

Research Paper

Diabetes and Risk of Renal Cell Carcinoma

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Abstract

Background and objectives: There is evidence that the incidence of solid tumors is markedly increased in patients with diabetes mellitus. In the current study, we investigate the association between diabetes and renal cancer.

Patients and Methods: A single-center retrospective analysis of 473 patients who underwent nephrectomy for renal cell carcinoma (RCC) was performed. Diabetic RCC patients were screened for age, gender, ethnicity, HgA1C, glucose levels and renal function.

Results: Of the 473 cases with RCC, we identified 120 patients (25.4%) with a history of diabetes. The incidence of diabetes in RCC patients was higher in female than male subjects and in Hispanic compared to White and Other ethnic backgrounds. At diagnosis, the majority of diabetic RCC patients were 50-59 years of age. In diabetic RCC cases, clear cell type histology (92.0%), nuclear grade 2 (56.1%) and tumor size range from 1-5 cm (65.7%) were the most common in each category.

Conclusion: Our findings indicate that diabetic RCC patients have a predominance of localized, small clear cell RCC. In addition, females with a history of RCC have a higher frequency of diabetes compared to males. This is the first report of clinical and histopathological features of RCC associated with diabetes.

Key words: RCC, diabetes, race, gender, tumor stage and HgA1C

1. Introduction

Epidemiologic studies have shown that patients with type 1 and type 2 diabetes mellitus (DM) are at higher risk than the general population for developing certain malignancies including kidney, liver, biliary tract, pancreas and colon [1-6]. In diabetics, cancer contributes 13% to mortality and these patients suffer from a high rate of cancer recurrence [7] Kidney cancer is the most common renal malignancy in adults and responsible for approximately 51,190 new cancer cases and accounting for 2.3% of all cancer deaths in

the United States [8]. RCC is more prevalent in men than in women and occurs most often 50-70 years of age. Cancer involving the renal parenchyma (renal cell cancer, RCC) accounts for the majority of cases, while the minority of cases are usually due to cancer of the renal pelvis [9]. The predominant subtype of RCC is clear cell type that represents 80% of RCC and is derived from the tubular epithelium [10]. Other types of RCC are papillary (15%), chromophobe (5%), and collecting duct (1%).

The risk factors for kidney cancer are smoking, obesity, hypertension, kidney transplantation, family history of the disease and exposure to certain toxins [12-16]. The importance of diabetes as a potential risk factor for cancer has been shown in clinical and autopsy studies [5]. A prior history of diabetes was associated with a three-fold increased risk for cancer in women [14]. In the retrospective International Cancer Study, a 5- to 10-year history of diabetes increased the relative risk of cancer by 40% in both men and women [15]. Several mechanisms implicated in the development of renal cancer in diabetes have included increased growth factors and/or their receptors, hyperinsulinemia and glucose availability [16-20].

As in other states in the U.S. DM is a serious public health problem in Texas. Of the 19.3 million individuals in the U.S. with diabetes, more than 1.8 million reside in Texas, with a high prevalence of Hispanic ethnicity [21]. Kidney cancer is one of the ten leading sites of cancer incidence in Texas; however, the association of DM and RCC histology has not been explored. To better understand this relationship between diabetes and renal cancer, all RCC cases at our center from 1994 to 2009 were analyzed with relation to history of diabetes, diabetic laboratory parameters gender, ethnicity, age and tumor morphology.

2. Materials and Methods

All RCC cases in patients who underwent nephrectomy at the University of Texas Health Science Center at San Antonio (UTHSC) from 1994 to 2009 were analyzed for gender, ethnicity and age at presentation. Results from laboratory tests including HgA1C (normal, 5.0-5.5%), glucose (normal, 80-100 mg/dL) and serum creatinine (normal, 0.6-1.2 mg/dl) were collected. RCC subtypes were classified according to WHO criteria. The Fuhrman nuclear grading system was used to classify RCC into different grades. Tumors were staged according to the American Joint Commission on Cancer (AJCC) tumor, nodes, and metastasis (TNM) system. We classified localized disease as TNM Stage I: tumors ≤ 7 cm, limited to the kidney or Stage II: tumors > 7 cm, limited to the kidney. Regional disease included TNM Stage III: tumor invasion of perinephric fat or adrenal gland but not beyond Gerota's fascia, with or without extension into the renal vein or vena cava. Metastatic disease refers to TNM Stage IV: tumor invades beyond

Gerota's fascia. The clinical database did not contain complete information regarding clinical presentation, type of DM, and length of diabetes, treatment modality or comorbid conditions; thus, these were not included in our study. The study was approved by the Institutional Review Board of The

University of Texas. Health Science Center at San Antonio, TX.

