Risk of Bladder Cancer Associated with Family History of Cancer: Do Low-Penetrance Polymorphisms Account for the Increase in Risk?

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Abstract

The relationship between family history of cancer in first-degree relatives and risk of bladder cancer was examined in the Spanish Bladder Cancer Study. Information on family history of cancer was obtained for 1,158 newly diagnosed bladder cancer cases and 1,244 controls included in 18 hospitals between 1998 and 2001. A total of 464 (40.1%) cases and 436 (35.1%) controls reported a family history of cancer in ≥1 relative [odds ratio (OR), 1.32; 95% confidence interval (95% CI), 1.11-1.59]; the OR was 1.23 (95% CI, 1.01-1.50) among those with only one relative affected and 1.67 (95% CI, 1.23-2.29) among those with ≥2 affected relatives (P_{trend} = 0.0004). A greater risk of bladder cancer was observed among those diagnosed at age ≤45 years (OR, 2.67; 95% CI, 1.10-6.50) compared with those diagnosed over age 45 years (OR, 1.27; 95% CI, 1.06-1.52). The OR of bladder cancer among subjects reporting a family history of cancer of the bladder was 2.34 (95% CI, 0.95-5.77). Statistically significant associations emerged between bladder cancer risk and family history of cancer of the esophagus, lung, prostate, and brain. The OR of bladder cancer for those reporting family history of bladder cancer was 4.76 (95% CI, 1.25-18.09) among *NAT2*-slow acetylators and 1.17 (95% CI, 0.17-7.86) among *NAT2*-rapid/intermediate acetylators ($P_{interaction}$ = 0.609). Among individuals with *GSTM1* null and present genotypes, the corresponding ORs were 2.91 (95% CI, 0.44-19.09) and 4.21 (95% CI, 1.26-14.14), respectively ($P_{interaction}$ = 0.712). Limitations of our study are small sample size in subgroup analyses, reliability of family history data, and possible residual confounding by shared environmental exposures. Overall, our findings support the hypothesis that genetic factors play a role in bladder cancer etiology. Whether these correspond to low-penetrance cancer-predisposing polymorphisms acting together and/or interacting with environmental factors warrants further research. (Cancer Epidemiol Biomarkers Prev 2007;16(8):1595–600)

Introduction

The incidence of bladder cancer in Spain is the highest in the western world and the second at the worldwide level after Egypt (1). In Egypt, most of the bladder cancers are of squamous histology, whereas in Spain they are urothelial cell carcinomas. It is estimated that ~12,215 new cases of bladder cancer occurred in Spain in 2002 (1). This makes bladder cancer the fourth most common cancer in men (33 new cases per 100,000 persons per year) and the 15th in women (3.5 per 100,000 persons per year). Tobacco smoking and occupational exposure to aromatic amines are the most important risk factors for this disease (2, 3) but other lifestyle/environmental as well as hereditary factors have also attracted much interest.

Among the hereditary factors involved in bladder cancer carcinogenesis, the role of variation in the genes coding for xenobiotic biotransforming enzymes such as *N*-acetyltransferase 2 (*NAT2*) and glutathione *S*-transferase M1 (*GSTM1*) has been most extensively studied (4-6). Recent meta-analyses of 31 case-control studies assessing the risk of bladder cancer conferred by *NAT2*-slow acetylating genetic variants and of 28 case-control studies assessing the risk of bladder cancer conferred by *GSTM1*-null variants estimated odds ratios (OR) of 1.4 [95% confidence interval (95% CI), 1.2-1.6] and 1.5 (95% CI, 1.3-1.6), respectively (6). Indeed, this is the tumor for which strongest evidence is available on a role of low-penetrance genetic variants in both increasing cancer risk and in gene-environment interactions (6). By contrast, research on familial aggregation of bladder cancer has been less extensive and the results of case-control studies remain controversial (7-11). Family history of other types of cancer such as lymphocytic leukemia, cervical, pancreas, kidney, thyroid, and nervous system cancer has also been associated with an increased risk of bladder cancer (12-16).

Several case reports of families with multiple affected relatives have been published (17-22) but high-penetrance genes have not been identified (23). Therefore, it is possible that, as in breast cancer, familial aggregation of cancer may be due to additive effects of several common, low-penetrance gene variants that cosegregate within families (24).

In this report, we assessed the relationship between bladder cancer risk and the reported history of any other type of cancer, including bladder cancer, among first-degree relatives using data from the Spanish Bladder Cancer Study. We have also investigated whether variants of *NAT2* and *GSTM1*

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modified, or accounted for, the increased risk of bladder cancer observed among those individuals with family history of cancer in first-degree relatives.

Materials and Methods

The Spanish Bladder Cancer Study is a hospital-based case-control study conducted between 1998 and 2001 in 18 hospitals in five areas of Spain: Asturias, Barcelona metropolitan area, Vallès Occidental/Bages, Alicante, and Tenerife.

