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Evaluation of mild cognitive impairment and dementia in patients with metastatic renal cell carcinoma

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Abstract

Background: Dementia and cancer are both more common in adults as they age. As new cancer treatments become more popular, it is important to consider how these treatments might affect older patients. This study evaluates metastatic renal cell carcinoma (mRCC) as a risk factor for older adults developing mild cognitive impairment or dementia (MCI/D) and the impact of mRCC-directed therapies on the development of MCI/D.

Methods: We identified patients diagnosed with mRCC in a Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset from 2007–2015 and matched them to non-cancer controls. Exclusion criteria included age <65 years at mRCC diagnosis and diagnosis of MCI/D within the year preceding mRCC diagnosis. The main outcome was time to incident MCI/D within one year of mRCC diagnosis for cases or cohort entry for non-cancer controls. Cox proportional hazards models were used to measure associations between mRCC and incident MCI/D as well as associations of oral anticancer agent (OAA) use with MCI/D development within the mRCC group.

Results: Patients with mRCC (n=2,533) were matched to non-cancer controls (n=7,027). mRCC (hazard ratio [HR] 8.52, p<0.001), being older (HR 1.05 per 1-year age increase, p<0.001), and identifying as Black (HR 1.92, p=0.047) were predictive of developing MCI/D. In addition, neither those initiating treatment with OAAs nor those who underwent nephrectomy were more likely to develop MCI/D.

Conclusions: Patients with mRCC were more likely to develop MCI/D than those without mRCC. The medical and surgical therapies evaluated were not associated with increased incidence of MCI/D. The increased incidence of MCI/D in older adults with mRCC may be the result of the pathology itself or risk factors common to the two disease processes.

Keywords

renal cell carcinoma; cognitive dysfunction; dementia; nephrectomy; antineoplastic agents

INTRODUCTION

Dementia and cancer are both more common in adults as they age.[1–5] Though the etiology is unclear, the prevalence of dementia is higher in those adults who also have cancer.[6–9] Several studies have evaluated different cancer treatments as risk factors for dementia, including chemotherapy[7,10–12], radiotherapy[7,12,13], and surgical procedures.[7,12,14] Terms such as ‘cancer-related cognitive impairment’[12], ‘post-chemotherapy cognitive impairment’[11], and ‘postoperative cognitive decline’[14] are now common in medical literature. Other groups that focused on the impact of tumor genetics and tumor biology on cognitive function showed both protective[15,16] and detrimental[17,18] effects of cancer.

Regardless of the pathogenesis, patients who carry both cancer and dementia diagnoses are more difficult to care for and experience worse outcomes than those with just a single diagnosis. Their cancer diagnoses are delayed[19], they have shorter median survival[9], and often require more complex and more substantial care from both their medical teams and their families.[20]

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As the population grows in number and in age, the incidence and prevalence of many cancers have increased. The incidence of kidney cancer is the most rapidly increasing in the United States, with estimates of 76,080 new cases in 2021.[21,22] Those with metastatic kidney cancer have only a 13% chance of surviving five years after their diagnosis.[22] Of these kidney cancers, 85% are renal cell carcinoma (RCC).[23] New treatment regimens have evolved as the burden of RCC on our healthcare system has increased, including different surgical procedures as well as the use of oral anticancer agents (OAAs) in patients with metastatic RCC (mRCC). These treatments have led to dramatic improvements in the overall survival for patients with mRCC.[24]

The impact of these treatments on cognitive function is less clear. At the time of their mRCC diagnosis, 3.4% of patients had pre-existing dementia.[25] Kinase inhibitors have been crucial in the treatment mRCC for many years, with studies showing significant improvements in progression-free survival starting in 2007.[26–29] More recently, kinase inhibitors have been used in conjunction with immune checkpoint inhibitors.[30] Currently, sunitinib and pazopanib are among the kinase inhibitors that are first-line agents used independently, while ipilimumab/nivolumab and pembrolizumab/axitinib regimens are first-line treatment combinations of kinase inhibitors and immune checkpoint inhibitors.[30] At present, there is conflicting evidence that suggests kinase inhibitors may play a role in the development of dementia. There is evidence that they may induce cognitive dysfunction in certain patient groups, perhaps the result of higher levels of inflammation in these patients.[31–33] Other studies show that they may improve cognitive function in patients with Alzheimer's Disease[34] and after heart transplant.[35]

In addition, the impact of nephrectomy on cognitive function in patients with RCC is not well described in the current literature. Nephrectomy was the standard of care for patients with mRCC prior to the advent of targeted immunotherapies. With the above treatment regimens gaining popularity in the last two decades, the role of nephrectomy in the treatment of mRCC is evolving.[36] Prior studies have established that radical nephrectomy is a predictor of chronic kidney disease, and as such may play a role in cognitive decline.[37]

The primary objective of this study was to investigate whether specific mRCC-directed medical or surgical therapies were associated with increased risk of MCI/D. Given the existing literature that describes the relationships between different cancer treatments and cognitive impairment, we hypothesized that patients with mRCC who had used OAAs or who had undergone partial or radical nephrectomy would show higher rates of MCI/D compared to patients with mRCC who had not. Prior to evaluating this potential association, this study addressed a secondary objective and examined the relationship between mRCC and incident MCI/D. This was done to establish whether patients with mRCC are at increased risk for developing MCI/D after their metastatic cancer diagnosis. We hypothesized that patients with mRCC would show higher incident rates of MCI/D compared to matched non-cancer controls.

