Type 2 Diabetes in Relation to the Risk of Renal Cell Carcinoma Among Men and Women in Two Large Prospective Cohort Studies

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

We assessed whether type 2 diabetes is associated with renal cell carcinoma (RCC), independent of key potential confounders, in two large prospective cohorts with biennially updated covariate data.

RESEARCH DESIGN AND METHODS

A total of 117,570 women from the Nurses' Health Study (NHS) and 48,866 men from the Health Professionals Follow-Up Study (HPFS) were followed from 1976 and 1986, respectively, through 2014. Multivariable Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% CIs for associations between type 2 diabetes and pathology-confirmed RCC, overall and by stage, grade, and histologic subtype.

RESULTS

During 38 years of follow-up in the NHS, we confirmed 418 RCC case subjects, including 120 fatal cases. Over 28 years in the HPFS, we confirmed 302 RCC case subjects, including 87 fatal cases. Women with type 2 diabetes had a significantly increased risk of RCC compared with women without type 2 diabetes (multivariable HR 1.53; 95% CI 1.14–2.04), with some evidence that the association was stronger for ≤5 (HR 2.15; 95% CI 1.44–3.23) than >5 (HR 1.22; 95% CI 0.84–1.78) years' duration of type 2 diabetes ($P_{difference}$ 0.03). Among men, type 2 diabetes was not associated with total RCC (HR 0.89; 95% CI 0.56–1.41) or with RCC defined by stage, grade, or subtype. Sample sizes for analyses by stage, grade, and subtype were limited.

CONCLUSIONS

We found that type 2 diabetes was independently associated with a greater risk of RCC in women but not in men.

Type 2 diabetes has been associated with increased incidence and poor oncologic outcomes across numerous cancers (1,2). Studies evaluating the association between type 2 diabetes and the risk of renal cell carcinoma (RCC) have yielded conflicting results. Given that there has been a steady rise in the incidence of type 2 diabetes and RCC in the U.S., understanding their association is imperative (3).

Because hypertension and obesity are established risk factors for RCC and are also strongly linked with type 2 diabetes, accounting for these conditions in evaluating the association of type 2 diabetes and RCC is critical. However, few studies evaluating this relationship have adjusted for these important confounders (4,5). A recent

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meta-analysis of 11 cohort and 7 case-control studies found a modest positive association between diabetes and kidney cancer. Only five, however, adjusted for obesity and only two for history of hypertension (5). The studies also varied in the ascertainment of diabetes status (physician-confirmed vs. self-reported), inclusion of patients with type 1 diabetes, and use of RCC versus total kidney cancer as the outcome. The independent association between type 2 diabetes and RCC thus remains unclear.

We previously reported that type 2 diabetes was associated with a 60% increased risk of RCC in women in the Nurses' Health Study (NHS) (6). In the current study, we sought to update the analysis in the NHS with additional follow-up time and cases and to replicate the analysis in a cohort of men from the Health Professionals Follow-Up Study (HPFS). We hypothesized that type 2 diabetes is associated with greater risks of both total and fatal RCC among women and men, independent of obesity, hypertension, and smoking.

RESEARCH DESIGN AND METHODS

Study Populations

The prospective NHS was established in 1976 when 121,701 female nurses age 30–55 years answered a baseline questionnaire concerning their medical histories and risk factors relating to chronic disease. In 1986, the HPFS enrolled 51,529 male medical professionals age 40–75 years who responded to a similar questionnaire. Since baseline, follow-up questionnaires have been sent every 2 years to update information on lifestyle factors and new disease diagnoses.

For this study, we excluded participants who reported cancer other than nonmelanoma skin cancer at baseline (NHS/HPFS: n = 3,290/2,077) and individuals with type 1 diabetes (554/351), diabetes before the age of 30 years (112/17), or missing date of diabetes diagnosis (0/181). Lastly, we excluded participants missing date of birth (175/36) and one individual (from the HPFS) with concomitant upper-tract transitional cell carcinoma. Our final study population included 117,570 participants in the NHS and 48,866 participants in the HPFS.

The NHS and HPFS were approved by the institutional review boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health (Boston, MA).

