

**Renal Cell Carcinoma in Arizona
American Indians/Alaska Natives**

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ABSTRACT

OBJECTIVE – This study assesses trends in the incidence of cancers of the kidney and renal pelvis (K&RP) with focus on renal cell carcinoma (RCC) from 1995-2009 among American Indian/Alaska Natives (AI/AN) residing in Arizona.

RESEARCH DESIGN AND METHODS – Using the Arizona Cancer Registry (ACR), we obtained the total number of new cases of cancers of the K&RP from 1995 through 2009. The incidence rates of these cancers, as well as the sub-group of RCC, were age-adjusted to the 2000 U.S. population for comparison between populations. Comparisons between demographic and tumor characteristics were also completed between AI/AN and non-Hispanic white cases.

RESULTS – Between 1995 and 2009, 502 cases of K&RP were diagnosed in AI/AN in Arizona, with a majority of these cases (463, 92.23% of cases) being RCC of the kidney parenchyma. Over the study period, the age-adjusted incidence per 100,000 population was 19.18 for all tumors of the K&RP and 17.65 for RCC. Comparing the average age-adjusted rate over the first third (1995-1999) of the study period versus the last third (2005-2009), the rate of RCC among AI/AN increased 12.30% from 16.55 to 18.58 per 100,000 population. When this rate was stratified by sex, AI/AN males showed the most striking increase - 54.56% (19.22 to 29.70 cases of RCC per 100,000 population). While AI/AN females showed a decrease in the rate of 28.24% (14.20 to 10.19 cases per 100,000 population).

CONCLUSIONS – The incidence rate of RCC has increased dramatically in Arizona AI/AN males. Research looking at this disease in this group is needed to determine which risk factors may be associated and to determine if any steps can be taken toward prevention or if there is a need for screening in this population.

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INTRODUCTION

The Arizona Cancer Registry (ACR) is the state agency within the Arizona Department of Health Services that is mandated by statute to monitor the incidence of cancer in Arizona.

This student project utilizes the resources of the ACR to conduct an epidemiologic assessment of kidney and renal pelvis (K&RP) cancer. By design, the project is limited in scope to an analysis of non-confidential data obtained from the ACR.

Background

The kidneys are a paired organ that serve several important functions, including the removal of waste products from the blood and maintaining homeostatic balance of fluids and solutes in the body.¹ A kidney is composed of a parenchyma and a collecting system. Cancers can arise from each of these components. The most common adult kidney cancer is adenocarcinoma, also called renal cell carcinoma (RCC), which arises from the renal parenchyma and accounts for about 90% of all adult kidney cancers.²⁻⁴ The renal pelvis gives rise to renal transitional cell carcinomas (RTCC), representing less than 10% of kidney carcinomas. Nephroblastoma, also called Wilms tumor, makes

up about 1.2% of all kidney cancers and is the most common kidney cancer in children.

Since the late 1970s, the incidence of kidney cancers increased through the mid-1990s, with most of the increase coming from increased diagnosis of early-stage RCC.¹ In the U.S., incidence rates of K&RP cancers differ among racial groups. Higher rates of RCC with steeper rates of increase are seen in African Americans, and lowest rates are seen among those of Asian descent.

The Arizona Cancer Registry (ACR) has observed an apparent increase in the incidence of kidney and renal pelvis (K&RP) cancer among American Indians/Alaska Natives (AI/AN) residing in Arizona. This observation was noted in data the ACR presented in 2008 to the Arizona Cancer Coalition in order to address cancer disparities and for the development of community-specific cancer interventions and research.⁵ The data in the disparity report, covering cases diagnosed in the years 1995-2004, showed that Arizona's AI/AN had the highest K&RP cancer incidence rates compared to the other races, and that the yearly count of cases appeared to be increasing among AI/AN. Furthermore, K&RP cancer was the second most common cancer (next

to breast cancer) and comprised 9.5% of all cancers. This proportion was 2-3 times higher than that of other races.

The purpose of this student project is to update the previous observation and to examine factors that characterize the nature of the increase, if it is still present. The project intends to inform the ACR and other interested parties about the known risk factors as they relate to the currently available data in Arizona. Additionally, the project intends to indicate the direction or topics that should be explored to advance the cause of controlling K&RP cancer.

Significance

Past reviews looking at rates of K&RP cancers among AI/AN have shown that this group has an increased risk of developing and dying of this cancer.⁶ The rates in Arizona may indicate that this population and cancer site deserves investigation to identify risk factors, indications for increased screening, and evaluations of interventions for prevention.

Aims/goals/hypothesis

The goals of this project are to characterize the incidence of cancer of the kidney and renal pelvis among American Indian/Alaska Natives, to determine whether the rate is changing, and to assess factors (age, sex, county) that may be contributing to the rate.

