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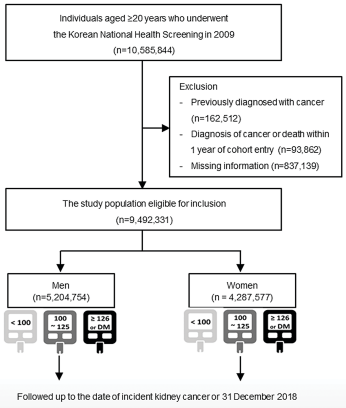
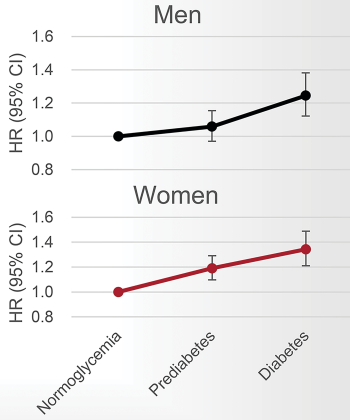
- Kidney cancer predominantly affects men, suggesting a biological protection against kidney cancer in women.
- We investigated the dose-response association between glycemic status and the risk of kidney cancer in men and women.





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ARTICLE HIGHLIGHTS

- **Why did we undertake this study?** Although kidney cancer predominantly affects men, the association between glycemic status and the risk of developing kidney cancer in men and women is unclear.
- **What is the specific question(s) we wanted to answer?** Dose the association between glycemic status and the risk of developing kidney cancer differs by sex?
- **What did we find?** Diabetes increases the risk of kidney cancer in men and women, and prediabetes increases the risk only in women.
- **What are the implications of our findings?** Diabetes may be a risk factor for kidney cancer in men and women, and women with prediabetes have an increased risk of kidney cancer.

Association Between Glycemic Status and the Risk of Kidney Cancer in Men and Women: A Nationwide Cohort Study

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Kidney cancer predominantly affects men, suggesting a biological protection against kidney cancer in women. We investigated the dose-response association between glycemic status and kidney cancer risk in men and women.

RESEARCH DESIGN AND METHODS

In this nationwide cohort study, 9,492,331 adults without cancer who underwent national health screening in 2009 were followed up until 31 December 2018. We estimated kidney cancer risk using multivariable Cox proportional hazard regression models after adjusting for potential confounders.

RESULTS

During the 78.1 million person-years of follow-up, incident kidney cancer occurred in 8,834 men and 3,547 women. The male-to-female ratio of the incidence rate was 2.1:1 in never-smokers with normoglycemia (17.8 vs. 8.5/100,000 person-years). Among never-smokers, men with diabetes, but not prediabetes, had an increased risk of kidney cancer (adjusted hazard ratio [aHR] 1.25 [95% CI 1.12–1.38] and 1.06 [0.97–1.15], respectively). Among never-smokers, women with both diabetes and prediabetes had an increased risk (aHR 1.34 [95% CI 1.21–1.49] and 1.19 [1.10–1.29], respectively) (P_{trend} <0.01). Among smokers, men and women with diabetes had 49% and 85% increased kidney cancer risk (aHR 1.49 [95% CI 1.37–1.61] and 1.85 [1.26–2.73], respectively).

CONCLUSIONS

Glycemic status and kidney cancer risk exhibited a dose-response association in women. Diabetes, but not prediabetes, was associated with an increased risk in men. Although women have a lower risk of kidney cancer than men, women with even prediabetes have an increased risk. These findings should not be overlooked when monitoring for kidney complications.

The incidence of kidney cancer is increasing, particularly among young populations in Europe and North America (1,2). Kidney cancer is predominant in men, with a 2:1 male-to-female incidence ratio that is consistent across time, geographic regions, and age groups, indicating a biological protection against kidney cancer in women (1–4). Therefore, sex differences should be considered when evaluating the association between risk factors and kidney cancer risk.

A large body of evidence suggests that type 2 diabetes (hereafter diabetes) increases the risk of diverse malignancies (5). However, the effects of prediabetes and

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diabetes on kidney cancer risk remain unclear. Although some cohort studies have examined the association between diabetes and kidney cancer risk after adjusting for smoking and obesity, they have reported inconsistent results: positive only in women (6), positive only in men (7), or null (8–11) associations. Moreover, these studies had limitations owing to self-reported diabetes assessments (6–9), lack of prediabetes data (6–9), and lack of adjustments for chronic kidney disease (6,7,9–11) or hypertension (5,7,10,11). Previous studies also had limited statistical power for sex-specific analysis (<60 kidney cancer cases in men or women with diabetes) (6,7) or no sex-specific analysis (8–11). Notably, there has been no evidence of a dose-response association between glycemic status and kidney cancer risk and whether the association differs by sex.