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MATERIALS & METHODS

Cohort Selection

This was a retrospective cohort study of Surveillance, Epidemiology, and End Results (SEER)-Medicare patients diagnosed with mRCC and matched non-cancer controls from 2007–2015 (Figure 1). The SEER-Medicare database is composed of patients with cancer identified in the SEER cancer registry who have Medicare insurance coverage. Non-cancer controls were identified from the 'non-cancer' Medicare 5% sample which is comprised of a random 5% sample of patients with Medicare and excludes all patients in the SEER cancer registry. Patients with mRCC were required to have had at least twelve months of continuous enrollment in Medicare fee-for-service parts A (inpatient facility, skilled nursing facility, hospice and home health services) and B (medically necessary doctor's services, outpatient care, and some preventative care) before their mRCC diagnosis, and in Parts A, B, and D (prescription medication coverage) for twelve months after the metastatic index date or until death. Patients with mRCC were excluded if their metastatic diagnosis occurred at autopsy or death, if they were less than 65 years of age at metastatic index date, or if they had a second primary diagnosis of cancer at another site between the initial SEER RCC diagnosis date (if they were initially diagnosed at Stage I, II, or III) and their metastatic diagnosis date. Patients were excluded from analysis if they had a claim with a diagnosis code indicating MCI/D (Appendix A) at any time during the twelve months prior to their date of metastatic diagnosis. Non-cancer matched controls selected from the Medicare 5% sample were required to be at least 65 years of age on July 1 of the year of their matched case's metastatic diagnosis, which served as the control's cohort entry date. Controls were required to be enrolled in Medicare fee-for-service parts A and B in the twelve months prior to July 1 of their entry year, and for twelve months following their entry or until death. Potential controls were excluded if they had a claim with a diagnosis code in any position indicating MCI/D (Appendix A) in the twelve months prior to cohort entry. Three controls were selected per case, and controls were matched using greedy match without replacement on year of entry (+/− two years), patient age (+/− five years), patient sex, patient race (matched Black/not Black), hypertension, cerebrovascular disease, hemiplegia/paraplegia and Charlson comorbidity score (+/− two) calculated from the twelve months preceding their entry date.

Development of mild cognitive impairment or dementia (MCI/D)

Patients were determined to have an incident diagnosis of mild cognitive impairment or dementia if they had a diagnosis code for MCI/D in any diagnosis position on an inpatient, outpatient, carrier, or home health Medicare claim in the twelve months following the patient's cohort entry date (Appendix A).[38] This cohort likely includes patients with cancer-related dementia and mild cognitive impairment as well as patients with MCI/D that may be unrelated to cancer. The date of the earliest claim with one of these codes served as the patient's MCI/D diagnosis date.

Patient characteristics

Patient demographics at metastatic diagnosis or cohort entry included self-reported race/ethnicity, age, sex, geographic region of residence, residence in a metropolitan region as

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defined by Rural-Urban Continuum Codes, and ZIP code of residence-level socioeconomic characteristics. ZIP-code-level socioeconomic characteristics are continuous variables that are presented in this analysis as quartiles, with quartile 4 (Q4) representing areas with the highest rates of households experiencing poverty, the highest percentage of Black residents, and the highest percentage of adults without a high school education. Validated coding algorithms were used to assess patient comorbidities of interest in the twelve months prior to the metastatic index date or cohort entry date using diagnosis codes (Appendix B) from inpatient, outpatient, and carrier Medicare claims files.[39] For patients with mRCC, we additionally assessed stage at initial RCC diagnosis, histology at initial RCC diagnosis, and marital status at initial RCC diagnosis.

Receipt of oral anticancer agents by mRCC patients

Utilization of an OAA was determined by the presence of a Part D prescription drug fill record for any of the following OAAs in the twelve months following metastatic diagnosis: sorafenib, sunitinib, pazopanib, everolimus, and axitinib. OAA utilization was treated as a binary time-varying exposure (never used/ever used an OAA), with the date of a patient's first OAA prescription claim serving as the date at which they began using an OAA.

