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Risk analysis of metformin use in prostate cancer: a national population-based study

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ABSTRACT

Introduction: Various approaches are required to prevent and treat heterogeneity-based prostate cancer. Here, we analyzed the anticancer effects of metformin, which has a good toxicity profile and is inexpensive.

Method: From January 2010 to December 2019, analysis was conducted retrospectively in a cohort from the National Health Insurance Service database. The wash-out period was set for cancer diagnosis in 2010 and 2011, and subjects (105,279) diagnosed with prostate cancer (ICD C61) from 2012 to 2014 were excluded The final subjects (105,216) were defined as the metformin administration group when they took metformin for 180 days or more from January 2012 to December 2019. The non-metformin group was defined as those who took less than 180 days from January 2012 to December 2019. The prevalence of prostate cancer according to metformin administration and the risk according to the cumulative duration of metformin were analyzed.

Results: A total of 105,216 people were included in this study, with 59,844 in the metformin group and 45,372 in the metformin non-administration group. When calculating HRs (Hazard Rate) according to the cumulative period of metformin administration, metformin administration period length was inversely associated with prostate cancer risk (Q2 HR = 0.791 95% CI: 0.773–0.81, Q3 HR = 0.634 95% CI: 0.62–0.649, Q4 HR = 0.571 95% CI: 0.558–0.585). HRs tended to decrease with the cumulative duration of metformin administration.

Conclusion: This study confirmed that prostate cancer risk decreased with increasing duration of metformin administration. Metformin should be considered as a new strategy in the treatment and prevention of prostate cancer characterized by heterogeneity.

Introduction

Prostate cancer (PCa) is a representative urological cancer, of which one-sixth of men are at risk [1]. The incidence rate has increased significantly in Asian countries over the past few decades. Therefore, various approaches to preventing and treating PCa based on heterogeneity are needed.

Hyperinsulinemia associated with type 2 diabetes can play an important role in cancer and can be negatively related to cancer prognosis [2,3]. Increased insulin levels in obese men can exacerbate PCa [3–5]. This is supported by laboratory evidence showing that hyperinsulinemia upregulates insulin receptors and increases tumor growth in PCa cells [6]. However, diabetes is associated with a reduction in diagnosis of PCa, potentially mediated by low testosterone level [7,8].

Metformin, a non-guanid drug, is the most widely used oral hypoglycemic agent in type 2 diabetes, with a good toxicity profile and low cost. Metformin is currently approved by the U.S. Food and Drug Administration (FDA) as an exercise and dietary supplement to enhance blood sugar control in adults and children with type 2 diabetes [9]. Its main mechanisms are to stimulate 50 AMP-activated protein kinase in the liver, inhibit gluconeogenesis, and reduce circulating insulin level [10]. In addition to other anti-tumor properties, such as a decrease in the c-myc tumor gene, metformin can also reduce insulin-stimulated cancer growth [11].

We hypothesized that metformin use would be associated with a reduced risk of PCa. Therefore, we conducted a large population-based study of metformin use and PCa. In addition, the effect of metformin

on PCa prognosis was analyzed according to treatment duration to provide a basis for including metformin in new strategies for the treatment of PCa characterized by heterogeneity.

Materials and methods

Study cohort

This study was approved by the Institutional Review Board of Hanyang University Hospital in Seoul (HYUH2020-10-004). The National Health Insurance Service (NHIS) database includes only anonymized data, so participant consent was not required [12]. The NHIS provides compulsory medical care to almost all Koreans and collects health data from nearly 50 million insured people, including hospitalization and outpatient visits, diagnosis, drug prescriptions, national health examination, and death data.

Classification of patient groups

This is a retrospective cohort study using the NHIS Database from January 2010 to December 2019. We set the washout period to exclude the canceller diagnosis with CCI for 2 years, from January 2010 to December 2011. Exclusion criteria included: (1) Those with a date of death before the diagnosis of cancer, (2) those younger than 20 years Subjects who met the inclusion criteria and who were newly diagnosed with prostate cancer (C61) between 2012 and 2014 were classified into a metformin-treated group and a group not treated with metformin. The metformin non-administration group was defined as subjects who had never been prescribed metformin during the study period (from January 2012 to December 2019) or those with a metformin usage period <180 days.

