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Original Article

Duration of diabetes mellitus and risk of kidney and bladder cancer: a longitudinal nationwide cohort study

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Abstract: Previous studies have suggested that diabetes mellitus (DM) may increase the risk of kidney and bladder cancer; however, little is known about the duration of DM. We aimed to analyze the risk of kidney and bladder cancer according to the duration of DM in a longitudinal nationwide cohort. This study was conducted in a cohort of 9,773,462 participants ≥ 20 years old who underwent a National Health Examination in 2009 and were followed up until December 2017. Cox-proportional hazard models were used to evaluate the risk of kidney and bladder cancer in relation to the duration of DM. During follow-up (mean 7.3 years), kidney and bladder cancer occurred in 11,219 and 13,769 participants, respectively. DM was associated with an increased risk of kidney and bladder cancer (hazard ratio (HR), 95% confidence interval (95% CI); 1.14, 1.09-1.20 and 1.23, 1.17-1.28, respectively). Compared to fasting glucose < 100 mg/dL, impaired fasting glucose (IFG) and longer DM duration were associated with increased risks (HR, 95% CI): IFG (1.05, 1.01-1.10), new-onset DM (1.13, 1.03-1.24), DM < 5 years (1.11, 1.02-1.20), and DM ≥ 5 years (1.25, 1.15-1.36) in kidney cancer; IFG (1.05, 1.01-1.09), new-onset DM (1.10, 1.01-1.19), DM < 5 years (1.26, 1.18-1.35), and DM ≥ 5 years (1.34, 1.26-1.43) in bladder cancer, respectively. Our findings suggest that the subjects with IFG and longer duration of DM had a higher risk for kidney and bladder cancer than those without DM.

Keywords: Kidney cancer, bladder cancer, type 2 diabetes mellitus, impaired fasting glucose, disease duration

Introduction

The prevalence of diabetes mellitus (DM) and impaired fasting glucose (IFG) has been increasing worldwide [1]. According to the IDF Diabetes Atlas, it was estimated that there were 451 million people with DM in 2017, and this number is expected to increase to 693 million by 2045 worldwide. Moreover, there were an estimated 374 million people with IFG, equaling 7.7% of the world population. DM is a leading cause of disability globally with higher medical care costs, reduced quality of life and increased mortality, ranking as the fourth leading cause of age-standardized years lived with disability in 2017 [2-4]. In particular, DM is associated with a 17% increased risk of developing any cancer and a 21% increased risk of death from any cancer [5-8]. Several meta-analyses have shown that DM increases the risk of genitourinary cancer, including kidney [9] and bladder cancer [10, 11], but not prostate cancer [12].

Kidney and bladder cancer are among the well-known DM-related human cancers. In 2018, there were an estimated 403,300 cases of kidney cancer and 549,400 cases of bladder cancer globally, with 175,100 and 199,900 resultant deaths, respectively [13]. Various modifiable and non-modifiable lifestyle, environmental, and biological factors are known to increase

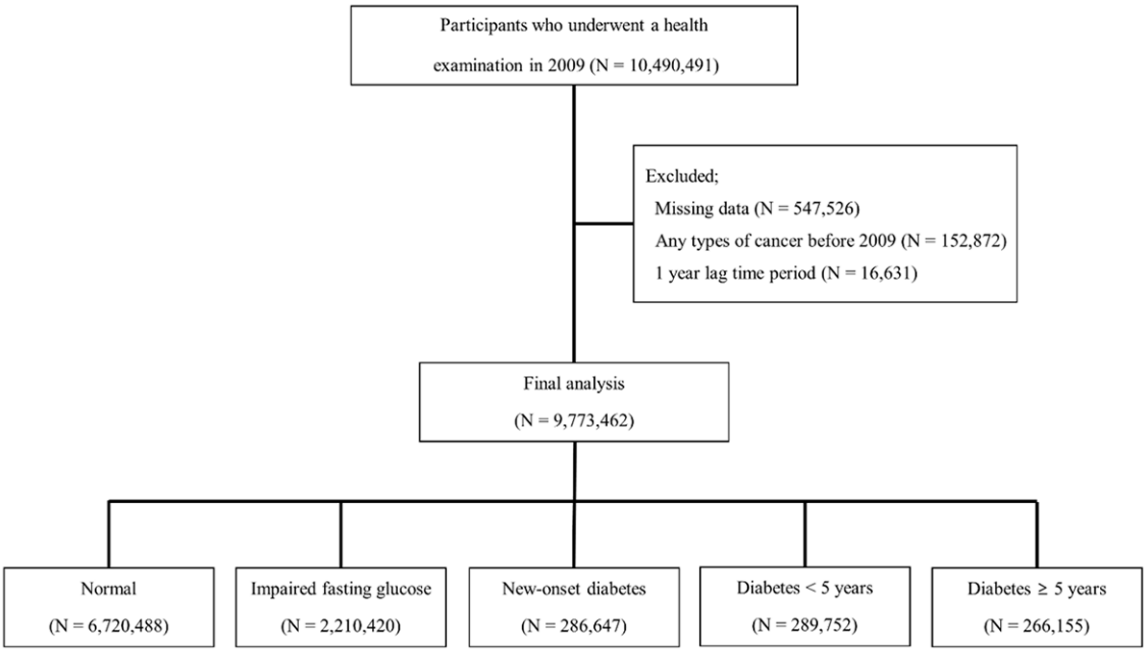

Figure 1. Flowchart of participant inclusion.

the risk of kidney and bladder cancer. Among these risk factors, several studies have suggested that hyperinsulinemia, hyperglycemia and insulin resistance are important risk factors for kidney and bladder cancer [14]. It may be the possible common biological links between DM and kidney and bladder cancer. Considering these mechanistic backgrounds, the association between DM and kidney and bladder cancer is relatively well established.

