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Epidemiology of Young Adult Renal Cell Carcinoma in Kentucky: Incidence, Clinicopathologic Features, and Cancer-specific Survival

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**Epidemiology of Young Adult Renal Cell Carcinoma in Kentucky:
Incidence, Clinicopathologic Features, and Cancer-specific Survival**

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Abstract:**Introduction:**

Renal cell carcinoma (RCC) is an important cause of morbidity and mortality in our country. Previously reported data suggest that the overall incidence of RCC continues to rise and may be accelerating even faster among younger adult patients.

Methods:

Data for analysis included the combined NPCR-SEER USCS public use database and the Kentucky Cancer Registry dataset. Incidence rates and trends by age group and location were calculated and tested. Clinicopathologic features of disease among Kentucky cases were analyzed by age group. Cancer-specific survival (CSS) analysis was performed, along with Cox proportional hazards regression to test for association of younger age with improved CSS.

Results:

Incidence of RCC is higher in KY than in the rest of the country, and the rate is increasing faster, especially among younger adults. Annual percent change (APC) for patients in the 20-39 year-old age group was 8.5% (95% CI 5.9-11.2%), compared to only 4.4% (95% CI 3.5-5.3%) for the same age group in the rest of the country. APC among older patients in KY was 5.4% (95% CI 3.4-7.5%) for ages 40-49 and 1.8% (95% CI 0.8-2.9%) for ages 50+. Younger adult patients in KY were significantly more likely to be diagnosed with RCC of lower stage, lower grade, and more favorable histologic subtype. Survival curves by age group were similar when stratified by disease stage. Cox proportional hazards regression analysis revealed hazard ratio (HR) of 0.72 (95% CI 0.47-1.09) for the 19-39 age group

and 0.61 (95% CI 0.49-0.76) for the 40-49 age group relative to the 50+ age group, adjusted for sex, stage, grade, and subtype.

Conclusion:

Young adults in Kentucky are increasingly likely to be diagnosed with RCC. However, they tend to have more favorable disease features compared to older adults, and possibly improved survival. More work will be needed to determine potential causes and implications of accelerating incidence, as well as to guide treatment decisions and post-treatment surveillance for these patients.

Background:

An estimated 64,000 patients were diagnosed with kidney cancers—overwhelmingly renal cell carcinoma (RCC)—in 2017, and over 14,000 patients died.¹ Among new cancer diagnoses, kidney cancers are the sixth most common in men and tenth among women in the United States, the ninth most common in Europe, and twelfth worldwide.^{1,2} While nationwide incidence of new cancer diagnoses continue to decline overall in our country, there is ample epidemiological evidence of a long-term increase in the incidence of renal cell carcinoma in the United States and in other developed nations.^{1,3–6} Daily clinical experience for many urologists and other providers suggests that an increasing proportion of these new RCC diagnoses occur in younger adults relative to the more typical RCC patients, who are classically diagnosed in their seventh or eighth decades. This anecdotal trend is substantiated by a small number of studies presenting data supporting that observation.^{3,7}

Over the last two decades, the epidemiology of renal cell carcinoma has been examined at state, regional, national, and international levels, and several centers have reported their experience with young adult patients in particular.^{8–20} A pivotal study by Chow and colleagues in 1999 using SEER data from the 9 geographic areas for the years 1975 through 1995 suggested that the observed “rapidly rising incidence of renal cell carcinoma in the United States” could not be explained merely by the increased use of abdominal imaging such as ultrasound, computed tomography (CT) scans, and magnetic resonance imaging (MRI) as had been suggested by other authors.²⁰ Since then, a similar

increase in incidence has been described in other reviews of large registry data in the US and other developed countries.¹¹

The most comprehensive contemporary review of national-level data in the United States was performed by King, et al and published in 2014.³ In their study, they used the United States Cancer Statistics (USCS) public use database, which is comprised of combined cancer incidence data from the Centers for Disease Control and Prevention's (CDC's) National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program registries, to examine incidence trends over the decade from 2001 to 2010. While they emphasize the high annual percent change (APC) in incidence rate seen in the 20-24 year-old age group over that span, review of their data demonstrates that in actuality all patient groups from 20-39 had consistently higher APC (6.3-7.5%) than older (0.9-4.1%) and younger (3.9%) age groups.³

While their findings generally corroborate those of others who have noted an overall slowing, or even leveling, of RCC incidence rates, the broader population coverage (91.3% of U.S. population) of their cohort makes the observation particularly compelling, and the granular incidence rate data for 5-year age categories seems to show a clear difference between the rates seen in each of the 20-39 age groups compared to the older groups. The APC for the 40-44 (4.1%) and 45-49 (3.2%) age groups seem to represent the transition period to the more typical RCC population, with all age groups 50 and older showing APC of 2.1% or lower. Despite this more attenuated rate increase among the older age groups, they still represent the demographic most

likely to be diagnosed with RCC, with incidence peaking in the 65-79 year-old age groups, which have incidence rates of 49.2 to 51.2 per 100,000 individuals (age-adjusted to 2000 U.S. Standard Population), compared to 13.1 or lower in all the age groups younger than 50 (and less than 1 in patients 20-29).³