PCa was defined as a code C61 claim from 2012 to 2014 according to the International Classification of Diseases (ICD-10), the age group was classified using a 10-year interval starting from the age of 20, and income groups were classified into quartiles. Residential areas were divided into Seoul, other metropolitan cities (Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan, and Gyeonggi-do), and rural areas.

Statistics

Continuous variables were described as mean and standard deviation for normally distributed variables and as median (Q1, Q3) for non-normally distributed variables. Independent t-tests were used to compare normally distributed variables, and Wilcoxon rank-sum

test was used to compare non-normally distributed variables. The chi-square and Fisher's exact test were used to compare categorical variables. P values < 0.05 were considered statistically significant. Statistical analysis was performed using SAS v9.4 (SAS Institute, Cary, NC) and R software (version 4.0.4 or newer; R Project for Statistical Computing).

Results

During this study, a total of 105,279 patients were diagnosed with PCa, of whom 105,216 were included in this study after the exclusion criteria were applied (Figure 1). The remaining patients were divided into the metformin group ($n = 59,844$) and the metformin non-administration group ($n = 45,372$). Table 1 shows demographic characteristics including age, sex, income, residential area, comorbidities, and CCI(Charlson comorbidity index). The metformin non-administration group was older than the metformin group and had a higher income level, while the metformin group had higher CCI and comorbidity.

Survival rate was analyzed among the administration and non-administration groups by age, income, and residential area subgroups in stratified analysis (Table 2). When stratified by age, income, and residential area, the survival rate of the administration group was higher than that of the non-administration group.

The survival curve during the follow-up period was estimated using the Kaplan-Meier method, and survival between groups was compared with the log-rank test. The survival rate varied significantly based on metformin use ($p < 0.001$) (Figure 2).

Causes of death in the total population of patients with PCa were malignant neoplasm (14,632), PCa (5782), other (4316), and respiratory disease (2943) (Table 3). Causes of death in the metformin administration group were malignant neoplasm (5129), other (2272), cardiovascular disease (2016), respiratory disease (1570), endocrine disease (1075), and PCa (1039). Causes of death in the metformin non-administration group were malignant neoplasm (9503), prostate cancer (4743), others (2044), cardiovascular diseases (4678), and respiratory disease (1373). HRs for cancer-related death were lower in the metformin administration group than those for the metformin non-administration group [malignant neoplasm (HR = 0.381, 95% CI: 0.368–0.394), PCa (HR = 0.154, 95% CI: 0.144-0.165) bladder cancer (HR = 0.24), and kidney cancer (HR = 0.24, 95% CI: 0.188–0.308)].

The incidence of PCa is expressed as the number of events per 100,000 people (PY), as shown in Table 4. The incidence of urological cancer was 59,844
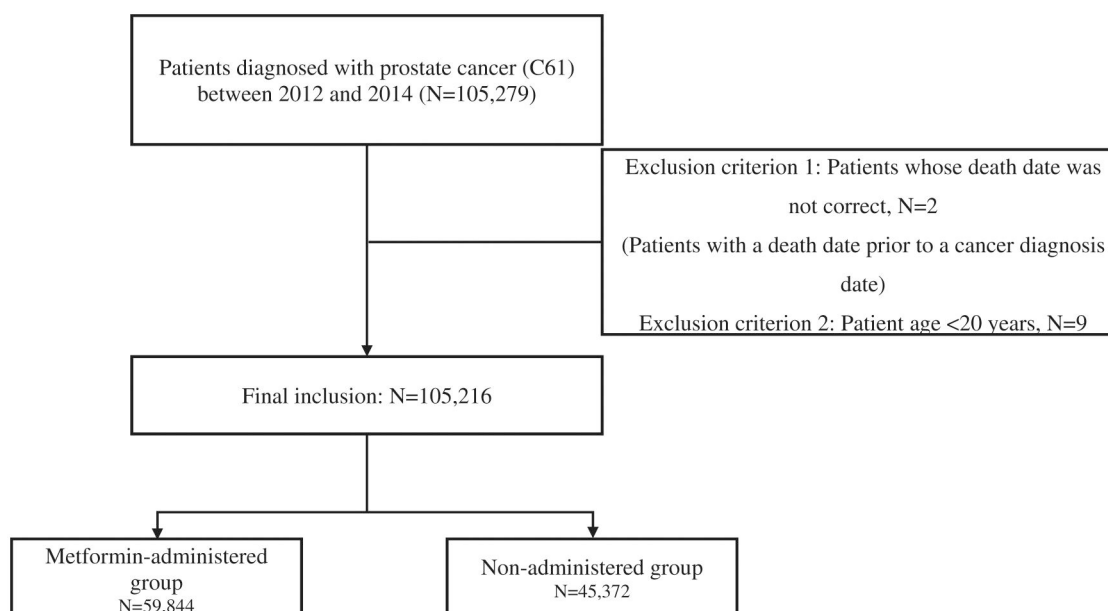
Figure 1. Flow chart of the study cohort.

