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Risk of Malignant Neoplasms of Kidney and Bladder in a Cohort Study of the Diabetic Population in Taiwan With Age, Sex, and Geographic Area Stratifications

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Abstract: Diabetes has been reported to increase the risk of malignant neoplasms of kidney and bladder, but the studies' results are still inconclusive. Age, sex, and geographical area-specific incidence and relative risks of above neoplasms are also scarce in the literature. We prospectively investigated the age, sex, geographical area-specific incidence and relative risks of kidney and bladder neoplasms in diabetic population of Taiwan.

Diabetic patients (n = 615,532) and age- and sex-matched controls (n = 614,871) were linked to inpatient claims (2000–2008) to identify the admissions for malignant neoplasm of kidney (International Classification of Diagnosis, 9th version, Clinical Modification: 189) and bladder (International Classification of Diagnosis, 9th version, Clinical Modification: 188). The person-year approach with Poisson assumption was used to evaluate the incidence density. We also estimated the age, sex, and geographical area-specific relative risks of above malignancy in relation to diabetes with Cox proportional hazard regression model.

The overall incidence density of malignant neoplasm of kidney for diabetic men and women were 3.87 and 4.28 per 10,000 patient-years, respectively; the corresponding figures for malignant neoplasm of bladder were 5.73 and 3.25 per 10,000 patient-years. Compared with the controls, diabetic men were at significantly increased hazards of kidney (covariate adjusted hazard ratio [aHR]: 1.31, 95% confidence interval [CI] 1.18–1.46) and bladder aHR: 1.13, 95% CI 1.04–1.23). Diabetic women, on the contrary, only experienced significantly elevated hazard of kidney neoplasm (aHR: 1.14, 95% CI 1.04–1.26). Diabetic men aged >65 years showed the most significantly increased hazard of developing neoplasm of kidney (aHR: 1.40) and bladder (aHR: 1.13). The most significantly increased hazard of kidney neoplasm was noted for women diabetic patients aged >65 years. There was also a significant interactive effect of geographic area with diabetes on the incidence of kidney and bladder neoplasms in both sexes.

Diabetic men >45 years and diabetic women >65 years were found to have significantly increased hazard of malignant neoplasm of kidney, but only diabetic men >65 years were at significantly increased hazard of bladder neoplasm. The significant geographic variations in incidence and relative hazard of kidney and bladder neoplasms warrant further investigations of the underlying reasons.

Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, HR = hazard ratio, ICD-9 CM = International Classification of Diagnosis, 9th version, Clinical Modification, NHI = National Health Insurance.

INTRODUCTION

Kidney and urinary bladder cancers, reported to be related to zinc transporters,[1] are the most frequent malignant tumors of the urinary tract. Both neoplasms together make up about 5% of all the cancers worldwide. They also represent the 14th and 11th leading cause of cancer, respectively in the ethnic Chinese population in terms of estimated age-standardized incidence rates.[2] Diabetes mellitus, whose global prevalence was estimated at 366 million in 2011,[3,4] has been reported to be associated with increased risks of malignant neoplasm of kidney[5−8] and bladder[9−12]; however, some other studies did not report such a putative association between diabetes and kidney[9,13−18] or bladder[5,7,8,13−15,17,18] neoplasms.

Interpretation of findings from many previous case−control studies[10,12−14,16] were limited by their small sample sizes. Some cohort studies[5,6,8,18] were conducted using only patients with diabetes from in-patient registries, which could result in underrepresentativeness of diabetic patients from outpatient settings. Additionally, several studies focused on specific study groups such as government employees,[9] veterans,[8] or women patients.[11] By far, there are limited data from population-based studies looking into the relationships between diabetes and malignant neoplasms of kidney and bladder. Moreover, the

information on the age, sex, and geographic area-specific relationship between diabetes and kidney/bladder cancer is also lacking.

