Metformin Use and the Risk of Cancer in Patients with Diabetes: A Nationwide Sample Cohort Study

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ABSTRACT

Metformin is known to have an antitumor effect; however, its effects in the prevention of cancer remain controversial. This study aimed to investigate the association of metformin therapy with the development of cancer. A population-based cohort study was conducted among adult patients with diabetes in 2010 using sample cohort data from the National Health Insurance Service. Metformin users were defined as those who had been prescribed repeated oral metformin administration over a period of ≥90 days. The primary endpoint of this study was the new development of cancer from January 1, 2011, to December 31, 2015. A total of 66,627 adult patients with diabetes were included in the final analysis; 29,974 were metformin users and 36,653 were controls. In the time-dependent Cox regression model, after multivariable adjustment, the risk for the development of cancer among metformin users was not significantly different from that among controls (HR = 0.96; 95% confidence interval, 0.89–1.03; $P = 0.250$). In the sensitivity analysis, neither low daily dosage (≤1 g/day, $P = 0.301$) nor high daily dosage (>1 g/day, $P = 0.497$) of metformin was significantly associated with the development of cancer between 2011 and 2015. We found no association between metformin therapy and the risk of cancer among patients with diabetes, even in the high daily dosage groups of metformin (>1 g/day). However, there might be residual confounders or bias; thus, further prospective, large population-based cohort studies are needed to confirm these findings.

Impact: This population-based cohort study suggested a lack of association between metformin therapy and the risk of cancer among patients with diabetes. Therefore, the relationship between metformin therapy and the risk of cancer is still controversial.

Introduction

Cancer is one of the most important causes of death worldwide (1). From 2006 to 2016, there were 17.2 million cancer patients worldwide, 8.9 million deaths caused by cancer, and the global incidence of cancer increased by 28% (2). Furthermore, the incidence of cancer is expected to increase in the future, and the prevention of cancer is important to reduce the global burden of disease in the future (3).

Metformin is a biguanide (N-N-dimethylbiguanide hydrochloride), which is most commonly prescribed for the management of type 2 diabetes mellitus (4). Metformin is known to reduce glycogenesis through adenosine monophosphate-activated kinase signaling, and it increases glucose uptake in muscle cells, leading to a decrease in glucose levels (5). Recently, there have been some reports that metformin has an antitumor effect that might be beneficial in cancer prevention and treatment (6, 7). The antitumor activity of metformin has been explained by both direct and indirect molecular mechanisms in preclinical and *in vitro* studies (8–10). Against this background, recent clinical- and population-based cohort studies have reported that metformin therapy in patients with diabetes is beneficial in the prevention of various cancers (11–13). However, another recent nationwide population-based cohort study conducted in Israel reported that there was no significant association between metformin therapy and the incidence of major cancer (14), and the debate is ongoing.

Therefore, this study was designed to investigate the association of metformin therapy in patients with diabetes with the development of cancer, using a sample cohort from South Korea. We hypothesized that metformin therapy lowers the risk of cancer in patients with diabetes.

Materials and Methods

Database and ethics statement

The "sample cohort database" of the National Health Insurance Service (NHIS) was developed to provide data for academic healthcare-related research among the general population in South Korea. The database included a stratified random sample of one million people who had registered with the NHIS since 2002. It was designed to be representative of the national population in terms of demographic and socioeconomic variables. The cohort was dynamic, and patients were followed up until the end of 2015. It was supplemented with additional data, including data on infants, to allow for attrition due to death and loss to follow up. The study protocol was approved by the

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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Cancer Prev Res 2020;13:195–202