Table 1. Descriptive characteristics of the study population with PCa.

	Total (%)	Metformin-administered group (%)	Non-administered group (%)	p-value
Subjects	105,216	59,844	45,372	
Age (years)	69 (62–75)	67 (60–73)	71 (64–77)	<0.0001
Age group				<0.0001
≤45	1624 (1.54)	1,140 (1.9)	484 (1.07)	
46~≤65 years	37,344 (35.49)	24,702 (41.28)	12,642 (27.86)	
66~≤75 years	41,940 (39.86)	23,192 (38.75)	18,748 (41.32)	
>75 years	24,308 (23.1)	10,810 (18.06)	13,498 (29.75)	
Sex				
Male	105,216 (100)	59,844 (100)	45,372 (100)	
Income quartile				<0.0001
Highest	22,226 (21.12)	11,979 (20.02)	10,247 (22.58)	
Middle-high	47,135 (44.8)	26,719 (44.65)	20,416 (45)	
Middle-low	19,943 (18.95)	11,711 (19.57)	8232 (18.14)	
Lowest	15,912 (15.12)	9435 (15.77)	6477 (14.28)	
Place of residence				0.0034
Seoul	22,099 (21)	12,397 (20.72)	9702 (21.38)	
Metropolitan city	44,544 (42.34)	25,578 (42.74)	18,966 (41.8)	
Rural	38,573 (36.66)	21,869 (36.54)	16,704 (36.82)	
Year of diagnosis of prostate cancer				<0.0001
2012	46,296 (44)	22,493 (37.59)	23,803 (52.46)	
2013	30,841 (29.31)	19,431 (32.47)	11,410 (25.15)	
2014	28,079 (26.69)	17,920 (29.94	10,159 (22.39)	
CCI	8 (3–11)	8 (4–12)	7 (2–10)	<0.0001
0	4730 (4.5)	888 (1.48)	3842 (8.47)	<0.0001
≤9	59,248 (56.31)	32,999 (55.14)	26,249 (57.85)	
≤19	40,965 (38.93)	25,805 (43.12)	15,160 (33.41)	
≥20	273 (0.26)	152 (0.25)	121 (0.27)	
Comorbidities				
Hypertension	72,378 (68.79)	45,463 (75.97)	26,915 (59.32)	<0.0001
Dyslipidemia	69,936 (66.47)	46,486 (77.68)	23,450 (51.68)	<0.0001
CVD	23,361 (22.2)	14,401 (24.06)	8960 (19.75)	<0.0001
COPD	11,760 (11.18)	6778 (11.33)	4982 (10.98)	0.0787

The criterion for metformin use versus non-use was used for 180 days or more.

(56.88%) in the metformin non-administration group, and the incidence rate per 100,000 PY was 18300.33 in the metformin non-administration group and 16,981.7 in the metformin group. The metformin group had a higher risk of prostate cancerPCa than the metformin non-administration group (HR = 1.141, 95% CI: 1.127–1.156).

The longer the cumulative duration of administration of metformin, the lower the HR for the risk of prostate cancer (Q2 HR = 0.791 95% CI: 0.773–0.81,

Table 2. Overall survival rate.

