

## Rate of Renal Cell Carcinoma Subtypes in Different Races

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### ABSTRACT

*Purpose:* We sought to identify racial differences among histological subtypes of renal cell carcinoma (RCC) between black and non-black patients in an equal-access health care system.

*Materials and Methods:* We established a multi-institutional, prospective database of patients undergoing partial or radical nephrectomy between January 1, 2000 and Sept 31, 2009. For the purposes of this study, data captured included age at diagnosis, race, tumor size, presence of lymphovascular invasion, presence of capsular invasion, margin status, and tumor histology.

*Results:* 204 kidney tumors were identified (Table-1). Of these, 117 (57.4%) were in black patients and 87 (42.6%) were in non-black patients. Age at surgery ranged from 37 to 87 with a median of 62. Tumor size ranged from 1.0 to 22.0 cm with a median of 5.0 cm. Overall, tumors were composed of clear cell RCC in 97 cases (47.5%), papillary RCC in 65 cases (31.9%), chromophobe RCC in 13 cases (6.4%), collecting duct/medullary RCC in 2 cases (1.0%), RCC with multiple histological subtypes in 8 cases (3.9%), malignant tumors of other origin in 6 cases (2.9%), and benign histology in 13 cases (6.4%). Among black patients, papillary RCC was seen in 56 cases (47.9%), compared to 9 cases (10.3%) among non-black patients ( $p < 0.001$ ) (Table-2). Clear cell RCC was present in 38 (32.5%) of black patients and in 59 (67.8%) of non-blacks ( $p < 0.001$ ).

*Conclusions:* In our study, papillary RCC had a much higher occurrence among black patients compared to non-black patients. This is the first study to document such a great racial disparity among RCC subtypes.

*Key words:* kidney neoplasm; renal cell; carcinoma

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### INTRODUCTION

Renal cell carcinoma (RCC) is the seventh most common human malignancy, having accounted for approximately 59,702 new cancer cases in the United States in 2009 (1). The histological classification of RCC has undergone several major revisions, with the current 2004 World Health Organization (WHO) guidelines incorporating new cytogenetic findings and molecular markers that help guide diagnosis, prognosis, and therapy (2). RCC is now recognized to be a complex neoplasm consisting of several different tumor subtypes, each with distinct

genetic and clinical features. Previous population-based studies on racial differences in incidence patterns and outcomes of RCC have failed to account for the different histological subtypes of RCC (3). We sought to identify racial differences in the patterns of histological subtypes of RCC in a racially diverse, equal-access health care system.

### MATERIALS AND METHODS

We performed a multi-institutional, retrospective review of patients undergoing partial or radical nephrectomy between January 1<sup>st</sup>, 2000 and Sept 31<sup>st</sup>,

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2009. Our hospitals included a tertiary care academic center, a veteran's administration hospital, and an inner-city county hospital, ensuring a mixed ethnic population. All slides underwent centralized pathology review using the WHO 2004 Classification of renal cell histology to classify tumors into clear cell, papillary, chromophobe, or medullary/collecting duct varieties. We did not differentiate between papillary RCC type 1 and papillary RCC type 2. Data was collected by reviewing patient charts and capturing the following parameters: age at diagnosis, race, tumor size, presence of lymphovascular invasion, presence of capsular invasion, margin status, and tumor histology.

## RESULTS

Two hundred and four kidney tumors were identified (Table-1). Of these, 117 (57.4%) were in black patients and 87 (42.6%) were in non-black patients. Age at surgery ranged from 37 to 87 with a median age of 62. Among black patients the age range was 37 to 82 with a median of 63 and among non-black patients the age range was 40 to 87 with a median of 60.

Tumor size ranged from 1.0 to 22.0 cm with a median of 5.0 cm. The size of tumors among blacks ranged from 1.4 to 20.0 cm and from 1.0 to 22.0 cm in

