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Original Article

New findings on the effects of diabetes and anti-diabetic drugs on prostate cancer

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Abstract: Although diabetes mellitus (DM) is known to be related to the risk of many cancers, there are few studies on the risk of prostate cancer (PC) depending on the status of hyperglycemia, such as prediabetes and DM. Thus, the objective of this study was to determine the effect of each status of hyperglycemia on the risk of PC. In a Korean National Health Insurance Service database cohort, a total of 560,413 individuals who were followed until 2018 were analyzed. The risk of PC in patients with impaired fasting glucose (IFG) and new onset DM as well as all DM was determined. Associations of metabolic syndrome (MetS) components with the risk of PC according to glycemic status were evaluated. The association of anti-diabetic drugs with the incidence of PC was also analyzed. The presence of new-onset and all DM showed a significant reduction of the risk of PC in adjusted models. There was a trend that the presence of DM reduced the risk of PC regardless of the presence of MetS components. Regarding associations of anti-diabetic drugs with the incidence of PC, DM patients who were taking less than three drugs of oral hypoglycemic agents including metformin showed a reduced risk of PC compared to patients without using metformin. This study supports an inverse relationship between DM and the risk of PC. However, the risk of PC can be different depending on glycemic status and sorts of anti-diabetic drugs.

Keywords: Diabetes mellitus, hypoglycemic agents, prostate neoplasms

Introduction

Although several factors have emerged as risk factors for prostate cancer (PC), the established risk factors are age, family history of the disease, and genetic factors [1]. A systematic review and meta-analysis reported smoking, diet, physical activity, certain medications and occupational factors as possible PC risk factors in 2022 [2]. Diabetes mellitus (DM) is known to increase the incidence and worsen the prognosis of various cancers [3-5]. However, an inverse relationship between DM and PC has been confirmed. A meta-analysis of studies from 1971 to 2005 has confirmed a reverse relationship between DM and PC (hazard ratio [HR]: 0.84, 95% confidence interval [CI]: 0.76, 0.93) [6].

There are few known studies on the risk of PC depending on the stage of DM such as prediabetes and DM including newly developed DM. Thus, the objective of this study was to determine the risk of PC in patients with impaired fasting glucose (IFG) and new-onset DM as well as all diabetes using large population-based data from the Korea National Health Insurance Service database (KNHIS).

In addition, studies have shown that metabolic syndrome (MetS) is a disease that is often accompanied by DM patients and increases the risk of PC [7, 8]. However, the EPICAP population-based control study did not find a significant association between MetS and the number of MetS criteria met with PC risk [9]. There are few studies on what happens to PC risks when MetS is accompanied by diabetes. Thus, in this study, we tried to identify PC risks according to the presence or absence of Mets components in IFG and DM patients.

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Studies on the correlation between anti-diabetic drugs and the risk of PC are also insufficient. In particular, several studies have shown inconsistencies in the effect of metformin, one of the most commonly used drugs for DM, on the risk of PC [10-13]. Thus, the risk of PC related to the use of anti-diabetic drugs including metformin and insulin was also investigated in this study. This study was conducted according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) reporting checklist.

Materials and methods

Patient cohort

The NHIS covers about 50 million people of Korean population. A total of 10,585,843 people who had undergone the health checkup of KNHIS in 2009 were assessed in this study. We excluded those aged younger than 65 years, females, and persons who had a history of cancer in recent one year. We analyzed 560,413 people and they were followed until 2018. PC patients were patients diagnosed with PC in this cohort in a 10-year follow-up period. Age, income status, body mass index (BMI), smoking history, alcohol consumption, regular exercise, comorbidities (DM, hypertension, dyslipidemia, chronic kidney disease), height, weight, waist circumference (WC), blood pressure, fasting blood glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride were examined.