The three most well-documented risk factors for renal cell carcinoma are smoking, obesity, and hypertension.²¹ A recent meta-analysis examined 109 case-control studies and 37 cohort studies and estimated the relative risk (RR) of RCC among current smokers to be 1.36 (95% CI 1.19-1.56).²² A meta-analysis of data regarding obesity and RCC incidence found that each 5 kg/m² increase in body mass index (BMI) confers a RR of 1.24 for men and 1.34 for women.²³ Finally, a meta-analysis published last year evaluating the risk of renal cell carcinoma in patients with hypertension reported a RR of 1.67 (95% CI 1.46-1.90).²⁴ Whether these risk factors alone account for the incidence trends seen in developed countries is unknown, although it has been suggested that they are at least partially responsible.³

Most patients who are ultimately diagnosed with renal cell carcinoma are initially found to have a “renal mass” on an abdominal imaging study. Few of these patients have a biopsy performed prior to making a treatment decision, usually either surgery, ablative therapy, or active surveillance.^{25,26} As a result, “risk stratification” at the time of initial diagnosis is a critical component of counseling and treatment decision-making in this setting.^{25,27} Multiple potential patient- and disease-specific features factor into the risk stratification process, and many investigators have examined them, including several who have focused on younger adult patients.

However, most of the studied cohorts are relatively small and/or span large time periods. For example, reports from Cleveland Clinic and Mayo Clinic spanned 20 and 30 years, respectively, and included just over a hundred patients each.^{8,9}

A multicenter review of 12 European centers also covered a twenty year period, which included only patients treated surgically, and identified nearly 5000 total patients.²⁸ Of these, only 288 were 40 years of age or younger and they were noted to have lower grade and stage and the time of diagnosis, as well as more favorable histologic subtype distribution. Multivariate analysis suggested that younger age was an independent positive prognostic factor.²⁸ Other studies have also suggested that younger age may be an independent favorable prognostic factor, or that younger patients with RCC tend to have more favorable clinicopathologic features, such as stage, grade, or histologic subtype.^{10,16,19} However, still other investigators have reported findings suggesting the opposite—that younger adult patients may have less favorable histologic features and higher rates of lymph node-positive disease.^{29,30} As a result, risk stratification and treatment recommendations lack the requisite evidence base in these patients to allow for informed decision-making.

Following treatment for RCC, the focus shifts to prognosis and surveillance. Ideally, we would be able to identify predictors for long-term cancer-specific and overall survival for these young adult patients, but to date there has not been robust literature characterizing these outcomes.³¹ As a result, counseling patients requires relying on the data that is currently available—again based on an older population who may not necessarily have the same disease. In the absence of good long-term outcome data, we

can look at those variables that we believe most importantly contribute to survival, both cancer-specific and overall, and try to draw conclusions from that data instead. The most important known prognostic factors for patients treated for RCC are tumor grade, disease stage, and histologic subtype.^{27,32,33} To date, there is debate about the role of younger age in cancer-specific outcomes in RCC.

The rising incidence of RCC in the young adult population presents challenges for providers as they try to provide evidence-based care to these patients. The majority of guidelines and evidence sources are primarily based on the more typical RCC patient population consisting of patients over 50 years of age. In the absence of more specific guidance, these general treatment and surveillance recommendations and protocols are then applied to the younger patients, some of whom will complete both treatment and prescribed post-treatment surveillance before they reach even 40 years of age. There is basically no literature to guide clinicians for these patients once they have completed the protocols, in terms of how to monitor, if at all, for disease recurrence over the several remaining decades of life expectancy for many of them.³¹

This challenge is magnified by the recognition that renal cell carcinoma in the adolescent population seems to be a different entity than that of the adult population in general, and if there is an age or time period at which one transitions to the other, it is unknown.³⁴⁻³⁶ Some authors have designated age less than 40 or 45 as the “young adult” population with regard to RCC, but there is no clear scientific basis for either cutoff point at this time.^{10,13,31,32,37} One study evaluating the differing presentations of hereditary RCC proposed a genetic testing cutoff age of 46 years, and is likely the most

rigorous attempt thus far to identify a specific age under which patients might appropriately be considered as a separate group.³⁸ However, at this time there is no consensus among clinicians or investigators regarding an age below which patients can or should be categorized as “young adult,” as opposed to a more typical RCC population.

The purpose of this study is to use high-quality, actively-collected cancer registry data to examine the epidemiology of renal cell carcinoma in the young adult population in Kentucky (KY) in an effort to better understand the incidence rates and trends, clinicopathologic features important to prognosis, and cancer-specific survival for these patients relative to the more typical, older adult cohort of RCC patients.