In Taiwan, malignant neoplasm of kidney is the 14th and 20th most common cancer in men and women, respectively, whereas the bladder cancer is the 9th and 16th commonest malignancy in men and women, respectively.[19] Our previous study showed significant geographic variation in relative risk of hip fracture in relation to diabetes, in which diabetes from rural areas in Taiwan experienced a higher relative risk of hip fracture. Such observation suggested possible inadequate health care services delivered to patients with diabetes from rural areas.[20] In addition, it was observed that people living in Southwestern coastal area of Taiwan had elevated standardized mortality ratio of kidney and bladder cancers due to high arsenic content in artesian well water.[21,22] Because both diabetes and certain environmental risk factors have been found to be associated with cancer risk, we examined in this study the possible interaction of diabetes and geographic area (a proxy of level of arsenic exposure) on the risk of kidney and bladder cancers. We speculated that patients with diabetes from South and rural areas of Taiwan could experience higher relative risk of kidney and bladder cancers.

The purpose of this study, therefore, was to use a nationally representative diabetic cohort selected from the National Health Insurance (NHI) database to estimate the incidence and relative risks of malignant neoplasms of kidney and bladder according to age, sex, and various geographical stratifications.

PATIENTS, MATERIALS, AND METHODS

Study Design

A universal NHI Program has been implemented by NHI Administration (previously called Bureau of NHI) under the jurisdiction of Ministry of Health and Welfare since March 1995. Approximately 96% of total Taiwanese population had enrolled in NHI Program by the end of 1996,[23] and NHI Administration had contracted 97% of hospitals and 90% of clinics all over Taiwan.[24] To ensure the accuracy of claim files, the NHI Administration performs quarterly expert reviews on a random sample for every 50 to 100 ambulatory and inpatient claims,[25] and information available is considered to be complete and accurate.[26] With the ethical approval from the Review Committee of National Health Research Institutes, we used data of diabetic ambulatory care claims (1997–2008), all inpatient claims (1997–2008), and the updated registry for beneficiaries (1995–2002) for this study. All the dataset can be interlinked through each individual's personal identification number.

Identification of Study Subjects

Details of the selection of diabetic patients and controls have been thoroughly reported before.[27] Briefly, all the patients who sought ambulatory cares for diabetes (International Classification of Diagnosis, 9th version, Clinical Modification [ICD-9-CM]: 250 or A-code: A181) in 2000 were recruited in the diabetic group. To ensure the accurate estimation of cancer incidence, we excluded those diabetes who had cancer diagnosis (ICD-9-CM: 140–208) between January 1, 1997 and the first clinical visit for diabetes in 2000. All cancer diagnoses were verified by major illness/injury certificates. The final diabetic cohort thus consisted of 615,532 patients. The index date for each patient with diabetes was the date of his/her first outpatient visit for diabetes in 2000 (Figure 1).

The control group was randomly selected from the all NHI beneficiaries registered in 2000, by matching diabetic group on the frequency of age and sex. People included in the control group must have no prior histories of diabetes and all-cause cancer in 1997 and 1999. We selected 614,871 controls in this study; and the index date for subjects in the control group was January 1, 2000 or the date of NHI enrollment, if their first date of NHI enrollment was after January 1, 2000.

The geographic area of each member's NHI unit, either the beneficiaries' residential area or location of their employment, was grouped into 4 geographic areas (North, Central, South, East) or 2 urbanization statuses (urban and rural) according to the National Statistics of Regional Standard Classification.[28] The information on clinical risk factors for neoplasm of kidney including hypertension (ICD-9-CM: 401–405, 437.2), acquired cystic disease of the kidney (ICD-9-CM: 593.2) was retrieved from the inpatient and outpatient medical claims between January 1997 and the index date.

Study Endpoints

All study subjects were followed from the index date to the occurrence of endpoints of interest (eg, malignant neoplasm of kidney [ICD-9-CM: 189] and bladder [ICD-9-CM: 188]), termination of NHI policy, or the end of 2008. Information on the endpoints was retrieved from the inpatient claims. To ensure the accuracy of the diagnoses of malignant neoplasm, only the cancer patients admitted with major illness/injury certificates were counted. We analyzed the association of diabetes with kidney and bladder cancers separately.

Statistical Methods

We first described and tested the characteristics between diabetic and no-diabetic groups. The age- and sex-specific incidence density rate was estimated with person-years as the denominator under the Poisson assumption. We then performed multiple Cox proportional hazard models to assess the independent effects of diabetes on the risks of malignant neoplasms of kidney and bladder. Adjustment for both geographic area and urbanization status was made for adjustment of possible geographic variations in cancer incidence and mortality in Taiwan.[29] Additionally, such adjustment may help reduce the presence of an urban–rural difference in accessibility to medical health services in Taiwan.[30] Inclusion of frequency of medical visit in the multiple regression model was to reduce the potential for surveillance bias, which arising from the likelihood that neoplasms of kidney and bladder in the diabetic group might be more likely to be detected simply because patients with diabetes usually have more clinical visits.