Receipt of nephrectomy by mRCC patients

Receipt of a partial or radical nephrectomy was assessed among RCC patients in the twelve months prior to and twelve months following metastatic diagnosis. Nephrectomies were identified by the presence of one of the following Healthcare Common Procedure Classification System (HCPCS) codes indicating nephrectomy on a Medicare carrier or outpatient claim in that time period: 50230, 50545, 50546, 50220, 50225, 50240, 50280, 50290, 50542, or 50543. Receipt of nephrectomy was coded as a time-varying exposure (has not had nephrectomy/had nephrectomy) beginning at the patient's metastatic diagnosis date. The date of the first Medicare claim with a nephrectomy HCPCS code served as the date at which a patient was classified as having a nephrectomy.

Statistical Methods

Patient demographics and clinical characteristics were presented stratified by case status. Continuous variables were described using mean (SD) or median (Q1, Q3). Categorical variables were described using N (%) and tested for differences between matched cases and controls using chi-square tests, Wilcoxon rank-sum tests/t-tests and standardized differences to assess the matches. Patient ZIP code, local education percentages, poverty percentages, and racial composition percentages were analyzed as quartiles. Baseline differences between the mRCC and non-cancer cohorts were assessed with standardized difference scores. The threshold for reporting was set at 10%, given that a standardized difference of less than 10% suggests balance between the case and control groups with respect to the variable in question.[40]

Cumulative incidence of MCI/D was calculated for mRCC patients and controls at one year from the cohort entry date based on estimates from the cumulative incidence function, to account for the high risk of death in this patient population. Patients were censored at one year following their cohort entry or at their death, whichever occurred first. The one-year

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cumulative incidence was stratified by case status, age group, and patient race/ethnicity. Group differences in the cumulative incidence function were evaluated using Gray's test. Kaplan-Meier curves were used to test the proportional hazards assumption.

Unadjusted and multivariable-adjusted Cox proportional hazards regression analyses were used to estimate the associations between mRCC case status and risk of developing MCI/D. Adjustment variables were pre-selected based on prior literature and clinical input. Models were adjusted for the following characteristics at the metastatic index date (mRCC cohort) or cohort entry (controls): patient age in years, sex, race/ethnicity, year of cohort entry, residence in a metropolitan area, geographic region, dual-enrollment in Medicaid and Medicare, previously-defined ZIP code-level socioeconomic measures, and patient comorbid conditions. In a post-hoc analysis to assess for potential residual confounding in the association between mRCC and MCI/D development, we tested the association between mRCC and a falsification endpoint, hospitalization for congestive heart failure (CHF) (Appendix A).

A cohort limited to mRCC patients was used to assess whether RCC-specific therapies increased the risk of developing MCI/D among mRCC patients in the twelve months following metastatic diagnosis. Univariable and multivariable adjusted time-varying Cox proportional hazards regression analyses were used to assess the associations between development of MCI/D and receipt of OAAs and receipt of partial or radical nephrectomy (as time-varying exposures), with additional adjustment for patient age, race/ethnicity, and other patient demographic and clinical factors, as previously described.

An alpha level of 0.05 was used to establish statistical significance of tests, and all tests were two-sided. All analyses were conducted using SAS version 9.4 (Cary, NC). The study protocol was reviewed by the Duke University Health System Institutional Review Board. It was initially approved and later determined to be exempt (Protocol Pro00101962).

RESULTS

Cohort selection

There were 2,792 patients who received an mRCC diagnosis in the given time period and who were over the age of 65 with the required periods of continuous enrollment both before and after diagnosis identified from the SEER-Medicare database. Of those patients, 259 with a prevalent diagnosis of MCI/D prior to their metastatic diagnosis were excluded, leaving 2,533 patients with mRCC. The final cohort consisted of 2,533 patients with mRCC and 7,027 non-cancer controls (Figure 1).

Demographics

Demographic variables were compared between patients with mRCC and non-cancer controls. Cases and controls were generally well-matched based on directly matched factors. Among all analyzed beneficiaries, mean age was 76.2 years (standard deviation = 6.7 years) and 42.3% were female. Patients with mRCC were less likely than controls to live in ZIP codes with adults who had less than a high school education (standardized difference 17.7%) and where households had incomes below the poverty line (standardized difference 16.0%).

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Patients with mRCC had higher incidence of mild liver disease (standardized difference 31.2%) and renal disease (standardized difference 20.0%) (Table 1).

Trends in incidence of MCI/D

Median available follow-up time in the cohort was 365 days (IQR 341 days– 365 days). The one-year cumulative incidence of MCI/D was greater in patients with mRCC than in non-cancer controls (6.0% vs 1.3%, Gray's P<.001) (Figure 2a). When patients with mRCC and patients without cancer were analyzed as one cohort, there was greater cumulative incidence of MCI/D in older patients (Gray's P<.001) (Figure 2b). There was not a statistically significant difference in cumulative incidence of MCI/D based on race/ethnicity (Gray's P=0.067) (Figure 2c).