Methods:

Appropriate institutional review board (IRB) approval was obtained from our institution, and data access request for the Kentucky Cancer Registry (KCR) was submitted and approved. Request documentation for access to the combined NPCR-SEER USCS public use dataset was also submitted and subsequently approved. The Kentucky Cancer Registry is the official population-based central cancer registry for the Commonwealth of Kentucky and reports its data to both SEER and NPCR. The USCS public use dataset includes cancer incidence data from registries covering the entire U.S. population, including central cancer registries reporting to NPCR in 45 states and the District of Columbia and to SEER in 5 states. These central cancer registries actively collect data for all new cancer diagnoses from patient records at various medical facilities and from

state vital records, and use uniform data items and codes which conform to the standards set by the North American Association of Central Cancer Registries.³⁹

Surveillance Research Program, National Cancer Institute SEER*Stat software version 8.3.5 was used to access and analyze the USCS data for the years 2001-2014, including only cases that meet USCS standard. Cases were further selected based on International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site recode 64.9, restricted to histology codes 8050/3, 8140/3, 8255/3, 8260/3, 8310/3, 8312/3, 8316/3, 8317/3, 8318/3, and 8320/3. Average annual rates per 100,000 population by age group (20-39, 40-49, and 50+) and registry location (Kentucky vs not) for the time period 2001-2014 were analyzed and compared. Rate denominators are based on annual county population estimates produced by the U.S. Census Bureau, in collaboration with CDC and supported by NCI, and are age-adjusted by the direct method to the 2000 U.S. standard population.⁴⁰ Percent change over the course of the study period was calculated using a two-year average for each end point. Annual percent change (APC) was used to quantify the change in rates over the course of the study period and was calculated using least squares regression. Two-sided *t*-test was used to test if the APC was different from zero.

The Kentucky Cancer Registry data for patients with topo code C64.9 were examined for the years 1995-2015. All KCR analyses were performed using age groups 19-39, 40-49, and 50+. Individual histology codes were grouped into subtypes as follows: Renal cell carcinoma (no subtype specified—NOS), 8312; clear cell subtype, 8005 and 8310; papillary subtype, 8050 and 8260; chromophobe subtype, 8317; and

remainder of codes were categorized as “other.” Race was categorized as “White,” “Black,” and “Other/Unknown.” The derived “Best Stage Group” variable was used to create the following stage groups for analysis and is based on the American Joint Committee on Cancer (AJCC), 6th edition stage groups: numeric codes <30: “Stage I”; codes 30-49: “Stage II”; codes 50-69: “Stage III”; codes 70-74: “Stage IV”; and codes 88 and 99: “N/A or Unknown.” Follow-up duration was determined using the date of diagnosis and the date of last contact or death, rounded to the nearest month. Cause of death codes “C64.9” and “189” were considered RCC disease-specific cause of death.

Differences in distribution of characteristics across all age groups were tested for using the chi-square test for independence for sex, race, grade, stage, and histologic subtype. Then the distribution of these variables for each specific young adult patient group was tested for differences against the older adult group (age 50+) using Pearson chi-square test.

Cancer-specific survival analysis was performed for the same age groups. Kaplan-Meier cancer-specific survival curves were created by age group, then by age group stratified by stage. Log-rank test was performed to test for equality of cancer-specific survival distributions for the three different levels of age group. Cox proportional hazards regression was performed for those patients with known sex, histologic subtype (clear cell, papillary, chromophobe, or other), grade, and stage.

Data from the SEER database was analyzed using SEER*Stat software version 8.3.5. The data from the Kentucky Cancer Registry was analyzed using SPSS v24 (IBM).

Results:

The USCS dataset included 12,059 cases in Kentucky and 678,042 cases outside Kentucky that met all selection criteria, while the KCR dataset included 13,564 patients. Incidence rate by year for each age group by KY and non-KY location are shown in Figure 1. Over the course of the study period, the overall percent change for the 20-39 age group in KY was 163.1%, compared to only 68.5% for the non-KY cases. The percent change for the 40-49 age group was also higher for KY, 88.6%, compared to 44.9% for non-KY cases, while percent change for the 50+ age group was similar for both locations (23.3% vs 20.8%). The annual percent change (APC) was significantly higher for the youngest patients in KY compared to the rest of the country, 8.5% (95% CI 5.9-11.2%) per year, compared to only 4.4% (95% CI 3.5-5.3%) per year ($p < 0.05$), as seen in Figure 2. The APC for the 40-49 and 50+ age groups were also higher for KY cases, but the confidence levels overlapped for these groups.

Age group characteristics for the KCR cases are shown in Table 1. About 2000 (16.5%) of the patients were under the age of 50 at the time of diagnosis, including over 600 (4.5%) who were less than 40. Median follow-up for the entire cohort was about three and a half years, while the median follow-up among the young adult groups was nearly five years. Race distribution was similar across the three age groups, but the younger groups had a significantly higher proportion of female cases, nearly 50%, compared to a more traditional 60% male-40% female distribution among the older age groups ($p < 0.001$).

Pathologic characteristics by age group are described in Table 2. Overall, the younger patients had statistically different and more favorable disease distribution. Over 70% of the 20-39 age group had Stage 1 disease, compared to less than half of the 50+ age group, and only 13% of the youngest group presented with advanced Stage 3 or 4 cancer, while over 30% of the oldest group did ($p < 0.001$). Younger patients had similarly lower rates of high grade disease compared to more traditional RCC patients, 59.1% vs 41.2%, although substantially more patients in the 50+ group had unknown grade—34.6% vs 18.1%. Analysis of histologic subtype was also hampered by many cases having either “other” (10.8%) or “non-specific” (35.9%) subtype. However, patients in the younger groups do seem to be somewhat more likely to be diagnosed with the (generally) more indolent chromophobe subtype.

