INVITED ARTICLE

Hereditary bladder cancer

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Abstract

First degree relatives of patients with bladder cancer have a two-fold increased risk of bladder cancer but high-risk bladder cancer families are extremely rare. There is no clear Mendelian inheritance pattern that can explain the increased familial risk. This makes classical linkage studies for the mapping of susceptibility genes impossible. The disease is probably caused by a combination of exposure to exogenous carcinogens and a large number of susceptibility genes with modest effects. Genome-wide association studies are better suited to identify these genes. Three such studies are currently underway and are expected to report their results in 2008.

Key Words: *Hereditary, bladder cancer, familial clustering*

Introduction

The study of hereditary cancer syndromes such as hereditary breast cancer and hereditary non-polyposis colorectal cancer has been very successful. During the past two decades several high-penetrance tumour suppressor genes and DNA repair genes have been discovered which have had important implications for clinical management and genetic counselling. Among the urological cancers, prostate and renal cell cancer are known to have hereditary subtypes and susceptibility genes have been identified. In this article, the evidence for the existence of a hereditary subtype of urinary bladder cancer is reviewed.

Anecdotal evidence for an inherited subtype

The first indication for the existence of an inherited subtype of bladder cancer comes from case reports. Thelen and Schaeuble were the first to report familial clustering of urothelial cell carcinoma (UCC) in 1957, when they described identical male twins with “benign transitional cell papillomas of the bladder” [1]. Later, Fraumeni and Thomas reported a family of Russian-Jewish origin with a

father (age at diagnosis 54 years) and three of his sons (aged 57, 64 and 64) affected by bladder cancer [2]. Benton and Henderson presented a 19-year-old patient with bladder cancer whose father was diagnosed with bladder cancer 1 year before. Although the son was occupationally exposed to glues and solvents and the father was a welder, the early ages at diagnosis argue against a pure exogenous cause [3]. A striking family was reported by McCullough et al. in six members of a two-generation family. Four affected patients were diagnosed before the age of 50 years, two before the age of 40. Two of the patients later developed upper urinary tract UCC and five had other tumours (basal cell, stomach, prostate, cervix uteri and unknown primary). An identical twin of one of the patients died of melanoma at the age of 63 years [4]. A germline mutation in one of the unaffected parents of three affected brothers seems likely in this extraordinary pedigree. Several other case reports [5–8] also suggest but cannot prove the existence of an inherited subtype of bladder cancer. More formal evidence for familial aggregation and segregation patterns must come from epidemiological studies, while linkage studies and/or modern molecular biology methods are

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needed for the mapping and identification of susceptibility genes.

Epidemiological evidence

Only a few epidemiological studies specifically addressed the issue of familial bladder cancer while controlling for the number, age and smoking status of family relatives. Kramer et al. collected demographic data and cigarette smoking status on all first degree relatives of 319 men with bladder cancer diagnosed in New York State and 319 neighbourhood controls [9]. The two cohorts of relatives were then linked to the New York State Tumor Registry to obtain valid data on cancer occurrence. Fourteen cases of bladder cancer were found among 1619 relatives of patients, while seven were found among 1773 relatives of controls [adjusted hazard ratio (HR) 1.9, 90% confidence interval (CI) 0.9–4.1]. Kiemeny et al. identified the first to third degree relatives of 190 patients with bladder, ureter or renal pelvis UCC diagnosed between 1983 and 1992 in Iceland through the Icelandic Cancer Family Resource. The records of these 12 328 relatives were subsequently linked to the 1965 to 1994 cancer registry. In 41 of the 190 pedigrees at least one relative had UCC of the urinary tract: observed to expected (O/E) ratio 1.2 (95% CI 0.9–1.7). Surprisingly, the O/E ratio was higher among second and third degree relatives than among first degree relatives, which argues against the existence of a hereditary subtype of bladder UCC, at least in the founder population of Iceland [10].