Definitions

DM was defined as a fasting plasma glucose (FPG) value of ≥ 126 mg/dL or International Classification of Diseases (ICD)-10 codes for DM (E11.x-E14.x) with a claim for antidiabetic medication, or both. Antidiabetic medications included sulfonylurea, metformin, dipeptidyl peptidase 4 (DPP-4) inhibitor, alpha-glucosidase inhibitor, meglitinide, thiazolidinedione, and insulins. Glycemic status was classified into four groups as follows: 1) normoglycemia (FPG < 100 mg/dL), 2) IFG (FPG 100-125 mg/dL), 3) new-onset DM (FPG ≥ 126 mg/dL at the index date and no claims for the ICD-10 code of DM or antidiabetic medication before the index date), and 4) all DM (defined as above).

Obesity was defined as a BMI ≥ 25 kg/m^2 by the Asia-Pacific criteria of the World Health Organization guidelines. Abdominal obesity was defined as a waist circumference ≥ 90 cm in men and ≥ 85 cm in women by the definition of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) guidelines. Hypertension was defined as a blood pressure ≥ 140/90 mmHg or at least one claim per year for the prescription of antihypertensive medication under ICD-10 codes I10-I13 and I15. Dyslipidemia was defined as serum total cholesterol ≥ 240 mg/dL or taking a lipid-lowering drug.

We defined the development of PC if the patient was given a diagnostic code of C61 according to ICD-10 or V193 according to special calculation. We excluded patients who were younger than 65 years or diagnosed with any cancer before 2009. Finally, we analyzed 560,413 men for 10 years (from 2009 to 2018).

Statistical analysis

We performed statistical analyses using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Baseline characteristics of study participants are expressed as means ± standard deviation for continuous variables and as a percentage of the number of categorical variables. Values were compared using the independent t-test for continuous variables and the chi-square test for categorical variables. The incidence of PC was measured by dividing the number of patients by 1,000 person-years. Cox proportional risk analysis was performed to evaluate the incidence of PC according to glycemic status. We adjusted variables such as age, BMI, smoking status, drinking level, regular exercise, hypertension, and dyslipidemia.

Results

Baseline characteristics

Characteristics comparing normal, IFG and DM are shown in **Table 1**. Among 560,413 participants, 156,396 (27.9%) were diagnosed with IFG and 117,194 (20.9%) were diagnosed with DM. The proportion of obesity with a BMI ≥ 30 kg/m^2 was significantly higher in those with IFG and DM than in the normal population (*P* <

Table 1. Comparison of baseline characteristics according to the presence of IFG and DM

n	Normal	IFG	DM	*p*-value
	286823	156396	117194	
Age, years	71 (66-76)	71 (66-76)	71 (66-75)	< .0001
Income, Lowest Q1	62172 (21.68)	34231 (21.89)	24878 (21.23)	0.0002
BMI 5Level				< .0001
< 18.5	15098 (5.26)	5515 (3.53)	2617 (2.23)	
< 23	123096 (42.92)	56550 (36.16)	36156 (30.85)	
< 25	75503 (26.32)	43490 (27.81)	33630 (28.7)	
< 30	69937 (24.38)	47943 (30.65)	41609 (35.5)	
≥ 30	3189 (1.11)	2898 (1.85)	3182 (2.72)	
Smoking				< .0001
Non	125677 (43.82)	69790 (44.62)	51820 (44.22)	
Ex	83522 (29.12)	49144 (31.42)	37276 (31.81)	
Current	77624 (27.06)	37462 (23.95)	28098 (23.98)	
Drinking				< .0001
Non	156407 (54.53)	75639 (48.36)	63147 (53.88)	
Mild	103519 (36.09)	62464 (39.94)	42079 (35.91)	
Heavy	26897 (9.38)	18293 (11.7)	11968 (10.21)	
Regular exercise	69698 (24.3)	40666 (26)	32281 (27.54)	< .0001
Hypertension	145412 (50.7)	93959 (60.08)	85383 (72.86)	< .0001
Dyslipidemia	52257 (18.22)	35773 (22.87)	40186 (34.29)	< .0001
Chronic kidney disease	33074 (11.53)	21277 (13.6)	22352 (19.07)	< .0001
Height, cm	164.39±5.85	164.74±5.79	165.04±5.7	< .0001
Weight, kg	62.49±9.08	64.37±9.21	65.97±9.14	< .0001
BMI, kg/m^2	23.09±2.88	23.68±2.9	24.19±2.89	< .0001
Waist Circumference, cm	83.41±8.02	85.13±7.99	87.15±7.91	< .0001
Fasting glucose, mg/dL	88.8±7.57	108.84±6.86	138.08±44.8	< .0001
Systolic BP, mmHg	128.93±16.01	131.58±16.16	131.71±16.31	< .0001
Diastolic BP, mmHg	78.16±10.05	79.22±10.15	78.17±10.28	< .0001
Total Cholesterol, mg/dL	188.52±35.16	193.46±36.82	184.35±38.82	< .0001
HDL -C, mg/dL	54.51±34.08	54.79±36.71	51.08±31.23	< .0001
LDL -C, mg/dL	110.94±37.7	112.64±38.92	104.2±40.56	< .0001
Triglyceride, mg/dL	110.62 (110.42-110.83)	123.32 (123-123.64)	133.48 (133.06-133.9)	< .0001

