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Metformin use reduced the overall risk of cancer in diabetic patients: A study based on the Korean NHIS-HEALS cohort

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Abstract *Background and aim:* Several studies have reported the preventive effect of metformin on cancer development. This study aimed to investigate the relationship between use of metformin and risk of cancer in Koreans.
Methods and Results: This study was designed retrospectively using the National Health Insurance Service-National Health Screening Cohort conducted between 2002 and 2015. 40 to 69-year-old subjects who received a health screening examination from 2002 to 2003 were enrolled. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer were estimated in a multivariate Cox proportional regression analysis.

A total of 323,430 subjects was enrolled (301,905 individuals without diabetes [No DM], 8643 diabetic patients with metformin treatment [metformin users], and 12,882 diabetic patients without metformin treatment [metformin non-users]). The median follow-up period was 12.7 years. Cumulative incidence of overall cancer was 7.9% (7.7, 10.3, and 11.1% in No DM, metformin users and non-users, respectively). Compared to metformin non-users, the fully adjusted HRs (95% CIs) of metformin users and No DM for overall cancer incidence were 0.73 (0.66–0.81) and 0.75 (0.64–0.88), respectively, in men and 0.83 (0.78–0.89) and 0.81 (0.72–0.92) in women.
Conclusions: Diabetic patients receiving metformin treatment, and individuals without diabetes were at lower risk for cancer incidence than diabetic patients without metformin treatment.

Introduction

Diabetes mellitus (DM) and cancer are prevalent worldwide, and the related mortality is increasing [1]. The number of individuals with diabetes was approximately 451 million in 2017, and that number is expected to be 693 million in 2025 [2]. The prevalence of diabetes in Korea has increased from 8.9% in 2005 to 11.1% in 2013–2015 [3]. Diabetes in Korea is the 6th most common cause of death, according to the recent Statistics Korea Report [4]. In

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addition, more than 210,000 new cases of cancer are diagnosed each year in Korea. Age-standardized cancer incidence in Korea was 286.8 cases per 100,000 persons in 2016 [5]. Fortunately, the five-year relative survival rate remarkably improved to 70.3% between 2010 and 2014 compared to 41.2% of cancers diagnosed between 1993 and 1995 [6]. Even though cancer survival rates have increased, malignant neoplasia is the number one cause of death in Korea [7]. In particular, diabetes and cancer are associated with complications and sequelae, resulting in increased medical expenses and social losses, great motivators of prevention and treatment. To control this increasing incidence, early detection and proper management are essential. Many diabetes-related academic societies, including the American Diabetes Association, recommend active lifestyle modification and metformin use as first-line treatment [8].

Also, to reduce cancer-related burden and mortality, various preventive strategies against cancer development, such as lifestyle modification and chemoprevention, should be adopted in addition to regular cancer screening. Avoiding known carcinogens, such as tobacco and alcohol use, is the easiest way to prevent cancer. In terms of chemoprevention, various drugs and phytochemicals can be applied [9,10]. Although there are inconsistent findings, several therapeutic agents, including statin and metformin, are considered candidates to play a functional role in preventing cancers [11,12].

Metformin is the first choice to treat type 2 DM [8]. Although metformin's mechanism of action in controlling DM is not fully elucidated, inhibition of hepatic gluconeogenesis and promotion of insulin sensitivity may be the major mechanisms [13]. Also, metformin can modulate adenosine monophosphate (AMP) kinase (AMPK) and the immune response through mammalian target of rapamycin (mTOR) [14]. Several studies demonstrated that metformin use is inversely associated with incidence of cancer [15–17].

However, there is a lack of evidence to support the inverse association between metformin use and cancer development in Korean.

This study aims to investigate whether metformin use in diabetic patients decreases cancer incidence using real-world data based on the National Health Insurance Service (NHIS)-National Health Screening Cohort Database (HEALS).

Methods

Cohort formation and study population

Data were derived from 514,794 examinees who received a general health screening between Jan 2002 and Dec 2003; these individuals were randomly extracted from the 5.15 million health examinees aged from 40 to 79 years receiving examination before, the end of December 2002. The cohort was followed until 2015. The data were deidentified by individual keys that created for the NHIS-HEALS so that it can be used for research purposes without patients' individual consent [18]. The Korean NHIS-HEALS database included death information; healthcare unit usage; socio-economic status; and medical information, including health examination information and diagnosis codes. Researchers can identify and analyze the association between medical use, medication prescription, socio-economic status, and health outcomes, based on these health examinations and claims.