doi: 10.1158/1940-6207.CAPR-19-0427

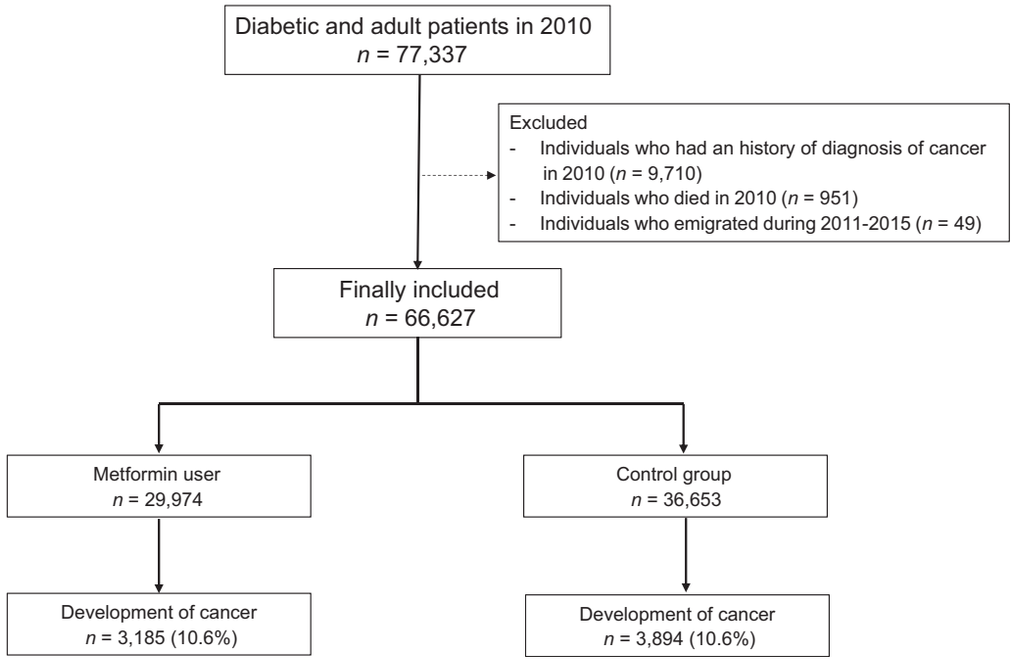

Figure 1.
Flow chart depicting patient selection.

Institutional Review Board of Seoul National University Bundang Hospital (X-1905-541-901) and the Health Insurance Review and Assessment Service (NHIS-2019-2-159).

Study population

We included all diabetic and adult patients (ages ≥18 years) in the 2010 cohort database of the NHIS. All subjects were registered with diagnoses of diabetes mellitus according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10; E10–E14) in the 2010 NHIS database. Next, we excluded individuals who died during 2010, individuals who emigrated between 2011 and 2015 due to inability to follow them up, and individuals who had a history of diagnosis of cancer in 2010, as our study focused on new diagnoses of cancer between 2011 and 2015.

Metformin use as an exposure variable

Among patients with diabetes in the NHIS 2010 cohort, metformin users were defined as those who had been prescribed a continuous supply of oral metformin over a period of ≥90 days. All other individuals were classified as the control group. The classification of metformin use in the 2010 cohort was based on the metformin prescription data from October 2009 to December 2010 because we aimed to exclude immediate exposure to metformin (<90 days) before evaluating cancer development since January 2011 via a lag-time approach (15). Metformin users were divided into the following two groups: high daily dosage group (>1 g/day) and low daily dosage group (≤1 g/day).

Development of cancer as the dependent variable

According to the ICD-10 diagnostic system, the development of cancer in this study was defined as newly registered diagnoses of any malignancy (C00–C96) between 2011 and 2015. In detail, the development of cancer was divided into gastric cancer (C16), esophageal cancer (C15), colorectal cancer (C18–C20), gall bladder and biliary tract cancer (C23–C24), head and neck cancer (C00–C14), brain cancer (C71), liver cancer (C22), pancreatic cancer (C25), lung cancer (C34), bone and articular cartilage cancer (C40–C41), neoplasms of breast and genital organs (C50–C63), urinary tract cancer (C64–C68), thyroid cancer (C73), and lymphoma or leukemia (C81–C96). The time to cancer diagnosis was calculated from January 1 to the date of diagnosis of cancer, as registered officially in the ICD-10 system. In South Korea, all patients diagnosed with cancer of any C-code should be registered in the NHIS database to receive special financial coverage; 95% of the total cost for cancer treatment is covered by the NHIS. Therefore, there was no patient whose diagnosis of cancer was not registered in the sample cohort of 2010 in South Korea.