Therefore, we conducted this nationwide cohort study and investigated the sex-specific dose-response association between glycemic status and kidney cancer risk after adjusting for potential confounders. We examined this association among never-smokers and smokers because smoking is a significant risk factor for kidney cancer (1,12). We followed up >9 million participants without cancer at baseline who underwent the Korean national health screening for 10 years.

RESEARCH DESIGN AND METHODS

Data Source and Study Population

The Korean National Health Insurance Service (KNHIS) is a national single-payer health insurance system that covers 97% of South Koreans, with the remaining 3% being covered by the Medical Aid Program. In addition, the KNHIS administers a standardized biennial national health examination to all citizens aged ≥40 years and all employees regardless of age (13). The overall participation rate of the eligible population was ∼72%. We obtained health examination results (laboratory test results, anthropometric measurements, and a self-administered questionnaire on health-related behavior) and claims data (medical treatment, prescription drugs, and disease diagnosis based on the ICD-10 Clinical Modification [ICD-10-CM] code) from the KNHIS database.

Figure 1 shows the flowchart of the study population. This study initially included 10,585,844 individuals aged ≥20 years who underwent KNHIS health examinations between 1 January and 31 December 2009. We excluded participants

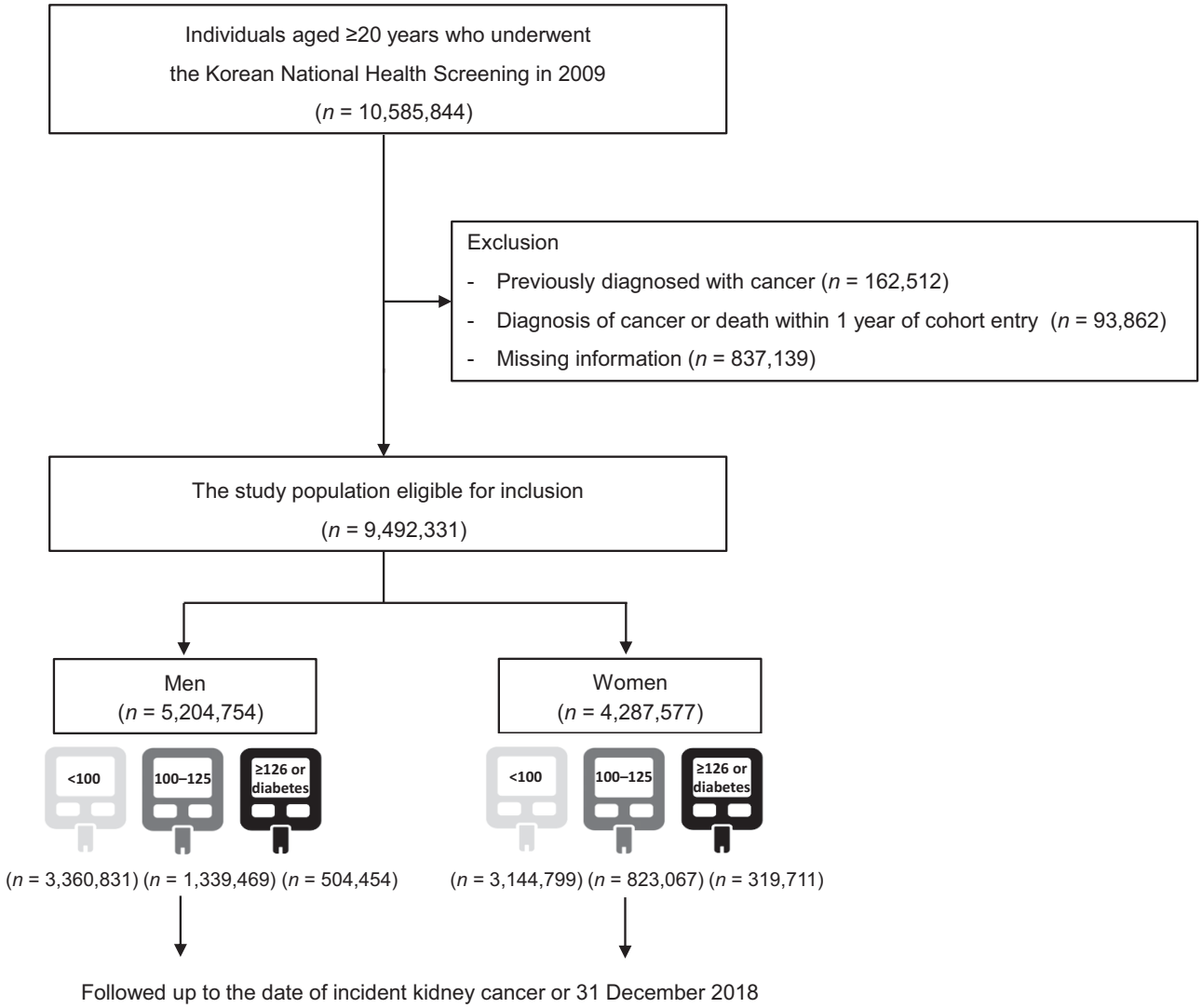

Figure 1—Selection flow of the study population. Glycemic status: normoglycemia (<100 mg/dL), prediabetes (100–125 mg/dL), and diabetes (≥126 mg/dL).

who had been diagnosed with cancer prior to cohort entry (n = 162,512). To minimize the effects of preexisting diseases and overestimation due to early detection bias (5), we excluded participants who developed cancer or died within the first year of cohort entry (n = 93,862). Those who lacked data on the variables used in this study were excluded (n = 837,139). In total, 9,492,331 individuals were enrolled in this study. The study participants were followed up until the date of kidney cancer development, death, or 31 December 2018, whichever came first.