We can speculate that the risk of kidney and bladder cancer may vary depending on the duration of type 2 DM considering the longer exposure to potential biological mechanisms, including hyperinsulinemia, hyperglycemia and insulin resistance. Thus, we conducted a longitudinal nationwide cohort study to evaluate the risk of kidney and bladder cancer according to the duration of DM using data from the Korean National Health Insurance Service (NHIS) database, which covers nearly the entire South Korean population.

Materials and methods

Data source

The NHIS is a national health care insurance system that covers 97% of the total Korean population. It provides mandatory health insurance that covers all forms of health services and contains a broad range of information including principal diagnosis classified by the International Classification of Disease, 10th revision (ICD-10). Details of the NHIS database have been described elsewhere [15]. The NHIS also provides health examinations, consisting of anthropometric measurements, laboratory tests, and standardized self-reported questionnaires, for all insured Koreans. After approval by the Institutional Review Board and NHIS, we extracted and analyzed the data from the NHIS database server. We followed recommendations of the REporting of studies Conducted using Observational Routinely collected health Data statement [16].

Study population

From the NHIS database, participants over 20 years old who had undergone a health examination in 2009 were included (n = 10,490,491). We excluded participants with missing data (n = 547,526), participants diagnosed with any type of cancer diagnosed before 2009 (n = 152,872) and participants diagnosed with any cancer within the first year from the index date (lag-time, n = 16,631). In total, 9,773,462 participants were included in the final analysis and followed up until December 2019 (**Figure 1**).

The primary endpoint was newly diagnosed kidney and bladder cancer, which was defined as C64 and C67 according to the ICD-10.

Definition of DM

Normal group was defined as a normal glucose level (< 100 mg/dL) and no previous history of DM. IFG was defined as baseline fasting glucose 100-125 mg/dL and no previous history of claim for DM prescription or diagnosis. Type 2 DM was defined as at least one claim per year for the prescription of antidiabetic medication under ICD-10 codes E10-14 or fasting glucose level ≥ 126 mg/dL in a health examination after an 8-hour fast [7]. Participants were categorized into five groups according to the baseline glycemic status and duration of DM: normal, IFG, new-onset DM, and duration of DM < 5 or ≥ 5 years. New-onset DM was defined as follows: (1) baseline fasting blood glucose ≥ 126 mg/dL measured in a health examination; (2) no previous history of claim for DM prescription or diagnosis; (3) taking antidiabetic medications within 1 year of the health examination [17].

Covariate assessment

Height, body weight, waist circumference, and systolic and diastolic blood pressure (BP) were measured, and body mass index (BMI) was calculated by dividing weight by the square of height. Standardized self-reported questionnaires were analyzed for the lifestyle of participants, including smoking, alcohol consumption, and regular physical activity. Participants were classified according to smoking status as non-smokers, ex-smokers, or current smokers. Participants who drank < 30 g of alcohol per day according to the questionnaire were defined as mild alcohol drinkers, and those who drank ≥ 30 g were defined as heavy alcohol drinkers [18]. Regular exercise was defined as strenuous exercise for at least 20 minutes at least once a week or moderate exercise for at least 30 minutes at least once a week [19]. Blood samples were collected after fasting for at least 8 hours, and serum glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels were measured.

Hypertension was defined according to the presence of at least one claim per year under ICD-10 codes I10-I13 and I15 as well as at least one claim per year for the prescription of an antihypertensive agent or systolic/diastolic BP ≥ 140/90 mmHg. Dyslipidemia was defined as a serum total cholesterol level ≥ 240 mg/dL or at least one claim per year for the prescription of a lipid-lowering medication under the ICD-10 code E78. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease equation [20]. Cardiovascular disease (CVD) was defined as a composite of ischemic heart disease (ICD-10 code I20-25), stroke (ICD-10 code I63-64), and congestive heart failure (ICD-10 code I50).

Statistical analysis

Statistical analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). Demographic data of participants are expressed as the mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. Comparison of demographic data was performed by analysis of variance (ANOVA) or independent t-test for continuous variables and by the chi-square test for categorical variables. Incidence rates of kidney and bladder cancer were calculated per 1,000 person-years. The cumulative incidence of kidney and bladder cancer was calculated using the Kaplan-Meier curve, and statistical significance was assessed using the log-rank test.

