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Research Report

Evolving Epidemiologic Trends of Renal Cell Cancer by Histologic Subtype: An Updated Analysis of the California Cancer Registry

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Abstract.
Background: While most renal cell carcinomas (RCC) are of the clear cell subtype, other histologic subtypes are well described and have distinct clinical behavior. This study seeks to evaluate survival of clear and non-clear cell RCC retrospectively from a large, population-based cancer registry.
Objectives: The key objectives of this study were to determine cancer-specific survival (CSS) and overall survival (OS) of RCC by histologic subtype and to examine survival by histologic subtype since the advent of anti-angiogenesis therapy in 2006.
Methods: Within the California Cancer Registry (CCR), we used multivariable Cox proportional hazards models to assess the association of histologic subtype with CSS and OS, adjusted for sociodemographic and clinical factors.
Results: In the CCR, 33,539 RCC patients were diagnosed between 2004 and 2014. The most common subtype, clear cell RCC, comprised 82.6% ($n = 27{,}717$) of cases. The next most common subtypes were papillary (8.8%, 2,948) and chromophobe (5.2%, 1,759). RCC was more common in men (62.9%, 21,097) compared to women (37.1%, 12,442). Across histologic subtypes, patients with low neighborhood socioeconomic status had lower CSS (HR = 1.07, 95% CI 1.02–1.13, $p = 0.011$) and OS (HR = 1.14, 95% CI: 1.10–1.19, $p < 0.001$). On multivariate analysis, we observed an interaction between histologic subtype and CSS, finding that patients in the anti-angiogenesis treatment era with clear cell had a significant improvement in CSS (HR: 0.87, 95% CI: 0.82–0.92, $p < 0.001$) as did patients with collecting duct subtype (HR: 0.25, 95% CI: 0.12–0.51, $p < 0.001$), while there were no differences in outcomes over time among patients with chromophobe or papillary subtypes. After 2006, compared to clear cell subtype, patients with chromophobe subtype had a better CSS (HR = 0.40, 95% CI: 0.30–0.53, $p < 0.001$), while those with collecting duct carcinomas had a poorer CSS (HR = 1.83, 95% CI: 1.29–2.59, $p = 0.001$).

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Conclusions: In the era following anti-angiogenesis therapy development, patients with chromophobe subtype RCC continue to have a better prognosis compared with clear cell RCC, and patients with collecting duct subtype continue to have a significantly worse prognosis, with more advanced disease at diagnosis. There have been improvements in CSS in patients with clear cell and collecting duct subtypes since the advent of anti-angiogenesis therapy.

Keywords: Chromophobe, papillary, collecting duct, epidemiology, kidney cancer

INTRODUCTION

The incidence of renal cell cancer (RCC) in the United States is an estimated 63,000 cases per year, with up to 13,000 attributable deaths per year [1]. Renal cell cancer is a clinically and histologically heterogeneous disease. While the clear cell histologic subtype of RCC (ccRCC) is most common, a number of other histologic subtypes exist with unique characteristics. These other histologies are referred collectively as non-clear cell RCC (nccRCC), but the World Health Organization (WHO) has recognized that these comprise of 16 histologically distinct subtypes [2]. The most common of these nccRCC subtypes are papillary and chromophobe RCC, but other subtypes such as medullary, collecting duct, and translocation-associated RCC are also well-characterized.

While ccRCC, whether hereditary or sporadic, has been long-known to be driven by alterations in the von Hippel-Lindau (VHL) gene [3], in recent years further genomic characterization of nccRCC subtypes have revealed distinct molecular drivers in these subtypes, such as MET alterations in type 1 papillary RCC (pRCC), fumarate hydratase mutations in type 2 pRCC [4]. Though these genomic drivers are an active area of research, at present they have not translated to a change in management. Thus, patients are still classified by WHO histologic subtypes.

Given the smaller populations and heterogeneity of nccRCC, most clinical trials in RCC have either excluded nccRCC patients or have enrolled few of these patients. Treatments available for ccRCC are largely employed in management of advanced nccRCC as well, but with limited supporting data. Further insight into nccRCC regarding patient populations and survival outcomes can be gained from retrospective analyses of large registries or administrative datasets. A previous study evaluated the California Cancer Registry (CCR) database between 1998–2009 for survival trends prior to the era of cytokine therapy and in the post-cytokine therapy era and found improved cancer-specific survival (CSS) and overall survival (OS) in the post-cytokine therapy era [5]. In this study, we re-analyze the CCR between 2004–2014 to provide updates on survival of nccRCC as compared to ccRCC given the advances in systemic therapy that have occurred since the emergence of anti-angiogenesis agents in 2006.

