0022-5347/96/1563-0867$03.00/0
THE JOURNAL OF UROLOGY
Vol. 156, 867–872, September 1996
Printed in U.S.A.

Review Article

FAMILIAL TRANSITIONAL CELL CARCINOMA

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ABSTRACT

Purpose: Bladder cancer is a common malignancy, and a frequent cause of urological consultation and surgical intervention. Except for smoking and certain occupational exposures, the etiology of bladder cancer is largely unknown. Although the majority of patients with bladder cancer do not have a family history of transitional cell carcinoma of the urinary tract, the study of familial transitional cell carcinoma may lead to knowledge of the pathogenesis of this disease.

Materials and Methods: To evaluate the current understanding of familial transitional cell carcinoma, we reviewed the contemporary literature for case reports and epidemiological studies about this disease.

Results: Numerous case reports document the clustering of transitional cell carcinoma in families, several of which demonstrate an extremely early age at onset of disease, which argues in favor of a genetic component to familial transitional cell carcinoma. The results of large epidemiological studies also suggest the existence of familial transitional cell carcinoma, and first degree relatives appear to have an increased risk for disease by a factor of 2. Familial clustering of smoking does not appear to be the cause of this increased risk.

Conclusions: Familial transitional cell carcinoma may be the result of a genetically transmitted predisposition to disease, at least in some affected families. Further studies are required to identify candidate genes that may be responsible for this form of bladder cancer.

KEY WORDS: carcinoma, transitional cell; bladder neoplasms; hereditary diseases

Bladder cancer is the fourth most common tumor among white men in Western Europe and the United States, following prostate, lung and colorectal cancer.[1–3] In the United States the annual age adjusted incidence is 32/100,000 men and the lifetime risk of bladder cancer among white men is 3.6%. The annual age adjusted incidence among white women is 8/100,000.[4] For undetermined reasons black men experience only half the risk of white men, whereas the risk for black women is essentially the same as that for white women.[4] Of bladder cancers 95% are transitional cell tumors. Overall, bladder cancer constitutes the bulk of urothelial transitional cell neoplasms, with upper tract lesions contributing less than 10% of all tumors arising from the urothelial cell surface.[5] Numerous epidemiological studies have shown that only smoking and certain occupational exposures (for example β-naphthylamine, benzidine and 4-aminobiphenyl) can be considered important environmental risk factors for bladder cancer development.[6] Similar data are available for transitional cell carcinoma in the upper urinary tract, the only difference being phenacetin use, which was identified as an additional important risk factor.[7–11]

Although attention has also been paid recently to genetic lesions hypothesized to contribute to transitional cell carcinoma, the role of familial transmission has yet to be completely explored. Case reports suggest a familial component to bladder cancer. In addition, there is strong evidence for an increased risk of ureteral and renal pelvic transitional cell carcinoma in families with hereditary nonpolyposis colon cancer.[12,13] We critically review the available data on familial clustering of transitional cell carcinoma.

FAMILIAL TRANSITIONAL CELL CARCINOMA OF THE BLADDER

Thelen and Schaeuble first reported familial clustering of transitional cell carcinoma in 1957, when they described identical male twins, both smokers, with "benign transitional cell papillomas" of the bladder.[14] Fraumeni and Thomas reported 4 cases of bladder cancer in a family of Russian-Jewish origin.[15] The father was diagnosed with invasive bladder cancer at age 54 years, and 3 sons had bladder cancer at ages 57 and 64 years (2 had well differentiated noninvasive papillary tumors and 1 had metastatic squamous cell carcinoma). All affected individuals in this kindred were heavy smokers but none was employed in a high risk occupation. The mother died of colon adenocarcinoma. In a followup study of this family, 2 sons with bladder cancer later had primary lung cancers.[16]

Benton and Henderson presented the occupational histories of 9 individuals with transitional cell carcinoma of the bladder diagnosed before age 25 years.[17] One patient was a 19-year-old repairman with exposure to glues and solvents. The father, a welder, was diagnosed with transitional cell carcinoma of the bladder 1 year before diagnosis in the son. Although chance occurrence is a possible explanation in this family, the young age at onset of disease strongly favors a hereditary etiology.

Familial bladder transitional cell carcinoma was also re-

Supported in part by a fellowship grant from the Dutch Cancer Society.