To adjust for the imbalance between the baseline characteristics according to the duration of DM, we used two different approaches. First, the hazard ratio (HR) and 95% confidence interval (CI) for kidney and bladder cancer were calculated using multivariate Cox proportional hazard regression analysis. We employed statistical models using gradually adjusted methods: Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, smoking status, alcohol consumption, regular activity, and BMI; Model 3, adjusted for age, sex, smoking status, alcohol consumption, regular activity, BMI, CKD, and CVD. Second, the inverse probability of treatment weighting (IPTW) analysis, based on propensity scoring, was used to eliminate possible confounding effects of imbalances in baseline characteristics [21]. The propensity for being in each group was calculated using a logistic regression model with baseline covari-

ates. To evaluate the balance of baseline characteristics among five groups according to the duration of DM, the maximum absolute standardized difference (ASD) was calculated in each covariate, and values less than 0.1 were considered negligible differences. The risk for kidney and bladder cancer of the five groups was obtained using weighted Cox proportional hazards regression models with IPTW. We also conducted clinically relevant subgroup analyses and calculated the *P*-values for interactions between the baseline glycemic status and duration of DM and subgroups in the development of kidney and bladder cancer using Cox proportional hazard regression analysis. All statistical tests were two-tailed, and the significance level was set at *P*-values less than 0.05.

Results

Baseline characteristics of the participants

The baseline characteristics of the participants according to the duration of DM are shown in **Table 1**. According to the duration of DM, there were significant differences in almost all baseline characteristics. Cardiometabolic parameters such as systolic and diastolic BP, serum fasting glucose, and total cholesterol levels were significantly higher in participants with IFG or DM than in the normal group. The prevalence of comorbidities such as hypertension, dyslipidemia, and chronic kidney disease increased as the duration of DM increased. However, the proportion of current-smokers and heavy alcohol drinkers decreased and the proportion of participants who performed regular exercise was increased as the duration of DM increased.

Incidence of kidney and bladder cancer according to the duration of DM

During the mean observation period of 7.3 years, 11,219 and 13,769 participants were newly diagnosed with kidney and bladder cancer, respectively (**Table 2**). The incidence of kidney cancer was 0.145 per 1,000 person-years (PY) in participants without DM, and 0.299 per 1,000 PY in participants with DM ($p < 0.0001$). Similarly, the incidence of bladder cancer with or without DM was 0.170 and 0.456 per 1,000 PY, respectively ($p < 0.0001$). When the participants were categorized according to the duration of DM, the incidence of kidney and bladder cancer increased significantly with increasing duration of DM as follows: 0.130 (normal), 0.191 (IFG), 0.247 (new-onset DM), 0.295 (DM < 5 years), and 0.360 (DM ≥ 5 years) per 1,000 PY for kidney cancer and 0.148 (normal), 0.237 (IFG), 0.314 (new-onset DM), 0.469 (DM < 5 years), and 0.596 (DM ≥ 5 years) per 1,000 PY for bladder cancer. The incidence probability of kidney and bladder cancer was significantly different according to the duration of DM (**Figure 2**).

Risk of kidney and bladder cancer according to the duration of DM

Table 2 shows the HRs of kidney and bladder cancer according to the duration of DM. After adjusting for confounding variables, participants with DM had increased HRs for kidney (1.14, 95% CI: 1.09-1.20) and bladder cancer (1.23, 1.17-1.28) compared to those without DM. A markedly increased incidence rate of kidney and bladder cancer was observed with increasing duration of DM. Compared to the normal group, the HRs (95% CI) for kidney cancer increased significantly with abnormal and longer diabetes duration: IFG (1.05, 1.01-1.10), new-onset DM (1.13, 1.03-1.24), DM < 5 years (1.11, 1.02-1.20) and DM ≥ 5 years (1.25, 1.15-1.36) (*P* for trend < 0.001) after adjusting for confounding variables (Model 2). Similar results were found in bladder cancer: IFG (1.05, 1.01-1.09), new-onset DM (1.10, 1.01-1.19), DM < 5 years (1.26, 1.18-1.35), and DM ≥ 5 years (1.34, 1.26-1.43) (*P* for trend < 0.001). Moreover, competing risk analysis consistently showed that the duration of DM was significantly associated with an increased risk of kidney and bladder cancer, even after completely adjusting for well-known complication of DM such as CKD and CVD (Model 3). In the original data set, baseline demographics were significantly different according to the duration of DM (**Table 1**). After IPTW, the baseline characteristics of the three groups were well-balanced (data not shown). The results of weighted Cox proportional hazards regression models with IPTW were also consistent with the main results.

Risk of kidney and bladder cancer in clinically relevant subgroups

We also conducted a subgroup analysis after categorizing participants according to several