MATERIALS AND METHODS

Patients with RCC were identified within the CCR, the population-based cancer surveillance system for the state comprising 4 National Cancer Institute Surveillance Epidemiology and Ends Results (SEER) registries. Amassing cancer incidence and mortality information since 1988, the CCR encompasses over 98% of statewide cancer diagnoses. First primary malignant RCC patients between 2004 and 2014 were identified in the CCR using SEER site recode 29020 and limited to clear-cell and the following non-clear cell histology groups: papillary, chromophobe, collecting duct, and other non-clear cell carcinoma histologies- these distinct groups were chosen on the basis of reliably coded data in the CCR database. All cases were pathologically confirmed, and diagnoses determined by autopsy or death certificate were excluded. This study was approved by the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the University of California, Davis, Institutional Review Boards.

From the CCR, we obtained date of diagnosis, stage at diagnosis (AJCC 7th edition), and initial course of surgical treatment. Initial course of surgical treatment was defined as no surgery, local excision/destruction, partial nephrectomy, complete nephrectomy, or unknown surgery. Additionally, we obtained patient demographics, including race/ethnicity, sex, age, residence, marital status, neighborhood socioeconomic status (nSES), and insurance type at time of diagnosis/initial treatment [6, 7]. Neighborhood SES were assigned at the Census block group level (2000 U.S. Census) and based on patient address at the time of initial diagnosis as reported in the medical record. Education, employment characteristics, median household income, proportion of the population living 200% below the federal poverty level, median rent, and

median housing value at the census tract level were utilized in determining the index characterized as nSES. A principal components analysis was used to identify quintiles, based on the distribution of census tracts in California of nSES ranging from 1 (lowest) to 5 (highest), with quintiles collapsed into low (quintiles 1–3) and high (quintiles 4–5). Treatment era cut-off was defined as prior to and after January 1, 2006 based on the Food and Drug Administration (FDA) approval of the first antiangiogenic agent for RCC, sorafenib, on 12/20/2005 [8]. CCR routinely collects follow-up information, including vital status and cause of death. RCC patients included in this study had complete follow-up through December 2014.

Descriptive statistics were used to generate demographic and tumor characteristics of all RCC patients in the cohort and by histologic subtype. The primary and secondary outcomes were RCC cause-specific survival (CSS) and overall survival (OS), respectively. Kaplan-Meier methodology was used to determine survival. To compare CSS and OS by histologic subtypes, we used multivariable Cox proportional hazards models, adjusted for gender, age at diagnosis, race/ethnicity, stage at diagnosis, nSES, health insurance type at diagnosis or initial treatment, surgical treatment, and era of diagnosis. Interactions between histology subtypes and race/ethnicity, gender, stage at diagnosis and era of diagnosis (2004–2005 vs 2006–2014) were assessed. Interactions were only significant for stage for OS and era of diagnosis for CSS. The proportional hazard assumption was assessed using Schoenfeld residuals [8]. Variables that violated proportional hazard assumptions (in the CSS or OS models) were included as stratification variables, including surgical treatment (both CSS and OS models), stage at diagnosis (CSS model) and age at diagnosis (OS model). All analyses were performed using SAS version 9.4. All statistical tests were two-sided, and a *P*-value of less than 0.05 was considered statistically significant. Results are presented as adjusted hazard ratios (HR) and 95% confidence intervals (CI).

RESULTS

A total of 33,539 RCC patients were identified in the CCR during the study period. Of these, 82.6% ($n = 27{,}717$) were ccRCC, while 17.4% (5,822) were characterized as nccRCC. The most common nccRCC subtypes found were papillary and chromophobe subtypes; collecting duct subtype only accounted for 0.2% (80) of all RCC cases. Characteristics of RCC patients by subtype are summarized in Table 1. Findings indicate a higher RCC frequency in males, with 62.9% (21,097) men as compared to 37.1% (12,442) women. Similar male predominance was seen across individual subtypes of clear cell, papillary, chromophobe, and collecting duct. However, this predominance was less marked in chromophobe subtype (55.8% [982] men vs 44.2% [777] women).