The study protocol was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea (approval number SMC2019–08–106). The requirement for written informed consent was waived because deidentified and anonymized information, as provided by the KNHIS, was used for the analysis. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Definition of Glycemic Status

The fasting plasma glucose (FPG) level of each participant was determined during the national health examinations. Blood samples were collected after overnight fasting by health care professionals at the KNHIS-certified hospitals. The glycemic status of the participants was categorized as normoglycemia (FPG $<$100 mg/dL), impaired fasting glucose (FPG 100–125 mg/dL), and diabetes (FPG $\geq$126 mg/dL or at least one claim per year of antidiabetic medication prescription under ICD-10-CM code E11.x–E14.x). This definition was based on a consensus of widely used results from previous studies (13–16). Prediabetes was defined using the impaired fasting glucose criterion based on the American Diabetes Association's three prediabetes criteria (17).

Definition of Incident Kidney Cancer

The end point of this study was a new diagnosis of kidney cancer. We identified new cases of kidney cancer between January 2009 and December 2018 using the ICD-10-CM code (C64, malignant neoplasm of the kidney except in the renal pelvis) during hospitalization and a reimbursement code for cancer (V193). Since 2006, the KNHIS policy has enhanced health coverage for intractable diseases, including cancer. The KNHIS registers all patients with a confirmed diagnosis of cancer by using a special reimbursement code (V193). Physicians and medical institutions need to certify cancer diagnosis to enable a patient to benefit from a reduced copayment rate of up to 5% for cancer-related examinations and treatments.

Definition of the Clinical Variables

Detailed information on health-related behaviors was obtained using a standardized self-administered questionnaire during the national health examinations. The participants were classified as never-smokers or smokers based on the smoking status. Never-smokers were defined as those who had smoked $<$100 cigarettes in their lifetime. To measure a person's cumulative exposure to tobacco, smokers were further categorized according to the smoking pack-years, which was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For alcohol consumption, participants were classified according to the average amount of alcohol consumed per day as follows: none, light-to-moderate ($<$30 g of alcohol/day), or heavy drinkers ($\geq$30 g of alcohol/day) (16,18). Regular physical activity was defined as performing $\geq$20 min of vigorous-intensity physical activity at least three times per week or $\geq$30 min of moderate-intensity physical activity at least five times per week.

Anthropometric measurements of the participants, including height, weight, and waist circumference, were measured directly during the national health examinations. BMI was calculated by dividing weight by height squared (kg/m^2). Systolic and diastolic blood pressure were measured in a seated position after at least 5 min of rest. Serum total cholesterol, HDL-cholesterol, LDL-cholesterol, and creatinine levels were measured. Estimated glomerular filtration rate (eGFR) was calculated using a creatinine-based equation from the MDRD (19). Chronic kidney disease was defined as an eGFR $<$60 mL/min/1.73 m^2 (20).

Dyslipidemia was defined based on serum total cholesterol levels $\geq$240 mg/dL or ICD-10-CM code (E78) with lipid-lowering drug prescriptions (21). Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or ICD-10-CM codes (I10–I13 and I15) with claims for antihypertensive medications. Low-income status included those in the lowest quartile of the required insurance fee or those who received free medical care.

Statistical Analysis

Baseline characteristics were compared using ANOVA for continuous variables and χ^2 test for categorical variables. The incidence rate of kidney cancer was calculated by dividing the number of incident cases by 100,000 person-years for each category of exposure in men and women. We conducted a sex-specific analysis of the dose-response association between glycemic status and kidney cancer risk in never-smokers and smokers. We used multivariable Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% CIs for kidney cancer development based on glycemic and smoking status in men and women. Model 1 was adjusted for age. Model 2 was adjusted for potential confounders, such as age, alcohol consumption, physical activity, income status, and BMI. Model 3 was adjusted for potential confounders and mediators, such as age, alcohol consumption, physical activity, income status, BMI, hypertension, dyslipidemia, and chronic kidney disease. We also conducted a sensitivity analysis of dose-response associations between glycemic status and kidney cancer risk in men and women, considering individuals who developed incident diabetes during the study follow-up. We censored individuals with normoglycemia and prediabetes when a claim was registered as a diagnostic code or a drug prescription for diabetes during the follow-up. All statistical tests were two-sided, and significance was set at $P < 0.05$. All statistical analyses were performed using the SAS software, version 9.3 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics of the Study Population

