Original Article

Kidney Cancer and Diabetes Mellitus: A Population-Based Case-Control Study in Taiwan

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Abstract

Introduction: The purpose of this study was to explore whether diabetes mellitus (DM) correlates with the risk of kidney cancer in Taiwan. Materials and Methods: We designed a population-based case-control study from the Taiwan National Health Insurance Database, which consisted of 116 patients with newly diagnosed kidney cancer as cases and 464 subjects without kidney cancer as controls in 2000 to 2009. Both cases and controls were aged ≥20 years. Baseline comorbidities were compared between kidney cancer cases and controls. Results: Multivariable analysis showed no association was detected between DM and kidney cancer (OR 1.06, 95% CI, 0.58 to 1.94). Hypertension (OR 2.05, 95% CI, 1.23 to 3.42), chronic kidney diseases (OR 2.57, 95% CI, 1.23 to 5.37), cystic kidney diseases (OR 18.6, 95% CI, 1.84 to 187.6) and kidney stones (OR 4.02, 95% CI, 2.43 to 6.66) were significant comorbidities associated with increased risk of kidney cancer. Use of alpha-glucosidase inhibitor was associated with increased risk of kidney cancer (OR 4.31, 95% CI, 1.07 to 17.3). Conclusion: DM does not correlate with the risk of kidney cancer. Hypertension, chronic kidney diseases, cystic kidney diseases, kidney stones and use of alpha-glucosidase inhibitors are associated with kidney cancer.

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Key words: Chronic kidney disease, Cystic kidney disease, Diabetes mellitus, Hypertension, Kidney cancer, Kidney stone

Introduction

Kidney cancer accounts for 3% to 4% of all cancers.[1] In a systematic review by Mathew and et al,[2] the incidence of kidney cancer was the highest in France (16.1 per 100,000 man-years) and the lowest in India (0.9 per 100,000 woman-years) during 1988 to 1992. A trend analysis in North America by Sun et al[3] showed that the age-adjusted incidence of renal cell carcinoma rose from 7.6 per 100,000 person-years in 1988 to 11.7 per 100,000 person-years in 2006. This incidence has been increasing substantially in the world, but varies markedly.[2,3] In Taiwan, kidney cancer was ranked the eighteenth leading cause of cancer death in 2010 and the current mortality rate was around 2.0 to 2.3 per 100,000 persons in 2006 to 2010.[4]

Kidney cancer includes renal cell carcinoma arising from renal parenchyma (accounting for 90% of kidney cancer), and transitional cell carcinoma arising from renal pelvis.[5,6] Although the real cause of kidney cancer remains unclear, to date, epidemiologic studies have shown that smoking, obesity, hypertension, end-stage renal disease, occupational

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exposure to chemical agents and genetic factors are risk factors that contribute to development of kidney cancer worldwide.[6-9] On the other hand, accumulating evidence has suggested that diabetes mellitus (DM) may affect the cancer risks of colon-rectum, liver and pancreas.[10,11] In 2 large cohort studies in Japan and in the United States, men with DM may have an increase of 1.1 to 1.9-fold risk of kidney cancer.[12,13] In a systematic review by Larsson et al,[14] DM might also increase 1.4-fold risk of kidney cancer (95% CI, 1.06 to 1.91), compared with non-diabetes.

There is no updated evidence about the association between DM and kidney cancer in Taiwan. Identifying the risk factors of kidney cancer is of importance to prevent this disease and further improve its prognosis. Therefore, we conducted this population-based case-control study using data from the National Health Insurance (NHI) programme in Taiwan to explore the following questions: (i) whether there is an association between DM and kidney cancer, (ii) the roles of other comorbidities on the risk of kidney cancer, (iii) the impact of anti-diabetic drugs on the risk of kidney cancer.

Materials and Methods

Data Sources

This case-control study used the research database of the NHI programme of Taiwan, which contains claims data of one million subjects randomly selected from all NHI beneficiaries. Details of the insurance programme and the research database can be found in previous studies.[15-18]

Design

This was a population-based case-control study. Cases were the subjects who were newly diagnosed with kidney cancer (renal cell carcinoma, ICD-9 189.0) during the period of 2000 to 2009 and aged 20 years and above at the date of diagnosis. The index date for each case was the date of diagnosis with kidney cancer, and we defined the index date of control subjects as the date of kidney cancer diagnosis of their corresponding cases. For each kidney cancer case, 4 controls were randomly selected from the same dataset, after excluding the subjects with kidney cancer, any other cancer (ICD-9 140-208) or kidney transplant (ICD-9 V42.0) before the index date. In order to explore the potential comorbidities associated with the risk of kidney cancer, we retrospectively screened the medical history for each subject. Comorbidities prior to the index date included are as follows: DM (ICD-9 250.xx), obesity (ICD-9 278.00, 278.01), hypertension (ICD-9 401-405), tobacco use (ICD-9 305.1), alcoholism (ICD-9 303, 305.00, 305.01, 305.02, 305.03 and V11.3), kidney infections (ICD-9 590.x), chronic kidney diseases (ICD-9 585, 586, 588.8 and 588.9), cystic kidney diseases (ICD-9 753.1x), and kidney stones (ICD-9 592.0, 592.1 and 592.9).