Racial/ethnic differences were observed across subtypes. Hispanic patients represented 28.6% ($n = 7{,}914$) of clear cell patients and 23.3% (409) of chromophobe subtype patients, but only 11.2% (330) of papillary subtype and 13.8% (11) of collecting duct subtype. While African-American patients represented 5.4% (1493) of clear cell subtype, these patients comprised 19.9% (588) of papillary, 7.8% (138) of chromophobe, and 15.0% (12) of collecting duct subtype. Asian/Pacific-Islander (PI) patients accounted for 8.8% (2,430) of clear cell, 5.1% (149) of papillary, 7.7% (136) of chromophobe, and 11.3% (9) of collecting duct subtype.

Stage of diagnosis was found to vary by subtype. Patients with clear cell subtype presented predominantly with Stage 1 disease (53.7%, $n = 14{,}894$), with 18.6% (5,144) patients having Stage 4 disease. Of papillary subtype, 69.5% (2,049) had Stage 1 disease while 6.8% (199) had Stage 4 disease. Similarly, among chromophobe patients, 63.4% (1,115) had Stage 1 disease while 2.8% (49) were diagnosed with Stage 4 RCC. With collecting duct subtypes, 27.5% (22) had Stage 1 disease, while 23.8% (19) and 41.3% (33) had Stage 3 and Stage 4 disease, respectively.

In Tables 2 and 3, multivariate analysis of CSS and OS are presented. Considering the interaction of histologic subtype and treatment era with CSS, there was a significant improvement in CSS seen in patients with ccRCC (HR = 0.87, 95% CI 0.82–0.93, $p < 0.001$) in the most recent era (Table 2). A significant improvement was not observed among the chromophobe or papillary subtype patients across eras. Patients with collecting duct subtype were found to have an improvement in CSS in the post-angiogenesis era (HR: 0.25, 95% CI 0.12–0.51, $p < 0.001$). In the post-angiogenesis era, compared to clear cell subtype, there was no significant difference in CSS in patients with papillary subtype RCC, but chromophobe subtype was associated with a better CSS (HR = 0.40, 95% CI 0.30–0.53, $p < 0.001$) and collecting duct subtype was associated with worse CSS (HR = 1.83, 95% CI 1.29–2.59, $p = 0.001$) (Supplemental Table). There was no interaction between treatment era and histology with respect to OS.

Table 1
Baseline characteristics among RCC patients diagnosed in California, 2004–2014