Predictors of MCI/D in case-matched cohort

Fully-adjusted Cox proportional hazards regression was used to identify predictors of incident MCI/D in the twelve months following mRCC diagnosis or entry to the case-matched cohort. This model included both patients with a diagnosis of mRCC and the non-cancer controls. Diagnosis of mRCC was a significant positive predictor of incident MCI/D (hazard ratio [HR] 8.52, 95% confidence interval [CI] 6.49–11.19, p<.001) (Table 2). Increased age (HR 1.05 per one-year, 95% CI 1.03–1.07, p<.001) as well as later year of cohort entry (HR 1.21 per one-year, 95% CI 1.14–1.28, p<.001) were significant positive predictors of incident MCI/D. Multiple comorbidities were associated with a higher hazard of incident MCI/D, including CHF (HR 1.44, 95% CI 1.07–1.94, p=.016), cerebrovascular disease (HR 1.40, 95% CI 1.05–1.87, p=.022), rheumatologic disease (HR 1.63, 95% CI 1.06–2.49, p=.025) and hemiplegia/paraplegia (HR 2.04, 95% CI 1.03–4.04, p=.042). Mild liver disease was found to be a negative predictor of MCI/D (HR 0.59, 95% CI 0.37–0.94, p=.027).

In the post-hoc falsification endpoint analysis, there was a borderline significant association between mRCC and CHF hospitalization (HR 1.32, 95% CI 1.01–1.72, p=.045).

Predictors of MCI/D in mRCC cohort

A second fully-adjusted Cox proportional hazards regression was used to identify predictors of incident MCI in the twelve months following mRCC diagnosis. This model included only those patients with a diagnosis of mRCC. Neither use of OAAs (HR 0.89, 95% CI 0.59–1.34) nor undergoing partial or radical nephrectomy (HR 0.78, 95% CI 0.52–1.17) was a significant predictor of incident MCI/D (Table 3). Increased age was a significant predictor of incident MCI/D (HR 1.06 per one-year, 95% CI 1.03–1.08, p<.001), as was self-identifying as non-Hispanic and Black when compared to those identifying as non-Hispanic and White (HR 1.92, 95% CI 1.02–3.59, p=.042). Mild liver disease was found to be a negative predictor of incident MCI/D (HR 0.55, 95% CI 0.32–0.95, p=.033).

DISCUSSION

This study evaluated mRCC as a risk factor for development of MCI/D in older adults and whether OAAs or nephrectomy predicted incident MCI/D in older patients with mRCC.

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These data indicate that older adults with mRCC are more likely than those without cancer to develop MCI/D even when controlling for demographic variables and comorbid conditions. In addition, these analyses suggest that this increased incidence of MCI/D in older adults with mRCC is not driven by treatment with OAAs or by partial or radical nephrectomy.

Our results are consistent with previous findings that mRCC is a potential risk factor for development of incident MCI/D in older adults. Multiple mechanisms have been proposed to explain the development of MCI/D in patients with cancer, including cancer treatments[10,11,13] and the emotional toll that a cancer diagnosis can take on a patient.[12] This increased incidence of dementia developed after cancer diagnosis has been observed in patients with many types of cancer including breast,[41] gynecologic,[41] colon,[42] and hematologic.[41] We have also seen that despite achieving successful remission of their cancer, many patients who develop dementia will continue to experience cognitive deficits for years after they complete their cancer treatment.[43] Based on this study, healthcare providers should be mindful of this increased incidence of MCI/D in patients with mRCC and be vigilant in their assessments for cognitive decline.

This study also provides evidence that the higher incidence of MCI/D in patients with mRCC is unlikely to be related to treatment with OAAs or with nephrectomy. Prior studies have recognized the higher incidence of cognitive dysfunction in patients with cancer, and have shown the predictive values of treatments with various chemotherapies[7,10–12] as well as invasive surgeries.[7,12,13] This study suggests that these prior findings of increased incidence of MCI/D for patients receiving chemotherapy or having surgery may not hold true for patients with mRCC taking OAAs or undergoing nephrectomy. It should be noted that this study specifically evaluates patients who have received sorafenib, sunitinib, pazopanib, everolimus, and axitinib, and therefore, these data do not allow for extrapolation to the effects of all kinase inhibitors. Regardless of the etiology of the increased incidence of MCI/D, this is an impactful finding in that it does not discourage the use of these specific treatments for patients who are particularly concerned about the potential for cognitive side effects of mRCC treatment. Future research might investigate the potential presence of a dose-response relationship to ensure that higher incidence of MCI/D is not seen in patients taking higher doses of OAAs.