Specifically, we address the following study questions:

1. With the addition of four years of data (through 2009), what do the race-specific counts and rates indicate about the rate among AI/AN?
2. How does the rate among AI/AN compare to that of the state?
3. Among the AI/AN population are there unusual factors associated with the distribution of cases including patient's age, sex, cancer site, histology, and tumor size compared to the reference group of non-Hispanic whites (NHW).

RESEARCH MATERIALS AND METHODS

Arizona Cancer Registry

The Arizona Cancer Registry (ACR) provided the data to assess trends in the incidence of cancers of the kidney and renal pelvis among Arizona residents. The ACR is a population-based surveillance system

that has been collecting and analyzing cancer case data in Arizona since 1981.⁷ These data were initially collected from hospitals who reported the information voluntarily, but reporting has been mandatory for hospitals, clinics, physicians, dentists, nurse practitioners, and doctors of naturopathic medicine since 1992 when Arizona Revised Statue §36-133 came into effect. The year that the ACR became complete in achieving statewide coverage was 1995. Data from Indian Health Service (IHS) facilities in Arizona are reported to the ACR from the New Mexico Tumor Registry.

In December 2011, a dataset of non-confidential variables was obtained from the ACR. The dataset included demographic, tumor, follow-up, and mortality information for cases of primary K&RP cancers in Arizona diagnosed from 1995-2009. Cases included in the dataset were limited to patients who were Arizona residents at the time of diagnosis with a malignant neoplasm (behavior code/3) of the kidney parenchyma (ICD-O-3 code C64.9) or renal pelvis (C65.9). Cases were excluded if they were missing demographic information (age, sex, or race) (See Table 1). Patients with a race designation of “White” were sub-classified as non-Hispanic or Hispanic using the

Table 1. Kidney cancer incidence by type among Arizona residents, 1995-2009

Type of disease (ICD-O-3 morphology codes)	Cases: All	%	Cases: NHW	%	Cases: AI/AN	%
Total kidney cancer (including renal pelvis)	10,959	100.0	8,349	100.0	503	100.0
Of which*						
Excluded cases: missing race	91	0.83	-	-	-	-
Excluded cases: missing sex	3	0.03	2	0.02	1	0.20
Excluded cases: missing age	3	0.03	2	0.02	0	0.00
Included cases	10,888	99.35	8,345	99.95	502	99.80
Of which†						
Other‡	2	0.02	2	0.02	0	0.00
Ill-defined (8000-8046)	522	4.81	407	4.88	23	4.58
Nephroblastoma (Wilms tumor; 8960)	105	0.97	62	0.74	5	1.00
Sarcomas, other (8800-9540; except 8960)	51	0.47	30	0.36	3	0.60
Carcinomas (8050-8575)	10,182	93.74	7,844	94.00	471	93.82
Of which§						
Transitional cell/squamous cell (RTCC; 8050-8131 [renal pelvis/ parenchyma])	887	8.71	806	10.28	7	1.49
Adenocarcinoma [RCC; 8140-8575 [renal pelvis])	16	0.16	13	0.17	1	0.21
Adenocarcinoma [RCC; 8140-8575 [renal parenchyma])	9,279	91.13	7,025	89.56	463	98.30

Type of disease (ICD-O-3 morphology codes)	Cases: All	%	Cases: NHW	%	Cases: AI/AN	%
Of which						
RCC, NOS (8312)	5,504	59.32	4,184	59.56	271	58.53
Clear cell (8310)	2,478	26.71	1,780	25.34	152	32.83
Papillary (8260)	512	5.52	431	6.14	9	1.94
Chromophobe (8270, 8317)	335	3.61	277	3.94	4	0.86
Adenocarcinoma, NOS	90	0.97	72	1.02	3	0.65
Tubular (8211)	6	0.06	6	0.09	0	0.00
Granular cell (8320)	95	1.02	84	1.20	3	0.65
Other [¶]	259	2.79	191	2.72	21	4.54

Data are taken from the Arizona Cancer Registry for cases of malignant neoplasm of the kidney parenchyma or renal pelvis. *Proportion of total kidney cancer. †Proportion of cases with complete demographic data (race, sex, age). ‡Includes granulosa cell tumor and granular cell tumor. §Proportion of kidney and renal pelvis carcinomas with complete demographic data. ||Proportion of adenocarcinomas with complete demographic data. ¶Includes mixed cell types, adenocarcinoma not otherwise specified, and other rarer adenocarcinomas. Abbreviations: RCC, renal cell carcinoma; RTCC, renal transitional cell carcinoma; ICD, International Classification of Diseases; NHW, non-Hispanic white; AI/AN, American Indian/Alaska Native; NOS, not otherwise specified.

NHIA (NAACCR Hispanic Identification Algorithm) derived Hispanic origin classification system.

Statistical analyses

Statistical analysis was performed using Intercooled Stata, version 10.1 (Stata Corp., College Station, TX).