Variables	All		Clear cell		Papillary		Chromophobe		Collecting duct		Other non-clear	
	N	%	*N*	col %	*N*	col %	*N*	col %	*N*	col %	*N*	col %
All	33,539	100.0%	27,717	100.0%	2,948	100.0%	1,759	100.0%	80	100.0%	1,035	100.0%
Gender												
Female	12,442	37.1%	10,451	37.7%	706	23.9%	777	44.2%	21	26.3%	487	47.1%
Male	21,097	62.9%	17,266	62.3%	2,242	76.1%	982	55.8%	59	73.8%	548	52.9%
Race/ethnicity												
Non-Hispanic White	18,986	56.6%	15,500	55.9%	1,857	63.0%	1,060	60.3%	48	60.0%	521	50.3%
African-American	2,347	7.0%	1,493	5.4%	588	19.9%	138	7.8%	12	15.0%	116	11.2%
Hispanic	8,964	26.7%	7,914	28.6%	330	11.2%	409	23.3%	11	13.8%	300	29.0%
Asian/Pacific Islander	2,811	8.4%	2,430	8.8%	149	5.1%	136	7.7%	9	11.3%	87	8.4%
Other/Unknown	431	1.3%	380	1.4%	24	0.8%	16	0.9%	.	.	11	1.1%
Age at diagnosis												
<40	1,922	5.7%	1,271	4.6%	111	3.8%	171	9.7%	7	8.8%	362	35.0%
40–69	21,942	65.4%	18,226	65.8%	2,019	68.5%	1,188	67.5%	49	61.3%	460	44.4%
≥70	9,675	28.8%	8,220	29.7%	818	27.7%	400	22.7%	24	30.0%	213	20.6%
Year of diagnosis												
2004–2005	5,330	15.9%	4,430	16.0%	402	13.6%	230	13.1%	17	21.3%	251	24.3%
2006–2007	5,693	17.0%	4,736	17.1%	458	15.5%	269	15.3%	17	21.3%	213	20.6%
2008–2009	6,390	19.1%	5,269	19.0%	565	19.2%	345	19.6%	13	16.3%	198	19.1%
2010–2011	6,384	19.0%	5,251	18.9%	614	20.8%	354	20.1%	9	11.3%	156	15.1%
2012–2014	9,742	29.0%	8,031	29.0%	909	30.8%	561	31.9%	24	30.0%	217	21.0%
Stage at diagnosis												
Stage 1	18,363	54.8%	14,894	53.7%	2,049	69.5%	1,115	63.4%	22	27.5%	283	27.3%
Stage 2	3,305	9.9%	2,592	9.4%	317	10.8%	341	19.4%	4	5.0%	51	4.9%
Stage 3	4,607	13.7%	3,997	14.4%	294	10.0%	225	12.8%	19	23.8%	72	7.0%
Stage 4	5,571	16.6%	5,144	18.6%	199	6.8%	49	2.8%	33	41.3%	146	14.1%
Stage Unknown	1,693	5.0%	1,090	3.9%	89	3.0%	29	1.6%	2	2.5%	483	46.7%
First course of treatment-surgery												
No Surgery	5,100	15.2%	4,732	17.1%	170	5.8%	41	2.3%	13	16.3%	144	13.9%
Local excision/destruction	1,335	4.0%	1,096	4.0%	174	5.9%	49	2.8%	.	.	16	1.5%
Partial Nephrectomy	7,646	22.8%	5,782	20.9%	1,110	37.7%	583	33.1%	3	3.8%	168	16.2%
Complete Nephrectomy	19,418	57.9%	16,070	58.0%	1,493	50.6%	1,086	61.7%	64	80.0%	705	68.1%
Unknown Surgery	40	0.1%	37	0.1%	1	0.0%	.	.	.	.	2	0.2%
Neighborhood socioeconomic status at diagnosis												
Low SES (1, 2, 3)	19,198	57.2%	16,154	58.3%	1,491	50.6%	863	49.1%	46	57.5%	644	62.2%
High SES (4, 5)	13,340	39.8%	10,760	38.8%	1,363	46.2%	821	46.7%	32	40.0%	364	35.2%
SES Unknown	1,001	3.0%	803	2.9%	94	3.2%	75	4.3%	2	2.5%	27	2.6%
Marital status at diagnosis												
Never Married	5,816	17.3%	4,529	16.3%	537	18.2%	306	17.4%	18	22.5%	426	41.2%
Married	20,531	61.2%	17,072	61.6%	1,870	63.4%	1,107	62.9%	45	56.3%	437	42.2%
Previously Married	6,341	18.9%	5,417	19.5%	474	16.1%	288	16.4%	16	20.0%	146	14.1%
Unknown Marital Status	851	2.5%	699	2.5%	67	2.3%	58	3.3%	1	1.3%	26	2.5%
Residence at time of diagnosis												
Rural	1,317	3.9%	1,127	4.1%	83	2.8%	58	3.3%	3	3.8%	46	4.4%
Urban	32,222	96.1%	26,590	95.9%	2,865	97.2%	1,701	96.7%	77	96.3%	989	95.6%
Health insurance at diagnosis												
No insurance/Self Pay	596	1.8%	520	1.9%	34	1.2%	29	1.6%	1	1.3%	12	1.2%
Private Insurance	18,087	53.9%	14,764	53.3%	1,636	55.5%	1,102	62.6%	50	62.5%	535	51.7%
Medicaid/Government	3,296	9.8%	2,705	9.8%	224	7.6%	131	7.4%	8	10.0%	228	22.0%
Medicare	11,038	32.9%	9,258	33.4%	1,031	35.0%	487	27.7%	19	23.8%	243	23.5%
Unknown Insurance	519	1.5%	467	1.7%	23	0.8%	10	0.6%	2	2.5%	17	1.6%
Vital status (through 12/31/2014)												
Overall Death	10,155	30.3%	8,948	32.3%	614	20.8%	181	10.3%	56	70.0%	356	34.4%
RCC Death	6,243	18.6%	5,650	20.4%	286	9.7%	60	3.4%	42	52.5%	205	19.8%