The Cox regression model considered the following as the censoring event whichever came first: in-hospital mortality for causes other than neoplasm of kidney or bladder, withdrawal from NHI, and December 31, 2008. All the statistical analyses were performed using the Statistical Analysis Software (version 9.4; SAS Institute, Cary, NC). A P value of < 0.05 was considered statistically significant.

RESULTS

The characteristics of study subjects are shown in Table 1. Distribution of geographic area and level of urbanization between diabetic and controls were also comparable. On the contrary, diabetic patients tended to have higher prevalence of selected clinical risk factors for kidney or bladder neoplasm.
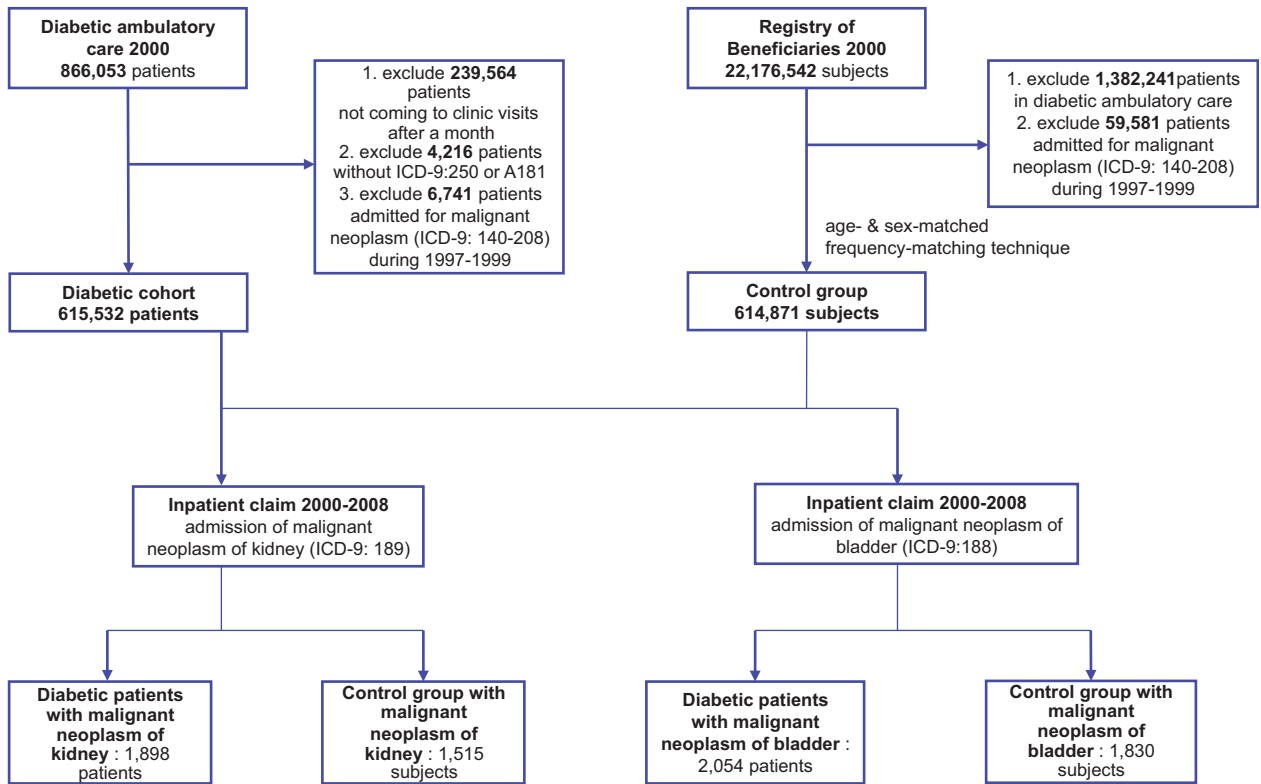
FIGURE 1. Flowchart for identification of diabetic cohort and control group.