Table 1. Comparison by Sociodemographic Factors and Other Medical Conditions Between Kidney Cancer Cases and Controls

	Kidney cancer				*P* value
	No n = 464		Yes n = 116		
	n	(%)	n	(%)	
Sex					1.00
Women	192	(41.4)	48	(41.4)	
Men	272	(58.6)	68	(58.6)	
Age (Mean and SD, years)†	62.4	16.0	61.3	14.3	0.52
Comorbidities					
Diabetes mellitus	68	(14.7)	21	(18.1)	0.36
Obesity	1	(0.22)	2	(1.72)	0.04
Hypertension	194	(41.8)	69	(59.5)	0.0006
Tobacco use	4	(0.86)	3	(2.59)	0.13
Alcoholism	9	(1.94)	1	(0.86)	0.43
Kidney infections	28	(6.03)	14	(12.1)	0.02
Chronic kidney diseases	23	(4.96)	17	(14.7)	0.0002
Cystic kidney diseases	1	(0.22)	4	(3.45)	0.0008
Kidney stones	58	(12.5)	45	(38.8)	<0.0001

Data are presented as the number of subjects in each group, with percentages given in parentheses.
Chi-square test and †t test comparing patients with and without kidney cancer.

Table 2. Crude and Adjusted Odds Ratios and 95% Confidence Intervals of Kidney Cancer Associated with Diabetes and Covariates

Variable	Crude	Adjusted†	
	OR (95%CI)	OR (95%CI)	*P* value
Sex			
Women	1.00	1.00	
Men	1.00 (0.66-1.51)	0.83 (0.53-1.29)	0.41
Age (per one year)	0.99 (0.98-1.01)	0.98 (0.97-0.99)	0.03
Diabetes mellitus			
No	1.00	1.00	
Yes	1.29 (0.75-2.21)	1.06 (0.58-1.94)	0.86
Obesity			
No	1.00	1.00	
Yes	8.12 (0.73-90.4)	NIL	
Hypertension			
No	1.00	1.00	
Yes	2.04 (1.35-3.09)	2.05 (1.23-3.42)	0.006
Tobacco use			
No	1.00	1.00	
Yes	3.05 (0.67-13.8)	NIL	
Alcoholism			
No	1.00	1.00	
Yes	0.44 (0.06-3.51)	NIL	
Kidney infections			
No	1.00	1.00	
Yes	2.14 (1.09-4.21)	1.01 (0.47-2.18)	0.98
Chronic kidney diseases			
No	1.00	1.00	
Yes	3.29 (1.70-6.39)	2.57 (1.23-5.37)	0.01
Cystic kidney diseases			
No	1.00	1.00	
Yes	16.5 (1.83-149.2)	18.6 (1.84-187.6)	0.01
Kidney stones			
No	1.00	1.00	
Yes	4.44 (2.79-7.06)	4.02 (2.43-6.66)	<0.0001

†Adjusted for sex, age, diabetes mellitus, hypertension, kidney infections, chronic kidney diseases, cystic kidney diseases and kidney stones.
OR: odds ratio; CI: confidence interval

Statistical Analysis

We compared the differences in sex, age, and comorbidities between the kidney cancer cases and the controls using the chi-square test and t test. The significant variables were further included in the multivariable logistic regression analysis to measure odds ratio (OR) and 95% confidence interval (CI) for kidney cancer. The statistical significance level was set at probability value of <0.05 (SAS software version 9.1, SAS Institute Inc., Cary, North Carolina, USA).

Ethical Considerations

All types of personal identification on files connected with the present study were scrambled using surrogate identification numbers to secure patient privacy. The present study was exempted from a full review by the Institutional Review Board at College of Public Health, China Medical University.

Results

Baseline Characteristics of the Study Population

From 2000 to 2009, we identified 116 new cases of kidney cancer. Table 1 compares the demographic characteristics and comorbidities between kidney cancer cases and controls. The cases were more likely to have obesity, hypertension, kidney infections, chronic kidney diseases, cystic kidney diseases and kidney stones.

Related Factors for Kidney Cancer by Multivariable Logistic Regression

The results of multivariable logistic regression analysis showed no association was observed between DM and kidney cancer (OR 1.06, 95% CI, 0.58 to 1.94) after adjusting for variables that were significantly related to kidney cancer from the crude analysis (Table 2). Hypertension (OR 2.05, 95% CI, 1.23 to 3.42), chronic kidney diseases (OR 2.57, 95% CI, 1.23 to 5.37), cystic kidney diseases (OR 18.6, 95% CI, 1.84 to 187.6) and kidney stones (OR 4.02, 95% CI, 2.43 to 6.66) were independent comorbidities significantly associated with kidney cancer. The further analysis was performed using only the diabetic cases. After adjusting for variables, diabetic duration was not significantly related to the risk of kidney cancer (Table 3).