The details of the study have been described elsewhere (6). Briefly, 1,219 newly diagnosed cases of bladder cancer, ages 21 to 80 years, admitted to the Study hospitals to perform transurethral resection were included. All cases were histologically confirmed by a panel of pathologists using the 1999 WHO classification system (25). Only patients with urothelial cell carcinoma of the bladder were included in this analysis (n = 1,209). Controls were 1,271 subjects selected from participating hospitals with diagnoses thought to be unrelated to the exposures of interest. The most common reasons for hospitalization of controls were surgery for abdominal hernia or hydrocele, diseases of the digestive system (e.g., intestinal obstruction and appendicitis), and injuries (e.g., fractures; Table 1). Controls were individually matched to the cases by age at diagnosis (±5 years), gender, race, and region. Six non-White individuals (five cases, one control) were excluded from the analyses.

Written informed consent was obtained from all subjects, and the study was approved by the Institutional Review Board of the U.S. National Cancer Institute and the local Institutional Ethics Committees.

Computer-assisted personal interviews, carried out at the hospitals by trained interviewers, included information on sociodemographic characteristics, smoking habits, environmental exposures, previous history of cancer, and family history of cancer. Subjects were specifically asked the number of brothers and sisters they had and whether parents, siblings, or offspring had ever had cancer. Tumors reported among family members were coded according to the 9th revision of the International Classification of Diseases (ICD-9). For each relative with a history of cancer, the subjects were asked to specify the site of the tumor and age at diagnosis. To verify the information related to bladder cancer in the family, we contacted by phone the relatives, mainly wives and sisters, of the 16 cases and 9 controls that reported a family history of bladder cancer. Relatives of 3 cases and 6 controls failed to confirm the information provided by the patient.

Subjects were classified as never smokers if they had smoked fewer than 100 cigarettes in their lifetime and as ever smokers otherwise. Ever smokers were further classified as regular smokers if they had smoked at least one cigarette per day for ≥6 months and occasional otherwise. Regular smokers were subsequently classified as former or current smokers if they stopped or continued smoking 1 year before their inclusion to the study, respectively. Furthermore, regular smokers were classified into two groups according to the duration smoked, <20 or ≥20 years (26). To adjust analyses by environmental shared risk factors among first-degree relatives, we considered exposure to environmental tobacco smoke (ETS) among nonsmokers, which was assessed by asking subjects for the number of persons who smoked around them at every residence and every job held (26) and lifelong average residential trihalomethane levels (μg/L), as recorded by Villanueva et al. (27).

Polymorphisms in *NAT2* and *GSTM1* were investigated using germ-line DNA from blood and buccal cell samples as previously described (6). The genotype assays were done at the Core Genotyping Facility at the U.S. National Cancer Institute using TaqMan (Applied Biosystems). Details on genotyping assays have been reported elsewhere (6).[9] Individuals homozygous for *NAT2* rapid-acetylator alleles (*NAT2**4, *NAT2**11A, *NAT2**12A, *NAT2**12B, *NAT2**12C, and *NAT2**13) were classified as rapid-acetylator phenotype; individuals homozygous for slow-acetylator alleles were classified as slow-acetylator phenotype; and heterozygous individuals (one rapid and one slow *NAT2* allele) were classified as intermediate-acetylator phenotype. *GSTM1* genotypes were defined as present if one (+/−) or two (+/+) of gene copies were present and absent/null (−/−) if the two alleles were null. All genotypes were in Hardy-Weinberg equilibrium among the control population.

Table 1. Distribution of cases and controls according to selected characteristics

Characteristics	Cases (n = 1,158)	Controls (n = 1,244)
	n (%)	n (%)
Region*		
Barcelona	218 (18.8)	244 (19.6)
Vallès Occidental/Bages	179 (15.5)	189 (15.2)
Elche	86 (7.4)	84 (6.8)
Tenerife	211 (18.2)	217 (17.4)
Asturias	464 (40.1)	510 (41.0)
Age (y)*		
<55	176 (15.2)	205 (16.5)
55-64	247 (21.3)	306 (24.6)
65-69	255 (22.0)	286 (23.0)
70-74	248 (21.4)	243 (19.5)
≥75	232 (20.0)	204 (16)
Gender*		
Male	1,012 (87.4)	1,080 (86.8)
Female	146 (12.6)	164 (13.2)
Education level		
Less than primary	532 (45.9)	575 (46.2)
Primary and less than high school	451 (38.9)	485 (39.0)
At least high school	158 (13.6)	164 (13.2)
Other	14 (1.2)	15 (1.2)
Missing	1 (0.1)	— (—)
No. siblings		
0-2	295 (25.5)	345 (27.7)
3-4	252 (21.8)	273 (21.9)
≥5	371 (32.0)	396 (31.8)
Missing	240 (20.7)	230 (18.5)
Smoking status		
Nonsmoker	160 (13.8)	363 (29.2)
Occasional	47 (4.1)	95 (7.6)
Former	472 (40.8)	499 (40.1)
Current	474 (40.9)	281 (22.6)
Missing	5 (0.4)	6 (0.5)
Average lifetime trihalomethane levels (μg/L)		
0-15	356 (30.7)	423 (34.0)
16-50	414 (35.8)	400 (32.2)
≥51	317 (27.4)	350 (28.1)
Missing	71 (6.1)	71 (5.7)
Diagnoses of controls		
Ophthalmology diseases		15 (1.2)
Circulatory system diseases		46 (3.7)
Hernia of abdominal cavity		450 (36.2)
Other general surgery/ digestive diseases		149 (12.0)
Skin and subcutaneous tissue diseases		145 (2.2)
Male genital organs diseases, hydrocele		27 (11.7)
Fractures		300 (24.1)
Other injuries/orthopedics		93 (7.5)
Other conditions		19 (1.5)

*Cases and controls were matched on these variables.