The median time of follow-up was similar at 8.9 years for both groups.

Incidence and Relative Hazards of Malignant Neoplasm of Kidney

Over 9 years of follow-up, 1898 diabetic patients were admitted for kidney neoplasm, and 1515 control were admitted for the same diagnosis. The overall incidence density for diabetic men and women was 3.87 and 4.28 per 10,000 patient-years, respectively, whereas the corresponding figures for control men and women were 2.75 and 3.21 per 10,000 patient-years. The incidence density increased with age in both diabetic and control groups irrespective of sex. Compared with the controls, diabetic men and women showed moderately but significantly increased risks of malignant neoplasm of kidney with a hazard ratio (HR) of 1.31 (95% confidence interval [CI] 1.18–1.46) and 1.14 (95% CI 1.04–1.26), respectively, after adjustment for potential confounders. Although small, the difference in sex-specific HR of kidney neoplasm was significant statistically ($P < 0.001$). Because there was also a significant interaction of diabetes with age ($P < 0.001$) for both men and women, we also evaluated the age-specific HRs for each sex. In diabetic men, the adjusted HR increased with age, and the highest age-specific HR was observed for the diabetic men aged >65 years (HR: 1.40; 95% CI 1.21–1.63). The highest age-specific HR was noted for diabetic women aged >65 years (HR: 1.14; 95% CI 1.00–1.28) (Table 2). We also evaluated the geographic area-specific incidence densities and relative hazards of malignant neoplasm of kidney in the diabetic and control groups (Table 3). Irrespective of diabetic status, people

in southern Taiwan had the highest incidence densities of kidney neoplasm in both men and women. Compared with those residing or working in the same area, the diabetic men from areas other than East all showed significantly higher HRs of malignant neoplasm of kidney. For women, only those from Northern Taiwan showed significantly increased risk of kidney cancer.

Incidence and Relative Hazards of Malignant Neoplasm of Bladder

There were 2054 diabetic patients and 1830 controls were admitted for malignant neoplasm of bladder during the study period. The incidence densities of bladder neoplasm for diabetic men and women were 5.73 and 3.25 per 10,000 patient-years, and the same figures for control men and women were 4.70 and 2.65 per 10,000 patient-years (Table 4). In both diabetic men and women, the incidence density of bladder neoplasm increased with age, and the highest incidence density was observed among those aged >65 years (men: 10.37, women: 5.20 per 10,000 person-years). After controlling for potential confounders, diabetic patients were found to have a modestly but significantly increased risk of developing malignant neoplasm of bladder, with an overall adjusted HR of 1.09 (95% CI 1.02–1.17). With further sex-stratified analysis, however, only diabetic men had significantly higher risk of bladder cancer (HR: 1.13; 95% CI 1.04–1.23), and analysis of age-specific HR further suggested that only men aged >65 years experienced a significantly increased risk of bladder neoplasm.

People from Southern Taiwan had the highest incidence densities of malignant neoplasm of bladder regardless of

TABLE 1. Characteristics of the Study Subjects

Variables[*]	Control Group		Diabetic Group		P Value[†]
	n	%	n	%	
Sociodemographic characteristics					
Age					
<45	69,617	11.32	69,825	11.34	0.9176
45−64	296,810	48.27	297,142	48.27	
>64	248,444	40.41	248,562	40.39	
Mean age (±SD)	60.00	12.84	60.09	12.73	0.9018
Sex					
Female	319,308	51.93	319,310	51.93	0.9991
Male	295,563	48.07	295,566	48.07	
Geographic area					
Northern	269,239	44.29	269,920	44.41	<0.001
Central	151,693	24.96	141,321	23.25	
Southern	168,995	27.80	178,627	29.39	
Eastern	17,938	2.95	17,944	2.95	
Urbanization status					
Urban area	407,323	66.81	415,154	68.16	<0.001
Rural area	202,343	33.19	193,949	31.84	
Comorbidity					
Hypertension					
Yes	334,908	54.47	460,889	74.88	<0.001
No	279,963	45.53	154,643	25.12	
Acquired cystic disease of the kidney					
Yes	9695	1.58	11,259	1.83	<0.001
No	605,176	98.42	604,273	98.17	
Mean ambulatory care visit in 2000 (±SD)	20.76 (±18.08)		34.17 (±20.84)		<0.001
Total	614,871	100.00	615,532	100.00	

SD = standard deviation.