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ported by McCullough et al in 6 members of a 2-generation family.[18] Four affected patients were diagnosed before age 50 years and 2 before age 40 years. Two of these patients later had upper urinary tract transitional cell carcinoma and 5 had other tumors (basal cell, stomach, prostate, cervix uteri and unknown primary). Other tumors were also diagnosed among the nonaffected siblings in this kindred, including 1 with leukemia at age 20 years and 1 with breast cancer at age 40 years. Interestingly, an identical twin of a patient in this kindred with transitional cell carcinoma died of melanoma at age 63 years. Although 4 individuals with transitional cell carcinoma were smokers and 2 had high risk occupations (painter and printer), a germline mutation in 1 unaffected parent of 3 affected brothers, resulting in a genetic susceptibility for cancer (especially transitional cell carcinoma) seems likely in this extraordinary pedigree.

Three interesting case reports appeared in the late 1970s and early 1980s.[19–21] Lynch et al reported on 3 siblings diagnosed with bladder cancer before age 50 years.[19] Purtilo et al described 13 cases of bladder transitional cell carcinoma in 6 unrelated families in Massachusetts.[20] The study is interesting because 5 of the 6 families were identified from a registration of 162 incident cases of bladder cancer, yielding a 3% prevalence estimate of familial bladder cancer, and all 3 affected individuals in 1 family were diagnosed with disease at young ages (19, 28 and 33 years old, respectively). Mahboubi et al reported 3 cases of transitional cell carcinoma in a nuclear family.[21]

Bladder cancer within a familial context is often seen in association with carcinomas of nongenitourinary origin. The association with retinoblastoma is especially noteworthy. Chan and Pratt described the family of an 11-year-old white girl with bilateral retinoblastoma and multiple nonradiation induced osteosarcomas.[22] The mother had unilateral retinoblastoma. The maternal grandfather and 1 of his brothers were diagnosed with bladder transitional cell carcinoma at ages 60 and 47 years, respectively. Aherne described a family with retinoblastoma and osteosarcoma in which the mother of 2 affected children had bladder cancer at age 40 years.[23] Aherne also summarized 5 other British cases of retinoblastoma. The father of 1 patient died of bladder cancer at age 50 years. Although based on small numbers, subsequent studies confirmed the greater risk of bladder cancer among relatives of retinoblastoma patients.[24–26] This greater risk appeared to be confined to known carriers of the mutated retinoblastoma gene.

FAMILIAL TRANSITIONAL CELL CARCINOMA OF THE UPPER URINARY TRACT

There are several cases of familial transitional cell carcinoma of the upper urinary tract, the rarity of which favors a genetic origin. Some of these cases were reported before the risk of this tumor was suggested to be great in families with hereditary nonpolyposis colon cancer.[12] Therefore, it is not always possible to evaluate whether familial transitional cell carcinomas of the ureter and renal pelvis occur in a site specific manner. Burkland and Juzek reported on a 68-year-old white woman and her 53-year-old son, both of whom had transitional cell carcinoma of the right ureter.[27] Her oldest sister died of intestinal cancer at age 60 years. Orphali et al described 3 siblings with transitional cell carcinoma of the upper urinary tract.[28] Another sibling had cervical cancer and the father was diagnosed with lymphosarcoma at a late age. Three paternal uncles, both grandfathers, 1 maternal uncle and 1 maternal aunt had unspecified cancers.

Other reports underscore the fact that transitional cell carcinoma of the upper urinary tract may represent a significant expression of hereditary nonpolyposis colon cancer.[29–35] In the Japanese family reported on by Chiba et al the proband was diagnosed with transitional cell carcinoma of the renal pelvis at age 49 years and she subsequently had endometrial carcinoma at age 50 years.[33] The 3 brothers of this patient were diagnosed with colorectal cancer before age 45 years. One brother subsequently had transitional cell carcinoma of the left ureter at age 49 years and multiple bladder tumors at age 51 years. One brother had adenocarcinoma of the stomach and transitional cell carcinoma of the renal pelvis at age 45 years. Greenland et al reported on 4 male siblings with transitional cell carcinoma, 3 of whom had renal pelvis cancer.[35] Two of the 4 siblings and 2 of their children had colorectal adenocarcinoma. A surprising detail in this report is that the family came to attention after the wrong set of records was produced for 1 case. Before that time neither the patients themselves nor the urologist who treated 3 cases was aware of the familial clustering.