Figure 1 is the flowchart of inclusions and exclusions for this study. Of the initial 514,794 participants, 191,364 were excluded based on criteria of 1) aged 70 years or older at the time of the initial screening (n = 38,519); 2) previously diagnosed with malignant neoplasm (C00–C97) or in situ neoplasm (D00-04, 09, D_group) based on the 10th edition of the International Classification of Diseases [ICD-10] between 2002 and 2004 (n = 35,136) ; 3)any past medical history of cancer in self-reported questionnaires (n = 3243); 4) death from any cause between 2002 and 2004 (n = 2526);5) prescription of insulin for more than 90 days between 2002 and 2003 (n = 73); 6) new diagnosis with diabetes between 2004 and 2015 (n = 74,569); 7) prescription of metformin before diabetes diagnosis between 2002 and 2003 (n = 1028) or without diagnosis of diabetes between 2002 and 2015 (n = 2667); 8) prescription of metformin for less than 90 days between 2002 and 2003 and more than 90 days during the total study period between 2002 and 2015 (n = 21,167); 9) a total study duration of 30 days or less between 2002 and 2015 (n = 147); and 10) missing values (n = 20,030). The above exclusion conditions were not mutually exclusive. After full exclusion, the remaining eligible participants numbered 323,430 (175,495 men and 147,935 women).

The Institutional Review Board of Chungbuk National University approved the present study (CBNU-201903-BMETC-802-01), which adhered to the Declaration of Helsinki (1975).

The operational definitions of subject groups, cancer, index date, and dosage of metformin use

We defined a subject as a DM patient if the participant satisfied one of the following conditions (1) a record of diabetes diagnosis (ICD-10 code E11-14) and prescription of any anti-diabetic drugs (insulin, sulfonylurea, metformin, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, α-glucosidase inhibitor, sodium-glucose cotransporter-2 inhibitor, glucagon-like peptide (GLP)-1 agonist, and other anti-diabetic drugs) for more than 90 days, or as (2) a fasting blood glucose level $\geq$ 126 mg/dL on health screening.

We categorized study subjects into three groups as follows: 1) metformin users, diabetic patients who were prescribed metformin over 90 days during 2002–2003 (n = 8643); 2) metformin non-users, diabetic patients who were never prescribed metformin or used metformin for less than 90 days but used other oral glucose-lowering medication (n = 12,882); and 3) No DM, participants without personal history of DM and who were prescribed anti-diabetic medications for less than 90 days during