One of the largest studies has been conducted in the Netherlands. Using a family case-control design, 1193 patients, newly diagnosed with UCC of the bladder, ureter, renal pelvis or urethra, were contacted. Information on the patients' first degree relatives was collected by postal questionnaires and subsequent telephone calls. The patients' partners filled out a similar questionnaire on their relatives. All reported occurrences of UCC among the 8014 first degree case-relatives and 5673 control-relatives were verified using medical records. Among the case-relatives, 101 individuals were diagnosed with cancer of the bladder ($n=97$), ureter ($n=3$) and renal pelvis ($n=1$), compared with 38 individuals among the control-relatives (bladder $n=36$, ureter $n=1$ and urethra $n=1$). In six case-families and two control-families, two affected first degree relatives were found. Overall, 8% of the patients had a positive family history of UCC compared with 4% of the controls. The mean age at diagnosis of patients with a positive family history was similar to that of patients with a negative family history (62 years). The mean age at diagnosis of UCC among

affected case-relatives was only slightly lower than that of affected control-relatives (64 vs 66 years). The cumulative risk of UCC among case-relatives was 3.8% compared with 2.1% among control-relatives. The age, gender and smoking-adjusted random effect hazard ratio of UCC for case-relatives compared with control-relatives was 1.8 (95% CI 1.3–2.7). This risk appeared to be higher among women (HR = 3.2) and among non-smokers (HR = 3.9), but stratification by probands with upper versus lower urinary tract UCC, by probands with a pTa versus pT1+ tumour and by younger and older probands did not suggest different results. Also, there was no striking clustering of tumours at other sites among all case-relatives. Among case-relatives with a positive family history of UCC, there was a non-significant clustering of tumours of the female genital organs, non-UCC urinary tract tumours and cancer of the haematolymphopoietic system [11]. (See Box 1 for a summary of the features of familial bladder cancer.)

Another large case-control study from Spain among 1158 bladder cancer cases and 1244 controls found an increased risk of bladder cancer by a factor of 2.34 (95% CI 0.95–5.77) for those reporting a positive family history of bladder cancer [12]. This

Box 1. Features of familial bladder cancer (BIC) as assessed in the Dutch familial bladder cancer study.

- Approximately 8% of patients with BIC have a first degree relative with BIC.
- Less than 1% have two first degree relatives with BIC.
- The risk of BIC cancer is increased by around two-fold with one first degree relative with BIC.
- This risk may be somewhat higher among women and among non-smokers.
- Increased risk is not due to familial correlation of smoking.
- Increased risk is not very different for relatives of pTa and pT1+ cases.
- The age at diagnosis of patients with and without a positive family history is not very different.
- There is no strong familial clustering of BIC with other types of cancer.
- The familial clustering cannot easily be explained by a Mendelian inheritance pattern.

Source: Aben et al. [11,17].

familial risk was stronger, although not significantly so, among *NAT2* slow-acetylators and among those with a *GSTM1* non-null genotype. In this study, the risk of bladder cancer was also increased with a positive family history of oesophageal [odds ratio (OR) = 2.7], lung (OR = 1.6), prostate (OR = 2.2) and brain cancer (OR = 2.9) but there was no verification of these cancer occurrences among relatives.

Goldgar et al. [13] estimated O/E ratios in the Utah Population Database by identifying all cases of cancer in first degree relatives of patients. The first degree relatives of bladder cancer probands were found to have an increased risk of bladder cancer of 1.5 (95% CI 1.0–2.2) (not adjusted for smoking). When only relatives of young probands (age < 60 years) were considered, the familial risk was 5.1 (95% CI 1.0–12.5). Among these relatives of young probands, a 3.7-fold increase (95% CI 1.1–7.4) in the risk of lymphocytic leukaemia was found.

The cause of familial clustering

The epidemiological studies suggest that the risk of bladder cancer is increased approximately two-fold with a positive family history of bladder cancer, but the cause of this clustering remains unclear. In a twin study from Denmark, Sweden and Finland, Lichtenstein et al. reported a three- to four-fold higher relative risk of bladder cancer among monozygotic twins (6.6; 95% CI 2.6–16.9) than among dizygotic twins (1.7; 95% CI 0.4–6.9). Assuming that the correlation in environmental risk factors is similar among monozygotic and dizygotic twins, this finding suggests the existence of a genetic aetiology of bladder cancer [14].