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IFG, impaired fasting glucose; DM, Diabetes mellitus.

0.001). There was a significant difference in life style such as smoking, drinking, and regular exercise according to the presence of IFG and DM. The proportion of hypertension, dyslipidemia, and chronic kidney disease was significantly higher in those with IFG and DM than in those without abnormal blood glucose levels. Waist circumference, fasting glucose, blood pressure, and serum triglyceride were significantly higher in those with IFG and DM than in those without abnormal blood glucose levels (all $P < 0.001$).

Relationship between glycemic status and the incidence of PC

Over a 10-year follow-up period, 17,638 people were newly diagnosed as PC. **Table 2** presents results of the association between glycemic status and the risk of PC through COX regression analysis. The presence of new-onset and all DM showed a significant reduction in the risk of PC. The presence of IFG was not related to a significant risk of PC by unadjusted models (1) and adjusted models (2 to 4).

Table 2. Multivariate Cox proportional hazard model for incidence of PC according to glycemic status

	N	Event	Duration	IR, per 1000 PY	Model 1	*p*-value	Model 2	*p*-value	Model 3	*p*-value	Model 4	*p*-value
DM						0.0009		0.0027		< .0001		< .0001
No	443,219	14,265	3,331,030	4.282	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Yes	117,194	3,373	843,199	4.000	0.938 (0.904, 0.974)		0.944 (0.909, 0.980)		0.916 (0.882, 0.952)		0.904 (0.870, 0.939)	
DM 4Level						0.002		0.0041		< .0001		< .0001
Normal	286,823	9,163	2,154,857	4.252	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
IFG	156,396	5,102	1,176,173	4.338	1.020 (0.986, 1.056)		1.025 (0.990, 1.061)		1.003 (0.969, 1.038)		0.997 (0.963, 1.032)	
New onset DM	26,559	773	192520	4.015	0.948 (0.880, 1.020)		0.956 (0.888, 1.029)		0.936 (0.869, 1.007)		0.928 (0.862, 0.999)	
All DM	117,194	3,373	843,199	4.000	0.945 (0.908, 0.983)		0.952 (0.916, 0.991)		0.917 (0.881, 0.955)		0.903 (0.867, 0.940)	

Model 1: Non-adjusted; Model 2: Adjusted for age; Model 3: Adjusted for age, BMI, income, smoking, drinking, and regular exercise; Model 4: Adjusted for age, BMI, income, smoking, drinking, regular exercise, hypertension, and dyslipidemia. PC, prostate cancer; IFG, impaired fasting glucose; DM, Diabetes mellitus; IR, incidence rate.