Confounding variables

Data regarding the following variables were collected as confounders in this study: (i) demographic information (age and sex); (ii) socioeconomic information [income level in deciles and place of residence in 2010 (Seoul, metropolitan cities, or others)]; (iii) comorbidities that had been registered from 2009 to 2010 using the ICD-10 code diagnostic system in the NHIS database [hypertension (I10–I16), coronary artery

disease (I20*–I25*), cerebrovascular disease (I60*–I69*), psychobehavioral disorder (F00–F99), musculoskeletal disorders (M00–M99), chronic kidney disease (N18*), dyslipidemia (E78.0), anemia (D64*), chronic obstructive pulmonary disease (J44*), arrhythmia (I49*), and liver cirrhosis (K74*)]; (iv) receipt of surgery in 2010; (v) total number of hospital visit days in 2010; and (vi) use of other antidiabetic medications (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, and insulin). The number of hospital visit days included the number of hospital outpatient clinic visits and days spent on admission, but did not include outpatient visits to primary care physicians. For example, an individual who visited a hospital outpatient clinic five times and was admitted to the hospital for 3 days would be considered to have eight hospital visit days. In the analysis, the number of hospital visit days was categorized into five groups (0, 1–7, 8–29, 30–90, and >90 days).

Study endpoint

The primary endpoint of this study was the new development of cancer from January 1, 2011, to December 31, 2015, among patients with diabetes registered in the NHIS sample cohort of 2010 in South Korea.

Statistical analysis

The baseline characteristics of patients are presented as means with standard deviations for continuous variables or frequencies with percentages for categorical variables. First, because our study focused on time-dependent exposure to metformin in the 2010 cohort from 2011 to 2015, we investigated the proportion of patients with diabetes that went off metformin therapy or started using it during the follow-up period (2011–2015). Exposure to metformin in both the metformin and control groups in 2010 varied throughout the follow-up period (Supplementary Table S1). Therefore, we investigated the association between exposure to metformin and the new development of cancer using a time-dependent Cox regression model. In this model, exposure to metformin was considered as a time-dependent variable, and all other covariates were included in the time-dependent Cox regression model for multivariable adjustment. As a first sensitivity analysis, we performed a time-dependent Cox regression analysis of the development of cancer according to the daily dosage of metformin in the high daily dosage (>1 g/day) and low daily dosage ($\leq$1 g/day) groups. In addition, we performed a time-dependent Cox regression analysis of the development of cancer in detail via the same method to investigate whether the association differed according to the type of cancer.

To enhance the robustness of our study findings, we performed propensity score (PS) matching, which is known to reduce confounders in cohort studies (16), using the nearest neighbor method with a 1:1 ratio, without replacement, and a caliper width of 0.2. Logistic regression analysis was performed to calculate PS values as a logistic model, and all covariates were included in the PS model. The absolute value of the standardized mean difference (ASD) was used to determine the balance between the metformin and control groups before and after PS matching. The ASDs between the two groups before and after PS matching were set to below 0.1 to determine if the two groups were well balanced.

After confirming adequate balance between the two groups after PS matching, we performed a time-dependent Cox regression analysis of the development of cancer between 2011 and 2015 in the PS-matched cohort. The results of the Cox regression models are presented as HRs with 95% confidence intervals (CI), and it was confirmed that there was no

Table 1. Baseline characteristics of diabetic patients in 2010 NHIS cohort.

Variable	Total (n = 66,627)	Mean (SD)
Age, year		60.1 (13.2)
Sex, male	33,168 (49.8)	
Income level (deciles distribution ratio)		
First (Lowest income level)	5,352 (8.0)	
Second	3,714 (5.6)	
Third	4,222 (6.3)	
Fourth	4,561 (6.8)	
Fifth	4,926 (7.4)	
Sixth	10,690 (16.0)	
Seventh	6,523 (9.8)	
Eighth	7,357 (11.0)	
Ninth	8,770 (13.2)	
Tenth (highest income level)	10,512 (15.8)	
Residence		
Capital city (Seoul)	13,718 (20.6)	
Metropolitan city[a]	16,132 (24.2)	
Others	36,777 (55.2)	
Underlying disease in 2010		
Hypertension [I10–I16]	42,654 (64.0)	
Coronary artery disease [I20*–I25*]	12,038 (18.1)	
Cerebrovascular disease [I60*–I69*]	9,444 (14.2)	
Psycho-behavioral disorder [F00–F99]	21,106 (31.7)	
Musculoskeletal disease [M00–M99]	46,841 (70.3)	
Chronic kidney disease [N18*]	1,537 (2.3)	
Dyslipidemia [E78.0]	39,184 (58.8)	
Anemia [D64*]	3,529 (5.3)	
Chronic obstructive pulmonary disease [J44*]	2,339 (3.5)	
Arrhythmia [I49*]	1,734 (2.6)	
Liver cirrhosis [K74*]	631 (0.9)	
Surgery at 2010	14,950 (22.4)	
Metformin user	29,974 (45.0)	
>1 g/day	8,903 (13.4)	
Other diabetic medication use		
Sulfonylureas	25,099 (37.7)	
Alpha-glucosidase inhibitors	8,315 (12.5)	
Thiazolidinediones	4,273 (6.4)	
Insulin	2,268 (3.4)	
Hospital visit in 2010,[b] day		
0	48,385,(72.6)	
1–7	8,548 (12.8)	
8–30	6,395 (9.6)	
30–90	1,980 (3.0)	
>90	1,319 (2.0)	