Influence of Anti-Diabetic Drugs on the Risk of Kidney Cancer

Table 4 shows the effects of anti-diabetic drugs on the risk of kidney cancer. After adjustments for potential confounders, the OR for use of alpha-glucosidase inhibitor vs no use was 4.31 (95% CI, 1.07 to 17.3). No significant association was found between other anti-diabetic drugs and the risk of kidney cancer.

Table 3. Adjusted Odds Ratios of Kidney Cancer in Relation to Duration of Diabetes

Duration of diabetes (years)	Case	Control		
	Number (%)		Odds ratio†	(95% CI)
<2	4 (19.1)	4 (5.88)	1.00	
≥2	17 (81.0)	64 (94.1)	0.18	(0.03-1.01)

†Adjusted for sex, age, hypertension, kidney infections, chronic kidney diseases, cystic kidney diseases and kidney stones.
This analysis was performed using only the diabetic cases.

Discussion

Though not novel, to the best of our knowledge, this is the first case-control study to discuss the association between DM and kidney cancer in Taiwan, making this a timely contribution to the growing literature on diabetes and cancers. A large cohort study in Japan by Inoue et al[12] found that after exclusion of kidney cancer diagnosed within 5 years of baseline, the hazard ratio of kidney cancer remained high in diabetic patients (HR 2.41, 95% CI, 1.22 to 4.78). A large cohort study in US by Atchison et al[13] showed that the relative risk of kidney cancer was 1.24 after 2 to 5 years between diagnoses of DM and kidney cancer (95% CI, 1.11 to 1.38), 1.09 after 6 to 10 years (95% CI, 0.97 to 1.22) and decreasing to 1.00 after >10 years (95% CI, 0.91 to 1.10). However, a cohort study in Japan by Washio et al[19] showed that though DM showed an increased risk of kidney cancer death in age- and sex-adjusted model (HR 2.22, 95% CI, 1.04 to 4.70), after controlling for covariates, it did not achieve statistical significance (HR 1.52, 95% CI, 0.60 to 3.85).[19] In this study, we did not observe an association between DM and kidney cancer, irrespective of the diabetic duration. Because this was an observational study, we do not have a plausible explanation why no association was detected between DM and kidney cancer in Taiwan. However, the different populations may partially account for the conflicting results between the present study and the others.

The other medical conditions significantly associated with kidney cancer found in the present study are consistent with the established evidence in literature.[6-8, 20, 21] These conditions include hypertension (OR 2.05), chronic kidney diseases (OR 2.57), cystic kidney diseases (OR 18.6) and kidney stones (OR 4.02). This further confirms that the aetiology of kidney cancer is multi-factorial. However, detection bias should be considered, because patients with these above conditions would receive much more attention such as frequent kidney imaging, and small renal masses that might not otherwise be discovered could be identified and treated.

In the present study, the use of alpha-glucosidase inhibitor was found to be associated with the risk of kidney cancer

Table 4. Adjusted Odds Ratios of Kidney Cancer in Relation to Use of Anti-diabetic Drugs

Use of anti-diabetic drugs	Case	Control	Odds ratio†	(95% CI)
	Number (%)			
Insulin				
never use	97 (83.6)	416 (89.7)	1.00	
ever use	19 (16.4)	48 (10.3)	1.38	(0.72-2.64)
Metformin				
never use	98 (84.5)	402 (86.6)	1.00	
ever use	18 (15.5)	62 (13.4)	0.86	(0.45-1.62)
Sulfonylurea				
never use	97 (83.6)	411 (88.6)	1.00	
ever use	19 (16.4)	53 (11.4)	1.18	(0.62-2.24)
Thiazolidinedione				
never use	113 (97.4)	451 (97.2)	1.00	
ever use	3 (2.59)	13 (2.80)	0.80	(0.20-3.19)
Alpha-glucosidase inhibitor				
never use	111 (95.7)	460 (99.1)	1.00	
ever use	5 (4.31)	4 (0.86)	4.31	(1.07-17.3)

†Adjusted for sex, age, hypertension, kidney infections, chronic kidney diseases, cystic kidney diseases and kidney stones.

(OR 4.31). Because there was no similar report previously and the case number was small in the present study, we could not make a plausible explanation why the use of alpha-glucosidase inhibitor is associated with the increased risk of kidney cancer.

It should be noted that there were some limitations in the present study. First, because there was an inherent limitation of using health insurance dataset, a number of suspected risk factors of kidney cancer were not available in this dataset, such as exposure to chemical agents and genetic factors. Second, we could not quantitatively adjust for many covariates of interest, including smoking, body mass index, and drinking. That was also due to the inherent limitation of this dataset. Though we included these covariates by using ICD-9 codes, only small case numbers could be found. Third, the information about tumour stage, tumour size, kidney function, blood glucose level, and HbA1c were also not available because of the inherent limitation of this dataset. Further studies including these related factors are needed to clarify the issue of kidney cancer.

Conclusion

This study suggests that: (i) DM does not correlate with the risk of kidney cancer, (ii) hypertension, chronic kidney diseases, cystic kidney diseases and kidney stones are associated with kidney cancer, and (iii) the use of alpha-glucosidase inhibitor is associated with kidney cancer.

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