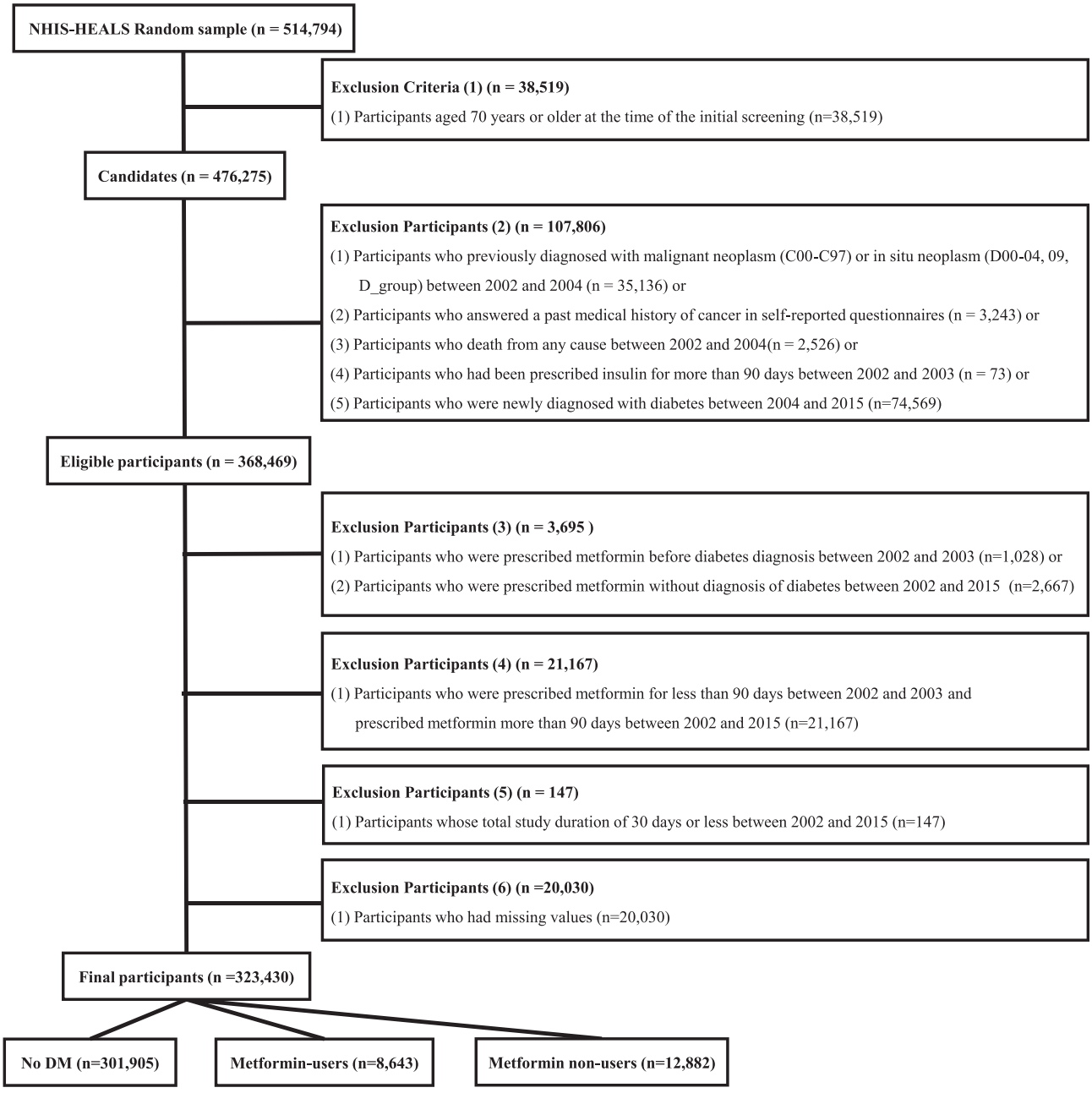

Figure 1 Flowchart of inclusion and exclusion.

2002−2015 (n = 301,905). In total, 1554 individuals in the No DM group were prescribed anti-diabetic drugs (including all types).

Cancer incidence event was defined as the first record of cancer (ICD-10 code C00−C97) as a primary diagnosis code of hospitalization since January 1, 2005.

The research start date of metformin users and metformin non-users was defined as the earlier date between 1) the first date when participants were prescribed anti-diabetic drugs and were diagnosed with diabetes (ICD-10 code E11-14) or 2) the date of health examination with a fasting glucose level $\geq$ 126 mg/dL. The start date of No DM was defined as the day of the first health examination between 2002 and 2003. For participants diagnosed with cancer during 2005−2015, the initial diagnosis date of cancer was the end date. If participants died before cancer occurred or cancer did not occur within the study period, their study end date was defined as the date of death. In the other cases, the study end date was defined as the date of the last health screening, the date of the last outpatient clinic visit, or the last date on which the prescribed medication was taken (available only for metformin users).

The cumulative defined daily dose (DDD) was calculated to analyze the metformin dosage effect. We obtained the prescription date, daily dose, and the number of days' supply from the NHIS-HEALS prescription database. Also, we used the DDD recommended by the World Health Organization of 2000 mg/day to quantify metformin usage [19][19]. The cumulative metformin DDD (cDDD) was calculated as the total amount of prescribed metformin for individual patients during the entire study period divided by its DDD (2000 mg).

Definition of covariates

In this study, analyses were conducted by controlling for confounding variables such as age, systolic blood pressure (SBP), body mass index (BMI), serum fasting glucose, total cholesterol, alanine aminotransferase (ALT) level, personal history of hypertension, smoking status, alcohol consumption, physical activity, and household income levels between 2002 and 2003.

BMI (unit kg/m^2) was defined as body mass in kg divided by the square of height in meter. History of hypertension, smoking status, alcohol consumption, and physical activity data were collected through self-questionnaires. Smoking status was categorized as ever smokers or non-smokers. Ever smokers were defined as individuals who had smoked in the past or during the relevant research period. Alcohol consumption was classified as rare (less than twice per month), sometimes (twice per month to twice per week), and often (three or more times per week). Physical activity was divided into three categories of rare (rarely exercised), sometimes (exercised one to four times a week), and regular (exercised five or more times a week). Household income was categorized into three groups of 1) low, 0−3rd deciles; 2) middle, 4th -7th deciles; and 3) high, 8th −10th deciles.

Statistical analysis

Continuous variables are expressed as the mean ± standard error (SE). Categorical variables are expressed as number of participants and percentage. For group comparison, ANOVA and Chi-square tests were used for continuous and categorical variables, respectively. If there were significant results in the ANOVA and Chi-square test, post hoc analysis was performed for pair-wise comparison. Here, p-values were adjusted based on the Bonferroni method.