[a]Metropolitan city include Incheon, Kwangju, Busan, Ulsan, Daegu, and Daejeon.
[b]Hospital visit days included the number of hospital outpatient clinic visits, and days as a hospital inpatient, but did not include outpatient visits to primary care physicians.

Table 2. Multivariable time-dependent Cox regression model for development of cancer from 2011 to 2015 among entire diabetic cohort in 2010.

Metformin group (vs. control group)	Multivariable model HR (95% CI)	*P* value
Overall cancer (n = 7,079)	0.96 (0.89–1.03)	0.250
Sensitivity analysis according to daily dosage of metformin		
Low daily dosage of metformin group	0.97 (0.92–1.03)	0.301
High daily dosage of metformin group	1.02 (0.95–1.11)	0.497
Specific cancer type		
Gastric cancer (C16) (n = 570)	0.91 (0.74–1.12)	0.376
Esophageal cancer (C15) (n = 37)	0.74 (0.32–1.67)	0.461
Colorectal cancer (C18–C20) (n = 917)	1.01 (0.86–1.19)	0.892
GB and biliary tract cancer (C23–C24) (n = 124)	0.83 (0.52–1.27)	0.364
Head and Neck cancer (C00–C14) (n = 46)	0.64 (0.30–1.38)	0.255
Brain cancer (C71) (n = 24)	1.76 (0.63–4.90)	0.277
Liver cancer (C22) (n = 1,197)	0.96 (0.83–1.11)	0.552
Pancreatic cancer (C25) (n = 485)	0.88 (0.70–1.11)	0.277
Lung cancer (C34) (n = 711)	1.23 (0.94–1.39)	0.075
Bone and articular cartilage cancer (C40–C41) (m = 12)	0.53 (0.13–2.18)	0.379
Neoplasms of breast and genital organs (C50–C63) (n = 1,683)	0.90 (0.78–1.04)	0.162
Urinary tract cancer (C64–C68) (n = 357)	1.01 (0.77–1.33)	0.944
Thyroid cancer (C73) (n = 252)	0.95 (0.61–1.33)	0.751
Lymphoma or Leukemia (C81–C96) (n = 203)	1.03 (0.71–1.48)	0.894

Note: All covariates were included for adjustment in time-dependent multivariable Cox regression model.
Abbreviation: GB, gall bladder.

multicollinearity in all multivariable models of the entire cohort with a variance inflation factor of <2.0. All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria), and $P < 0.05$ was considered statistically significant.

Results

Population

In total, 77,337 adult patients with diabetes were screened initially. Next, we excluded individuals who died in 2010 (n = 952), individuals who emigrated between 2011 and 2015 (n = 49) due to inability to follow them up, and individuals who had a history of cancer in 2010 (n = 9,710). Finally, 66,627 adult diabetes patients were included in the analysis. Among them, 7,079 (10.6%) patients (3,185 in the metformin group and 3,894 in the control group) were newly diagnosed with cancer between 2011 and 2015 (**Fig. 1**). **Table 1** shows the characteristics of the entire study cohort.