[9] http://snp500cancer.nci.nih.gov

Statistical Analysis. Unconditional logistic regression using the maximum likelihood estimate (28) was done by use of STATA version 8.0 (StataCorp 2003), adjusting for age in four categories: gender, study area, smoking status (nonsmoker and occasional, former, and current smoker), and average residential trihalomethane levels (μg/L). Because risk estimators and 95% CIs for family history of cancer did not vary significantly when duration of tobacco consumption and ETS variables were included in the models, we did not consider them further in the analyses. The association between bladder cancer risk and family history of all cancers combined, as well as specifically by cancer site or organ system, was investigated. Subjects without family history of cancer were considered the reference group. Smoking-related cancers included tumors of the oral cavity and pharynx, respiratory organs, esophagus, pancreas, urinary bladder, and kidney. We have also investigated the effect of family history of cancer, stratifying by gender, smoking status, age of the subjects, previous history of cancer, and polymorphisms in *NAT2* and *GSTM1*. ORs and 95% CIs were calculated from the coefficients in the regression models. Interaction effects between the family history of cancer, gender, smoking status, age of the case, and *NAT2* and *GSTM1* were assessed by fitting the model with and without the interaction parameters and conducting a likelihood ratio test.

Results

Overall, 1,158 patients with urothelial cell carcinoma of the bladder and 1,244 controls were included in the analysis; 3.8% of the cases and 2.1% of the controls were excluded because of missing information on family history of cancer.

The distribution of cases and controls is shown in Table 1. The mean age for cases and controls was 65.8 and 64.7 years, respectively. Males accounted for 87.4% of the cases and 86.8% of the controls. Case patients were more often current smokers (40.9%) than controls (22.6%). Number of siblings was similar between cases (mean, 4.3) and controls (mean, 4.1).

Table 2. ORs and 95% CIs for bladder cancer associated with family history of cancer, stratified by selected characteristics of relatives

Cancer in relatives	Cases, *n* (%)	Controls, *n* (%)	OR* (95% CI)
First-degree relative with cancer			
None†	694 (59.9)	808 (64.9)	Reference (—)
Any	464 (40.1)	436 (35.1)	1.32 (1.11-1.59)
No. first-degree relatives with cancer‡			
1	339 (29.3)	345 (27.7)	1.23 (1.01-1.50)
≥2	125 (10.8)	91 (7.4)	1.67 (1.23-2.29)
Age at diagnosis of cancer in family member§			
≤45	62 (6.0)	57 (4.9)	1.42 (0.95-2.11)
>45	280 (27.0)	288 (25.0)	1.25 (1.01-1.54)
Family member with history of cancer			
Parents	308 (30.7)	287 (26.2)	1.39 (1.13-1.71)
Mother	135 (16.3)	124 (13.3)	1.38 (1.03-1.85)
Father	191 (21.6)	183 (18.5)	1.42 (1.11-1.82)
Siblings	203 (22.6)	187 (18.8)	1.27 (1.00-1.62)
Sister	88 (11.3)	74 (8.4)	1.36 (0.96-1.94)
Brother	138 (16.6)	131 (14.0)	1.21 (0.91-1.60)
Offspring	25 (3.5)	12 (1.5)	2.24 (1.07-4.66)
Daughter	14 (2.0)	8 (1.0)	2.12 (0.86-5.27)
Son	11 (1.6)	4 (0.5)	2.46 (0.71-8.47)

*After adjustment by unconditional logistic regression for age, gender, area, and smoking status of the subjects and average lifetime trihalomethane levels (μg/L).
†Reference category for all comparisons.
‡χ^2 test for trend, $P = 0.0004$.
§If more than one first-degree relative had cancer, the youngest at age at diagnosis was considered.

Table 3. ORs and 95% CIs for bladder cancer associated with family history of cancer, stratified by selected characteristics of the individuals

Characteristics	Cases, *n* (%)*	Controls, *n* (%)*	OR† (95% CI)
Age (y)			
≤45	27/51 (52.9)	18/61 (29.5)	2.67 (1.10-6.50)
>45	437/1,107 (39.5)	418/1,183 (35.3)	1.27 (1.06-1.52)
Gender			
Male	396/1,012 (39.1)	376/1,080 (34.8)	1.31 (1.07-1.59)
Female	68/146 (46.6)	60/164 (36.6)	1.64 (0.99-2.72)
Smoking status			
Never	67/160 (41.9)	146/363 (40.2)	1.17 (0.78-1.78)
Ever	397/998 (39.8)	290/880 (33.0)	1.36 (1.11-1.65)
Previous history of cancer			
No	441/1,115 (39.6)	397/1,173 (33.8)	1.35 (1.12-1.63)
Yes	21/41 (51.2)	37/67 (55.2)	1.83 (0.58-5.78)

*Percentage of respondents with this characteristic and a positive family history of cancer.
†After adjustment by unconditional logistic regression for age, gender, area, and average lifetime trihalomethane levels (μg/L), and smoking status of the subjects when appropriate. Subjects having no first-degree relative diagnosed of cancer were taken as the reference category for al comparisons.