Table 1. Demographics according to the duration of DM

	Duration of DM						DM		
	Normal	IFG	New-onset	< 5 years	≥ 5 years	*p*-value	No	Yes	*p*-value
No. of patients	6,720,488	2,210,420	286,647	289,752	266,155	-	8,930,908	842,554	-
Age (years)[a]	44.8 ± 13.8	49.6 ± 13.3	51.9 ± 12.7	58.3 ± 11.1	61.9 ± 9.9	< 0.0001	46.0 ± 13.9	57.2 ± 12.0	< 0.0001
Sex[b]						< 0.0001			< 0.0001
Male	3,470,802 (51.7)	1,370,317 (62.0)	204,155 (71.2)	168,595 (58.2)	145,126 (54.5)		4,841,119 (54.2)	517,876 (61.5)	
Female	3,249,686 (48.3)	840,103 (38.0)	82,492 (28.8)	121,157 (41.8)	121,029 (45.5)		4,089,789 (45.8)	324,678 (38.5)	
Height (cm)[a]	164.0 ± 9.2	164.3 ± 9.2	164.7 ± 8.9	161.7 ± 9.2	160.8 ± 9.0	< 0.0001	164.1 ± 9.2	162.5 ± 9.2	< 0.0001
Weight (kg)[a]	63.0 ± 11.5	66.0 ± 11.6	68.1 ± 12.0	66.5 ± 11.4	64.1 ± 10.6	< 0.0001	63.7 ± 11.6	66.3 ± 11.5	< 0.0001
BMI (kg/m^2)[a]	23.3 ± 3.1	24.4 ± 3.2	25.0 ± 3.4	25.4 ± 3.3	24.7 ± 3.1	< 0.0001	23.6 ± 3.2	25.0 ± 3.3	< 0.0001
WC (cm)[a]	78.9 ± 8.9	82.4 ± 8.6	85.0 ± 8.5	86.2 ± 8.4	85.3 ± 8.2	< 0.0001	79.7 ± 9.0	85.5 ± 8.4	< 0.0001
sBP (mmHg)[a]	120.5 ± 14.4	125.8 ± 15.0	129.8 ± 15.8	128.7 ± 15.5	129.0 ± 15.8	< 0.0001	121.8 ± 14.7	129.2 ± 15.7	< 0.0001
dBP (mmHg)[a]	75.3 ± 9.8	78.3 ± 10.0	80.6 ± 10.4	79.0 ± 9.9	77.6 ± 9.9	< 0.0001	76.0 ± 9.9	79.1 ± 10.1	< 0.0001
Smoking[b]						< 0.0001			< 0.0001
Non-smoker	4,131,690 (61.5)	1,205,429 (54.5)	133,638 (46.6)	166,974 (57.6)	167,567 (63.0)		5,337,119 (59.8)	468,179 (55.6)	
Ex-smoker	852,085 (12.7)	385,025 (17.4)	52,277 (18.2)	53,894 (18.6)	47,209 (17.7)		1,237,110 (13.9)	153,380 (18.2)	
Current-smoker	1,736,713 (25.8)	619,966 (28.1)	100,732 (35.1)	68,884 (23.8)	51,379 (19.3)		2,356,679 (26.3)	220,995 (26.2)	
Alcohol consumption[b]						< 0.0001			< 0.0001
None	3,483,576 (51.8)	1,041,417 (47.1)	123,148 (43.0)	175,251 (60.5)	178,143 (66.9)		4,524,993 (50.7)	476,542 (56.6)	
Mild	2,772,330 (41.3)	935,640 (42.3)	122,782 (42.8)	88,365 (30.5)	69,771 (26.2)		3,707,970 (41.5)	280,918 (33.3)	
Heavy	464,582 (6.9)	233,363 (10.6)	40,717 (14.2)	26,136 (9.0)	18,241 (6.9)		697,945 (7.8)	85,094 (10.1)	
Regular exercise[b]	1,160,912 (17.3)	419,514 (19.0)	54,368 (19.0)	64,290 (22.2)	64,758 (24.3)	< 0.0001	1,580,426 (17.7)	183,416 (21.8)	< 0.0001
Hypertension[b]	1,289,456 (19.2)	726,496 (32.9)	124,866 (43.6)	180,281 (62.2)	177,589 (66.7)	< 0.0001	2,015,952 (22.6)	482,736 (57.3)	< 0.0001
Dyslipidemia[b]	937,961 (14.0)	495,737 (22.4)	81,941 (28.6)	140,161 (48.4)	125,542 (47.2)	< 0.0001	1,433,698 (16.1)	347,644 (41.3)	< 0.0001
Chronic kidney disease[b]	326,694 (4.9)	146,988 (6.67)	21,662 (7.6)	31,508 (10.9)	45,832 (17.2)	< 0.0001	473,682 (5.3)	99,002 (11.8)	< 0.0001
Cardiovascular disease[b]	150,481 (1.8)	84,050 (3.0)	10,161 (2.7)	21,668 (4.3)	26,158 (5.3)	< 0.001	234,531 (2.1)	57,987 (4.2)	< 0.001
Fasting glucose (mg/dL)[a]	87.5 ± 7.7	107.8 ± 6.6	153.3 ± 37.0	137.4 ± 47.1	146.4 ± 50.8	< 0.0001	92.5 ± 11.5	145.6 ± 45.7	< 0.0001
Total cholesterol (mg/dL)[a]	192.5 ± 35.3	201.9 ± 37.3	207.5 ± 41.0	195.3 ± 41.5	188.4 ± 40.2	< 0.0001	194.9 ± 36.1	197.3 ± 41.6	< 0.0001
LDL cholesterol (mg/dL)[a]	112.2 ± 32.5	117.6 ± 35.1	116.7 ± 38.6	109.7 ± 37.8	105.9 ± 36.2	< 0.0001	113.5 ± 33.3	110.9 ± 37.8	< 0.0001
HDL cholesterol (mg/dL)[a]	56.1 ± 18.6	54.7 ± 18.7	52.9 ± 19.1	51.4 ± 21.4	51.0 ± 21.8	< 0.0001	55.8 ± 18.6	51.8 ± 20.8	< 0.0001
Triglyceride (mg/dL)[a]	123.4 ± 84.6	151.3 ± 103.3	195.9 ± 140.9	177.3 ± 120.9	163.2 ± 109.1	< 0.0001	130.3 ± 90.4	179.2 ± 125.4	< 0.0001

[a]Values are presented as mean ± standard deviation. [b]Values are presented as number (percentage). IFG, impaired fasting glucose; BMI, body mass index; WC, waist circumference; sBP, systolic blood pressure; dBP, diastolic blood pressure.