Ascertainment of Type 2 Diabetes

On baseline and all subsequent biennial questionnaires, we asked participants whether they had been diagnosed with either type 1 or type 2 diabetes by a physician. Participants with self-reported diabetes provided additional information about diagnostic symptoms, tests, and treatments. Participants diagnosed before 1998 were considered to have "definite" type 2 diabetes if they met the National Diabetes Data Group (NDDG) Criteria (7) and, after 1998, if they met the American Diabetes Association criteria (8). "Probable" type 2 diabetes was defined as self-reported diabetes plus at least one of the following: *1*) elevated random plasma glucose or elevated glucose after fasting and oral glucose testing, *2*) drug therapy, or *3*) classic symptoms and positive urine dipstick for glucose. "Definite" type 2 diabetes was used as the exposure definition for our main analyses, and "probable" type 2 diabetes was included in sensitivity analyses. The validity of supplementary questionnaires to confirm and characterize diabetes type has previously been evaluated in random subsamples of NHS and HPFS participants (9,10).

Ascertainment of RCC and Death

Self-reported RCC diagnosis was ascertained on each biennial questionnaire. Pathology-confirmed diagnoses of RCC were considered case subjects. We included clear cell, papillary, chromophobe, collecting duct, and unspecified RCC histologies and excluded oncocytoma (11). TNM stage (2010 criteria) and Fuhrman grade (1–4) or differentiation (well, moderately, poorly, and undifferentiated) were obtained from pathology reports.

Deaths were identified by reports from family members in response to follow-up questionnaires, postal authorities, and the National Death Index (NDI), and cause of death was assigned by an end points committee based on review of all available medical and autopsy reports. Participants with RCC-specific deaths were considered fatal RCC case subjects in these analyses. Follow-up for mortality in these study populations was roughly 98% (12).

Statistical Analysis

We treated type 2 diabetes as a time-dependent exposure, wherein individuals contributed non–type 2 diabetes person-time prior to type 2 diabetes diagnosis and type 2 diabetes person-time after diagnosis. Person-time was calculated from the return date of the baseline questionnaire until the first of RCC diagnosis, death from any cause, or end of follow-up (June 2014 in NHS and January 2014 in HPFS).

We used Cox proportional hazards models stratified by age and calendar time to evaluate associations of type 2 diabetes with total and fatal RCC (using the diagnosis date of RCC that went on to become fatal as the event date). Multivariable models were adjusted for BMI (<23, 23 to <25, 25 to <27, or ≥ 27 kg/m^2), history of hypertension (yes or no), smoking status (never, past, or current), pack-years (continuous), physical activity (quartiles of MET h/week, assessed beginning in 1986 for the NHS), duration of non-aspirin nonsteroidal anti-inflammatory drug use (<5 years or ≥ 5 years, assessed beginning in 1990 for the NHS), parity (0, 1–2, 3, or ≥ 4 children [NHS only]), and alcohol intake (by quartiles, assessed beginning in 1980 for the NHS). All covariates, other than parity, were updated in each questionnaire cycle; pregnancy information was updated until 1996. In sensitivity analyses, with adjustment for BMI as a continuous variable and for race and fruit and vegetable intake, results were essentially unchanged compared with the multivariable models presented herein. Results from simple and multivariable models were combined across the NHS and HPFS with random effects meta-analysis.

Next, we evaluated whether type 2 diabetes was uniquely associated with RCC defined by histologic subtype (clear cell or non–clear cell), pathologic stage (localized or advanced), and grade (low-grade: Fuhrman grade 1–2 or well/moderately differentiated, or high-grade: Fuhrman grade 3–4 or poorly/nondifferentiated) (13). Heterogeneity tests were performed to evaluate differences across RCC subtypes. We assessed the risk of RCC relative to duration of diabetes as a marker of overall duration of exposure to elevated insulin levels. We also conducted analyses stratified by hypertension and BMI (both of which are highly associated with type 2 diabetes and established risk factors for RCC) and tested for interaction using likelihood ratio tests comparing models with and without a cross-product term between diabetes and the stratification variable.

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In sensitivity analyses, we updated covariates until the time of diabetes diagnosis (if any) and held them steady thereafter. We also explored confounding by imaging frequency by stratifying by time period (before 1994 vs. 1994 and beyond). Because the inclusion of prevalent type 2 diabetes at baseline may induce bias, we also ran models including only incident type 2 diabetes (14). Lastly, we excluded RCC case subjects diagnosed within the first 2 years after a type 2 diabetes diagnosis to address possible detection bias or increased medical surveillance after a type 2 diabetes diagnosis.

Statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC). All *P* values were two tailed; $P < 0.05$ was considered statistically significant.