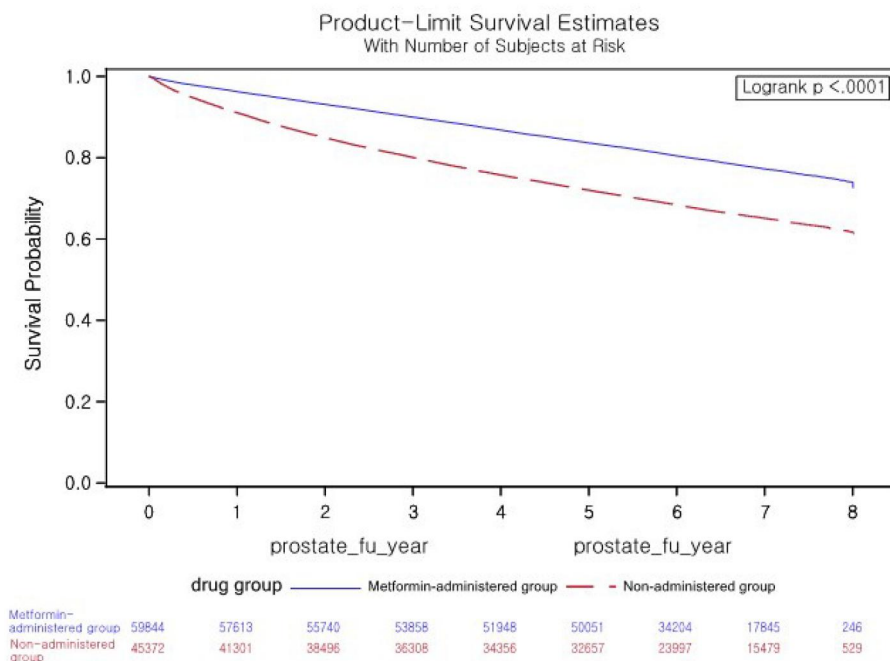|	Survival							
	1 year		3 years		5 years		8 years	
	Metformin-administered group (95% CI)	Non-administered group (95% CI)	Metformin–administered group (95% CI)	Non-administered group (95% CI)	Metformin–administered group (95% CI)	Non-administered group (95% CI)	Metformin–administered group (95% CI)	Non-administered group (95% CI)
All patients	0.9627 (0.961–0.964)	0.91 (0.907–0.913)	0.8999 (0.898–0.902)	0.8001 (0.796–0.804)	0.8363 (0.833–0.839)	0.7197 (0.716–0.724)	0.7255 (0.734–0.745)	0.6158 (0.610–0.622)
Age (years)								
≤45	0.993 (0.987–0.997)	0.9174 (0.891–0.940)	0.9763 (0.966–0.984)	0.8554 (0.822–0.885)	0.957 (0.944–0.968)	0.8285 (0.794–0.861)	0.9336 (0.931–0.958)	0.8113 (0.776–0.846)
46~≤65	0.9821 (0.980–0.984)	0.9498 (0.946–0.953)	0.9522 (0.949–0.955)	0.8902 (0.885–0.896)	0.9235 (0.920–0.927)	0.8504 (0.844–0.857)	0.8801 (0.875–0.886)	0.8066 (0.791–0.817)
66~≤75	0.9646 (0.962–0.967)	0.9335 (0.930–0.937)	0.9022 (0.898–0.906)	0.8434 (0.838–0.849)	0.8351 (0.830–0.840)	0.7777 (0.772–0.784)	0.7297 (0.721–0.739)	0.6803 (0.673–0.688)
>75	0.9111 (0.905–0.916)	0.8407 (0.834–0.847)	0.7679 (0.760–0.776)	0.6539 (0.646–0.662)	0.6272 (0.618–0.636)	0.513 (0.504–0.521)	0.4231 (0.422–0.448)	0.3525 (0.343–0.362)
Income								
Highest	0.9673 (0.964–0.970)	0.9252 (0.920–0.930)	0.9074 (0.902–0.913)	0.8351 (0.828–0.842)	0.8464 (0.840–0.853)	0.7581 (0.750–0.766)	0.7474 (0.737–0.760)	0.6575 (0.647–0.668)
Middle-high	0.9642 (0.962–0.966)	0.9156 (0.912–0.919)	0.9047 (0.901–0.908)	0.8067 (0.801–0.812)	0.8437 (0.839–0.848)	0.729 (0.723–0.735)	0.7489 (0.745–0.759)	0.6205 (0.618–0.636)
Middle-low	0.9649 (0.962–0.968)	0.906 (0.899–0.912)	0.9052 (0.900–910)	0.7948 (0.786–0.803)	0.8476 (0.841–0.854)	0.7185 (0.709–0.728)	0.7585 (0.750–0.772)	0.6078 (0.605–0.631)
Lowest	0.9501 (0.945–0.954)	0.8754 (0.867–0.883)	0.8707 (0.864–0.877)	0.7315 (0.721–0.742)	0.789 (0.781–0.797)	0.6316 (0.620–0.643)	0.6725(0.650–0.685)	0.5119 (0.498–0.526)
Place of residence								
Seoul	0.9663 (0.963–0.969)	0.9349 (0.930–0.940)	0.9133 (0.908–0.918)	0.8404 (0.833–0.848)	0.8529 (0.846–0.859)	0.771 (0.763–0.779)	0.7588 (0.753–0.773)	0.6648 (0.662–0.685)
Metropolitan city	0.9695 (0.967–0.972)	0.9157 (0.912–0.920)	0.9119 (0.908–0.915)	0.8142 (0.809–0.820)	0.8519 (0.847–0.856)	0.739 (0.733–0.745)	0.7545 (0.746–0.764)	0.6329 (0.629–0.649)
Rural	0.9528 (0.950–0.955)	0.8898 (0.884–0.894)	0.8785 (0.874–0.883)	0.761 (0.754–0.767)	0.8089 (0.804–0.814)	0.6682 (0.661–0.675)	0.7079 (0.700–0.717)	0.5553 (0.546–0.564)