Table 2. Hazard ratios of kidney and bladder cancer according to the duration of DM

		No.	Event	Person-years	Incidence rate[a]	HR (95% CI)			
						Model 1[b]	Model 2[c]	Model 3[d]	Post-IPTW
Kidney cancer	DM duration								
	Normal	6,720,488	6,376	48,995,139	0.13	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	IFG	2,210,420	3,058	16,013,317	0.19	1.12 (1.07, 1.17)	1.05 (1.01, 1.10)	1.05 (1.00, 1.09)	1.00 (0.95, 1.04)
	New-onset	286,647	505	2,045,827	0.25	1.25 (1.14, 1.37)	1.13 (1.03, 1.24)	1.11 (1.01, 1.22)	1.08 (0.97, 1.21)
	< 5 years	289,752	610	2,066,518	0.30	1.26 (1.16, 1.37)	1.11 (1.02, 1.20)	1.09 (1.00, 1.19)	1.24 (1.11, 1.38)
	≥ 5 years	266,155	670	1,859,191	0.36	1.37 (1.26, 1.48)	1.25 (1.15, 1.36)	1.21 (1.11, 1.31)	1.50 (1.34, 1.66)
	DM								
	No	8,930,908	9,434	65,008,457	0.15	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Yes	842,554	1,785	5,971,536	0.30	1.25 (1.18, 1.31)	1.14 (1.09, 1.20)	1.12 (1.06, 1.18)	1.20 (1.13, 1.27)
Bladder cancer	DM duration								
	Normal	6,720,488	7,256	48,993,557	0.15	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	IFG	2,210,420	3,794	16,011,835	0.24	1.06 (1.02, 1.10)	1.05 (1.01, 1.09)	1.04 (1.00, 1.08)	0.93 (0.90, 0.97)
	New-onset	286,647	643	2,045,392	0.31	1.14 (1.05, 1.23)	1.10 (1.01, 1.19)	1.09 (1.00, 1.18)	0.98 (0.89, 1.08)
	< 5 years	289,752	969	2,065,502	0.47	1.31 (1.22, 1.40)	1.26 (1.18, 1.35)	1.24 (1.16, 1.33)	1.27 (1.15, 1.40)
	≥ 5 years	266,155	1,107	1,857,998	0.60	1.37 (1.29, 1.46)	1.34 (1.26, 1.43)	1.32 (1.23, 1.40)	1.63 (1.48, 1.78)
	DM								
	No	8,930,908	11,050	65,005,392	0.17	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Yes	842,554	2,719	5,968,893	0.46	1.26 (1.21, 1.32)	1.23 (1.17, 1.28)	1.21 (1.16, 1.26)	1.22 (1.16, 1.28)

[a]Incidence per 1,000 person-years. [b]Model 1 was adjusted for age and sex. [c]Model 2 was adjusted for age, sex, smoking status, alcohol consumption, regular activity, and BMI. [d]Model 3 was adjusted for age, sex, smoking status, alcohol consumption, regular activity, BMI, CKD, and CVD. IFG, impaired fasting glucose; HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; IPTW, inverse probability of treatment weighting.

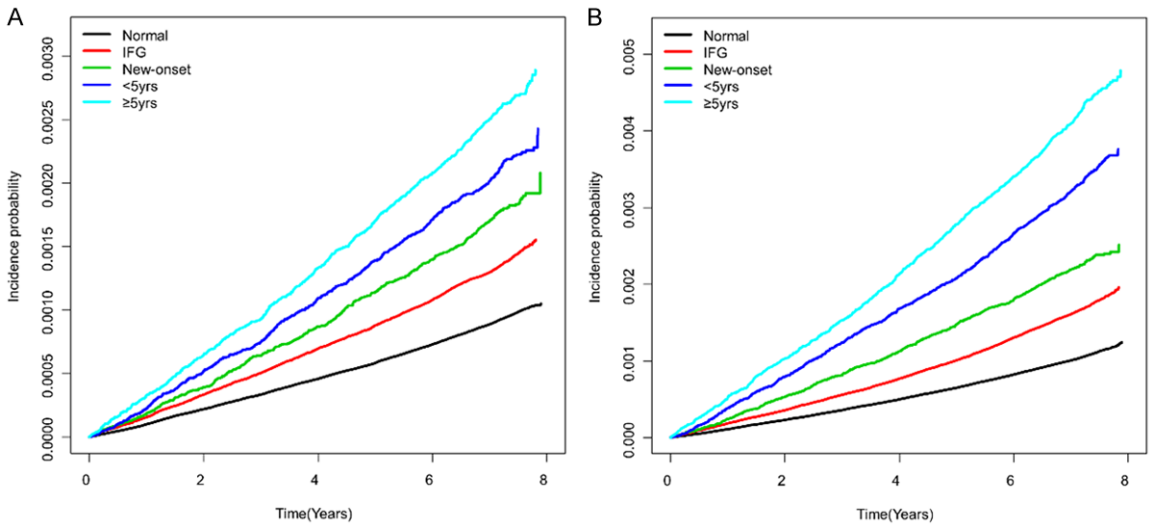

Figure 2. Incidence probability of kidney and bladder cancer according to the duration of DM. A. Incidence probability of kidney cancer. B. Incidence probability of bladder cancer.

variables (**Figure 3**). We found similar trends of increasing risk of kidney and bladder cancer in participants according to the duration of DM in subgroup analyses. The risk of kidney cancer according to the duration of DM was more prominent in non-obese participants (*P* for interactions = 0.0162) and in younger participants (*P* for interactions = 0.0789). Additionally, the risk of bladder cancer according to the glycemic status and duration of DM was more prominent in younger participants (*P* for interactions = 0.0001).