A history of cancer in at least one first-degree relative was reported in 40.1% of the cases compared with 35.1% of the controls (adjusted OR, 1.32; 95% CI, 1.11-1.59; Table 2). The risk of bladder cancer increased with increasing numbers of affected first-degree relatives ($P_{trend} = 0.0004$). No differences were observed related to age at diagnosis of cancer in family members. The increased risk of bladder cancer was observed among all relatives with a history of cancer. However, a significant increase was found among those subjects with affected parents; the greatest increase was observed among those individuals with affected offsprings.

Table 3 shows the familial risks of bladder cancer stratified by selected characteristics of the probands. The risk associated with family history of cancer was higher among those cases diagnosed at age ≤45 years (OR, 2.67; 95% CI, 1.10-6.50) than among older cases (OR, 1.27; 95% CI, 1.06-1.52), but the test for interaction did not reach statistical significance ($P = 0.103$). There was little or no association between bladder cancer and family history of cancer among never smoker subjects or among those with previous history of cancer. Again, *P* values for interaction between these variables and family history of cancer were not significant.

Table 4 shows the risk of bladder cancer according to family history of cancer at specific sites. Sixteen (1.4%) cases and 9 (0.7%) controls reported at least one first-degree relative with bladder cancer (OR, 2.34; 95% CI, 0.95-5.77). Only one case, diagnosed at age 56 years, had two affected relatives with bladder cancer (the father, diagnosed at age 70 years, and a brother diagnosed at age 50 years). Furthermore, three cases and their relatives were diagnosed with bladder cancer before age 60 years. A family history of tobacco-related cancers was associated with a significantly increased risk for bladder cancer (OR, 1.69; 95% CI, 1.28-2.23). In addition, statistically significant associations emerged between bladder cancer risk and family history of cancer of the esophagus (OR, 2.73; 95% CI, 1.07-6.97), lung (OR, 1.64; 95% CI, 1.14-2.36), prostate (OR, 2.15; 95% CI, 1.28-3.61), and brain (OR, 2.88; 95% CI, 1.00-8.27).

Because polymorphisms in *NAT2* and *GSTM1* are well-established susceptibility factors for this tumor, we have analyzed the relationship between family history of some types of cancer and bladder cancer risk after stratification according to *NAT2* and *GSTM1* genotypes (Table 5). The effect of overall family history of cancer was similarly significant among cases with rapid/intermediate versus slow *NAT2* acetylators and among *GSTM1* present versus null genotypes. However, and despite the small number of cases, the risk of

Table 4. ORs and 95% CIs for bladder cancer according to family history of selected cancers

Family-history cancer site	Cases (n = 1,158)	Controls (n = 1,244)	OR* (95% CI)
None	694	808	Reference (—)
All sites	464	436	1.32 (1.11-1.59)
Urinary bladder	16	9	2.34 (0.95-5.77)
Tobacco-associated sites †	168	125	1.69 (1.28-2.23)
Non–tobacco-associated sites	300	288	1.18 (0.96-1.44)
Lip, oral cavity, and pharynx	11	10	1.34 (0.53-3.40)
Esophagus	16	8	2.73 (1.07-6.97)
Stomach	54	57	1.10 (0.72-1.68)
Intestine	38	48	0.93 (0.58-1.49)
Liver	40	46	1.04 (0.65-1.67)
Pancreas	14	10	1.43 (0.60-3.44)
Larynx	24	23	1.46 (0.77-2.79)
Lung	90	67	1.64 (1.14-2.36)
Bone	10	11	0.90 (0.36-2.26)
Female breast	57	43	1.50 (0.95-2.37)
Uterus, unspecified	18	19	1.41 (0.70-2.84)
Ovary	5	10	0.75 (0.25-2.31)
Prostate	43	29	2.15 (1.28-3.61)
Kidney	5	6	1.12 (0.30-4.09)
Brain	13	6	2.88 (1.00-8.27)
All lymphomas	3	2	1.83 (0.27-12.5)
Leukemia, unspecified	19	17	1.47 (0.71-3.02)

*After adjustment by unconditional logistic regression for age, gender, area, and smoking status of the subjects and average lifetime trihalomethane levels (μg/L).
†Include cancers of the oral cavity and pharynx, respiratory organs, esophagus, pancreas, urinary bladder, and kidney.

bladder cancer for those reporting a family history of bladder cancer was 4.76 (95% CI, 1.25-18.09) among *NAT2*-slow acetylators and 1.17 (95% CI, 0.17-7.86) among *NAT2*-rapid/intermediate cases ($P_{interaction}$ = 0.609). Interestingly, family history of tobacco-related cancers did not show a different risk according to *NAT2* phenotype. For the *GSTM1* genotype, *GSTM1*-null subjects and *GSTM1*-present subjects reporting a history of bladder cancer among their first-degree relatives had risks of 2.91 (95% CI, 0.44-19.09) and 4.21 (95% CI, 1.26-14.14), respectively ($P_{interaction}$ = 0.712).