To determine the association between metformin use and cancer incidence, we estimated and compared cancer-free survival rates using the Kaplan−Meier method based on the log-rank test. Cox proportional hazard regression models were adopted to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) after controlling for confounding factors. Four Cox proportional hazards regression models were considered: (1) Model 1: age only; (2) Model 2: age, smoking status, alcohol consumption, and physical activity; and (3) Model 3: BMI, SBP, total cholesterol, ALT level, hypertension history, and household income in addition to the variables in Model 2; and (4) Model 4: adjusted fasting glucose in addition to the variables in Model 3.

All p-values reported are two-sided, and statistical significance was set at p-value <0.05. The statistical package SAS enterprise guide version 7.1 (SAS Inc., Cary, NC) and R studio version 3.3.3 were used to perform the analyses in this study.

Results

Table 1 shows the baseline characteristics of the study population according to metformin usage (metformin users, vs. non-users) and DM diagnosis (No DM). The total study population numbered 323,430 (175,495 male and 147,935 female), and the median follow-up duration was 12.7 years. Metformin users were prescribed metformin for a mean of 3062 days (from 90 days to 7472 days). Individuals with DM (metformin users and non-users) were older and had higher levels of BMI, SBP, fasting glucose, and ALT, compared with the No DM group. A personal history of hypertension was more prevalent in DM patients than in No DM patients. In post hoc analyses through the Bonferroni method, both male and female metformin users had higher BMI, fasting glucose level, and ALT level than other groups. Both male and female metformin users also exercised more regularly, had higher household income, and had lower total cholesterol levels than metformin non-users (all p-values < 0.05). Also, male metformin users had a lower percentage of ever smokers.

Figure 2 shows a cumulative incidence of cancer-based on a Kaplan−Meier's survival curve. Cumulative incidence was highest in metformin non-users and lowest in No DM in both sexes (Log-rank test p-values < 0.05). Cancer incidence was 25,646, accounting for 7.9% of the total subjects. Among them, 23,333 patients (7.7%) had No DM, 888 patients (10.3%) used metformin, and 1425 patients (11.1%) were metformin non-users. At the end of follow-up, the estimated cumulative incidences of overall cancer in metformin non-users, users, and No DM were 14.72, 13.07, and 9.95%, respectively, in men and 11.04, 8.71, and 7.48% in women.

To quantify the cancer risk according to presence or absence of DM and use of metformin, we used Cox proportional hazards regression models. The results are presented in Table 2. Note that the metformin non-users group was set as the reference. The estimates of HRs (95% CIs) for cancer incidence in metformin users and No DM were 0.71 (0.64−0.79) and 0.76 (0.71−0.81), respectively, in men and 0.79 (0.67−0.92) and 0.78 (0.70−0.87) in women after adjusting for age only (Model 1). Compared to metformin non-users, HRs (95% CIs) of metformin users and No DM were 0.74 (0.66−0.81) and 0.77 (0.72−0.82), respectively, in men and 0.79 (0.67−0.92) and 0.78 (0.70−0.88) in women

Table 1 Baseline characteristics of study participants according to diabetes and metformin usage.