RESULTS

At baseline in 1976, 0.72% of women had type 2 diabetes, increasing to 12% by the end of follow-up. At baseline among men in 1986, 1.3% had type 2 diabetes, increasing to 9.4% by the end of follow-up. Table 1 describes the age-adjusted characteristics of the NHS and HPFS cohorts according to diabetes status in 1994, partway through follow-up, when 4.7% of women and 3.4% of men had type 2 diabetes. Individuals with type 2 diabetes in both cohorts had higher BMI and prevalence of hypertension, were less physically active, and consumed less alcohol. In the NHS, smoking patterns were similar for women with and without type 2 diabetes. In the HPFS, men with type 2 diabetes were less likely to be never smokers.

During 38 years of follow-up in the NHS, there were 418 incident RCC case subjects, including 120 fatal cases (Table 2). Women with type 2 diabetes had a statistically significant greater risk of developing RCC than women without type 2 diabetes (multivariable hazard ratio [HR] 1.53; 95% CI 1.14–2.04). The HR was nonsignificant for fatal RCC (HR 1.35; 95% CI 0.72–2.55). During 28 years of follow-up in the HPFS, there were 302 incident RCC case subjects, including 87 fatal cases. Men with type 2 diabetes did not have a greater risk of total RCC (HR 0.89; 95% CI 0.56–1.41) or fatal RCC (HR 1.23; 95% CI 0.54–2.76). Numbers of RCC case subjects diagnosed after each number of years since diabetes diagnosis are summarized in Supplementary Table 1. In both cohorts, adjustment for hypertension accounted for the largest portion of the difference between the age-adjusted and fully adjusted estimates (data not shown).

Table 1—Age-adjusted characteristics of study participants in 1994 according to type 2 diabetes status

	Women (NHS)		Men (HPFS)	
	No Diabetes	Diabetes	No Diabetes	Diabetes
Number	105,979	5,265	44,786	1,594
Age, years*	60.6 (7.2)	63.4 (6.5)	61.6 (9.6)	66.6 (8.5)
Duration of type 2 diabetes, years	—	8.6 (7.1)	—	6.7 (6.6)
Caucasian	93.8	90.6	95.6	92.1
BMI, continuous, kg/m^2	26.1 (5.1)	31.4 (6.4)	25.9 (3.6)	28.5 (5.0)
BMI, categorical, kg/m^2				
<25	48.1	14.5	41.9	24.3
25–29.9	32.7	31.2	47.2	46.2
≥30	19.2	54.3	10.9	29.6
History of hypertension	35.3	71.8	31.8	56.4
Smoking status				
Never	43.3	44.7	46.8	38.1
Former	40.9	41.6	45.7	53.2
Current	15.9	13.7	7.5	8.7
Pack-years of smoking†	24.9 (21.0)	27.0 (22.1)	25.0 (19.5)	29.2 (20.9)
Physical activity, MET h/week	17.3 (24.0)	13.3 (20.5)	29.6 (29.9)	21.9 (24.5)
Regular use of nonaspirin NSAIDs	32.7	29.5	11.0	9.7
Parity (no. of children)	3.2 (1.5)	3.2 (1.6)	—	—
Alcohol intake, g/day	5.2 (9.4)	2.1 (6.9)	11.0 (14.9)	7.5 (13.1)
Fruit intake, servings/day	2.3 (1.2)	2.4 (1.2)	2.5 (1.5)	2.5 (1.4)
Vegetable intake, servings/day	2.9 (1.3)	2.9 (1.3)	3.2 (1.6)	3.4 (1.7)

Data are percentages or means (SD) unless otherwise indicated. Percentages may not add up as expected as a result of rounding. NSAIDs, nonsteroidal anti-inflammatory drugs. *Not adjusted for age. †For the HPFS, calculated among 22,939 ever smokers without type 2 diabetes and 992 ever smokers with type 2 diabetes; for the NHS, calculated among 59,993 ever smokers without type 2 diabetes and 2,900 ever smokers with type 2 diabetes.

Sensitivity analyses in which covariates were only updated until the time of diabetes diagnosis (if any) yielded materially similar results (Supplementary Table 2). Analyses stratified by time period, excluding case subjects with prevalent type 2 diabetes, and those including case subjects with "probable" type 2 diabetes along with case subjects with "definite" diabetes also yielded largely similar results (data not shown). Exclusion of case subjects diagnosed within the first 2 years after a type 2 diabetes diagnosis attenuated the association between type 2 diabetes and risk of RCC in the NHS (HR 1.29; 95% CI 0.94–1.76). It did not materially change results in the HPFS (HR 0.85; 95% CI 0.53–1.35).