On multivariate analysis, OS was noted to be slightly better in women (HR = 0.95, 95% CI 0.91–0.99, $p = 0.013$) but there was no difference in CSS between genders (Tables 2 and 3). Hispanic patients had a slightly better CSS (HR = 0.92, 95% CI 0.86–0.98, $p = 0.007$) and OS (HR = 0.89, 95% CI 0.85–0.94, $p < 0.001$) when compared to non-Hispanic White patients. No significant differences in CSS were seen in African-American or Asian/Pacific-Islander patients; however, OS

Table 2
Renal cell carcinoma (RCC) specific survival among RCC patients in California, 2004–2014

Variable	HR	95% CI	*P*-value
Histology * Treatment Era^			
Clear Cell			
2004–2005	Ref	–	–
2006–2014	0.87	(0.82, 0.93)	<0.001
Papillary			
2004–2005	Ref	–	–
2006–2014	0.89	(0.68, 1.17)	0.409
Chromophobe			
2004–2005	Ref	–	–
2006–2014	1.35	(0.72, 2.55)	0.349
Collecting Duct			
2004–2005	Ref	–	–
2006–2014	0.25	(0.12, 0.51)	<0.001
Other non-clear cell			
2004–2005	Ref	–	–
2006–2014	0.80	(0.59, 1.07)	0.132
Gender			
Female	1.04	(0.99, 1.10)	0.158
Male	Ref	–	–
Race/Ethnicity			
Non-Hispanic White	Ref	–	–
African American	0.95	(0.86, 1.06)	0.377
Hispanic	0.92	(0.86, 0.98)	0.007
Asian/Pacific Islander	0.99	(0.91, 1.08)	0.862
Other/Unknown	0.78	(0.60, 1.00)	0.054
Age at Diagnosis			
<40	Ref	–	–
40–69	1.24	(1.05, 1.46)	0.011
≥70	1.68	(1.42, 2.00)	<0.001
Neighborhood Socioeconomic Status (SES)			
Low SES	1.07	(1.02, 1.13)	0.011
High SES	Ref	–	–
SES unknown	0.91	(0.78, 1.07)	0.273
Health Insurance at Diagnosis			
Self-Pay/none	1.08	(0.90, 1.29)	0.402
Private Insurance	Ref	–	–
Medicaid/Government	1.04	(0.95, 1.13)	0.380
Medicare	0.96	(0.91, 1.02)	0.230
Unknown Insurance	1.40	(1.21, 1.62)	<0.001

^A significant interaction between histologic subtype and treatment era, p-value = 0.0070. Proportional hazard assumption was violated, therefore the CSS model was stratified by stage at diagnosis and first course of treatment-surgery.

was slightly poorer in African-American patients (HR = 1.08, 95% CI: 1.00–1.17, $p = 0.059$) and slightly better in Asian/Pacific-Islander patients (HR = 0.91, 95% CI 0.84–0.98, $p = 0.009$). Patients with low nSES had a slightly worse CSS (HR = 1.07, 95% CI 1.02–1.13, $p = 0.011$) and OS (HR = 1.14, 95% CI 1.10–1.19, $p < 0.001$).

We observed an interaction of histologic subtype and stage with OS ($p = 0.02$) (Table 3). Across all stages, OS was similarly improved in patients with chromophobe subtype compared to ccRCC. Collecting duct subtype patients had significantly worse OS as compared to ccRCC, except for Stage II patients where there were only 4 patients with collecting duct subtype. No differences were seen in OS in papillary subtypes compared to ccRCC across stages.

DISCUSSION

This study updates survival outcomes for histologic subtypes of RCC in California. Compared to ccRCC, patients with chromophobe subtype continue to have a better CSS and OS, and those with collecting duct have a poorer CSS and OS. There was not a significant difference in CSS and OS between papillary subtype and ccRCC. Those with collecting duct RCC had a poor prognosis regardless of stage. These trends are similar to those previously reported [5, 9].