It is possible that the increased incidence of MCI/D seen in patients with mRCC may be due to the cancer itself. Many paraneoplastic syndromes have been linked to RCC.[44,45] Among them, several are known to cause cognitive dysfunction, including hypercalcemia[46], amyloidosis[15,47], and nephropathy. Specifically, previous work has shown that renal dysfunction is more prevalent among adults with mRCC than in those without, possibly the result of tumor invasion and destruction of the renal parenchyma.[48–50] Another possible explanation for this increased incidence of MCI/D is an accelerated aging process resulting from the cancer pathology. Increasing evidence of accelerated aging has been reported in older adults with cancer[51],specifically in those receiving cancer treatment.[52]

These data also show that self-identified non-Hispanic Black patients with mRCC are more likely to develop MCI/D than those identifying as a different race. This has not

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been previously shown in patients with mRCC. However, prior studies have identified and established many racial disparities in the outcomes experienced by patients with cancer. Black patients with cancer experience higher mortality and worse outcomes than White patients with cancer.[53] These differences are more pronounced in solid tumor malignancies and for which treatment is an important prognostic factor, both of which apply to RCC.[54] In addition, Black patients experience higher prevalence and incidence of dementia than White patients.[55,56] Thus, while the finding that identifying as non-Hispanic Black may be predictive of MCI/D in patients with mRCC is novel, it is not unexpected. Clinicians should be mindful of this finding when evaluating the cognitive function of their patients, and further research is required into the potential role of structural determinants of health as a cause of this disparity.

Limitations

Many of this study's limitations are inherent to the SEER-Medicare database. First, we were unable assess renal function in our mRCC or non-cancer control cohorts because the database is not linked to patient laboratory data. Renal dysfunction may contribute to the increased incidence of MCI/D seen in patients with mRCC; future studies might include serum calcium or creatinine levels, or creatinine clearance in the regression model used to predict incident MCI/D. Second, it was challenging to evaluate the impact of prior cancer treatments on MCI/D and to identify patients with current cancer diagnoses given that our database was limited to a one-year look-back period. Next, the ability to identify the progression of localized disease to metastatic disease using SEER-Medicare data is not complete.[57] Thus, there may be patients who were initially diagnosed with stage I, II or III RCC and who progressed to mRCC who were not included in this study. Finally, we cannot account for the impact of individuals' education on cognition because the SEER-Medicare database does not record this information.

There are also limitations inherent to claims analysis. Some patients with mRCC who experienced cognitive deficits may not have been assigned MCI/D International Classification of Diseases (ICD) diagnosis codes in the SEER-Medicare database because of coding practices in a real-world sample. These deficits may have been identified objectively on neuropsychological tests or subjectively by patients themselves, and can substantially impact the quality of life experienced by these patients.[33] However, given that both patients with mRCC and non-cancer controls were subject to this limitation, it is unlikely that the inability to capture all MCI/D cases alters the difference in incident MCI/D that we detected between groups. Though we are unaware of existing studies that validate the ICD codes for mild cognitive impairment, this does not preclude impactful research findings utilizing these claims.

We acknowledge that a portion of the increased incidence in MCI/D observed in patients with mRCC may be the result of residual confounding or detection bias. While we did observe a borderline significant association between mRCC and our CHF hospitalization endpoint, the magnitude of the hazard ratio and strength of the association seen in the p-value were both considerably smaller than those observed for the association between mRCC and incident MCI/D. Mild cognitive impairment or dementia may have been more

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frequently diagnosed in patients with mRCC in the setting of more frequent contact with the healthcare system. If so, this bias would overestimate the hazard ratio for developing MCI/D in those patients with mRCC. The literature describes the potential for this bias, but confirms these measures still provide valuable insight into patients suffering from MCI/D.[58,59]

Finally, the control group selected in this study comprises patients who did not have any diagnosis codes related to cancer. This is similar to previous works that evaluated the effect of cancer on cognitive decline.[60–62] While this study does not offer insight into the possible differences in MCI/D seen in patients with different types of cancer, its relevance lies in establishing the evidence for providers to have a lower threshold for cognitive screening in patients who are newly diagnosed with mRCC.

Conclusions

Older adults with mRCC have higher one-year cumulative incidence of MCI/D than those without cancer. This finding is significant to primary care providers, oncologists and surgeons in that each must be aware of the increased risk for cognitive decline in their patients with mRCC. It may be beneficial to integrate cognitive screening in treatment models. In addition, involvement of patients' families shortly after diagnosis can be encouraged in the event that patients become unable to make decisions for themselves.

Among patients with mRCC, neither treatment with OAAs nor partial or radical nephrectomy was associated with an increased risk of developing MCI/D. These findings suggest that while a diagnosis of mRCC in older adults should raise concern for the possibility of developing MCI/D, neither of these treatment options should be avoided in the hope of avoiding MCI/D.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest:

Dr. Zhang receives research funding (to Duke) from Pfizer, Janssen, Acerta, Abbvie, Novartis, Merrimack, OmniSeq, PGDx, Merck, Mirati, and Astellas; consulting/speaking with Genentech Roche, Exelixis, Genomic Health, and Sanofi Aventis; and consulting/advisory board with AstraZeneca, Bayer, Exelixis, Pfizer, Foundation Medicine, Janssen, Amgen, BMS, MJH Associates, Calithera, Dendreon, and IQVIA. Stock ownership/employment/consulting (spouse) from Capio Biosciences, Archimmune Therapeutics, & Nanorobotics.