Table 3. Associations of metabolic syndrome components and the risk of PC according to glycemic status

		DM 3Level	N	PROSTATE	DURATION	RATE	HR (95% C.I)	*p* for interaction
Age	< 75 years	Normal	231258	7387	1791892.75	4.12246	1 (Ref.)	0.9301
		IFG	128169	4186	991733.31	4.22089	1.000 (0.962, 1.038)	
		DM	97157	2806	721062.7	3.89148	0.901 (0.862, 0.942)	
	≥ 75 years	Normal	55565	1776	362963.97	4.89305	1 (Ref.)	
		IFG	28227	916	184439.79	4.96639	0.987 (0.912, 1.069)	
		DM	20037	567	122136.53	4.64235	0.910 (0.827, 1.000)	
Obesity	No	Normal	213697	6601	1588220.57	4.15622	1 (Ref.)	0.549
		IFG	105555	3281	783097.22	4.18977	0.990 (0.949, 1.032)	
		DM	72403	1941	509207.87	3.8118	0.888 (0.843, 0.935)	
	Yes	Normal	73126	2562	566636.15	4.52142	1 (Ref.)	
		IFG	50841	1821	393075.88	4.63269	1.014 (0.955, 1.077)	
		DM	44791	1432	333991.36	4.28754	0.928 (0.869, 0.990)	
Abdominal obesity	No	Normal	222757	6959	1666443.88	4.17596	1 (Ref.)	0.0664
		IFG	111021	3433	831286.42	4.12974	0.972 (0.933, 1.013)	
		DM	72806	2009	519002.97	3.87088	0.901 (0.857, 0.948)	
	Yes	Normal	64066	2204	488412.84	4.51258	1 (Ref.)	
		IFG	45375	1669	344886.68	4.83927	1.061 (0.996, 1.131)	
		DM	44388	1364	324196.27	4.20733	0.918 (0.857, 0.982)	

Hypertension	No	Normal	141411	4303	1073445.92	4.00859	1 (Ref.)	0.702
		IFG	62437	1943	473618.02	4.10246	1.009 (0.956, 1.065)	
		DM	31811	847	232646.73	3.64071	0.888 (0.825, 0.956)	
	Yes	Normal	145412	4860	1081410.81	4.49413	1 (Ref.)	
		IFG	93959	3159	702555.08	4.49644	0.990 (0.946, 1.035)	
		DM	85383	2526	610552.5	4.13724	0.907 (0.864, 0.952)	
Dyslipidemia	No	Normal	234566	7393	1760116.66	4.20029	1 (Ref.)	0.7344
		IFG	120623	3854	904792.05	4.25954	0.994 (0.956, 1.033)	
		DM	77008	2137	550367.03	3.88286	0.893 (0.851, 0.938)	
	Yes	Normal	52257	1770	394740.06	4.48396	1 (Ref.)	
		IFG	35773	1248	271381.05	4.5987	1.010 (0.940, 1.086)	
		DM	40186	1236	292832.21	4.22085	0.925 (0.860, 0.995)	

PC, prostate cancer; IFG, impaired fasting glucose; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval.

Table 4. Multivariate Cox proportional hazard model for incidence of PC according to anti-diabetic drug