In order to control for confounding as a result in differences in age distributions between populations, all incidence rates per 100,000 were age-adjusted using the 2000 U.S. standard calculated by the direct method. 95% confidence intervals were calculated for these incidence rates. Age-adjusted incidence rates were calculated for all cases of K&RP tumors in Arizona, cases among AI/AN, and cases among non-Hispanic whites (NHW).

As it was found that RCC of the kidney parenchyma composed the majority of cases of K&RP in the AI/AN population, the remainder of the analyses focused on this sub-group. Comparisons in demographic and tumor characteristics between AI/AN and NHW were completed using Chi-squared tests for categorical variables and Wilcoxon rank sum test for continuous variables. The overall and annual (new tumors/population per 100,000 occurring each year) RCC incidence

rates were age-adjusted to the 2000 U.S. standard population using the direct method. Simple linear regression was used to calculate the annual change in the best-fit line of the annual age-adjusted rates.

RESULTS

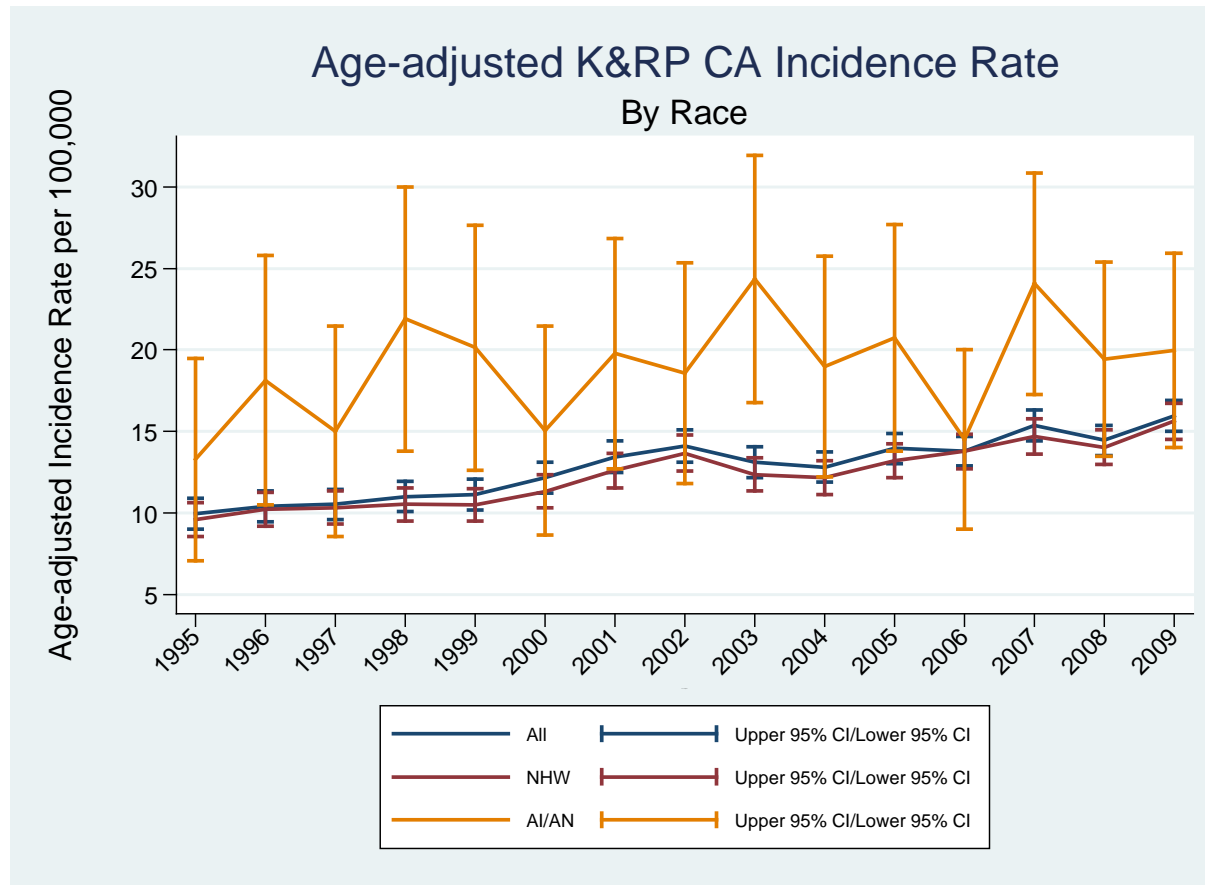
K&RP

From 1995-2009, there were 10,959 cases in the ACR dataset. Of these cases, 10,888 (99.35%) were eligible for inclusion in this analysis (Table 1). Of the cases included in the analysis, 76.64% (n = 8,345) were NHW (n = 5,208, 62.41% males; n = 3,137, 37.59% females), and 4.61% (n = 502) are AI/AN (n = 308, 62.47 males; n = 185, 37.53% females).