[*] Data are n (%) or mean (±SD). Inconsistency between total population and population summed for individual variable was due to missing information.

[†] Based on the chi-square test for categorical variables and Student t test for continuous variables.

diabetic status and sex (Table 5). Further analysis revealed that diabetic men living or working in the Southern (HR: 1.24; 95% CI 1.09−1.42) and Northern areas (HR: 1.17; 95% CI 1.03−1.34) had modestly but significantly higher risks of malignant neoplasm of bladder compared with those control men from the same areas. On the contrary, geographic area did not significantly modify the HR of bladder neoplasm in women with diabetes.

DISCUSSIONS

Incidence and Relative Hazards of Malignant Neoplasm of Kidney

Literature regarding the age- and sex-specific incidence of malignant neoplasm of kidney in diabetic patients is scarce. In our study, the overall incidence densities of kidney neoplasms in diabetic patients were higher than those of control groups. The incidence increased with age, and those aged >65 had the highest incidence of above malignancy in both groups.

The plausible mechanism between diabetes and malignant neoplasm of kidney has not been clearly identified. Hyperinsulinemia associated with diabetic patients might be an operative mechanism for transformation to malignancy. Insulin serves as a growth factor for epithelial tumors in vitro, and increases the bioavailability of insulin-like growth factor-1, which is another tumor growth factor.[31] Obesity, frequently associated with diabetes, in which fat cells also release several kinds of cytokines and probably promote tumor growth.[32]

Incidence and Relative Hazards of Malignant Neoplasm of Bladder

Our study showed that the age-specific incidence density of malignant neoplasm of bladder increased with age, and it was higher in men than in women irrespective of diabetic status. Compared with age- and sex-matched control group, there was 13% increased risk of bladder neoplasm in diabetic men. The risk estimates and corresponding CIs were comparable with those reported from the studies of US veterans[8] and Korean men,[9] but lower than those of case−control studies from New England[12] and Israel.[10] With further age stratification, the statistical significance of HR was lost in diabetic men <65 years old. Actually, there were many articles reporting negative association between bladder neoplasm in diabetic men,[5,7,8,13] diabetic women,[5,7,13] or overall diabetic patients.[14,15,17,18] The overall and age-stratified risk estimates of our diabetic women revealed no association between diabetes and malignant neoplasm of bladder.

TABLE 2. Overall and Age- and Sex-Specific Incidence Densities and Relative Hazards of Malignant Neoplasm of Kidney (ICD-9: 189) in the Diabetic and Control Groups

Variables*	Control Group			Diabetic Group			Adjusted HR (95% CI) in Association With Diabetic Group
	No of Patients	No of Events	ID (Per 10,000 Patient-Years) (95% CI)†	No of Patients	No of Events	ID (Per 10,000 Patient-Years) (95% CI)†	
Men							
<45	40,537	18	0.52 (0.31−0.82)	40,537	30	0.90 (0.60−1.28)	1.23 (0.65−2.33)‡
45−65	141,899	281	2.32 (2.05−2.60)	141,899	371	3.32 (2.99−3.67)	1.19 (1.00−1.40)‡
>65	113,127	359	4.33 (3.89−4.80)	113,129	448	6.04 (5.49−6.62)	1.40 (1.21−1.63)‡
Total	295,563	658	2.75 (2.55−2.97)	295,566	849	3.87 (3.61−4.14)	1.31 (1.18−1.46)§
Women							
<45	29,080	8	0.31 (0.14−0.62)	29,079	13	0.53 (0.28−0.90)	0.90 (0.33−2.46)‡
45−65	154,911	317	2.33 (2.08−2.60)	154,911	436	3.43 (3.11−3.76)	1.13 (0.97−1.32)‡
>65	135,317	532	5.04 (4.62−5.48)	135,318	600	6.45 (5.95−6.99)	1.14 (1.00−1.28)‡
Total	319,308	857	3.21 (3.00−3.43)	319,310	1049	4.28 (4.03−4.55)	1.14 (1.04−1.26)§
Overall	614,871	1515	2.99 (2.84−3.15)	615,532	1898	4.08 (3.90−4.27)	1.22 (1.13−1.31)‖

CI = confidence interval, HR = hazard ratio, ICD-9 = International Classification of Diagnosis, 9th version, ID = incidence density. The interaction of diabetes and sex, and the interactions of diabetes and age in both sexes were all significant statistically (*P* < 0.001).

