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E D I T O R I A L

Genetic Basis of Bilateral Renal Cancer: Implications for Evaluation and Management

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Kidney cancer is estimated to affect more than 54,000 individuals in the United States each year and to be responsible for 13,000 deaths in the United States annually.[1] When a patient with localized kidney cancer is treated surgically, 5- and 10-year disease-specific survival can approach 95%. However, despite the remarkable recent advances in targeted therapeutics for kidney cancer, this disease is still fatal for the majority of patients who present with advanced disease.

In this issue of *Journal of Clinical Oncology,* Wiklund et al[2] report an elegant study of the risk of bilateral kidney cancer. In this population-based study from Norway and Sweden, the authors defined the risk of development of bilateral kidney cancer in 28,642 patients observed for an average of 4.4 years. They found asynchronous renal cell cancer in 86 patients. One hundred twelve metachronous bilateral kidney cancer cases were detected during 126,493 person years of follow-up, revealing an overall relative risk of 3.1, with a cumulative incidence of 0.85 after 20 or more years of follow-up. A striking observation in the current work was the finding of a significant increase in relative risk of bilateral disease for young patients diagnosed with this kidney cancer. When compared with the general population, Wiklund et al found a 90% increase in risk for contralateral disease when a patient 60 years or older was diagnosed with kidney cancer, whereas in patients younger than 40 years of age, there was an 1,800% increased risk for the development of cancer in the remaining kidney.[2]

This article raises a number of important issues in the evaluation and management of patients with kidney cancer. Does bilateral disease represent metastasis of the cancer from one kidney to the other, or does it result from a genetic predisposition? In some patients with widespread metastatic disease, metastases may account for tumors in the contralateral kidney. However, in the great majority of patients, the multiple/bilateral tumors seem to arise independently, as occurs in a number of the inherited forms of kidney cancer, such as von Hippel-Lindau (VHL) and Birt-Hogg-Dubé syndrome (Table 1).[3,4] It is also likely that in most instances of nonfamilial bilateral, multifocal kidney cancer, the tumors arise independently. Wiklund et al[2] report on the incidence of bilateral kidney cancer; however, because of the magnitude and nature of this large study, the authors were not able to categorize the tumors by histologic type or to assess the prevalence of multifocality within an individual kidney. If a tumor is bilateral, it is, by definition, multifocal. The nature of this large study likely underestimates the true incidence of bilateral kidney cancer (given that the surveillance was limited to 4 years) and it is likely that in many of the patients there was occult intrarenal multifocality. The finding of bilateral tumors in such a large percentage of patients with this disease suggests that these patients have a genetic predisposition to develop renal cell cancer, and that a single gene alteration is responsible for the development of each of the tumors. This raises the possibility that many patients carry a hereditary predisposition to develop kidney tumors, and their management should be based on the expectation that additional kidney tumors may develop in these patients. If so, removing the entire kidney may be suboptimal, because much of the remaining kidney at the time of surgery may be disease free and functional, and it may be needed in the future.

Table 1. Hereditary Renal Cancer Syndromes

Syndrome	Histology	Gene
von Hippel-Lindau	Clear cell Renal cysts	*VHL*
Hereditary papillary renal cell carcinoma	Type 1 papillary	*MET*
Birt-Hogg-Dubé	Chromophobe Hybrid-oncocytic Clear cell Oncocytoma Renal cysts	*BHD*
Hereditary leiomyomatosis renal cell carcinoma	Type 2 papillary Renal cysts	*FH*
Tuberous sclerosis	Angiomyolipoma Clear cell Oncocytoma	*TSC1* *TSC2*
Succinate dehydrogenase B–associated renal cancer	Clear cell Chromophobe Type 2 papillary Oncocytoma	*SDHB*

Abbreviation: FH, fumarate hydratase.

It has been estimated that 5% to 10% of renal cancers are hereditary. However, 5% to 10% is most likely a significant underestimate of the true hereditary predisposition to renal cancer Important insight into this question comes from the study of Gudbjartsson et al,[5] who studied all patients in Iceland who had renal cancer from 1955 to 1999. When Gudbjartsson et al evaluated whether these individuals with kidney cancer had a relative with kidney cancer, they found a much higher risk in first-degree relatives as well as a significantly higher risk for renal cancer in members of the extended family of an affected individual.[5] The Icelandic study suggests that there may be a genetic predisposition in nearly 60% of patients with kidney

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cancer. The results from the current study of Wiklund et al[2] suggest that young patients with kidney cancer should be actively monitored for the development of recurrence of cancer in the ipsi- or contralateral kidney, and that the possibility of hereditary kidney cancer should be considered.

