

KIDNEY CANCER UPDATE

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Genetic Conditions Associated With a Predisposition to Kidney Cancer

Based on a presentation by W. Marston Linehan, MD, at the ASCO Genitourinary Cancers Symposium

Scientists have identified at least 13 genes that predispose patients to the development of kidney cancer, according to W. Marston Linehan, MD. A better understanding of these gene pathways can aid in the diagnosis, management, and treatment of inherited kidney cancer, he said, and can even serve as a “bit of a Rosetta Stone” for understanding sporadic disease.

Dr Linehan, who is surgeon-in-chief at the National Institutes of Health and chief of the Urologic Oncology Branch at the Center for Cancer Research of the National Cancer Institute (NCI) in Bethesda, Maryland, made his remarks during the renal cancer keynote lecture at the 2017 Genitourinary Cancers Symposium of the American Society of Clinical Oncology (ASCO) in Orlando, Florida. His talk focused on several genetic conditions that can lead to kidney cancer (Table): Von Hippel-Lindau (VHL) syndrome, which increases the risk for clear cell renal cell carcinoma (RCC); Birt-Hogg-Dubé (BHD) syndrome, which increases the risk for chromophobe or hybrid RCC; and mutations in the microphthalmia transcription factor gene (*MITF*), which increase the risk for papillary and clear cell RCC. He also discussed hereditary papillary renal carcinoma (HPRC), which increases the risk for papillary type 1 RCC, and hereditary leiomyomatosis and RCC (HLRCC), which increases the risk for papillary type 2 RCC.

“When we started working on kidney cancer 32 years ago, in the early 80s, kidney cancer was viewed as a single disease,” said Dr Linehan. Scientists now know that kidney cancer encompasses multiple types of cancer that vary in histology, clinical course, and response to treatment. These various forms of cancer are caused by different genes.

Von Hippel-Lindau Syndrome

The best-known form of hereditary kidney cancer is caused by VHL syndrome. Patients with this syndrome are at elevated risk for the development of tumors in several organs, including the kidneys. The renal tumors that

are associated with VHL syndrome are always the clear cell form of kidney cancer.

Patients with VHL syndrome–associated clear cell kidney cancer generally undergo nephron-sparing enucleation to remove the tumors. “We’ve taken out as many

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as 92 tumors from 1 kidney in a single patient, and we have taken out more than 50 tumors robotically,” said Dr Linehan. What is notable, he observed, is that metastatic disease has not developed in any of the patients at the NCI who underwent surgery when the largest tumor reached 3 cm.

Patients with a diagnosis of metastatic disease used to have no treatment options, which is what prompted the NCI investigators to use genetic linkage analysis to search for the underlying genetic defect in families. In 1993, the team identified *VHL* as the gene responsible for clear cell kidney cancer in patients with VHL syndrome. The team has identified *VHL* mutations in 100% of nearly 400 families with the syndrome. These were intragenic mutations in 65% of patients, partial or complete deletions in 30% of patients, and splicing defects in 5% of patients. The clinical phenotype varied depending on the type and location of the mutation.

In 1994, Dr Linehan’s team showed that patients with sporadic clear cell RCC also have mutations in *VHL*.

Table. Genetic Conditions Associated With Increased Risk for Kidney Cancer

Condition Increasing Risk	Type of Kidney Cancer
Von Hippel-Lindau syndrome	Clear cell RCC
Birt-Hogg-Dubé syndrome	Chromophobe or hybrid RCC
Mutations in <i>MITF</i>	Papillary and clear cell RCC
Hereditary papillary renal carcinoma	Papillary type 1 RCC
Hereditary leiomyomatosis and RCC	Papillary type 2 RCC

MITF, microphthalmia transcription factor gene; RCC, renal cell carcinoma.

“This was the first indication to us that there is a genetic predisposition to kidney cancer.” They have now detected *VHL* gene mutations in nearly 90% of clear cell renal tumors.

Dr Linehan said that his NCI colleagues and other groups learned over time that the VHL protein is a component of a complex that targets other proteins—such as hypoxia-inducible factor 1 (HIF-1) and HIF-2—for degradation. The VHL complex is an oxygen sensor. When a cell contains a normal amount of oxygen, the VHL complex targets HIF for degradation. When a cell is hypoxic and the complex is unable to target HIF for degradation, HIF accumulates. An overaccumulation of HIF drives the transcription of several genes important in cancer, such as vascular endothelial growth factor (*VEGF*), platelet-derived growth factor (*PDGF*), and transforming growth factor alpha (*TGF- α*). Mutations in *VHL* can cause the VHL protein to behave as if it is hypoxic, leading to the accumulation of HIF and downstream effects on *VEGF*, *PDGF*, and *TGF- α* . This may explain why tumors in clear cell RCC are highly angiogenic and continue to grow.

The elucidation of the VHL pathway by several outstanding scientific groups provided the foundation for the development of therapeutic approaches targeting the VHL/HIF pathway: 9 drugs over the past 12 years that have achieved response rates as high as 45%.¹ The addition of immunologic treatments or other agents may improve results further.

