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# Comparison of Papillary Renal Cell Carcinoma Type 1 and Type 2: A Secondary Data Analysis Using the Cancer Genome Atlas

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COMPARISON OF PAPILLARY RENAL CELL CARCINOMA TYPE 1 AND TYPE 2:
A SECONDARY DATA ANALYSIS USING THE CANCER GENOME ATLAS

A Dissertation
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy
Healthcare Genetics

by
Melissa Paquin
December 2020

Accepted by:
Dr. Tracy Fasolino, Committee Chair
Dr. Joseph Bible
Dr. Mary Beth Steck
Dr. Joel Williams

# Abstract

The first chapter in this manuscript serves as an overview of the background, significance, and theological framework of this study, comparison of papillary renal cell carcinoma type 1 and type 2: a secondary analysis. The body of this work focuses on the topics of the current knowledge, genetic variations and syndromes, demographics, increased risk factors, and pathways associated with type 1 and type 2 papillary renal cell carcinoma.

The second chapter is a review of the literature to discuss the current working knowledge on papillary renal cell carcinoma including genetic underpinnings, disease management and histological subtyping. This chapter was designed to give clinicians a better working knowledge on papillary renal cell carcinoma. The results of this review highlight the importance of discovering discernible differences between type 1 and type 2 papillary renal cell carcinoma tumors.

The third chapter is a review of the most common hereditary renal cell syndromes that are associated with an increased risk of developing renal cell carcinomas. This review covered Hereditary Leiomyomatosis and Renal Cell Cancer, a renal cancer syndrome that is characterized by benign neoplasms and is associated with an increased risk of developing type 2 papillary renal cell carcinoma. The results of this review highlighted the complex genetic nature of papillary renal cell carcinoma and provided the background for a variable used in the secondary data analysis.

The fourth chapter describes the dissertation work and was a secondary data analysis on papillary renal cell carcinoma using The Cancer Genome Atlas – Cervical Kidney Renal

Papillary Cell Carcinoma and cBioPortal databases. The analysis focused on determining the epidemiological, increased risk factor and pathway preference differences between type 1 and type 2 papillary renal cell carcinoma. The results of this study showed that while there are some significant differences between tumor types, further studies are warranted.

The final chapter is a synthesis of all the manuscripts related to papillary renal cell carcinoma type 1 and type 2 tumors. This chapter provides a cohesive discussion of all three manuscripts and provides suggestions for future research specific to type 1 and type 2 papillary renal cell carcinoma. The result of all three manuscripts is to better provide an understanding of papillary renal cell carcinoma as a disease and to define differences between type 1 and type.

**Dedication**

I would like to dedicate my dissertation work to my family and friends. I would like to give special consideration to my husband, Mark Paquin, whose support and encouragement gave me the strength needed to complete this program. I'd also like to give a special acknowledgment to my children, Jacoby, Ophelia, Tobin and Callum, who silently sacrificed with me and never ceased to amaze me with their interest and support. Additionally, I would like to recognize my parents, Donna and Brian Eaton for their continued to support and raising me to believe I can do all things.

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**Chapter I**

**Introduction**

**Statement of the Problem**

Renal cell carcinoma (RCC) is among the top ten most commonly occurring cancers in the United States. The American Cancer Society (ACS) estimates around 74,000 new cases will be diagnosed and 15,000 deaths will occur from RCC in 2020 (ACS, 2020). Clear cell renal cell carcinoma (ccRCC) is the most common RCC subtype and as such has been the focus of the majority of RCC research. Specifically, known epidemiological data such as demographics and increased risk factors, have been based on the ccRCC subtype.

Papillary renal cell carcinoma (PRCC) is the second most common RCC subtype comprising 15-20% of total RCC cases (Pal et al. 2018). PRCC is considered a heterogenous disease and is further divided into multiple subtypes, with the two most common subtypes being type 1 and type 2. Current PRCC research has been dedicated to determining the cellular molecular components of the disease, with no significant research distinguishing between type 1 and type 2 PRCC subtypes (MacLennan & Cheng 2020: Lineman et al 2015). However, research has shown that the different PRCC subtypes have varying patient outcomes. Specifically, type 1 tumors tend to be diagnosed at a lower grade and have a better prognosis than type 2 tumors. Furthermore, there are numerous genetic variations in both PRCC tumor subtypes that are not seen in other RCC subtypes, making traditional drug treatment therapies ineffective (Lineman et al 2015; Ahrens et al. 2019).

There are significant gaps in the literature concerning other RCC subtypes in which researchers are striving to address. Such gaps include understanding the epidemiology, genetics and risk factors associated with subtypes other than ccRCC. The goal of this dissertation is to

expand the state of the science regarding type 1 and type 2 PRCC tumors and the genetic relationships.

Papillary renal cell carcinoma (PRCC) is the second most common RCC subtype comprising 15-20% of total RCC cases (Pal et al. 2018). PRCC is considered a heterogenous disease and is further divided into multiple subtypes, with the two most common subtypes being type 1 and type 2. Current PRCC research has been dedicated to determining the cellular molecular components of the disease, with no significant research distinguishing between type 1 and type 2 PRCC subtypes (MacLennan & Cheng 2020: Lineman et al 2015). However, research has shown that the different PRCC subtypes have varying patient outcomes. Specifically, type 1 tumors tend to be diagnosed at a lower grade and have a better prognosis than type 2 tumors. Furthermore, there are numerous genetic variations in both PRCC tumor subtypes that are not seen in other RCC subtypes, making traditional drug treatment therapies ineffective (Lineman et al 2015; Ahrens et al. 2019).

The aim of this research was to determine if there were significant discernible differences, specifically demographics, increased risk factors and genetic pathway preferences between type 1 and type 2 PRCC tumors. The premise for the research was to gain expanded knowledge of type 1 and type 2 PRCC subtypes so clinicians will be able to better identify patients at risk for each subtype and subsequently development appropriate evidence-based treatment plans.

**Significance of the Problem**

PRCC is often difficult to detect with only 5% to 10% of patients presenting with symptoms of hematuria, flank pain and palpable abdominal masses. Furthermore, these symptoms generally occur in advanced stages of the disease when kidney function has been

compromised (Maclennan & Cheng 2020; Diaz de Leon & Pedrosa 2018).  The other 90 to 95% of PRCC tumors are generally found via incidental findings during kidney imaging for other maladies such as hypertension or chronic kidney disease. Traditionally, tumors that are diagnosed early tend to be smaller, less invasive and have a better prognosis than tumors that are found at more advanced stages.  Additionally, PRCC type 1 tumors have higher survival rates and more positive outcomes as compared to type 2 tumors (Grande & Fidler 2015; MacLennan & Cheng 2020).

### *Treatment*

Treatment options for PRCC remains limited with nephrectomy being the standard strategy. Typically, nephrectomy involves the partial or total removal of the kidney, which can results in decrease kidney function. Patients who undergo nephrectomies are at an increased risk of developing hypertension and chronic kidney disease (Glazar et al. 2014). Up to 20% of patients that undergo localized treatment or nephrectomy experience cancer reoccurrence. Even with the reoccurrence rates, there are concerns that partial nephrectomies are too invasive. Thus, surveillance is often recommended as an alternative. Recent technology advances have provided less invasive procedures to help maintain proper kidney function, but not all patients are suitable for these procedures. Currently, there are no successful adjuvant (after surgery) therapies to treat RCCs (Redig et al. 2019; Chien et al. 2020). Targeted treatment therapies have been found to be helpful in the effective treatment of RCCs. These therapies target cancer specific genes or proteins and is the basis of precision cancer treatment. However, current drug therapy options are designed for clear cell renal cell carcinoma and are not specific for treating PRCC. There are several clinical trials in progress but no drug therapy specific to PRCC (Redig et al. 2018; Dengina et al. 2017; Ahrens et al. 2019).

*Monetary Impact*

Along with the physical impact of cancer, there is also a significant burden associated with RCC. Currently, the United States has an annual cost of $600 million, up to $5.2 billion US dollars for all cancers and the cost continues to rise. Specifically, technological advances have increased the cost of localized treatments and nephrectomy for RCC, which can be $20,000 to $50,000. The cost of nephrectomy does not include any additional treatments that may be needed, such drug therapies or necessary dialysis (Jeong et al. 2019; Chien et al. 2020). Moreover, drug treatment therapies have varying costs depending on the drug and whether the drug is a first line or second line treatment therapy. First line treatments can $150,000 whereas second line treatments cost $60,000 to $120,000. However, second line treatments are utilized in conjunction with first line treatments which raises their cost to approximately $350,000. Treatment costs increase with cancer metastasis since more aggressive treatments are needed (Deniz et al. 2019; Chien et al. 2020). These costs reflect the cost of the drug therapy themselves, and do not include doctor visits, lost wages or other costs associated with cancer treatments.

Providing a comprehensive understanding of the epidemiology of PRCC will allow clinicians to distinguish between subtypes at earlier stages. Focusing on the individual risk factors and preferred genetic pathways displayed by each of the two subtypes supports the next stages of genetic research. This new avenue of research will ultimately supply vital criteria to develop individualized treatment plans that will lower treatment costs and increase treatment success rates.

**Theoretical Framework Supporting the Primary Dissertation Problem/Issue**

The theoretical framework for this research project is the integrative cancer theory. Given that PRCC is a heterogenous disease that encompasses a large number of genetic variations,

clinical and epidemiological features, the integrative cancer theory supports the research directive. This theory was developed from the comprehensive integrative theory, which is widely used in psychiatry. The integrative theory views illness, both mental and biological, as a complex disease that needs to be viewed at multiple angles. The theory states that looking at illness from a variety of perspectives will lead to more comprehensive and personalized treatment plans (Lake 2007; Lake 2008). The integrative cancer theory specifically includes three domains: genetic variations, epidemiological factors and environmental risk factors. Each one of the three domains adds to the metabolic imbalance between host and tumor, allowing further tumor proliferation (Luo & Liu 2019).  By looking at PRCC as a complicated disease with multiple components in each domain, disease risk factors will be determined, and treatment plans will be personalized.

The integrative theory for cancer is utilized to conceptualize cancer as a linked genetic disease. In this theory, chronic irritations, defined as any metabolic imbalance (including chronic inflammation, unstable glucose levels and lack of vital nutrients), provoke tumors with genetic alterations and rapid proliferative ability. These tumor cells reprogram their metabolic systems and employ aerobic glycolysis to sustain the rapid growth. Further proliferation occurs in patients with certain characteristics, such as advanced age, obesity, and diabetes (both Type I and Type II). These co-existing conditions trigger a metabolic imbalance between the patient and tumor resulting in catastrophe events of invasion, metastasis, and necrosis (Luo and Liu, 2019). PRCC is a genetically linked disease that encompasses multiple genetic pathways which allow cancer cells to override normal cell signaling.  By overriding normal cytogenetic pathways, PRCC tumors grow, invade surrounding tissue and kill normal cells (Maclennan & Cheng 2020). Therefore, PRCC as a disease follows the conceptual model presented by the integrative cancer theory.

# Integrative Cancer Theory
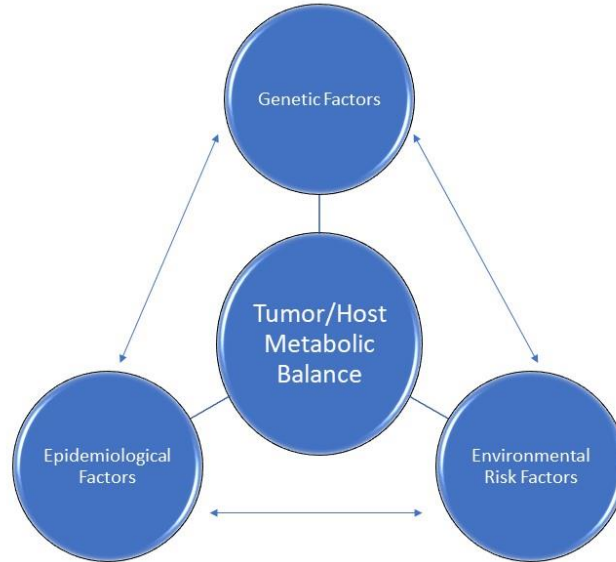


Fig. 1.1 Integrative Cancer Theory

This research views PRCC as a complex heterogenous disease that is not limited to one risk factor or genetic pathway. Furthermore, this study sought to define differences in each of the three domains as described in the integrative theory for cancer. Due to the complex genetic nature of PRCC, genetic pathways were used to fulfil the first domain. Cancer cells will turn off or increase the host and tumor metabolic imbalance on certain genes to manipulate cellular pathways (Luo & Liu 2019). Therefore, looking at PRCC genetic pathways sufficiently satisfies the conditions of the first domain. The second (epidemiological factors) and third (environmental risk factors) domains were categorized as demographics and associated risk factors specific for to this research study. The target demographic variable included in this research were age, ethnicity, gender, and race. Each of these variables have the potential to increase the tumor/host imbalance and promote tumor development. The associated risk factors

examined were body mass index (BMI), smoking history, neoplasm (non-malignant tumor) history, and malignancy history. The integrative cancer theory is appropriate to provide the framework for this dissertation since this research looks at the three domains of PRCC as described in the theory in an effort to identify differences between PRCC subtypes.