Time-dependent Cox regression model for the entire cohort

The results of the time-dependent Cox regression analysis of the development of cancer after multivariable adjustment are presented in **Table 2**. There was no significant difference in the hazard for the development of cancer between the metformin and control groups (HR = 0.96; 95% CI, 0.89–1.03; P = 0.250). In the sensitivity analysis according to daily dosage, there was no significant difference in the hazard for the development of cancer in both the low daily dosage of metformin group (HR = 0.97; 95% CI, 0.92–1.03; P = 0.301) and high daily dosage of metformin group (HR = 1.02; 95% CI, 0.95–1.11; P = 0.497), compared with the control group. In addition, there was no significant difference in the hazard for the development of any cancer type between the metformin and control groups (all $P > 0.05$).

Time-dependent Cox regression model after PS adjustment

The results of the comparison of characteristics between the metformin and control groups before and after PS adjustment are shown in **Table 3**. The characteristics of both the metformin and control groups were well balanced as the ASDs of all variables were below 0.1 after PS matching. In the time-dependent Cox regression model of the PS-matched cohort, there was no significant difference in the hazard for the development of cancer between the metformin and control groups (HR = 0.96; 95% CI, 0.90–1.04; P = 0.320; **Table 4**). In addition, there were no differences in the hazards for the development of any cancer type between the metformin and control groups in the PS-matched cohort (all $P > 0.05$).

Discussion

This population-based cohort study showed that metformin therapy was not significantly associated with a lower risk of cancer among patients with diabetes. This association did not significantly differ according to the daily dosage of metformin. Our finding is similar to that of a recent cohort study conducted by Dankner and colleagues (14), and suggested that the relationship between metformin therapy and the risk of cancer remains controversial.

Table 3. Comparison of characteristics between metformin users and control group among patients with diabetes before and after PS matching.

	Entire cohort (n = 36,653)			PS-matched cohort (n = 29,974)		
Variables	**Metformin user n = 29,974**	**Control n = 36,653**	**ASD**	**Metformin user n = 19,546**	**Control n = 19,546**	**ASD**
Age, year	60.6 (12.0)	60.0 (14.1)	0.077	60.5 (13.3)	60.3 (12.2)	0.019
Sex: male	15,772 (52.6)	17,396 (47.5)	0.103	10,362 (53.0)	10,274 (52.6)	0.009
Income level (deciles distribution ratio)						
First (lowest income level)	2,430 (8.1)	2,922 (8.0)		1,561 (8.0)	1,525 (7.8)	
Second	1,707 (5.7)	2,007 (5.5)	0.009	1,063 (5.4)	1,067 (5.5)	<0.001
Third	1,899 (6.3)	2,323 (6.3)	<0.001	1,224 (6.3)	1,207 (6.2)	0.004
Fourth	2,103 (7.0)	2,458 (6.7)	0.012	1,305 (6.7)	1,323 (6.8)	0.004
Fifth	2,236 (7.5)	2,690 (7.3)	0.004	1,393 (7.1)	1,429 (7.3)	0.007
Sixth	4,655 (15.5)	6,035 (16.5)	0.026	2,982 (15.3)	2,993 (15.3)	0.002
Seventh	3,031 (10.1)	3,492 (9.5)	0.019	2,034 (10.4)	1,925 (9.8)	0.019
Eighth	3,356 (11.2)	4,001 (10.9)	0.009	2,211 (11.3)	2,260 (11.6)	0.008
Ninth	3,921 (13.1)	4,849 (13.2)	0.004	2,593 (13.3)	2,625 (13.4)	0.005
Tenth (highest income level)	4,636 (15.5)	5,876 (16.0)	0.016	3,180 (16.3)	3,192 (16.3)	0.002
Residence						
Capital city (Seoul)	5,937 (19.8)	7,781 (21.2)		4,187 (21.4)	4,096 (21.0)	
Metropolitan city[a]	7,422 (24.8)	8,710 (23.8)	0.023	5,040 (25.8)	4,874 (24.9)	0.020
Others	16,615 (55.4)	20,162 (55.0)	0.008	10,319 (52.8)	10,576 (54.1)	0.027
Hypertension	20,231 (67.5)	22,423 (61.2)	0.135	13,282 (68.0)	13,185 (67.5)	0.011
Coronary artery disease	5,033 (16.8)	7,005 (19.1)	0.062	3,404 (17.4)	3,365 (17.2)	0.005
Cerebrovascular disease	3,913 (13.1)	5,531 (15.1)	0.060	2,644 (13.5)	2,609 (13.3)	0.005
Psycho-behavioral disorder	8,311 (27.7)	12,795 (34.9)	0.160	5,439 (27.8)	5,499 (28.1)	0.007
Chronic kidney disease	257 (0.9)	1,280 (3.5)	0.286	234 (1.2)	224 (1.1)	0.006
Dyslipidemia	18,529 (61.8)	20,655 (56.4)	0.113	12,844 (65.7)	12,234 (62.6)	0.064
Anemia	1,240 (4.1)	2,289 (6.2)	0.106	838 (4.3)	783 (4.0)	0.014
Chronic obstructive pulmonary disease	822 (2.7)	1,517 (4.1)	0.086	548 (2.8)	562 (2.9)	0.004
Arrhythmia	539 (1.8)	1,195 (3.3)	0.110	383 (2.0)	361 (1.8)	0.009
Liver cirrhosis	200 (0.7)	431 (1.2)	0.062	160 (0.8)	139 (0.7)	0.013
Surgery at 2010	6,246 (20.8)	8,704 (23.7)	0.072	4,157 (21.3)	4,016 (20.5)	0.018
Hospital visit in 2010,[b] day (including admission)						
0	22,982 (76.7)	25,403 (69.3)		14,930 (76.4)	15,086 (77.2)	
1–7	3,376 (11.3)	5,172 (14.1)	0.090	2,227 (11.4)	2,231 (11.4)	<0.001
8–30	2,543 (8.5)	3,852 (10.5)	0.073	1,654 (8.5)	1,589 (8.1)	0.012
30–90	757 (2.5)	1,223 (3.3)	0.052	469 (2.4)	453 (2.3)	0.005
>90	316 (1.1)	1,003 (2.7)	0.164	266 (1.4)	189 (1.0)	0.039
Other diabetic medication use						
Sulfonylureas	17,277 (57.6)	7,822 (21.3)	0.735	7,698 (39.4)	7,733 (39.6)	0.004
Alpha-glucosidase inhibitors	6,638 (22.1)	1,677 (4.6)	0.423	2,198 (11.2)	1,648 (8.4)	0.068
Thiazolidinediones	2,750 (9.2)	1,523 (4.2)	0.174	2,028 (10.4)	1,470 (7.5)	0.098
Insulin	1,279 (4.3)	989 (2.7)	0.078	938 (4.8)	765 (3.9)	0.044

