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Metformin reduces the risk of cancer in patients with type 2 diabetes

An analysis based on the Korean National Diabetes Program Cohort

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Abstract

The epidemiological literature suggests that insulin resistance, hyperinsulinemia, and increased levels of insulin-like growth factors place patients with type 2 diabetes mellitus (T2DM) at greater risk of cancer. The association between cancer incidence and the use of antidiabetic medications in patients with T2DM has been recently examined. There have been conflicting reports regarding an association between metformin and cancer risk. The aim of this study was to investigate the relationship between metformin use and the incidence of cancer in Koreans with T2DM.

Data from The Korean National Diabetes Program (KNDP, 2006–2014), a nationwide, large-scale, prospective, multicenter cohort study in Korea, were used to study patients with T2DM. Patients ≥30 years old whose complete medical records were available were included in this study. Patients with a history of any cancer on KNDP registration or those who had been diagnosed with any type of cancer within 1 year of metformin use were excluded. Survival curves with respect to the incidence of cancer were plotted using the Kaplan–Meier method. Hazard ratios and 95% confidence intervals for cancer were estimated in a Cox proportional hazards regression analysis.

During a mean 5.8 years of follow-up, 164 of the 1918 study patients (335 metformin nonusers and 1583 metformin users) developed cancer. The incidence per 1000 person-years was 21.8 in metformin nonusers and 13.2 in metformin users. Metformin users had a reduced risk of cancer, even after adjustment for demographic characteristics, metabolic parameters, diabetic complications, and other antidiabetic medications (hazard ratio 0.513, 95% confidence interval 0.318–0.826, $P=.0060$). Subgroup analysis of metformin users showed a reduced risk of cancer in males, patients < 65 years of age, patients with a T2DM duration < 5 years, nonobese patients, nonsmokers, and good glycemic control group.

This large-scale, prospective, multicenter cohort study demonstrated an association between metformin use and reduced cancer risk in patients with T2DM.

Abbreviations: BMI = body mass index, CI = confidence intervals, DPP4 = dipeptidyl peptidase 4, HbA1c = glycated hemoglobin, HOMA-IR = homeostasis model assessment of insulin resistance, HR = hazard ratios, IGF = insulin-like growth factors, KNDP = Korean National Diabetes Program, T2DM = type 2 diabetes mellitus.

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1. Introduction

The prevalence of both type 2 diabetes mellitus (T2DM) and cancer are increasing worldwide, and an increased risk of a variety of cancers in patients with T2DM has been reported in many countries.[1] The American Diabetes Association and American Cancer Society reported an approximately twofold increased risk of cancers of the liver, pancreas, and endometrium and a 1.2 to 1.5-fold increased risk of cancers of the colon and rectum, breast, and bladder in patients with T2DM.[1] Several observational studies found that newly diagnosed cancer patients have a higher prevalence of diabetes,[2,3] and a bidirectional association between these 2 diseases has been suggested.[2,3]

T2DM and cancer share several common potential risk factors, including aging, obesity, physical inactivity, and poor dietary and lifestyle habits. The epidemiological literature shows that the increased risk of cancer in patients with T2DM is related to the insulin resistance, hyperinsulinemia, and elevated levels of insulin-like growth factors (IGFs) that characterize T2DM.[1] Consequently, the association between cancer incidence and the use of antidiabetic medications in patients with T2DM has been examined in several studies.[3,4]

Metformin is commonly used and recommended as the first-line drug for the management of T2DM. Although its mechanism of action is not fully understood, metformin reduces insulin resistance and fasting plasma insulin levels.[5] Several animal and cell-based studies, as well as epidemiological and clinical investigations, have revealed an association between metformin use and the prevention or reduced risk of cancer,[4,6–8] and this has drawn attention to the drug's potential anticancer effect. The anticancer activity of metformin is thought to involve AMP-activated protein kinase (AMPK) activation and inhibition of the mammalian target of rapamycin complex 1 (mTORC1).[9] Although the results of several studies support an association between metformin and the reduced risk of cancer,[6–8] other studies found no association.[10–12] Some studies were limited by their failure to include potentially important confounding factors. Several of the previous studies investigating the association between metformin use and cancer incidence were retrospective cohort studies, which are difficult to evaluate in terms of medical history, laboratory findings, and diabetic complications. Large-scale prospective observational studies in humans are lacking. Moreover, few studies have investigated metformin use and cancer risk in Korean patients with T2DM.[13,14] Therefore, we investigated the relationship between metformin use and cancer incidence in Korean patients with T2DM using the Korean National Diabetes Program (KNDP) database, a large-scale, prospective, multicenter, cohort study that includes data on a large number of possible confounding factors.