Discussion

In this study, we analyzed data from 9,773,462 participants in a nationwide population-based cohort study with a mean observation period of 7.3 years and found an increased risk of kidney and bladder cancer according to the duration of DM. Many previous studies have reported the association between DM and the risk of kidney and bladder cancer. To the best of our knowledge, however, this is the first study in which the risk of kidney and bladder cancer increases in participants with IFG, a non-diabetic hyperglycemic status, and the risk of kidney and bladder cancer is proportional according to the duration of DM rather than simply being dependent on the presence of DM. These results were consistent after adjusting for various confounding factors.

DM has been suggested as an important risk factor for kidney and bladder cancer; however, conflicting results have been presented in this regard [19, 22-26]. In a nationwide cohort study of 9,777,133 participants from Korea, the incidence rate of kidney and bladder cancer showed a remarkable increase in participants with DM regardless of combined obesity [19]. In a prospective analysis of 118,177 women in the Nurses' Health Study, the multivariate adjusted HR of kidney cancer in women with DM was 1.60 (95% CI 1.19-2.17) [22]. In two large prospective cohort studies of 117,570 women from the Nurses' Health Study and 48,866 men from the Health Professionals Follow-Up Study, DM was associated with an increased risk of kidney cancer in women by 53% but not in men [24]. Similarly, for bladder cancer, DM was related to an increased risk of bladder cancer (adjusted odds ratio = 2.2, 95% CI, 1.3 to 3.8) in a small case-control study [23]. In a cohort analysis of 41,836 women from the Iowa Women's Health Study, the HR of bladder cancer in women with DM was 1.69 (95% CI 1.40-2.41) [25]. However, a recent meta-analysis with bias analysis for unmeasured confounding in 151 cohorts assessed the robustness of the observational associations between DM and cancer to unmeasured confounding [26]. Although this meta-analysis showed that DM was associated with an increased risk of kidney (HR 1.32, 95% CI 1.21-1.44) and bladder (1.19; 1.09-1.29) cancer, bias analysis for unmeasured confounding showed that the association with kidney cancer was less robust to unmeasured