Note: Data are presented as number (percentage) or mean (SD).

[a]Metropolitan city include Incheon, Kwangju, Busan, Ulsan, Daegu, and Daejeon.

[b]Hospital visit (day) includes numbers of the outpatient clinic and admission day in hospital, whereas it did not include outpatient clinic by primary physician.

Recently, some previous studies have reported that metformin therapy might have a potential benefit for the prevention of cancer development (6, 7, 17). This effect was supported by the *in vitro* evidence that metformin has a direct antitumor effect, and might suppress tumor proliferation, induce apoptosis, and arrest the division of cancer cells (8–10). Furthermore, metformin is known to confer an indirect antitumor effect by inhibiting protein phosphatase 2A (18). In this context, metformin therapy was expected to be beneficial in preventing cancer among patients with diabetes in population-based cohort and clinical studies (19–24). However, both our study and the study conducted by Dankner and colleagues (14) failed to show that metformin use yielded a potential benefit for the prevention of cancer among patients with diabetes.

Several observational studies have shown that metformin therapy confers a protective effect on cancer development or progression. Specifically, metformin therapy is reported to lower the risk of overall cancer (19–21), as well as colorectal cancer (22), esophageal cancer (23), and endometrial cancer (24). However, Suissa and colleagues reported that these observational studies mostly suffered from time-related bias such as immortal time bias, which might result in an overestimation of the effect of metformin on cancer development (25). Immortal time bias refers to a period of follow-up during which the study outcome cannot occur due to the

Table 4. Time-dependent Cox regression model for development of cancer from 2011 to 2015 among PS-matched diabetic cohort in 2010.