The age-adjusted rate of K&RP tumors for the study period was 13.04 (95% CI 12.80, 13.29), 12.48 (95% CI 12.21, 12.75), and 19.18 (95% CI 17.42, 20.93) for all races, NHW, and AI/AN, respectively. In general, rates of K&RP rose over the study period for all races, NHW, and AI/AN as illustrated in Figure 1.

Carcinomas made-up over 90% of cases of tumors of the K&RP, with the majority of these cases being further classified as adenocarcinomas

Figure 1. Age-adjusted* incidence rate of kidney and renal pelvis tumors, 1995-2009



*Age-adjusted to the 2000 U.S. standard population. Abbreviations: K&RP, kidney and renal pelvis; NHW, Non-Hispanic White; AI/AN, American Indian/Alaskan Native.

of the renal parenchyma (also known as renal cell carcinomas [RCC]). RCC of the renal parenchyma was over-represented as the histological type of K&RP carcinomas compared to those in NHW ($P < 0.001$).

RCC: Tumor characteristics

In the analysis of RCC, 9,279 cases were included. This included 7,025 cases among NHW and 463 cases among AI/AN (Table 2). Among cases of RCC, the clear cell histology sub-type was over-represented with fewer than expected cases of papillary and chromophobe compared to NHW ($P < 0.001$). However, the histology of the tumors was significantly less likely to have been microscopically confirmed in AI/AN ($P = 0.001$).

While the majority of tumors are smaller than 7.0 cm, tumors diagnosed in AI/AN were overall significantly larger than in NHW patients ($P = 0.003$). The SEER summary stage also showed a higher stage with increased spread of the cancer to distant sites or lymph nodes and few cases which are discovered when they are limited to the local site in AI/AN ($P = 0.003$). The size of the tumor and stage are indicators of patients' prognosis. Indeed, this is reflected in the cancer and vital statuses of patients at follow-up. American Indian/Alaska

Table 2. Demographics and clinical characteristics of renal cell carcinoma among all Arizona residents, Arizona non-Hispanic whites, and Arizona American Indians/Alaska Natives, 1995-2009

Characteristic	Cases: All	%	Cases: NHW	%	Cases: AI/AN	%	NHW vs. AI/AN*
Total cases	9,279	100.0	7,025	75.71†	463	4.99†	
Year of diagnosis							
1995	364	3.92	289	4.11	18	3.89	
1996	377	4.06	304	4.33	22	4.75	
1997	414	4.46	335	4.77	21	4.54	
1998	433	4.67	340	4.84	28	6.05	
1999	475	5.12	367	5.22	29	6.26	
2000	536	5.78	404	5.75	20	4.32	
2001	602	6.49	455	6.48	25	5.40	
2002	664	7.16	523	7.44	29	6.26	P = 0.54
2003	644	6.94	480	6.83	41	8.86	
2004	656	7.07	489	6.96	32	6.91	
2005	705	7.60	515	7.33	35	7.56	
2006	723	7.79	565	8.04	26	5.62	
2007	882	9.51	643	9.15	50	10.80	
2008	847	9.13	616	8.77	42	9.07	
2009	957	10.31	700	9.96	45	9.72	
Sex:							
Male	5,815	62.67	4,449	63.33	292	63.07	P = 0.91
Female	3,464	37.33	2,576	36.67	171	36.93	

Characteristic	Cases: All	%	Cases: NHW	%	Cases: AI/AN	%	NHW vs. AI/AN*
Age group (in years)							
Less than 1	1	0.01	1	0.01	-	-	
1-4	-	-	-	-	-	-	
5-9	1	0.01	1	0.01	-	-	
10-14	-	-	-	-	-	-	
15-19	4	0.04	3	0.04	-	-	
20-24	17	0.18	9	0.13	3	0.65	
25-29	35	0.38	17	0.24	2	0.43	
30-34	91	0.98	49	0.70	7	1.51	
35-39	213	2.30	119	1.69	13	2.81	P < 0.001
40-44	423	4.56	250	3.56	30	6.48	
45-49	640	6.90	413	5.88	36	7.78	
50-54	892	9.61	639	9.10	64	13.82	
55-59	1,097	11.82	771	10.98	81	17.49	
60-64	1,218	13.13	932	13.27	63	13.61	
65-69	1,371	14.78	1,095	15.59	48	10.37	
70-74	1,205	12.99	996	14.18	48	10.37	
75-79	1,055	11.37	863	12.28	32	6.91	
80-84	633	6.82	542	7.72	24	5.18	
85+	383	4.13	325	4.63	12	2.59	