Table 3
Overall Survival (OS) among RCC patients in California, 2004–2014

Variable	HR	95% CI	*P*-value
Stage * Histologic Subtype^			
Stage I			
Clear cell	Ref	–	–
Papillary	1.03	(0.90, 1.16)	0.701
Chromophobe	0.54	(0.43, 0.67)	<0.001
Collecting Duct	3.53	(2.00, 6.24)	<0.001
Other non-clear cell	0.93	(0.70, 1.24)	0.630
Stage II			
Clear cell	Ref	–	–
Papillary	0.91	(0.70, 1.18)	0.471
Chromophobe	0.54	(0.38, 0.77)	0.001
Collecting Duct	1.93	(0.27, 13.73)	0.512
Other non-clear cell	0.82	(0.45, 1.49)	0.516
Stage III			
Clear cell	Ref	–	–
Papillary	1.02	(0.83, 1.25)	0.872
Chromophobe	0.52	(0.37, 0.73)	0.001
Collecting Duct	3.91	(2.21, 6.90)	<0.001
Other non-clear cell	1.16	(0.82, 1.65)	0.406
Stage IV			
Clear cell	Ref	–	–
Papillary	1.02	(0.87, 1.19)	0.837
Chromophobe	0.62	(0.43, 0.89)	0.010
Collecting Duct	1.90	(1.32, 2.75)	0.001
Other non-clear cell	1.14	(0.95, 1.36)	0.159
Stage Unknown			
Clear cell	Ref	–	–
Papillary	0.40	(0.26, 0.63)	<0.001
Chromophobe	0.49	(0.24, 0.98)	0.045
Collecting Duct	8.75	(2.19, 34.97)	0.002
Other non-clear cell	1.24	(1.01, 1.51)	0.039
Gender			
Female	0.95	(0.91, 0.99)	0.013
Male	Ref	–	–
Race/Ethnicity			
Non-Hispanic White	Ref	–	–
African American	1.08	(1.00, 1.17)	0.059
Hispanic	0.89	(0.85, 0.94)	<0.001
Asian/Pacific Islander	0.91	(0.84, 0.98)	0.009
Other/Unknown	0.72	(0.58, 0.88)	0.002
Neighborhood Socioeconomic Status (SES)			
Low SES	1.14	(1.10, 1.19)	<0.001
High SES	Ref	–	–
SES unknown	0.98	(0.86, 1.11)	0.739
Health Insurance at Diagnosis			
Insurance-Self Pay/none	1.05	(0.91, 1.23)	0.495
Private Insurance	Ref	–	–
Medicaid/Government	1.15	(1.07, 1.24)	<0.001
Medicare	1.13	(1.08, 1.19)	<0.001
Unknown Insurance	1.42	(1.25, 1.61)	<0.001
Year of Diagnosis			
2004–2005	Ref	–	–
2006–2007	0.94	(0.89, 1.00)	0.053
2008–2009	0.93	(0.87, 0.98)	0.012
2010–2011	0.91	(0.85, 0.97)	0.004
2012–2014	0.82	(0.77, 0.88)	<0.001

^A significant interaction between stage at diagnosis and histologic subtype, p-value = 0.0161. Proportional hazard assumption was violated, therefore the OS model was stratified by age (category) at diagnosis and first course of treatment-surgery.

We extended our evaluation of the CCR to evaluate survival prior to and after the era of angiogenesis therapy; patients with ccRCC and collecting duct subtype enjoyed improvements in CSS in the era after angiogenesis therapy, while there were no differences in survival over time in patients with chromophobe and papillary subtypes.

A recent study evaluating survival by histologic subtype of RCC using the Surveillance, Epidemiology and End Results (SEER) database from 2001 to 2013 showed that clear cell RCC was most common, followed by papillary and chromophobe subtype, much as our study demonstrates [9]. The SEER analysis showed differences in chromophobe and collecting duct subtype CSS and OS compared to ccRCC similar to our study findings. The SEER analysis looked at one and three-year relative survival in the era prior to and after angiogenesis therapy, and found a modest improvement in relative survival in patients with ccRCC over time, but not in other subtypes. This differs somewhat from our findings for CSS, as we also found improvement in CSS in collecting duct subtype over time. Both our study and the SEER analysis indicate that advances in ccRCC treatment have not translated to benefit in papillary and chromophobe subtypes, further supporting the need for more clinical research in these patients.

