8,841	98.80		
Bladder cancer (second-degree)						
Yes	39	2.60	16	0.77	<0.001	
No	1,461	97.40	2,070	99.23		
Other urologic cancer (first-degree)						
Yes	55	2.16	126	1.84	0.015	
No	2,489	97.84	6,717	98.16		
Other urologic cancer (second-degree)						
Yes	25	1.68	17	0.82	0.020	
No	1,467	98.32	2,054	99.18		
Nonurologic cancer (first-degree)						
Yes	535	12.36	1,575	17.60	<0.001	
No	3,792	87.64	7,373	82.40		
Nonurologic cancer (second-degree)					<0.001	
Yes	117	7.78	95	4.54		
No	1,387	92.22	1,997	95.46		
Number of family history (first-degree)						
0	793	61.62	3,503	68.58	<0.001	
1	419	32.56	1,299	25.43		
>1	75	5.83	306	5.99		
Number of family history (second-degree)						
0	1,387	92.22	1,997	95.46	<0.001	
1	102	6.78	81	3.87		
>1	15	1.00	14	0.67		

Note: $P < 0.05$ was considered statistically significant and $P_{interaction} < 0.05$ was considered statistically significant.

Abbreviation: SD, standard deviation.

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

[b]To evaluate potential effect modification, $P_{interaction}$ was calculated by adding the main interaction term between family history (with or without any relative affected by cancer) of cancer and age, sex, and smoking status to the age (continuous, years), sex (male or female), ethnicity (Caucasian or non-Caucasian), smoking status (never, current, or former) and smoking pack-years (continuous).

[c]Age at the time of recruitment.

[d]Pack-years was defined as the number of cigarettes smoked per day multiplying the years of smoking.

The stratified analysis, shown in **Table 4** that most of the results were consistent with results of the overall population, also showing that for both male and female the bladder cancer risk ($P_{interaction} = 0.321$) increases with having first-degree relatives affected by either bladder cancer (OR, 2.16; 95% CI, 1.53–3.07; 2.11; 95% CI, 1.14–3.89) or a nonbladder cancer type (OR, 1.22; 95% CI, 1.06–1.41; 1.27; 95% CI, 1.08–1.80) for males and females, respectively, and having second-degree relatives affected by either bladder cancer (OR, 2.82; 95% CI, 1.39–5.73; 2.12; 95% CI, 1.10–5.38) or a nonbladder cancer type (OR, 1.74; 95% CI, 1.21–2.49; 2.05; 95% CI, 1.10–3.84) for males and females, respectively.

Both current and former smokers were at an increased bladder cancer risk for individuals having a first-degree relative affected by either bladder cancer (OR, 1.77; 95% CI, 1.10–2.84; 1.83; 95% CI, 1.14–2.94) or a nonbladder cancer type (OR, 1.29; 95% CI, 1.05–1.57; 1.22; 95% CI, 1.01–1.50) for current and former smokers, respectively, and having second-degree relatives affected by either bladder cancer (OR, 3.06; 95% CI, 1.42–8.04; 3.92; 95% CI, 1.26–7.15) or a nonbladder cancer type (OR, 2.12; 95% CI, 1.22–3.69; 1.61; 95% CI, 1.01–2.58) for current and former smokers, respectively, while never-smokers only showed null associations. When considering the combined effect of a positive family history of bladder cancer and smoking, smokers without having a positive first-degree relative showed a positive association with bladder cancer risk compared with never-smokers without having a positive relative (OR, 1.65; 95% CI, 1.45–1.87). This positive association doubled in magnitude for current and former smokers having a positive first-degree relative (OR, 3.43; 95% CI, 2.39–4.91). Among never-smokers having a positive first-degree relative there was a nonstatistically significant association with bladder cancer risk compared with never-smokers without having a positive relative (OR, 1.67; 95% CI, 0.88–3.17). A similar pattern was shown for second-degree relatives (Supplementary Table S2).

Similar results under fully adjustment model (model 3) were obtained after additionally adjusting for passive smoking (Supplementary Table S3), or removing the case–cohort study from the analysis (Supplementary Table S4S and S5). In addition, the meta-analysis approach also showed the consistent results: there was a significant increased bladder cancer risk for individuals having a first- or second-degree bladder cancer affected relative (OR, 1.68; 95% CI, 1.23–2.12; OR 1.47; 95% CI, 1.12–1.82, respectively); and current and former smokers with family history of all cancers showed a significantly increased risk of bladder cancer compared with never-smokers without a positive family history (OR, 3.97; 95% CI, 2.82–5.12; 1.98; 95% CI, 1.45–2.52, respectively; Supplementary Fig. S2).