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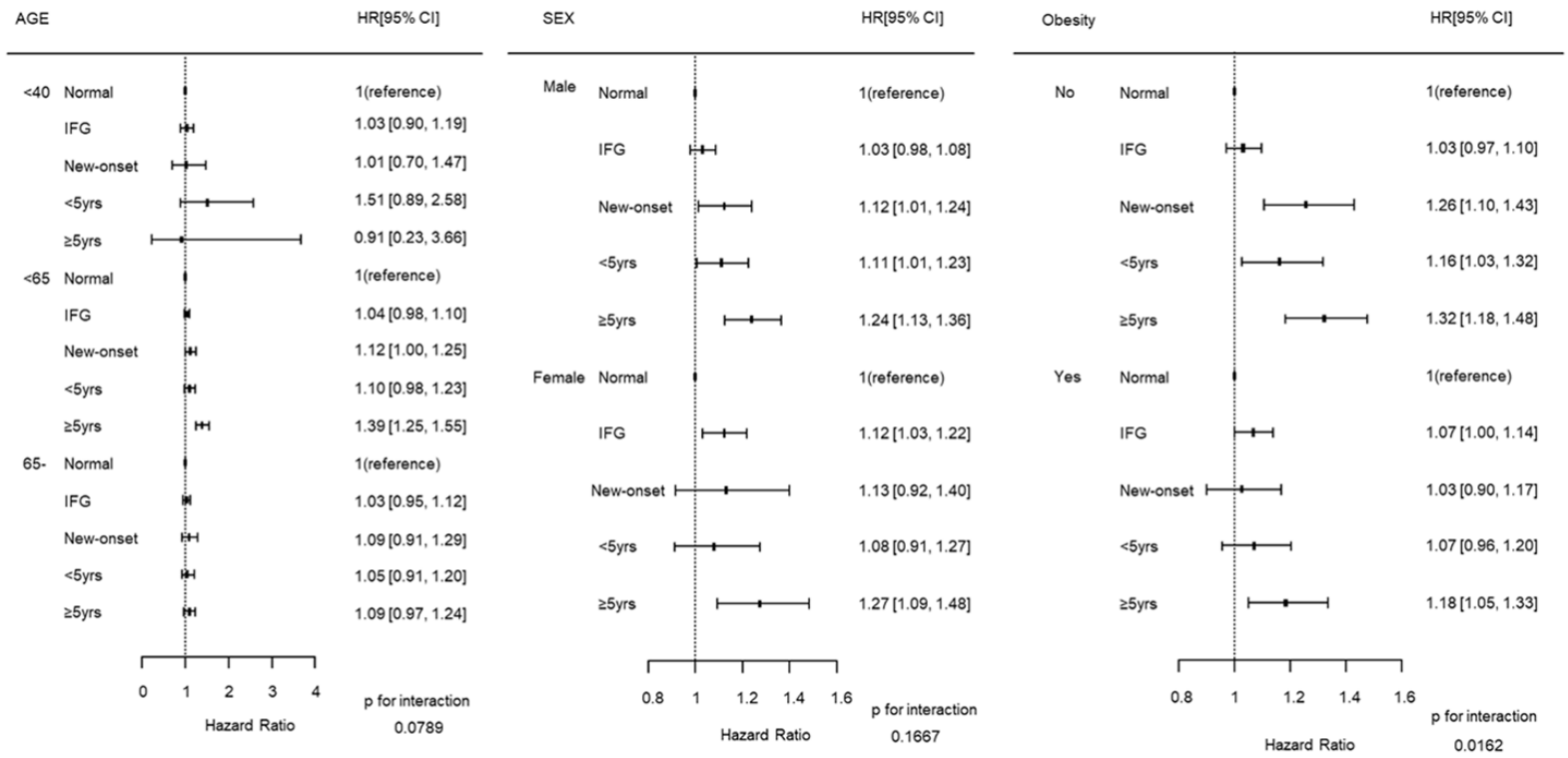
AGE
HR[95% CI]
<40 Normal 1(reference)
IFG 1.03 [0.90, 1.19]
New-onset 1.01 [0.70, 1.47]
<5yrs 1.51 [0.89, 2.58]
≥5yrs 0.91 [0.23, 3.66]
<65 Normal 1(reference)
IFG 1.04 [0.98, 1.10]
New-onset 1.12 [1.00, 1.25]
<5yrs 1.10 [0.98, 1.23]
≥5yrs 1.39 [1.25, 1.55]
65- Normal 1(reference)
IFG 1.03 [0.95, 1.12]
New-onset 1.09 [0.91, 1.29]
<5yrs 1.05 [0.91, 1.20]
≥5yrs 1.09 [0.97, 1.24]
0 1 2 3 4
Hazard Ratio
p for interaction
0.0789
SEX
HR[95% CI]
Male Normal 1(reference)
IFG 1.03 [0.98, 1.08]
New-onset 1.12 [1.01, 1.24]
<5yrs 1.11 [1.01, 1.23]
≥5yrs 1.24 [1.13, 1.36]
Female Normal 1(reference)
IFG 1.12 [1.03, 1.22]
New-onset 1.13 [0.92, 1.40]
<5yrs 1.08 [0.91, 1.27]
≥5yrs 1.27 [1.09, 1.48]
0.8 1 1.2 1.4 1.6
Hazard Ratio
p for interaction
0.1667
Obesity
HR[95% CI]
No Normal 1(reference)
IFG 1.03 [0.97, 1.10]
New-onset 1.26 [1.10, 1.43]
<5yrs 1.16 [1.03, 1.32]
≥5yrs 1.32 [1.18, 1.48]
Yes Normal 1(reference)
IFG 1.07 [1.00, 1.14]
New-onset 1.03 [0.90, 1.17]
<5yrs 1.07 [0.96, 1.20]
≥5yrs 1.18 [1.05, 1.33]
0.8 1 1.2 1.4 1.6
Hazard Ratio
p for interaction
0.0162