During the 78.1 million person-years of follow-up, 12,381 (8,834 men and 3,547 women) were newly diagnosed with kidney cancer. Table 1 shows the baseline characteristics of the study population according to the glycemic status in men and women. Normoglycemia, prediabetes, and diabetes were found in 3,360,831

Table 1—Baseline characteristics of the study population

	Men				Women			
	Normoglycemia (*n* = 3,360,831)	Prediabetes (*n* = 1,339,469)	Diabetes (*n* = 504,454)	*P* value	Normoglycemia (*n* = 3,144,799)	Prediabetes (*n* = 823,067)	Diabetes (*n* = 319,711)	*P* value
Age (years), mean ± SD	43.3 ± 13.3	47.7 ± 12.8	54.9 ± 11.9	<0.001	46.7 ± 14.2	52.8 ± 13.3	60.9 ± 11.3	<0.001
Anthropometrics, mean ± SD								
BMI (kg/m^2)	23.9 ± 3.0	24.6 ± 4.0	25.0 ± 3.1	<0.001	22.8 ± 3.2	24.1 ± 4.3	25.2 ± 3.6	<0.001
Waist circumference (cm)	82.6 ± 8.1	84.7 ± 8.1	87.0 ± 8.3	<0.001	75.0 ± 8.9	78.7 ± 9.2	83.3 ± 9.2	<0.001
Systolic BP (mmHg)	123.0 ± 13.5	127.0 ± 14.4	129.5 ± 15.5	<0.001	117.9 ± 15.1	124.0 ± 16.0	128.9 ± 16.5	<0.001
Diastolic BP (mmHg)	77.2 ± 9.4	79.5 ± 9.9	80.0 ± 10.2	<0.001	73.3 ± 9.9	76.6 ± 10.3	77.9 ± 10.2	<0.001
Laboratory findings, mean ± SD								
Fasting glucose (mg/dL)	87.7 ± 7.8	108.0 ± 6.6	150.1 ± 51.1	<0.001	87.3 ± 7.6	107.3 ± 6.4	141.7 ± 46.9	<0.001
Total cholesterol (mg/dL)	192.5 ± 38.7	200.1 ± 43.4	195.2 ± 47.8	<0.001	193.3 ± 40.2	206.0 ± 44.5	202.5 ± 48.8	<0.001
HDL-cholesterol (mg/dL)	54.1 ± 32.3	53.8 ± 31.2	51.5 ± 33.0	<0.001	60.9 ± 34.7	59.1 ± 33.6	55.1 ± 37.4	<0.001
LDL-cholesterol (mg/dL)	111.7 ± 38.6	114.3 ± 38.9	106.8 ± 43.2	<0.001	113.5 ± 37.7	123.0 ± 38.6	117.2 ± 42.6	<0.001
eGFR (mL/min/1.73 m^2)	89.3 ± 54.7	85.6 ± 37.9	85.0 ± 38.9	<0.001	88.4 ± 36.7	84.4 ± 28.9	80.9 ± 29.9	<0.001
Alcohol consumption, *n* (%)				<0.001				<0.001
None	994,717 (29.6)	366,550 (27.4)	179,464 (35.6)		2,261,912 (71.9)	624,764 (75.9)	280,193 (87.6)	
Light-to-moderate	1,937,190 (57.6)	750,041 (56.0)	242,295 (48.0)		846,429 (26.9)	187,925 (22.8)	37,402 (11.7)	
Heavy	428,924 (12.8)	222,878 (16.6)	82,695 (16.4)		36,458 (1.2)	10,378 (1.3)	2,116 (0.7)	
Smoking status, *n* (%)				<0.001				<0.001
Never	1,042,497 (31.0)	404,475 (30.2)	157,359 (31.2)		2,985,479 (94.9)	784,826 (95.4)	305,400 (95.5)	
Ever	2,318,334 (69.0)	934,994 (69.8)	347,095 (68.8)		159,320 (5.1)	38,241 (4.6)	14,311 (4.5)	
Regular exercise, *n* (%)	649,550 (19.3)	275,714 (20.6)	122,027 (24.2)	<0.001	478,043 (15.2)	134,800 (16.4)	56,945 (17.8)	<0.001
Low-income status, *n* (%)	495,643 (14.8)	187,253 (14.0)	87,615 (17.4)	<0.001	660,664 (21.0)	174,922 (21.3)	63,658 (19.9)	<0.001
Comorbidities, *n* (%)								
Hypertension	675,397 (20.1)	433,714 (32.4)	277,677 (55.1)	<0.001	588,807 (18.7)	279,995 (34.0)	196,614 (61.5)	<0.001
Dyslipidemia	426,907 (12.7)	257,769 (19.2)	180,168 (35.7)	<0.001	482,492 (15.3)	224,732 (27.3)	157,990 (49.4)	<0.001
Chronic kidney disease	169,092 (5.0)	90,614 (6.8)	49,286 (9.8)	<0.001	206,741 (6.6)	77,992 (9.5)	53,954 (16.9)	<0.001
Hypoglycemic medications, *n* (%)								
Insulin	0 (0)	0 (0)	37,453 (7.4)	—	0 (0)	0 (0)	33,725 (10.6)	—
Sulfonylurea	0 (0)	0 (0)	234,073 (46.4)	—	0 (0)	0 (0)	181,561 (56.8)	—
Metformin	0 (0)	0 (0)	225,964 (44.8)	—	0 (0)	0 (0)	178,355 (55.8)	—
Thiazolidinedione	0 (0)	0 (0)	42,021 (8.3)	—	0 (0)	0 (0)	29,609 (9.3)	—
Dipeptidyl peptidase 4 inhibitors	0 (0)	0 (0)	25,331 (5.0)	—	0 (0)	0 (0)	19,711 (6.2)	—

