

# HOSPITAL PHYSICIAN®

## ONCOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

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## Kidney Cancer

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# Kidney Cancer

Leonard J. Appleman, MD, PhD

## OVERVIEW

### EPIDEMIOLOGY

Approximately 30,000 Americans are diagnosed each year with kidney cancer (renal cell carcinoma), and nearly 12,000 will die of the disease.<sup>1</sup> Renal cell carcinoma is most commonly diagnosed in patients aged 50 to 70 years, and men are affected more frequently than women. Tobacco and occupational chemical exposures are known environmental risk factors for renal cell carcinoma.<sup>2</sup> Renal cell carcinoma is a component of inherited cancer syndromes including von Hippel-Lindau (VHL) disease,<sup>3</sup> tuberous sclerosis,<sup>4</sup> hereditary papillary renal cancer (HPRC),<sup>5</sup> Birt-Hogg-Dubé (BHD) syndrome,<sup>6</sup> and hereditary leiomyomatosis and renal cell cancer syndrome.<sup>7</sup>

### PATHOLOGY AND MOLECULAR PATHOGENESIS

Clear cell renal carcinoma is the most common histological subtype of kidney cancer, accounting for 75% to 85% of all cases. Papillary (chromophilic) carcinomas comprise 10% to 15% of renal cell cancers. Chromophobe, renal medullary, and collecting duct tumors are less common. Oncocytomas are uncommon, well-differentiated renal tumors that are histologically similar to chromophobe carcinoma and carry little or no risk of metastasizing.<sup>8,9</sup>

Other tumors can arise in the kidneys that are not considered renal carcinoma. Transitional cell carcinomas of the renal pelvis can appear on computed tomography (CT) scan as tumors of the kidney. However, they are histologically similar to the urothelial cancers that arise from the bladder and ureters. Sarcomas, lymphomas, and metastatic tumors from other sites are occasionally seen in the kidneys. Wilms' tumor (nephroblastoma) is the most common kidney tumor of childhood.

Clear cell cancers, which arise from the proximal renal tubules, are a clinical feature of VHL disease. This autosomal dominant cancer syndrome is caused by mutation or deletion of the VHL tumor suppressor gene on human chromosome 3p.<sup>3</sup> Patients with VHL can develop renal cysts and clear cell renal carcinoma,

often with multiple bilateral tumors. Other clinical features include hemangioblastomas of the retina, brain and spine, pheochromocytoma, and cysts of the pancreas and epididymis.

Most sporadic clear cell carcinomas have undergone mutation and/or deletion of both alleles of the VHL gene,<sup>2,10,11</sup> implicating loss of VHL function in the pathogenesis of this histological subtype. The product of the VHL gene, pVHL, is a subunit of a ubiquitin ligase that targets other proteins for degradation.<sup>12</sup> Hypoxia-inducible factor-1 and -2 (HIF1 and HIF2) are transcription factors that are abundant in response to cellular hypoxia. The alpha subunits of the HIF proteins are targeted for degradation by the pVHL ubiquitin ligase in the presence of normal levels of molecular oxygen. Cells that have lost pVHL function therefore have inappropriate overabundance of HIF proteins. Transcriptional targets of HIF, including genes involved in cell growth, survival, and metabolism, are therefore overexpressed. Overexpression of these genes, which are normally under the control of VHL, has been implicated in kidney cancer tumorigenesis. Vascular endothelial growth factor (VEGF) is an HIF transcriptional target that is overexpressed in clear cell kidney cancer. Inappropriate expression of VEGF is implicated in formation of the rich blood supply found in clear cell kidney cancers and the hemangioblastomas associated with VHL syndrome.<sup>12</sup>

Papillary renal cell carcinoma is not commonly associated with loss of the VHL tumor suppressor. HPRC has been linked to activating mutations in the MET tyrosine kinase proto-oncogene,<sup>5</sup> and these mutations have been identified in sporadic papillary RCC as well.<sup>5</sup>

The BHD syndrome is an autosomal dominant cancer syndrome characterized by benign hair follicle hamartomas, renal tumors, lung cysts, and spontaneous pneumothorax.<sup>13</sup> The renal tumors seen in this condition may be clear cell, chromophobe, oncocytoma, or papillary histology.<sup>13,14</sup> The BHD gene on human chromosome 17p encodes a protein known as folliculin, which does not share homology to any proteins of known function but is highly conserved across species. Loss of BHD function through missense mutation, deletion or promoter methylation has been associated with sporadic renal carcinoma.<sup>15,16</sup>