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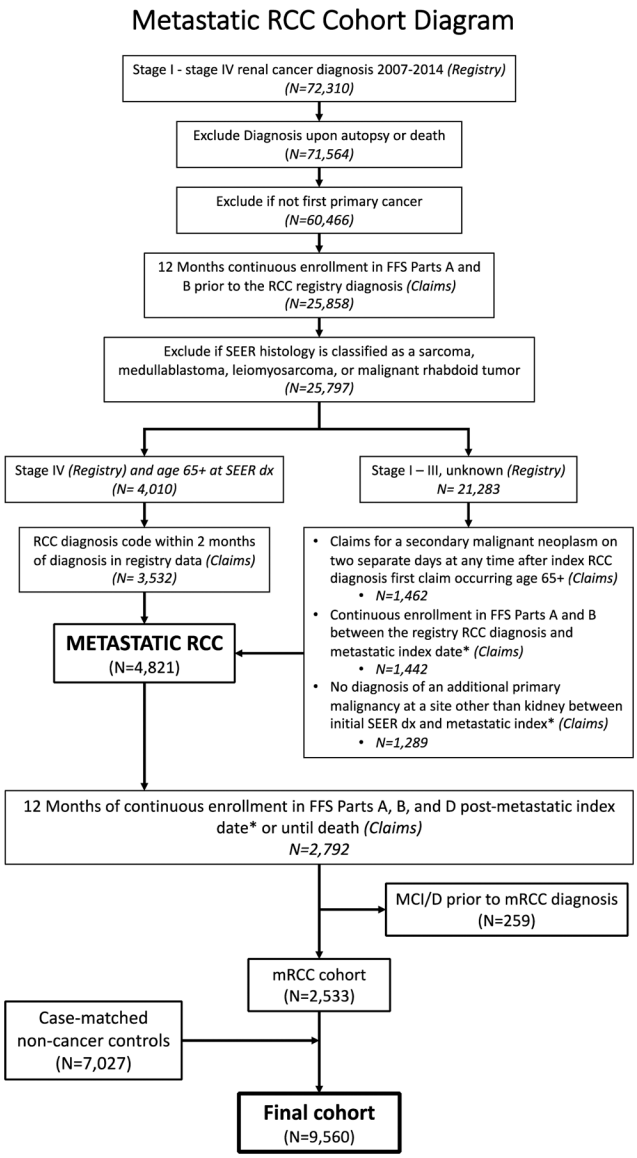

Figure 1:

mRCC cohort diagram

* Metastatic index date: date of the first metastatic claim for Stages I - III or first diagnosis on a claim for Stage IV

mRCC - metastatic renal cell carcinoma; RCC - renal cell carcinoma; MCI/D - mild cognitive impairment or dementia; FFS - Fee-for-Service; SEER - Surveillance, Epidemiology, and End Results; Dx - diagnosis

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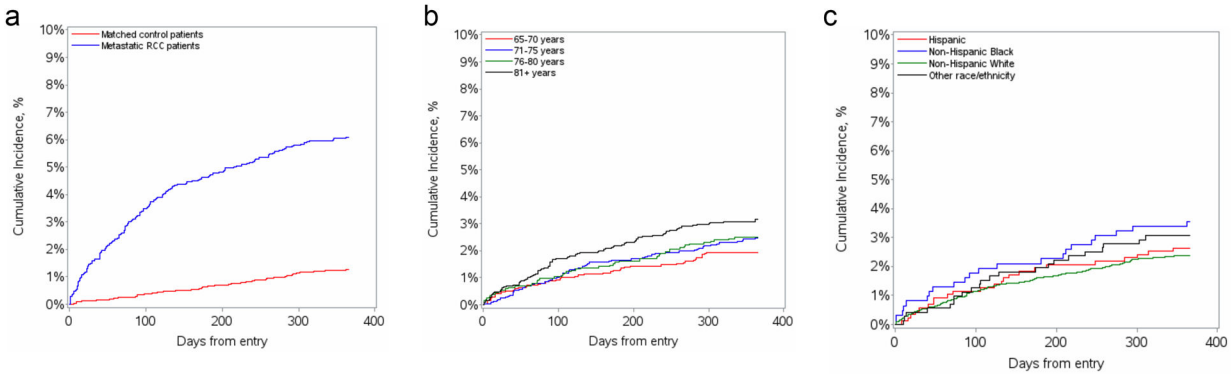

Figure 2a: One-year cumulative incidence of cognitive impairment and dementia by case status

Figure 2b: One-year cumulative incidence of cognitive impairment and dementia by age

Figure 2c: One-year cumulative incidence of cognitive impairment and dementia by race/ethnicity

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Table 1:

