The prognostic value of family history among patients with urinary bladder cancer

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A history of urinary bladder cancer (UBC) in first-degree relatives increases UBC risk by twofold. The influence of positive family history on UBC prognosis is unknown. Here, we investigated association of first-degree UBC family history with clinicopathological characteristics and prognosis of UBC patients. Detailed clinical data of 1,465 non-muscle-invasive bladder cancer (NMIBC) and 250 muscle-invasive or metastatic bladder cancer (MIBC) patients, diagnosed from 1995 to 2010, were collected through medical file review. Competing risk analyses were used to compare recurrence-free survival (RFS) and progression-free survival (PFS) of NMIBC patients according to self-reported UBC family history. Overall survival in MIBC patients was estimated using Kaplan-Meier analysis. The added value of family history in prediction of NMIBC prognosis was quantified with Harrell's concordance-index. Hundred (6.8%) NMIBC and 14 (5.6%) MIBC patients reported UBC in first-degree relatives. Positive family history was statistically significantly associated with smaller tumor size and non-significantly with more favorable distribution of other tumor characteristics. In univariable analyses, positive family history correlated with longer RFS ($p = 0.11$) and PFS ($p = 0.04$). Hazard ratios for positive vs. negative family history after adjustment for clinicopathological characteristics were 0.75 (95% CI = 0.53–1.07) and 0.45 (95% CI = 0.18–1.12) for RFS and PFS, respectively. Five familial and 48 sporadic MIBC patients (Kaplan-Meier 10-year risk: 41% and 25%) died within 10 years. Family history did not improve the c-index of prediction models. This study shows that a first-degree family history of UBC is not clearly associated with NMIBC prognosis. Family history does not aid in prediction of NMIBC recurrence or progression.

Urinary bladder cancer (UBC) ranks ninth in worldwide cancer incidence with approximately 430,000 new cases diagnosed each year.[1] UBC is known as a complex disease to which both environmental and genetic factors contribute.[2] A positive family history is a risk factor for UBC: first-degree relatives of UBC patients have a twofold increased risk to develop UBC themselves.[3,4] The influence of family history on prognosis in UBC patients, however, is still unclear.

The prognosis of UBC is heterogeneous; oncologic outcomes and, therefore, management vary considerably between patients.[5,6] According to the 2013 European Association of Urology (EAU) guidelines, treatment of patients with non-muscle-invasive bladder cancer (NMIBC) should be based on tumor stage, grade, size, and focality, concomitant carcinoma in situ (CIS), and prior recurrence rate. Using these characteristics, patients are classified in a low, intermediate or high

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What's new?

If you have a family history of cancer, you have reason to be concerned. But can your family history help clinicians accurately predict the course of your disease? In this study, the authors compared the prognosis of urinary bladder cancer patients with a positive and a negative first-degree family history – the first ever such investigation. While those who had a relative with the disease did seem to have smaller tumors and slightly more favorable outcomes, the authors could claim no strong statistical correlation between family history of UBC and prognosis.

risk group for recurrence and progression with different chemotherapy or immunotherapy instillation policies.[7] However, accurate identification of NMIBC patients who will actually experience recurrence or progression to muscle-invasive disease remains difficult.[8,9] Therefore, there is a need for additional prognostic factors.

In addition to the potential value for outcome prediction and clinical management decisions, assessment of the prognostic impact of UBC family history could fuel our mechanistic understanding of disease etiology and progression.

For several other cancer types, differences in prognostic outcomes have been found between sporadic and familial patients, although with different directions of effect.[10–16] For UBC, studies that investigated the possible influence of a positive family history on tumor characteristics and prognostic outcomes are scarce. Analysis of the Swedish Family-Cancer Database revealed that overall and bladder cancer-specific survival was similar for familial and sporadic UBC patients.[17] Studies that looked into the relation between family history and UBC stage and grade at diagnosis reported absence of association.[3,4] So far, the effect of a positive family history on recurrence and progression in UBC patients has not been described in the literature.