Men	No DM	Metformin users	Metformin non-users	p-value
Number of subjects	161,377	4886	9232	N.A
Age, yr	50.4 ± 7.8	55.0 ± 7.8	52.4 ± 8.1	<0.001
BMI, kg/m^2	23.8 ± 2.8	24.6 ± 2.8	24.1 ± 3.1	<0.001
SBP, mmHg	126.7 ± 16.7	132.2 ± 17.3	133.4 ± 18.6	<0.001
Fasting glucose, mg/dL	90.5 ± 12.3	161.0 ± 68.9	149.5 ± 77.8	<0.001
Total cholesterol, mg/dL	197.5 ± 36.0	197.2 ± 40.3	200.3 ± 47.9	0.001
ALT, IU/L	28.2 ± 20.5	34.2 ± 25.6	32.8 ± 28.9	<0.001
Hypertension, N (%)	8135 (5.0)	709 (14.5)	750 (8.1)	<0.001
Ever smokers, N (%)	93,177 (57.7)	2695 (55.2)	5632 (61.0)	<0.001
Alcohol consumption, N (%)				<0.001
Rare	55,292 (34.3)	2098 (42.9)	3027 (32.8)	
Sometimes	76,502 (47.4)	1988 (40.7)	4087 (44.3)	
Often	29,583 (18.3)	841 (17.2)	2118 (22.9)	
Physical activity, N (%)				<0.001
Rare	77,966 (48.3)	2098 (42.9)	4645 (50.3)	
Sometimes	68,871 (42.7)	2065 (42.3)	3668 (39.7)	
Regular	14,540 (9.0)	723 (14.8)	919 (10.0)	
Household income, N (%)				<0.001
Low	25,368 (15.7)	1001 (20.5)	2304 (25.0)	
Middle	51,994 (32.2)	1582 (32.4)	3394 (36.8)	
High	84,015 (52.1)	2303 (47.1)	3534 (38.3)	
Women	No DM	Metformin users	Metformin non-users	p-value
Number of subjects	140,528	3757	3650	N.A
Age, yr	51.6 ± 8.1	58.0 ± 7.3	55.8 ± 8.3	<0.001
BMI, kg/m^2	23.7 ± 3.0	25.2 ± 3.3	24.5 ± 3.2	<0.001
SBP, mmHg	122.8 ± 18.0	132.0 ± 18.7	130.9 ± 19.8	<0.001
Fasting glucose, mg/dL	88.9 ± 11.5	160.4 ± 73.3	159.9 ± 116.6	<0.001
Total cholesterol, mg/dL	200.0 ± 37.6	207.3 ± 42.2	210.6 ± 62.0	<0.001
ALT, IU/L	20.1 ± 15.6	28.5 ± 19.7	23.7 ± 17.7	<0.001
Hypertension, N (%)	9750 (6.9)	873 (23.2)	461 (12.6)	<0.001
Ever smokers, N (%)	4652 (3.3)	154 (4.1)	150 (4.1)	0.001
Alcohol consumption, N (%)				<0.001
Rare	114,186 (81.3)	3400 (90.5)	3073 (84.2)	
Sometimes	23,704 (16.9)	313 (8.3)	503 (13.8)	
Often	2638 (1.9)	44 (1.2)	74 (2.0)	
Physical activity, N (%)				<0.001
Rare	92,284 (65.7)	2318 (61.7)	2628 (72)	
Sometimes	35,738 (25.4)	884 (23.5)	689 (18.9)	
Regular	12,506 (8.9)	555 (14.8)	333 (9.1)	
Household income, N (%)				<0.001
Low	37,956 (27.0)	1025 (27.3)	1263 (34.6)	
Middle	46,496 (33.1)	1338 (35.6)	1263 (34.6)	
High	56,076 (39.9)	1394 (37.1)	1124 (30.8)	

Values are presented as n (%) or mean ± standard errors.
In the post hoc analysis, we performed the pair-wise comparisons among the three groups. After Bonferroni adjustment, multiplying p-values by three (the number of comparisons), all the comparisons were still significant at level 0.05 except the comparison of smoking status between metformin non-users and users in women.

after adjusting for age, smoking status, alcohol consumption, and physical activity (Model 2). After additional adjustment for BMI, SBP, total cholesterol level, serum ALT level, personal history of hypertension, and household income in addition to Model 2, HRs (95% CIs) for cancer incidence of metformin users and No DM were 0.73 (0.66–0.81) and 0.80 (0.75–0.85), respectively, in men and 0.75 (0.64–0.88) and 0.80 (0.71–0.89) in women (Model 3). To control for hyperglycemic effect on cancer incidence, fasting glucose level was adjusted in Model 4. After full adjustment, HRs (95% CIs) for cancer incidence of in metformin users and No DM were 0.73 (0.66–0.81) and 0.83 (0.78–0.89), respectively, in men and 0.75 (0.64–0.88) and 0.81 (0.72–0.92) in women (Model 4).

We analyzed overall risk of cancer incidence according to metformin use dosage using cDDD (see Table 3). Metformin users were divided into quartile groups according to the cDDD; Q1 $<$ 968, Q2 968 to $<$ 1777, Q3 1777 to $<$ 2611, and Q4 $\geq$ 2611 for men and Q1 $<$ 1051, Q2 1051 to $<$ 1856, Q3 1856 to $<$ 2634, and Q4 $\geq$ 2634 for women. A Cox proportional hazard regression was performed and the results are shown in Table 3. Compared to metformin non-users, the metformin users fully adjusted HRs (95% CIs) of the first quartile group (Q1) for overall cancer incidence were 1.74 (1.53–1.99) in men and 2.12 (1.76–2.55) in women. Also, except for the first quartile group, higher cumulative metformin doses significantly lowered the overall cancer incidence. Additionally, compared to