Figure 2. Kaplan–Meier survival analysis of time to death.

Q3 HR = 0.634 95% CI: 0.62–0.649, Q4 HR = 0.571 95% CI: 0.558–0.585). HR tended to decrease with the cumulative duration of metformin administration.

If the reference is group 1 of the non-treated group, it can be seen that HRs decrease according to the duration of treatment in comparison with the

Table 3. Hazard ratios for mortality in PCa patients.

	Total	Metformin-administered group	Non-administered group	p-Value	HR (95% CI)	Subdistribution HR (95% CI)
			Mortality rate			
Number of subjects	105,216	59,844	45,372			
Cause of death						
Prostate cancer (C61)	5782	1039	4743	<0.0001	0.154 (0.144–0.165)	0.161 (0.151–0.173)
Genitourinary cancer	1391	311	1080	<0.0001	0.203 (0.179–0.23)	0.218 (0.192–0.248)
Bladder cancer (C67,D09.0)	335	85	250	<0.0001	0.24 (0.188–0.308)	0.26 (0.203–0.332)
Kidney cancer (C64)	335	85	250	<0.0001	0.24 (0.188–0.308)	0.26 (0.203–0.332)
Malignant neoplasm (C00-D48)	14,632	5129	9503	<0.0001	0.381 (0.368–0.394)	0.386 (0.373–0.4)
Cardiovascular disease (I00-I99)	3694	2016	1678	0.0040	0.847 (0.794–0.904)	0.936 (0.877–0.998)
Hypertension (I10-I15)	240	134	106	0.7301	0.893 (0.692–1.153)	0.988 (0.765–1.275)
Ischemic heart disease (I20-I25)	1002	568	434	0.9025	0.918 (0.81–1.041)	1.017 (0.897–1.152)
Cerebrovascular disease (I60-I69)	1398	752	646	0.0190	0.82 (0.738–0.911)	0.905 (0.815–1.005)
Respiratory disease (J00-J99)	2943	1570	1373	0.0001	0.812 (0.755–0.873)	0.9 (0.837–0.968)
Pneumonia (J12∼J18)	1569	860	709	0.0961	0.864 (0.782–0.954)	0.962 (0.871–1.063)
Chronic lower respiratory disease (J40-J47)	715	337	378	<0.0001	0.63 (0.543–0.729)	0.696 (0.601–0.806)
Endocrine disease (E00-E90)	1565	1075	490	<0.0001	1.555 (1.397–1.731)	1.711 (1.537–1.905)
Gastrointestinal disease (K00-K93)	799	439	360	0.2679	0.862 (0.749–0.991)	0.945 (0.822–1.087)
Neurological disease (G00-G99)	575	347	228	0.0920	1.07 (0.905–1.265)	1.196 (1.012–1.413)
Mental or behavioral disorder (F01-F99)	0	0	0		–	–
Musculoskeletal or connective tissue disease (M00-M99)	84	38	46	<0.0001	0.581 (0.378–0.894)	0.642 (0.417–0.988)
Bone fracture in neoplastic diseases (M90.7)	0	0	0		–	–
Other	4316	2272	2044	<0.0001	0.786 (0.74–0.834)	0.865 (0.815–0.918)

