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ORIGINAL ARTICLE

Metformin use reduced the risk of stomach cancer in diabetic patients in Korea: an analysis of Korean NHIS-HEALS database

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Abstract

Background Diabetes mellitus (DM) increases atherosclerotic cardiovascular complications and cancer risks. Stomach cancer is the most common cancer in Korea. Although the survival rate of stomach cancer has improved, the disease burden is still high.

Methods This retrospective study investigated the association between metformin use and stomach cancer incidence in a Korean population using the National Health Insurance Service-National Health Screening Cohort database. Participants aged 40–80 years old at the baseline period (2002–2003) were enrolled. The study population was categorized into three groups of metformin non-users with DM, metformin users with DM, and individuals without DM (No DM group).

Results A total of 347,895 participants (14,922 metformin non-users, 9891 metformin users, and 323,082 individuals without DM) were included in the final analysis. The median follow-up duration was 12.70 years. The estimated cumulative incidence of stomach cancer was highest in metformin non-users and lowest in the No DM group (men vs. women: 3.75 vs. 1.97% in metformin non-users, 2.91 vs. 1.53% in metformin users, and 2.54 vs. 0.95% in the No DM group). Compared with metformin non-users, the hazard ratios (95% confidence intervals) for stomach cancer incidence of metformin users and the No DM group were 0.710 (0.579–0.870) and 0.879 (0.767–1.006) in men and 0.700 (0.499–0.981) and 0.701 (0.544–0.903) in women, respectively, after full adjustment.

Conclusions Metformin users with DM in the Korean population were at lower risk of stomach cancer incidence after controlling for potential confounding factors.

Keywords Metformin · Diabetes mellitus · Stomach neoplasm · Incidence

Introduction

Malignant neoplasms are the leading cause of death in Korea, and among them, stomach cancer is the most common [1]. The age-standardized incidence rate per 100,000

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persons for stomach cancer was 34.0 in 2016 [1]. The Korean National Health Insurance Service (NHIS) provides a biennial national cancer screening program for early detection of five major cancers (stomach, colorectum, liver, breast, and uterine cervix) in persons aged over 40 years. Biennial check-up using endoscopy or barium radiography is recommended for stomach cancer screening. This cancer screening program likely contributes to an improvement of stomach cancer survival, as the 5 year relative survival rate for stomach cancer has been improved from 42.8% in 1993–1995 to 76.0% in 2012–2016 [1].

Diabetes is prevalent in Korea and is expected to steadily increase [2]. Its prevalence was 11.1% in 2013–2015 and it is the sixth leading cause of death in Korea [1, 3]. Diabetes is a threat to public health in itself, but its macro- and microvascular complications, such as retinopathy, nephropathy, neuropathy, and atherosclerotic cardio-cerebro-vascular diseases, also contribute to public health burdens. These complications increase the healthcare expenditures and mortality and decrease patients' quality of life. To prevent and manage diabetes mellitus (DM), lifestyle modifications, such as maintaining a normal body weight and regular exercise, are required. In addition to lifestyle modifications, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend metformin use as the first therapeutic option to manage type 2 DM [4, 5]. Metformin has pleiotropic functions, although its principal action is glucose lowering. Through inhibition of hepatic gluconeogenesis and improvement of insulin sensitivity, it may result in lower blood glucose levels, although its exact mechanisms of action are not fully elucidated [6]. Additionally, metformin can activate 5′-adenosine monophosphate (AMP)-activated protein kinase (AMPK), which modulates carcinogenesis [7].

Chemopreventive effects of commonly prescribed drugs, such as metformin, could additively reduce the burden of stomach cancer. Therefore, we aimed to investigate the association between metformin use and stomach cancer incidence using data from the Korean NHIS–National Health Screening Cohort (HEALS) of the general Korean population.

Methods

Study population

The NHIS-HEALS is a cohort of individuals who participated in Korean national health screening programs. The NHIS biennially provides a general health screening program for eligible adults aged 40 years or older. The cohort includes 514,794 individuals (about 10%) who were randomly selected from all of the health screening participants between 2002 and 2003 and who received follow-up evaluations until 2015. The primary information collected regarding the NHIS cohort is the claim data, such as the diagnosis code, and prescription details. In addition, the NHIS-HEALS includes health screening results, such as laboratory data and surveys, along with socioeconomic status and death records. More detailed information on the cohort was described in previous study [8].

Figure 1 provides the flowchart indicating how the participants were included and excluded in this research. Of the initial 514,794 participants, 347,895 participants were selected for our analysis. To determine whether metformin use is associated with the incidence of stomach cancer, participants were stratified into three groups: metformin users, metformin non-users, and No DM. Detailed definitions of each group are described in the next section.

Study participants who had initially been diagnosed with serious illnesses, who were at risk for complications, or who died during the study window were excluded, because the effects of these external factors could not be separated from the effects of metformin. Of the total 514,794 participants in the NHIS-HEALS cohort, 117,438 were excluded by exclusion criteria (1). This included participants who were diagnosed with cancer (ICD-10 code, C00-C97 or any D_code) between 2002 and 2004 ($n = 38,982$), who answered cancer in self-reported questionnaire between 2002 and 2004 ($n = 3,752$), or who died between 2002 and 2004 ($n = 3,774$). In addition, participants who were newly diagnosed with diabetes between 2004 and 2015 were excluded from the data ($n = 79,925$) under exclusion criteria (1). It should be noted that these criteria were not mutually exclusive. Participants who were prescribed metformin before diabetes occurred between 2002 and 2015 or those who were not diagnosed diabetes but prescribed metformin between 2002 and 2015 were excluded by exclusion criteria (2) ($n = 4,286$). Some participants were prescribed very low cumulative metformin dose in our study period. Because it made difficult to separate the effect of metformin, we excluded participants who were prescribed metformin for less than 90 days between 2002 and 2003 and prescribed metformin for more than 90 days between 2002 and 2015 ($n = 23,264$) (exclusion criteria [3]). Besides, participants whose study duration was 30 days or less between 2002 and 2015 were also eliminated ($n = 157$) (exclusion criteria [4]) to remove bias caused by extremely short observed period. Finally, participants with incomplete data for the confounding covariates were excluded ($n = 21,754$) (exclusion criteria [5]).