Characteristic	Cases: All	%	Cases: NHW	%	Cases: AI/AN	%	NHW vs. AI/AN*
Tumor sequence							
Only tumor	6,923	74.61	5,099	72.58	379	81.86	
First of >1	675	7.27	546	7.77	23	4.97	
Second	1,415	15.25	1,151	16.38	54	11.66	P = 0.001
Third	225	2.42	191	2.72	6	1.30	
Fourth	35	0.38	32	0.46	1	0.22	
Fifth	6	0.06	6	0.09	-	-	
RCC tumor sequence							
Only RCC tumor	8,963	96.59	6,781	96.53	445	96.11	
First of >1 RCC tumors	157	1.69	121	1.72	9	1.94	P = 0.943
Second RCC tumor	157	1.69	121	1.72	9	1.94	
Third RCC tumor	2	0.02	2	0.03	-	-	
RCC histology sub-type (ICD-O-3)							
RCC, NOS (8312)	5,504	59.32	4,184	59.56	271	58.53	
Clear cell (8310)	2,478	26.71	1,780	25.34	152	32.83	P < 0.001
Papillary (8260)	512	5.52	431	6.14	9	1.94	
Chromophobe (8270, 8317)	335	3.61	277	3.94	4	0.86	
Other	450	4.85	353	5.02	27	5.83	
Microscopically confirmed							
Yes	8,514	92.97	6,441	93.00	403	88.96	
No	644	7.03	485	7.00	50	11.04	P = 0.001
Unknown	121		99		10		

Characteristic	Cases: All	%	Cases: NHW	%	Cases: AI/AN	%	NHW vs. AI/AN*
Tumor size (largest dimension, in cm)[†]							
Less than 4.0	3,279	39.25	2,550	40.25	125	31.65	P = 0.003
4.0-6.9	2,687	32.16	2,024	31.95	133	33.67	
7.0-9.9	1,470	17.60	1,088	17.17	87	22.03	
More than 10.0	918	10.99	673	10.62	50	12.66	
Missing	925		690		68		
SEER summary stage							
Localized only	5,807	67.90	4,427	68.35	267	62.82	P = 0.003
Regional	1,420	16.60	1,067	16.47	67	15.76	
Distant site(s) or node(s)	1,325	15.49	983	15.18	91	21.41	
Missing	727		548		116		
Median follow-up at last contact (in years)							
(25 th percentile, 75 th percentile)	2 (0, 5)		2 (1, 5)		2 (0, 4)		P = 0.01
Missing	3		1		-		
Vital status at last contact							
Living	5,295	57.06	3,952	56.26	231	49.89	P = 0.008
Deceased	3,984	42.94	3,073	43.74	232	50.11	
Cancer status at last contact							
No evidence of tumor	4,536	67.62	3,421	68.08	174	55.95	P < 0.001
Evidence of tumor	2,172	32.38	1,604	31.92	137	44.05	
Missing	2,571		2,000		152		

Characteristic	Cases: All	%	Cases: NHW	%	Cases: AI/AN	%	NHW vs. AI/AN*
<p>*χ^2 test for categorical variables and Wilcoxon rank-sum test for years of follow-up care. †Percent of all cases. ‡Per 100,000 population. §Adjusted to the 2000 U.S. standard population, per 100,000 population. ¶Includes mixed cell types, adenocarcinoma not otherwise specified, and other rarer adenocarcinomas. ¶Categories of tumor size based on TNM classification. Abbreviations: NHW, non-Hispanic White; HW, Hispanic White; AI/AN, American Indian/Alaskan Native; RCC, renal cell carcinoma; NOS, not otherwise specified.</p>							

Natives are seen to have a higher proportion of tumor at follow-up (44.05% vs. 31.92% in NHW patients). Mortality also shows disparity between NHW and AI/AN. More than half (56.26%) of NHW patients were reported to be alive at follow-up, but less than half (49.89%) of AI/AN were (See Table 2).