Kaplan-Meier curves for cancer-specific survival by age group are seen in Figure 3. Log-rank test for difference between older and younger age groups revealed $p < 0.001$. However, Kaplan-Meier curves for cancer-specific survival by age group stratified by stage (Figure 4) show similar curves across all three age groups out to 10 years. Results of Cox proportional hazards regression are shown in Table 3. Results suggest that younger age may be an independent favorable prognostic factor, with hazard ratio (HR) of 0.72 (95% CI 0.47-1.09) for the 19-39 age group and 0.61 (95% CI 0.49-0.76) for the 40-49 age group relative to the 50+ age group when accounting for sex, stage, grade, and subtype.

Discussion:

Classically, renal cell carcinoma has been considered a disease of older adults, and the preponderance of clinical data and guidelines are based on studies of these patients.

However, as our data demonstrate, and other studies have suggested, the proportion of young adult patients diagnosed has been steadily increasing, both nationally and within Kentucky. As we encounter more young adult patients with RCC, the clinician is faced with the question of whether the accumulated literature regarding the disease process in older adults also applies to these patients for purposes of risk stratification, treatment counseling and decision-making, and post-treatment surveillance.

A few other investigators have described the higher APC among younger adults previously, although this is the first to include national data beyond 2010.^{3,13}

Interestingly, we also see that this trend is even more pronounced in Kentucky. There are several known risk factors that have been identified for RCC among adults—smoking, obesity, and hypertension the most commonly described—and these may be contributing to the increased incidence and rate of growth in Kentucky.^{5,11,41} However, whether these risk factors alone are able to explain the incidence trends nationwide or in Kentucky is unknown at this time.

It also remains to be seen whether the RCC incidence trends we have seen nationwide and within KY will continue their current course. These patients already comprise a larger proportion of RCC patients than ever before, and that proportion may continue to grow. Several investigators have noted an apparent plateau in overall RCC incidence, while the younger group rates continue to accelerate.^{3,12,13} Data about the

behavior of the disease in these patients will be increasingly important for providers as they guide the patients through treatment choices, treatment itself, and the post-treatment surveillance process.⁴² Current guidelines from the American Urological Association and European Urological Association do not give any guidance for surveillance of these patients beyond the generic prescription for all patients, despite the fact that they may have decades more survival time ahead of them than the typical patient.^{25,26}

Our analysis sheds some light on the question of disease behavior in the young adult population. Young adults in Kentucky are more likely to be diagnosed with renal cell carcinoma with favorable pathologic features—grade, stage, and histologic subtype—than their older counterparts. The stage difference, at least, could be a function of earlier diagnosis, but the grade and subtype are more likely to be related to differences in tumor biology. Our data do not corroborate other studies that have suggested more aggressive disease in these patients, but rather are more consistent with those who have identified more favorable features.^{10,16,29,30}

These more favorable pathologic features are important for risk stratification and treatment planning. These patients are more likely to be candidates for nephron-sparing surgery, and with data demonstrating the long-term mortality associated with chronic kidney disease, such approaches might be especially important among young adult patients with their prolonged life expectancy relative to older patients.⁴³

The cancer-specific survival data for these younger patient age groups are important for clinicians who are treating and counseling patients who present with

possible RCC or are diagnosed and treated for it. In particular, the survival curves and regression analysis suggest that prognosis for these patients is at least as good as their older counterparts, and potentially even better. Hazard ratio estimate for the youngest group was 0.72, but with a wide confidence interval that included 1, likely due to the relatively low number of these patients in the model. The HR for the 40-49 group was lower still, at 0.61, with a much narrower 95% CI of 0.49-0.76. As the most important known prognostic factors (grade, stage, and histology) are included in the model, it is suggested that there is truly a cancer-specific survival advantage for these patients that is independent of the known pathologic features, as has been seen in studies of other populations.^{16,19,37}

As with all registry-based studies, there are potential weaknesses or concerns about interpreting the results. We are subject to the quality of the data collection, which is inevitably imperfect. A meaningful proportion of the patients had incomplete and/or non-specific data regarding stage and grade, for example. Generalizability is sometimes an issue when dealing with registry data; however, by using the combined NPCR-SEER data for the incidence analyses, we hopefully have captured a much broader population than most similar studies. For the Kentucky data, all cases should be collected, but it is possible that some were missed or were never diagnosed based on the limited access to care of some KY patients. Longer follow-up data would have been ideal for the cancer-specific survival analyses. Finally, residual confounding is certainly a concern as there is important data about risk factors that we do not have, as well as other potential unknown variables of importance.⁴⁴

Moving forward, there is more to be done as we try to better understand the young adult RCC patient cohort. We need to determine how to follow these patients long-term. Registry data may provide those answers someday, but to date there is no specific guidance for surveillance for these patients. At the individual patient level, better molecular testing and analysis of these tumors may provide insights into the basic tumor biology underlying the clinical manifestations and potentially give clues as to better targeted or personalized therapies for advanced disease. Finally, the American Urological Association (AUA) released specific guidelines in 2017 about genetic testing for patients under the age of 45 who are diagnosed with RCC.²⁵ As more patients are tested and genetic data accumulates, we may find guidance for how to treat and follow these patients based on underlying genetic determinants and risk factors for recurrence.