	N	Event	Duration	IR, per 1000 PY	Model 1	*p*-value	Model 2	*p*-value	Model 3	*p*-value	Model 4	*p*-value
Normal	286,823	9,163	2154857	4.252	1 (ref.)	0.0025	1 (ref.)	< .0001	1 (ref.)	< .0001	1 (ref.)	< .0001
OHA < 3 Without Metformin	21,305	652	154865	4.210	0.994 (0.918, 1.076)		0.996 (0.920, 1.078)		0.949 (0.877, 1.028)		0.933 (0.861, 1.011)	
OHA < 3 With Metformin	37,088	1,072	273326	3.922	0.925 (0.868, 0.985)		0.935 (0.877, 0.996)		0.894 (0.839, 0.952)		0.878 (0.823, 0.836)	
OHA ≥ 3 Without Metformin	308	4	2131	1.877	0.445 (0.167, 1.185)		0.447 (0.168, 1.192)		0.426 (0.160, 1.136)		0.415 (0.156, 1.106)	
OHA ≥ 3 With Metformin	18,921	573	135729	4.222	0.998 (0.917, 1.086)		1.008 (0.926, 1.096)		0.974 (0.895, 1.060)		0.955 (0.878, 1.040)	
Insulin	13,013	299	84628	3.533	0.842 (0.750, 0.994)		0.846 (0.754, 0.949)		0.815 (0.726, 0.914)		0.794 (0.707, 0.892)	

Model 1: Non-adjusted; Model 2: Adjusted for age; Model 3: Adjusted for age, BMI, income, smoking, drinking, and regular exercise; Model 4: Adjusted for age, BMI, income, smoking, drinking, regular exercise, hypertension, and dyslipidemia. PC, prostate cancer; OHA, oral hypoglycemic agents.

Association of metabolic syndrome components and PC by glycemic status

There was a trend that the presence of IFG and DM reduced the risk of PC regardless of the presence of the component of Mets (**Table 3**). The presence of MetS components such as obesity, abdominal obesity, hypertension, and dyslipidemia did not have a significant effect on the risk of PC according to glycemic status (*p*-value for interaction > 0.05).

Relationship between anti-diabetic drugs and the incidence of PC

We studied the association between anti-diabetic drugs and the incidence of PC. Those who were using metformin did not show a significant risk of PC compared to those without prescribing metformin (Model 1: HR = 0.965 (0.885-1.052), Model 2: HR = 0.974 (0.893-1.062), Model 3: HR = 0.982 (0.900-1.071), Model 4: HR = 0.981 (0.900-1.070)). However, for DM patients who were taking less than three drugs of oral hypoglycemic agents (OHA), using metformin reduced the risk of PC compared to those without using metformin (**Table 4**). This trend was not shown for DM patients who were taking more than three drugs of OHA. Those who were using insulin showed a significantly lower risk of PC compared to those without abnormal blood glucose levels in the adjusted model.

Discussion

Many studies have reported an inverse relationship between DM and PC. In an analysis of men aged 67-74 years in the 2014-2015 SEER-Medicare data, men with diabetes had a significantly lower incident rate of PC compared with men without diabetes in both 2006-2011 [RR = 0.89, 95% confidence interval (CI) 0.87-0.91] and 2012-2015 (RR = 0.92, 95% CI: 0.89-0.95) [14]. Other study has reported that the preventive effect of DM on the prevalence of PC is greater in patients with long-term type 2 DM than in short-term type 2 DM patients [15]. The EPICAP population-based control study, which included 819 incident prostate cancer cases and 879 controls analyzed in 2012-2013, also showed that PC risk decreased with increasing duration of diabetes (p-trend = 0.008) [9].

Studies in other countries and races have shown similar results on the relationship between DM and PC. A prospective cohort study in 23 centers in Europe showed that those with diabetics had a 26% decrease in PC risk compared to those without DM (HR, 0.74; 95% CI, 0.63-0.86) [16]. In a population-based study of a multiethnic cohort, the risk of PC in diabetics was lower than in those without DM (relative risk = 0.81, 95% CI: 0.74, 0.87). The inverse association was identified in all ethnicities and relative risk was ranged from 0.65 (95% CI: 0.50, 0.84) in European Americans to 0.89 (95% CI: 0.77, 1.03) in African Americans (*p*-heterogeneity, 0.32) [17]. A study using SEER-Medicare data from 2011-2015 compared the relationship between DM and PC in Black Non-Hispanic (BNH) men and White Non-Hispanic (WNH) men. In WNH men, the overall age-adjusted incidence rate of PC was significantly lower in men with diabetes [RR = 0.88, 95% Confidence Interval (CI) 0.86-0.90]. However, in BNH men, there was no difference in the incidence rate of PC by diabetes status (RR = 1.01, 95% CI: 0.96-1.07) [18]. These results suggest that the effect of diabetes on PC risk may differ by race, and larger studies with more diverse populations are needed to analyze the effects of diabetes on PC risk.