RCC: Age-adjusted incidence rates

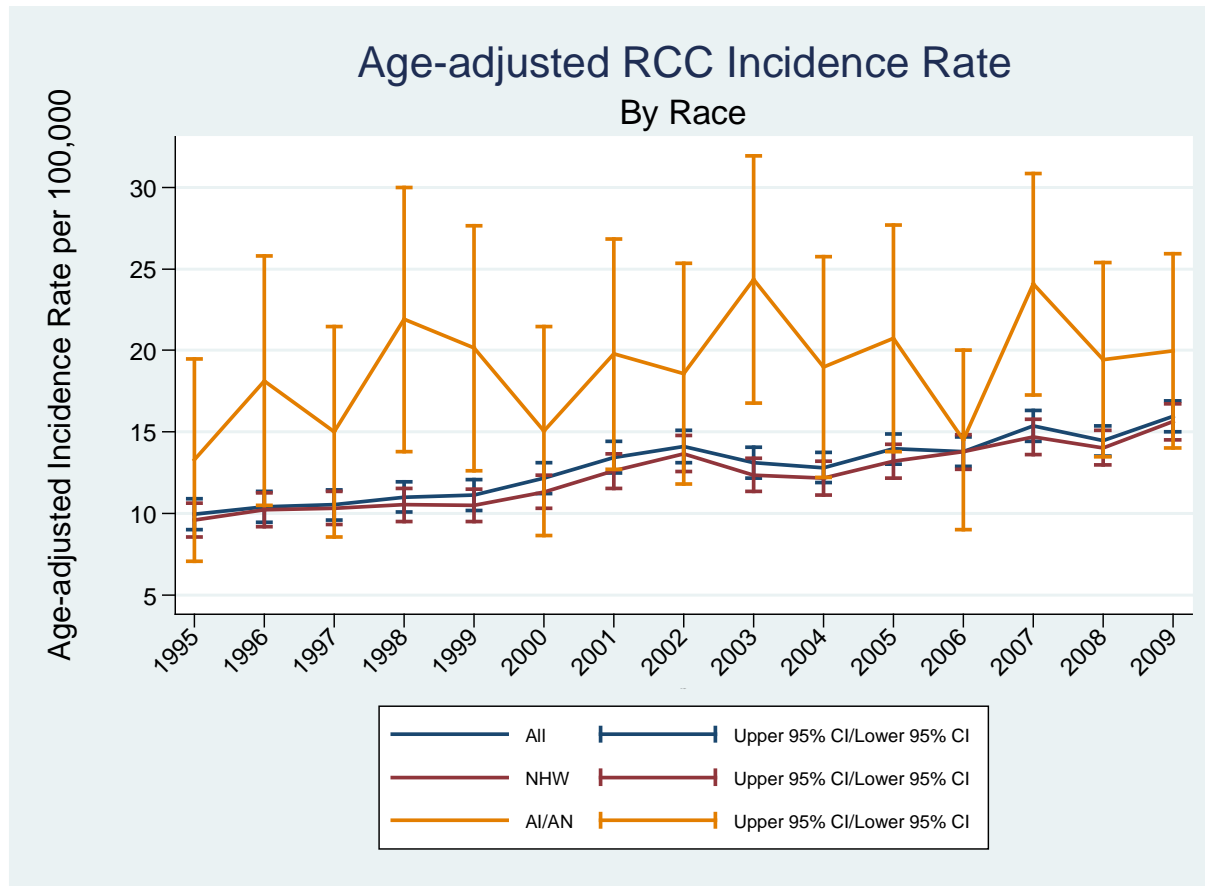
When rates were age-adjusted for comparison between populations, the age-adjusted incidence rate of RCC in Arizona from 1995-2009 was 11.13 per 100,000 population with an increase of 0.38 cases per 100,000 per year over the study period (Table 3, Figure 2a). The percent increase in the average age-adjusted rate from the first three years of the study period (1995-1997) to the final three years (2007-2009) were 48.30%, 47.07%, and 36.68% for all races, NHW, and AI/AN, respectively. When these rates are stratified by sex, males showed an increase of 40.09% (all races), 36.71% (NHW), and 83.57% (AI/AN). Females from all races had an increase of 59.30%, and NHW females had an increase of 9.17%, while AI/AN females had a decrease of 7.78%.

Table 3. Arizona Renal Cell Carcinoma: Number and rates of cases for all races, NHW, and AI/AN (1995-2009)					
Race	Sex	Cases	Crude-rate*	Age-adjusted rate (95% CI)*	Change in age-adjusted rate/year (95% CI)*†
All	All	9,279	12.96	11.13 (10.91, 11.36)	0.38 (0.30, 0.45)
All	Males	5,815	16.32	14.96 (14.57, 15.34)	0.41 (0.27, 0.55)
All	Females	3,464	10.71	7.85 (7.59, 8.11)	0.33 (0.28, 0.37)
NHW	All	7,025	15.11	10.54 (10.29, 10.79)	0.37 (0.29, 0.44)
NHW	Males	4,449	19.52	14.26 (13.84, 14.69)	0.40 (0.27, 0.53)
NHW	Females	2,576	11.71	7.31 (7.02, 7.60)	0.32 (0.26, 0.39)
AI/AN	All	463	18.08	17.65 (15.97, 19.32)	0.33 (-0.08, 0.73)
AI/AN	Males	292	23.83	25.42 (22.32, 28.51)	1.14 (0.56, 1.72)
AI/AN	Females	171	12.80	11.60 (9.81, 13.38)	-0.26 (-0.66, 0.14)