2.1. Statistics

Data are presented as mean \pm standard error and frequency counts with percentages where means were not appropriate. Where expected cell counts were below 5, the exact likelihood ratio chi-square test was used for a more appropriate statistical test of association. Statistical differences were determined using contingency table chi-square analysis and Analysis of Variance (ANOVA) followed by multiple comparisons of subgroup means. *P*-values less than 0.05 were considered statistically significant. Software used was the Statistical Analysis Systems' version 9.1.3 for window.

3. Results

A total of 473 cases of RCC were identified at our institution from 1994 to 2009. Table 1 shows that males comprised 56.9% of the cohort and were more prevalent than females (43.1%) ($p=0.003$). Of the RCC cases, 120 (25.4%) had a history of diabetes and, within this group, a greater proportion ($p=0.01$) of females (31.4%) had diabetes compared to males (20.8%) (Table 1).

Table 1: Distribution of RCC subjects with and without diabetes according to the gender.

Gender	RCC Cases Frequency (%)	RCC+diabetes Cases Frequency (%)
Male	269 (56.9) ^a	56 (20.8)
Female	204 (43.1)	64 (31.4) ^b
Total	473 (100)	120 (25.4)

a. $P=0.003$ Unequal proportions of males and females.

b. $P=0.01$ Unequal proportions of males and females.

Analysis of RCC cases for ethnic background and gender together is shown in Table 2. In both RCC and diabetes mellitus (DM) cases with RCC, there was a predominance of Hispanics (63.9 and 75%, respectively) with fewer Whites (28.7 and 19.2%, respectively) and Other ethnic groups (7.4 and 5.8%, respectively). This is not unexpected due to the prominent Hispanic population at our center. In addition, this difference may have occurred since Whites were less likely to have diabetes compared to Hispanics and Other ethnicities (refer to Table 2, $P=0.01$). When these data were analyzed for an association of gender and ethnicity, we found that in RCC cases, female and

male genders were not differently distributed ($p=0.76$) among the Hispanic (female 131/302, 43.4%), White (female 60/136, 44.1%) and Other (female 13/35, 37.4%) ethnic groups (Table 2). In addition, males were more predominant than females among all ethnic groups of RCC cases (Table 1, $P=0.003$; Table 2). In contrast, in RCC cases with DM, females predominated Table 2 and the predominance was similar ($P=0.76$) across all ethnic groups [Table 2, Hispanic (51.1%), White (60.9%) and Other (57.1%)]. However, the percentage of RCC cases with DM significantly differed ($P=0.01$) among ethnic groups: Hispanics (90/302, 29.8%), Whites (23/136, 16.9%) and Others (7/35, 20%).

Subsequently, the RCC and RCC cases with a history of DM were further examined for an association with age and gender. Table 3 shows that the dominant age groups of patients with RCC were 50 to 59 years of age (36.4%) and, to a lesser extent of 60 to 69 (23.1%), and 40-49 (22.3%) years of age. Within each age group, males consistently predominated ($P=0.45$) compared to females for RCC cases (Table 3). In contrast, females predominated (64/120, 53.3%) compared to males (56/120, 46.7%) and were similarly distributed within age groups ($p=0.57$) in cases of RCC with DM (Table 3). There were no significant differences of male and female mean HgA1C ($P=0.73$), serum creatinine ($p=0.14$) or blood glucose levels ($P=0.74$) (Table 3).

Table 2: Distribution of RCC subjects (frequency,%) with and without diabetes according to the ethnicity and gender.

Ethnic group	RCC Cases Gender ^a			RCC+diabetes Cases Gender ^b			% RCC with DM ^c
	F	M	Total (%)	F	M	Total (%)	
Hispanic	131 (43.4)	171 (56.6)	302 (63.9)	46 (51.1)	44 (48.9)	90 (75)	29.8
White	60 (44.1)	76 (55.9)	136 (28.7)	14 (60.9)	9 (39.1)	23 (19.2)	16.9
Other	13 (37.4)	22 (62.9)	35 (7.4)	4 (57.1)	3 (42.9)	7 (5.8)	20.0
Total	204 (43.1)	269 (56.9)	473 (100)	64 (53.3)	56 (46.7)	120 (100)	25.4

a. $P=0.76$ (gender vs ethnic group in RCC cases).

b. $P=0.76$ (gender vs ethnic group in diabetic RCC cases).

c. $P=0.01$ (unequal ethnic group proportions among diabetic RCC cases).