Metformin group (vs. control group)	Multivariable model HR (95% CI)	*P* value
Overall cancer ($n = 4{,}118$)	0.96 (0.90–1.04)	0.320
Gastric cancer (C16) ($n = 343$)	0.92 (0.72–1.18)	0.921
Esophageal cancer (C15) ($n = 20$)	0.38 (0.13–1.13)	0.080
Colorectal cancer (C18–C20) ($n = 539$)	1.03 (0.84–1.26)	0.771
GB and biliary tract cancer (C23–C24) ($n = 71$)	0.78 (0.46–1.35)	0.381
Head and Neck cancer (C00–C14) ($n = 25$)	0.56 (0.20–1.53)	0.256
Brain cancer (C71) ($n = 24$)	1.49 (0.45–4.93)	0.514
Liver cancer (C22) ($n = 680$)	1.08 (0.90–1.29)	0.410
Pancreatic cancer (C25) ($n = 304$)	0.77 (0.59–1.00)	0.053
Lung cancer (C34) ($n = 368$)	1.20 (0.95–1.45)	0.075
Bone and articular cartilage cancer (C40–C41) ($m = 6$)	0.22 (0.02–2.33)	0.209
Neoplasms of breast and genital organs (C50–C63) ($n = 1{,}683$)	0.90 (0.78–1.04)	0.162
Urinary tract cancer (C64–C68) ($n = 357$)	0.94 (0.69–1.29)	0.708
Thyroid cancer (C73) ($n = 129$)	0.86 (0.57–1.29)	0.452
Lymphoma or leukemia (C81–C96) ($n = 203$)	1.12 (0.72–1.76)	0.618

Abbreviation: GB, gall bladder.

study design, death, or the study outcome (26). In addition, Wei and colleagues reported that the association between metformin therapy and survival among patients with pancreatic cancer had been greatly exaggerated in previous cohort studies due to the wide presence of immortal time bias (27). Immortal time bias might be present in our study. For instance, the risk of cancer in the control group might be higher if patients in the metformin group died due to any other disease (e.g., cardiovascular disease) in 2011 before cancer development and the control group lived beyond 2011. However, immortal bias is known to be overcome in epidemiological studies via two statistical methods (28): time-dependent techniques and matching. We used both time-dependent Cox regression analysis and PS matching in this study. Furthermore, we considered as many comorbidities as possible with socioeconomic status-related confounders for PS matching, which might be closely related to death due to other diseases, before cancer development.

Second, there might be protopathic bias. This arises when a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been detected diagnostically (29). For example, the results might be biased due to inadequate duration of exposure for the event to occur if a patient received a prescription for metformin from December 2010 within 30 days. To minimize this bias, we defined metformin users using a lag-time approach as those who received prescriptions for metformin over 90 days until December 2010 (15, 30). By this approach, we excluded immediate exposure to metformin among patients with diabetes before evaluating the development of cancer from January 2011. Considering that protopathic bias may affect the association between exposure to metformin and the development of cancer, our study is notable with regard to using the lag time approach.

This study has several limitations. First, some important variables, such as body mass index, were not included in the statistical adjustment because they were not included in the NHIS data set. Second, we defined the comorbidities using ICD-10 codes registered in the NHIS database. The diseases specified by the ICD-10 codes might differ from the actual underlying diseases in all patients. Third, PS adjustment and multivariable adjustment could control only known confounders; thus, there might be residual confounders that could affect the study results. Fourth, we based the analysis on metformin prescription data and did not assess actual adherence or compliance among those classified as metformin users. Finally, we classified neoplasms of the breast and genital organs (C50–C63) as one group among specific cancer sites in this study, because the NHIS database contained one C-code (C_) for breast or genital organ cancer (C50–C63). Therefore, we could not evaluate the association between exposure to metformin and the development of cancer of the prostate, breast, or cervix; this could be a limitation of this study.

In conclusion, this population-based cohort study suggested a lack of association between metformin therapy and the risk of cancer among patients with diabetes, even in those receiving high daily doses (>1 g/day). However, there might be residual confounders or bias; thus, further prospective, large population-based cohort studies are needed to confirm these findings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: T.K. Oh, I.-A. Song
Development of methodology: T.K. Oh