Discussion

In this multicentric study, we found that a first- and second-degree relative affected by bladder cancer increases the risk of bladder cancer. In addition, bladder cancer risk increased with an increment of relatives affected by any cancer type. Moreover, these findings were also found among never-smokers (although weaker), suggesting an independent effect of family history.

Findings of the current article are in line with most of the previously epidemiologic studies on the effect of family history

Table 2. Bladder cancer risk for individuals with a positive family history of cancer in first- and second-degree relatives.

Family history	Case (*N*)	Model 1[a] OR (95%)	Model 2[b] OR (95%)	Model 3[c] OR (95%)
First-degree				
Bladder cancer				
No	4,210	1.00	1.00	1.00
Yes	155	2.81 (1.62–4.85)	2.66 (1.52–4.63)	2.72 (1.55–4.77)
Other urologic cancer				
No	2,489	1.00	1.00	1.00
Yes	55	1.99 (1.06–3.75)	1.73 (0.91–3.28)	1.83 (0.96–3.50)
Nonurologic cancer				
No	3,792	1.00	1.00	1.00
Yes	575	1.82 (1.36–2.43)	1.58 (1.17–2.13)	1.61 (1.19–2.18)
Second-degree				
Bladder cancer				
No	1,461	1.00	1.00	1.00
Yes	46	1.91 (1.44–2.52)	1.82 (1.31–2.53)	1.71 (1.22–2.40)
Other urologic cancer				
No	1,476	1.00	1.00	1.00
Yes	16	1.26 (0.90–1.76)	1.25 (0.89–1.76)	1.27 (0.90–1.80)
Nonurologic cancer				
No	1,387	1.00	1.00	1.00
Yes	124	1.20 (1.06–1.35)	1.18 (0.97–1.41)	1.06 (0.76–1.42)

Note: Reference group was non-family history.
[a]Model 1: crude model without any adjustment.
[b]Model 2: Adjusted for age (years, continuous), sex (male or female), ethnicity (Caucasian or non-Caucasian).
[c]Model 3: In addition, smoking status (never, current, or former) and smoking pack-years (continuous).

Table 3. Bladder cancer risk by the number of affected relatives.

Family history	Case (*N*)	Model 1[a] OR (95%	Model 2[b] OR (95%	Model 3[c] OR (95%)	P_{trend}
Number of first degree					0.032
0	1,387	1.00	1.00	1.00	
1	571	1.56 (1.11–2.20)	1.51 (1.07–2.14)	1.42 (1.02–2.04)	
>1	129	2.62 (1.87–3.66)	2.56 (1.81–3.63)	2.67 (1.84–3.86)	
Number of second degree					0.048
0	1,005	1.00	1.00	1.00	
1	109	1.72 (0.82–2.64)	1.73 (0.82–2.65)	1.86 (0.88–2.06)	
>1	15	1.81 (1.32–2.48)	1.80 (1.31–2.47)	1.88 (1.35–2.56)	

Note: Reference group was non-family history and $P_{trend} < 0.05$ was considered statistically significant.
[a]Model 1: Crude model without any adjustment.
[b]Model 2: Adjusted for age (years, continuous), sex (male or female), ethnicity (Caucasian or non-Caucasian).
[c]Model 3: In addition, smoking status (never, current, or former) and smoking pack-years (continuous).

and bladder cancer risk, including a recent case–control study (Turati and colleagues, 2017; ref. 13), reporting a roughly 2-fold bladder cancer risk for individuals having a bladder cancer affected relative. In addition, some earlier studies also demonstrated an elevated bladder cancer risks associated with an affected relative with bladder cancer, with estimates ranging from 1.20 to 4.0 (14, 16, 29–35). However, all previous studies were only based on first-degree relatives, thereby, lacking evidence for the effect of having more distant affected relatives. To our knowledge, this is the first study showing a 70% increased bladder cancer risk for individuals having a second-degree affected relative, which strengths the evidence of inherited bladder cancer risk in more distant genetic relationships. If this finding is validated, family history among second-degree relatives could be considered when assessing an individual's bladder cancer risk. In addition, family history in second-degree relatives only increased the bladder cancer risk when the second-degree relative was affected by bladder cancer, this could be explained that patients with bladder cancer may remember bladder cancers among relatives better than other cancers.