In the present study, we investigated whether a positive first-degree UBC family history is associated with differences in tumor characteristics and recurrence-free, progression-free, or overall survival among a large population-based series of UBC patients.

Material and Methods

Study population

This study used data of the Nijmegen Bladder Cancer Study (NBCS).[18] In the NBCS, UBC patients diagnosed in one of seven hospitals in the mid-eastern part of the country were identified through the population-based Netherlands Cancer Registry (NCR) held by the Comprehensive Cancer Center the Netherlands (IKNL). The study population consists of UBC patients diagnosed under the age of 75 years from 1995 to 2010. The age threshold was chosen to decrease non-response. Patients were invited to the NBCS by IKNL on behalf of the patients' treating physicians. The NBCS started in May 2007 with invitation of UBC patients diagnosed in 1995 to 2006 who were still alive (prevalent sampling). Later, the NBCS was expanded with three more recently diagnosed patient cohorts (2006–2008, 2008–2009, 2009–2010) in three

phases (January 2009, November 2010, February 2012, respectively). Of all the invitees, 66% agreed to participate. Vital status of patients at December 31st 2012 was obtained through record linkage of NCR data with the Dutch Municipal Personal Records Database. Detailed data on the clinico-pathological characteristics of the primary UBC tumor, treatment, and clinical outcome of participants were collected by a retrospective medical file review. Treatment and follow-up of patients was in accordance with the EAU guidelines.[7,19] All participants gave written informed consent and the study was approved by the Institutional Review Board of the Radboud university medical center, Nijmegen, the Netherlands.

Ascertainment of family history

At study inclusion, patients were asked to fill out a questionnaire that, among others, contains questions on the occurrence of cancer in first-degree family members. Participants were asked to fill out whether a parent, sibling, or child ever had cancer, and if so, of what type and year of diagnosis. A positive family history was defined as having at least one first-degree relative with UBC.

Verification of family history

A small survey was performed to verify and to check validity of self-reported UBC family history. When patients filled out an unclear cancer type for a family member that could indicate UBC, such as "abdominal cancer", or did not specify the cancer type, the cancer type was verified in the NCR. Verification was only possible if the diagnosis was made after January 1, 1989, the starting date of the NCR. For 17 out of 26 relatives with an unclear reported type of cancer, full name and date of birth could be ascertained via a phone call to the NBCS participant. Only seven out of these 17 (41%) relatives could be linked to the NCR; one was found to have (had) UBC. The lack of linkage for the other 10 relatives could be caused by incorrect statement of date of birth or, more likely, could indicate that the family member actually did not have cancer. Furthermore, 11 randomly chosen patients who reported bladder cancer in first-degree relatives were contacted by telephone to ascertain full name and date of birth of these relatives. All were indeed diagnosed with UBC according to the NCR. Based on this survey, the unclear diagnoses reported above were not interpreted as UBC and self-reported first-degree UBC family history was considered to be valid.

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Prognostic endpoint definitions and statistical analyses

χ^2 and Fisher's exact tests were used when appropriate to compare distribution of patient and tumor characteristics according to family history status. Muscle-invasive (stage $\geq$T2) or metastatic bladder cancer (MIBC) patients were omitted from these analyses, as the group with a positive family history ($n = 14$) was too small.