2. Methods

2.1. Study subjects

We analyzed the database of patients with T2DM obtained from the KNDP, a nationwide, large-scale, prospective, multicenter, observational cohort study, to assess the prevention, treatment, and management of T2DM in Korean patients.[15] The primary outcomes of the KNDP cohort were mortality, diabetes-related microvascular complications, and macrovascular complications. The secondary outcomes were the factors causing diabetes-related mortality and complications. The first patient was enrolled in the KNDP in May 2006, and by the end of the study in March 2014, the database included primary observations for 4540 registered participants from 13 university hospitals. Medical histories, physical examinations, laboratory tests, surveys, and diabetic complication studies were regularly conducted according to the KNDP protocol. All patients were managed by specialists according to standard practice guidelines.[15]

Our study was based on the data of patients ≥30 years old whose complete medical records were available. Patients with a history of any cancer on KNDP registration or those who had been diagnosed with any type of cancer within 1 year of metformin use were excluded, as the causal relationship between metformin use and cancer is unclear. Thus, our study included 1918 patients with T2DM.

All KNDP patients had previously submitted written informed consent. The relevant data for the KNDP cohort were registered at www.ClinicalTrials.gov (NCT01212198). Our study was approved by the Institutional Review Board of each participating hospital.

2.2. Data collection

The following characteristics of the patients were surveyed at the time of KNDP cohort registration: age, sex, diabetes duration, income, smoking habits, height, weight, blood pressure, and other baseline clinical characteristics. Blood samples were taken for fasting plasma glucose and insulin, glycated hemoglobin (HbA1c), and serum lipid profiles as well as other biochemical tests at the time of cohort registration. A radio-immunoassay kit (Linco Research Inc, St. Louis, MO) was used to measure insulin levels. Homeostasis model assessment of insulin resistance (HOMA-IR) ([fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5) was calculated as an index of insulin resistance, and HOMA of β-cell function (HOMA-β) ([20 × fasting insulin (μU/mL)/fasting glucose (mmol/L)] − 3.5) was calculated as an index of beta cell function.

Macrovascular complications consisted of cardiovascular disease (including myocardial infarction, angina, heart failure, and cardiovascular complications with congestive heart failure) and cerebrovascular accident (including cerebral infarction, cerebral hemorrhage, and transient ischemic attack). Microvascular complications consisted of diabetic retinopathy (including nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, macular edema, and blindness), neuropathy (diabetic peripheral neuropathy, autonomic neuropathy), and nephropathy (including dialysis and renal transplantation). All microvascular and macrovascular complications, as well as a history of hypertension, were defined according to the baseline medical history of the patient.

Antidiabetic drugs were classified into 6 categories: metformin, sulfonylurea, alpha glucosidase inhibitor, thiazolidinedione, insulin, and dipeptidylpeptidase-4 (DPP4) inhibitor. Patients with a history of using metformin (≥90 days) and not using metformin throughout the KNDP were categorized as metformin users (including metformin monotherapy and metformin in combination with other antidiabetic agents) and metformin nonusers, respectively, and their data were analyzed. For both groups, demographic and laboratory data, and data on other antidiabetic medication use and complication status at the time of cohort registration were used in the analysis.

Information on the incidence of cancer, defined as all types of cancer occurring 1 year after KNDP registration, was obtained from the medical records of each institution.

Table 1

Demographic and clinical characteristics of patients according to metformin use.