Dong and Hemminki [15] used the Swedish Family-Cancer Database to quantify the risk of cancer in more than 5.5 million offspring from more than 2 million nuclear families where one of the parents had cancer or one or more of the siblings had cancer. The risk of bladder cancer for offspring was increased by a factor of 1.5 (95% CI 1.1–2.0) if one of the parents had bladder cancer. If one of the siblings had bladder cancer, the risk was increased by a factor of 3.3 (95% CI 1.7–5.8). The higher (relative) risk in the case of an affected sibling was considered to be an indication of a recessive or X-linked transmission model. Because only one of the 12 offspring with bladder cancer who had an affected sibling was female, the authors suggested that an X-linked model was most likely [15]. However, ascertainment bias due to cohort effects in, for example, diagnostic procedures and data quality, may also result in higher risks for siblings. The same holds for a higher correlation in environmental exposures

between siblings compared with parents and offspring. With respect to the latter possibility, in a later study on the Swedish Family-Cancer Database by the same group, it was estimated that 7% of the occurrence of bladder cancer is due to genetic effects, 12% to shared environmental effects, 4% to childhood environmental effects and 77% to non-shared environmental effects [16].

The family case-control study from the Netherlands performed complex segregation analysis to evaluate the segregation pattern of bladder cancer within the 1193 families of probands with UCC. Strong evidence for a Mendelian inheritance pattern of UCC through a single major gene was not found. The “no major gene” (or sporadic) model seemed to be the most parsimonious one to describe the occurrence of UCC in these families. However, none of the Mendelian models could be clearly rejected, which means that an inherited subtype of UCC cannot be excluded. A major gene may segregate in some families, but this effect may have been masked by a background of high sporadic incidence. In addition, the families consisted of first degree relatives only, which make the power of segregation analyses fairly limited, despite the large number of families [17]. The same group also evaluated whether mutagen sensitivity plays a role in developing UCC and whether this sensitivity is different in familial and non-familial cases. Intrinsic susceptibility was quantified by a mutagen sensitivity assay [mean number of chromatid breaks per cell (PBLs) after damage induction with bleomycin in the late S-G₂ phase of the cell cycle]. UCC patients showed a higher mutagen sensitivity score than control subjects (mean number of chromatid breaks per cell: 0.91, 95% CI 0.84–0.97, and 0.74, 95% CI 0.69–0.79, respectively; $p = 0.001$). Sporadic and familial patients exhibited the highest susceptibility (0.94, 95% CI 0.82–1.06, and 0.93, 95% CI 0.83–1.03, respectively). Hereditary patients (0.79, 95% CI 0.72–0.86) showed a susceptibility similar to controls [18]. From this study, it can be concluded that mutagen sensitivity (i.e. genetic susceptibility) increases the risk of non-hereditary UCC. The relatively low mutagen sensitivity score among hereditary patients may point to a different carcinogenic pathway.

Recently, Kiemeney et al. [19] performed high-density array comparative genomic hybridization (CGH) studies in probands from 10 families suggestive of hereditary bladder cancer. In all probands large-scale copy number variations were detected, 41 in total, but all variations were already known as polymorphisms.

High-penetrance bladder cancer susceptibility genes

Quite a few genes are known to increase modestly the risk of bladder cancer (reviewed elsewhere in this issue). Only two “high-penetrance” genes are known so far: *RB1* and *CDC91L1*.

RB1

Chan and Pratt described the family of an 11-year-old white girl with bilateral retinoblastoma and multiple non-radiation-induced osteosarcomas [20]. The mother had unilateral retinoblastoma. The maternal grandfather and one of his brothers were diagnosed with bladder UCC at the ages of 60 and 47 years, respectively. Aherne described a family with retinoblastoma and osteosarcoma in which the mother of two affected children had bladder cancer at the age of 40 years [21]. He also summarized five other British cases of retinoblastoma. The father of one patient died of bladder cancer at the age of 50. Three relatively small cohort studies in the 1980s confirmed the increased risk of bladder cancer among relatives of retinoblastoma patients [22–24]. This increased risk appeared to be confined to known carriers of the mutated retinoblastoma gene. Because the protein encoded by the retinoblastoma 1 gene, p105 Rb, functions in cell proliferation, DNA replication, DNA repair and cell-cycle checkpoint control, and because *RB1* mutations are frequently found in bladder tumours, it is possible that hereditary retinoblastoma survivors run an increased risk of bladder cancer. Recently, in a long-term follow-up study from the UK, five bladder cancer cases were found among 144 hereditary retinoblastoma cases, an O/E ratio of 26.3 (95% CI 8.5–61.4) [25]. This study shows that hereditary retinoblastoma patients should also be checked for bladder cancer during lifetime follow-up. Case reports also suggest the occurrence of leiomyosarcomas of the bladder among retinoblastoma survivors [26–28].