Conclusion:

Young adults in Kentucky are increasingly likely to be diagnosed with RCC. However, they tend to have more favorable disease features compared to older adults, and likely improved cancer-specific survival as well. More work will be needed to determine potential causes and implications of the accelerating incidence, as well as to guide treatment decisions and post-treatment surveillance for these patients.

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Figure 1: Incidence rates by year and age group for patients in KY vs the rest of the United States (“Non-KY”). USCS data, 2001-2014

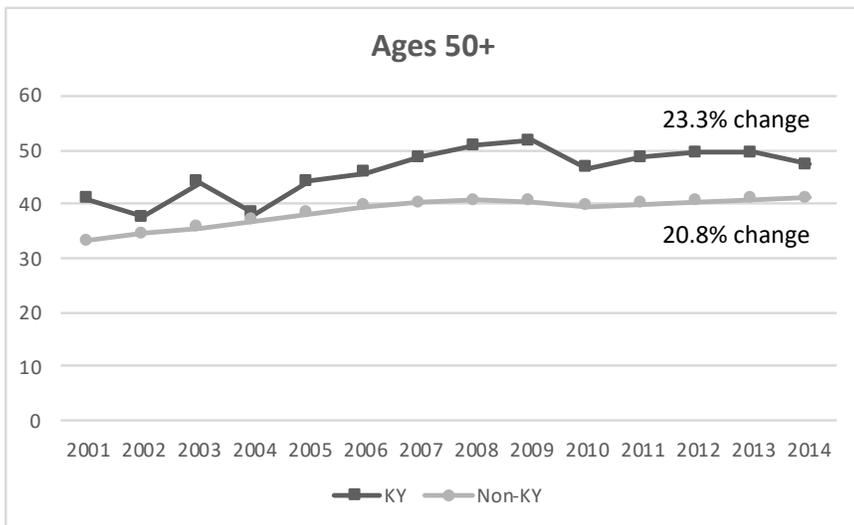
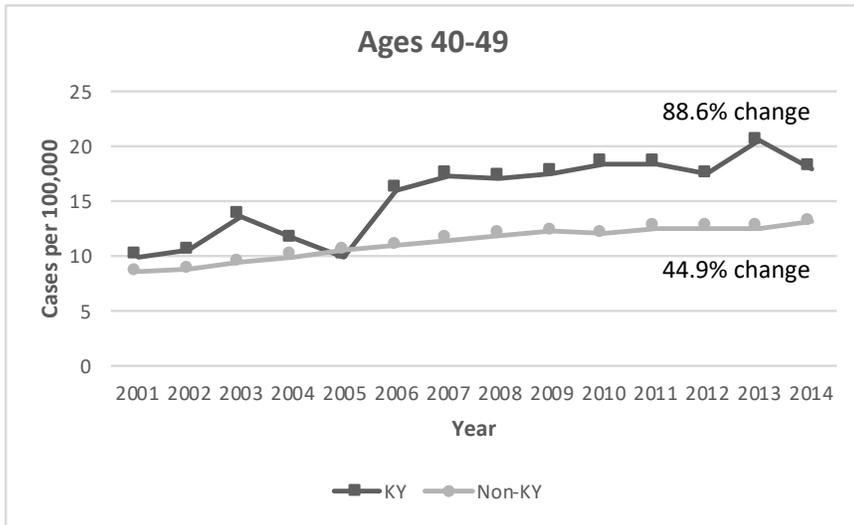
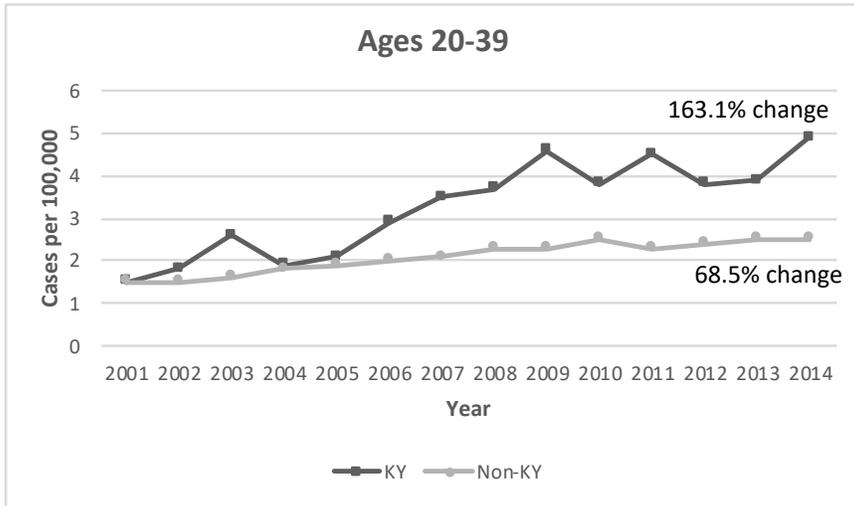


Figure 2: Annual percent change and confidence intervals by age group, KY vs “Non-KY” for the years 2001-2014