Table 4. Hazard ratios for prostate cancer incidence.

Metformin use	Number of prostate cancer patients	Person-years	Incidence of prostate cancer (per 100,000 person-years)	Hazard ratio of prostate cancer (95% CI)
Non-administered group	45,372 (43.12%)	247,930	18,300.33	Reference
Metformin-administered group	59,844 (56.88%)	352,402.9	16,981.7	1.141 (1.127–1.156)
Cumulative duration (day/month)				
Q1	14,101	64022.55	22,025.05	Reference
Q2	14,969	86,357.9	17,333.68	0.791 (0.773–0.81)
Q3	15,342	99,509.67	15,417.6	0.634 (0.62–0.649)
Q4	15,432	102,512.8	15,053.73	0.571 (0.558–0.585)

Q1 to Q4 are quartiles of the metformin group.

metformin-treated group quartile group (group 5: HR = 0.926 95% CI: 0.88–0.975, group 6: HR = 0.735 95% CI: 0.699–0.773, group 7: HR = 0.593 95% CI: 0.563–0.623, group 8: HR = 0.535 95% CI: 0.509–0.563) (Table 5).

In relative 5-year survival rate, the 1-year, 3-year, 5-year, and 8-year survival rates of the metformin group were 99.7%, 94.7%, 88.2% and 78.5%, respectively, and those in the metformin non-administration group were 96.7%, 85.6%, 76.2%, and 65.4%, respectively (Table 6).

Discussion

Using a large population-based longitudinal cohort study, we investigated prostate cancer risk according to the use and cumulative duration of metformin.

Studies on the link between metformin and PCa have shown that cancer rates have reduced diabetes and metformin's risk of PCa by 44% [13]. A Scottish study reported that diabetics taking metformin had a 23% lower overall risk of cancer compared to those not taking metformin [14]. The study observed and reported risk reduction for the longest metformin use period.

In a large Finnish population-based registry study, a reduction in the risk of PCa was observed with the use of all diabetes drugs [15]. The study showed that treatment of diabetes, rather than specific drugs, was inversely proportional to the risk of PCa. Other studies have reported differences between ethnic groups, including that African and European Americans showed a different association between PCa and diabetes [16].

Table 5. Hazard ratio for prostate cancer incidence by the group.

Metformin use		Prostate cancer	Person-years	Incidence of prostate cancer (per 100,000 person-years)	Hazard ratio of prostate cancer (95% CI)
Cumulative duration (day/month)					
Non-administered group	group1	1658	7153.252	23,178.27	Reference
	group2	1745	7900.293	22,087.79	0.92 (0.86–0.984)
	group3	1700	7816.263	21,749.52	0.85 (0.794–0.909)
	group4	1692	7245.636	23,351.99	0.958 (0.895–1.025)
Metformin-administered group	group5	14,101	64,022.55	22,025.05	0.926 (0.88–0.975)
	group6	14,969	86,357.9	17,333.68	0.735 (0.699–0.773)
	group7	15,342	99,509.67	15,417.6	0.593 (0.563–0.623)
	group8	15,432	102,512.8	15,053.73	0.535 (0.509–0.563)

*Groups 1 to 4 are quartiles of the non-metformin use group.
*Groups 5 to 8 are quartiles of the metformin-administered group.