Discussion

Findings from this study add further evidence that bladder cancer has a familial component. We observed an increase in bladder cancer risk of ~32% among subjects with one or more first-degree relatives with history of cancer and the risk increased with increasing number of family members with cancers. The higher risk observed among bladder cancer patients diagnosed at younger ages also supports the familial aggregation hypothesis.

A higher risk of bladder cancer was observed for patients with family history of bladder cancer (OR, 2.34; 95% CI, 0.95-5.77). Excess risk of similar magnitude has been reported in other case-control studies. The largest population case-control study of 2,982 bladder cancer patients and 5,782 controls conducted in the United States on family history of cancer found a risk of 1.45 (95% CI, 1.2-1.8) for those with a first-degree relative with cancer of the genitourinary tract (8). When we added kidney and ureter sites in a joint category of urinary tract cancers among first-degree relatives, the risk of bladder cancer decreased to 1.93 (95% CI, 0.93-3.97).

Kantor et al. (8) reported a higher risk among younger patients (OR, 2.7; 95% CI, 0.8-2.9) and among women (OR, 1.8; 95% CI, 1.1-2.7); the former observation is also confirmed in our study and the latter cannot be appropriately assessed because of the lower incidence of bladder cancer among women in Spain, where the male/female ratio of bladder cancer is 7.4:1 (1). In a population-based family case-control study in Netherlands based on patients with urothelial cell carcinoma of the bladder, ureter, renal pelvis, and urethra, the risk of bladder cancer among cases with a positive family history was 1.8 (95% CI, 1.3-2.7) compared with controls after adjusting by age, gender, and smoking status of relatives (14). In a hospital-based case-control study in Germany, a significant increase in risk among subjects with family history of bladder cancer was reported (OR, 2.5; 95% CI, 1.1-5.8; ref. 11). On the other hand, several older studies have not found statistically significant increases in risk associated with familial history of cancer (7, 9, 29-33).

We have also evaluated the effect of family history of cancer at specific sites and the association remained statistically significant only for those reporting a family history of tobacco-related cancer, specifically lung and esophagus. The fact that both family history of tobacco-related cancer and personal history of smoking were associated with an increased risk for bladder cancer points to two potential explanations: first, that shared exposures within families such as *in utero* exposure to tobacco compounds, exposure to tobacco carcinogens through breast-feeding, and ETS during childhood, as well as the intensity of the smoking habit among relatives, may account for cancer clusters in relatives (34); second, that a susceptibility polymorphism, or a combination of them, is segregated within families predisposing relatives to cancer in the presence of tobacco exposure. We explored the hypothesis that ETS might contribute to the familial clustering of bladder cancer among the nonsmoker subjects by adjusting the logistic regression models for childhood ETS. Nevertheless, no significant variation of the risk was observed in the nonsmoker group, suggesting that childhood ETS exposure may not explain the clusters of cancer in relatives. Unfortunately, we could not examine to which extent the amount of tobacco smoked among relatives could explain the excess risk because the study lacks this information.

In addition, we found a statistically significant increase in risk among subjects reporting a family history of cancer of the prostate and brain. A family history of bladder cancer was previously reported in a case-control study including 1,294 men with prostate cancer and 1,451 controls, the risk of prostate cancer being 3.5 (95% CI, 1.6-7.4; ref. 35). Furthermore, several studies have reported a high frequency of a concomitant history of bladder and prostate cancer. Kinoshita et al. (36) reported both a significantly increased risk of bladder

Table 5. ORs and 95% CIs for bladder cancer according to family history of bladder cancer stratified by *NAT2* and *GSTM1* polymorphisms

Genotype	Subjects with family history of bladder cancer (cases/controls)	Subjects without family history of bladder cancer (cases/controls)	OR* (95% CI)	$P_{interaction}$
NAT2-slow	14/3	414/412	4.76 (1.25-18.09)	
NAT2-rapid/intermediate	2/4	247/313	1.17 (0.17-7.86)	0.609
GSTM1-null	5/2	423/365	2.91 (0.44-19.09)	
GSTM1-present	11/5	240/363	4.21 (1.26-14.14)	0.712

*After adjustment by unconditional logistic regression for age, gender, area, and smoking status of the subjects and average lifetime trihalomethane levels (μg/L).

cancer after prostate cancer diagnosis and of prostate cancer after bladder cancer diagnosis. Recently, a report on subsequent primary cancers in a large cohort of patients with a first urinary tract cancer described significant excess risk of prostate cancer among those subjects diagnosed of bladder cancer (37). In addition to misreporting of bladder-prostate cancers, increased medical surveillance of patients with bladder cancer as well as secondary effects of bladder cancer treatment should be considered in interpreting these results.

With regard to brain cancer, we have no specific hypothesis to account for the findings. Although the risk estimate was high (OR, 2.88), the statistical significance was borderline. No specific brain cancer histology could be assigned and brain metastases, especially from lung cancer, cannot be completely excluded. Other studies have also reported clustering of bladder cancer with other tumors such as those of the hematopoietic system (12, 14, 37), cervix (12), pancreas (15, 37), kidney, and thyroid (13, 16, 37). Our results did not confirm the familial clustering of bladder cancer with these tumors.