There are also studies on associations of obesity, MetS, and DM with PC risk. The inverse relationship between body mass index (BMI) and PSA levels has been shown by several previous studies of various races [17, 19]. However, in a study of the UK Biobank, MetS was not significantly associated with PC risk (hazard ratio [HR] = 0.99, 95% confidence interval [CI] = 0.92-1.06). In addition, the components of MetS, such as triglyceride, HDL, BP, and WC were not associated with PC risk [20]. A study using two-sample Mendelian randomization found that unfavorable adiposity, favorable adiposity, and BMI were not associated with PC risk, suggesting that adiposity is unlikely to be associated with PC risk through these metabolic factors [21]. However, a population-based study of the Korea Nationwide cohort has confirmed that the risk of PC is increased when BMI is increased (18.5 to 22.9 kg/m^2) in diabetics, suggesting a possible relationship between obesity and PC in diabetics [22]. Thus, based on the previous findings, obesity and MetS do not appear to have an established association with PC risk in DM patients.

Several hypotheses could explain the inverse relationship between DM and PC. First, DM can

lower the concentration of testosterone circulating in the bloodstream, which is known to have a significant role in the growth of the prostate and the development of PC [23-25]. Second, DM patients are characterized by hyperglycemia and relative hypoinsulinemia. Therefore, insulin reduction can have a growth-inhibitory effect on PC cells [26, 27]. Third, DM can be associated with low prostate-specific antigen (PSA) concentration, increased prostate size, and lower prevalence in screening tests for PC, which can eventually explain a decrease in the detection of localized biopsy-detected PCs [1, 28-30]. Finally, there are studies suggesting that diabetes medications especially metformin may reduce the risk of PC. A study from Lithuania with a retrospective cohort design showed a significantly lower risk of PC in diabetics in all age groups, with a further risk reduction in metformin users (SIR 0.71, 95% CI: 0.68-0.75) compared to never-users (SIR 0.88, 95% CI: 0.80-0.96) [31]. From the retrospective analysis of the KNHIS database, PC risk was reduced in the metformin group, with HRs decreasing with cumulative duration of metformin treatment [32].

However, there are conflicting findings regarding the effect of metformin on PC risk. In a cohort study of PC Data Base Sweden 3.0, the diabetic patients who used metformin did not have a significant reduction in the risk of PC (HR = 0.96, 95% CI = 0.77-1.19), while diabetic patients who used insulin or sulfonylurea had a reduced risk (HR = 0.73, 95% CI = 1-955) compared to patients without using anti-diabetic medications [15]. For another study analyzed on metformin, in 2018, a meta-analysis of 18 cohort or nested case-control studies from PubMed and Web of Science databases showed no significant association of metformin use with PC risk (RR 0.97, 95% CI: 0.80-1.16, P = 0.711) [33]. In the meta-analysis of observational studies from systematic literature search (PubMed, Embase and Cochrane Library), there was no significant association between the use of metformin, thiazolidinedione, sulfonylureas, insulin or dipeptidyl peptidase-4 inhibitors and PC risk (All *p*-values > 0.05) [34].