Variable		Total n (%) or mean ± SD	Metformin		*P* value
			Nonusers n (%) or mean ± SD	Users n (%) or mean ± SD	
N		1918 (100.0)	335 (17.5)	1583 (82.5)	
Sex	Male	1090 (56.8)	203 (60.6)	887 (56.0)	.126
	Female	828 (43.2)	132 (39.4)	696 (44.0)	
Age, years		54.8 ± 9.8	56.7 ± 10.5	54.4 ± 9.6	<.001
DM duration, years	<5	957 (49.9)	144 (43.0)	813 (51.4)	.005
	≥5	961 (50.1)	191 (57.0)	770 (48.6)	
Income, $/month	≤1700	727 (42.5)	134 (45.4)	593 (41.9)	
	1701–3400	527 (30.8)	91 (30.9)	436 (30.8)	.385
	>3400	457 (26.7)	70 (23.7)	387 (27.3)	
BMI, kg/m^2	<25.0	959 (50.1)	196 (58.9)	763 (48.3)	<.001
	≥25.0	954 (49.9)	137 (41.1)	817 (51.7)	
Smoking	Current	381 (20.4)	56 (17.3)	325 (21.1)	.142
	Past	529 (28.3)	104 (32.2)	425 (27.5)	
	Never	957 (51.3)	163 (50.5)	794 (51.4)	
Hypertension		952 (49.6)	164 (49.0)	788 (49.8)	.784
SBP, mm Hg		125.9 ± 15.4	125.3 ± 15.1	126.0 ± 15.4	.416
DBP, mm Hg		78.3 ± 9.9	77.7 ± 9.7	78.4 ± 10.0	.265
FBG, mg/dL		146.9 ± 49.1	141.3 ± 56.6	148.1 ± 47.4	.067
HbA1c (%)		7.8 ± 1.8	7.5 ± 2.0	7.8 ± 1.7	.006
Fasting Insulin, μU/mL		9.4 ± 8.6	8.8 ± 6.3	9.5 ± 8.9	.269
HOMA-IR		3.5 ± 3.8	4.0 ± 7.5	3.4 ± 2.7	.224
HOMA- ß		59.6 ± 88.4	77.6 ± 129.4	56.4 ± 78.3	.023
Total cholesterol, mg/dL		178.7 ± 40.2	179.8 ± 42.1	178.5 ± 39.8	.596
Triglyceride, mg/dL		159.3 ± 131.3	143.7 ± 111.4	162.5 ± 134.9	.009
HDL-C, mg/dL		47.2 ± 12.9	47.1 ± 14.2	47.3 ± 12.7	.843
LDL-C, mg/dL		99.5 ± 36.3	103.8 ± 39.2	98.6 ± 35.6	.039
Antidiabetic medication					
Sulphonylurea		1185 (61.8)	176 (52.5)	1009 (63.7)	<.001
α-GI		310 (16.2)	80 (23.9)	230 (14.5)	<.001
Thiazolidinedione		190 (9.9)	23 (6.9)	167 (10.6)	.040
DPP4 inhibitor		620 (32.3)	28 (8.4)	592 (37.4)	<.001
Insulin		707 (36.9)	164 (49.0)	543 (34.3)	<.001
Diabetic complications					
Cardiovascular disease		149 (7.8)	27 (8.1)	122 (7.7)	.827
Cerebrovascular disease		146 (7.6)	26 (7.8)	120 (7.6)	.910
Neuropathy		689 (35.9)	151 (45.1)	538 (34.0)	<.001
Retinopathy		383 (20.0)	88 (26.3)	295 (18.6)	.002
Nephropathy		320 (16.7)	68 (30.3)	252 (15.9)	.051

All values were assessed using data collected at the time of patient registration.

α-GI = alpha glucosidase inhibitor, BMI = body mass index, DBP = diastolic blood pressure, DPP4 = dipeptidyl peptidase 4, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure.