The risk of transitional cell carcinoma is also reported to be greater in families with the Muir-Torre syndrome, a rare autosomal dominant condition characterized by at least 1 sebaceous tumor and at least 1 visceral malignancy (predominantly proximal colon cancer). The clinical features of this syndrome can overlap with those of hereditary nonpolyposis colon cancer.[36,37] Families with the Muir-Torre syndrome have an increased risk of upper and lower urinary tract transitional cell carcinoma, in contrast to families with hereditary nonpolyposis colon cancer, in which there is no clear increased risk of bladder cancer.[12,38,39]

Another study suggests that familial transitional cell carcinoma of the upper urinary tract can occur in other settings. Marchetto et al reported on a 48-year-old woman with transitional cell carcinoma of the ureter who had endometrial cancer 2 years later.[40] Her mother had transitional cell carcinoma of the ureter and renal cell carcinoma at age 57 years, and bladder cancer 3 years later. A 69-year-old cousin of the mother had transitional cell carcinoma of the bladder and ureter, and she was diagnosed with endometrial cancer 1 year previously. Four siblings of the mother had breast cancer, liver cancer, gastric adenocarcinoma and lung cancer. The maternal grandfather died of a brain tumor at age 42 years. No colorectal tumors were identified in this pedigree.

Strong familial clustering of transitional cell carcinoma of the upper and lower urinary tract has also been found in some rural areas of the Balkan states of eastern Europe.[41–43] It is likely that the site specific familial clustering in these areas is related to Balkan endemic nephropathy and exposure to environmental causes, such as ochratoxin A.[44] The high risk of transitional cell carcinoma among consanguineous married persons and the low risk among relatives who moved to nonendemic villages strongly argue against a genetic origin.

EPIDEMIOLOGICAL STUDIES

Case-control studies. A variety of studies have examined familial clustering of bladder cancer (see table).[10,45–64] Most studies were small and used an ill-defined definition of family history. However, 3 studies will be highlighted for different reasons. The largest study is a population based examination of 2,982 patients and 5,782 controls conducted in 1978 (the United States national bladder cancer study).[51] Of the cases 6% versus 4% of the controls identified at least 1 member in the immediate family (that is parents and siblings) who had genitourinary cancer. The odds ratio adjusted for race, sex, smoking and age was 1.5 (95% confidence interval 1.2 to 1.8), which can be interpreted as a 50% greater risk of bladder cancer if there is a first degree relative with cancer of the genitourinary tract. This risk appeared to be somewhat greater in persons younger than 45 years (odds ratio 2.7, 95% confidence interval 0.8 to 2.9) and in female patients (odds ratio 1.8, 95% confidence interval 1.1 to 2.7). Unfortunately, examination of family history was not a major objective of this study. Therefore, the authors were unable to

Case-control studies of transitional cell carcinoma in which family history was evaluated

Reference (country)	Disease (No. pts.)	No. Controls	Exposure Measurement	% Prevalence in Controls	Odds Ratio	Adjustment for Smoking	Comment
Morganti et al (Italy)[45]	Bladder Ca (160)	160 Hospital	Bladder Ca in men of first and second degree	1.2	2.0	No	Brief report
Wynder et al (United States)[46]	Bladder Ca (370)	370 Hospital	"Family history" (ill-defined)	?	?	?	No correlation with bladder Ca
Miller et al (Canada)[47]	Bladder Ca (264)	528 Hospital	Family history of Ca	32	1.0	No	Retrospective study
Cartwright (United Kingdom)[48]	Bladder Ca	Hospital	Bladder Ca in first and second degree relatives	?	1.35	?	Total study population 1,261, total prevalence 7.6%, preliminary report, final results never published
Sullivan (United States)[49]	Bladder Ca (82)	169 Population	Family history of urinary Ca	?	?	?	Nonsignificant higher frequency among cases
Najem et al (United States)[50]	Prevalent bladder Ca (75)	142 Hospital	Family history of Ca	?	?	?	No statistically significant difference
Kantor et al (United States)[51]	Bladder Ca (2,900)	5,684 Population	Ca of urinary tract in parents or siblings	3.8	1.5*	Yes	Higher risk in younger pts., women and smokers
Piper et al (United States)[52]	Bladder Ca (162 women 20–49 yrs. old)	162 Population	Bladder/kidney Ca in first degree relatives	0.6	4.0	No	Of 5 pos. answers 3 concern kidney Ca
Bravo et al (Spain)[53]	Bladder Ca (406)	406 Hospital	Family history of Ca	?	?	Yes	Family history improved the multivariate model (but significance level unknown)
Ross et al (United States)[10]	Renal pelvis and/or ureter Ca (187)	187 Neighborhood	Family history of kidney/bladder Ca	0/3.7	∞*/0.6	Yes/No	—
You et al (China)[54]	Bladder Ca (317)	317 Hospital	Family history of bladder/other Ca	?/?	1.29/1.66	No	Brief description of the methods makes interpretation difficult
Akdas et al (Turkey)[55]	Bladder Ca (194)	194 Hospital	Family history	?	?	?	Family history had no impact on the risk of bladder Ca
Kunze et al (Germany)[56]	Benign and malignant tumors of urinary tract (675)	675 Hospital	Bladder Ca in first degree relatives	?	2.5 Men*/ 1.5 women	Yes	—