Table 3: Distribution of RCC and RCC+diabetic subjects according to age.

Age	RCC ^a			RCC+Diabetes ^b		
	Male	Female	Total (%)	Male	Female	Total
30-39	31	17	48 (10.3)	9	6	15 (12.5)
40-49	63	41	109 (22.3)	10	13	23 (19.2)
50-59	91	79	170 (36.4)	19	29	48 (40.0)
60-69	57	51	108 (23.1)	13	14	27 (22.5)
70-81	23	14	37 (7.9)	5	2	7 (5.8)
Total	265	202	467 (100)	56	64	120 (100)
HgA1C average (%) ^c				7.7±0.37	7.5±0.45	7.59±0.30
Creatinine average (ng/dl) ^d				1.42±0.20	1.06±0.14	1.22±0.12
Glucose (mg/dL) ^e				146.6±10.2	146.9±9.4	146.8±6.9

a. $P=0.45$ (gender vs age group for RCC cases).

b. $P=0.57$ (gender vs age group for DM cases).

c. $P=0.73$ (ANOVA, mean +/- SE).

d. $P=0.14$ (ANOVA, mean +/- SE).

e. $P=0.74$ (ANOVA, mean +/- SE).

Next the RCC with DM cases (n=113) were analyzed for tumor morphology and size (Table 4). In this cohort, clear cell type (104/113, 92.0%), nuclear grade 2 (60/107, 56.1%) and 1-5 cm tumor size (65/99, 65.7%) were more predominant among all tumors. Analysis of the distribution of histological cell types among ethnic groups found significant differences (P=0.01) existed (Table 4) primarily in papillary cell type. Cell chi-square statistical results showed decreased papillary cell type in Hispanics whereas it increased in Whites (4/7). On the other hand, no difference in the distribution of nuclear grades (P=0.55) was observed across ethnic groups. The distribution of tumor size was significantly different (P=0.03) among ethnic groups due to decreased frequency of small (1-5 cm) and increased frequency of medium (>5-10 cm) tumors in the Other ethnic group (Table 4). Interestingly, average of HgA1C was significantly higher (P=0.05) in Hispanic patients compared to Whites and Other ethnicities (Table 4) by the least significant difference (LSD) pairwise comparison test following a one-way ANOVA. Blood glucose and creatinine mean values were not significantly different for the ethnic groups (P=0.84 and P=0.88, respectively).

To identify the association between tumor sizes within the RCC diabetic cohort, we analyzed all RCC

diabetic subjects for tumor size and diabetic parameters. Data in Table 5 show that total of 65 cases have tumor size 1-5 cm, 31 cases with >5-10 cm and 3 cases with >10cm. Interestingly, the average of HgA1C was significantly higher (8.1, P=0.05) in patients with tumor size 1-5 cm compared to tumor size >5-10 cm (Table 5). In addition, the average of glucose level was slightly higher in patients with tumor size of 1-5 cm; however, significant differences among the tumor size groups for serum glucose and creatinine were not detected (Table 5).

The association between tumor stage, HgA1C, creatinine and glucose levels among all ethnic groups is shown in Table 6. Among all ethnic groups, tumor stage I was the predominant stage (79/109, 72.5%) compared to advanced stage III (22/109, 20.2%) and IV (5/109, 4.6%) (Table 6). Interestingly, the HgA1C average (8.2) was higher in patients with tumor stage IV compared to patients with other tumor stages, although this was not statistically significant. In addition, tumor stage was significantly associated with the ethnicity (P=0.03) due to small frequency differences (Whites had decreased Stage III and Others had increased Stage II), whereas no significant association was identified between creatinine and glucose levels and tumor stages (Table 6).

Table 4: Distribution of RCC diabetic subjects according to cell type, nuclear grade, tumor size and HgA1C.