2.3. Statistical analyses

Variables are described as means and standard deviations (SD) for continuous variables and percentages for categorical variables. The demographic characteristics of subjects (metformin users and nonusers) were analyzed using descriptive statistics followed by two-sided independent Student's *t* tests for the continuous variables, and the chi-squared (χ^2) test for the categorical variables. The incidence of cancer was calculated at the end of follow up. Survival probabilities were estimated with Kaplan–Meier plots between groups, and Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) of cancer, adjusting for demographic factors, HbA1c, BMI, duration of diabetes, diabetes medication, and complications. All statistical analyses were performed using Statistical Analysis System (SAS) version 9.3 (SAS Institute, Inc., Cary, NC). A *P* value <.05 was considered to indicate statistical significance.

3. Results

The 1918 patients included in the study consisted of 335 metformin nonusers and 1583 metformin users. The mean ages at the time of registration were 56.7 ± 10.5 and 54.4 ± 9.6 years ($P < .001$), respectively, and the percentage of subjects with diabetic durations < 5 y at the time of registration was 43.0% and 51.4% ($P = .005$) in metformin nonusers and metformin users, respectively. The percentage of subjects with BMI ≥ 25 kg/m^2 was 41.1% and 51.7% ($P < .001$), and the mean HbA1c were 7.5 ± 2.0% and 7.8 ± 1.7% ($P = .006$) in metformin nonusers and metformin users, respectively. In terms of combination therapy, metformin users received sulfonylurea, thiazolidinediones, and DPP4 inhibitors more often compared to metformin nonusers, whereas alpha glucosidase inhibitors and insulin were used less often. The prevalences of diabetic neuropathy and diabetic retinopathy were higher in metformin nonusers than in metformin users (Table 1).

Table 2

Cumulative incidence rate of cancer per 1000 person-years.

	Case number	Cases of cancer n (%)	Person-years	Incidence rate per 1000 person-years	*P* value
Total	1918	164 (8.6)	11043	14.7	
Metformin nonusers	335	42 (12.5)	1879	21.8	.004
Metformin users	1583	122 (7.7)	9164	13.2	

During a mean follow-up period of 5.8 ± 1.4 years, 164 of the 1918 study patients developed cancer: 42 (12.5%) metformin nonusers and 122 (7.7%) metformin users. The type of cancer was, in order of prevalence, prostate cancer (n = 10), colorectal cancer (n = 10), liver cancer (n = 8), and thyroid cancer (n = 6) in metformin nonusers; and thyroid cancer (n = 24), prostate cancer (n = 23), colorectal cancer (n = 20), and liver cancer (n = 19) in metformin users (Supplemental Table 1, http://links.lww.com/MD/C147). The incidence per 1000 person-years was 21.8 for metformin nonusers and 13.2 for metformin users (Table 2).

Metformin users had a reduced risk of cancer, even after adjusting for demographics (age, sex, duration of diabetes, income, and smoking), metabolic parameters (BMI, HbA1c, fasting blood glucose, HOMA-IR, blood pressure, and lipid profile), diabetic complications, and other antidiabetic medications (HR = 0.513, 95% CI: 0.318–0.826, $P = .006$; Table 3). The cumulative probabilities of cancer incidence based on metformin use, adjusted for demographics, metabolic parameters, diabetic complications, and antidiabetic medications, is shown in Figure 1.

In a subgroup analysis of metformin users, males, patients < 65 years of age, patients with a T2DM duration < 5 years, nonobese patients (BMI < 25.0 kg/m^2), nonsmokers (never and former smokers), and good glycemic control group (HbA1c < 7%) had a lower risk of cancer (Table 4).

4. Discussion

In this large-scale, prospective, multicenter cohort study, we demonstrated an association between metformin use and reduced cancer risk in patients with T2DM. Metformin users had a reduced risk of cancer, even after adjusting for demographic characteristics, metabolic parameters, diabetic complications, and other antidiabetic medications.

Table 3

Adjusted hazard ratios with 95% confidence intervals for cancer in metformin users based on a Cox hazard model.

	Hazard ratio	95% Confidence interval	*P* value
Model I	0.604	0.425–0.858	.005
Model II	0.633	0.443–0.906	.012
Model III	0.500	0.318–0.787	.003
Model IV	0.513	0.318–0.826	.006

Reference is metformin nonusers.

Model I: Unadjusted.

Model II: Adjusted for demographic characteristics (age, sex, duration of diabetes, income, and smoking), BMI, and HbA1c.