**An Overview of the Important Literature**

PRCC tumors are characterized by solid well-defined lesions in the renal papillae or tubulopapillae that are formed by a single layer of cuboidal cells (Grande & Fidler 2015; MacLennan & Cheng 2020). Furthermore, PRCC tumors tend to be multifocal (multiple tumors arise from one tumor in the same location) and necrotic (dead renal cells are present in the tumor). PRCC consists of multiple genetic variations and can be sporadic and hereditary (inherited) with most cases being the sporadic form. Hereditary PRCC is most commonly characterized by mutations in the oncogene Mesenchymal Epithelial Transition (*MET*), although there are multiple genetic variations associated with both sporadic and hereditary PRCC (MacLennan & Cheng 2020). PRCC subtypes are most frequently characterized by histomorphological features, although recent studies suggest using cytomorphological structures to better distinguish between subtypes. Type 1 PRCC tumors are defined as having a single layer of cells with sparse basophilic cytoplasm and small round nuclei. Conversely, type 2 PRCC is defined as a pseudostratified layer of cells with eosinophilic cytoplasm and large spherical nuclei (MacLennan & Cheng 2020; Magers et al. 2019).

Risk factors associated with RCC are supported by current literature, though still limited because they focus on the ccRCC subtype. The first category of risk factors are demographics with certain factors associated with an increased risk for RCC. Research suggests that RCC is less prevalent in women with men being diagnose Men have higher prevalence, 2:1, at a lower

median age of diagnosis of 50-59 years compared to women. In fact, RCC risk increases with age within all sexes until a plateau occurs around 70 years. RCC rates vary by ethnicity/race with the lowest incidence seen in Asian Americans, 8.8 cases per 100,000 and the highest incidence seen in African Americans, 17.5 cases per 100,000 (Hsieh et al. 2019; Diaz de Leon et al. 2017; Howlader et al. 2020). Additionally, there are number of increased risk factors that increase an individual's chance of developing RCC such as increased Body Mass Index (BMI) and the use of tobacco products. One study has shown that BMI and tobacco use were factors in at least half of PRCC cases. Smoking cessation may decrease PRCC risk but limited to those who have quit for ten years or longer (Hsieh et al. 2019; Diaz de Leon et al. 2017).

There are several renal cell cancer syndromes that predispose an individual to the development of RCC. Not only do these renal cell cancer syndromes provide evidence for the genetic variables used in this research study, many of them present with benign neoplasms. BRCA1 Associated Protein-1 (*BAP1*) tumor predisposition syndrome, Birt-Hogg-Dubé syndrome, and Cowden syndrome present with benign tumor growths with associated increased risk for developing RCC. Another example is von Hippel-Lindau syndrome, which is the most common renal cell cancer syndrome and characterized by variations in the Von Hippel–Lindau Tumor Suppressor (*VHL*) gene (Paquin & Fasolino 2020). Additionally, there are numerous genetic variations that have been associated with RCC. At least eleven genes have been linked to hereditary RCC including, Folliculin (*FLCN*), Fumarate Hydratase (*FH*), Phosphatase and Tensin Homolog (*PTEN*), Succinate Dehydrogenase Complex Iron Sulfur Subunit B (*SDHB*), *and* TSC Complex Subunit 1 (*TSC1*). Variations in *MET* have been found in as many as 20% of hereditary PRCC cases as well as in sporadic cases. *MET* variations have been seen in both type 1 and type 2 PRCC tumors (Hsieh et al. 2019; Albiges et al. 2015). However, genetic variations

in RCC are not limited to genetic mutations and include chromosomal copy number variations. Type 1 PRCC shows copy number gains in chromosome 7, whereas type 2 PRCC show losses in chromosome 9 (Modi & Singer 2016). Due to the large number of genetic variations, utilizing genetic pathways may be a more efficient process for comparing type 1 and type 2 PRCC instead of genetic sequencing. Utilizing genetic pathways will cover a larger number of genes allowing the treatment of more patients at once and decreasing cost.

Three manuscripts have been submitted to fulfill the specific aims of this research project. Collectively, the three manuscripts offer a comprehensive view of the differences between type 1 and type 2 PRCC. The target audiences for these manuscripts have been direct patient care clinicians, healthcare clinicians who directly provide patient care, in order to advance their knowledge of the differences in epidemiology, risk factors and genetic pathways associated with type 1 and type 2 PRCC. The following offers detailed information on the three papers:

The first manuscript (Chapter 2) is entitled "Papillary Renal Cell Carcinoma: Epidemiology, Subtype Classification, and Various Genetic Pathways of the Disease" (Under Review). Papillary renal cell carcinoma (PRCC) is a subset of renal cell carcinoma (RCC). PRCC is a heterogenous disease that consists of multiple subtypes, diverse genetic makeups, and a continually changing epidemiology. Similarly, the management of PRCC reflects the complexity of the disease. Clinicians should possess a basic knowledge of the subtype classification, genetic pathways and epidemiology of PRCC in order to develop effective management plans. This paper presented the current applicable knowledge of PRCC as it relates to healthcare clinicians (Paquin & Fasolino, under review).

The second manuscript (Chapter 3) is entitled "Renal Cell Cancer Syndromes: Identification and Management of Patients and Families at Increased Risk" (Paquin & Fasolino 2020). There are many inherited renal cancer syndromes that increase an individual's risk of developing renal cell cancer (RCC). The major autosomal dominantly inherited RCC syndromes include: von Hippel-Lindau syndrome (VHL); Lynch Syndrome/ Hereditary Non-Polyposis Colorectal Cancer (HNPCC); Tuberous Sclerosis Complex (TSC); Birt-Hogg-Dubé Syndrome (BHD); Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC); Cowden Syndrome; and BAP1 Tumor Predisposition Syndrome. The age of onset for these RCC syndromes range from infancy through 65 years. Clinical manifestations vary widely, and multiple body systems can be involved and present unique challenges to the healthcare team. With the advancement of genetic panels, clinicians can screen individuals with known hereditary syndromes for genetic mutations. This paper presented clinically relevant information on specific to the major renal cancer syndrome focusing on the gene mutation, incidence, and clinical implications (Paquin and Fasolino 2020).

The third manuscript (Chapter 4) is entitled Comparison of Papillary Renal Cell Carcinoma Type 1 and Type 2: A Secondary Data Analysis using The Cancer Genome Atlas" (under review). This manuscript is a secondary data analysis using The Cancer Genome Atlas Kidney Renal Papillary Cell Carcinoma (TCGA-KIRP) and cBioPortal data to determine if there were significant differences between type 1 and type 2 PRCC tumors. Demographic, increased risk factor and preferred genetic pathway data were determined for each PRCC tumor type. Then a logistic regression was performed on each variable to determine the probability of that variable being exhibited by type 2 PRCC tumors. This study found that higher age at diagnosis was statistically more likely to be associated with type 2 tumors. Furthermore, type 2 tumors

were found to prefer the PI3K pathway. Being African American had a negative association with type 2 tumors. No increased risk factor variable was found to be significant, however further research is needed to better understand how these variables can be used in determining tumor subtype (Paquin et al., under review).

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**Chapter II**

**Papillary Renal Cell Carcinoma: Epidemiology, subtype classification, and various genetic pathways of the disease.**

**Overview**

      Papillary renal cell carcinoma (PRCC) is a subset of renal cell carcinoma (RCC). PRCC is a heterogenous disease that consists of multiple subtypes, diverse genetic makeups, and a continually changing epidemiology. Similarly, the management of PRCC reflects the complexity of the disease. Clinicians should possess a basic knowledge of the subtype classification, genetic pathways and epidemiology of PRCC in order to develop effective management plans.

**Keywords:** Papillary renal cell carcinoma, cancer treatment, cancer genetics

*Introduction*

      Renal cell carcinoma (RCC) is the 14th most common cancer type worldwide with approximately 430, 262 new cases and 175,098 deaths in 2018 (WHO, 2020). Papillary renal cell carcinoma (PRCC) comprises 15-20% of all RCCs and is the second most common RCC subtype. PRCC is largely considered a heterogenous disease given the histologically and genetically distinct subtypes that vary in prognosis and disease progression. This heterogeneity makes it difficult to diagnose and manage with approximately 20-50% of tumors being discovered incidentally (Fernandes & Lopes 2015; Steffen et al. 2012). Mostly, PRCC is divided into two subtypes, type 1 and type 2 (Pal et al. 2019). The aim of this paper is to provide the clinician with an overview of PRCC inclusive of the epidemiology, subtype classification, and various genetic pathways of the disease so that an appropriate management plan can be created.

*Staging & Grading*

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Typically, renal cancer is asymptomatic and any symptoms that occur are generally attributed to other kidney diseases. Currently, 20-50% of PRCC tumors are discovered through incidental findings (Fernandes & Lopes 2015; Steffen et al. 2012). Similarly, distinguishing between type 1 and type 2 tumors can be difficult as well given the heterogeneity (Fernandes & Lopes 2015; Modi and Singer 2015). Type 1 tumors are diagnosed at a younger age compared with type 2 tumors. Additionally, type 2 tumors present with a poorer prognosis than type 1 tumors (Ahrens et al. 2019).

Tumor stage is a key prognostic parameter in cancer diagnosing. The most common staging system is TNM where each tumor is given a letter and a number stage.  In the TNM system the T represents the size and extent of the main or primary tumor. Similarly, the N represents the extent of lymph node involvement and lastly the M represents the extent of metastasis. The letters representing the aforementioned TNM and the numbers range from 0 (cannot be found) to 3 or more (the higher the number the larger the tumor, the greater the number of involved lymph nodes and the greater the metastasis). If there is an x after the letter then the tumor cannot be found (National Cancer Institute, 2020; Table 1. TNM Staging System).  However, tumors can also be staged in five less descriptive categories. Stage I tumors are confined to the kidney and less than 7.0 cm in size. Stage II tumors are also confined to the kidney but are greater than 7.0 cm with no spread to lymph nodes or distant organs. Stage III tumors have spread into the lymph nodes adjacent to the kidney or large vessels but no invasion in adjacent organs or distant metastasis. Lastly, Stage IV tumors have invaded adjacent organs and possibly distant metastases. spread to lymph nodes and possibly distant organs (National Cancer Institute, 2020).

The grading schema of RCC is based on the microscopic morphology of a neoplasm with hematoxylin and eosin (H&E) staining. The most popular and used widely system for grading RCC has been a nuclear grading system described in 1982 by Fuhrman et al (1982), which concurrently evaluates nuclear size and shape, and nucleolar prominence. Grade one tumors have round small nuclei (<10 micrometers) with small smooth nuclear contours and either absent or inconspicuous nucleoli. Grade two tumors have slightly larger (15 micrometers) and irregular nuclei with small not easily visible nucleoli. Grade three tumors have large (20 micrometers) nuclei with prominent nucleoli (Cornejo et al. 2015). Lastly, grade four tumors have the largest (> 20 micrometers) nuclei, with macro-nucleoli that have multi-lobation that exhibit pleomorphism (Table 2. PRCC Fuhrman Nucleolar Grading System).

There are some criticisms of the Fuhrman Grading System, primarily the lack of inclusion of recent subtypes of RCC. The grading system is designed so that each parameter will increase in parallel and as each parameter increases, so will the tumor grade. However, studies have shown that the importance of nuclear shape and tumor prognosis varies with RCC subtype. Another limitation of the grading system is the lack of guidance as to which parameter should be prioritized in variances (Delahunt et al. 2016). The initial results from the original study that produced the Fuhrman Grading System have been difficult to replicate. Also, there is wide variation among tumors within each tumor grade, further adding to the difficult reproducibility (Delahunt el al. 2016). Considering there are no concrete alternatives, the Fuhrman Grading System still remains the most widely used grading for RCC tumors.