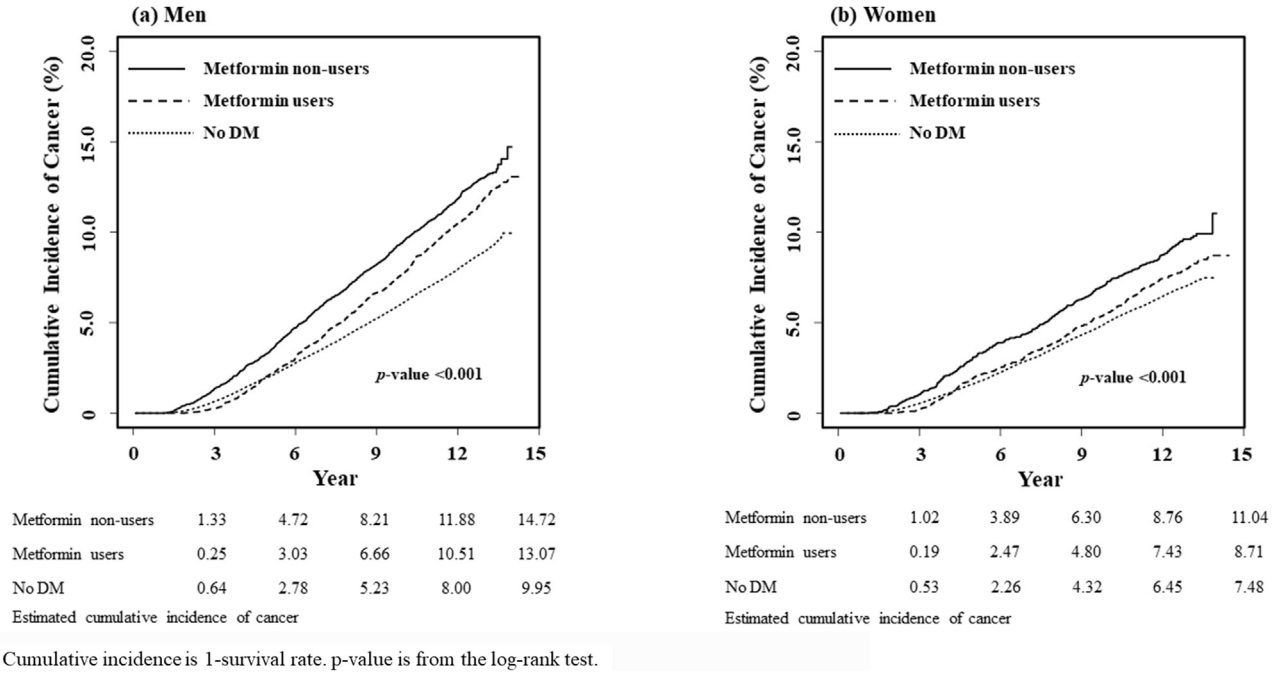

Figure 2 The estimated cumulative incidence of cancer according to diabetes and metformin usage by sex.

Table 2 Cox proportional hazards regression results for cancer incidence according to metformin usage and diabetes.

HRs (95% CIs)	Men			Women		
	Metformin non-users	Metformin users	No DM	Metformin non-users	Metformin users	No DM
Model 1	1	0.71 (0.64–0.79)	0.76 (0.71–0.81)	1	0.79 (0.67–0.92)	0.78 (0.70–0.87)
Model 2	1	0.74 (0.66–0.81)	0.77 (0.72–0.82)	1	0.79 (0.67–0.92)	0.78 (0.70–0.88)
Model 3	1	0.73 (0.66–0.81)	0.80 (0.75–0.85)	1	0.75 (0.64–0.88)	0.80 (0.71–0.89)
Model 4	1	0.73 (0.66–0.81)	0.83 (0.78–0.89)	1	0.75 (0.64–0.88)	0.81 (0.72–0.92)

Model 1: adjusted for age.
Model 2: adjusted for smoking status, alcohol consumption, and physical activity in addition to Model 1.
Model 3: adjusted for body mass index, systolic blood pressure, serum total cholesterol level, serum ALT level, past hypertension history, and household income, in addition to Model 2.
Model 4: adjusted for fasting glucose levels, in addition to Model 3.

Table 3 Cox proportional hazard regression results for cancer incidence according to metformin dosage.

HRs (95% CIs)	Metformin non-users	Metformin users				No DM
		Q1	Q2	Q3	Q4	
3-a. Men						
Model 1	1	1.69 (1.48–1.92)	0.77 (0.65–0.91)	0.41 (0.33–0.51)	0.23 (0.17–0.30)	0.76 (0.71–0.81)
Model 2	1	1.75 (1.53–2.00)	0.79 (0.67–0.93)	0.42 (0.34–0.52)	0.24 (0.18–0.31)	0.77 (0.72–0.82)
Model 3	1	1.75 (1.53–1.99)	0.79 (0.7–0.93)	0.42 (0.34–0.52)	0.23 (0.18–0.31)	0.80 (0.75–0.85)
Model 4	1	1.74 (1.53–1.99)	0.79 (0.67–0.93)	0.42 (0.34–0.52)	0.23 (0.17–0.31)	0.84 (0.78–0.90)
3-b. Women						
Model 1	1	2.19 (1.82–2.63)	0.78 (0.61–1.00)	0.32 (0.22–0.45)	0.17 (0.11–0.28)	0.78 (0.70–0.87)
Model 2	1	2.18 (1.82–2.62)	0.78 (0.61–1.00)	0.32 (0.22–0.45)	0.17 (0.11–0.28)	0.78 (0.70–0.87)
Model 3	1	2.12 (1.76–2.54)	0.75 (0.58–0.96)	0.30 (0.21–0.43)	0.16 (0.10–0.26)	0.80 (0.71–0.89)
Model 4	1	2.12 (1.76–2.55)	0.75 (0.58–0.96)	0.30 (0.21–0.43)	0.16 (0.10–0.26)	0.81 (0.72–0.92)