**Table 1 – Baseline characteristics.**

	Black # (%)	Non-Black # (%)	Total	
<b>Patient characteristics</b>				
Number of patients	117 (57.4)	87 (42.6)	204 (100)	
<b>Age</b>				
Range	37 - 82	40 - 87	37 - 87	
Mean	60.3	64.1	61.9	
Median	63	60	62	
Under 65 years old	74/117 (63.2)	52/87 (59.8)	126/204 (61.8)	
65 years old or older	43/117 (36.8)	35/87 (40.2)	78/204 (38.2)	p = 0.61
<b>Tumor characteristics</b>				
<b>Size (cm)</b>				
Range	1.4 – 20.0	1.0 – 22.0	1.0 – 22.0	
Mean	5.9	5.1	5.6	
Median	5.0	4.9	5.0	
4 cm or less	41/113 (36.3)	35/82 (42.7)	76/195 (39.0)	
Greater than 4 cm and less than or equal to 7 cm	38/113 (33.6)	31/82 (37.8)	69/195 (35.4)	
Greater than 7 cm	34/113 (30.1)	16/82 (19.5)	50/195 (25.6)	p = 0.25
<b>Lymphovascular invasion</b>				
Yes	5/115 (4.3)	10/84 (11.9)	15/199 (7.5)	
No	110/115 (95.7)	74/84 (88.1)	184/199 (92.5)	p = 0.05
<b>Capsular invasion</b>				
Yes	10/115 (8.7)	11/84 (13.1)	21/199 (10.6)	
No	105/115 (91.3)	73/84 (86.9)	178/199 (89.4)	p = 0.32
<b>Margin status</b>				
Positive	6/115 (5.2)	5/84 (6.0)	11/199 (5.5)	
Negative	109/115 (94.8)	79/84 (94.0)	188/199 (94.5)	p = 0.82

non-blacks. There was no statistically significant difference in tumor size between blacks and non-blacks when subdivided into groups of 4 cm or less, greater than 4 cm and less than or equal to 7 cm, and greater than 7 cm ( $p = 0.25$ ).

The majority of tumors in blacks and non-blacks had absence of lymphovascular invasion (4.3% and 11.9%,  $p = 0.05$ ), absence of capsular invasion (91.3% and 86.9%,  $p = 0.32$ ), and negative surgical margins (94.8% and 94.0%,  $p = 0.82$ ).

Overall, tumors were composed of clear cell RCC in 97 cases (47.5%), papillary RCC in 65 cases (31.9%), chromophobe RCC in 13 cases (6.4%), collecting duct/medullary RCC in 2 cases (1.0%), RCC with multiple histological subtypes in 8 cases (3.9%), malignant tumors of other origin in 6 cases (2.9%), and benign histology in 13 cases (6.4%). Among black patients, papillary RCC was seen in 56 cases (47.9%), compared to 9 cases (10.3%) among non-black patients ( $p < 0.001$ ) (Table-2). Clear cell RCC was present in 38 (32.5%) of black patients and in 59 (67.8%) of non-blacks ( $p < 0.001$ ).

**COMMENTS**

Our study found a greater than four-fold increase in occurrence of papillary RCC in blacks when compared to non-blacks. This is the first study to document such a large ethnic disparity among RCC subtypes.

This phenomenon of neoplastic variability among different races has been observed in other urologic cancers. Prostate cancer is a well-studied malignancy that tends to behave differently among different races. Compared with whites, blacks are more likely to be diagnosed with prostate cancer at a younger age (4). Black patients with prostate cancer are also less likely to be treated with surgical intervention and have an overall lower survival (5).

There are many previously reported, large, population-based studies elucidating the racial disparities among patients with RCC. These reports, however, have focused on topics such as overall survival and access to health care. A recent paper by Stafford et al. found that blacks had an overall increase in incidence of renal cell carcinoma and decrease in survival rate when compared to other ethnicities (6). Zini et al. concluded that black patients with RCC were 50% less likely to undergo nephrectomy compared to white patients (7). A study by Brendt et al. also addresses the lower survival rate among blacks with renal cell carcinoma and proposes that this may be explained by both a higher number of comorbidities and lower rate of surgical treatment (8). While these studies have unearthed many interesting data trends among RCC cases, none have included information on histological subtypes of RCC.

Beyond the well-described association of renal medullary carcinoma with sickle-cell disease and trait in black patients, there has been very little reported regarding racial differences for the other RCC

*Table 2 – Race and tumor histology.*

<b>Tumor Histology</b>	<b>Black # (%)</b>	<b>Non-black # (%)</b>	<b>Total # (%)</b>	
RCC clear cell	38 (32.5)	59 (67.8)	97 (47.5)	$p < 0.001$
RCC papillary	56 (47.9)	9 (10.3)	65 (31.9)	$p < 0.001$
RCC chromophobe	6 (5.1)	7 (8.0)	13 (6.4)	$p = 0.40$
RCC collecting duct / medullary	2 (1.7)	0 (0.0)	2 (1.0)	$p = 0.22$
RCC multiple histologies	6 (5.1)	2 (2.3)	8 (3.9)	$p = 0.30$
Other malignancy	2 (1.7)	4 (4.6)	6 (2.9)	$p = 0.23$
Benign	7 (6.0)	6 (6.9)	13 (6.4)	$p = 0.79$
Total	117	87	204	

*RCC = renal cell carcinoma.*

histologies (9). Historically, clear cell tumors have accounted for 70-80% of RCC, followed by 10-15% for papillary, 3-5% for chromophobe, and 1-2% for medullary/collecting duct (10). Our reported 47.9% incidence of papillary tumors among black patients is the first of its kind and is more than four-fold the incidence of papillary tumors among non-black patients in our study. One explanation for this observation may be a genomic predisposition for blacks to express genes unique for the development of papillary RCC.