*Epidemiology of PRCC*

The demographic variables associated with PRCC are under investigation. Therefore, the risk factors and epidemiology associated with PRCC are umbrellaed under the more general

RCC. In general, RCC is twice as likely to occur in men than women. In fact, RCC is the 6th most common cancer in men and 8th in women (Fernandes & Lopes 2015). The reasoning behind the disparity is unclear but current theory attributes the increased likelihood to environment exposures in the workplace. There are also a number of medical conditions that increase the risk of renal cancer. Obesity, especially caused by a diet rich in fat, increases renal cancer risk. Other conditions such as high blood pressure also may increase risk, although it is unclear if the condition itself increases the risk or the medication (specifically diuretics). However, no specific antihypertension drug has been linked to RCC, leading researchers to believe that hypertension is the risk factor. However, it is unclear if RCC tumors are responsible for the development of high blood pressure (Fernandes & Lopes 2015; Woldu et al. 2014).

More recent studies that have focused specifically on PRCC have shown that ethnicity plays a role in the prognosis and treatment of PRCC with African Americans having poorer survival rates compared to Caucasians (Paulucci et al. 2017). Similarly, given the genetic heterogeneity of PRCC, a wide range of age groups are expected to be affected. Individuals with hereditary papillary renal cell carcinoma generally develop PRCC type 1 tumors around the age of 50 (Fernandes & Lopes 2015). Conversely, individuals with known Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC), may develop PRCC type 1 tumors between the age of 18 and 50, with an average age of 25 (Skala, Dhanaesekaran, & Mehra, 2018). Furthermore, there is strong evidence that end stage renal disease (ESRD) is a strong risk factor for developing PRCC. Studies have also shown that renal insufficiency, either chronic or episodic renal failure, are corelated to an in increased risk of PRCC (Fernandes & Lopes 2015; Woldu et al. 2014).

There are a number of disorders that increase an individual's risk of developing PRCC. von Hippel-Lindau disease is the most common inherited disorder that is associated with renal tumor development. Individuals with von Hippel-Lindau disease have a 40% risk of developing renal tumors. von Hippel-Lindau disease is an inherited disorder characterized by the formation of tumors and fluid-filled sacs (cysts) and *VHL* gene mutation. However, the loss of *VHL* function is not sufficient to develop malignant tumors (Gupta et al. 2017; Gossage et al. 2013). Likewise, HLRCC also known as Reed's Disease, has been linked with the development of PRCC type 2. HRLCC is an autosomal dominant condition in which individuals are at risk for developing cutaneous leiomyomas, early onset multiple uterine leiomyomas, uterine fibroids and PRCC type 2. The link between HRLCC and PRCC type 2 is found with *fumarate hydratase* (FH) gene mutation. The *FH* gene codes for a critical Krebs cycle protein allowing the cell to utilize oxygen to produce energy. *FH* mutation leads to cellular hypoxia which in turn leads to tumor development (Skala, Dhanaesekaran, & Mehra, 2018).

Similarly, individuals with hereditary papillary renal cell carcinoma (HPRCC) disorder have germline *MET* mutations and therefore have a higher risk for PRCC type 1 tumor development. In fact, according to some estimates, individuals with HPRC have an almost 100% risk of developing PRCC type 1. Although individual's with HPRC have a greater risk of developing PRCC, HPRC itself is a rare disorder (Haas and Nathanson, 2014). Interestingly, individuals with a sibling who has a history of renal cancer (without having any of the previously listed disorders) have a higher risk of developing renal cancer, including PRCC (Fernandes & Lopes 2015).

*Subtypes and Clear Cell Papillary Renal Cell Carcinoma*

An aspect of management is understanding the different subtypes associated with PRCC given each subtype utilizes different diagnostic and treatment plans (Figure 1: Visual breakdown of renal cell carcinoma subtypes). There are two main subtypes of PRCC, type 1 and type 2, and are generally accepted as distinct enough to be defined given the heterogeneity. PRCC type 1 tumor morphology is seen in sporadic and hereditary forms of PRCC.  PRCC type 1 tumors are histologically characterized by having a single layer of small cells with sparse, basophilic cytoplasm and small oval nuclei that cover renal papillae or tubules (Marsaud et al 2015; Prochazkova et al. 2018).

In contrast, PRCC type 2 is generally more heterogenous and comprises less than a third of PRCC cases (Marsaud et al 2015; Prochazkova et al. 2018). PRCC type 2 tumors are histologically characterized by large pseudostratified cells that have a large spherical nucleus with prominent nucleoli and eosinophilic cytoplasm that cover the renal papillae (Yin et al. 2015).  If a tumor presents with a combination of type 1 and type 2 histological features, it would be classified by the most predominant subtype. Similarly, if a tumor has an approximately equal amount of type 1 and 2 features are classified as mixed (Sukov et al. 2011).

Recently, clear cell renal cell carcinoma (ccPRCC) has been recognized as a third subtype of RCC. ccPRCC is histologically characterized by small to medium sized cuboidal cells with ample cytoplasm that cover the renal papillae (Wang et al. 2020). ccPRCC shares similar features with both PRCC and clear cell carcinoma but is distinct enough and does not fall under either RCC subtype. For instance, ccPRCC tumors are surrounded by a fibrous capsule with both papillary and clear cell morphology. Furthermore, ccPRCC tumors can appear to be densely packed due to papillae branching (Morlote et al. 2019). ccPRCC is similar to PRCC in that individuals are asymptomatic and tumors are found through incidental findings. Thus far

ccPRCC can be found individuals of all ages with no race or age predilection. ccPRCC tumors have favorable prognosis with low metastasis and reoccurrence rates. Similarly, if ccPRCC are found early they may be managed with increased surveillance or minimal surgical means (Zhao and Eyzaguirre, 2019). Although ccPRCC is not a subtype of PRCC, the name can be misleading and it is important to recognize ccPRCC as distinct subtype of RCC.

*Genetic Underpinning*

In order to understand PRCC subtypes, an overview of the various genetic pathways involved in tumor development is necessary. Given the heterogenous state of PRCC, a number of genetic pathways exist and present as both sporadic (no inherited genetic changes) and hereditary (inherited genetic changes) depending on the type of mutation exhibited in the tumor. Evidence suggests that type 1 and type 2 tumors arise from a similar cytogenic pathway. Type 1 tumors show significantly more gains in chromosomes 7p and 17p as compared to type 2 (Modi and Singer 2015). Chromosomal gain or loss is significant in cancer cells because this allows for tumor development by either gaining additional copies of oncogenes (tumor promoting) or losing copies of tumor suppressor genes. Type 2 tumors are more genetically diverse compared to type 1 tumor and there are theories that type 2 tumors evolved from type 1 tumors after acquiring more genetic mutations (Marsuad et al. 2015).

There are a number of genetic changes associated with PRCC type 1 tumors, either sporadic or inherited. Approximately 20% of PRCC type 1 tumors are associated with mutations of the protooncogene (a normal gene that when mutated becomes an oncogene) mesenchymal transition factor (*MET*). The *MET* gene codes for the protein c-MET, which is a tyrosine kinase receptor (RTK) protein. RTK proteins play a diverse role in the regulation of multiple cellular processes including differentiation, proliferation and the regulation of the cell cycle (Albiges et

al. 2014). Changes in *MET* generally allow for the continued growth and migration of cancerous

cells, which in turn increases tumor growth and invasion into healthy tissue.  Hereditary PRCC

stems from a gain of chromosome 7, that contains a non-random mutated copy of the *MET* gene,

which results in the overexpression of the c-MET protein. Given that hereditary PRCC is rare,

familial non-random *MET* mutations are uncommon (Yin et al. 2015). Conversely, although

some studies suggest that *MET* mutations are found in approximately 13% of sporadic PRCC

type 1 tumors, it is believed that *MET* mutations do not play a major role in the development of

these tumors (Marsuad et al. 2016). Other studies have correlated gains of chromosome 17p with

type 1 tumors. There are several oncogenes that are located on chromosome 17p including

*HER2, TOP2A* and *TAU*. Additionally, 17p houses the tumor suppressor genes *p53, BRCA1* and

*HIC-1*. The genes located on 17p have been linked to the initiation of tumor growth, tumor

progression, and tumor response to drug therapy. *HER2* and *TAU* overexpression are correlated

with poor chemotherapy response and poor prognosis. *TOP2A* is involved with DNA replication

and *TOP2A* overexpression has been linked to tumor proliferation (Yu et al., 2013).  Likewise,

*p53* plays a critical role in tumor suppression and DNA repair, serving as a check point gene that

induces apoptosis when critical nonrepairable DNA errors are found. When *p53* mutations occur,

DNA instability and unchecked cell proliferation occur. *BRCA1* is similar to *p53* in that it plays a

role in DNA regulation and repair. *HIC-1* mutations are generally found in conjunction with *p53*

to inhibit apoptosis (Yu et al., 2013).

Type 2 tumors have been associated with a mutation in the tumor suppressor gene,

fumarate hydratase *(FH)*. In healthy cells, *FH* acts as a catalyst for the conversion of fumarate

into malate during the Krebs cycle. PRCC type 2 *FH* mutations inactivate the FH protein causing

an accumulation of fumarate.  The accumulation of fumarate then activates hypoxia inducible

factor (and associated genes), which prompts the activation of other genes that increase tumor cell survival and proliferation (Gardie et al. 2011). Additionally, mutations in the vascular endothelial growth factor (*VEGF)* gene, specifically amplification, promote angiogenesis and cellular migration. Furthermore, PRCC type 2 has been associated with a loss of chromosome 3 and 14.  Chromosome 3 is the home for several tumor suppressor genes including, *VHL* which plays a role in angiogenesis regulation. When *VHL* is suppressed hypoxia-inducible factor is allowed to go unchecked which in turn leads to angiogenesis. Likewise, chromosome 14 houses genes that are responsible for cellular regulation and apoptosis (Modi and Singer 2015: TCGA, 2016: Marsuad et al. 2015).  Some studies have associated gains of chromosomes 7 and 17 with type 2 tumors but to a lesser extent than type 1 (Yu et al., 2013).

Sporadic PRCC type 1 and type 2 share a number of genetic variations.  For instance, chromosome 17 gain has a high association with sporadic PRCC and is rarely found in non-renal cancers (Marsuad et al. 2016). Specifically, a duplication of the 17q21 region, which contains the oncogene *HER2*, was found to be associated with a large number of sporadic PRCC tumors (Marsuad et al. 2016; Banumathy and Cairns, 2014). Allelic loss (loss of a specific gene variation) has also been associated with sporadic PRCC tumor development, specifically loss of the 7q31 region which contains the aphidicolin-inducible fragile site (FRA7G*).* The FRA7G site contains the tumor suppressor genes, *CAV1, CAV2* and *TESTIN*. Fragile sites such as FRA7G, aid in tumorigenesis because they are easily susceptible to breakage, leading to chromosomal translocation, deletion or amplification. Similarly, duplication of chromosome 20 and loss of chromosome 9p are also common in sporadic PRCC tumors (Modi and Singer 2016; Marsuad et al. 2016; Banumathy and Cairns 2014). Research is ongoing to determine what other genetic factors play a role in PRCC tumor development.

*Management*

There are a limited number of treatment options available for PRCC. Traditional treatment therapies are targeted towards clear cell renal cell carcinoma and are generally unsuccessful treating PRCC. Currently, nephrectomy is the most effective treatment option for PRCC tumors regardless of tumor stage. Likewise, partial nephrectomy is the preferred treatment choice since this option is nephron sparing and there are no after surgery treatment options available (Dengina et al. 2017). Individual's with advanced PRCC, characterized as stage 3 or greater, are recommended to seek out clinical trials. Clinical trials are generally focused on inhibiting specific cellular molecular pathways that are used by cancerous cells. Currently, the m-TOR inhibitors, temsirolimus and everolimus, have proven more effective on non-clear cell renal cell carcinomas (including but not limited to PRCC) as compared to interferon -α. Similarly, smaller clinical trials with the *VEGF* inhibitor, sorafenib, has shown efficacy treating PRCC. Efficacy was measured in progression free survival (PFS) and was shown to be 8.5 months for sorafenib as compared to 5.6 months for everolimus. Conversely, *MET* and *EGFR* inhibitors, such as erlotinib, have not yet proven to be an effective treatment option for PRCC. Current clinical trials do not differentiate between all the various types of non-clear cell carcinomas and therefore no treatment can be specified for PRCC (Ahrens et al. 2019).

