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The genetic basis of bilateral renal cancer: implications for evaluation and management

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Kidney cancer is estimated to affect over 54,000 Americans each year and to be responsible for 13,000 deaths in the U.S. annually.(1) When a patient with localized kidney cancer is treated surgically, 5- and 10-year disease-specific survival can approach 95%. However, in spite of 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 followed for an average of 4.4 years. They found asynchronous renal cell cancer in 86 patients. One hundred and 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 .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 1800% increased risk for the development of cancer in the remaining kidney.(2)

This paper 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 appear to arise independently, as occurs in a number of the inherited forms of kidney cancer, such as von Hippel-Lindau and Birt-Hogg-Dubé syndrome.(3, 4) It is also likely that in most instances of non-familial bilateral, multifocal kidney cancer, the tumors arise independently. Wiklund et al. reported 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.(2)

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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 (as the surveillance was limited to four years) and it is likely that in many of the patients there was occult intra-renal 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.

It has been estimated that 5–10% of renal cancers are hereditary. However, 5–10% is most likely a significant under-estimate of the true hereditary predisposition to renal cancer. Important insight into this question comes from the study of Gudbjartsson *et al* who studied all patients in Iceland who had renal cancer from 1955 to 1999.(5) When Gudbjartsson *et al* evaluated whether or not 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 cancer. The results from the current study of Wiklund *et al.* 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.(2)

The results demonstrating an increased incidence both synchronous as well as 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 is 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 under the age of 40 reinforces the need to search for a genetic cause of kidney cancer in patients with bilateral disease, particularly among those under 40.

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 von Hippel-Lindau.(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 von Hippel-Lindau (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-oncocyctic 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, FRO patients do not have pulmonary cysts or fibrofolliculoma and do not have germline mutation of the *BHD* gene. The renal tumors in FRO patients 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 TS renal tumor is a benign angiomyolipoma, although TSC patients 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 very 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 very aggressive tumors that tend to spread to lymph nodes and can metastasize when the primary tumor is very small (less than 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 *SDHB* PGL families.(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.

Although Wiklund et al. were not able to ascertain histologic subtypes in this study, clinical management of patients with bilateral, multifocal renal cancer (BMF) 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.

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Table 1

Hereditary Renal Cancer Syndromes

Syndrome	Histology	Gene
von Hippel-Lindau (VHL)	Clear Cell Renal Cysts	<i>VHL</i>
Hereditary Papillary Renal Cell Carcinoma (HPRCC)	Type 1 Papillary	<i>MET</i>
Birt-Hogg-Dubé (BHD)	Chromophobe Hybrid-Oncocytic Clear Cell Oncocytoma Renal Cysts	<i>BHD</i>
Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC)	Type 2 Papillary Renal cysts	<i>FH</i>
Tuberous Sclerosis (TSC)	Angiomyolipoma Clear Cell Oncocytoma	<i>TSC1</i> <i>TSC2</i>
Succinate Dehydrogenase B (SDHB)-associated renal cancer	Clear Cell Chromophobe Type 2 papillary Oncocytoma	<i>SDHB</i>

Abbreviations: FH, fumarate hydratase