Model 1–4 are same as in Table 2.
Metformin users were divided into quartile group according to cDDD: Q1 $<$ 968, Q2 968 to $<$ 1777, Q3 1777 to $<$ 2611, and Q4 $\geq$ 2611 for men and Q1 $<$ 1051, Q2 1051 to $<$ 1856, Q3 1856 to $<$ 2634, and Q4 $\geq$ 2634 for women.

metformin non-users, the metformin users fully adjusted HRs (95% CIs) for overall cancer incidence in the Q2, Q3, and Q4 quartile groups were 0.79 (0.67–0.93), 0.42 (0.34–0.52), and 0.23 (0.17–0.31) in men and 0.75 (0.58–0.96), 0.30 (0.21–0.43), and 0.16 (0.10–0.26) in women, respectively.

Discussion

This study retrospectively analyzed the association between metformin use and cancer risk using the NHIS-HEALS date representative of the Korean population. Metformin usage in diabetic patients reduced the risk of cancer development. In addition, individuals without DM were at a lower risk of overall cancer incidence than metformin non-user diabetics. Based on the Cox proportional hazard regression models, metformin use seems to be associated with a lower overall risk of cancer in a dose-response manner.

Several studies have reported an increased risk of cancer in patients with diabetes or high fasting blood glucose [20–22]. The increased risk of cancer in patients with DM or high fasting glucose is thought to be associated with obesity, hyperinsulinemia, and hyperglycemia [20]. In this study, diabetic patients without metformin treatment were at higher risk of cancer development than participants without DM. This finding is consistent with the previous studies [23].

Several observational and meta-analysis studies showed that use of metformin lowered the incidence of cancer, which supports our laboratory findings [15–17]. According to Zhang et al.'s meta-analysis of 37 analytical and experimental studies of cancer incidence in people with diabetes, the relative risk (RR) (95% CI) for all cancer incidence of metformin users was 0.73 (0.64–0.83) compared to metformin non-users [15]. A meta-analysis of 17 other studies revealed that use of metformin was associated with a lower risk of all cancers (0.61, 0.54–0.70) [16]. In a meta-analysis involving two randomized controlled studies (RCTs), overall cancer incidence was significantly lower in metformin users than in metformin non-users (pooled RR 0.67, 95% CI 0.53–0.85) [17].

This result is similar to previous studies on metformin use and cancer risk [19,24,25]. In a population-based cohort study conducted by Lin et al., the cancer onset time was delayed by metformin treatment in a dose-dependent manner [19]. A study by Cho et al. showed that the incidence of thyroid cancer was significantly decreased by metformin depending on the dose and duration of treatment, especially in diabetic individuals [24]. And in a study conducted by Chang et al., the risk of colorectal cancer decreased progressively with a higher cumulative dose or higher intensity of metformin use [25].

However, there is still controversy over the findings. In meta-analyses analyzing only RCT and a retrospective study using cohort data from Israel showed conflicting results from the above studies. Dankner et al. analyzed metformin use and the risk of cancer incidence from a total of 320,000 diabetic individuals [26]. As a result, overall risk of cancer except for pancreatic and prostate cancer was not significantly different between metformin users and non-users. Also, a meta-analysis using RCT did not show that metformin use reduced the risk of cancer (RR 1.03, 95% CI 0.82–1.28) [27]. The higher risk of overall cancer incidence in Q1 of metformin users, compared to metformin non-users, appears to be partly due to low patient adherence to metformin doses, or more vigilant surveillance of health problems. Carstensen et al. reported that cancer diagnose increased within the first five years after patients were diagnosed with diabetes [28]. The surveillance for health problems such as cancer tends to increase after a diabetes diagnosis, and there is a possibility that hidden malignancy may accelerate the development of diabetes [29].

Evidence on the association between metformin usage and cancer risk in the Korean population is lacking. In all Korean studies, either only a small number of participants were enrolled, or only one type of cancer was investigated as the primary outcome [30,31]. In addition, these studies have shown conflicting results [30–32].