A role for a genetic component in bladder cancer development has also been suggested by other types of studies. Lichtenstein et al. (38) estimated the effects of heritable and environmental factors in the causation of cancer in a cohort of 44,000 twins from Sweden, Denmark, and Finland. They estimated that the proportion of variance corresponding to inherited factors for bladder cancer was 31%, although the estimate was not statistically significant. A recent publication failed to identify candidate regions associated with familial bladder cancer through a genome-wide tiling resolution comparative genomic hybridization array (39). Based on the strong evidence that *NAT2*-slow acetylator and *GSTM1*-null genotypes increase the risk of bladder cancer (4-6), we examined the potential contribution of polymorphisms in *NAT2* and *GSTM1* to the increased risk of bladder cancer associated with a family history of cancer. The results from our study suggest a potential role for the studied polymorphisms in familial bladder cancer clustering, although the small sample size for some genotype strata hampers drawing definitive conclusions. However, it is noteworthy that, as expected, *NAT2*-slow individuals showed a higher increased risk of bladder cancer associated with a family history of bladder cancer than *NAT2*-rapid/intermediate subjects. Whether the differential risk was due to a cosegregation of the polymorphism and the disease within the families or a residual confounding by passive smoking cannot be completely ruled out. In addition to bladder cancer, increased risk of other tumors including those of the esophagus, lung, and prostate (40-44) have been associated with polymorphisms in these genes. These findings would agree with the notion that susceptibility alleles may increase the risk of different types of cancer within families. This is the first study analyzing this hypothesis and our findings support the notion that further work is warranted.

Results of studies evaluating family history of cancer as a risk factor require careful interpretation. Contradictory findings may be explained by the different distributions of both genes and shared environmental exposures among family members, methodologic flaws, and chance. One of the limitations of our study is the lack of information on environmental or lifestyle exposures among family members in our study, possibly leading to false-positive findings. With regard to misclassification of cancer sites among tumors in relatives, some studies have shown that the recall of cancer in first-degree relatives is satisfactory and comparable in cases and controls for some types of cancer (45). Moreover, the quality of the information may vary according to primary site. Pinsky et al. (46) found that family history of some types of cancer, including bladder cancer, was underreported among subjects enrolled in a cancer screening trial in the United States. Metastatic cancer sites can also be mistaken as the primary site. Airewele et al. (47) evaluated the accuracy of cancer reports by comparing information from interviews with data obtained from medical records and death certificates and found high agreement for lung and brain cancer. We assessed the reliability of history of cancer data in families by contacting wives and sisters of those subjects who reported bladder cancer in their relatives. Whereas a patient-relative agreement was observed in 80% of cases, it was only present in 33% of controls, wives and sisters having reported less affected relatives. Therefore, we may be underestimating the actual risk estimates if controls have overreported family history of bladder cancer. Furthermore, some authors have discussed the limitations of the use of case-control studies to assess familial aggregation of cancer (48, 49). They suggest that, even when cases and controls are similar in terms of family size and age of relatives, the association with family history may overestimate ORs.

Our study has relevant strengths. First, it is one of the largest case-control studies to date to assess bladder cancer risk conferred by a family history of cancer in first-degree relatives. Second, the distribution of superficial (76.6%) and invasive (23.4%) cancers among our case series is similar to that described in the general population, indicating that the case series reflects the disease in the general population. We further assessed the association of family history of cancer at any site, as well as family history of bladder cancer, with grade/stage among the cases of our study. In addition, we stratified the analysis in two groups according to age, <45 and ≥45 years. We did not observe any significant association between family history of cancer and stage or grade in the global series nor in any of the age subgroups. Hence, we can rule out a selection bias toward more aggressive disease. Third, environmental exposures shared within families due to ETS and chlorination-by-products were considered in the analysis. Fourth, this is the first report assessing the combined role of family history of cancer and polymorphisms in *NAT2* and *GSTM1*, the genes with the strongest evidence of a role in bladder carcinogenesis. Finally, most of the results present a false positive report probability value below the worthiness cutoff point of 0.2 according to the Wacholder et al. proposal test (50). Even taking into account the low statistical power of *NAT2*-slow result, the false positive report probability for this finding was below 0.5, which is considered important because it is a primary result needed to be replicated in further studies.

In conclusion, family history of cancer in first-degree relatives is associated with an increased risk of bladder cancer, the association being stronger among younger cases. Whereas residual confounding by shared environmental exposure cannot be excluded, these results support the hypothesis that genetic factors play a role in the etiology of bladder cancer. Our results do not have immediate implications on genetic counseling for this disease but should stimulate additional work on the role of low-penetrance cancer-predisposing polymorphisms acting together and/or interacting with environmental factors.