A role for a familial component in bladder cancer development has also been suggested by other studies. Genome-wide association studies (GWAS) have identified many SNPs related to bladder cancer occurrence, including the identification of the NAT2-slow acetylator and GSMT1-null genotypes, which are highly associated with an increased bladder cancer risk (36–38). In addition, it was reported that the overall proportion of variance corresponding to inherited factors for bladder cancer was 31% (39). Recent data suggested that up to 13.4% of patients with bladder cancer have (likely) pathogenic mutations in previously identified cancer genes (40). Moreover, a recent GWAS investigating the heritability and genetic correlation attributable to the additive effects of common SNPs found that the bladder cancer familial relative risk was 1.37, defined as the increase in risk associated with the effects of GWAS identified SNPs (10).

In the current study, only weak association between bladder cancer and having a relative affected with urologic cancer types other than bladder cancer and nonurologic cancer types, suggesting that the influence of adjacent urinary tract or other sites on bladder cancer is limited. This is in line with a recent study which showed no association of bladder cancer risk and family history of nonbladder cancer sites (13); however, the specific cancer type was unable to be examined because of the lack of sufficient data.

Because smoking is the most important independent risk factor for bladder cancer risk and might interact with genetic defects for causing bladder cancer, this risk factor should be carefully considered when assessing the association between positive family history and bladder cancer. Smoking behavior tends to cluster in families, thereby making it challenging to differentiate between smoking-related exposures, environmental exposures, and shared genes (41). In the current study, the combined effect of smoking and a positive bladder cancer family history yielded an almost 3.5-fold increased bladder cancer risk, while smoking and a positive family history alone yielded a roughly 1.5-fold increased bladder cancer risk. Although the effect of a positive family history was not statistically significant among never-smokers, this was likely due to the low statistical power. Nonetheless, the findings of current study suggest an independent effect of both factors on bladder cancer risk.

For the current study, data were pooled from seven case–control and one case–cohort study, to obtain a sample size, large enough to permit detailed analyses with good precision. The study has some limitations; first, data on family history were self-reported; therefore, measurement error and misclassification due to recall bias are unavoidable, particularly for cancer types. It is suggested that individuals who suffer from a cancer tend to know other family members diagnosed with cancer, while those who are cancer free will be less informed on diagnosed family members, resulting in differential misclassification. However, it has been observed previously that the accuracy of reporting cancers in the first-degree relatives is generally high (34). Unfortunately, this cannot be confirmed for second-degree relatives' data. Second, we did not have information about all other possible risk factors consistently across all studies included in these pooled analyses, other than age, sex, ethnicity, and smoking, such as body mass index,

Table 4. Bladder cancer risk for having a positive family history stratified for sex and smoking status.