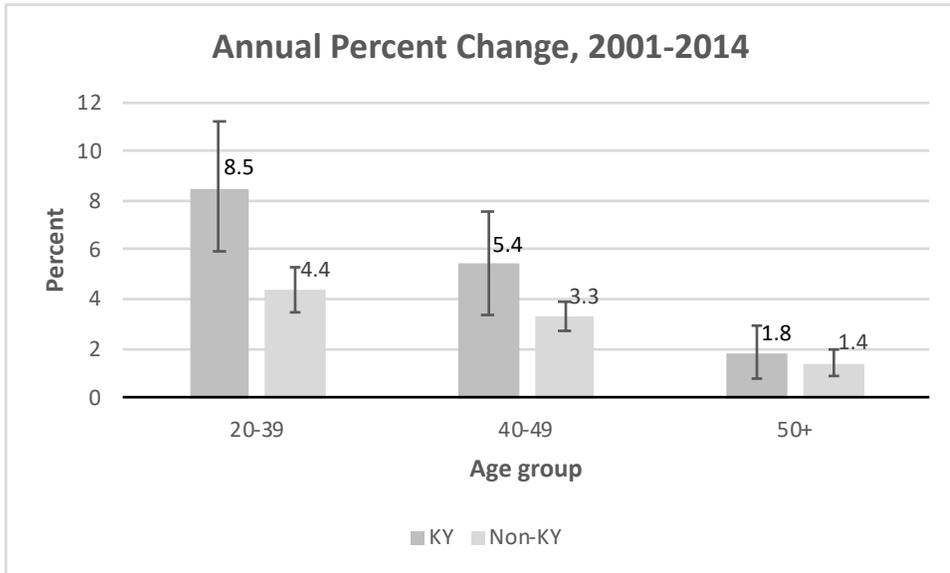


Table 1: Basic demographics by age group; KCR 1995-2015

		19-39	40-49	50+	Total
		N= 614 (4.5%)	N= 1620 (11.9%)	N=11,330 (83.5%)	N=13.564
Sex	Male	319 (52.0%)*	1016 (62.7%)	6892 (60.8%)	8227 (60.7%)
	Female	295 (48.0%)*	604 (37.3%)	4438 (39.2%)	5337 (39.3%)
Race	White	550 (89.6%)	1488 (91.9%)	10491 (92.6%)	12529 (92.4%)
	Black	55 (9.0%)	120 (7.4%)	798 (7.0%)	973 (7.2%)
	Other/Unk	9 (1.5%)	12 (0.7%)	41 (0.4%)	62 (0.5%)
Follow-up months		58 (24, 93)	57 (21, 104)	39 (11, 85)	42 (13, 88)

*p<0.001 for difference relative to age 50+

Table 2: Pathologic characteristics by age group; KCR 1995-2015

		19-39	40-49	50+	Total
Histology	RCC NOS	139 (22.6%)	511 (31.5%)	4216 (37.2%)	4866 (35.9%)
	Clear cell	339 (55.2%)	808 (49.9%)	4638 (40.9%)	5785 (42.6%)
	Papillary	48 (7.8%)	121 (7.5%)	960 (8.5%)	1129 (8.3%)
	Chromophobe	37 (6.0%)	44 (2.7%)	241 (2.1%)	322 (2.4%)
	Other	51 (8.3%)	136 (8.4%)	1275 (11.3%)	1462 (10.8%)
			p<0.001*	p<0.001*	Reference
Grade	Low	363 (59.1%)	867 (53.5%)	4673 (41.2%)	5903 (43.5%)
	High	140 (22.8%)	413 (25.5%)	2738 (24.2%)	3291 (24.3%)
	Unknown	111 (18.1%)	340 (21.0%)	3919 (34.6%)	4370 (32.2%)
			p<0.001*	p<0.001*	Reference
Stage	I	440 (71.7%)	934 (57.7%)	5576 (49.2%)	6950 (51.2%)
	II	62 (10.1%)	210 (13.0%)	1159 (10.2%)	1431 (10.5%)
	III	41 (6.7%)	179 (11.0%)	1479 (13.1%)	1699 (12.5%)
	IV	40 (6.5%)	209 (12.9%)	1946 (17.2%)	2195 (16.2%)
	Unknown	31 (5.0%)	88 (5.4%)	1170 (10.3%)	1289 (9.5%)
			p<0.001*	p<0.001*	Reference

*Chi square test for difference in distribution relative to reference group – age 50+

Figure 3: Kaplan-Meier curve for CSS to 15 years by age group.