* Inconsistency between total population and population summed for individual variable was due to missing information.

† Based on Poisson assumption.

‡ Based on Cox proportional hazard regression with adjustment for geographic area, urbanization status, hypertension, acquired cystic disease of the kidney, and frequency of medical visit.

§ Based on Cox proportional hazard regression with adjustment for age, geographic area, urbanization status, hypertension, acquired cystic disease of the kidney, and frequency of medical visit.

‖ Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, urbanization status, hypertension, acquired cystic disease of the kidney, and frequency of medical visit.

TABLE 3. Overall and Geographic Area-Specific Incidence Densities and Relative Hazards of Malignant Neoplasm of Kidney (ICD-9-CM: 189) in the Diabetic and Control Groups

Variables*	Control Group			Diabetic Group			Adjusted HR (95% CI) in Association With Diabetic Group
	No of Patients	No of Events	ID (Per 10,000 Patient-Years) (95% CI)†	No of Patients	No of Events	ID (Per 10,000 Patient-Years) (95% CI)†	
Men							
Eastern	8996	18	3.08 (1.66−4.51)	8428	11	2.08 (0.85−3.31)	0.71 (0.33−1.50)‡
Southern	80,441	242	4.58 (4.00−5.15)	86,256	311	5.72 (5.08−6.35)	1.25 (1.06−1.48)‡
Central	71,724	140	2.96 (2.47−3.44)	65,181	158	3.81 (3.22−4.41)	1.26 (1.00−1.59)‡
Northern	130,931	251	2.93 (2.57−3.29)	132,076	363	4.39 (3.94−4.84)	1.38 (1.17−1.62)‡
Total	295,563	658	2.75 (2.55−2.97)	295,566	849	3.87 (3.61−4.14)	1.31 (1.18−1.46)§
Women							
Eastern	8942	23	3.88 (2.29−5.46)	9511	25	4.11 (2.50−5.73)	1.05 (0.59−1.85)‡
Southern	88,554	326	5.56 (4.95−6.16)	92,314	380	6.45 (5.81−7.10)	1.09 (0.94−1.27)‡
Central	79,969	225	4.24 (3.69−4.80)	76,101	257	5.27 (4.62−5.91)	1.14 (0.95−1.37)‡
Northern	138,308	279	3.05 (2.69−3.41)	137,620	382	4.38 (3.94−4.82)	1.29 (1.10−1.50)‡
Total	319,308	857	3.21 (3.00−3.43)	319,310	1049	4.28 (4.03−4.55)	1.14 (1.04−1.26)§
Overall	614,871	1515	2.99 (2.84−3.15)	615,532	1898	4.08 (3.90−4.27)	1.22 (1.13−1.31)‖

CI = confidence interval, HR = hazard ratio, ICD-9 = International Classification of Diagnosis, 9th version, ID = incidence density. The interactions of diabetes and geographic area in both sexes were all significant statistically (*P* < 0.001).

* Inconsistency between total population and population summed for individual variable was due to missing information.

† Based on Poisson assumption.

‡ Based on Cox proportional hazard regression with adjustment for geographic area, urbanization status, hypertension, acquired cystic disease of the kidney, and frequency of medical visit.

§ Based on Cox proportional hazard regression with adjustment for age, geographic area, urbanization status, hypertension, acquired cystic disease of the kidney, and frequency of medical visit.

‖ Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, urbanization status, hypertension, acquired cystic disease of the kidney, and frequency of medical visit.