Appendix A. Participating Study Centers in Spain

Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra, Barcelona—Coordinating Center (M. Sala, G. Castaño, M. Torà, D. Puente, C. Villanueva, C. Murta-Nascimento, J. Fortuny, E. López, S. Hernández, R. Jaramillo); Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona (J. Lloreta, S. Serrano, L. Ferrer, A. Gelabert, J. Carles, O. Bielsa, K. Villadiego), Hospital Germans Trias i Pujol, Badalona, Barcelona (L. Cecchini, J.M. Saladié, L. Ibarz); Hospital de Sant Boi, Sant Boi de Llobregat, Barcelona (M. Céspedes); Consorci Hospitalari Parc Taulí, Sabadell (D. García, J. Pujadas,

R. Hernando, A. Cabezuelo, C. Abad, A. Prera, J. Prat); Centre Hospitalari i Cardiològic, Manresa, Barcelona (M. Domènech, J. Badal, J. Malet); Hospital Universitario de Canarias, La Laguna, Tenerife (J. Rodríguez de Vera, A.I. Martín); Hospital Universitario Nuestra Señora de la Candelaria, Tenerife (FJ. Taño, F. Cáceres); Hospital General Universitario de Elche, Universidad Miguel Hernández, Elche, Alicante (F. García-López, M. Ull, A. Teruel, E. Andrada, A. Bustos, A. Castillejo, J.L. Soto); Universidad de Oviedo, Oviedo, Asturias; Hospital San Agustín, Avilés, Asturias (J.L. Guate, J.M. Lanzas, J. Velasco); Hospital Central Covadonga, Oviedo, Asturias (J.M. Fernández, J.J. Rodríguez, A. Herrero), Hospital Central General, Oviedo, Asturias (R. Abascal, C. Manzano, T. Miralles); Hospital de Cabueñes, Gijón, Asturias (M. Rivas, M. Arguelles); Hospital de Jove, Gijón, Asturias (M. Díaz, J. Sánchez, O. González); Hospital de Cruz Roja, Gijón, Asturias (A. Mateos, V. Frade); Hospital Alvarez-Buylla (Mieres, Asturias): P. Muntañola, C. Pravia; Hospital Jarrio, Coaña, Asturias (A.M. Huescar, F. Huergo); Hospital Carmen y Severo Ochoa, Cangas, Asturias (J. Mosquera).