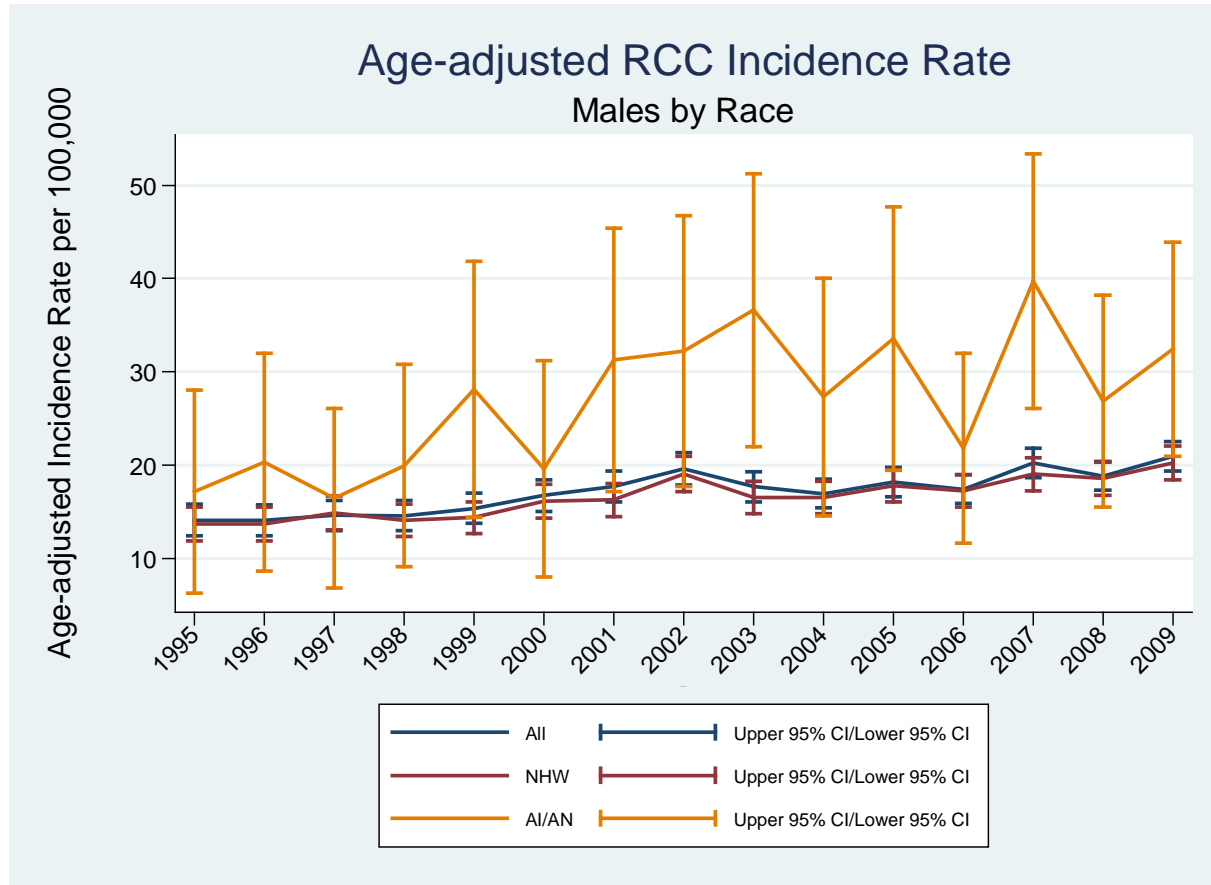
*Rates are per 100,000 population. †From simple linear regression. Abbreviations: NHW, non-Hispanic White; AI/AN, American Indian/Alaskan Native; 95% CI, 95% Confidence Interval.

Figure 2a. Age-adjusted* incidence rate of renal cell carcinomas for males and females, 1995-2009; 2b. Males only; 2c. Females only.