BP, blood pressure.

(64.6%), 1,339,469 (25.7%), and 504,454 (9.7%) men and 3,144,799 (73.3%), 823,067 (19.2%), and 319,711 (7.5%) women, respectively. Individuals with diabetes were the oldest and had the highest proportion of nondrinkers and regular exercisers (all $P < 0.01$).

Supplementary Table 1 shows the baseline characteristics of the study population according to sex with and without kidney cancer. Both men and women with kidney cancer were older and had higher FPG levels and BMI than those without kidney cancer (all $P < 0.01$). Patients with kidney cancer had a higher proportion of nondrinkers than those without kidney cancer (all $P < 0.01$). Patients with kidney cancer had a higher proportion of individuals with diabetes, hypertension, dyslipidemia, and chronic kidney disease (all $P < 0.01$).

Sex-Specific Dose-Response Association Between Glycemic Status and Kidney Cancer Risk in Never-Smokers

As shown in Table 2, among never-smokers with normoglycemia, the male-to-female ratio of the incidence rate was 2.1 (17.8 vs. 8.5/100,000 person-years). Among never-smokers, men with diabetes, but not prediabetes, had an increased kidney cancer risk, after adjusting for all potential confounders (model 2: HR 1.25 [95% CI 1.12–1.38] and 1.06 [0.97–1.15], respectively). However, never-smoking women with diabetes and prediabetes had an increased kidney cancer risk, after adjusting for all potential confounders (model 2: HR 1.34 [95% CI 1.21–1.49] and 1.19 [1.10–1.29], respectively) ($P_{trend} < 0.01$). Among never-smokers, a dose-response association was observed between glycemic status and kidney cancer risk in women. Even after adjusting for all mediators (model 3), the results for women remained statistically significant (Supplementary Table 2). Sensitivity analysis considering individuals who developed incident diabetes during the study follow-up also showed similar results for both men and women (Supplementary Table 3).

Sex-Specific Dose-Response Association Between Glycemic Status and Kidney Cancer Risk in Smokers

Among ever-smokers with diabetes, the male-to-female ratio of the incidence rate was 1.6 (36.7 vs. 22.9/100,000 person-years) (Table 3). Among smokers, individuals with diabetes had the highest risk of kidney cancer in both men and women (all $P < 0.01$).

Men with diabetes who smoked had a 49% increased kidney cancer risk (HR 1.49 [95% CI 1.37–1.61]) compared with never-smoking men with normoglycemia. Women with diabetes who smoked had an 85% increased kidney cancer risk (HR 1.85 [95% CI 1.26–2.73]) compared with never-smoking women with normoglycemia. Even after adjusting for mediators (model 3), the results remained significant (Supplementary Table 4). The results were similar in the sensitivity analysis, considering individuals who developed incident diabetes during the study follow-up (Supplementary Table 5). A detailed analysis was conducted on men according to the smoking pack-years (Supplementary Table 6), daily smoking amount (cigarettes per day) (Supplementary Table 7), and smoking duration (years) (Supplementary Table 8) because of the adequate sample size of smoking men. Men with diabetes had the highest risk of developing kidney cancer across all smoking categories.

Kidney Cancer Risk According to Antidiabetic Medication Use Among Never-Smokers With Diabetes

We performed further analysis on the risk of kidney cancer according to antidiabetic medication use among never-smoking men and women with diabetes (Supplementary Table 9).

There was no significant association between specific antidiabetic medications and the risk of kidney cancer in men. In women, dipeptidyl peptidase 4 inhibitor users had a lower risk of kidney cancer than nonusers (model 2: HR 0.45 [95% CI 0.16–0.92]).