Recurrence- and progression-free survival (RFS and PFS) were determined for NMIBC patients (stage Ta/CIS/T1). Recurrence was defined as a new, histologically confirmed bladder or prostatic urethra tumor following at least one tumor-negative urethrocystoscopy (UCS) or following two surgical resection attempts for the primary bladder tumor. Progression was defined as first occurrence of grade progression, stage progression, local or distant metastasis, and/or cystectomy for therapy-resistant disease. A more detailed description of these prognostic endpoint definitions was published previously.[20] To evaluate the association between family history and NMIBC recurrence and progression, competing risk analyses were conducted. RFS and PFS were defined as the time period between date of the initial transurethral resection of the tumor (TURT) and date of first event (recurrence or progression, respectively), date of last urological check-up, date of death (during urological follow-up), or date of 5-year follow-up, whichever came first. Death was treated as competing event. Cumulative incidence curves (CICs) were constructed and compared between groups using Gray's test.[21] Univariable and multivariable competing risk regression analyses according to the method of Fine and Gray were used to calculate subdistribution hazard ratios (sHRs) and 95% confidence intervals (CIs).[22] In multivariable analyses, patient age at diagnosis, gender, smoking status, number of brothers, number of sisters, initial treatment, concomitant CIS, and tumor stage, grade, and focality were included as covariables. Missing treatment values were imputed with the most frequent treatment category in the dataset for each corresponding combination of tumor stage, grade, and concomitant CIS. Multiple imputation of missing values for tumor focality was conducted using SPSS based on joint distribution of tumor stage, grade, concomitant CIS, treatment, recurrence status, and tumor focality. Five imputations for each missing value were generated. Model estimates of multivariable regression analyses were pooled across the five resulting datasets.

Kaplan-Meier (KM) analysis was used to estimate overall survival (OS) in both familial and sporadic MIBC patients. OS was defined as the time from the initial TURT until death resulting from any cause, date of censoring (December 31st 2012), or date of 10-year follow-up, whichever came first. Because of the low MIBC patient number, no further statistical analyses were performed to compare OS between the family history groups.

The improvement in discrimination performance by including family history in a model with prognostic factors underlying the European Organisation for Research and Treatment of Cancer (EORTC) risk tables for recurrence and progression[23] was assessed by Harrell's concordance(c)-index (adapted to the competing risks setting).[24] First, the available EORTC predictors were included in a competing risk regression model for recurrence and progression, respectively: tumor focality (multifocal *vs.* solitary), stage (T1 *vs.* Ta), grade (high *vs.* low), and concomitant CIS (yes *vs.* no). Patients with primary CIS were excluded in accordance with the EORTC model. Next, family history (yes *vs.* no) was added to the model to determine the incremental predictive value of family history.

Analyses were performed using SPSS v20.0 (IBM Corp., Armonk, NY, USA) and R v3.0.1 (packages: cmprsk, mitools, riskRegression, and pec).

Results

Association of family history with prognosis in NMIBC

Questionnaire and clinical data were available for 1,465 NMIBC patients. Of these, 100 (6.8%) had at least one first-degree relative with UBC. Table 1 presents NMIBC patient and tumor characteristics according to family history status. No statistically significant differences in the distribution of age, gender, or smoking status were noted between family history groups. Familial patients were more likely to have a larger number of siblings than sporadic patients. Overall, familial patients tended to have more favorable tumor characteristics. Familial patients presented more often with Ta stage, absence of concomitant CIS, and a low tumor grade than sporadic patients, although not statistically significant. Familial patients had a tumor size $\geq$3 cm less often than patients with a negative family history ($p = 0.05$). However, information about tumor size was recorded in the medical files of only 20% of patients.

Median follow-up time (time from initial TURT until last urological check-up) of the NMIBC subgroup was 4.6 (interquartile range (IQR): 3.2–7.5) years. In Figure 1, the CICs for NMIBC recurrence and progression by family history status are shown. Five-year cumulative incidence of recurrence was 43% for patients with a positive UBC family history, compared to 48% for patients with a negative UBC family history (Gray's $p = 0.11$). Five-year cumulative incidence of progression was 5% for familial patients and 14% for sporadic patients (Gray's $p = 0.04$). The crude sHRs for family history were 0.76 (95% CI: 0.54–1.07) for recurrence and 0.41 (95% CI: 0.17–0.99) for progression. In multivariable analyses, the adjusted sHRs for recurrence and progression were 0.75 (95% CI: 0.53–1.07) and 0.45 (95% CI: 0.18–1.12), respectively (Table 2).