Baseline characteristics of patients with mRCC and non-cancer controls

Variable	mRCC cases (%)	Controls (%)	Standardized Difference
N	2,533	7,027	
Characteristics			
Age at entry, Mean (SD) *	76.0 (6.7)	76.3 (6.8)	4.1%
Race/ethnicity			8.3%
Hispanic	275 (10.8)	594 (8.4)	
Non-Hispanic Black *	164 (6.5)	453 (6.4)	
Non-Hispanic White *	1,913 (75.5)	5,444 (77.3)	
Other	181 (7.1)	536 (7.61)	
Female sex *	1,058 (41.8)	2,988 (42.5)	1.5%
Charlson comorbidity score, mean (SD) *	3.6 (2.5)	3.5 (2.4)	6.5%
Myocardial infarction	240 (9.5)	699 (9.9)	1.6%
Hypertension *	2,198 (86.8)	6,078 (86.5)	0.8%
Peripheral vascular disease	653 (25.8)	1,800 (25.6)	0.4%
Congestive heart failure	557 (22.0)	1,765 (25.1)	7.4%
Cerebrovascular disease *	544 (21.5)	1,498 (21.3)	0.4%
Chronic obstructive pulmonary disease	818 (32.3)	2,513 (35.8)	7.3%
Rheumatologic disease	120 (4.7)	491 (6.9)	9.6%
Peptic ulcer disease	75 (3.0)	198 (2.8)	0.9%
Mild liver disease	385 (15.2)	405 (5.7)	**31.2%**
Moderate/severe liver disease	<11	38 (0.5)	2.1%
Chronic kidney disease	750 (29.6)	1,473 (21.0)	**20.0%**
Diabetes with complications	398 (15.7)	1,196 (17.0)	3.5%
Hemiplegia or paraplegia *	60 (2.4)	98 (1.4)	7.2%
Year of cohort entry *			**10.8%**
2007	225 (8.9)	607 (8.6)	
2008	239 (9.4)	592 (8.4)	
2009	234 (9.2)	650 (9.3)	
2010	244 (9.6)	656 (9.3)	
2011	284 (11.2)	772 (11.0)	
2012	305 (12.0)	796 (11.3)	
2013	353 (13.9)	879 (12.5)	
2014	357 (14.1)	1,039 (14.8)	
Lives in a metropolitan area	2,006 (79.2)	5,315 (75.6)	8.5%
Lives in rural area	85 (3.3)	251 (3.6)	1.2%
Dual-enrolled in Medicaid	732 (28.9)	2,360 (33.6)	**10.1%**
Geographic region			**20.3%**
Midwest	334 (13.2)	719 (10.2)	
Northeast	493 (19.5)	1,053 (15.0)	

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Variable	mRCC cases (%)	Controls (%)	Standardized Difference
South	645 (25.5)	2,332 (33.2)	
West	1,024 (40.4)	2,789 (39.7)	
NA/Missing	37 (1.5)	134 (1.9)	
ZIP code: % residents identifying as Black (quartiles)			**8.1%**
Q1- lowest percentage of Black residents	710 (28.0)	1,976 (28.1)	
Q2	650 (25.7)	1,640 (23.3)	
Q3	623 (24.6)	1,670 (23.8)	
Q4- highest percentage of Black residents	550 (21.7)	1,741 (24.8)	
ZIP code: % adults 25+ without a high school degree (quartiles)			**17.7%**
Q1- lowest percentage without degree	824 (32.5)	1,855 (26.4)	
Q2	653 (25.8)	1,645 (23.4)	
Q3	543 (21.4)	1,757 (25.0)	
Q4- highest percentage without degree	513 (20.2)	1,770 (25.2)	
ZIP code: % households experiencing poverty (quartiles)			**16.0%**
Q1- lowest percentage experiencing poverty	824 (32.5)	1,856 (26.4)	
Q2	630 (24.9)	1,665 (23.7)	
Q3	556 (21.9)	1,735 (24.7)	
Q4- highest percentage experiencing poverty	523 (20.6)	1,771 (25.2)	

* Variables directly included in the greedy match.

SD - standard deviation; mR CC - metastatic renal cell carcinoma; NA - not applicable

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Table 2:

Adjusted Cox proportional hazards regression evaluating for predictors of MCI/D in case-matched cohort