CONCLUSIONS

In this large-scale nationwide cohort study, we found that both prediabetes and diabetes were associated with an increased risk of kidney cancer in a dose-response manner in women who had never smoked. In men who had never smoked, diabetes, but not prediabetes, was associated with an increased risk. Among smokers, men and women with diabetes had the highest risk of kidney cancer compared with normoglycemic men and women. The relative excess risk of kidney cancer associated with diabetes and prediabetes was slightly higher in women than in men regardless of the smoking status. Sex differences in the dose-response association between glycemic status and kidney cancer risk were observed in our study. Although women are less likely to develop kidney cancer, women with prediabetes are at an increased risk of kidney cancer among never-smokers and smokers.

Some cohort studies have reported inconsistent results regarding the association between diabetes and kidney cancer risk after adjusting for smoking and BMI. In the Nurses' Health Study and the Health Professionals Follow-Up Study, diabetes was associated with an increased risk of renal cell carcinoma only in women (HR 1.53 [95% CI 1.14–2.04];

Table 2—Sex-specific dose-response associations between glycemic status and kidney cancer risk in never-smokers

						HR (95% CI)	
	Glycemic status	*n*	Events, *n*	Person-Years	IR[a]	Model 1	Model 2
Men	Normoglycemia	1,042,497	1,533	8,589,563	17.8	1 (reference)	1 (reference)
	Prediabetes	404,475	783	3,307,184	23.7	1.33 (1.22–1.45)	1.06 (0.97–1.15)
	Diabetes	157,359	474	1,241,761	38.2	2.15 (1.94–2.38)	1.25 (1.12–1.38)
Women	Normoglycemia	2,985,479	2,108	24,786,760	8.5	1 (reference)	1 (reference)
	Prediabetes	784,826	823	6,489,438	12.7	1.49 (1.38–1.62)	1.19 (1.10–1.29)
	Diabetes	305,400	471	2,472,833	19.0	2.24 (2.03–2.48)	1.34 (1.21–1.49)

Model 1: nonadjusted; model 2: adjusted for age, alcohol consumption, physical activity, income, and BMI. [a]Incidence rate (IR) of kidney cancer per 100,000 person-years.

Table 3—Sex-specific dose-response associations between glycemic status and kidney cancer risk in ever-smokers

	Glycemic status	*n*	Events, *n*	Person-years	IR[a]	HR (95% CI) Model 1	HR (95% CI) Model 2
Men							
Never-smokers	Normoglycemia	1,042,497	1,533	8,589,563	17.8	1 (reference)	1 (reference)
Smokers	Normoglycemia	2,318,334	3,306	19,091,408	17.3	0.97 (0.91–1.03)	1.12 (1.06–1.19)
	Prediabetes	934,994	1,724	7,646,836	22.5	1.27 (1.18–1.36)	1.22 (1.14–1.31)
	Diabetes	347,095	1,014	2,762,062	36.7	2.07 (1.91–2.24)	1.49 (1.37–1.61)
Women							
Never-smokers	Normoglycemia	2,985,479	2,108	24,786,760	8.5	1 (reference)	1 (reference)
Smokers	Normoglycemia	159,320	77	1,312,993	5.9	0.69 (0.55–0.87)	0.91 (0.73–1.15)
	Prediabetes	38,241	42	312,390	13.4	1.58 (1.17–2.15)	1.56 (1.15–2.13)
	Diabetes	14,311	26	113,408	22.9	2.71 (1.84–3.99)	1.85 (1.26–2.73)

Model 1: nonadjusted; model 2: adjusted for age, alcohol consumption, physical activity, income, and BMI. [a]Incidence rate (IR) of kidney cancer per 100,000 person-years.

59 cases of diabetes), but not in men (HR 0.89 [95% CI 0.56–1.41]; 21 cases of diabetes) (6). However, in a cohort study in Japan, men with diabetes had an increased risk of kidney cancer (HR 1.92 [95% CI 1.06–3.46]; 13 cases of diabetes), but not women (HR 1.36 [95% CI 0.32–5.78]; 2 cases of diabetes) (7). Other cohort studies did not show an association between diabetes and kidney cancer risk after adjusting for confounders (8–11). Moreover, these previous studies had limited statistical power to determine sex differences in the association because of the inclusion of a small number of kidney cancer cases in men or women with diabetes (6,7) or did not present the result by sex (8–11). Furthermore, these studies assessed diabetes solely through self-report (6–9). Thus, misclassification of the diabetes status may exist, and information on prediabetes was not obtained. A systematic review and meta-analysis regarding the sex differences in the association between diabetes and cancer reported diabetes as a risk factor for kidney cancer in both women and men, and the excess risk of cancer associated with diabetes is greater in women than in men. These findings are consistent with our findings (22).

To the best of our knowledge, this is the first study to show a dose-response association between glycemic status and kidney cancer risk in women but a null association in men using large-scale nationwide health screening and health insurance claims data.