Dr Linehan and his colleagues have evaluated several therapeutic approaches to downstream VHL/HIF pathway targets in patients who have kidney cancer associated with VHL syndrome. To identify a more effective approach with a potentially lower toxicity rate, Dr Linehan and his colleague, Dr Ramaprasad Srinivasan, are

preparing to initiate a clinical trial evaluating the effect of a new agent that targets transcription of the critical HIF-2 pathway. In 2016, the journal *Nature* published 2 studies validating the use of HIF-2 as a target in clear cell RCC.^{2,3}

Hereditary Papillary Renal Carcinoma and *MITF*

Regarding non-clear cell RCC, Dr Linehan described 3 patients he saw in the 80s and early 90s who died after being given a diagnosis of papillary renal carcinoma. The first of these cases was found to be caused by a fusion of the *TFE3* gene, a member of the MiTF transcription factor family. Alterations affecting the MiTF genes (*TFE3*, *TFEB*, and *MITF*) can cause both the hereditary and sporadic forms of kidney cancer, and they appear in nearly 2% of all kidney cancers and in 20% to 45% of kidney cancers occurring in children and young adults. When physicians find it difficult to identify the type of RCC, they should consider mutations in *TFE3* or *TFEB*. *TFE3*-fusion kidney cancer is especially aggressive, and patients do not do well with active surveillance. In families with a history of both kidney cancer and melanoma, physicians should look for germline mutations in *MITF* and *BAP1*.

Another of these early patients was found to have HPRC. HPRC is a hereditary cancer syndrome in which affected individuals are at risk for the development of bilateral, multifocal type 1 papillary RCC. HPRC is caused by germline mutation of the *MET* gene. The *MET* protein is the cell surface receptor for the ligand HGF. In a multicenter trial, researchers at the NCI found that the use of a dual-kinase VEGFR and *MET* inhibitor was able to shrink tumors significantly in patients with germline *MET* gene mutations.⁴ In addition, The Cancer Genome Atlas found in 2016 that more than 80% of patients with type 1 papillary kidney cancer have either a *MET* mutation, an increase in *MET* protein, an increase in phosphorylation, an increase in structural changes, or an increase in *MET* copy number.⁵ The NCI currently is conducting a trial of an agent targeting the *MET* pathway in patients who have papillary renal carcinoma.

Birt-Hogg-Dubé Syndrome

In 1977, Birt, Hogg, and Dubé described BHD syndrome as an inherited condition in which cutaneous fibrofolliculomas tend to develop in affected individuals.⁶ Subsequently, patients affected with BHD syndrome were found to be at risk for the development of kidney tumors.⁷ The tumors in this syndrome can be either solitary or multifocal, and either unilateral or bilateral. Unlike in VHL syndrome, in which the pathology is always of

the clear cell type, or HPRC, in which it is always type 1 papillary RCC, the pathology in BHD is variable. The tumors are mostly chromophobe and hybrid, but clear cell pathology can also be seen, as well as oncocytic and papillary types.⁸

Dr Linehan said that he and his team take the same approach of performing surgery when the largest tumor reaches 3 cm, and metastatic disease has not developed in any patient in whom this approach was used. To identify the gene for BHD disease, folliculin (*FLCN*), the researchers undertook genetic linkage analysis. Dr Linehan's group has found mutations of *FLCN* in 98% of families with BHD syndrome. "We have shown that folliculin binds to FNIP1 and FNIP2, as well as to AMPK (adenosine monophosphate-activated protein kinase), the energy-sensing superhighway of the cell." Folliculin gene mutation also leads to alterations in mammalian target of rapamycin 1 (mTOR1) and mTOR2. The NCI is currently conducting a clinical trial of an agent that targets the mTOR pathway in patients who have BHD syndrome and kidney cancer.

Hereditary Leiomyomatosis and Renal Cell Cancer

Dr Linehan said that "the most humbling disorder" he has studied is HLRCC, which can predispose patients to the development of kidney cancer. The first patient he saw with this disorder—although it was not identified as such at the time—was an 18-year-old woman who died 7 months after presenting to the NCI in 1989. Dr Linehan said that HLRCC is a much more common condition than many people might think. Patients with HLRCC are at risk for the development of cutaneous and uterine leiomyomas, and for the development of a highly aggressive form of type 2 papillary kidney cancer.

The cutaneous leiomyomas can be minimal, or they can be severe and highly symptomatic. Women with the syndrome are at risk for the development of uterine leiomyomas, also known as fibroids, early in life. Dr Linehan

said that in his initial report, 50% of the women with HLRCC had undergone a hysterectomy in their 20s. "So if you have a type 2 papillary renal carcinoma and early fibroids in the family, please think of this." He explained that over an 18-year period, not only the initial patient, but also her mother, brother, uncle, grandmother, and great-aunt, had died of kidney cancer. In patients with HLRCC, surgery rather than active surveillance is recommended. Surgical margins should be wide.

Conclusion

Dr Linehan concluded by saying he is hopeful that understanding the genetic basis of kidney cancer, along with knowing that kidney cancer actually comprises several different types of cancer, will enable physicians to improve the diagnosis and management of hereditary as well as sporadic (nonhereditary) cases of RCC. "We hope that this work will continue to provide the foundation for the development of effective forms of therapy for every patient with this disease," he said.⁹

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