Parameter	Partially adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Metastatic RCC diagnosis (ref=Control)	4.48 (3.54–5.67)	**8.52 (6.49–11.19)**
Race/ethnicity (ref=Non-Hispanic White)		
Hispanic	1.14 (0.78–1.67)	0.93 (0.57–1.52)
Non-Hispanic Black	1.77 (1.19–2.62)	1.52 (0.92–2.52)
Other	1.14 (0.73–1.77)	1.16 (0.71–1.91)
Age		**1.05 (1.03–1.07)**
Female sex		1.22 (0.94–1.59)
Region (ref=West)		
Midwest		1.00 (0.62–1.63)
Northeast		1.37 (0.93–2.02)
South		1.05 (0.71–1.55)
NA/Missing		1.40 (0.54–3.61)
Lives in a metropolitan area		1.18 (0.79–1.77)
Dual-enrolled in Medicaid		1.33 (0.98–1.80)
ZIP code: % poverty (ref=Q1 lowest percentage)		
Q2		1.30 (0.87–1.95)
Q3		1.42 (0.85–2.37)
Q4		1.16 (0.62–2.17)
ZIP code: % Black residents (ref=Q1 lowest percentage)		
Q2		1.28 (0.88–1.86)
Q3		1.14 (0.77–1.68)
Q4		1.05 (0.67–1.65)
ZIP code: % residents without a HS degree (ref=Q1 lowest percentage)		
Q2		0.80 (0.54–1.19)
Q3		1.00 (0.63–1.56)
Q4		0.85 (0.48–1.49)
Myocardial infarction		1.39 (0.96–2.02)
Hypertension		0.92 (0.59–1.44)
Peripheral vascular disease		1.06 (0.79–1.40)
Congestive heart failure		**1.44 (1.07–1.94)**
Cerebrovascular disease		**1.40 (1.05–1.87)**
Rheumatologic disease		**1.63 (1.06–2.49)**
Peptic ulcer disease		0.78 (0.34–1.76)
Mild liver disease		0.59 (0.37–0.94)
Moderate/severe liver disease		1.24 (0.16–9.39)
Chronic kidney disease		1.15 (0.86–1.53)
Diabetes with complications		1.28 (0.93–1.76)
Hemiplegia or paraplegia		**2.04 (1.03–4.04)**
Year of diagnosis		**1.21 (1.14–1.28)**

MCI/D – metastatic cognitive impairment or dementia; SD - standard deviation; CI - confidence interval; HR - hazard ratio; RCC - renal cell carcinoma; Ref – reference; NA - not applicable; HS - high school

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Table 3:

Adjusted Cox proportional hazards regression evaluating for predictors of MCI/D in patients with mRCC

Parameter	Partially adjusted HR (95%CI)	Fully adjusted HR (95% CI)
OAA use (ref=has not started an OAA)	0.52 (0.36–0.75)	0.89 (0.59–1.34)
Partial or radical nephrectomy	0.61 (0.41–0.91)	0.78 (0.52–1.17)
Race/ethnicity (ref=Non-Hispanic White)		
Hispanic	1.13 (0.66–1.91)	1.09 (0.60–1.98)
Non-Hispanic Black	1.91 (1.13–3.25)	**1.92 (1.02–3.59)**
Other	1.54 (0.88–2.69)	1.26 (0.66–2.41)
Age		**1.06 (1.03–1.08)**
Female sex		1.15 (0.82–1.61)
Region (ref=West)		
Midwest		1.06 (0.59–1.93)
Northeast		1.53 (0.95–2.46)
South		0.72 (0.42–1.24)
NA/Missing		1.39 (0.39–4.94)
Lives in a metropolitan area		1.23 (0.70–2.16)
Dual-enrolled in Medicaid		1.17 (0.77–1.77)
ZIP code: % poverty (ref=Q1 lowest percentage)		
Q2		1.24 (0.75–2.04)
Q3		1.31 (0.68–2.53)
Q4		0.93 (0.41–2.10)
ZIP code: % Black residents (ref=Q1 lowest percentage)		
Q2		1.18 (0.73–1.90)
Q3		1.18 (0.72–1.94)
Q4		1.17 (0.65–2.11)
ZIP code: % residents without a HS degree (ref=Q1 lowest percentage)		
Q2		0.79 (0.48–1.29)
Q3		1.14 (0.65–2.01)
Q4		1.00 (0.49–2.06)
Myocardial infarction		1.03 (0.61–1.75)
Hypertension		0.90 (0.52–1.54)
Peripheral vascular disease		1.08 (0.75–1.55)
Congestive heart failure		1.46 (1.00–2.14)
Hemiplegia or paraplegia		1.33 (0.92–1.92)
Rheumatologic disease		1.59 (0.89–2.83)
Peptic ulcer disease		0.65 (0.20–2.10)
Mild liver disease		**0.55 (0.32–0.95)**
Moderate/severe liver disease		2.48 (0.31–19.73)
Chronic kidney disease		1.02 (0.71–1.47)
Diabetes with complications		1.38 (0.91–2.09)
Hemiplegia/paraplegia		1.93 (0.87–4.27)

Parameter	Partially adjusted HR (95%CI)	Fully adjusted HR (95% CI)
Year of diagnosis		1.06 (0.99–1.13)

MCI/D – mild cognitive impairment or dementia; SD - standard deviation; CI - confidence interval; HR - hazard ratio; mRCC - metastatic renal cell carcinoma; OAA – oral anticancer agent; Ref – reference; NA - not applicable; HS - high school

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