TABLE 4. Overall and Age- and Sex-Specific Incidence Densities and Relative Hazards of Malignant Neoplasm of Bladder (ICD-9: 188) in the Diabetic and Control Groups

Variables[*]	Control Group			Diabetic Group			Adjusted HR (95% CI) in Association With Diabetic Group
	No of Patients	No of Events	ID (Per 10,000 Patient-Years) (95% CI)[†]	No of Patients	No of Events	ID (Per 10,000 Patient-Years) (95% CI)[†]	
Men							
<45	40,537	15	0.43 (0.24−0.71)	40,537	23	0.69 (0.44−1.03)	1.20 (0.61−2.40)[‡]
45−65	141,899	387	3.19 (2.88−3.52)	141,899	466	4.17 (3.79−4.56)	1.09 (0.94−1.25)[‡]
>65	113,127	721	8.71 (8.09−9.37)	113,129	768	10.37 (9.65−11.13)	1.13 (1.02−1.26)[‡]
Total	295,563	1123	4.70 (4.43−4.98)	295,566	1257	5.73 (5.42−6.05)	1.13 (1.04−1.23)[§]
Women							
<45	29,080	9	0.35 (0.16−0.67)	29,079	10	0.40 (0.19−0.74)	0.83 (0.31−2.21)[‡]
45−65	154,911	226	1.66 (1.45−1.89)	154,911	303	2.38 (2.12−2.66)	1.08 (0.90−1.30)[‡]
>65	135,317	472	4.47 (4.07−4.89)	135,318	484	5.20 (4.75−5.69)	1.01 (0.89−1.16)[‡]
Total	319,308	707	2.65 (2.46−2.85)	319,310	797	3.25 (3.03−3.49)	1.04 (0.93−1.16)[§]
Overall	614,871	1830	3.62 (3.45−3.79)	615,532	2054	4.42 (4.23−4.61)	1.09 (1.02−1.17)[‖]

CI = confidence interval, HR = hazard ratio, ICD-9 = International Classification of Diagnosis, 9th version, ID = incidence density. The interaction of diabetes and sex, and the interactions of diabetes and age in both sexes were all significant statistically ($P < 0.001$).

[*] Inconsistency between total population and population summed for individual variable was due to missing information.
[†] Based on Poisson assumption.
[‡] Based on Cox proportional hazard regression with adjustment for geographic area, urbanization status, and frequency of medical visit.
[§] Based on Cox proportional hazard regression with adjustment for age, geographic area, urbanization status, and frequency of medical visit.
[‖] Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, urbanization status, and frequency of medical visit.

TABLE 5. Overall and Geographic Area-Specific Incidence Densities and Relative Hazards of Malignant Neoplasm of Bladder (ICD-9-CM: 188) in the Diabetic and Control Groups

Variables[*]	Control Group			Diabetic Group			Adjusted HR (95% CI) in Association With Diabetic Group
	No of Patients	No of Events	ID (Per 10,000 Patient-Years) (95% CI)[†]	No of Patients	No of Events	ID (per 10,000 Patient-Years) (95% CI)[†]	
Men							
Eastern	8996	26	4.45 (2.74−6.16)	8428	22	4.16 (2.42−5.90)	1.04 (0.59−1.84)[‡]
Southern	80,441	387	7.32 (6.59−8.05)	86,256	481	8.85 (8.06−9.64)	1.24 (1.09−1.42)[‡]
Central	71,724	286	6.04 (5.34−6.74)	65,181	252	6.08 (5.33−6.83)	0.99 (0.84−1.18)[‡]
Northern	130,931	402	4.69 (4.23−5.15)	132,076	495	6.00 (5.47−6.53)	1.17 (1.03−1.34)[‡]
Total	295,563	1123	4.70 (4.43−4.98)	295,566	1257	5.73 (5.42−6.05)	1.13 (1.04−1.23)[§]
Women							
Eastern	8942	15	2.53 (1.25−3.81)	9511	20	3.30 (1.85−4.74)	1.21 (0.62−2.38)[‡]
Southern	88,554	264	4.50 (3.96−5.05)	92,314	301	5.11 (4.53−6.59)	1.08 (0.91−1.27)[‡]
Central	79,969	188	3.55 (3.04−4.05)	76,101	179	3.66 (3.13−4.20)	0.97 (0.79−1.19)[‡]
Northern	138,308	233	2.55 (2.22−2.88)	137,620	280	3.21 (2.83−3.58)	1.14 (0.96−1.36)[‡]
Total	319,308	707	2.65 (2.46−2.85)	319,310	797	3.25 (3.03−3.49)	1.04 (0.93−1.16)[§]
Overall	614,871	1830	3.62 (3.45−3.79)	615,532	2054	4.42 (4.23−4.61)	1.09 (1.02−1.17)[‖]

CI = confidence interval, HR = hazard ratio, ICD-9 = International Classification of Diagnosis, 9th version, ID = incidence density. The interactions of diabetes and geographic area in both sexes were all significant statistically ($P < 0.001$).