CDC91L1

A new bladder cancer gene was discovered by a research group from Baltimore [29]. In 1996, the Baltimore group identified a family in which a male was diagnosed with grade 2 superficial UCC of the bladder at the age of 29 years. He subsequently developed renal pelvis UCC. His mother died of metastatic UCC of the bladder at the age of 65. Because both the proband’s wife and his mother had a history of miscarriages, a karyogram was made which showed a balanced germline translocation t(5;20)(p15;q11) [30]. The group zoomed in at the breakpoints of this translocation, resulting in the

discovery of a new bladder cancer gene at 20q11 [29]. This gene, *CDC91L1* encoding CDC91L1, also called phosphatidylinositol glycan class U (PIGU), has a role in the glycosylphosphatidylinositol (GPI) anchoring pathway. The authors suggested that the gene is amplified and overexpressed in as many as one-third of bladder cancers and primary tumours, indicating that *CDC91L1* should be regarded as an oncogene. The translocation led to overexpression of the gene and, probably, to both bladder cancers in this pedigree. Carriers of the translocation in this family were therefore genetically susceptible for bladder cancer. Because the exact translocation site should be regarded as an extremely rare phenomenon, this gene should not be considered as a candidate for the genetic cause of many patients with hereditary bladder cancer. In addition, the frequent overexpression in bladder tumours was not confirmed in a study from the Netherlands [31]. Thus, the exact role of *CDC91L1* has yet to be established.

Screening in families with bladder cancer

The cumulative risks for a 50-year-old man and woman of developing (non-pTa) bladder cancer before the age of 60 are approximately 0.25% (1 in 400) and 0.07% (1 in 1400), respectively. For male and female 40-year-olds, the risks of developing non-pTa bladder cancer within the next 10 years are 0.06% (1 in 1600) and 0.02% (1 in 5000). In cases with one first degree relative with bladder cancer, these risks are doubled [11]. The absolute risk of bladder cancer for a person with a positive family history is therefore still very small, and probably not a reason for screening. There are too few data to deduce the absolute risk of bladder cancer for people with two first degree relatives with bladder cancer (or one first and one second degree relative in either the paternal or maternal lineage). There are also no data supporting the efficacy of screening unaffected relatives of (at least) two patients. Nevertheless, it seems logical to offer a routine check-up for such relatives. The protocol for such a screening may be:

- starting at the age of 40, or 5 years earlier than the age of the youngest patient in the family
- ultrasonography of the bladder and upper urinary tract at the first screening only
- sediment and cytology once every year (possibly including a marker such as NMP22).

Conclusions

A large number of case reports suggest that UCC of the bladder clusters in families. Epidemiological

studies have shown that the risk of bladder cancer is increased approximately two-fold in case of a positive family history. The cause of this familial clustering is still subject to speculation but several lines of evidence suggest a contributing genetic factor. This genetic factor is rare but its penetrance may be quite high, although not as high as in, for example, hereditary breast, prostate or colorectal cancer. The effect of the genetic factor is probably site specific: there is not a strong clustering of other types of cancers in bladder cancer families. The study of hereditary forms of common cancers has yielded important clues about the aetiology and pathogenesis of both inherited and sporadic forms of these tumours. It has also led to possibilities for genetic testing, early detection and even primary prevention of cancer, as in the case of colorectal cancer and breast cancer. A worldwide collaborative effort to identify and study high-risk bladder cancer families may move the field forward. An alternative approach is genome-wide association (GWA) studies in a classical case-control design. Such studies have recently resulted in very interesting results in other cancer sites. Three GWA studies in bladder cancer are currently underway and the results are expected in 2008.

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