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References

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide, version 1.0. IARC CancerBase No. 5. Lyon: IARC Press; 2004.
2. Kogevinas M, Trichopoulos. Urinary bladder cancer. In: Adami HO, Hunter D, Trichopoulos D, editors. Textbook of cancer epidemiology. New York: Oxford University Press; 2002. p. 446–66.
3. Silverman DT, Devesa SS, Moore LE, Rothman N. Bladder cancer. In: Schottenfeld D, Fraumeni J, editors. Cancer epidemiology and prevention. 3rd ed. New York: Oxford University Press; 2006.
4. Marcus PM, Vineis P, Rothman N. NAT2 slow acetylation and bladder cancer risk: a meta-analysis of 22 case-control studies conducted in the general population. Pharmacogenetics 2000;10:115–22.
5. Engel LS, Taioli E, Pfeiffer R, et al. Pooled analysis and meta-analysis of glutathione *S*-transferase M1 and bladder cancer: a HuGE review. Am J Epidemiol 2002;156:95–109.
6. García-Closas M, Malats N, Real FX, et al. Polymorphisms in *N*-acetyltransferase and glutathione transferase genes and the risk of bladder cancer: Spanish Bladder Cancer Study and meta-analysis. Lancet 2005;366:649–59.
7. Cartwright RA. Genetic association with bladder cancer. Br Med J 1979; 2:798.
8. Kantor AF, Hartge P, Hoover RN, Fraumeni JF, Jr. Familial and environmental interactions in bladder cancer risk. Int J Cancer 1985;35:703–6.
9. Piper JM, Matanoski GM, Tonascia J. Bladder cancer in young women. Am J Epidemiol 1986;123:1033–42.
10. Kramer AA, Graham S, Burnett WS, Nasca P. Familial aggregation of bladder cancer stratified by smoking status. Epidemiology 1991;2:145–8.
11. Kunze E, Chang-Claude J, Frentzel-Beyme R. Life style and occupational risk factors for bladder cancer in Germany. A case-control study. Cancer 1992;69:1776–90.
12. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst 1994;86:1600–8.
13. Plna K, Hemminki K. Familial bladder cancer in the National Swedish Family Cancer Database. J Urol 2001;166:2129–33.
14. Aben KK, Witjes JA, Schoenberg MP, Hulsbergen-van de Kaa C, Verbeek AL, Kiemeney LA. Familial aggregation of urothelial cell carcinoma. Int J Cancer 2002;98:274–8.
15. Hemminki K, Li X. Familial and second primary pancreatic cancers: a nationwide epidemiologic study from Sweden. Int J Cancer 2003;103: 525–30.
16. Czene K, Hemminki K. Familial papillary renal cell tumors and subsequent cancers: a nationwide epidemiological study from Sweden. J Urol 2003;169: 1271–5.
17. Fraumeni JF, Jr., Thomas LB. Malignant bladder tumors in a man and his three sons. J Am Med Assoc 1967;201:507.
18. McCullough DL, Lamma DL, McLaughlin AP III, Gittes RF. Familial transitional cell carcinoma of the bladder. J Urol 1975;113:629–35.
19. Sharma SK, Bapna BC, Singh SM. Familial profile of transitional cell carcinoma. Br J Urol 1976;48:442.
20. Lynch HT, Walzak MP, Fried R, Domina AH, Lynch JF. Familial factors in bladder carcinoma. J Urol 1979;122:458–61.
21. Purtilo DT, McCarthy B, Yang JP, Friedell GH. Familial urinary bladder cancer. Semin Oncol 1979;6:254–6.
22. Mahboubi AO, Ahlvin RC, Mahboubi EO. Familial aggregation of urothelial carcinoma. J Urol 1981;126:691–2.
23. Aben KK, Baglietto L, Baffoe-Bonnie A, et al. Segregation analysis of urothelial cell carcinoma. Eur J Cancer 2006;42:1428–33.
24. Antoniou AC, Pharoah PD, McMullan G, Day NE, Ponder BA, Easton D. Evidence for further breast cancer susceptibility genes in addition to BRCA1 and BRCA2 in a population-based study. Genet Epidemiol 2001;21:1–18.
25. Mostofi FK, Davis CJ, Sesterhen I. Histological typing of urinary bladder tumours. Worlf Health Organization international classification of histological tumours. Berlin: Springer Verlag; 1999.
26. Samanic C, Kogevinas M, Dosemeci M, et al. Smoking and bladder cancer in Spain: effects of tobacco type, timing, ETS and gender. Cancer Epidemiol Biomarkers Prev 2006;15:1348–54.
27. Villanueva CM, Cantor KP, Grimalt JO, et al. Assessment of lifetime exposure to trihalomethanes through different routes. Occup Environ Med 2006;63:273–7.
28. Hosmer DW, Lemeshow S. Applied logistic regression. 2nd ed. New York: John Wiley & Sons; 2000.
29. Wynder EL, Onderdonk J, Mantel N. An epidemiological investigation of cancer of the bladder. Cancer 1963;16:1388–407.
30. Sullivan JW. Epidemiologic survey of bladder cancer in greater New Orleans. J Urol 1982;128:281–3.
31. Iscovich J, Castelletto R, Esteve J, et al. Tobacco smoking, occupational exposure and bladder cancer in Argentina. Int J Cancer 1987;40:734–40.
32. Akdas A, Kirkali Z, Bilir N. Epidemiological case-control study on the etiology of bladder cancer in Turkey. Eur Urol 1990;17:23–6.
33. You XY, Chen JG, Hu YN. Studies on the relation between bladder cancer and benzidine or its derived dyes in Shanghai. Br J Ind Med 1990; 47:544–52.
34. Hemminki K, Chen B. Parental lung cancer as predictor of cancer risks in offspring: clues about multiple routes of harmful influence? Int J Cancer 2006;118:744–8.
35. Negri E, Pelucchi C, Talamini R, et al. Family history of cancer and the risk of prostate cancer and benign prostatic hyperplasia. Int J Cancer 2005;114: 648–52.
36. Kinoshita Y, Singh A, Rovito PM, Jr., Wang CY, Haas GP. Double primary cancers of the prostate and bladder: a literature review. Clin Prostate Cancer 2004;3:83–6.
37. Wilson RT, Silverman DT, Fraumeni JF, Curtis RE. New malignancies following cancer of the urinary tract. In: Curtis ER, Freedman DM, Ron E, et al., editors. New malignancies among cancer survivors. SEER Cancer Registries, 1973-2000. NIH Publication No. 05-5302. Bethesda, MD, 2006.
38. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78–85.
39. Kiemeney LA, Kuiper RP, Pfundt R, et al. No evidence for large-scale germline genomic aberrations in hereditary bladder cancer patients with high-resolution array-based comparative genomic hybridization. Cancer Epidemiol Biomarkers Prev 2006;15:180–3.
40. Chen S, Xue K, Xu L, Ma G, Wu J. Polymorphisms of the CYP1A1 and GSTM1 genes in relation to individual susceptibility to lung carcinoma in Chinese population. Mutat Res 2001;458:41–7.
41. Pinarbasi H, Silig Y, Cetinkaya O, Seyfikli Z, Pinarbasi E. Strong association between the GSTM1-null genotype and lung cancer in a Turkish population. Cancer Genet Cytogenet 2003;146:125–9.
42. Taioli E, Gaspari L, Benhamou S, et al. Polymorphisms in CYP1A1, GSTM1, GSTT1 and lung cancer below the age of 45 years. Int J Epidemiol 2003;32: 60–3.
43. Xing D, Tan W, Lin D. Genetic polymorphisms and susceptibility to esophageal cancer among Chinese population [review]. Oncol Rep 2003;10: 1615–23.
44. Hamasaki T, Inatomi H, Katoh T, et al. *N*-Acetyltransferase-2 gene polymorphism as a possible biomarker for prostate cancer in Japanese men. Int J Urol 2003;10:167–73.
45. Murff HJ, Spigel DR, Syngal S. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. JAMA 2004;292:1480–9.
46. Pinsky PF, Kramer BS, Reding D, Buys S; PLCO Project Team. Reported family history of cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Am J Epidemiol 2003;157:792–9.
47. Airewele G, Adatto P, Cunningham J, et al. Family history of cancer in patients with glioma: a validation study of accuracy. J Natl Cancer Inst 1998; 90:543–4.
48. Khoury MJ, Flanders WD. Bias in using family history as a risk factor in case-control studies of disease. Epidemiology 1995;6:511–9.
49. Liang KY, Beaty TH. Statistical designs for familial aggregation. Stat Methods Med Res 2000;9:543–62.
50. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst 2004;96:434–42.

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