Metformin seems to mainly act on liver, muscle, and intestine. Metformin inhibits glucose production in the liver, increases glucose utilization by the intestine, increases GLP-1 level, and alters the microbiome [33]. In addition to glycemic control, metformin can affect diseases by having beneficial effects on cardiovascular function, aging, neurodegeneration, and cancer development [34–37]. Several mechanisms by which metformin prevents carcinogenic changes in precancerous and cancerous lesions were presented. The indirect mechanism is thought to be deceleration of tumor proliferation through the insulin-lowering effect in individuals with hyperinsulinemia. Metformin directly inhibits respiratory complex I in mitochondria, resulting in decreased ATP synthesis and energetic stress. To compensate for energetic stress, metformin alters the AMPK/mTOR balance. AMPK is activated by energetic stress, and mTOR is inhibited. Through these serial processes, cancerous cells become cytostatic, and oncogenic transformation is inhibited [38]. Metformin increases insulin sensitivity and modulates immune responses. In addition, tumor cell invasiveness and cancer suppression seem to be associated with metformin usage [37]. In addition to use of metformin, other factors affect cancer development. Common risk factors for diabetes and cancer include older age, obesity, physical inactivity, and smoking [39]. Even though metformin users were older and more obese than other groups, these patients had the highest rate of regular physical activity and the lowest rate of smoking experience. These healthier behaviors may compensate for cancer risks from other common risk factors such as older age and obesity. Although multiple factors were complicated in a carcinogenic effect, metformin may have an additive effect on cancer prevention.

There are several limitations in our study. First, since the NHIS-HEALS does not include data on glycated hemoglobin (HbA1c) and insulin levels, we could not adjust based the model for the degree of glycemic based on those

factors. Instead, we used serum glucose levels to control for the effect of DM severity, based on previous studies demonstrated fasting blood glucose levels showed a linear relationship with an increased risk of developing cancer [40,41]. Therefore, Model 4 was adjusted for fasting glucose levels, instead of HbA1c and insulin levels. Second, correction for all confounding factors that affect diagnosis and development of cancer was not possible. These factors include dietary patterns, cancer screenings, and individual genetic vulnerabilities. Even if we adjusted for clinically implicating risk factors as much as possible, there could be some residual effects of confounding factors that were not adjusted. Third, due to the complexity of the data, analysis of factors that may affect the treatment of diabetes, which includes the dosage of metformin and use of combination treatment of metformin with other anti-diabetic drugs, was not possible. Also, the cumulative dose of metformin might not be accurate because it was not possible to confirm the actual doses of patient taking and had to rely on only prescription data in the NHIS-HEALS. Fourth, we wanted to exclude individuals with in situ tumors (ICD D00-09) that could affect cancer development; however, in the NHIS-HEALS database, in situ tumor codes, except D00-04 and D08, were included in the D_group which cannot be individualized. This D_group includes hormone-related tumors (such as breast, cervix, endometrium, prostate, and other unspecified genital organs) and other diseases, such as sickle-cell disorder (ICD D568), neutropenic fever (ICD D 700), and combined immunodeficiencies disease (ICD D81). Therefore, excluding individuals with D_group diagnoses resulted in the exclusion of more subjects than the researchers intended. Fifth, C codes include various cancers. Each cancer is caused by various pathogenic mechanisms such as genetic mutation regulating cell signaling, infection, unhealthy lifestyle, and exogenous carcinogen exposure. Carcinogenic mechanisms are diverse and complex. All factors could not be controlled in this study.

However, this study has the advantages of analyzed the incidence of overall cancer according to the amount or dose of metformin used, using a longer follow up period and real-world data, unlike previous studies. In addition, a conservative approach was employed by defining the diagnosis of cancer as a primary diagnosis at the time of admission.

Comparing the general population without diabetes and metformin users and metformin non-users with type 2 DM was another strength of our study. Previous carcinoma studies have been limited to comparing the risk of cancer in general subjects without diabetes to diabetic patients using metformin [42].

Based on these findings, further studies should be undertaken to assess cancer incidence risk according to type of cancer, type or combination of anti-diabetic agents, and degree of glycemic control.

Clinically, diabetic patients can be educated on these study results when applied metformin. In addition to proper glycemic control and prevention of long-term complications and mortality, metformin is useful to prevent cancer development in diabetic patients.

Conclusions

DM patients who use metformin have a lower risk of developing cancer than DM patients who do not use metformin. This result has clinical importance. The risk of cancer development in DM patients who use metformin is similar to the risk of cancer in individuals without diabetes.

Declarations of interest

None.

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