The mechanisms by which diabetes and prediabetes increase the risk of kidney cancer may include the mitosis-promoting effect of insulin on tumor cells (23), cell proliferation via IGF-I activation (23), chronic oxidative stress (24), DNA damage caused by proinflammatory cytokine induction (24–26), and a weakened immune response by hyperglycemia (27–29). However, it is unclear why these proposed mechanisms may be more significantly applicable in women with hyperglycemia than in men during kidney cancer development. Notably, kidney cancer is one of the most immunogenic cancers, and immunotherapy is a critical component of medical treatment (30,31). Growing evidence suggests that the immunologic protection against kidney cancer development in women largely contributes to the male predominance in the incidence of kidney cancer (1,3). Generally, adult females have stronger innate and adaptive immune responses than males, which may enhance the surveillance of cancerous and precancerous cells, contributing to a lower incidence of kidney cancer in women (32,33). Given that hyperglycemia impairs the immune response (27–29), the immunologic protection against kidney cancer in females may be offset by hyperglycemia-mediated pathophysiology. Thus, kidney cancer risk in women may increase more significantly than that in men when exposed to hyperglycemia. In addition, a combination of hyperglycemia and smoking may cause synergistic detrimental effects on kidney cancer risk via a variety of possible biological mechanisms, including the synergism of immune response weakening, chronic oxidative stress, inflammation, DNA damage, and cytotoxicity (24,25,27–29,34–36). Hyperglycemia, which is associated with renal vascular damage (24) and altered urine filtration (37), can also affect the exposure of the kidney to tobacco carcinogens.

The strengths of this study are as follows: first, this study is one of the largest cohort studies based on data of >9 million individuals with a follow-up period of 10 years. The KNHIS database accurately tracked the clinical course after cohort entry. Secondly, we used longitudinally collected blood test results, lifestyle factors, anthropometric parameters, and comprehensive medical records. The glycemic status of each participant was determined using the FPG level, diagnostic code, and antidiabetic medication. Thus, the prediabetic status could be defined, and there was no recall bias associated with the definition of diabetes. Third, we used both ICD-10 CM diagnostic codes (C codes) during hospitalization and national registration codes (V codes) to identify kidney cancer with high diagnostic accuracy. Fourth, we performed the analysis after adjusting for potential confounders, including chronic kidney disease, smoking, hypertension, and BMI. Fifth, newly diagnosed individuals with diabetes and prediabetes may have had an early detection bias, in which they might have been diagnosed with kidney cancer earlier because of more frequent physician visits, which may have overestimated their risk of developing kidney cancer (5). To address this issue, we excluded those who developed cancer or died within the first year of cohort entry.

Our study had some limitations. First, data on family history of kidney cancer were not considered because of lack of data. Second, pathological subtypes

of kidney cancer were not considered. However, renal cell carcinoma accounts for 85–90% of all kidney cancer types (38). Third, we lacked information on HbA_{1c}, postload plasma glucose, and random plasma glucose levels. A possible misclassification of glycemic status and underestimation of the prevalence of diabetes may exist. Therefore, the risk of diabetes-associated kidney cancer may be underestimated. Fourth, individuals excluded due to missing data (7.9%) may have characteristics different from those of included participants. There may have been selection bias. Fifth, our nationwide cohort was large, with a general population of over nine million individuals. However, our findings were based on the population of a single country, and we were unable to determine whether ethnic differences existed.

In conclusion, we revealed that diabetes was associated with an increased risk of kidney cancer in both men and women, regardless of smoking status. Prediabetes was associated with an increased risk of kidney cancer in women but not in men. The relatively increased risk of kidney cancer associated with diabetes and prediabetes was higher in women than in men. Although kidney cancer is predominant in men, women with prediabetes are at an increased risk of kidney cancer. This finding should not be overlooked during the monitoring of individuals with hyperglycemia for kidney complications. In addition, given the increasing incidence of kidney cancer, particularly in the younger population, adequate management of diabetes and prediabetes may help to reduce the risk of developing kidney cancer. Our findings provide important insights into the sex-specific pathophysiological role of hyperglycemia in kidney cancer development, warranting further investigation.