A new treatment option immune check point therapy, which has been shown to be effective for clear cell carcinoma, is currently undergoing research for PRCC. Immune check point therapy works to block proteins from binding with their receptors that would inhibit immune cell activation. Thus, allowing the activation of immune cells such as T-cells to kill cancerous cells. However, as of now, PRCC is treated the same as clear cell carcinoma or with nephrectomy (Ahrens et al. 2019; Tsimafeyeu et al. 2017).

**Conclusion**

      PRCC is a complicated disease that consists of multiple subtypes and genetic pathways. It is important for clinicians to have a basic understanding of PRCC in order to develop effective personalized management plans. Furthermore, since PRCC remains difficult diagnose, clinicians should be able to recognize at risk individuals. As research continues on PRCC, new management techniques will be developed, having knowledge on the mechanism of the disease will allow clinicians to provide the best individualized care possible.

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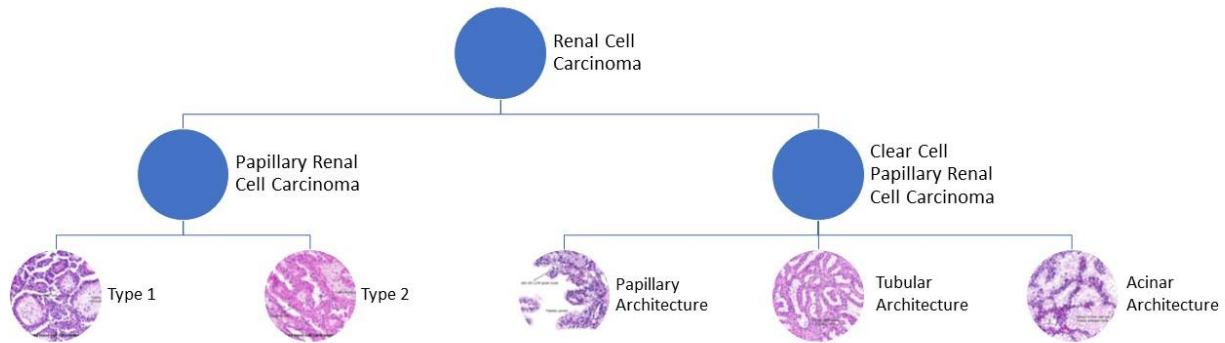
**Graphic 1.** Visual breakdown of renal cell carcinoma subtypes.

| | T (Tumor) | N (Lymph node involvement) | M (Metastasis) |
|---|---|---|---|
| **X** | Cannot be measured | Cannot be measured | Cannot be measured. |
| **0** | Cannot be found | Cannot be found | Has not spread. |
| **≥1** | Size and extent of main tumor. A larger number indicates greater size or infestation of surrounding tissue. | Number and location of involved lymph nodes. The higher the number, the more lymph nodes involved. | Has spread to other parts of the body. |

*Table 2.1. TNM Staging System (National Cancer Institute, 2020)*

| Tumor Grade | Size and Shape of Nuclei | Tumor Size | Tumor Location |
| --- | --- | --- | --- |
| 1 | round small nuclei (<10 micrometers) with small smooth nuclear contours and either absent or inconspicuous nucleoli | confined to the kidney | less than 7 centimeters across |
| 2 | slightly larger (15 micrometers) and irregular nuclei with small not easily visible nucleoli | confined to the kidney | larger than 7 centimeters across |
| 3 | large (20 micrometers) nuclei with prominent nucleoli | surrounding tissues or major veins but no lymph nodes | larger than 7 centimeters across |
| 4 | largest (> 20 micrometers) nuclei, with macro-nucleoli that have multi-lobation that exhibit pleomorphism | lymph nodes and possibly distant organs | larger than 7 centimeters across |

*Table 2.2. PRCC Furhman Fuhrman Nucleolar Grading System (Cornejo et al. 2015)*

| PRCC Subtype | Whole Chromosome Gain | Whole Chromosome Loss | Common Associated Oncogenes | Allelic Loss | Allelic Gain |
|---|---|---|---|---|---|
| Type 1 | 7p, 17p, 20 | 9 | *MET* | 7q31 | 17q21 |
| Type 2 | 20 | 3,14,9 | *FH, VEGF, HER2, TOP2A, TAU, p53, BRCA1, HIC-1* | 7q31 | 17q21 |

*Table 2.3. PRCC Genetic Variation Summary Table (Banumathy and Cairns, 2014Modi and Singer 2015; Marsuad et al. 2015; Yin et al. 2015; Yu et al., 2013)*

<div align="center">**Chapter III**</div>

**Genetic Manifestations of Hereditary Renal Cancer: Identification and Management of Patients and Families at Increased Risk**

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Overview: There are many inherited renal cancer syndromes that increase an individual's risk of developing renal cell cancer (RCC). The major autosomal dominantly inherited RCC syndromes include: von Hippel-Lindau syndrome (VHL); Lynch Syndrome/ Hereditary Non-Polyposis Colorectal Cancer (HNPCC); Tuberous Sclerosis Complex (TSC); Birt-Hogg-Dubé Syndrome (BHD); Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC); Cowden Syndrome; and BAP1 Tumor Predisposition Syndrome. The age of onset for these RCC syndromes range from infancy through 65 years. Clinical manifestations vary widely, and multiple body systems can be involved and present unique challenges to the healthcare team. With the advancement of genetic panels, clinicians can screen individuals with known hereditary syndromes for genetic mutations. This paper will present clinically relevant information on specific to the major renal cancer syndrome focusing on the gene mutation, incidence, and clinical implications.

Key Words: Hereditary renal cancer syndromes; autosomal dominant; renal cell cancer; gene mutation

**Introduction**

Individuals with inherited renal cancer syndromes develop kidney cancer at an earlier age with notable features of heterogeneous, multifocal, and bilateral tumors. Several of the syndromes have renal cell cancer (RCC) as a primary feature, including von Hippel-Lindau and Birt-Hogg-Dubé syndrome, whereas others, such as Lynch syndrome and Cowden syndrome, have RCC as a secondary feature. Most hereditary renal cancer syndromes are autosomal dominant, meaning that only one copy of the mutated gene is needed to present to express the disease. The mutated gene predisposes affected individuals to tumor development often with early onset malignancy (da Costa et al. 2017). Children of parents with autosomal dominant diseases have a 50% chance of inheriting the syndrome. Each hereditary renal cancer syndrome manifests with different clinical symptoms and is correlated with varying risks of developing RCC. This paper will present clinically relevant information of hereditary renal cancer syndromes associated with RCC with a focus on the incidence, background and clinical implications (Table 1).

**Von Hippel-Lindau Syndrome**

Von Hippel-Lindau (VHL) syndrome, is the most common hereditary renal syndrome. It is characterized by visceral cysts and benign tumors that have the potential to become malignant. In fact, individuals with *VHL* have a 40% chance of developing RCC (Gupta et al. 2017). However, the loss of *VHL* gene function alone is not enough for patients to develop RCC. Other gene mutations in conjunction with *VHL,* including *BAP1*, *PBRM1*, *JARID1c*, *SETD2*, and *KDM6A,* have been found in patients with RCC, indicating that multiple gene mutations are involved with RCC development (Gossage et al. 2013). More recently, *SDHB* and *TMEM127* alterations have been linked to *VHL* mutations but their connection to RCC is unclear. (Gupta et

al. 2017). Further research is necessary to determine the exact relationship between *SDHB*, *TMEM127*, *VHL* and RCC.

**Lynch Syndrome (LS)/Hereditary non-polyposis colorectal cancer (HNPCC)**

LS, synonymous with HNPCC, is a condition that predisposes individuals to increased risk of colorectal cancer (CRC), endometrial cancer, upper tract urothelial cancers, and other types of cancers. (Lynch et al. 2015). A number of germline mutations are associated with LS, specifically in the mismatch repair genes (*MMR*). These genes are responsible for correcting mismatched nucleotides when DNA is copied in preparation for cell division. Germline mutations in the *MSH2, MSH6, MLH1* and *PMS2* genes (members of the MMR gene family) are the most common cause of LS (Ziada-Bouchaar et al. 2017). Furthermore, deletions in the *EPCAM* gene, a gene that codes for a cell adhesion protein, can result in silencing of the *MSH2* gene, which can lead to EPCAM-associated Lynch Syndrome.

**Tuberous Sclerosis Complex (TSC)**

TSC is a rare, multisystem disease characterized by multiple benign tumors found in the brain, spinal cord, kidneys, heart, and other areas due to mutation in the tumor suppression genes, *TSC1* or *TSC2.* Each of these genes code for proteins involved in cell proliferation. Typically, individual's with TSC present with benign renal tumors (Leech et al. 2018). However, when both copies of the gene are mutated, an individual has a greater chance of developing malignant renal tumors

**Birt-Hogg-Dube Syndrome (BHD)**

BHD syndrome is an extremely rare complex disorder characterized by deletion of the *folliculin* gene (*FCLN*) (Centini et al. 2018). The *FLCN* gene transports instructions to produce folliculin, a protein whose precise function is not known but seems to interact with proteins

involved in cell growth, energy production, and metabolism. As a tumor suppressor gene, FLCN gene aids in apoptosis but mutations predispose individuals to cancer development

**Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC)**

HLRCC, otherwise known as Reed's syndrome, is a syndrome characterized by the presence of one or more of the following: cutaneous leiomyomas (average age of occurrence is 25), uterine leiomyomas/fibroids (average age of occurrence is 30), and renal cell cancer (RCC) (National Cancer Institute, 2019). The pattern of renal cancer in HLRCC differs from other inherited renal cancer syndromes in that the tumors tend to be solid, unilateral, and more aggressive (Skala, Dhanaesekaran, & Mehra, 2018). HRLCC is caused by a germline mutation in the *FH* gene, which codes for an enzyme that catalyzes the conversion of fumarate into L-malate during the Krebs Cycle (Valencia et al. 2017). Fumarase, or fumarate hydratase, allows the cells to use oxygen and generate energy. Excesses of fumarate may interfere with cellular oxygen levels, yielding chronic hypoxia leading to tumor formation and tendency to develop leiomyomas and RCC.

**Cowden Syndrome**

Cowden Syndrome (CS) is a relatively rare condition that predisposes individuals to developing renal tumors and is characterized by multiple, noncancerous growths (called hamartomas) at various sites of the body. Nearly all patients with CS will present with benign growths on the skin, mouth and along the inner lining of the gastrointestinal tract by the end of their 20s (Eng, 2016).  Mutations in four different genes, *PTEN, SDHB, SDHD,* and *KLLN,* have been identified in people with CS. Of interest is the tumor suppressor gene, *PTEN*, which codes for a protein involved in cell proliferation (Breuksch et al. 2018). Additionally, *SDHB-B* and *KLLN* have been found to contribute to CS even in the absence of a *PTEN* mutation. However,

individuals with a *KLLN* mutation have a higher risk of developing RCC as compared to individuals with a *SDHB-B* mutation. Currently, testing for the *KLLN* mutation is not readily available (Mahdi et al. 2015).

**Implications for Nurses**

Hereditary renal cancer syndromes account for approximately 5% of all kidney cancers, though this number is probably underestimated (Kallinikas et al, 2017). The number of families identified with hereditary conditions leading to RCC continues to increase as germline genetic testing is being utilized more frequently. As presented, RCC can either be a major or a minor feature of the cancer susceptibility syndrome. However, RCC is not limited to hereditary renal cancer syndromes or the gene mutation discussions. In fact, mutations in the *MET*, *MITF*, and *SDH* genes also have a strong association with an increased risk of RCC.

Early age of onset, unusual or pathognomonic pathology, and multiple tumors in a patient with renal cancer raises concern for hereditary renal cancer syndromes. Accurate, ongoing, and complete assessment of family history is the first step in identifying individuals who may be at risk for hereditary renal cancer syndromes. Nurses need to inquire about the type of kidney cancer as well as the presence of other indicators of hereditary risk particularly dermatologic and other unusual findings. Families with unusual histories should be referred for further evaluation and possible genetic testing to credentialed genetics professional.

The identification of known mutation carriers enables the implementation of aggressive and often complex surveillance in those likely to benefit and prevents unnecessary aggressive surveillance in those who do not have an inherited risk. The complexity of screening for those with hereditary risk requires regular coordination. Surveillance and prevention recommendations

should be reviewed annually by genetics professional to verify that they are still current and evidence based.