In the present study, the relative 5-year survival rate was higher in the metformin group than in the non-administration group. These findings are in agreement with the results of previous papers. This study presents the results of showing the anticancer effect of metformin on prostate cancer through the analysis of the incidence and survival rate of prostate cancer according to the cumulative dose of metformin.

The specific mechanism of action of metformin has not been identified, but it (1) inhibits cellular respiration in mitochondria, (2) activates AMPK, and (3) prevents increases in cAMP concentration induced by glucagon, consequently inhibiting protein kinase A activity and affecting normal gut bacteria [17–19]. Metformin is involved in cellular apoptosis through the activation of AMPK and complete inhibition of phosphorylation, and it has been suggested that the apoptosis induced by energy stress due to AMPK is mediated by a combination of metformin and 2DG [20]. p53 regulates the induction of apoptosis mediated by metformin/2DG, and the combination of metformin and 2DG strongly induces the expression of p53 [20].

The drug biguanide was developed in Europe in the 1920s, but its interest has declined due to insulin and has returned to the spotlight. Metformin lowers blood sugar with few side effects and is inexpensive, making it the most cost-effective diabetes treatment currently available. For these reasons, it is widely used. Additional large-scale, big-data research is expected to provide a new treatment strategy for PCa based on heterogeneity.

The findings of this research indicated that the risk of PCa changes according to the cumulative quantity of metformin taken, with risk decreasing as the cumulative amount increases. The key result of this study is that the longer the cumulative period of metformin use is, the lower the risk of PCa, confirming a preventive effect of PCa through long-term cumulative use.

The death rate from PCa was lower in the group taking metformin compared with the non-administration group. Such results may have been shown because PCa includes cancers with a relatively mild prognosis enough to be called turtle cancer, but significant differences in causes of death between the metformin and non-administration groups indicate that metformin has anticancer effects.

Metformin is not without disadvantages. Diarrhea, nausea, vomiting, drainage, and poor appetite are the most common side effects of metformin use. It has been reported that 41.7% of Koreans who took atrioventricular formulations of metformin before taking Western formulations experienced gastrointestinal side effects [21]. However, these side effects are not serious, and the administration of metformin should be actively considered in applicable cases. In addition, in the case of the Western type, side effects are less likely. Since this study confirmed that the mortality rate from PCa decreases with metformin use, metformin treatment should be recommended regardless of stage or progression.

This study has several limitations. First, due to the characteristics of NHIS data, it was not possible to analyze the information on the test number, which is actual clinical information. No information was available on PSA level or Gleason score, both of which are important clinical indicators of PCa. Therefore, an analysis of biochemical recurrence could not be conducted. Second, the absence of clinical information prohibited the analysis of patient groups according to the stage. This is also linked to the limitations, and if there was an analysis according to the risk, it would be possible to know which patient group could be used more effectively. Despite these limitations, metformin was effective against the development of PCa as well as decreasing associated mortality. In addition, there were differences in effect depending on the cumulative amount of metformin taken. To overcome

Table 6. Conditional relative 5-year survival.