In our study, Hispanic patients were found to have a small but significantly better CSS compared to non-Hispanic White patients. No other significant race/ethnicity differences were seen in CSS. The finding of better cancer-specific survival in Hispanic patients is novel. A recent small study evaluating patients treated in Tucson, Arizona found that Hispanic patients were more likely to be diagnosed at an earlier age and with clear-cell subtype; however, that study did not evaluate survival [10]. Our analysis indicates that both Hispanic and Asian patients have a high proportion of clear cell subtype among kidney cancer diagnoses. This enrichment of clear cell histology may lead to differences in survival, though CSS was not significantly better in Asian patients. The prior analysis of the CCR, capturing patients diagnosed between 1998 and 2009, found African-Americans to experience worse CSS, in contrast to our findings [5]. This may indicate that in the era after anti-angiogenesis therapy, survival by race/ethnicity may have changed. Of course, we are unable to conclude this definitively as the CCR does not capture specific treatment data.

Patients residing in low nSES neighborhoods had a worse prognosis in terms of both CSS and OS, independent of histologic subtype, in this study. This was not observed in the prior analysis of the CCR [5]. Our findings with more recent data may relate to varying access to newer disease-directed therapies, such as vascular endothelial growth factor tyrosine kinase inhibitors (VEGF TKIs) and mTOR inhibitors by SES, as many of these therapies are costly oral therapies.

Treatment for ccRCC has been well defined by clinical studies, which have evaluated the utility of nephrectomy, adjuvant therapy, and systemic therapy for metastatic disease in large prospective clinical trials. In these studies, nccRCC patients were largely excluded or underrepresented. To date, two randomized Phase 2 studies evaluated sunitinib versus everolimus in patients with nccRCC, demonstrating an OS and progression-free survival (PFS) benefit with sunitinib [11, 12]. This led to the adoption of VEGF TKI therapy for metastatic nccRCC, and there are current larger trials looking at specific therapies for papillary subtype RCC patients. Moreover since that time, immune checkpoint inhibitor therapy has been found to be an important therapy in the treatment of metastatic ccRCC in both the first- and second-line settings [13–16]. Small retrospective analyses do suggest a response to immune checkpoint inhibitor therapy in patients with nccRCC [17]. More recently, pembrolizumab has been studied in a single-arm, open-label, Phase 2 study (KEYNOTE-427), with a cohort of nccRCC patients who were treatment naïve [18]. This study of 165 patients demonstrated an objective response rate (ORR) of 24.8% overall; there was a suggestion towards differences in responses by subtype, with an ORR of 25.4% seen in patients with papillary subtype and of 9.5% seen in patients with chromophobe subtype. Another Phase 2 study recently evaluated the combination of atezolizumab plus bevacizumab in nccRCC patients as well as patients with sarcomatoid ccRCC [19]. Of the 56 patients evaluable for response in the study, 39 had nccRCC. The ORR was 26% in patients with nccRCC. Immune checkpoint inhibitor therapy, a significant advance in the treatment of metastatic RCC, was not approved for treatment until 2015, and thus meaningful survival analysis using the most current treatment paradigms are unable to be captured with this study. We plan to update our analysis in the future to include patients treated after 2015, which may demonstrate further changes in survival, given the benefits seen with immune checkpoint therapy as well as ongoing clinical trials evaluating specific histologic subtypes.

Our analysis is subject to some limitations. This retrospective analysis of the CCR does not include evaluation of systemic treatments received, as details of systemic therapy are not routinely available in the registry. Papillary subtype in the CCR is coded together and not delineated as Type 1 versus Type 2. The separate papillary subtypes have different genomic characteristics, which also may correlate to varying responses to systemic therapy. Thus, there could be differences in outcomes within that group that are not adequately captured in this analysis. While California represents a large population with diverse representation, regional differences in the population of California does somewhat limit the generalizability of this analysis. Finally, the number of collecting duct subtype patients was small ($n = 80$), making outcome conclusions about these patients tenuous.

In the era following anti-angiogenesis therapy development, patients with chromophobe subtype RCC continue to have a better prognosis compared with ccRCC in California. Patients with collecting duct subtype continue to have a significantly worse prognosis with more advanced disease at diagnosis. There have been improvements in CSS in patients with clear cell and collecting duct subtypes since the advent of anti-angiogenesis therapy. More clinical trials are needed to evaluate nccRCC patients specifically.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

SUPPLEMENTARY MATERIAL

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