Known carriers may have concerns and dilemmas about reproduction and the possibility of passing a mutation to offspring. These individuals often require ongoing psychosocial support to manage the consequences of their genetic predisposition. Oncology nurses can offer support to these individuals and families and refer them to resources (see Figure 1).

**Conclusion**

Management of individuals with hereditary polyposis syndromes demands accurate assessment of patients' personal and family history, referral for genetic evaluation and testing, and implementation of complex surveillance plans to ultimately decrease the morbidity and mortality associated with these syndromes. Oncology nurses play an integral role in supporting these patients and families as they manage the complexities of their diagnoses and ongoing care.

**Nursing Implications**

1. Renal cell cancer syndromes are autosomal dominant and increase an individual's risk of developing renal cell cancer and other malignancies.

2. The age of onset for renal cell cancer ranges from infancy through 65 years with a wide range of clinical manifestations that include benign and malignant histology.

3. Heightened surveillance and pre-emptive management of individuals with known renal cell cancer syndromes can improve outcomes and quality of life.

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**Figure 3.1**

**Resources for Hereditary Cancer Syndromes**

**General Resources**

- Kidney Cancer Association   www.kidneycancer.org
- National Cancer Institute – Genetics of Kidney cancer
  https://www.cancer.gov/types/kidney/hp/kidney-genetics-pdq#_362_toc

**Birt Hogg Dube**

- National Library of Medicine Genetics Home
  Reference  https://ghr.nlm.nih.gov/condition/birt-hogg-dube-syndrome
- Genetic and Rare Disease Center https://rarediseases.info.nih.gov/diseases/2322/birt-hogg-dube-syndrome
- Gene Reviews: https://www.ncbi.nlm.nih.gov/books/NBK1522/
- BHD Foundation:  https://www.bhdsyndrome.org/

**Von Hippel Lindau**

- National Library of Medicine Genetics Home Reference
  https://ghr.nlm.nih.gov/condition/von-hippel-lindau-syndrome
- Genetic and Rare Disease Center: https://rarediseases.info.nih.gov/diseases/7855/von-hippel-lindau-disease
- National Institute of Neurological Diseases and Stroke
  https://www.ninds.nih.gov/Disorders/All-Disorders/Von-Hippel-Lindau-Disease-VHL-Information-Page
- Gene Reviews https://www.ncbi.nlm.nih.gov/books/NBK1463/
- VHL Alliance: https://www.vhl.org/

**Lynch Sydrome**

- National Library of Medicine Genetics Home Reference
  https://ghr.nlm.nih.gov/condition/lynch-syndrome
- Genetic and Rare Disease Center https://rarediseases.info.nih.gov/diseases/9905/lynch-syndrome
- Gene Reviews  https://www.ncbi.nlm.nih.gov/books/NBK1211/
- Lynch Syndrome International: https://lynchcancers.com/

**Tuberous Sclerosis Complex**

- National Library of Medicine Genetics Home Reference
  https://ghr.nlm.nih.gov/condition/tuberous-sclerosis-complex
- Genetic and Rare Disease Center:
  https://rarediseases.info.nih.gov/diseases/7830/tuberous-sclerosis
- Gene Reviews https://www.ncbi.nlm.nih.gov/books/NBK1220/

- Tubular Sclerosis Complex https://www.tsalliance.org/

**Hereditary Leiomyomatosis Renal Cell Carcinoma**

- National Library of Medicine Genetics Home Reference
  https://ghr.nlm.nih.gov/condition/hereditary-leiomyomatosis-and-renal-cell-cancer
- Genetic and Rare Disease Center:
  https://rarediseases.info.nih.gov/diseases/10096/hereditary-leiomyomatosis-and-renal-cell-cancer
- HLRCC Family Alliance http://hlrccinfo.org/

**Cowden Syndrome**

- National Library of Medicine Genetics Home Reference
  https://ghr.nlm.nih.gov/condition/cowden-syndrome
- Genetic and Rare Disease Center
  https://rarediseases.info.nih.gov/diseases/6202/cowden-syndrome
- Gene Reviews: https://www.ncbi.nlm.nih.gov/books/NBK1488/

**BAP1 Tumor Predisposition Syndrome**

- National Library of Medicine Genetics Home Reference
  https://ghr.nlm.nih.gov/condition/bap1-tumor-predisposition-syndrome
- Genetic and Rare Disease Center https://rarediseases.info.nih.gov/diseases/13219/bap1-tumor-predisposition-syndrome

Table 3.1. Summary of Hereditary Renal Cancer Syndromes.

| Hereditary Syndrome | Incidence | Average Age of Onset | Clinical Manifestations | Genes | Screening Surveillance |
|---|---|---|---|---|---|
| *von Hippel-Lindau (VHL)* | 1 in 36,000 people (10,000 cases in the US and 200,000 cases worldwide), Males and females equally affected | Mean age of onset is 26 years with most patients presenting with symptoms by 65 | Hemangioblastomas of the eye, brain and spinal cord<br><br>Pheochromocytomas<br><br>Endolymphatic sac tumors<br><br>RCC | *VHL* | Yearly physical and eye exams to monitor for small asymptomatic lesions as well as detect new early stage lesions.<br><br>24-hour urine test for elevated catecholamines beginning at age 5<br><br>abdominal ultrasound (teen years) or magnetic resonance imaging (adulthood) to assess the kidney, pancreas, and adrenal glands. |
| *Lynch Syndrome/ Hereditary non-polyposis colorectal cancer (HNPCC)* | Estimated frequency is 1:370 to 1:2000. Approximately 140,000 new cases of colon cancer yearly in the US; 3-5% of these caused by Lynch Syndrome | Mean age of onset is 40 years | Early onset colon cancer<br><br>Endometrial cancer<br><br>Ovarian cancer<br><br>Sebaceous adenomas<br><br>Pancreatic cancer<br><br>RCC | *MSH2, MSH6, MLH1, PMS2, EPCAM* | Colonoscopy every 12 to 24 months starting at age 20 to 25 or two to five years before the youngest diagnosis of colon cancer in the family<br><br>Risk reducing hysterectomy with bilateral salpingoophorectomy when childbearing is complete<br><br>Esophagogastroduodenoscopy every 3 to 5 years starting at age 30. Treatment of H pylori infections<br><br>Annual urinalysis starting at age 30<br><br>Consider pancreatic screening |
| *Tuberous Sclerosis Complex (TSC)* | 25,000 to 40,000 individuals in the US and nearly 1 million worldwide | Infancy | Numerous benign growths<br>Developmental delay<br>Seizures<br>Lymphangioleiomyomatosis (LAM)<br>Polycystic kidney disease<br>RCC | *TSC1, TSC2,* | Evaluate for seizures. Obtain routine EEG in individuals with known or suspected seizure activity. The frequency of routine EEG should be determined by clinical need.<br><br>Imaging for benign growths, and psychiatric evaluation beginning in childhood. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Obtain MRI of the brain every one to three years in asymptomatic persons by age 25<br><br>MRI of abdomen to assess for angiomyolipoma & renal cysts by age 25 every 1 to 3 years<br><br>Assess renal function (including determination of GFR) and blood pressure at least annually by age 25.<br><br>Perform clinical screening (targeted history) for LAM symptoms including exertional dyspnea and shortness of breath at each clinic visit for women older than age 18 years or those who report respiratory symptoms. Counseling regarding smoking risk and estrogen use should be reviewed at each clinic visit for individuals at risk for LAM.<br><br>Perform detailed clinical dermatologic inspection/exam annually. |
| *Birt-Hogg-Dube Syndrome (BHD)* | 200 and 600 families worldwide | Unknown | Lung cysts<br><br>Benign skin tumors: Fibrofolliculomas, Trichodiscomas, Angiofibromas, Acrochordons and Perifollicular fibromas<br><br>Spontaneous pneumothorax<br><br>Renal tumors including hybrid oncocytic renal cell carcinoma, oncocytoma, chromophobe renal cell carcinoma, and clear cell renal cell carcinoma | *FCLN* | Renal imaging is appropriate for individuals age 18 years or older. Yearly MRI of the kidneys is the optimal screening modality to assess for kidney lesions.<br><br>Abdominal/pelvic CT scan with contrast is an alternative when MRI is not an option. However, the long-term effects of cumulative radiation exposure in individuals with BHDS is unknown and has not been studied.<br><br>Annual full body skin examination<br><br>Avoid |

| | | | | | -Cigarette smoking

-High ambient pressures, which may precipitate spontaneous pneumothorax

-Radiation exposure |
|---|---|---|---|---|---|
| *Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC)* | Unknown | 25-30 years of age | Cutaneous leiomyomas Uterine leiomyomas (fibroids) Kidney cancer | *FH* | Annual full body dermatologic examination

Annual gynecologic consultation is recommended to assess severity of uterine fibroids and to evaluate for changes suggestive of leiomyosarcoma.

Yearly examination with abdominal MRI is recommended for individuals with normal initial baseline or follow-up abdominal MRI. MRI is preferred because of the potential added radiation exposure associated with CT over lifetime. |
| *Cowden Syndrome* | Unknown | Late 20s | Hamartomas (benign growths) on the skin, mouth and gastrointestinal tract.

Macrocephaly

Trichilemmomas and papillomatous papules

Benign breast, thyroid and endometrial diseases.

Kidney cancer and congenital kidney anomalies

Lhermite -Dulcos Disease, autism spectrum disorder, intellectual disabilities and vascular abnormalities. | *PTEN* | Children (age <18 years). Yearly thyroid ultrasound from the time of diagnosis and skin check with physical examination.

Adults. Yearly thyroid ultrasound and dermatologic evaluation.

Women beginning at age 30 years. Monthly breast self-examination; annual breast screening (at minimum mammogram; MRI may also be incorporated) and transvaginal ultrasound or endometrial biopsy.

Colonoscopy beginning at age 35 years with frequency dependent on degree of |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | polyposis identified; biennial (every 2 years)

Renal imaging (CT or MRI preferred) beginning at age 40 years.

Those with a family history of a particular cancer type at an early age. Consider initiating screening 5-10 years prior to the youngest age of diagnosis in the family. |
| *BAP1 Tumor Predisposition Syndrome* | Unknown | 20s | Mesothelioma

Uveal melanoma.

Atypical Spitz tumors

Melanoma

Clear cell kidney carcinoma

Basal cell skin cancer

Cholangiocarcinoma | *BAP1* | Yearly dilated eye examinations and imaging by an ocular oncologist beginning around age 11 years for uveal melanoma

Annual evaluation is recommended for late manifestations of mesothelioma, which can include chest pain, cough, fever, shortness of breath, dysphagia, hoarseness, weight loss, fever, upper body and face edema (chest mesothelioma) and abdominal pain, ascites, nausea, vomiting, and/or constipation (peritoneal mesothelioma). Annual physical examination is recommended to look for signs of pleurisy (pleural inflammation), peritonitis, ascites and/or pleural effusion.

Annual full body dermatologic examinations beginning around age 20 years

Annual abdominal ultrasound examination; consideration of annual urinalysis and abdominal MRI every two years to monitor for renal cancer |

Based on information from (Colorectal Cancer Alliance, 2019; Gupta et al. 2017; Therkildsen et al. 2016; National Comprehensive Cancer Network, 2019; National Institute of Neurological Disorders & Stroke, 2019; Menko et al 2017; Masoomian et al. 2018; National Institute of Neurological Disorders and Stroke, 2019 a,b,c,d

**Chapter IV**

**Background**

Renal cell carcinoma (RCC) is the 14th most common cancer worldwide and was the cause of 175,098 deaths in 2018 (WHO, 2020). RCC consists of numerous subtypes including clear cell renal carcinoma, papillary renal cell carcinoma and most recently clear cell papillary renal cell carcinoma. Currently, papillary renal cell carcinoma (PRCC) is the second most common type of RCC, after clear cell renal cell carcinoma, comprising approximately 15-20% of all RCC cases (Fernandes & Lopes 2015; Steffen et al. 2012). PRCC is considered to be a heterogeneous disease that consists of two subtypes; type 1 and type 2. PRCC subtypes are primarily distinguished by their histology and vary in prognosis, treatment and patient outcomes. Type 1 is histologically characterized by a single layer of cells with sparse basophilic cytoplasm and small oval shaped nuclei that are present in either the renal tubules or renal papillae. Type 1 tumors can be associated with both hereditary and sporadic PRCC (Marsaud et al 2015; Prochazkova et al. 2018). Conversely, type 2 tumors are histologically characterized by large pseudostratified cells with eosinophilic cytoplasm with large spherically shaped nuclei that are present in the renal papillae. Type 2 tumors can be associated with hereditary PRCC but are more often associated with the sporadic form of PRCC (Yin et al. 2015). Furthermore, research has shown that patients with PRCC type 2 tumors are correlated with a higher rate of metastasis and have a lower overall survival rate compared with patients with type 1 tumors (Wong et al. 2019).