Not listed in the table are studies in which questions were asked about family history of bladder cancer but that did not yet supply results (possibly indicating negative findings), including studies from Denmark,[57,58] Canada,[59,60] Italy,[61] China,[62] and Iowa.[63] Another study with positive results on family history was reported in the Russian literature only.[64]

* Statistically significant.

distinguish bladder cancer from kidney cancer, for example, and were not able to verify reports of familial cancer. A later study acknowledged that family history was not clearly associated with tumor stage and grade at diagnosis.[65]

Piper et al performed a case-control study in young women, the group with a greater than average odds ratio for family history in the aforementioned United States national bladder cancer study.[52] A total of 162 women with bladder cancer 20 to 49 years old was matched to population controls and asked about the history of bladder or kidney cancer (renal cell and transitional cell carcinoma) in first degree relatives. Four patients (2.5%) and 1 control subject (0.6%) reported a positive family history, yielding an insignificant odds ratio of 4.0. Only 1 individual reported bladder cancer in a parent, and 1 reported that a sister had papillary cancer of the kidney and ureter. The remaining 2 patients and 1 control subject reported kidney cancer in the father. Thus, there is a striking difference between the prevalence of a positive history in this study and that in the United States national bladder cancer study. Of course, young women usually have young relatives with a low risk of bladder cancer. However, in the national bladder cancer study the prevalence was also much greater among female controls only (3.3%) and among controls younger than 45 years (2.0%). The reason for this difference remains unknown.

In a German study conducted by Kunze et al 675 cases of histologically confirmed benign or malignant epithelial tumors of the bladder, ureters, renal pelves and urethra were compared to matched controls with nonneoplastic diseases of the lower urinary tract (predominantly prostatic hyperplasia in men and urinary tract infection in women).[56] An interviewer administered questionnaire noted bladder cancer in first degree relatives. In a multivariate analysis, controlling for smoking status, occupational exposures and phenacetin use, a positive family history showed an odds ratio of 2.5 (95% confidence interval 1.1 to 5.8) in men and a statistically insignificant odds ratio of 1.5 in women. This greater risk in men is in contrast with the findings from the United States national bladder cancer study.[52]

Other epidemiological studies. A disadvantage of the aforementioned case-control studies is that the exposure (bladder cancer in the family) was examined by simple questions asked the patients and controls. No adjustment could be made for total number of relatives, age, sex, smoking status and age of the relatives at cancer diagnosis. However, 1 study specifically addressed the issue of familial bladder cancer, and 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 neighborhood controls.[66] The 2 cohorts of relatives were then linked to the New York State Tumor Registry to obtain valid data on cancer occurrence. A total of 14 cases of bladder cancer was found among 1,619 relatives of patients and 7 were found among 1,773 relatives of controls. In a multivariate proportional hazards regression model with age, sex and smoking status, the hazard ratio of case-control status was 1.9 (90% confidence interval 0.9 to 4.1). According to the authors, there were no instances in which more than 1 first degree relative within a family was affected. Thus, the prevalence of a pos-

itive family history among the controls can be estimated at 2.2%.

In a small hospital based study by Lynch et al the cumulative risk of bladder cancer among first and second degree relatives of 49 consecutively ascertained bladder cancer cases was compared to the expected risk based on the United States third national cancer survey.[67] The cumulative risk among relatives of the patients was 1.63 times greater than expected. The same comparison was made for the relatives of 3 other cancer groups (254 patients with lung cancer, 138 with other smoking related cancers and 564 with nonsmoking related cancers). The risk for the relatives of these patients was not increased. This finding supports a nonenvironmental cause of familial clustering. In an additional analysis the authors found significant heterogeneity of risk across families, and only 3 of the 49 families studied (6%) were at high risk. In contrast, in a study of Danish twins no differences were found between the concordance rate of urinary system cancers in 1,528 monozygotic twin pairs and in 2,609 same sexed, dizygotic twin pairs.[68] In fact, in neither group was a pair with both twins affected found. This result has been used as an argument against a hereditary subtype of bladder cancer. However, the concordance rates of breast cancer and intestinal tumors (for which hereditary forms are known to exist) were also not greater in monozygotic twins.