A meta-analysis of the NHS and HPFS results did not yield evidence of an association between type 2 diabetes and risk of RCC (HR 1.20; 95% CI 0.71–2.03; $P_{heterogeneity}$ 0.05) or fatal RCC (HR 1.30; 95% CI 0.79–2.15; $P_{heterogeneity}$ 0.85). Because of heterogeneity in the results for RCC risk across the two cohorts, we present the remaining analyses stratified by sex.

In the NHS, analyses of RCC by histologic subtype suggested a stronger association for type 2 diabetes with non–clear cell RCC (HR 2.68; 95% CI 1.32–5.44) than with clear cell RCC (HR 1.35; 95% CI 0.94–1.93) ($P_{difference}$ 0.09) (Table 2). Tests for heterogeneity across RCC pathologic characteristics defined by stage and differentiation were not significant. However, type 2 diabetes was significantly associated with risk of low-grade and localized disease. In the HPFS, there were no significant associations between type 2 diabetes status and risk of RCC according to histologic subtype, stage, or differentiation.

Relative to women without type 2 diabetes, women with a duration of type 2 diabetes ≤5 years showed a statistically significant association with RCC risk (HR 2.15; 95% CI 1.44–3.23), while women with a duration >5 years did not (HR 1.22; 95% CI 0.84–1.78) ($P_{difference}$ = 0.03) (Table 3). Among men, there was no association for either duration category. We found

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Table 2—HRs and 95% CIs for associations between type 2 diabetes and risk of various RCC outcomes from the NHS (1976–2014) and HPFS (1986–2014)

	Women (NHS)			Men (HPFS)		
	No. of RCC case subjects without diabetes/with diabetes	Age-adjusted HR (95% CI)*	Multivariable HR (95% CI)†	No. of RCC case subjects without diabetes/with diabetes	Age-adjusted HR (95% CI)*	Multivariable HR (95% CI)†
RCC	359/59	2.15 (1.62–2.84)	1.53 (1.14–2.04)	281/21	1.20 (0.76–1.88)	0.89 (0.56–1.41)
Fatal RCC	108/12	1.86 (1.02–3.42)	1.35 (0.72–2.55)	80/7	1.76 (0.80–3.89)	1.23 (0.54–2.76)
Histology						
Clear cell RCC	249/39	1.93 (1.37–2.73)	1.35 (0.94–1.93)	168/17	1.73 (1.04–2.88)	1.29 (0.77–2.17)
Non–clear cell RCC	44/11	3.10 (1.58–6.07)	2.68 (1.32–5.44)	52/4	0.98 (0.35–2.75)	0.72 (0.25–2.05)
$P_{difference}$		0.22	0.09		0.33	0.32
Pathologic stage‡						
Localized RCC	168/33	2.32 (1.59–3.40)	1.72 (1.15–2.55)	138/8	0.84 (0.41–1.73)	0.64 (0.31–1.32)
Advanced RCC	179/25	2.05 (1.33–3.14)	1.44 (0.92–2.24)	134/13	1.78 (0.99–3.20)	1.28 (0.70–2.33)
$P_{difference}$		0.66	0.56		0.11	0.15
Differentiation§						
Low-grade	169/30	2.04 (1.37–3.02)	1.47 (0.97–2.21)	111/9	1.22 (0.62–2.44)	0.92 (0.46–1.86)
High-grade	73 / 17	2.58 (1.50–4.42)	2.07 (1.17–3.66)	70/6	1.24 (0.53–2.89)	0.89 (0.37–2.12)
$P_{difference}$		0.49	0.34		0.98	0.95

*Adjusted for age and calendar time. †Additionally adjusted for BMI (<23, 23 to <25, 25 to <27, or ≥27 kg/m^2), history of hypertension (yes or no), smoking status (never, past, or current), pack-years (continuous), physical activity (quartiles of MET h/week), duration of nonaspirin nonsteroidal anti-inflammatory drug use (<5 years or ≥5 years), parity (NHS only) (0, 1–2, 3, or ≥4 children), and alcohol intake (quartiles). ‡Localized, pT1N0M0 at diagnosis and not fatal; advanced, pT2-4NxMx, TxN1Mx, or TxNxM1 at diagnosis and/or fatal. §Low-grade: well/moderately differentiated or Fuhrman grade 1–2; high-grade: poorly/undifferentiated RCC or Fuhrman grade 3–4.

no statistically significant interactions between type 2 diabetes and hypertension or obesity (Table 4). However, power was low for these analyses, particularly for the type 2 diabetes–RCC association among those without hypertension.