Association of family history with overall survival in MIBC

The MIBC group consisted of 250 patients, of whom 14 (5.6%) had a positive UBC family history. Median follow-up time (time from initial TURT until December 31st 2012) was 8.4 years (IQR: 5.3–11.8). Five familial patients (Kaplan-Meier (KM) 10-year risk: 41%) and 48 sporadic patients (KM 10-year risk: 25%) died within 10 years. Because of the small sample size, in particular of the positive family history group,

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Table 1. Baseline patient and tumor characteristics of included non-muscle-invasive bladder cancer (NMIBC) patients by first-degree family history of urinary bladder cancer

	FH− (n = 1,365)		FH+ (n = 100)		
	No.	%	No.	%	p
Gender					
Male	1,133	83.0	78	78.0	0.20
Female	232	17.0	22	22.0	
Age at diagnosis (yrs)					
<65	741	54.3	46	46.0	0.11
≥65	624	45.7	54	54.0	
No. brothers					
0	234	17.5	5	5.0	1.1×10^{-5}
1−2	648	48.4	39	39.0	
≥3	458	34.2	56	56.0	
Unknown	25		−		
No. sisters					
0	269	20.0	10	10.0	0.03
1−2	633	47.2	48	48.0	
≥3	440	32.8	42	42.0	
Unknown	23		−		
Smoking status at diagnosis					
Never smoker	250	18.6	16	16.2	0.78
Former smoker	665	49.6	49	49.5	
Lifetime number of cigarettes (cig/d)[1]	15.2	± 9.0	16.2	± 11.2	
Smoking duration (yrs)[1]	26.3	± 12.6	25.7	± 11.3	
Age at start smoking (yrs)[1]	17.1	± 3.2	17.7	± 4.3	
Time since quitting smoking (yrs)[1]	18.5	± 11.2	19.4	± 10.6	
Current smoker	427	31.8	34	34.3	
Lifetime number of cigarettes (cig/d)[1]	15.8	± 6.9	16.0	± 6.7	
Smoking duration (yrs)[1]	37.2	± 12.7	38.2	± 14.3	
Age at start smoking (yrs)[1]	17.1	± 4.0	18.3	± 8.6	
Unknown	23		1		
Tumor stage					
Ta	946	70.5	70	72.9	0.81
CIS	50	3.7	4	4.2	
T1	346	25.8	22	22.9	
Unknown	23		4		
Concomitant CIS					
No	1,235	91.8	93	95.9	0.15
Yes	110	8.2	4	4.1	
Unknown	20		3		
Tumor grade[2]					
Low	862	64.0	69	69.7	0.25
High	485	36.0	30	30.3	
Unknown	18		1		

Table 1. Baseline patient and tumor characteristics of included non-muscle-invasive bladder cancer (NMIBC) patients by first-degree family history of urinary bladder cancer (Continued)

	FH− (n = 1,365)		FH+ (n = 100)		
	No.	%	No.	%	p
Tumor histology					
Urothelial cell carcinoma[3]	1,355	99.9	100	100	1.00
Other	2	0.1	–	–	
Unknown	8		–		
Tumor diameter (cm)					
<3	178	61.6	16	84.2	0.05
≥3	111	38.4	3	15.8	
Unknown	1,076		81		
Tumor focality[4]					
Solitary	739 (778)	57.6 (57.0)	52 (57)	57.8 (57.0)	0.98
Multifocal	543 (586)	42.4 (43.0)	38 (43)	42.2 (43.0)	
Unknown	83 (1)		10 (–)		
Initial treatment[5]					
TURT only (±one immediate p.o. i.v. chemotherapy instillation)	627 (642)	47.5 (47.2)	43 (47)	45.3 (47.0)	0.80
Adjuvant i.v. chemotherapy	411 (430)	31.1 (31.6)	33 (34)	34.7 (34.0)	
Adjuvant i.v. immunotherapy	248 (253)	18.8 (18.6)	16 (16)	16.8 (16.0)	
Both adjuvant i.v. chemo- and immunotherapy	16 (16)	1.2 (1.2)	2 (2)	2.1 (2.0)	
Immediate cystectomy	18 (18)	1.4 (1.3)	1 (1)	1.1 (1.0)	
Other	1 (1)	0.1 (0.1)	– (–)	– (–)	
Unknown	44 (5)		5 (–)		