Family history		Case (*N*)	Model 1[a] OR (95%)	Model 2[b] OR (95%)	Model 3[c] OR (95%)
First-degree					
Bladder cancer					
Male	No	3,411	1.00	1.00	1.00
	Yes	93	2.24 (1.59–3.17)	2.25 (1.59–3.18)	2.16 (1.53–3.07)
Female	No	799	1.00	1.00	1.00
	Yes	22	2.11 (1.15–3.90)	2.13 (1.15–3.94)	2.11 (1.14–3.89)
Current smoker	No	1,673	1.00	1.00	1.00
	Yes	49	1.69 (1.06–2.70)	1.78 (1.11–2.87)	1.77 (1.10–2.84)
Former smoker	No	1,760	1.00	1.00	1.00
	Yes	47	1.84 (1.15–2.95)	1.89 (1.18–3.02)	1.83 (1.14–2.94)
Never smoker	No	777	1.00	1.00	1.00
	Yes	19	1.44 (0.81–2.58)	1.45 (0.81–2.59)	1.38 (0.77–2.47)
Non–bladder cancer					
Male	No	3,083	1.00	1.00	1.00
	Yes	423	1.25 (1.08–1.44)	1.26 (1.09–1.47)	1.22 (1.06–1.41)
Female	No	709	1.00	1.00	1.00
	Yes	112	1.26 (1.03–1.76)	1.25 (1.06–1.76)	1.27 (1.08–1.80)
Current smoker	No	1,512	1.00	1.00	1.00
	Yes	210	1.25 (1.02–1.53)	1.28 (1.05–1.57)	1.29 (1.05–1.57)
Former smoker	No	1,582	1.00	1.00	1.00
	Yes	226	1.24 (1.02–1.51)	1.26 (1.03–1.55)	1.22 (1.01–1.50)
Never smoker	No	698	1.00	1.00	1.00
	Yes	99	1.13 (0.87–1.48)	1.12 (0.87–1.47)	1.12 (0.86–1.46)
Second-degree					
Bladder cancer					
Male	No	1,127	1.00	1.00	1.00
	Yes	29	3.10 (1.53–6.28)	2.75 (1.35–5.58)	2.82 (1.39–5.73)
Female	No	334	1.00	1.00	1.00
	Yes	10	2.55 (1.15–5.67)	2.21 (1.13–6.63)	2.12 (1.10–5.38)
Current smoker	No	474	1.00	1.00	1.00
	Yes	12	2.98 (1.40–7.78)	3.01 (1.46–8.97)	3.06 (1.42–8.04)
Former smoker	No	634	1.00	1.00	1.00
	Yes	20	3.99 (1.29–7.38)	3.55 (1.14–7.08)	3.92 (1.26–7.15)
Never smoker	No	353	1.00	1.00	1.00
	Yes	7	1.51 (0.54–4.24)	1.14 (0.39–3.32)	1.57 (0.56–4.43)
Non–bladder cancer					
Male	No	3,429	1.00	1.00	1.00
	Yes	77	1.66 (1.16–2.37)	1.67 (1.17–2.38)	1.74 (1.21–2.49)
Female	No	781	1.00	1.00	1.00
	Yes	40	1.76 (0.95–3.27)	2.20 (1.17–4.14)	2.05 (1.10–3.84)
Current smoker	No	1,696	1.00	1.00	1.00
	Yes	26	2.56 (0.85–4.68)	2.07 (1.20–3.57)	2.12 (1.22–3.69)
Former smoker	No	1,760	1.00	1.00	1.00
	Yes	48	1.52 (0.95–2.42)	1.66 (1.03–2.68)	1.61 (1.01–2.58)
Never smoker	No	754	1.00	1.00	1.00
	Yes	43	1.19 (0.77–1.84)	1.39 (0.92–2.10)	1.40 (0.92–2.13)

Note: Reference group was non-family history.
[a]Model 1: Crude model without any adjustment.
[b]Model 2: Adjusted for age (years, continuous), sex (male or female), ethnicity (Caucasian or non-Caucasian).
[c]Model 3: In addition, smoking status (never, current, or former) and smoking pack-years (continuous).

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 bladder cancer cases can be attributed to these factors (42), and their correlation with family history is not well understood for all. Third, the lack of information on either number of relatives or family size might introduce bias caused by different cancer occurrence rates among families. In addition, the lack of information on the age of siblings might influence the results, because the chance of having an affected sibling is greater among individuals with older siblings compared with individuals having younger siblings. Fourth, for some bladder cancer subtypes, that is, nonurothelial bladder cancer, it is known that they are mainly affected by infections (e.g., schistosomal and

chronic cystitis) rather than genetic susceptibility, thereby possibly affecting our results. Unfortunately, due to lack of data on bladder cancer subtypes, we were unable to exclude nonurothelial cancer types. However, considering the proportion of nonurothelial bladder cancer is less than 3%–5% (43), the influence of this cancer type on our results are negligible. Finally, although status as well as duration and intensity of smoking were considered, 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 (44). Moreover, we lacked information on smoking history among relatives.

Conclusion

In summary, our results confirm previous epidemiologic data reporting an increased bladder cancer risk with a positive bladder cancer family history in first- and second-degree relatives, and indicates a possible increased effect of a positive family history with an increment of numbers of affected relatives. Moreover, our findings suggest an added effect of smoking with family history on bladder cancer risk, and underline the importance of avoiding smoking, particularly in subjects with a family history of cancer.

Authors' Disclosures

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Authors' Contributions

E.Y.-W. Yu: Conceptualization, software, formal analysis, investigation, visualization, methodology, writing–original draft, writing–review and editing. **M.C. Stern:** Resources, validation. **X. Jiang:** Resources, validation. **L. Tang:** Resources, validation. **P.A. van den Brandt:** Resources, validation. **C.-M. Lu:** Resources, validation. **M.R. Karagas:** Resources, validation. **C. La Vecchia:** Resources, validation. **C. Bosetti:** Resources, validation. **J. Polesel:** Resources, validation. **K. Golka:** Resources, validation. **Z.-F. Zhang:** Resources, validation. **P. Villeneuve:** Resources, validation. **M.P. Zeegers:** Data curation, supervision, funding acquisition, project administration. **A. Wesselius:** Data curation, supervision, project administration.

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