Ethnicity	Hispanic	White	Other	Total (%)
Number	86	20	7	113(100)
Histological Cell type				
Clear cell	83	16	5	104 (92.0) ^a
Papillary	2	4	1	7 (6.2)
Chromophobe	1	0	1	2 (1.8)
Nuclear grade				
1	19	4	0	23 (21.5)
2	45	12	3	60 (56.1) ^b
3	14	3	3	20(18.7)
4	3	1	0	4 (3.7)
Tumor size				
1-5 cm	54	11	0	65 (65.7)
>5-10 cm	23	4	4	31 (31.3) ^c
>10 cm	3	0	0	3 (3.0)
HgA1C average^d	8.0	6.1	6.3	
Glucose^e	148.4	146.1	131.4	
Creatinine^f	1.2	1.3	1.1	

a. P=0.01 (Ethnicity vs cell type).

b. P=0.55 (Ethnicity vs nuclear grade).

c. P=0.03 (Ethnicity vs tumor size.)

d. P=0.05 (for Hispanics vs Whites following ANOVA with p=0.11).

e. P=0.84 (ANOVA).

f. P=0.88 (ANOVA).

Table 5: Association of tumor size with diabetic parameters.

Tumor size ^a	Hispanic	White	Other	Total (%)	HgA1C ^b	Creatinine ^c	Glucose ^d
1-5 cm	54	11	0	65 (65.7)	8.1	1.10	148.7
>5-10 cm	23	4	4	31 (31.3)	6.7	1.34	146.6
>10 cm	3	0	0	3 (3.0)	5.5	0.95	85.0

a. P=0.03 (Ethnicity vs tumor size).

b. P=0.11, ANOVA, but only 1-5 cm vs >5-10 cm p=0.05; 1-5 cm vs >10 cm p=0.30.

c. P=0.68 (ANOVA).

d. P=0.49 (ANOVA).

Table 6: Association of tumor stage with diabetic parameters.

Tumor stage ^a	Hispanic	White	Other	Total (%)	HgA1C ^b	Creatinine ^c	Glucose (mg/dL) ^d
I	60	16	3	79 (72.5)	7.61	1.18	148.3
II	1	1	1	3 (2.7)	5.90	1.15	107.5
III	21	0	1	22 (20.2)	7.66	1.14	147.2
IV	4	1	0	5 (4.6)	8.20	0.73	144.0
Total	86	18	5	109 (100)			

a. P=0.03 (Ethnicity vs tumor stage).

b. P=0.90 (ANOVA).

c. P=0.91 (ANOVA).

d. P=0.90 (ANOVA).

4. Discussion

This is the first report to characterize RCC cases in a South Texas population with respect to ethnicity, age, gender, laboratory parameters and tumor morphology. Our data indicate that a high proportion of RCC cases are associated with diabetes (25.4%), suggesting that diabetes one of the factors for the development of RCC. At our institution, when RCC subjects were screened for a history of diabetes, we observed a higher incidence of diabetes in female RCC subjects compared to male subjects. RCC cases with diabetes were also more prevalent in Hispanics compared to White and Other subjects and the majority of diabetic patients were diagnosed with RCC at 50-59 years of age. In addition, diabetic RCC patients had a predominance of the clear cell type RCC, nuclear grade II, tumor size 1-5 cm and tumor stage I. The average HgA1C level was significantly higher in Hispanic patients compared to Whites and Other ethnicities. Moreover, the average HgA1C level was higher in patients with tumors size 1-5 compared to those >5-10 cm. The high incidence of localized cancer may be largely due to the increased incidental detection of RCC through the ultrasound and CT for non-renal cancer-related problems [22-24].

RCC is the most common renal malignancy in adults, with a greater incidence in males than females and average age at diagnosis in the early 60s [25].

Similarly, the incidence of RCC was predominated in males dominant age range at presentation being 50-59 years. This is slightly younger than the mean age of presentation reported by most case series and may be due to early detection within our population. A similar age range was observed in our RCC cases with diabetes; however, females were more prevalent, consistent with other series. In a previous study, a prior history of diabetes was associated with a three-fold increase in the relative risk for renal cancer in women [21]. These findings indicate that the gender distribution of diabetic RCC is different from its nondiabetic counterpart, suggesting that there may also be differences in the biology of RCC in these patients.

Adult RCC has been demonstrated to have a slightly greater incidence in African Americans than in Whites [26]. Our data shows that the majority of RCC patients with or without a history of diabetes have Hispanic backgrounds. Few studies have examined cancer in U.S. Hispanics, and results showed that the incidence of kidney cancer varies depending on the geographic location of the Hispanic population analyzed [27,28]. In South Texas, Hispanics comprise a large portion of the population and the prevalence rate of diabetes in Mexican Americans is 1.9 fold higher than that in non-Hispanic Whites. Moreover, our study supports the observation that Hispanics have higher HgA1C levels than non-Hispanic Whites

[29]. In epidemiological and autopsy studies, elevated fasting serum glucose and diabetes were risk factors for the development of cancer in several organs including kidney [18] and the risk of cancer has been reported to increase in proportion to HgA1C levels in diabetes [13,14].