Missing data were not included in the calculation of the *p* values.
[1]Smoking variables are described as mean ± SD.
[2]Low grade: WHO 1973 differentiation grade 1 or 2, WHO/ISUP 2004 low-grade, or Malmström (Modified Bergkvist) grade 1 or 2a; High grade: WHO 1973 differentiation grade 3, WHO/ISUP 2004 high-grade, or Malmström (Modified Bergkvist) grade 2b or 3.
[3]Pure UCC or mixed with other morphologies.
[4]Between brackets are the pooled numbers and percentages based on the five imputed datasets (in each dataset 92 missing values for tumor focality were imputed).
[5]Between brackets are the numbers and percentages after single imputation of 44 missing values for treatment.
Abbreviations: FH = family history; cig = cigarettes; CIS = carcinoma *in situ*; TURT = transurethral resection of the tumor; p.o. = post-operative; i.v. = intravesical.

we did not perform further statistical analyses or testing to evaluate the impact of family history on OS in MIBC patients.

Prediction of NMIBC recurrence and progression
Harrell's c-index of the model for recurrence that included tumor focality, stage, grade, and concomitant CIS was only 0.54. With the addition of family history the c-index was approximately the same (*c* = 0.55). For progression, the c-index of the model with the four tumor characteristics was 0.66. Including family history resulted again in only a minor increase of the *c*-index (*c* = 0.67).

Discussion
In this study, we investigated the association of first-degree UBC family history with the clinicopathological characteristics and prognosis of UBC patients. Although firm statistical evidence is lacking, this study suggests that familial NMIBC patients show a slightly more favorable tumor profile and have better disease prognosis. As (to our knowledge) we are the first to report on the association between UBC family history and NMIBC recurrence and progression, there are no other studies to refer to.