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References

1. Scelo G, Larose TL. Epidemiology and risk factors for kidney cancer. J Clin Oncol 2018;36:3574–3581
2. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol 2010;7:245–257
3. Scelo G, Li P, Chanudet E, Muller DC. Variability of sex disparities in cancer incidence over 30 years: the striking case of kidney cancer. Eur Urol Focus 2018;4:586–590
4. Lucca I, Klatte T, Fajkovic H, de Martino M, Shariat SF. Gender differences in incidence and outcomes of urothelial and kidney cancer. Nat Rev Urol 2015;12:585–592
5. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. Diabetes Care 2015;38:264–270
6. Graff RE, Sanchez A, Tobias DK, et al. Type 2 diabetes in relation to the risk of renal cell carcinoma among men and women in two large prospective cohort studies. Diabetes Care 2018;41:1432–1437
7. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006;166:1871–1877
8. Macleod LC, Hotaling JM, Wright JL, et al. Risk factors for renal cell carcinoma in the VITAL study. J Urol 2013;190:1657–1661
9. Khan M, Mori M, Fujino Y, et al.; Japan Collaborative Cohort Study Group. Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study. Asian Pac J Cancer Prev 2006;7:253–259
10. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194–202
11. Setiawan VW, Stram DO, Nomura AM, Kolonel LN, Henderson BE. Risk factors for renal cell cancer: the multiethnic cohort. Am J Epidemiol 2007;166:932–940
12. Capitanio U, Bensalah K, Bex A, et al. Epidemiology of renal cell carcinoma. Eur Urol 2019;75:74–84
13. Lee YH, Han K, Ko SH, Ko KS; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Data analytic process of a nationwide population-based study using national health information database established by National Health Insurance Service. Diabetes Metab J 2016;40:79–82
14. Ko SH, Han K, Lee YH, et al.; TaskForce Team for the Diabetes Fact Sheet of the Korean Diabetes Association. Past and current status of adult type 2 diabetes mellitus management in Korea: a National Health Insurance Service database analysis. Diabetes Metab J 2018;42:93–100
15. Kim WJ, Lee SJ, Lee E, Lee EY, Han K. Risk of incident dementia according to glycemic status and comorbidities of hyperglycemia: a nationwide population-based cohort study. Diabetes Care 2022;45:134–141
16. Park JH, Hong JY, Han K, Park YS, Park JO. Light-to-moderate alcohol consumption increases the risk of biliary tract cancer in prediabetes and diabetes, but not in normoglycemic status: a nationwide cohort study. J Clin Oncol 2022;40:3623–3632
17. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S13–S27
18. Park JH, Han K, Hong JY, Park YS, Park JO. Association between alcohol consumption and pancreatic cancer risk differs by glycaemic status: a nationwide cohort study. Eur J Cancer 2022;163:119–127
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–470
20. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–147
21. Park JH, Han K, Hong JY, et al. Changes in metabolic syndrome status are associated with altered risk of pancreatic cancer: a nationwide cohort study. Gastroenterology 2022;162:509–520.e7
22. Ohkuma T, Peters SAE, Woodward M. Sex differences in the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events. Diabetologia 2018;61:2140–2154
23. Ibrahim YH, Yee D. Insulin-like growth factor-I and cancer risk. Growth Horm IGF Res 2004;14:261–269
24. Tabak O, Gelisgen R, Erman H, et al. Oxidative lipid, protein, and DNA damage as oxidative stress markers in vascular complications of diabetes mellitus. Clin Invest Med 2011;34:E163–E171
25. Pereira CS, Molz P, Palazzo RP, et al. DNA damage and cytotoxicity in adult subjects with prediabetes. Mutat Res 2013;753:76–81
26. Kosti A, Harry Chen HI, Mohan S, Liang S, Chen Y, Habib SL. Microarray profile of human kidney from diabetes, renal cell carcinoma and renal cell carcinoma with diabetes. Genes Cancer 2015;6:62–70
27. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 1999;26:259–265
28. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 diabetes and its impact on the immune system. Curr Diabetes Rev 2020;16:442–449
29. Daryabor G, Atashzar MR, Kabelitz D, Meri S, Kalantar K. The effects of type 2 diabetes mellitus on organ metabolism and the immune system. Front Immunol 2020;11:1582
30. Díaz-Montero CM, Rini BI, Finke JH. The immunology of renal cell carcinoma. Nat Rev Nephrol 2020;16:721–735

31. Xu W, Atkins MB, McDermott DF. Checkpoint inhibitor immunotherapy in kidney cancer. Nat Rev Urol 2020;17:137–150
32. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016;16: 626–638
33. Haupt S, Caramia F, Klein SL, Rubin JB, Haupt Y. Sex disparities matter in cancer development and therapy. Nat Rev Cancer 2021;21: 393–407
34. Stämpfli MR, Anderson GP. How cigarette smoke skews immune responses to promote infection, lung disease and cancer. Nat Rev Immunol 2009;9:377–384
35. Sopori M. Effects of cigarette smoke on the immune system. Nat Rev Immunol 2002;2: 372–377
36. Abe R, Yamagishi S. AGE-RAGE system and carcinogenesis. Curr Pharm Des 2008;14:940–945
37. Wasada T, Kuroki H, Arii H, et al. Hyperglycemia facilitates urinary excretion of C-peptide by increasing glomerular filtration rate in non-insulin-dependent diabetes mellitus. Metabolism 1995;44:1194–1198
38. Shuch B, Amin A, Armstrong AJ, et al. Understanding pathologic variants of renal cell carcinoma: distilling therapeutic opportunities from biologic complexity. Eur Urol 2015;67: 85–97