Chromophobe Renal Cell Carcinoma is the Most Common Nonclear Renal Cell Carcinoma in Young Women: Results from the SEER Database

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Purpose: The renal cell cancer incidence is relatively low in younger patients, encompassing 3% to 7% of all renal cell cancers. While young patients may have renal tumors due to hereditary syndromes, in some of them sporadic renal cancers develop without any family history or known genetic mutations. Our recent observations from clinical practice have led us to hypothesize that there is a difference in histological distribution in younger patients compared to the older cohort.

Materials and Methods: We queried the SEER (Surveillance, Epidemiology and End Results) 18-registry database for all patients 20 years old or older who were surgically treated for renal cell carcinoma between 2001 and 2008. Patients with unknown race, grade, stage or histology and those with multiple tumors were excluded from study. Four cohorts were created by dividing patients by gender, including 1,202 females and 1,715 males younger than 40 years old, and 18,353 females and 30,891 males 40 years old or older. Chi-square analysis was used to compare histological distributions between the cohorts.

Results: While clear cell carcinoma was still the most common renal cell cancer subtype across all genders and ages, chromophobe renal cell cancer was the most predominant type of nonclear renal cell cancer histology in young females, representing 62.3% of all nonclear cell renal cell cancers ($p < 0.0001$). In all other groups papillary renal cell cancer remained the most common type of nonclear renal cell cancer.

Conclusions: It is possible that hormonal factors or specific pathway dysregulations predispose chromophobe renal cell cancer to develop in younger women. We hope that this work provides some new observations that could lead to further studies of gender and histology specific renal tumorigenesis.

Key Words: kidney; carcinoma, renal cell; female; anatomy and histology; tumorigenesis

Abbreviations and Acronyms

AML = angiomyolipoma

RCC = renal cell carcinoma

TSC = tuberous sclerosis

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THE incidence of RCC has been increasing in recent years. In 2015 an estimated 61,560 new cases were diagnosed in the United States.[1] RCC is known to be a heterogeneous group with a histological spectrum of specific genetic alterations and prognoses. Several studies demonstrated that after adjusting for stage the histology of the tumor has a major role in patient outcomes.[2–4] The classic histological distribution of renal tumors is that clear cell is the most common type, followed by papillary (usually

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combined with type 1 or 2), followed by chromophobe RCC. The number of young patients diagnosed with RCC has been between 3% and 7%.[5–10]

Average age at onset of RCC is the seventh decade of life and the young patient classification is considered to include those younger than 40 years.[5,6,8–10] Due to the rarity of young patients with RCC there is limited and often conflicting literature regarding these patients. Often younger patients are grouped together with older patients when describing RCC treatments and various demographic descriptors, making the sparse literature that is available limited to guide the treatment of a young patient found to have RCC.

While a few groups analyzing younger patients have evaluated histological rates of RCC subtypes, the findings appear limited by single center analyses and contradictory findings.[5,6,8–14] In addition, to our knowledge there is no analysis describing the effects of gender on histological subtype. Our recent observations in clinical practice led us to hypothesize that age and gender affect the histological distribution of RCC with younger female patients presenting with chromophobe RCC more commonly than expected.

METHODS

The SEER 18-registry database was queried for all patients diagnosed with RCC between 2001 and 2008. This range was selected because several nonclear cell RCC subtypes were added to the ICD-O code established in 2000 and used starting in 2001.[15] Patients with unknown histology and those with likely hereditary syndromes (age less than 20 years with multiple or bilateral tumors) were excluded from study.

The histologies selected for were clear cell (8310), granular (8320), papillary (8260), chromophobe (8317) and collecting duct (8319) RCC. Granular tumors were combined with clear cell lesions during analysis as they are now considered 1 histological entity. Two cohorts were created, including age less than 40 years (younger cohort) and age 40 years or greater (older cohort). These groups were then subdivided by gender into 1,187 younger females, 1,683 younger males, 17,904 older females and 29,984 older males. Patients with a nonclear cell histology (papillary and chromophobe) were further divided by race.

Patient demographic variables included age, gender and race. Tumor variables included grade, histology and stage. Chi-square analysis was done to compare patient demographics, tumor characteristics and histological distributions among the cohorts. Statistical significance was considered at $p \leq 0.05$ for all variables. Prism® was used to perform statistical analysis.

RESULTS

For all patients significant differences were seen among all groups in race, grade and T stage (each $p < 0.0001$, table 1). Older patients had higher grade and stage RCC. Comparisons of histology in all groups demonstrated that clear cell was still the most common type of RCC in all subgroups. Chromophobe RCC in young women was the second most common type of tumors with double the frequency of papillary RCC (table 1). The overall histological distribution significantly differed among the groups ($p < 0.0001$). The figure shows significant differences in nonclear cell histologies when patients were stratified by age and gender. Table 2 lists histology distributions stratified by age, gender and race. Young white females had the highest rate of chromophobe histology while older black females had the highest rate of papillary tumors.

Males presented with higher grade disease than females ($p < 0.0001$). This difference was also observed in the older cohorts, which had higher grade disease than their younger counterparts. In addition, older patients were diagnosed with higher tumor stages than the respective younger genders ($p < 0.0001$). Females had more T1 disease than males ($p < 0.0001$). In contrast males were diagnosed with more T3 disease than females ($p < 0.0001$).

DISCUSSION

The current SEER analysis revealed that the histological distribution of RCC depends on patient age, gender and race. Chromophobe RCC is more common in younger patients, especially in young

Table 1. *Patient demographics, and tumor characteristics and histology*

	No. Younger (%)		No. Older (%)	
	Females	Males	Females	Males
Overall	1,202	1,715	18,353	30,891
Race:*				
White	934 (77.7)	1,360 (79.3)	15,215 (82.9)	25,808 (83.5)
Black	161 (13.4)	180 (10.5)	1,905 (10.4)	2,916 (9.4)
Other	107 (8.9)	175 (10.2)	1,233 (6.7)	2,167 (7)
Grade:*				
1	196 (16.3)	240 (14)	2,531 (13.8)	2,904 (9.4)
2	592 (49.3)	802 (46.8)	7,918 (43.1)	12,565 (40.7)
3	179 (14.9)	321 (18.7)	3,472 (18.9)	7,640 (24.7)
4	27 (2.2)	63 (3.7)	988 (5.4)	1,948 (6.3)
Unknown	208 (17.3)	289 (16.9)	3,444 (18.8)	5,834 (18.9)
T stage:*				
T1	898 (74.7)	1,229 (71.7)	11,999 (65.4)	17,901 (57.9)
T2	174 (14.5)	222 (17.8)	2,103 (11.5)	3,925 (12.7)
T3	88 (7.3)	178 (4.2)	3,050 (16.6)	6,752 (21.9)
T4	19 (1.6)	42 (2.4)	680 (3.7)	1,168 (3.8)
Tx	23 (1.9)	44 (2.6)	521 (2.8)	1,145 (3.7)
Histology:*	1,187	1,683	17,904	29,984
Clear cell	857 (72.2)	1,264 (75.1)	14,632 (81.7)	22,762 (75.9)
Papillary	106 (8.9)	242 (14.4)	1,734 (9.7)	5,197 (17.3)
Chromophobe	215 (18.1)	169 (10.0)	1,462 (8.2)	1,859 (6.2)
Collecting duct	9 (0.8)	8 (0.5)	76 (0.4)	166 (0.6)

* Each $p < 0.0001$.