Research has shown that malignant tumors utilize a wide variety of genetic alterations to modify the normal cell cycle in order to be able to divide and grow without restrictions. These modifications are accomplished by altering cell signaling pathways to promote cell growth,

angiogenesis and obstruct apoptosis (Sanchez-Vega et al. 2018). Considering the heterogeneous nature of PRCC, there are numerous genetic alterations that occur within both type 1 and type 2 PRCC. Approximately 20% of hereditary type 1 tumors have been associated with variations in the protooncogene mesenchymal epithelial transition (*MET*). However, sporadic type 1 tumors have numerous genes associations as well as chromosomal abnormalities. Type 2 tumors have also been correlated with a large number of genetic and chromosomal alterations (Marsuad et al. 2016; Linehan et al. 2015). Similarly, research has shown that renal cancers in general utilize several signaling pathways. The alteration of *MET* has been shown to activate the MAPK and PI3K pathways as well as other proteins involved with tumor growth (COJOCARU et al. 2015). However, research still needs to be done to determine if there is a preference of pathways specific to type 1 or type 2 PRCC tumors.

The epidemiology and risk factors for PRCC are largely based on the broader RCC. However, there are certain conditions that may increase an individual's risk of developing PRCC. For instances individuals with Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) have a greater chance of developing PRCC type 1. Furthermore, there is some evidence that suggests individuals with renal insufficiencies have a greater risk of developing PRCC (Paquin & Fasolino 2020; Fernandes & Lopes 2015; Woldu et al. 2014). Ethnicity has also been found to contribute to the risk of developing an RCC with African Americans having the highest incidence of RCCs in the United States. Sankin et al. (2011) found that African Americans had a four times greater incidence of PRCC as compared to non-African Americans (Hsieh et al. 2017; Sankin et al. 2011). However, research is still needed to further understand the risk factors specific to PRCC. Currently there are limited treatment options available for both types of PRCC. Presently, the standard treatment is partial or full nephrectomy. Individual's with

higher grade tumors are encouraged to seek out clinical trials, which tend to be developed based on specific cellular molecular pathways. Similarly, the prognosis of PRCC is dependent on tumor type (Dengina et al. 2017; Ahrens et al. 2019).

Most research on PRCC has either been umbrellaed under RCC or has been focused on developing a basic understanding of the disease. Furthermore, there is limited research focusing on the differences between type 1 and type 2 PRCC tumors. Given the findings in Wong *et al.* (2019) with respect to survival rates associated with type 1 and type 2 PRCC and the fact that the data we collected contained overall (presumably, all-cause mortality survival times) as well as demographic, environmental as well as gene pathway information our research plan is four-fold. First, we will analyze the all-cause mortality investigate whether we see discrepancies in survival rates between type 1 and 2 PRCC. The second phase will consist of selecting a demographic (baseline) model which will identify a set of demographic variables that are likely to be associated with the two different types of PRCC. In the third and fourth phases we will investigate environmental and gene pathway associations with prevalence of the two types of PRCC. The overall aim of these analyses is to determine if there are significant differences between type 1 and type 2 PRCC that can be utilized by healthcare providers. Specifically, this study sought to determine if there are clinically significant differences in survival, demographics (age, ethnicity, gender, and race), increased risk factors (body mass index [BMI] smoking history, neoplasm history, and malignancy history) and preferential genetic pathways between type 1 and type 2 PRCC tumors.

**Methods**

***Sample***

This study was a secondary data analysis using data from The Cancer Genome Atlas Kidney Renal Papillary Cell Carcinoma (TCGA-KIRP). A review of the literature was conducted to determine the appropriate inclusion criteria which were: 1) PRCC tumors, 2) distinguishes between type 1 and type 2, 3) demographics data ,gender, race, age and ethnicity, 4) clinical data, prognosis, treatment, preexisting conditions, 5) increased risk factors, smoking history, BMI, prior neoplasms and prior malignancies and 6) genetic analysis of the tumors. A further review of the literature revealed that TCGA-KIRP is the most current and appropriate dataset to use for this secondary data analysis. The cBioPortal for cancer genomics (cBioPortal) was also used to analyze the TCGA-KIRP data.

TCGA- Kidney Renal Papillary Cell Carcinoma (KIRP) data was collected from 41 institutions from 1996 to 2013. TCGA adheres to a strict inclusion policy for data to be included on the website. TCGA tumors are untreated samples that were snap frozen. Each tumor sample has to have a matched normal sample from the same patient which generally comes in the form of the patient's blood. The tumors and subsequent molecular data are cross referenced by Biospecimen Core Resource (BCR) to ensure validity. Furthermore, the BCR analyzes each sample for pathological quality control. This maintains that TCGA has a high-quality tumor samples as well as consistent molecular data (TCGA, 2020). Additionally, each sample was reviewed by a panel of six experienced pathologist to in order to be classified into type 1, type 2 or unclassified PRCC. Moreover, any samples that were pre-classified were reassessed by the same panel to ensure proper classification (TCGA, 2020).

The cBioPortal is a resource that incorporates data from TCGA and other reliable sources, when possible, into a more researcher-friendly resource. The BCR provides an interactive resource that can be used for a more comprehensive secondary data analysis. For

example, the cBioPortal separates PRCC genetic variations into categories such as copy number variations and mutations. Furthermore, the cBioPortal predetermines and denotes driver genes through specific algorithms. Additionally, the cBioPortal allows the user to analyze specific genes as opposed to TCGA which only allows users to view the dataset as a whole and does not denote potential driver genes. Even though the cBioPortal contains the same data as TCGA, the cBioPortal was used to aid in the analysis of TCGA data.

*Data Extraction*

A total of 292 cases were available on the listed datasets. The first step in evaluating the dataset was determining the clinical and demographic data. TCGA contains a manifest that includes all relevant clinical, demographic and environmental data. This manifest was downloaded and converted into an Excel file. Once retrieved the dataset was combed and irrelevant data was eliminated from the dataset. Irrelevant data included data categories with n/a, data categories on serum levels, blood cell counts, etc. Data categories that were redundant were also eliminated.

Next, the cBioPortal resource was used to determine pertinent genetic information related to PRCC. The first step was to download the copy number alteration (CNA) data from the cBioPortal website. A total of 10,837 genes exhibited a copy number variation. Genes that were not considered to be driver genes according to the GISTIC algorithm were eliminated from the dataset. This elimination left a total of 426 driver genes with CNA. The driver genes were then put into the BCG query to determine how many cases included one or more of the driver CNA genes. It was found that 193 of the cases or 66% contained one of the driver CNA genes. In order to increase the sample population, mutated driver genes (as determined by Mutsig) were added to the query bringing the total of genes up to 517. This addition brought the number of cases to 255

or 87% of the dataset. 36 cases did not have an association with one of the 517 driver genes and were therefore eliminated for continuity of the data. The driver genes were also divided into categories based on their cytoband for future reference.

Subsequently, the remaining 255 cases were reviewed to determine whether or not they were designated type 1 or type 2 PRCC. Out of the 255 cases, 115 cases had an NA designation in the type category. The pathology report of each of the 115 cases was reviewed to see if a pathologist had designated the tumor as either type 1 or type 2. At the conclusion of this analysis 88 cases were type 2, 69 cases were type 1 and 83 cases remained NA. The 83 NA cases were subsequently removed from the dataset in order to preserve the validity and continuity of the data. Furthermore, seven cases were determined to be a mix of type 1 and type 2 histology and were also removed. Additionally, eight more cases were determined to favor a different cancer type per the reviewing pathologist. These eight cases did not include a TCGA addendum that disputed the cancer typing and therefore were removed from this dataset. (See Figure 1)
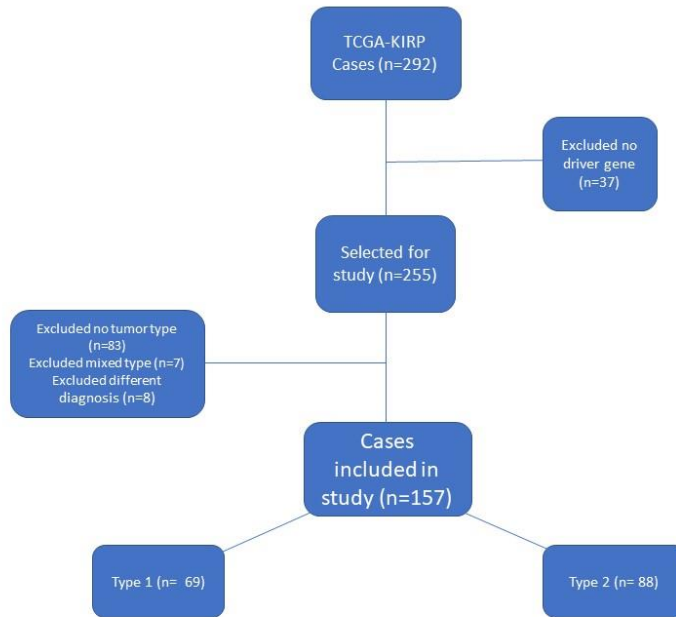
Fig. 1 Consort diagram describing TCGA-KIRP data extraction.

*Analysis*

*Descriptive Statistics and Survival Analysis*

First descriptive statistics were determined using excel for each of the domains; demographics, increased risk factors and genetic pathways. Then a survival analysis was conducted for the TCGA-KIRP analytic file using R version 3.6.2. A cox-proportional hazard model was fitted on the overall survival times of 156 patients (1 had a survival time of 0 indicating that they were diagnosed post-mortem or there was an error in entry) to determine if there were evidence that survival rates differ between Type 1 and 2 PRCC.

*Logic Regression*

For the next three phases of our investigation statistical analysis for this data was performed using SAS program software package for Windows. The demographic model selection included age at diagnosis, race, ethnicity and sex, as candidate descriptors relating to PRCC tumor type. The demographic model selection utilized forward selection with a relaxed p value (<0.1) to determine the appropriate variables to be included in the model. The selected demographic model included Age at Diagnosis (OR 1.045 95% CI 1.014, 1.078 Table 5) as well as 3 Category Race (which was not significant at the .1 level when included in the final candidate model but had a sufficient p-value to be selected for inclusion) was used as the baseline model for the increased risk factor variables. Each increased risk factor variable, BMI, smoking status, prior neoplasms and prior malignancies, were added univariately to the demographic model controlling for age at diagnosis and race to identify associations.

**Results**

*Descriptive Statistics*

Of the 69 type 1 tumors, 50 were male and 19 were female with a median age of 60 (range 28 to 82). In terms of race 46 were white, 18 were black or African American, 5 were unspecified and for ethnicity 62 were non-Hispanic or Latino, 2 were Hispanic or Latino and 5 were unspecified. Of the 88 type 2, 61 were male and 27 were female with a median age of 65 (range 28 to 88). In terms of race 66 were white, 15 were black or African American, 7 were unspecified and for ethnicity 75 were non-Hispanic or Latino, 5 were Hispanic or Latino and 8 were unspecified (Table 1). Due to the sparsity in the demographic factor levels the following variable levels were collapsed; Asian and American Indian. Smoking categories were defined as life-long non-smoker (1), current smoker (2), reformed smoker >15years (3), reformed smoker <15 years (4) and reformed smoker unknown length (5). For type 1 tumors 30 were category 1,

10 were category 2, 10 were category 3, 7 were either category 4 or 5 smokers and 11 were unspecified. For type 2 PRCC tumors 36 were category 1, 11 were category 2, 14 were category 3, 20 were category 4 or 5 and 7 were unspecified. Once again due to sparsity in the increased risk factor levels the following variables were collapsed; smoking category 4 and 5. Prior neoplasms were defined as either yes or no with 2 yes in type 1 and 9 in type 2. Similarly, prior malignancies were also defined as either yes or no with 16 yes in type 1 and 14 in type 2 (Figure 2). Lastly the most common pathway in type 1 was the MAPK pathway and in type 2 was the PI3K pathway Figure 3).