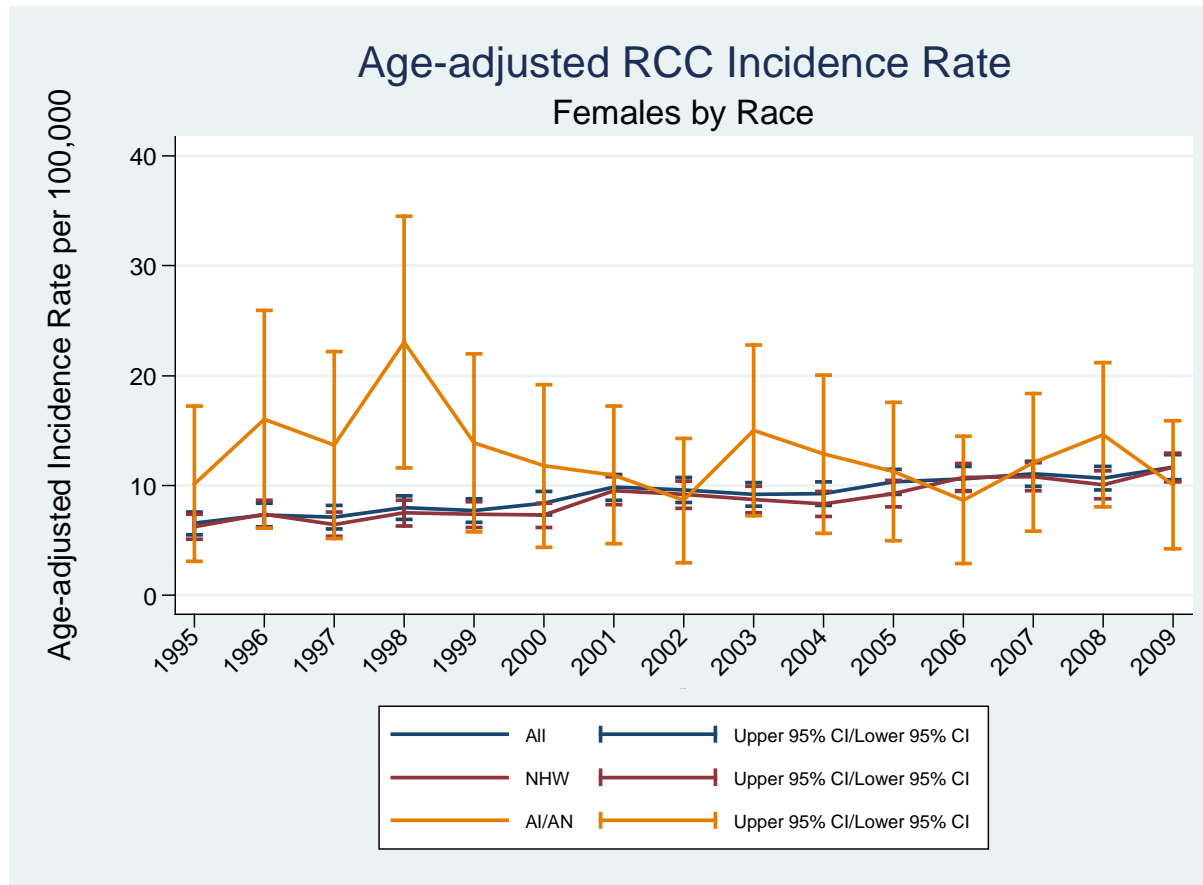
2a.



2b.



2c.



*Age-adjusted to the 2000 U.S. standard population. Abbreviations: RCC, renal cell carcinoma; NHW, Non-Hispanic White; AI/AN, American Indian/Alaskan Native.

DISCUSSION

Previous studies looking at cancers of the kidney and renal pelvis have shown an increase in the incidence of this category of cancers. Much of this increase has been attributed to an increase in incidentally detected tumors.⁸ This was supported by recent trends in stabilizing or decreasing rates of these cancers and increased survival.¹ However, in this analysis, the rates of cancers of the kidney and renal pelvis have shown an overall increase in incidence, particularly among AI/AN males (from 28.14 per 100,000 in 1995 to 32.43 per 100,000 in 2009).

Our study has several limitations. As in all studies that depend on data obtained from a registry, patients are excluded from all or part of the analyses due to missing data and can represent potential biases.

Data are also not available for the circumstances of diagnosis.

Therefore, it is not possible to determine whether the tumor was discovered because it was symptomatic or if it was found incidentally.

For example, AI/AN may undergo abdominal imaging more frequently for abdominal pain because this population has higher rates of cholelithiasis.⁹ AI/AN also have higher rates of diabetes which could be associated with more frequent urinalysis for microalbumin screening

which might lead to the discovery of a kidney tumor.⁹ Data are also not available for RCC-associated risk factors such as smoking, obesity, hypertension, or family history. Although it is unclear if a bias could develop, information on cancer cases among Arizona AI/AN seen in the Indian Health Service care system are first reported to the New Mexico Tumor Registry which then sends the information to the Arizona Cancer Registry for inclusion in the database. With this extra layer in the reporting, there is potential for missing or miscoded data.

In the data obtained from the ACR, residence information was not provided so we were not able to discriminate whether or not there were any geographic groupings of cases which may suggest an environmental component to the increase in incidence. We were also not able to determine whether specific tribes were over-represented with this disease.

The protocol for data entry of multiple tumors at diagnosis also changed in the study period; before 2007, if tumors were found in both kidneys, a single entry might reflect this. After 2007, an entry would be made for each of the tumors into the registry. This may have caused an apparent increase in the incidence following 2007. Because of the

increased risk of RCC in the AI/AN population, further study is recommended. Next steps may include a case-control study to find if known risk factors, including smoking, obesity, hypertension, or family history, or other factors unique to this population are related.

CONCLUSIONS

American Indian/Alaska Natives in Arizona are disproportionately affected by cancers of the kidney and renal pelvis, in particular American Indian/Alaska Native males. The change in incidence does not appear to be leveling off or decreasing as in other populations. Additional research is needed to determine whether this group is disproportionately affected by risk factors that have been shown to be associated with these cancers or if these populations have unique risk factors of their own. The increased rate may indicate a need for screening for these cancers, in particular among those with known risk factors, especially given that it appears that cases are diagnosed at a later stage as indicated by the larger tumor sizes and decreased survival as compared to white patients with the same cancers in Arizona.

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