[*] Inconsistency between total population and population summed for individual variable was due to missing information.
[†] Based on Poisson assumption.
[‡] Based on Cox proportional hazard regression with adjustment for geographic area, urbanization status, and frequency of medical visit.
[§] Based on Cox proportional hazard regression with adjustment for age, geographic area, urbanization status, and frequency of medical visit.
[‖] Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, urbanization status, and frequency of medical visit.

There are various hypotheses postulating possible mechanism between diabetes and malignant neoplasm of bladder. Apart from mitogenic properties of insulin and insulin-like growth factor-1,[31] alteration of urothelial-structure-like membrane glycoprotein cadherins and integrins distribution change in diabetic nephropathy were reported to be implicated in the pathogenesis of bladder cancer.[33] The process of glycosaminoglycan degradation taken place in bladder urothelium of diabetic patients may have predisposed to carcinogen exposure, tumor cell adherence and implantation.[10] Recently, use of oral hypoglycemic agent pioglitazone was also reported to be associated with increased risk of bladder cancer.[34,35]

Geographical Variation of Risks of Malignant Neoplasm of Kidney and Bladder

To our knowledge, geographic variation of malignant neoplasms of kidney and bladder was scarcely reported in the literature. Interestingly, the incidences of kidney and bladder neoplasms were highest in Southern areas regardless of sexes in our study. Southwest coast of Taiwan has been an endemic area of black foot disease resulting from high-arsenic artesian well water.[21] Chronic ingestion of inorganic arsenic in drinking water was reported to have cancer potential in liver, lung, kidney, and bladder.[21,22,36] Additionally, chloroform, the major species of trihalomethanes especially found in the water plant of south Taiwan, might have contributed the majority of the lifetime cancer risks (range: 87.5%–92.5% of total risks) from the 3 water supply areas in Taiwan.[37] Our study revealed diabetic men residing or working in Southern and Northern areas have increased absolute and relative risk of malignant neoplasm of kidney and bladder, whereas diabetic women from Northern area were prone to suffer from kidney neoplasm. Whether such observation might have reflected the interaction of diabetes with the above-mentioned environmental factors deserves further investigation.

Methodologic Consideration and Conclusion

There are several strengths involved in this study. Firstly, data analyzed in this study were based on Taiwan's NHI database, in which the medical claims are highly representative of the whole population of Taiwan. Secondly, with such a large sample size, our study was able to perform detailed stratified analyses according to age, sex, and geographic area.[38] Thirdly, according to the literature from Taiwan and the USA, there are truly geographic variations in medical resources[39] and cancer diagnostic technique.[40] The Northern Taiwan is usually with greater medical resources,[39] which could lead a spuriously higher cancer incidence. To account for such variations, we managed to adjust for geographic area and urbanization level in an attempt to reduce such potential geographic- and urbanization-related confounding.

Some limitations also must be mentioned. Firstly, the potential disease misclassification could happen to our study because we relied on the medical claims to get the information of disease diagnosis. A previous validation study reported that some 25.4% of diabetes shown in NHI claims are not accurate.[41] In addition, although we used major illness/injury certificates, the cancer diagnosis is still subject to a chance of error because there are no detailed pathologic data available from the medical claims. Such potential disease misclassification is likely to be nondifferential, which tends to underestimate the true relative risks.[42] Secondly, we only identified a study subject's residential area or location of employment from the year of 2000 (ie,

the baseline year), and did not take into account possible multiple residential areas/employment locations for a study subject during the follow-up period. This might have entailed certain residual confounding by geographic area. Lastly, our study was unable to take into account a comprehensive list of environmental/occupational risk factors for kidney and bladder cancers.

CONCLUSIONS

Diabetic men >45 years and diabetic women >65 years were found to have significantly increased hazard of malignant neoplasm of kidney, but only diabetic men >65 years were at significantly increased hazard of bladder neoplasm. The significant geographic variations in incidence and relative hazard of kidney and bladder neoplasms suggest a possible interaction of diabetes with certain environmental factors, which warrants further investigation.

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