### *Overall Survival*

The hazard ratio (comparing Type 2 to 1, with Type one being the reference group) was 2.459 (with 95% CI 0.9723, 6.217) which does not provide sufficient evidence at the $\alpha = .05$ level that the two types differ significantly in all-cause survival. However, given the relatively small sample size and high rate of censoring (70.3% for Type 1 and 52% for Type 2, which consequently prevents us from being able to report median survival without making parametric assumptions) it is not surprising that our results do not provide as striking a contrast between the two as was found in Wong *et al.* (2019). Survival rates are illustrated via the Kaplan Meier curve included in Figure 2.

### *Logistic Regression*

Odd ratios (OR) and confidence intervals (CI) are reported in Tables 5 and 6 for each variable in the increased risk factor and pathway analyses. Out of the increased risk factor variables investigated we found that smoking appeared to be associated with increased risk of Type 2. Specifically, being a reformed smoker of unknown length or less than 15 years (these two categories were grouped together due to sparsity) was positively associated with Type 2

PRCC compared to life-long non-smokers (OR 3.241 95% CI 1.066, 9.853 Table 5). None of the other increased risk factors had a significant association with tumor type. In the pathways analysis we observed one significant association and that was a significant difference between MAPK and PI3K with PI3K being significantly associated with Type 2 (OR 4.968 95% CI 1.759, 14.031 Table 6). In all analyses Type 1 was used as the reference level for each model and the OR correspond to odds of Type 2 vs 1.

**Discussion**

To the best of our knowledge our study is the first to collectively examine the demographic, increased risk and pathway associations between type 1 and type 2 PRCC tumors. Furthermore, while our findings with respect to the survival analysis were not significant at the $\alpha = .05$ level (in our setting p=.0573), it does provide marginal evidence to confirm the findings of Wong *et al.* (2019) in that survival rates for Type 2 are on average shorter than those for Type 1. Our secondary data analysis was limited to a small population sample with a lot of missingness among the dataset. None the less, our study certain variables were found to have an increased probability of being associated with type 2 PRCC tumors. The first variable found to be significant was age at diagnosis with an increase in age at diagnosis being indicative of an increased risk of type 2. This finding is supported by the fact that 20% of type 1 tumors have an association with a germline *MET* mutation and literature has shown that having a germline mutation is positively associated with a younger diagnosis age (Lineman et al. 2015). Although there are germline mutations associated with type 2 PRCC tumors, they are less prominent than type 1 (Lineman et al. 2015; Hsieh et al. 2018).

Smoking was the only increased risk factor that was significant in determining the probability of having the type 2 tumor type. Individuals who were reformed smokers of less than

15 years (as well as reformed smokers of unknown length) had a greater risk of developing a type 2 tumor as compared to lifelong non-smokers. Furthermore, type 2 PRCC tumors tend to be sporadic as compared to type 1, meaning that increased risk factors may have a greater impact on the development of type 2 tumors (Yin et al. 2015). However, further research needs to be conducted on the effects of smoking on the growth of specific tumor subtypes. Additionally, the increased risk factor dataset had a large amount of missingness with prior neoplasm having the most missingness (n=90). Further research should be conducted on a larger sample size with less missingness to compare increased risk factors variables between tumor types, specifically prior neoplasms. Neoplasms have been associated with a number of renal cell cancer syndromes that are considered to increase the risk of PRCC. The most common renal cell cancer syndrome, von Hippel-Lindau syndrome, is characterized by benign tumor growths and has a 40% chance of developing renal cancer, including type 2 PRCC. Additionally, hereditary leiomyomatosis and renal cell cancer (HLRCC), is characterized by harmatomas and also an increased risk of developing type 2 PRCC (Paquin & Fasolino 2020; Modi & Singer 2016). Considering the number of renal cell cancer syndromes that are both associated with an increased PRCC risk and are characterized by neoplasms; further research should be conducted to determine if prior neoplasms is a determining factor in PRCC subtype.

The findings in this study have potential implications for future treatment avenues. The higher rate of MAPK pathway in type 1 supports the ongoing studies of the use of *MET* in clinical trials. *MET* codes for c-Met, a tyrosine kinase protein that is involved with the MAPK pathway. When c-Met binds to its ligand, HGF, a downstream cascade is started that leads to the activation of the MAPK pathway which promotes cell migration and tumor proliferation (Zhang et al. 2018). Seeing as 20% of type 1 tumors contain a *MET* mutation, it is not surprising that

MAPK is the preferred pathway of type 1 tumors. Furthermore, the PI3K pathway was found to be significant in the probability of having a type 2 tumor as well as being the preferred pathway of type 2. The findings in this study support the ongoing efforts in determine drug treatment therapies that target the PI3K pathway. PI3K is comprised of lipid kinases that once activated, begin a downstream cascade that leads to cell growth and survival. PI3K pathway has a strong association with the inactivation of *PTEN,* which has been correlated poor patient outcomes (Yang et al. 2019; Bazzichetto et al. 2019).

**Conclusion**

Despite the imperfect database this study found that there is a trend in the data that is clinically significant. Furthermore, this study provides the framework for future more comprehensive research on the demographic, increased risk factor and genetic pathway differences between PRCC type 1 and type 2 tumors. Future investigations should include a more complete dataset with additional potential risk factors. Given the differences in survival rates, such investigations will provide clinicians a better understanding of tumor types allowing for quicker more accurate diagnosis and evidence based treatment plans.

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Fig. 4.2 Descriptive Statistics for Demographic Factors

|  | Type 1 | Type 2 |
|---|---|---|
| Gender (n=158) |  |  |
| Male | 50 | 61 |
| Female | 19 | 27 |
| Race (n=149) |  |  |
| White | 46 | 66 |
| Black or African American | 18 | 15 |
| Other | 0 | 4 |
| Mean Age (n= 156) | 60 (Range 28 to 82) | 64.5 (Range 28-88) |
| Ethnicity (n= 144) |  |  |
| Hispanic or Latino | 2 | 5 |
| Not Hispanic or Latino | 62 | 75 |

Fig. 4.3 Descriptive Statistics for Increased Risk Factors

|  | Type 1 | Type 2 |
|---|---|---|
| Smoking History Category (n=146) |  |  |
| 1 | 30 | 36 |
| 2 | 10 | 11 |
| 3 | 10 | 14 |
| 4/5 | 7 | 20 |
| Prior Neoplasm (n= 95) |  |  |
| Yes | 2 | 9 |
| No | 36 | 48 |
| Prior Malignancy (n= 156) |  |  |
| Yes | 16 | 14 |
| No | 55 | 77 |
| Mean BMI (n=123) | 35.88 | 27.72 |

Fig. 4.4 Descriptive Statistics for Pathways

|  | Type 1 | Type 2 |
|---|---|---|
| Pathway (n=157) |  |  |
| MAPK | 31 | 23 |
| HIPPO | 2 | 3 |
| PI3K | 8 | 27 |
| P53 | 13 | 16 |
| WNT | 7 | 6 |
| NOTCH | 5 | 9 |
| TGF | 2 | 3 |

| | | |
|---|---|---|
| TNF | 1 | 1 |

Table 4.1. Demographics Model

| | OR | 95% CI for OR | |
|---|---|---|---|
| Age at Diagnosis | 1.045 | 1.014 | 1.078 |
| White | Reference | - | - |
| Black or African American | 0.677 | 0.301 | 1.525 |
| Other | 5.601 | 0.54 | 58.089 |

Odds ratios (ORs) associated with the selected demographic model. The model was selected using forward selection (criteria for entry p<.1) from a candidate model including age at diagnosis, race, sex, and ethnicity. The final model had an effective sample size of 150.

Table 4.2. Increased Risk Factor Model

| Variable | Level | OR | 95% CI for OR | |
|---|---|---|---|---|
| BMI (n=121) | | 0.989 | 0.963 | 1.015 |
| Smoking (n=131) | Smoke 1 | Reference | - | - |
| | Smoke 2 | 1.141 | 0.381 | 3.415 |
| | Smoke 3 | 0.916 | 0.322 | 2.611 |
| | Smoke 4or 5 | 3.241 | 1.066 | 9.853 |
| Malignancy (n=150) | No | Reference | - | - |
| | Yes | 0.614 | 0.265 | 1.421 |
| Neoplasm (n=91*) | No | Reference | - | - |
| | Yes | 3.736 | 0.698 | 19.999 |

Odds ratios and associated confidence intervals for increased risk factor variables. Each variable, BMI, smoking, malignancy and neoplasm were added to the demographic model (i.e. the model containing Age at Diagnosis and Race) one at a time and the odds ratios for each variable and level are reported here, controlling for age at diagnosis and race. Effective sample sizes are included under the variable labels.

Table 4.3. Pathway Model

| Pathway | OR | 95% CI for OR | |
|---|---|---|---|
| MAPK | Reference | - | - |
| HIPPO | 7.43 | 0.58 | 95.242 |
| NOTCH | 3.076 | 0.768 | 12.32 |
| P53 | 1.783 | 0.678 | 4.69 |
| PI3K | 4.968 | 1.759 | 14.031 |
| TGF | 2.264 | 0.313 | 16.35 |
| TNF | 0.767 | 0.041 | 14.309 |
| WNT | 1.232 | 0.341 | 4.455 |

Odds ratios and associated confidence intervals for individual pathways. Note that the CI for PI3K does not contain 1 which indicates that PI3K is (significant and) positively associated with Type 2. ORs were obtained by adding pathway to the demographic model controlling for age at diagnosis and race.

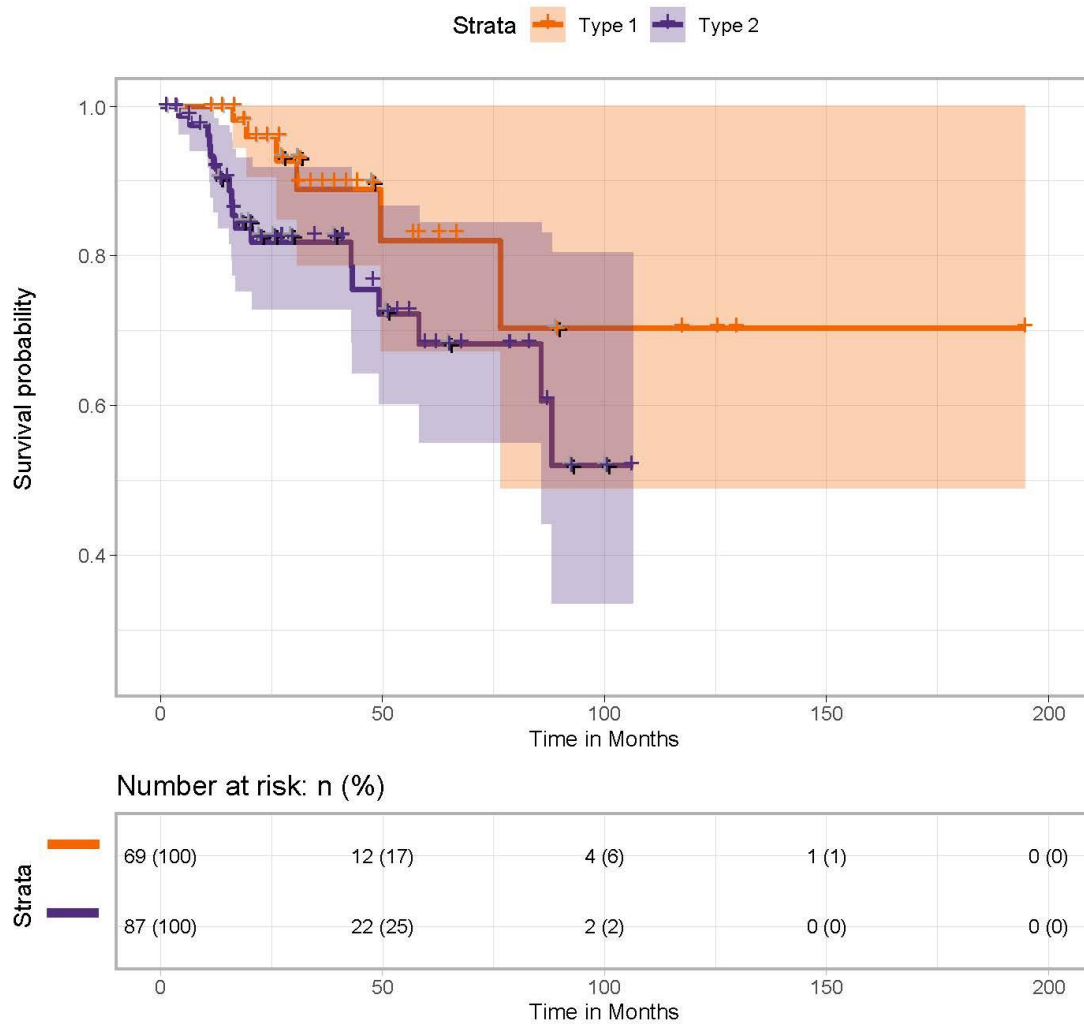## Kaplan Meier Curves for Type 1 and 2 PRCC Survival



Fig. 4.5. Kaplan-Meier survival curve for type 1 PRCC tumors as compared to type 2 PRCC tumors.

