Genitourinary Cancer Predisposition Syndromes

David J. Gallagher, MB, BCh, BAO[a,b,*], Andrew Feifer, MD[c], Jonathan A. Coleman, MD[c]

KEYWORDS

• Genitourinary • Cancer • Predisposition • Genetic

Genitourinary malignancies comprise a heterogenous group of cancers of the prostate, bladder, kidney, and testis that either, only (prostate and testis), or, more commonly (bladder male/female ratio 3:1; kidney male/female ratio 2:1),[1] occur in men. Early epidemiologic studies recognized a hereditary component to all 4 cancers, and subsequent linkage studies identified several rare syndromes whose phenotypes include a genitourinary malignancy (**Table 1**). Among these 4 cancers, testicular cancer seems to have the highest familial clustering, followed by prostate, kidney, and then bladder cancer.[2]

Prostate cancer is the most frequent nondermatologic malignancy in the United States and the second commonest cause of cancer death in men, after lung cancer.[1] Despite evidence from segregation analyses supporting the existence of prostate cancer susceptibility genes, few have been identified. BRCA is a rare exception that has been consistently replicated and seems to explain 2% to 5% of familial prostate cancer (**Table 2**). The discovery of germline determinants of bladder cancer has been similarly elusive. Familial bladder cancer is well recognized but its genetic cause has not yet been explained, and associations with rare predisposition syndromes such as Lynch syndrome (LS) or hereditary retinoblastoma (RB) explain only a minority of its inheritance. The incidence of renal cell cancer is increasing annually, largely because of the incidental discovery of small kidney tumors on imaging whose cause remains poorly understood. Birt-Hogg-Dubé (BHD) syndrome, hereditary leiomyomatosis

Supported by The Sidney Kimmel Center for Prostate and Urologic Cancers and funds provided by David H. Koch through the Prostate Cancer Foundation.

[a] Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA
[b] Genitourinary Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA
[c] Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA
* Corresponding author. Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.
E-mail address: gallaghd@mskcc.org

Hematol Oncol Clin N Am 24 (2010) 861–883
doi:10.1016/j.hoc.2010.06.002 **hemonc.theclinics.com**
0889-8588/10/$ – see front matter

Table 1
Predisposition syndromes whose phenotype contains a genitourinary malignancy

Cancer	Predisposition Syndrome
Prostate	HBOC
Urothelial	Lynch Hereditary RB Costello Apert
Testicular	Peutz–Jeghers Carney complex
Kidney	Birt–Hogg–Dubé HLRCC Von Hippel–Lindau HPRCC WAGR Tuberous sclerosis

Abbreviations: HBOC, hereditary breast-ovarian cancer; HLRCC, hereditary leiomyomatosis and renal cell cancer; HPRCC, hereditary papillary renal carcinoma; RB, retinoblastoma; WAGR, Wilms tumor-aniridia-genitourinary anomalies-mental retardation.

and renal cell cancer syndrome (HLRCC), von Hippel-Lindau (VHL) syndrome and Wilms tumor-aniridia-genitourinary anomalies-mental retardation (WAGR) explain some, but, again, a minority of hereditary kidney cancer. Testicular cancer is most common in white men with a 75% lower incidence reported in African American men, and, like kidney cancer, its incidence is increasing annually. The cause of this increased incidence is unknown, but sons and brothers of affected men have a six- to tenfold increased risk of developing testicular cancer, and family history is the strongest risk factor for the disease, suggesting a strong genetic component.

PROSTATE CANCER

The Evidence for Hereditary Prostate Cancer

Prostate cancer is an umbrella term for a clinically heterogenous group of diseases with distinct natural histories.[3] Despite strong evidence for the existence of prostate cancer susceptibility genes,[4–8] family-based linkage studies have been unable to identify compelling candidates.[8–25] This raises the possibility that the clinical heterogeneity may be further complicated by an underlying genetic heterogeneity that the studies performed to date have been underpowered to detect.

Age, ethnicity, and family history are the principal risk factors for prostate cancer. Family history has been confirmed as a risk factor for prostate cancer irrespective of age, race, or ethnicity, with a reported odds ratio of 2.5 (95% confidence interval [CI], 1.9–3.3) after adjusting for age and ethnicity. In Sweden, a population-based study suggested that approximately 11.6% of all prostate cancer can be accounted for by familial factors alone.[26] A meta-analysis of 33 studies investigating familial clustering suggested that risk was greater for men with affected brothers (risk ratio [RR], 3.4; 95% CI, 1.8–5.7) than for men with affected fathers (RR, 2.2; 95% CI, 1.9–2.5), and risk increased with the number of close relatives affected. Second-degree relatives (RR, 1.7; 95% CI, 1.1–2.6) conferred a lower risk than first-degree relatives, and 2 or more first-degree relatives (RR, 5.1; 95% CI, 2.6–4.2) conferred increased risk compared with 1 (RR, 3.3; 95% CI, 2.6–4.2).[27] Twin studies have further investigated this familial clustering and confirmed a strong genetic component, with a concordance among monozygotic twins of 27% compared with 7.1% between