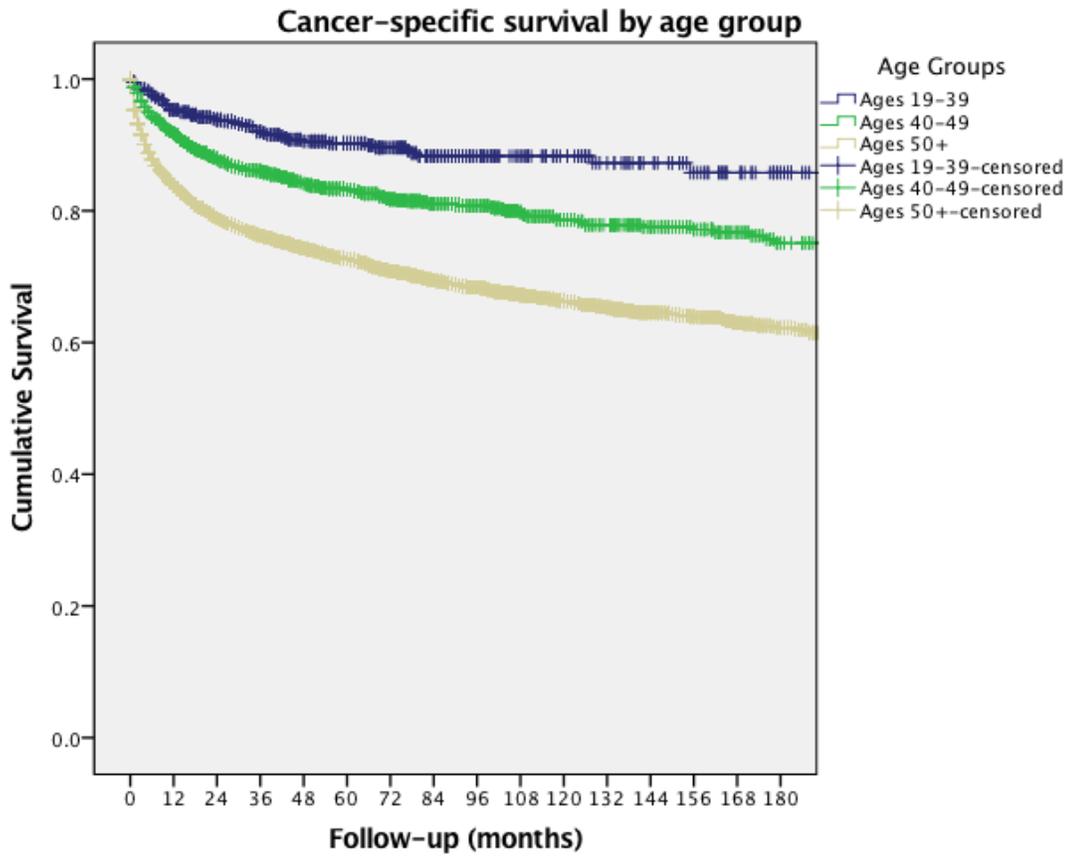
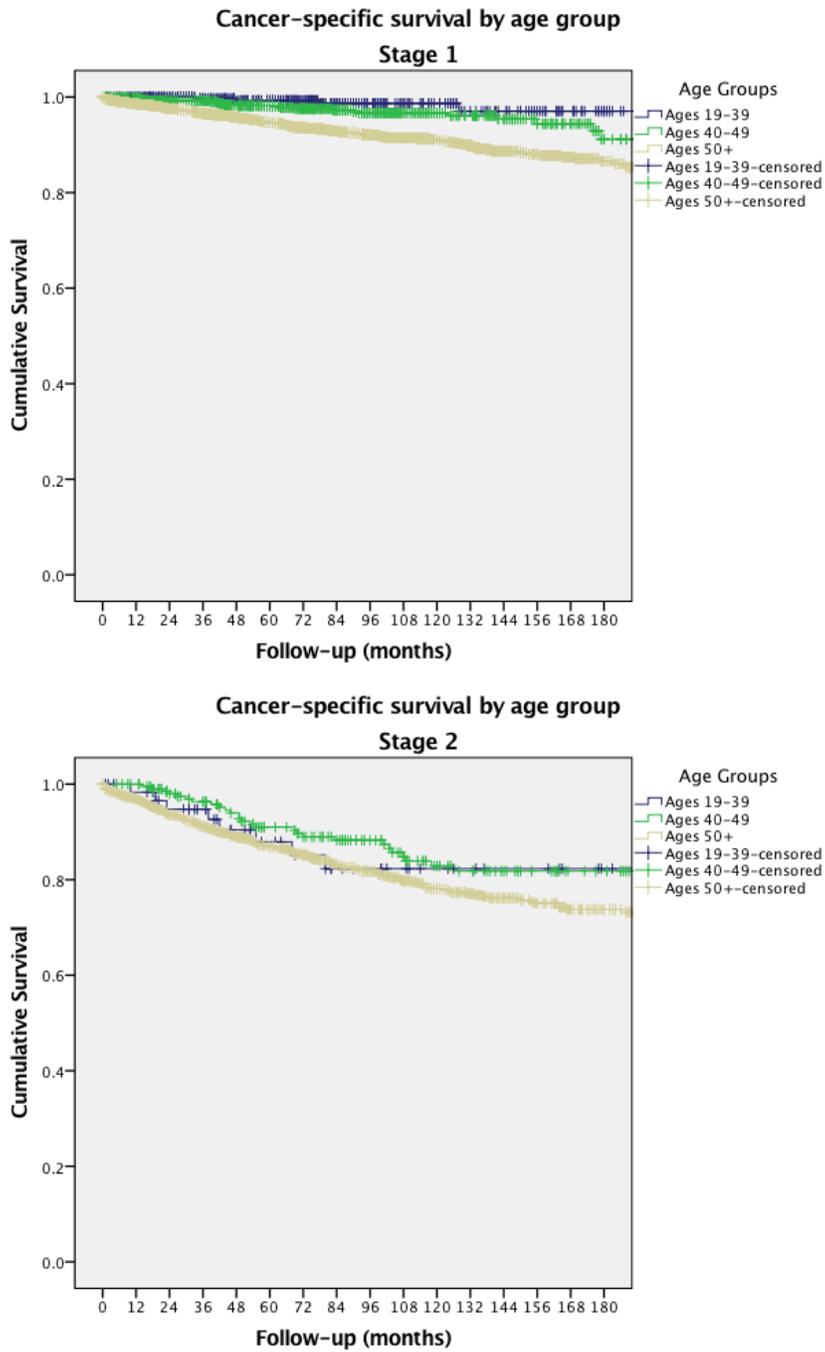
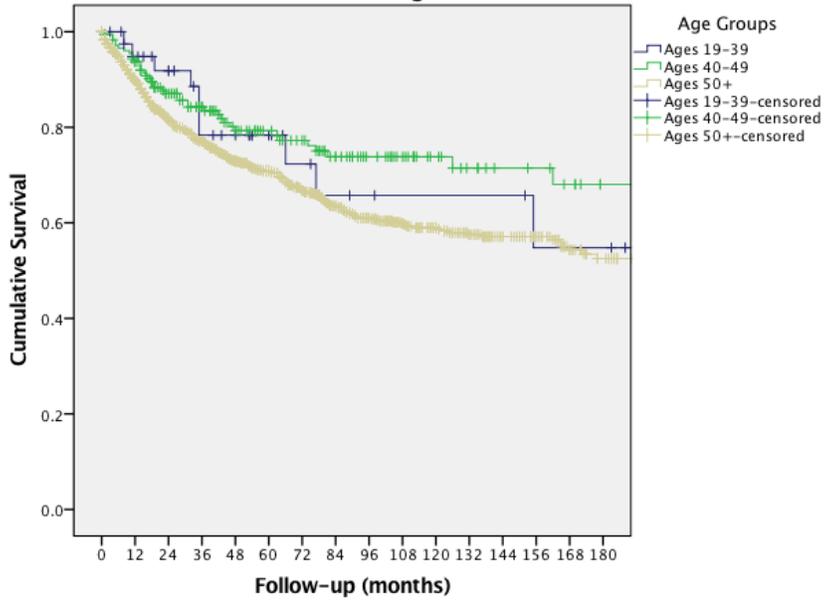