# Chapter V

## *Synthesis of Manuscripts*

Papillary renal cell carcinoma (PRCC) is the second most common renal cell carcinoma (RCC), following clear cell, comprising of 15-20% of all RCCs. PRCC is a heterogenous disease that consists of two histologically distinct subtypes; type 1 and type 2. PRCC is often asymptomatic and difficult to detect with as many as 20-50% of tumors being discovered incidentally (Marsaud et al 2015; Prochazkova et al. 2018). Furthermore, the treatment options remain limited for PRCC tumors with nephrectomy continuing to be the preferred treatment. Until recently research has been focused on the more common RCC subtype, clear cell. Additionally, PRCC studies have been broadly based with little research being done on comparing PRCC tumor subtypes. PRCC subtypes are genetically diverse and present with varying patient outcomes (Fernandes & Lopes 2015; Pal et al. 2019). Considering that healthcare providers are at the forefront of the diagnosis and treatment of PRCC, it is imperative that they be able to distinguish between PRCC subtypes.

All the chapters in this dissertation work together to create a cohesive and comprehensive understanding of PRCC as a whole, as well as understanding PRCC subtypes 1 and 2. The purpose of this body of work was first to discuss the status of the current literature on PRCC including subtypes, genetic underpinnings, epidemiology and treatment options. The second purpose was to define what is known on differentiating between PRCC subtypes and to perform a secondary data analysis to determine if there were clinically relevant differences between PRCC type 1 and type 2 tumors.

In order to better understand PRCC as a disease, the first manuscript (chapter 2) performed a comprehensive review and synthesis of the literature discussing the subtype

classification, genetic pathways and epidemiology of the disease as it relates to clinicians. This review found that PRCC is a genetically diverse disease with multiple subtypes. Currently, there are two main histologically diverse subtypes; type 1 and type 2. Type 1 tumors are characterized by a single layer of basophilic cells with sparse cytoplasm and small oval nuclei. Type 1 tumors can be sporadic or hereditary and 20% of type 1 tumors present with a mesenchymal epithelial transition (*MET)* gene variation (Marsuad et al. 2016). Conversely, type 2 tumors present with a pseudostratified layer of cells with eosinophilic cytoplasm and large nuclei. Type 2 tumors can also be sporadic or hereditary and have been associated with fumarate hydratase *(FH)* as well as vascular endothelial growth factor (*VEGF)* gene variations (Modi and Singer 2015: TCGA, 2016: Marsuad et al. 2015). This literature review found that there is a lack of knowledge concerning the epidemiology of type 1 and type 2 PRCC tumors. Furthermore, this review found that PRCC tumors are treated the same as clear cell tumors with nephrectomy being the preferred treatment method (Fernandes & Lopes 2015; Dengina et al. 2017). This manuscript differs from the others in that it is a description of PRCC as whole and provides the necessary background for manuscripts two and three.

After careful review of the literature, the second manuscript (chapter 3) aimed to further examine the genetic underpinnings of PRCC tumors. The purpose of this literature synthesis was to describe the various renal cell cancer syndromes that are associated with RCC. The most common renal cancer syndrome is von Hippel-Lindau Syndrome which is characterized by mutations in the VHL gene. Individual's with von Hippel-Lindau Syndrome have a 40% chance of developing an RCC, including the PRCC subtype (Gupta et al. 2017). Similarly, Hereditary Leiomyomatosis and Renal Cell Cancer is characterized by mutations in the *FH* gene and has been associated with the development of type 2 PRCC tumors (Arenas Valencia et al., 2017).

Considering that numerous renal cancer syndromes present with benign neoplasms, this literature review provided the basis for using prior neoplasms as a variable for the secondary data analysis (Paquin & Fasolino 2020). The second manuscript differs from the first manuscript in that it focuses specifically on hereditary causes of PRCC. Furthermore, this manuscript is a narrow-based literature review unlike manuscript 3, which is original research.

The third manuscript (chapter 4) in this dissertation performed a secondary data analysis using The Cancer Genome Atlas- Kidney Renal Papillary Cell Carcinoma (TCGA-KIRP) data to determine if there were significant differences between type 1 and type 2 PRCC tumors that can be utilized by clinicians. The secondary data analysis focused on epidemiological factors, age, ethnicity, gender, race; increased risk factors, body mass index (BMI), smoking history, neoplasm history, and malignancy history; and tumor subtype pathway preference. This analysis found that older age at diagnosis was significant in the probability of having a type 2 PRCC tumor. Similarly, this study also found that being African American had a negative probability of having a type 2 tumor. In terms of pathway preference, type 2 tumors were found to significantly prefer the PI3K pathway and type 1 tumors utilized the MAPK pathway. Lastly, this study found that there is a significant difference in overall survival rates between tumor types with type 2 tumors having a lower overall survival rate. Manuscript three is an original study that is based on the literature reviews performed in manuscripts one and two.

*Contribution to the Knowledge of PRCC and Healthcare Genetics*

Up until recently research has been based on the clear cell subtype of RCC and what research that has been done specifically on PRCC, has focused on the cellular molecular components of the disease. Furthermore, there is a gap in the knowledge concerning the clinically significant differences between type 1 and type 2 PRCC tumors (MacLennan & Cheng

2020: Lineman et al 2015). This dissertation contributed to the current knowledge of PRCC by determining that there are certain significant differences, age at diagnosis, race, genetic pathway preference, and overall survival, between type 1 and type 2 PRCC tumors. The findings in this dissertation are relevant to healthcare genetics because they provide the foundation for evidence-based practice concerning the diagnosis, prognosis and treatment of PRCC tumors. Furthermore, this dissertation provides the background needed for future research initiatives that focus on further defining the differences between type 1 and type 2 PRCC tumors.

*Knowledge Gaps and Future Directions*

Although this dissertation presented a comprehensive overview of PRCC and the subtypes associated with the disease, there are still gaps in the knowledge. The first gap is that although type 1 and type 2 PRCC tumors are the most recognized, there are more than two subtypes associated with PRCC. Additionally, tumors can be heterogenous and present with features of both type 1 and type 2 subtypes (Marsaud et al 2015; Prochazkova et al. 2018). This dissertation was limited to the data currently available and therefore restricted to type 1 and type 2 PRCC tumors, not accounting for additional subtypes. Another limitation was that this dissertation did not cover all known renal cancer syndromes. There are other syndromes, specifically hereditary papillary renal cell carcinoma (HPRCC) which is characterized by *MET* variations, that predispose individual's to PRCC. Although quite rare, HPRCC is associated with an almost 100% chance of developing type 1 PRCC tumors (Maher 2018). This dissertation focused on the most common renal cancer syndromes and is not a comprehensive list. Lastly, this dissertation was limited to a small sample population of already collected data, thus the research questions were limited to those that could be answered by the available data. Additionally, the sample size was further limited with each variable tested in the final

manuscript. This means that a larger sample size could provide additional insights into variables that can distinguish between type 1 and type 2 PRCC tumors.

The findings in this study indicate the need for further research to better distinguish between type 1 and type 2 PRCC subtypes. First there has to be research to clearly designate what constitutes PRCC subtypes. Type 1 and type 2 subtypes have consistently been recognized as the primary PRCC subtypes. However, these two subtypes have been characterized by their histology and a recent study has proposed other options for tumor typing (Mager et al. 2019). Having a clear system to properly subtype PRCC tumors is needed to insure the validity of future PRCC research.

Second, there is a need for a new descriptive and comprehensive PRCC dataset. Currently, the TCGA-KIRP remains the only source for a large collection of PRCC data that includes clinical, genetic and risk factor information. However, this dataset is largely incomplete and the last sample was collected in 2013 (Lineman et al, 2016). There is a need for new research that is more current and is comprised of more complete increased risk factor data, including chemical exposure, prior neoplasms, renal cancer syndrome status, and smoking history. Furthermore, this study must also include the specific subtype of each PRCC tumor as defined by the current literature.

Thirdly, additional research on PRCC preferred genetic pathways should be conducted to better understand what role pathways play in determining PRCC subtypes. Pathway preference is important in the development of tumor specific treatment options. Given the heterogenous nature of both types of PRCC, understanding the preferred genetic pathways of each subtype will lead to better evidence-based treatment options. Current clinical trials are focused on specific genes (namely *MET*) or individuals with certain renal cancer syndromes (Clinicaltrials.gov, 2020).

Focusing treatment research on genetic pathways as opposed to specific genes, will lead to the ability to treat a larger variety of PRCC tumors.

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# Appendices

## Appendix 1
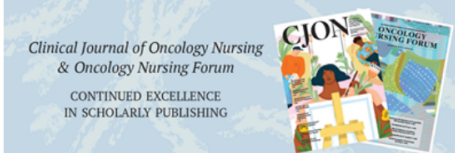
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**Rachel Geffrey**
Thu, Nov 5, 8:11 AM
to me

Hi Melissa,

We do not allow published articles to be made open access, but if your dissertation will be in an open access repository you can instead include the raw manuscript that has not been edited or designed. If you have any other questions, please don't hesitate to ask.

Best,

**Rachel Geffrey**
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# List of Acronyms

*Cancers*

ccRCC – Clear Cell Renal Cell Carcinoma

ccPRCC= Clear Cell Papillary Renal Cell Carcinoma

PRCC – Papillary Renal Cell Carcinoma

RCC – Renal Cell Carcinoma

*Genes/Proteins*

*BAP1* - BRCA1 Associated Protein-1

*BRCA1* = Breast Cancer type 1 Susceptibility Protein

*EGFR* = *E*pidermal Growth Factor Receptor

*FH*- Fumarate Hydratase

*FLCN* – Folliculin

*FRA7G* = Aphidicolin-Inducible Fragile Site

*HER2* = human epidermal growth factor receptor 2

*HGF* = Hepatocyte growth factor

*HIC-1* = Hypermethylated in Cancer 1

*KLLN* = Killin

*MET* – Mesenchymal Epithelial Transition

*MITF* = Melanocyte Inducing Transcription Factor

*P53* = Tumor Protein 53

*PTEN* = Phosphatase and Tensin Homolog

*RTK* = Tyrosine Kinase Receptor

*SDH* = Succinate Dehydrogenase Complex Iron Sulfur

*SDHB* = Succinate Dehydrogenase Complex Iron Sulfur Subunit B

*SDHD* = Succinate Dehydrogenase Complex Iron Sulfur Subunit D

*TAU*= microtubule-associated protein tau

*TOP2A*= topoisomerase 2-alpha

*TSC1*- TSC Complex Subunit 1

*VEGF* = Vascular Endothelial Growth Factor

*VHL* - Von Hippel–Lindau tumor suppressor

**Pathways**

MAPK = Mitogen Activated Protein Kinase

P53 = Tumor Protein 53 pathway

PI3K = Phosphoinositide 3-kinases

TGF = Transforming growth factor beta

TNF = Tumor Necrosis Factor

WNT = blending of Wingless and Int-1

**Syndromes/Diseases**

BHD = Birt-Hogg-Dubé Syndrome

CS = Cowden Syndrome

ESRD = End Stage Renal Disease

HRLCC= Hereditary Leiomyomatosis and Renal Cell Cancer

HNPCC = Lynch Syndrome/ Hereditary Non-Polyposis Colorectal Cancer

HPRCC = Hereditary Papillary Renal Cell Carcinoma

TSC = Tuberous Sclerosis Complex

VHL = von Hippel-Lindau Disease

**Databases**

BCR= Biospecimen Core Resource

cBioPortal = cBioPortal for cancer genomics

TCGA-KIRP- The Cancer Genome Atlas- Kidney Renal Papillary Cell Carcinoma

**Terms**

BMI – Body Mass Index

CNA = Copy Number Alteration

CI = Confidence Interval

OR = Odds Ratio