	Conditional relative 5-year survival (95% CI)							
	1 year		3 years		5 years		8 years	
	Metformin-administered group (95% CI)	Non-administered group (95% CI)	Metformin-administered group (95% CI)	Non-administered group (95% CI)	Metformin-administered group (95% CI)	Non-administered group (95% CI)	Metformin-administered group (95% CI)	Non-administered group (95% CI)
All patients	0.9965 (0.9960–0.9969)	0.9669 (0.9652–0.9684)	0.9471 (0.9454–0.9487)	0.8597 (0.8564–0.8624)	0.8819 (0.8796–0.8844)	0.7619 (0.7579–7656)	0.7848 (0.7811–0.7879)	0.6536 (0.6485–0.6573)
Age								
≤45	1.00 (1.00–1.00)	0.9835 (0.9710–0.9938)	0.9912 (0.9851–0.9956)	0.9070 (0.8780–0.9360)	0.9746 (0.9667–0.9825)	0.8512 (0.8182–0.8843)	0.9474 (0.9351–0.9605)	0.8140 (0.7789–0.8512)
46~≤65	0.9987 (0.9983–0.9992)	0.9843 (0.9822–0.9862)	0.9753 (0.9733–0.9772)	0.9250 (0.9208–0.9298)	0.9447 (0.9419–0.9475)	0.8727 (0.8676–0.8792)	0.9009 (0.8973–0.9048)	0.8244 (0.8181–0.8310)
66~≤75	0.9964 (0.9956–0.9972)	0.9763 (0.9735–0.9789)	0.9485 (0.9453–0.9512)	0.8921 (0.8872–0.8972)	0.8828 (0.8784–0.8874)	0.8125 (0.8057–0.8181)	0.7785 (0.7730–0.7838)	0.7135 (0.7071–0.7199)
>75	0.9913 (0.9898–0.9934)	0.9371 (0.9326–0.9415)	0.8749 (0.8697–0.8814)	0.7519 (0.7445–0.7601)	0.7269 (0.7194–0.7364)	0.5847 (0.5760–0.5920)	0.5157 (0.5064–0.5264)	0.4048 (0.3961–0.4131)
Income								
Highest	0.9965 (0.9954–0.9973)	0.9698 (0.9666–0.9733)	0.9512 (0.9471–0.9547)	0.8805 (0.8745–0.8871)	0.8880 (0.8822–0.8944)	0.7965 (0.7881–0.8026)	0.7923 (0.7844–0.7990)	0.6893 (0.6787–0.6967)
Middle-high	0.9964 (0.9957–0.9971)	0.9684 (0.9656–0.9704)	0.9494 (0.9468–0.9518)	0.8647 (0.8599–0.8685)	0.8869 (0.8829–0.8901)	0.7699 (0.7647–0.7748)	0.7946 (0.7894–0.7988)	0.6654 (0.6588–0.6713)
Middle-low	0.9976 (0.9968–0.9984)	0.9668 (0.9626–0.9705)	0.9518 (0.9484–0.9565)	0.8604 (0.8522–0.8684)	0.8918 (0.8866–0.8979)	0.7595 (0.7478–0.7690)	0.8017 (0.7947–0.8098)	0.6585 (0.6466–0.6691)
Lowest	0.9953 (0.9939–0.9967)	0.9577 (0.9534–0.9620)	0.9294 (0.9240–0.9342)	0.8103 (0.7993–0.8189)	0.8478 (0.8406–0.8554)	0.6850 (0.6738–0.6943)	0.7262 (0.7167–0.7344)	0.5541 (0.5417–0.5651)
Place of residence								
Seoul	0.9966 (0.9956–0.9977)	0.9778 (0.9751–0.9803)	0.9556 (0.9524–0.9591)	0.8893 (0.8834–0.8953)	0.8964 (0.8916–0.9023)	0.8080 (0.8010–0.8160)	0.8028 (0.7966–0.8096)	0.7103 (0.7006–0.7205)
Metropolitan city	0.9972 (0.9965–0.9980)	0.9669 (0.9646–0.9693)	0.9535 (0.9509–0.9561)	0.8691 (0.8647–0.8739)	0.8943 (0.8904–0.8979)	0.7782 (0.7716–0.7839)	0.8030 (0.7987–0.8080)	0.6778 (0.6718–0.6840)
Rural	0.9956 (0.9947–0.9964)	0.9606 (0.9577–0.9640)	0.9347 (0.9315–0.9374)	0.8319 (0.8261–0.8375)	0.8593 (0.8553–0.8636)	0.7167 (0.7093–0.7239)	0.7532 (0.7480–0.7584)	0.5935 (0.5864–0.6015)

these limitations, additional large-scale studies using actual clinical data should be performed.

Conclusions

In a real-world setting, a large, population-based study confirmed that metformin use is associated with a lower risk of PCa and death from PCa. This decrease in risk corresponds to the cumulative dose of metformin. Here, we present the basis for further studies on metformin as a new strategy in the treatment and prevention of PCa characterized by heterogeneity.

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