Model III: Adjusted for Model II + fasting blood glucose, HOMA-IR, systolic blood pressure, diastolic blood pressure, LDL cholesterol, triglyceride, and HDL cholesterol.

Model IV: Adjusted for Model III + other antidiabetic medications (sulfonylurea, thiazolidinedione, alpha glucosidase inhibitor, insulin), hypertension, cardiovascular disease, cerebrovascular disease, neuropathy, retinopathy, and nephropathy.

BMI = body mass index, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, LDL = low-density lipoprotein.

Studies of the association between diabetes and cancer development have proposed that insulin resistance and hyperinsulinemia in T2DM promotes malignant transformation, either directly or indirectly.[16,17] Hyperinsulinemia may take on the role of a growth factor by direct stimulation of insulin receptors expressed on cancer cell surfaces, linked to downstream signaling pathways involved in cell survival and mitogenesis.[18] It acts as a growth promoter of IGFs, which can modify downstream signaling pathways involved with cell proliferation and protection from apoptotic stimuli,[19] as well as an activator of chronic inflammatory processes that may trigger cancer initiation and progression.[20] Additionally, hyperglycemia may create a fuel-enriched environment for cancer progression.[17]

Previous findings have suggested that, among antidiabetic drugs, insulin and sulfonylurea may increase the risk of cancer by interacting with insulin and IGF-1 receptor signaling, which enhances proliferation and carcinogenesis.[7,21] However, the risk of cancer associated with use of these drugs remains uncertain, given the inconsistencies in the reported results and the limitations of observational studies.[4] By contrast, metformin has been reported to reduce cancer risk.[4,6–8,22]

There have been various epidemiological studies that have supported the anticancer activity of metformin. In a meta-analysis of 11 observational cohort trials, 3 randomized controlled studies (RCT), and 10 case–control studies, the risk of cancer was significantly lower in metformin users than nonusers (RR = 0.67, 95% CI = 0.53–0.85 for all cancer incidence).[6] In a retrospective cohort study, patients with T2DM were divided into 4 treatment groups: insulin, monotherapy with metformin or sulfonylurea, or combined therapy (metformin plus sulfonylurea). The adjusted HRs for metformin plus sulfonylurea, sulfonylurea monotherapy, and insulin-based regimens were 1.08 (95% CI: 0.96–1.21), 1.36 (95% CI: 1.19–1.54), and 1.42 (95% CI: 1.27–1.60), respectively. Combination therapy with metformin added to insulin reduced the development of cancer (HR = 0.54, 95% CI: 0.43–0.66) and diminished the excessive risk in patients treated with insulin or sulfonylurea.[7] In another cohort study, cancer was diagnosed in 7.3% of metformin users compared with 11.6% of metformin nonusers, with median times to cancer of 3.5 and 2.6 years, respectively ($P < .001$). The risk of cancer in metformin-treated patients was significantly reduced (HR = 0.63, 95% CI: 0.53–0.75) after adjusting for sex, age, BMI, HbA1c, deprivation, smoking, and other drug use.[8] However, other studies found no associations between metformin use and reduced cancer risk. A meta-analysis of prostate and breast cancer patients showed no association, with pooled cancer risk HRs of 0.92 (95% CI: 0.73 – 1.17) and 0.87 (95% CI: 0.69 – 1.10), respectively, in the metformin groups.[10] In a cohort study, metformin-treated patients with T2DM had a similar risk of developing cancer to those treated with sulfonylureas.[11] A meta-analysis of RCTs found no significant beneficial effect of metformin on cancer outcomes.[12] One possible reason for the discrepancy in previous studies might be the differences in comparator medications and combinations