There are two main hypotheses for the mechanisms of metformin's anti-cancer effects [35]. The first is the direct antitumor mechanism of metformin, which may exert its antitumor effects through activation of adenosine monophosphate-activated protein kinase (AMPK) and inhibition of mammalian target of rapamycin (mTOR) [36]. Second, there may be an indirect antitumor mechanism through the interaction of metformin with insulin. By inhibiting glycogenesis in the liver and increasing glucose uptake in muscle cells, metformin lowers serum glucose, which in turn lowers insulin levels and it could have anticancer effects by inhibiting the proliferation of cancer cells [37].

There are experimental studies about metformin use being associated with lower PC risk. Inappropriate activation of Nuclear factor-kB (NF-kB) is known to be involved in cellular senescence, apoptosis, immunity and inflammation, and may contribute to cancer, and metformin may reduce the incidence of cancer by inhibiting the expression of NF-kB [38]. In addition, epithelial-mesenchymal transition (EMT) is known to be an important mechanism for PC invasion and metastasis. There was a study aimed to determine whether metformin affects the EMT of PC cells through a micro-RNA (miRNA)-based mechanism. The authors found that metformin could inhibit EMT in PC cells through upregulation of miR30a and downregulation of SOX4 [39].

Until now, few studies have confirmed that the risk of PC varies according to the status of hyperglycemia. In the present study, IFG was not significantly associated with the risk of PC. However, DM including new-onset DM showed a significant reduction in the risk of PC in adjusted models. Because this study found that PC risk varied between IFG and all DM including new onset DM, it is meaningful to identify the different effects of hyperglycemia on PC at different stages.

There was a trend that DM reduced the risk of PC regardless of the presence of the component of Mets in the present study. This result was different from previous reports showing that the risk of PC increases with obesity and Mets in diabetics of Korean nationwide cohort [22].

Our study also determined the impact of anti-diabetic medications on PC risk and found that patients using insulin showed a significantly decreased risk of PC compared to the normal population in an adjusted model. This result is

consistent with the results of a previous study [40]. The National DM Register has reported that patients who use insulin have a longer period of type 2 DM and a higher level of glycated hemoglobin than the general population with type 2 DM [41]. High glycated hemoglobin and insulin resistance appear to be associated with a decrease in PC risk through several metabolic aberrations [42].

In the present study, when the use of metformin was analyzed, the number of OHA administered was also investigated. DM patients who were taking less than three drugs of OHA including metformin showed a reduced risk of PC compared to patients without using metformin. This result supports the possibility of a decrease in the risk of PC in patients using metformin. However, metformin use did not significantly reduce PC risk in patients who administered three or more types of OHA. In general, patients who administer three or more types of OHA usually have a poor glycemic control with high insulin resistance and low drug compliance. We could not pinpoint the exact cause of this result, however, this might have affected the non-significant result of reducing PC risk in patients taking three or more types of OHA.

This study has several limitations. First, the claim data was used in this study, so we could not include data about the status of PC such as PSA, pathology, or staging. Second, detection and selection bias might have an impact on the incidence of PC. Third, we did not check the compliance of insulin or OHA including metformin because it was difficult to find it in this claim data.

However, this was a large population-based observational study concerning the effects of glycemic status (IFG, new-onset DM, all DM) and metS component on the incidence of PC. Until now, most research has been conducted on populations of European ancestry. This study holds great significance as it analyzed large-scale data from Asians. We believe that this study has clinical significance, as few studies have analyzed the risk of PC in DM patients with 10-year follow-up in a healthy population. We thoroughly studied baseline characteristics including comorbidity, lifestyle, and parameters of metS. We also studied correlations of antidiabetic drugs (OHA, insulin) with the risk of PC. We especially analyzed the use of metformin and the number of OHA.

In conclusion, the risk of PC was statistically lower in newly onset DM and long standing DM. However, IFG and MetS components in DM patients did not have a significant effect on PC risk. If a patient with risk factors for PC develops early diabetes, using metformin can be an option to reduce PC risk. In the future, it needs to be confirmed by further experiments and prospective studies.

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Disclosure of conflict of interest

None.

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