Diabetes and kidney cancer:
A direct or indirect association?

Rohit P. Ojha[1,2], Eva L. Evans[2], Tabatha N. Offutt-Powell[2], Bahij S. Nuwayhid[3], Zuber D. Mulla[3]

[1]Division of Population Sciences, Dana-Farber Cancer Institute/Harvard Cancer Center; Boston, MA.
[2]Department of Epidemiology, University of North Texas Health Science Center; Fort Worth, TX.
[3]Department of Obstetrics and Gynecology, Texas Tech University Health Sciences Center; El Paso, TX.

I. INTRODUCTION

- A positive association between diabetes and kidney cancer has been reported in several investigations, but it is unclear whether diabetes or its complications account for this association.
- Recent advances in estimating direct associations may be useful for elucidating the association between diabetes and kidney cancer.

OBJECTIVE

We evaluated whether the direct association between diabetes and kidney cancer is the primary concern in this exposure-outcome relation.

II. METHODS

Data source
- We used discharge data (2001) for patients admitted to hospitals throughout Florida for our case-control analysis.

Study population
- Cases and controls were identified using the International Classification of Diseases, 9th Rev., Clinical Modification (ICD-9-CM).
- Cases (*n*=1,909) were defined as inpatients aged ≥45 years with a primary discharge diagnosis of malignant kidney cancer.
- Controls (*n*=6,451) were defined as inpatients aged ≥45 years with a diagnosis of motor vehicle accident in any of their discharge diagnosis fields but did not have a primary or secondary diagnosis of malignant kidney cancer.

Exposure ascertainment
- Patients with a primary discharge diagnosis of diabetes mellitus were defined as having diabetes.

Data analysis
- Covariates that required adjustment to estimate the total and direct associations between diabetes and kidney cancer were identified in a directed acyclic graph (DAG) that encoded causal assumptions derived from current evidence regarding factors relevant to the relation between diabetes and kidney cancer.
- Our DAG (*Figure 1*) indicated that age, gender, ethnicity, obesity, and smoking constituted a minimal sufficient set of covariates for adjustment when estimating the total association between diabetes and kidney cancer, whereas additional conditioning on hypertension and kidney disease (intermediates) would yield an estimate of the controlled direct association between diabetes and kidney cancer.

- Unconditional logistic regression was used to estimate the adjusted total and direct odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of kidney cancer for diabetics.
  - Age in years was included as a categorical covariate in the model (45 – 49 [reference category], 50 – 59, 60 – 69, 70 – 79, ≥80) because of a non-linear relation as a continuous covariate.
  - Race/ethnicity was categorized as non-Hispanic White [reference category], non-Hispanic Black, Hispanic White, and Other.
  - Sex (male/female), diabetes (diabetic/not diabetic), obesity (obese/not obese), smoking (smoker/non-smoker), hypertension (hypertensive, not hypertensive), and renal failure (acute, chronic or unspecified/no renal failure) were incorporated in the model as dichotomous covariates.

III. RESULTS

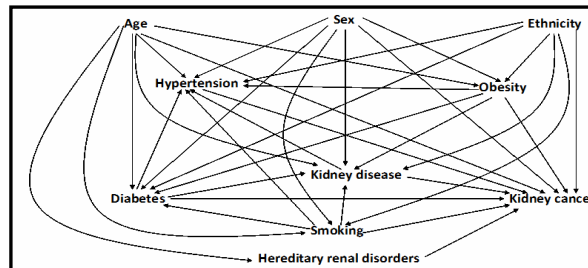*Figure 1. Proposed causal structure for the relation between diabetes and kidney cancer.*

Table 1. Demographic and clinical characteristics of kidney cancer cases and motor vehicle accident controls who were hospitalized throughout Florida and discharged in 2001.

Characteristic	Kidney Cancer Cases (n=1,909)	Motor Vehicle Accident Controls (n=6,451)
Age in years†, n (%)		
45 to 49	142 (7.4)	1,145 (17.8)
50 to 59	410 (21.5)	1,792 (27.8)
60 to 69	529 (27.7)	1,220 (18.9)
70 to 79	573 (30.0)	1,335 (20.7)
≥80	255 (13.4)	959 (14.9)
Race/ethnicity, n (%)		
Non-Hispanic White	1,565 (82.0)	4,763 (73.8)
Non-Hispanic Black	142 (7.4)	719 (11.2)
Hispanic White	167 (8.8)	750 (11.6)
Other	35 (1.8)	219 (3.4)
Sex, n (%)		
Female	693 (36.3)	2,995 (46.4)
Male	1,216 (63.7)	3,456 (53.6)
Diabetic, n (%)	337 (17.7)	813 (12.6)
Obese, n (%)	92 (4.8)	143 (2.2)
Smoker, n (%)	256 (13.4)	535 (8.3)
Hypertensive, n (%)	1,011 (53.0)	2,113 (32.8)
Renal failure (acute, chronic, or unspecified), n (%)	119 (6.2)	55 (0.9)

† Patients under age 45 years were excluded from the analyses.

IV. DISCUSSION

Table 2. Odds ratios for the type of association between diabetes and kidney cancer among patients aged ≥45 years discharged from Florida hospitals in 2001.

Type of association	Covariates adjusted	Odds ratio	95% CI	P-value
Crude	None	1.49	1.29 – 1.71	<0.0001
Total	Age, sex, race/ethnicity, obesity, smoking	1.27	1.10 – 1.47	0.001
Direct	Age, sex, race/ethnicity, obesity, smoking, hypertension, renal failure	1.08	0.93 – 1.25	0.34

Note: CI: Confidence interval

- The results of our case-control analyses indicate that inpatients discharged with a diabetes diagnosis have a 27% greater odds of kidney cancer than inpatients discharged without a diabetes diagnosis, which is generally consistent with previous studies in direction and magnitude regarding the total association between diabetes and kidney cancer.
- However, our results for the direct association indicate only an 8% greater odds of kidney cancer among diabetics. An estimate of the direct association has not been previously reported in the literature.
- We recognized *a priori* that our estimates would be susceptible to Berkson's bias because of our hospital-based case-control design and thus our estimates would likely be biased toward the null. We used data from patients with motor vehicle accident discharge diagnoses as the control group because of greater probability that they may represent the base population (the prevalence of diabetes in this group was closest to the Florida population).
  - *Sensitivity analysis*: We evaluated the impact of control selection on the estimates by re-analyzing our data using alternate control groups and observed considerable variation (range: OR=0.99 – 1.34) in the total association when patients with fractures, mental disorders, or asthma constituted the control groups.

CONCLUSIONS

- Our findings provide preliminary insight that the direct association between diabetes and kidney cancer may not be the primary concern in this exposure-outcome relation; indirect pathways (i.e. diabetic complications) may have greater influence on this relation.
- A similar analysis using longitudinal data with appropriately measured covariates may provide more definitive conclusions and could have implications for kidney cancer prevention among diabetics.