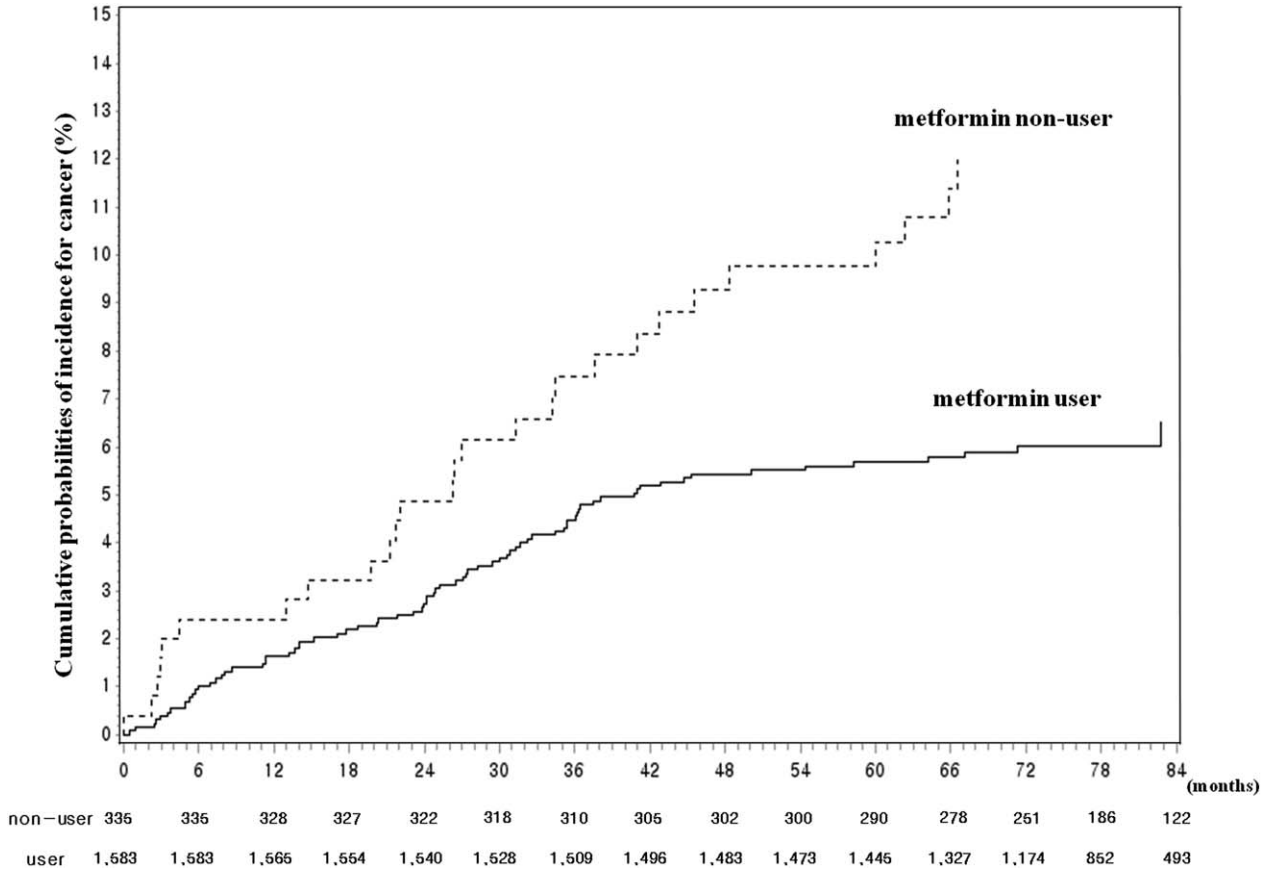

Figure 1. Cumulative probabilities of cancer incidence by use of metformin. Cumulative probabilities of incidence for cancer were significantly lower in metformin users than nonusers during follow up. Adjusted for demographics (age, sex, duration of diabetes, income, and smoking), metabolic parameters (BMI, HbA1c, fasting blood glucose, HOMA-IR, systolic blood pressure, diastolic blood pressure, LDL cholesterol, triglyceride, and HDL cholesterol), other antidiabetic medications (sulfonylurea, thiazolidinedione, alpha glucosidase inhibitor, insulin), hypertension, cardiovascular disease, cerebrovascular disease, neuropathy, retinopathy, and nephropathy. BMI = body mass index, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, LDL = low-density lipoprotein.

of medications. In addition, differences in the cancer types included in the analysis, and differences between the study populations, could have caused the conflicting results. To determine the relationship between metformin and cancer risk, well-designed, large-scale, randomized clinical trials are needed.