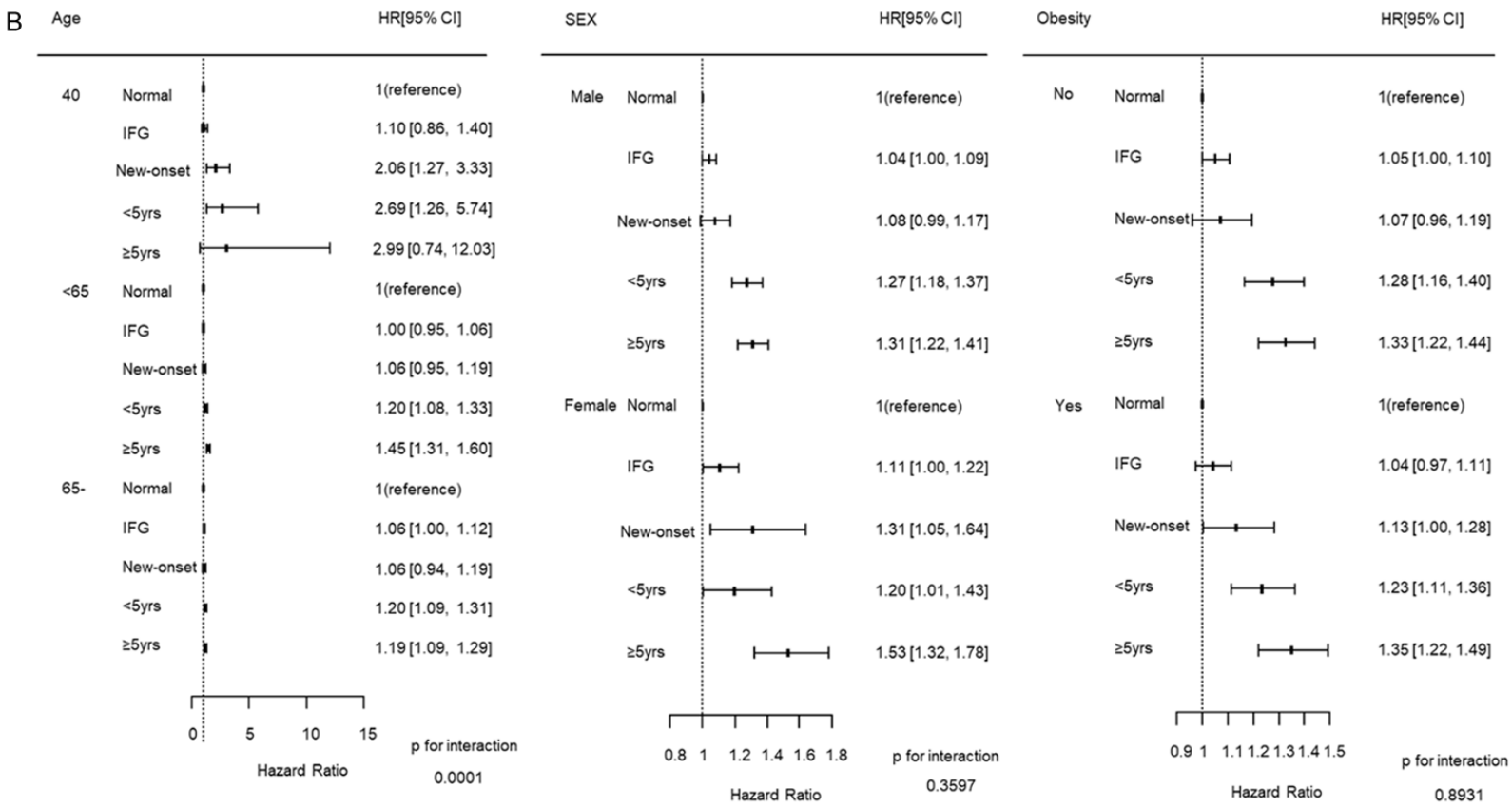

Figure 3. Hazard ratios (95% CI) of kidney and bladder cancer according to the duration of DM in clinically relevant subgroups. A. Kidney cancer. B. Bladder cancer

confounding and the association with bladder cancer was unlikely to be causal. In our study, after adjusting for potential confounders, we found that DM was associated with an increased risk of kidney cancer by 14% and bladder cancer by 23%.

The underlying mechanism linking DM and cancer has not been fully elucidated. Several well-known biological links between DM and cancer are as follows: 1) abnormal insulin/insulin-like growth factor axis activity, 2) hyperglycemia, 3) inflammatory cytokines, 4) sex hormone biosynthesis pathway, and 5) increased oxidative stress responsible for DNA damage [27]. In addition to these common mechanisms, a recent experiment suggests that the accumulation of oxidative DNA damage through the hyperactivation of the Akt/tuberin/mTOR pathway in DM may play an important role in the development of kidney cancer [28]. Another explanation for the pathogenesis of bladder cancer includes urinary tract infections that occur frequently in patients with DM. Bacterial cell components can produce inflammation and cellular proliferation, possibly promoting carcinogenesis [29]. It can be assumed that the risk of kidney and bladder cancer increases as different biological mechanisms of DM complimentarily accumulate over time.

There are two notable points in our study. First, IFG was associated with an increased risk of kidney (HR 1.05, 95% CI: 1.01-1.10) and bladder cancer (1.05, 1.01-1.09). In a recent meta-analysis, IFG was associated with an overall 15% increased risk of cancer (particularly stomach/colorectum, liver, pancreas, breast, and endometrium), but was not associated with the risk of kidney or bladder cancer [30]. However, when we further analyzed the previous studies included in the meta-analysis in detail, the included studies for meta-analysis were not about the risk of cancer incidence but about the cancer mortality [31, 32]. Thus, our study is the first to show that IFG increases the risk of kidney and bladder cancer. More importantly, our study suggests that IFG, as well as DM, may be considered as a surrogate sign for risk factors for kidney and bladder cancer.

Another interesting detail of our study is that the risk of kidney and bladder cancer is proportional according to the duration of DM. Very few studies have been reported on the relationship between the risk of kidney and bladder cancer and the duration of DM. A cohort study linking the Danish National Diabetprostes Register and Cancer Registry reported significantly different results from our findings [33]. The general shape of the overall cancer risk by duration of DM showed a high risk at the beginning and a subsequent decrease during the first year. This may be due to the indication bias, a potential mix-up between cause and effect. The probability of detecting prevalent asymptomatic cancers might increase due to many medical tests performed on participants early in the diagnosis of DM. We tried to overcome this bias by adding a lag-time into the exposure [34]. Similar to ours, another cohort study using the Reggio Emilia diabetes registry reported an increasing overall cancer risk for DM duration up to 10 years from diagnosis [35].

We should consider some limitations of this study. First, because information about TNM staging and histologic subtypes of kidney and bladder cancer was not included, the impact of the duration of DM on the prognosis of kidney and bladder cancer could not be evaluated. Second, due to the nature of national health screening, effect of glycemic control status was not considered sufficiently. Additionally, information on the diverse combinations of antidiabetic medications used in the participants was not analyzed. Finally, this finding is confined to one Asian ethnic group. However, our study was based on a large cohort encompassing the entire South Korean population, allowing us to make comprehensive adjustments for confounding variables and to perform clinically relevant subgroup analyses.

The novel result of our study is that the risk of kidney and bladder cancer increased in participants with IFG, as well as DM. Additionally, a longer duration of DM was significantly associated with an increased incidence of kidney and bladder cancer. These findings suggest that participants with IFG and DM, especially those with longer than 5 years, should be considered a more vulnerable population in need of early detection of kidney and bladder cancer.

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Disclosure of conflict of interest

None.

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