CONCLUSIONS

In this large prospective study, we found that type 2 diabetes was associated with a significantly greater risk of RCC in women, independent of obesity, hypertension, and smoking. The association was strongest for non–clear cell RCC. Type 2 diabetes was not significantly associated with risk of fatal RCC in women or with overall or fatal RCC in men.

A meta-analysis of 18 studies found a positive association between diabetes and kidney cancer (relative risk [RR] 1.40; 95% CI 1.16–1.69) (5). Among studies that looked separately by sex, there was a significant positive relationship among both women (RR 1.47; 95% CI 1.18–1.83 [10 studies]) and men (RR 1.28; 95% CI 1.10–1.48 [11 studies]). However, only 8 of the 18 studies focused on RCC alone, only 7 restricted to type 2 diabetes, and only 2 controlled for obesity/BMI, hypertension, and smoking. A recent prospective cohort study including 249 case subjects found a nonsignificant association between diabetes and RCC after adjustment for BMI, hypertension, smoking, and other risk factors; its HR of 1.39 (95% CI 0.92–2.09) was the same as that seen in the meta-analysis. However, the study did not present results by sex (4).

It is possible that our results suggest underlying biologic differences by which type 2 diabetes affects RCC risk for women and men. Men are at greater risk of RCC than women, with a 2:1 male:female incidence ratio observed consistently over time and across geographical regions that does not seem to be explained by differences in prevalence of known risk

Table 3—HRs and 95% CIs for associations between duration of type 2 diabetes and risk of RCC from the NHS (1976–2014) and HPFS (1986–2014)

	Women (NHS)			Men (HPFS)		
	No. of RCC case subjects	Age-adjusted HR (95% CI)*	Multivariable HR (95% CI)†	No. of RCC case subjects	Age-adjusted HR (95% CI)*	Multivariable HR (95% CI)†
No type 2 diabetes	359	1.00 (ref)	1.00 (ref)	281	1.00 (ref)	1.00 (ref)
Diabetes duration ≤5 years	27	3.09 (2.08–4.59)	2.15 (1.44–3.23)	6	0.96 (0.42–2.16)	0.70 (0.31–1.60)
Diabetes duration >5 years	32	1.70 (1.18–2.46)	1.22 (0.84–1.78)	15	1.34 (0.79–2.27)	1.00 (0.59–1.71)
P_{trend}‡		0.001	0.21		0.29	0.92
$P_{difference}$§		0.03	0.03		0.49	0.47

*Adjusted for age and calendar time. †Additionally adjusted for BMI (<23, 23 to <25, 25 to <27, or ≥27 kg/m^2), history of hypertension (yes or no), smoking status (never, past, or current), pack-years (continuous), physical activity (quartiles of MET h/week), duration of nonaspirin nonsteroidal anti-inflammatory drug use (<5 years or ≥5 years), parity (NHS only) (0, 1–2, 3, or ≥4 children), and alcohol intake (quartiles). ‡Based on a linear test for trend across categories of duration by modeling their median values as continuous variables. §Based on a χ^2 test for the difference between estimates for ≤5 years and >5 years.

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Table 4—HRs and 95% CI for associations between type 2 diabetes and risk of RCC stratified by hypertension and obesity status, NHS (1976–2014) and HPFS (1986–2014)

	Women (NHS)			Men (HPFS)		
	No. of RCC case subjects without diabetes/with diabetes	Age-adjusted HR (95% CI)*	Multivariable HR (95% CI)†	No. of RCC case subjects without diabetes/with diabetes	Age-adjusted HR (95% CI)*	Multivariable HR (95% CI)†
Hypertension						
No	136/4	1.28 (0.47–3.47)	1.14 (0.41–3.14)	111/5	1.45 (0.58–3.64)	1.18 (0.47–2.99)
Yes	223/55	1.80 (1.33–2.42)	1.51 (1.11–2.06)	170/16	0.97 (0.57–1.63)	0.90 (0.53–1.52)
$P_{interaction}$‡		0.43	0.37		0.43	0.46
Obesity						
BMI <30 kg/m^2	270/21	1.68 (1.07–2.64)	1.28 (0.80–2.02)	235/13	1.07 (0.61–1.89)	0.78 (0.44–1.38)
BMI ≥30 kg/m^2	89/38	1.96 (1.32–2.90)	1.58 (1.06–2.38)	46/8	1.36 (0.61–3.02)	1.31 (0.58–2.96)
$P_{interaction}$‡		0.52	0.29		0.78	0.63