Several studies showed that Hispanics population have higher prevalence of obesity, type 2 diabetes, and high fat diet than non-Hispanic Whites [27,29,30]. These factors may play a major role in increase the incidence RCC There is evidence of a positive association between obesity and risk of RCC [31,32]. We could not differentiate the type of DM, although most cases among adults would be expected to be type 2. Laboratory values were obtained near the time of nephrectomy and represented the fasting glucose levels of all patients but lacked information regarding the body mass index, duration of diabetes, follow up the laboratory values and treatment. Such information is important for determining whether the severity and duration of diabetes is correlated with risk of developing RCC. Nevertheless, our findings showed that HgA1C values were significantly higher in patients with tumors 1-5 cm compared to >5-10 cm, suggesting that HgA1C may provide a useful marker for early detection of silent or small RCC before they manifest clinically. Serum glucose or creatinine levels were not associated with tumor size or stage. In previous studies, the incidence of end-stage renal disease due to DM was higher in minorities including Hispanics [30]; however, in our cohort, little or no increase in serum creatinine was observed at the time of nephrectomy.

The predominant subtype of RCC is clear cell type that represents 80% of RCC and is derived from the tubular epithelium [10]. Our data show that majority of tumors (92%, $P=0.01$) was clear cell type among all ethnic groups in RCC diabetic patients suggesting that diabetes may involve an increased risk of development of clear cell tumor. Recent work in the molecular pathogenesis of clear cell RCC has facilitated the development of therapeutic strategies to target this tumor type. However, few studies have examined who is at increased risk for this histologic variant. Obesity is associated with a higher risk of clear cell RCC than with other histologies [6,12,32]. Our results provide the first evidence that diabetic RCC patients have a predominance of clear cell subtype with nuclear grade 2. In 98% of these tumors, whether familial, sporadic or associated with Von Hippel-Lindau (VHL) syndrome, they typically result from a somatic mutation within the VHL tumor-suppressor gene found on the short arm of chromosome 3 3p25 [18, 19, 32]. Mutation of VHL

activates hypoxia-inducible factor-1 (HIF-1), leading to increased transcription of pro-angiogenic factors including PDGF and VEGF that play a key role in renal cell tumorigenesis. In diabetic patients, other pathogenetic mechanisms previously described may also contribute to clear cell RCC including: prolonged exposure to pro-insulin products with some homology to IGF-1, raised growth factors and growth factor receptors, increased endogenous estrogen levels, end-stage renal disease due to diabetic nephropathy and hypertension [5]. Interestingly, histologic type varied among ethnic groups, with papillary cell type increased in Whites, but decreased in Hispanics. Perhaps this reflects differences in the tumor biology or genetics in various ethnic groups.

The incidence of all stages of kidney cancer is increasing in the U.S., particularly T1 disease and primarily reflects small tumors discovered incidentally on abdominal imaging [33]. In agreement with this finding, our cohort of RCC cases with DM showed a predominance of tumor size 1-5 cm and, among all ethnic groups, stage I was more commonly observed than other stages. Tumor size and stage were associated with ethnicity as evidenced by a greater incidence of medium size (>5-10 cm) tumors and stage 2 in Other ethnicities and a reduction in stage 3 tumors in Whites. It is tempting to speculate that African Americans within the "Other" group, reported to have more aggressive disease than Whites, may have contributed to this ethnic diversity [33,34]. Tumor staging in adult RCC is a strong prognostic indicator and the presence of lower-stage tumors in DM patients suggests a favorable response to therapy and survival. Although HgA1C was slightly higher in patients with stage IV, we did not observe a statically significant association of HgA1C, blood glucose or creatinine with tumor stage. Further studies with larger cohorts of DM patients will be useful for increasing our understanding of the association of DM with clear cell RCC.

In conclusion, our findings indicate that diabetic RCC patients have a predominance of localized, small clear cell RCC. Prospective studies are needed to further evaluate the importance of glycemic control and effective reduction of glucose levels on the outcome of RCC. In addition, the results of our study may have implications in determining a patient's risk of harboring a clear cell RCC and subsequent therapeutic recommendations.

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Conflict of Interest

The authors have declared that no conflict of interest exists.

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