Survival benefit associated metformin was also observed after incident cancer in a retrospective cohort study. People with diabetes receiving metformin monotherapy for 90 days before cancer diagnosis had significantly reduced overall mortality (HR = 0.85, 95% CI: 0.78–0.93) compared to those without diabetes.[23] In a prospective cohort study involving 1353 T2DM patients, metformin use was associated with a 57% reduction in cancer-specific mortality.[24] A randomized study showed a preventive effect of metformin against cancer, where nondiabetic patients with 1 month of metformin had less rectal aberrant crypt foci, a surrogated marker of colorectal cancer, and a lower proliferating cell nuclear antigen index.[25]

Both insulin-dependent and -independent mechanisms have been proposed to explain the association between metformin and cancer development. Metformin lowers serum levels of insulin and IGF-1, thus reducing levels of the stimuli that promote cancer cell growth.[26] Metformin activates the serine–threonine liver kinase B1/AMPK pathway and may thus inhibit cancer cell growth by suppressing mTORC1, which plays an important role in the metabolism, growth, and proliferation of cancer cells.[9,27] Metformin also initiates AMPK-dependent cell-cycle arrest by phosphorylating p53.[28] An influence of metformin on chronic inflammation, an important factor in the initiation and promotion of carcinogenesis has also been suggested as another mechanism.[29]

Our study has several clinical implications. We demonstrated that metformin users had a lower risk of cancer, supporting the anticancer effect of metformin based on a large-scale, prospective, multicenter cohort, and adjusting for a wide range of potential confounders. Among the metformin users in our study, cancer risk was reduced in males, younger patients, patients with a shorter T2DM duration, nonobese patients, nonsmokers, and patients with good glycemic control. These novel findings suggest that the anticancer effect of metformin might be more marked in subjects without risk factors such as older age, obesity, smoking, and long-term T2DM.

Our study had several limitations. First, we could not analyze the relationships between metformin use and specific cancers due to the relatively low incidence of cancer and the relatively short duration of follow-up (5.8 years). Second, the data on demographics,

Table 4

Adjusted hazard ratios with 95% confidence intervals for cancer in metformin users by subgroup.

Subgroup	Hazard ratio	95% confidence interval	*P* value
Sex			
Male	0.388	0.227–0.661	<.001
Female	0.944	0.356–2.502	.907
Age, years			
< 65	0.578	0.338–0.987	.045
≥ 65	0.389	0.147–1.031	.389
Diabetes duration, years			
< 5	0.500	0.266–0.940	.031
≥ 5	0.559	0.279–1.118	.100
BMI, kg/m^2			
< 25.0	0.393	0.209–0.741	.004
≥ 25.0	0.724	0.362–1.448	.361
Smoking			
None	0.461	0.282–0.753	.002
Current	0.642	0.162–2.544	.528
HbA1c (%)			
< 7	0.495	0.256–0.958	.037
≥ 7	0.537	0.273–1.056	.072

Reference is metformin nonusers.

Adjusted for age, sex, income, smoking, BMI,duration of diabetes, HbA1c, fasting blood glucose, HOMA-IR, systolic blood pressure, diastolic blood pressure, LDL cholesterol, triglyceride, and HDL cholesterol.

BMI = body mass index, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, LDL = low-density lipoprotein.

laboratory parameters, other antidiabetic medications, and status of diabetic complications were collected at the time of cohort registration, and cannot fully reflect the entire follow-up period, which may have resulted in biased results. The demonstrated relationship between a reduced risk of cancer and metformin users with a shorter T2DM duration should be interpreted cautiously, because it was based on the duration of T2DM at the time of registration, and not at the time of cancer diagnosis or first metformin use. Third, the possibility of bias and residual confounding cannot be completely excluded, although multivariable models were used to improve the validity of inferences made from the data.

In conclusion, in a nationwide, large scale, prospective, multicenter cohort study in Korea, our results showed an association between metformin use and a reduced cancer risk. Further large-scale, prospective, randomized clinical trials are needed to definitively determine the effect of metformin on cancer risk.

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