In approximately 70% of the familial NMIBC patients, UBC diagnosis in the family member preceded diagnosis in the NBCS patient. It is possible that awareness is better in these families leading to an earlier diagnosis, and the somewhat more favorable tumor profile and prognosis among the familial patients in the NBCS series. However, the effect estimates for family history in relation to recurrence and progression were roughly similar prior to and after adjustment for tumor characteristics and other potentially confounding factors. This suggests that these clinical features cannot (fully) explain the favorable, though insignificant, effect on NMIBC
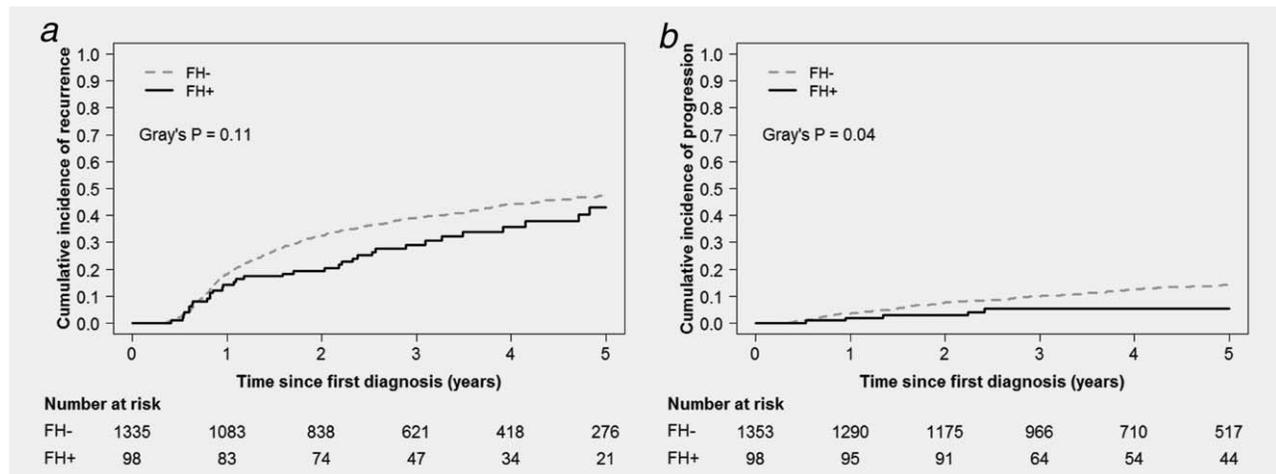
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Figure 1. Cumulative incidence curves for (a) recurrence and (b) progression in primary non-muscle-invasive bladder cancer (NMIBC) patients according to first-degree family history of urinary bladder cancer (UBC). Within five years after diagnosis, 34 NMIBC patients with a positive family history experienced recurrence and five of the familial patients developed progression. Among the sporadic NMIBC patients, 572 and 167 developed recurrence and progression, respectively, during the first five years after diagnosis. FH = (first-degree) UBC family history.

Table 2. Crude and adjusted subdistribution hazard ratios (sHRs) and 95% confidence intervals (CIs) for association between first-degree family history of urinary bladder cancer and recurrence-free and progression-free survival in NMIBC patients

Prognostic endpoint	Univariable analysis		Multivariable analysis[1]	
	FH−	FH+	FH−	FH+
Disease recurrence[2]				
No. at risk	1,335	98	1,260	94
No. events[3]	572	34	542	32
sHR (95% CI)[4]	1 (Ref)	0.76 (0.54–1.07)	1 (Ref)	0.75 (0.53–1.07)
p		0.11		0.11
Disease progression				
No. at risk	1,353	98	1,260	94
No. events[3]	167	5	156	5
sHR (95% CI)[4]	1 (Ref)	0.41 (0.17–0.99)	1 (Ref)	0.45 (0.18–1.12)
p		0.05		0.09

Recurrence and progression status could not be determined for two NMIBC patients with and 12 patients without a positive family history. Due to missing data for covariables, adjusted hazard ratios are based on a smaller number of patients.
[1]Adjusted for age at diagnosis (continuous), gender (male/female), smoking status (never/former/current), number of brothers (0/1–2/≥3), number of sisters (0/1–2/≥3), initial treatment (TURT only/adjuvant i.v. chemotherapy/adjuvant i.v. immunotherapy/both adjuvant i.v. chemo- and immuno-therapy), tumor stage (Ta/CIS/T1), tumor grade (low/high), concomitant CIS (no/yes), and tumor focality (solitary/multifocal). Effect estimates were pooled across the five datasets with imputations for missing values of tumor focality and treatment.
[2]Nineteen patients treated with immediate radical cystectomy were excluded from the recurrence-free survival analysis, as they were not at risk of (intravesical) recurrence.
[3]Number of events within five years after first UBC diagnosis.
[4]Effect estimates based on (Fine and Gray) competing risk regression.
Abbreviations: FH = family history; Ref = reference; NMIBC = non-muscle-invasive bladder cancer; sHR = subdistribution hazard ratio; CI = confidence interval.

prognosis. A difference in therapy between familial and sporadic patients is an implausible explanation for the better prognosis seen in patients with a positive family history, because treatments received did not differ between the two groups.