*Adjusted for age and calendar time. †Additionally adjusted for BMI (models stratified by hypertension status: <23, 23 to <25, 25 to <27, ≥27 kg/m^2; models stratified by obesity status: continuous), history of hypertension (models stratified by obesity status only; yes, no), smoking status (never, past, current), pack-years (continuous), physical activity (quartiles of MET h/week), duration of nonaspirin nonsteroidal anti-inflammatory drug use (<5 years, ≥5 years), parity (NHS only; 0, 1–2, 3, ≥4 children), and alcohol intake (quartiles). ‡Based on likelihood ratio tests between models with and without an interaction term.

factors (15). Hormone-related exposures in women such as oral contraceptives (16) and postmenopausal hormone use (17) have been studied with respect to RCC risk with conflicting results (18). Further studies are needed to determine whether differences in the hormonal milieu interact with type 2 diabetes to affect RCC risk differently in women than in men. Interestingly, the meta-analysis of 18 studies found a slightly stronger association in women than in men (RR 1.47 vs. 1.28), but both associations were statistically significant (5). The above-mentioned limitations of the studies included in this meta-analysis make it difficult to draw clear conclusions about possible sex differences in the association.

Among women, the risk of RCC was significantly higher within the first 5 years after type 2 diabetes diagnosis. It is possible that the association between diabetes and RCC is due to detection bias, particularly given the attenuated association when we excluded RCC case subjects diagnosed within the first 2 years after type 2 diabetes diagnosis. There is evidence that a diagnosis of type 2 diabetes increases the chance of diagnosis of multiple cancer types owing to increased medical scrutiny (1). Alternatively, increased risk of RCC sooner after type 2 diabetes may be related to hyperinsulinemia that occurs early in the course of type 2 diabetes (19). Insulin promotes tumor cell mitosis and cell proliferation through insulin-like growth factor-1 activation (20). In the setting of insulin resistance, changes in adipocytes lead to induction of proinflammatory cytokines, which may cause DNA damage, leading to carcinogenesis (21). Indeed, RCC in individuals with type 2 diabetes has been shown to have more DNA alterations compared with RCC in patients without diabetes (22). However, it is unclear why these proposed mechanisms would play a role in women but not in men with diabetes.

We did not find evidence of an increased risk of fatal RCC for women or men with type 2 diabetes. A meta-analysis of eight cohort studies of diabetes and kidney cancer–specific mortality found a nonsignificant suggestion of increased risk among individuals with diabetes (RR 1.12; 95% CI 0.99–1.20), but the studies included upper-tract transitional cell carcinoma and type 1 diabetes, making interpretation difficult (5). Our results are consistent with three retrospective studies that found no difference in grade or pathologic stage (23–25) and no difference in survival among RCC patients with versus without type 2 diabetes (26). However, two retrospective surgical series (27,28) found that individuals with diabetes were more likely to present with high-grade RCC, and a meta-analysis of 18 studies (29), consisting primarily of retrospective surgical cohorts, found that patients with diabetes had worse overall, recurrence-free, and cancer-specific survival than patients without diabetes, although hypertension was not considered as a confounder.

Our study had several limitations. First, we had limited power for analyses of fatal RCC, RCC subgroups, and interactions. We were unable to control for chronic kidney disease, which is also a risk factor for RCC (30). Our cohort is comprised of primarily Caucasian participants and, as a result, our results need to be validated in a more diverse population of patients. Finally, we could not directly assess the severity of type 2 diabetes and/or glucose control and did not have reliable information on types of medications used (e.g., metformin). The strengths of the study include its prospective design, a large number of RCC case subjects compared with other published prospective studies, extensive follow-up, biennial ascertainment of important RCC risk factors, and repeated ascertainment and confirmation of type 2 diabetes diagnosis. Unlike most studies included in the previous meta-analysis, we were able to carefully adjust for hypertension, BMI, and smoking at baseline and over time. In addition, we were able to evaluate the duration of diabetes.

In conclusion, type 2 diabetes was associated with a significantly greater risk of RCC in women but was not associated with RCC in men. These associations were independent of obesity, hypertension, and other RCC risk factors. Additional studies in populations with adequate confounder information are needed to confirm our findings and to further explore possible sex differences in the association between type 2 diabetes and RCC.

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