Figure 4: CSS by age group, stratified by stage at diagnosis



Cancer-specific survival by age group

Stage 3



Cancer-specific survival by age group

Stage 4

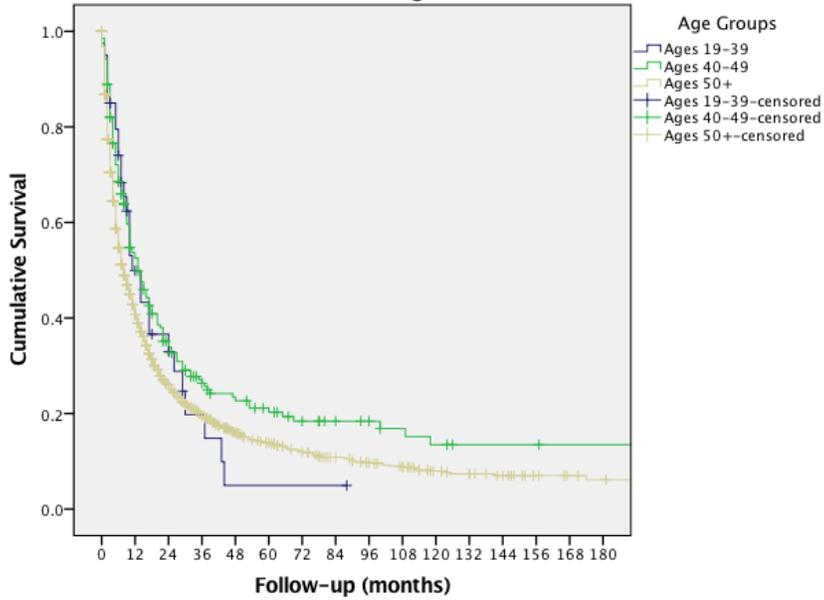


Table 3: Cox proportional hazards regression

	Hazard ratio	95% CI Lower	95% CI Upper	p
Age groups				
50+	Reference			<0.001
19-39	0.72	.474	1.090	.120
40-49	0.61	.490	.757	<0.001
Female vs Male	0.91	.790	1.045	.179
Stage				
Stage 1	Reference			<0.001
Stage 2	3.2	2.444	4.100	<0.001
Stage 3	6.1	4.962	7.484	<0.001
Stage 4	31.1	25.438	38.025	<0.001
Grade				
High vs Low	1.8	1.521	2.059	<0.001
Subtype				
Clear cell	Reference			<0.001
Papillary	0.82	.641	1.060	.132
Chromophobe	0.54	.290	1.015	.056
Other	1.8	1.557	2.148	<0.001

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