Skolnick et al,[69] and Bishop and Skolnick[70] presented the mean kinship coefficients of Mormon descendants registered in the Utah population based cancer registry. The kinship coefficient, which expresses the probability that randomly selected homologous genes from 2 individuals are identical by descent, was calculated by using the genealogy data base of the Utah Mormons.[71] They found that lip cancer, melanoma and skin cancer had the highest mean kinship coefficient, followed by ovarian, prostate, colon, breast, rectum and bladder cancer. Mean kinship coefficient for bladder cancer was 2.07×10^{-5}, which was only slightly lower than that for early onset (younger than 50 years) breast cancer (kinship coefficient 2.23×10^{-5}). In comparison, mean kinship coefficient for all cancer sites combined was 1.76×10^{-5} and that for a random sample of 3,000 Utah Mormons was 1.40×10^{-5}, which supports familial clustering of bladder cancer. However, the methodology is indirect and has many caveats. For example, mean kinship coefficient does not distinguish between genetic and environmental causes of familiality. Furthermore, a fairly large mean kinship coefficient may originate from only 1 or a few related individuals (for example 1 pair of siblings among 150 further unrelated bladder cancer patients would result in a kinship coefficient of 2.25×10^{-5}). A later article on the same study population reported that familiality of bladder cancer was greater among the youngest (less than 66 years old) and among female patients.[72]

Future studies. Analysis of currently available data on familial transitional cell carcinoma is flawed by incomplete data collection, and the complexity inherent in performing epidemiological studies on diseases that purportedly result from multifactorial ideologies. In an attempt to address the issue of familial transitional cell carcinoma, a study to confirm hereditary transitional cell carcinoma is about to begin in The Netherlands that will address issues, such as extent of transitional cell carcinoma clustering in families, extent to which this clustering is determined by hereditary factors, mode of inheritance of familial transitional cell carcinomas and whether common karyotypic abnormalities exist in transitional cell carcinoma families. In a recent study a family was identified in which the proband had germline translocation of the short arm of chromosome 5 to the long arm of chromosome 20.[73] Other members of the family had melanoma and transitional cell carcinoma, raising the possibility that this translocation may provide additional information about the genetic underpinnings of familial transmission of bladder cancer. A population based case-control study will be conducted in The Netherlands beginning in 1996 in which 1,000 cases of newly diagnosed transitional cell carcinoma of the bladder, ureter and renal pelvis will be selected from national cancer registries. A detailed family history of cancer in first and second degree relatives will be collected from the patients and spouses via a postal questionnaire. Smoking behavior and occupational exposure will be evaluated. Formal cluster and segregation analyses, as well as karyotypic analyses will be performed.

CONCLUSIONS

It is a well accepted fact that transitional cell carcinoma may cluster in certain cancer family syndromes, such as the Lynch type II (particularly ureter and renal pelvis tumors) and Muir-Torre (lower and upper urinary tract tumors) syndromes. A large number of case reports suggest that familial transitional cell carcinoma also exists as a unique entity despite the fact that it is difficult to draw firm conclusions from such reports. The causes of this familial clustering as well as its frequency are subject to speculation but a contributing genetic cause is likely considering the early age at onset of disease in some families in the literature. The pattern of occurrence is consistent with autosomal dominant inheritance of a major cancer predisposing gene that has decreased penetrance. Except for an early age at disease onset, and possibly clustering with other types of tumors, the case reports do not provide any clear indication about potential characteristics of familial transitional cell carcinoma (for example multiplicity, stage of disease and prognosis).

Evidence for familial transitional cell carcinoma from epidemiological studies is inconclusive. Studies with small sample sizes and those using an indirect approach to evaluate familiality suggest a weak or even absent familial clustering. Large case-control studies, as well as the only study that specifically addresses the issue of familial bladder cancer suggest a familial form of transitional cell carcinoma.[66]

Study of hereditary forms of cancers has yielded important clues about the etiology and pathogenesis of sporadic forms of these tumors. For example, the adenomatous polyposis coli gene is mutated in almost all colon cancers but was first mapped in pedigrees with familial adenomatous polyposis. Furthermore, knowledge of germline mutations may direct early detection of cancer, as is the case in hereditary nonpolyposis colon cancer and hereditary breast cancer. Therefore, it would seem important to confirm the existence of a familial subtype of transitional cell carcinoma, and to search for evidence that such familial clustering may be caused by specific genes.

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