Causes for a different prognosis may also be found in etiological factors that differ between familial and sporadic cases, and that are not reflected by the evaluated tumor characteristics. These may include genetic variants and environmental factors such as smoking that are shared among family members. We did not find differences in smoking history between familial and sporadic patients. Little is known about genetic factors that cause familial clustering of UBC, let alone their influence on disease outcome. Supported by the relative scarcity of families with multiple UBC cases, previous segregation analysis indicated there is not one major gene

underlying familial aggregation.[25] Yet there are a few examples of rare, high-penetrance susceptibility genes for UBC. Mutations in mismatch repair (MMR) genes (especially *MSH2*) related to Lynch syndrome lead to an increased risk of urinary tract cancer including UBC.[26,27] UBC with extremely early age at onset has been observed among patients with Costello syndrome, carrying de novo germline mutations in *HRAS*.[28] The prognostic implications of these syndrome-related mutations in UBC patients have not been studied yet. Alternatively, familial clustering of UBC could be due to multiple low-penetrance cancer-predisposing polymorphisms acting together and/or interacting with environmental factors.[3,4] A recent paper by our group describes results of a comprehensive evaluation of the prognostic relevance of all confirmed UBC susceptibility variants.[20] This study indicated that carriers of the UBC risk increasing allele of the rs9642880 single-nucleotide polymorphism (SNP) at the *MYC* locus have a better PFS. Suggestive evidence for prognostic influence of several other risk variants was found. Future research should shed further light on the genetic component underlying familial clustering of UBC, and the possible influence on disease outcome.

We investigated whether knowledge of family history status has the potential to improve the discriminative ability of the EORTC model.[23] Notably, we were not able to evaluate the complete EORTC model as described and disseminated via European clinical guidelines as tumor size and exact tumor number were poorly documented in the medical files of a large fraction of the patients. Prior recurrence rate, another EORTC predictor, was not incorporated in our prediction model, because we focused on the risk of a first recurrence and progression after diagnosis of the primary tumor. We found that prediction of recurrence and progression within five years by means of tumor focality, stage, grade, and concomitant CIS was rather poor in our data. Family history classification did not improve the prediction of either event.

In this study the occurrence of cancer among relatives was self-reported. In a previous study by our group we verified self-reported data on urinary tract cancer among relatives of almost 1,200 patients with urothelial cell carcinoma through medical records.[3] The self-reported family history data were found to be very valid; the questionnaire data appeared to be correct for all except one of the affected case- and control-relatives for whom verification was possible (56% and 63%, respectively). Verification of negative family history of cancer via linkage to the NCR showed good accuracy as well; only 2.6% of the relatives, who did not have any malignancies according to the questionnaire, could be linked to the cancer registry because of cancer at any site. Our current small validation study also indicated good validity of self-reported UBC family history based on linkage to the NCR.

A limitation of this study is that, despite the large study population, the subset of familial patients was relatively small. Only five of the 100 NMIBC patients that reported UBC among first-degree family members showed disease progression, and only five out of 14 familial MIBC patients died. Evaluation of the relationship between family history and a stricter definition of progression, *i.e.*, transition from NMIBC to MIBC, was hampered by even lower number of events in the positive family history group. In addition, because patients were selected on their vital status at inclusion (at most 12 years after initial diagnosis), those patients with the worst prognosis were less likely to be included. This selection of patients with a better prognosis may have biased study results, probably to a larger extent for progression than for recurrence. Strengths of this study are the detail at which clinical information was retrieved, the long follow-up, and the population-based setting.

To summarize, despite indications for slightly more favorable tumor characteristics and NMIBC prognosis, this study does not provide strong evidence that a positive history of UBC in first-degree relatives is correlated with disease prognosis. Family history does not contribute to prediction of NMIBC recurrence or progression in addition to currently used tumor characteristics. Investigation among independent patient series is required to validate our findings in NMIBC, and to draw conclusions about the value of family history information for counseling and clinical decision-making in MIBC patients.

Acknowledgements

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