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Received September 6, 2019; revised October 23, 2019; accepted October 31, 2019; published first November 7, 2019.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Global Burden of Disease Cancer C, Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the global burden of disease study. JAMA Oncol 2018;4:1553–68.
3. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 2017;3:524–48.
4. Bailey CJ. Metformin: historical overview. Diabetologia 2017;60:1566–76.
5. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 1995;333:550–4.
6. Saraei P, Asadi I, Kakar MA, Moradi-Kor N. The beneficial effects of metformin on cancer prevention and therapy: a comprehensive review of recent advances. Cancer Manag Res 2019;11:3295–313.
7. Kasznicki J, Sliwinska A, Drzewoski J. Metformin in cancer prevention and therapy. Ann Transl Med 2014;2:57.
8. Madiraju AK, Erion DM, Rahimi Y, Zhang XM, Braddock DT, Albright RA, et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature 2014;510:542–6.
9. Whitaker-Menezes D, Martinez-Outschoorn UE, Flomenberg N, Birbe RC, Witkiewicz AK, Howell A, et al. Hyperactivation of oxidative mitochondrial metabolism in epithelial cancer cells in situ: visualizing the therapeutic effects of metformin in tumor tissue. Cell Cycle 2011;10:4047–64.
10. Sekino N, Kano M, Matsumoto Y, Sakata H, Murakami K, Toyozumi T, et al. The antitumor effects of metformin on gastric cancer *in vitro* and on peritoneal metastasis. Anticancer Res 2018;38:6263–9.
11. Lu MZ, Li DY, Wang XF. Effect of metformin use on the risk and prognosis of ovarian cancer: an updated systematic review and meta-analysis. Panminerva Med 2019 [Epub ahead of print].
12. Kim HJ, Lee S, Chun KH, Jeon JY, Han SJ, Kim DJ, et al. Metformin reduces the risk of cancer in patients with type 2 diabetes: an analysis based on the Korean National Diabetes Program Cohort. Medicine 2018;97:e0036.
13. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One 2013;8:e71583.
14. Dankner R, Agay N, Olmer L, Murad H, Boker LK, Balicer RD, et al. Metformin treatment and cancer risk: Cox regression analysis with time-dependent covariates of 320,000 individuals with incident diabetes mellitus. Am J Epidemiol 2019;188:1794–800.
15. Arfe A, Corrao G. The lag-time approach improved drug-outcome association estimates in presence of protopathic bias. J Clin Epidemiol 2016;78:101–7.
16. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984;79:516–24.
17. Zi F, Zi H, Li Y, He J, Shi Q, Cai Z. Metformin and cancer: an existing drug for cancer prevention and therapy. Oncol Lett 2018;15:683–90.
18. Hanawa S, Mitsuhashi A, Shozu M. Antitumor effects of metformin via indirect inhibition of protein phosphatase 2A in patients with endometrial cancer. PLoS One 2018;13:e0192759.
19. Gandini S, Puntoni M, Heckman-Stoddard BM, Dunn BK, Ford L, DeCensi A, et al. Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev Res 2014;7:867–85.
20. Lin HC, Kachingwe BH, Lin HL, Cheng HW, Uang YS, Wang LH. Effects of metformin dose on cancer risk reduction in patients with type 2 diabetes mellitus: a 6-year follow-up study. Pharmacotherapy 2014;34:36–45.
21. Thakkar B, Aronis KN, Vamvini MT, Shields K, Mantzoros CS. Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. Metabolism 2013;62:922–34.
22. Singh S, Singh H, Singh PP, Murad MH, Limburg PJ. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2013;22:2258–68.
23. Becker C, Meier CR, Jick SS, Bodmer M. Case-control analysis on metformin and cancer of the esophagus. Cancer Causes Control 2013;24:1763–70.
24. Becker C, Jick SS, Meier CR, Bodmer M. Metformin and the risk of endometrial cancer: a case-control analysis. Gynecol Oncol 2013;129:565–9.
25. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 2012;35:2665–73.
26. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 2010;340:b5087.
27. Wei M, Liu Y, Bi Y, Zhang ZJ. Metformin and pancreatic cancer survival: real effect or immortal time bias? Int J Cancer 2019;145:1822–8.
28. Shariff SZ, Cuerden MS, Jain AK, Garg AX. The secret of immortal time bias in epidemiologic studies. J Am Soc Nephrol 2008;19:841–3.
29. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. Am J Med 1980;68:255–8.
30. Tamim H, Monfared AA, LeLorier J. Application of lag-time into exposure definitions to control for protopathic bias. Pharmacoepidemiol Drug Saf 2007;16:250–8.