The results demonstrating an increased incidence of both synchronous and metachronous bilateral kidney tumors will influence current thinking on the management of this disease. The increased incidence of bilateral kidney tumors provides an additional rationale for the use of partial nephrectomy in the management of patients with localized kidney cancer. If a patient were at increased risk of the development of another cancer in the contralateral kidney, the patient would often be better served by a nephron-sparing approach to therapy of the first kidney cancer. In addition, these results highlight the need to carefully evaluate and monitor the patient with localized kidney cancer for bilateral as well as multifocal disease. The finding that there is a 17-fold higher risk for the development of bilateral kidney cancer in patients younger than age 40 years reinforces the need to search for a genetic cause of kidney cancer in patients with bilateral disease, particularly among those younger than 40 years.

An important key to the evaluation and management of patients with bilateral or multifocal kidney cancer lies in the renal cancer pathology. Kidney cancer is not a single disease; it is made up of a number of different types of cancer that occur in the kidney.[6-8] The pathology of the kidney tumor, the patient's clinical phenotype, as well as family history guide the physician to the subsequent evaluation and management of the patient.

The first familial renal cancer gene identified was discovered in families with VHL.[9] There are now seven recognized familial renal cancer syndromes, each has a characteristic pathology, associated physical findings, and mutations in a specific gene that were discovered in extensive family studies.

Patients with VHL are at risk for the development of tumors in a number of organs, including the kidney.[10-12] A family history of retinal angioma, cerebellar or spinal hemangioblastoma, pancreatic neuroendocrine tumors, or pheochromocytomas strongly suggests VHL. In this instance, germline mutation testing for the *VHL* gene is recommended.

Patients affected with hereditary papillary renal carcinoma (HPRC) are at risk for the development of bilateral, multifocal type 1 papillary kidney cancer.[13,14] HPRC is caused by germline mutation of the *MET* gene.[15,16] Birt-Hogg-Dubé (BHD) patients are at risk for the development of bilateral, multifocal chromophobe, and hybrid-oncocytic renal tumors as well as benign cutaneous tumors, fibrofolliculomas,[17] pulmonary cysts, and recurrent pneumothorax.[18] BHD is characterized by germline mutation of the *BHD* gene.[19,20] In patients at risk for BHD, germline mutation testing for the *BHD* gene is recommended. Similar to VHL and HPRC, BHD-associated renal tumors are often managed expectantly until the largest tumor reaches approximately 3 cm in size.[21] Familial renal oncocytoma (FRO) is another familial syndrome in which affected individuals are at risk for the development of bilateral, multifocal oncocytoma.[22] FRO is often confused with BHD; however, patients with FRO do not have pulmonary cysts or fibrofolliculoma, and do not have germline mutation of the *BHD* gene. The renal tumors in patients with FRO are benign and managed expectantly. Patients affected with tuberous sclerosis (TSC) are at risk for manifestations in a number of organs, including the development of bilateral renal tumors, cutaneous lesions, CNS hamartomas, and pulmonary cysts.[23,24] The characteristic TSC renal tumor is a benign angiomyolipoma, although patients with TSC have also been found to have clear cell, chromophobe, and papillary renal tumors.

Hereditary leiomyomatosis renal cell carcinoma (HLRCC) is another hereditary renal cancer syndrome in which affected individuals are at risk for the development of bilateral kidney tumors and cysts as well as cutaneous and uterine leiomyomas.[25] HLRCC is characterized by germline mutation of the Krebs cycle enzyme, fumarate hydratase.[26,27] HLRCC-associated renal tumors are different from VHL, HPRC, or BHD kidney tumors. HLRCC-associated kidney tumors have a pathologic phenotype suggestive of type 2 papillary or collecting duct renal carcinoma, and are aggressive tumors that tend to spread to lymph nodes and can metastasize when the primary tumor is small (< 1 cm).[28,29] Familial pheochromocytoma/paraganglioma (PGL) is another hereditary kidney cancer syndrome in which affected individuals are at risk for the development bilateral and extra-adrenal pheochromocytoma or neck paraganglioma.[30-32] PGL is characterized by germline mutation of one of the B, C, or D isoforms of another Krebs cycle enzyme, succinate dehydrogenase (SDHB, SDHC, or SDHD). Recently, early-onset, bilateral, multifocal kidney cancer has been detected in families with *SDHB* PGL.[32-35] *SDHB* and fumarate hydratase germline mutation testing should be considered in patients with early-onset renal cancer, such as many of those described by Wiklund et al.[2]

Although Wiklund et al[2] were not able to ascertain histologic subtypes in this study, clinical management of patients with bilateral, multifocal renal cancer depends on the histologic type of the renal tumors as well as the patient's clinical phenotype and the family history. It is highly likely that many of the bilateral kidney cancers identified by Wiklund et al occur in individuals who have an underlying genetic abnormality, particularly in early-onset disease. Management of these patients is greatly improved by identifying the genetic cause of the disease. Understanding the genetic basis of bilateral, multifocal renal cancer and the characteristics of the hereditary types of renal cancer provides the foundation for rational evaluation and management of patients who develop kidney cancer.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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