Papillary RCC is commonly found in two classic genetic syndromes, hereditary papillary RCC and hereditary leiomyomatosis and renal cell cancer syndrome. Papillary tumors have also previously been reported to be associated with acquired renal cystic disease. The chromosomal abnormalities for papillary tumors are distinct from the chromosome 3 and Von-Hippel Lindau gene abnormalities of clear cell tumors. Papillary tumors typically demonstrate trisomy of chromosomes 7 and 17 and loss of the Y chromosome. Mutations in the met-oncogene, which encodes hepatocyte growth factor, is the usual mutation for papillary tumors, which usually display multicentricity and hypovascularity. As expected with the new era of targeted therapies for RCC, unique molecular agents separate from tyrosine kinase inhibitors are being developed for papillary tumors. If black patients with RCC truly have a predisposition for expression of papillary type tumors, they may benefit from early counseling and treatment with novel agents targeting this unique tumor.

More recently, papillary RCC has been subdivided into type 1 and type 2, with type 2 tumors exhibiting more aggressive clinicopathological features and worse prognosis (11). Our retrospective analysis does not allow statements regarding the influence of tumor subtype on clinical course and prognosis following treatment. As such, we do not present any outcomes data and do not differentiate between subtypes of papillary RCC. Of note, there have been studies demonstrating no differences in disease-free survival between papillary and clear cell RCC (12).

One must also consider the possible influence of confounding factors on the variable expression of RCC subtypes. Previous studies have shown that there is a predisposition among males and patients with end stage renal disease to develop papillary RCC (13,14).

This potential bias should be taken into consideration when designing future studies aimed to capture racial differences observed among RCC subtypes.

## CONCLUSION

We report for the first time, to our knowledge, that black patients seem to have an increased risk of developing papillary RCC than the general population. This result needs to be confirmed by large, population-based studies that examine different RCC histologies against a wide range of demographic, geographic, and environmental factors. Given the complex genetic and molecular basis for RCC and its role in response to adjuvant treatments, race and ethnicity may be important factors when counseling patients regarding prognosis and treatment outcomes.

## CONFLICT OF INTEREST

None declared.

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#### **EDITORIAL COMMENT**

We have known for a while that renal cell carcinomas (RCC) are more common in blacks compared to non-Blacks and Asians. Not only more common, RCC tend to be more aggressive in blacks, with a higher disease-specific mortality even when tumor size and stage are independent variables. Black patients have a significantly higher incidence rate and lower survival rate than all other races/ethnicities even when having more localized cancer.

This study lists the rates of different types of renal cell carcinoma in a population composed of many ethnicities. In blacks, almost half of all tumors were papillary RCC, compared to only 10% in non-blacks. This disparity is not commonly addressed. In addition, it found a much lower rate of clear cell

RCC in blacks, which is not a common finding in the literature. The readers could have benefited by data on survival or progression, which unfortunately the study lacks. Nonetheless, given such racial disparities in renal cell carcinoma incidence in this one study, one should consider expanding and confirming these findings that may help elucidate biological, behavioral and environmental factors that can potentially be addressed.

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**EDITORIAL COMMENT**

Renal cell carcinoma (RCC) tends to manifest variable prognoses and outcomes. Previous articles have already pointed toward prognostic parameters including pathological subtypes and ethnic origin. Yet the issue of race was not fully addressed. Epidemiologic literature showed shorter survival in Black Americans with RCC. Tripathi et al. concluded that the overall survival for metastatic RCC was significantly shorter for Black Americans. Vaishampayan et al. had a similar conclusion for local RCC, emphasizing a higher incidence, poorer outcome in Black patients with a similar age and stage. However, the histology subtypes disparities were not mentioned, demonstrating the advantage of the recent manuscript based on data that was retrieved from an equal-access health care system. Stafford published a major study comparing ethnic groups (White, Black, Hispanic and Asian -Pacific) concluding that Black patients tend to have a higher incidence and a shorter survival while Asian patients demonstrate the opposite. Yet even this article did not point to the histology subdivision.

Herein we can appreciate an important study advancing our knowledge regarding the correlation between race and RCC histology subtypes. Further studies should investigate the papillary predominance

of the RCC in the black population while paradoxically demonstrating a poorer prognosis than what was known previously for that histological subtype.

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