All procedures followed the 1964 Declaration of Helsinki, and the Institutional Review Board of Chungbuk National University approved this study (CBNU-201903-BMETC-802–01).

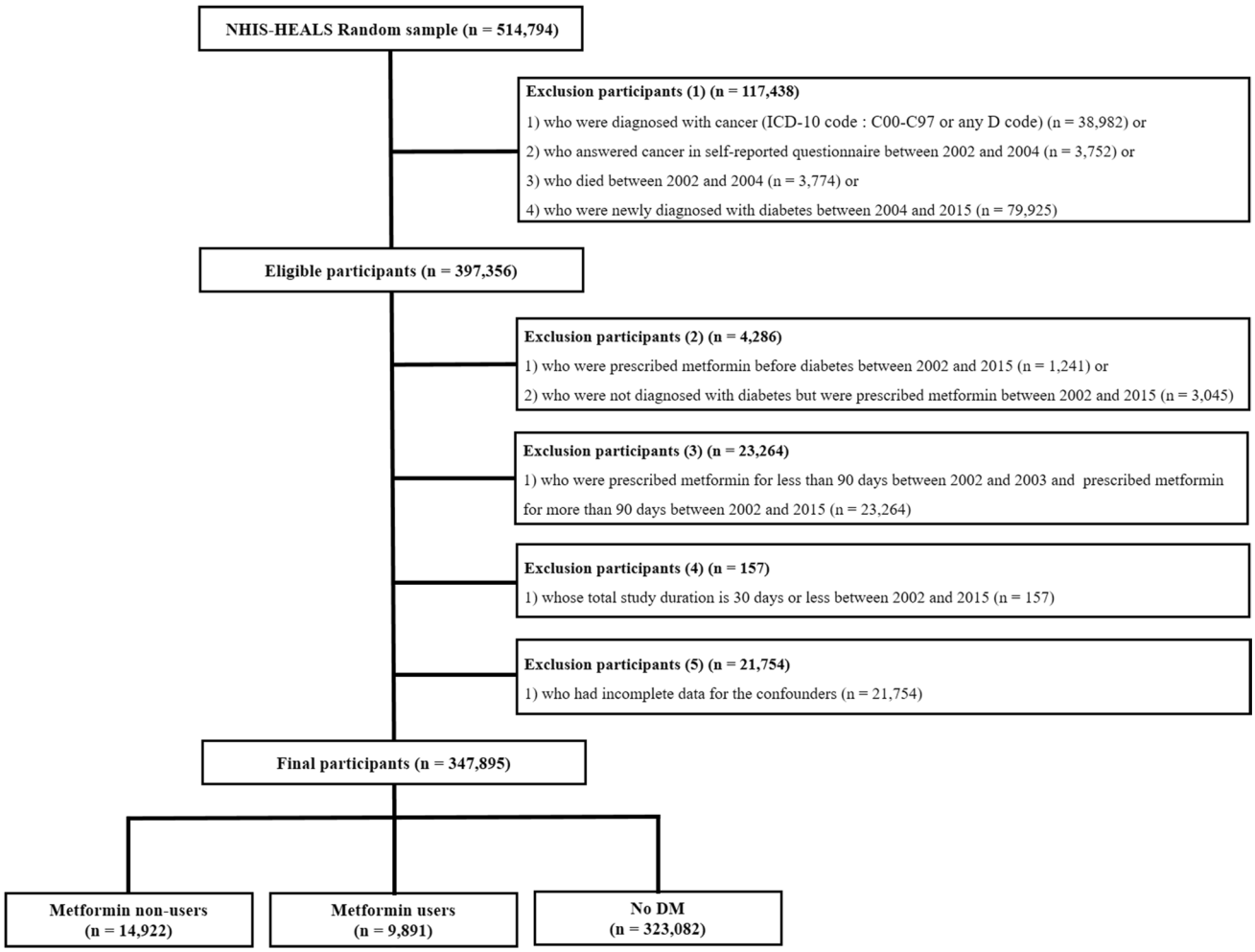


Fig. 1 Flowchart of inclusion and exclusion criteria

The operational definition of study groups, stomach cancer, and study date

DM was defined as meeting at least one of the following criteria: the first was a diagnosis code of diabetes (E11-14 according to ICD-10 code) and the prescription of any glucose-lowering agents including insulin, metformin, sulfonylurea, thiazolidinedione, α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium glucose cotransporter-2 inhibitor, glucagon-like peptide-1 analogue, or any other anti-diabetic drugs. The second criteria was a fasting blood glucose concentration ≥ 126 mg/dL from laboratory data taken during the national health screening.

Study participants were classified into three groups according to metformin usage in diabetic patients and the presence of DM: (1) metformin users, individuals with DM who were prescribed metformin for at least 90 days between 2002 and 2003 ($n = 9,891$); (2) metformin non-users, individuals with DM who were prescribed for less than 90 days, but had used other oral anti-diabetic drugs except metformin ($n = 14,922$); 3) No DM group, individuals without a personal history of DM ($n = 323,082$). Metformin users were further stratified into four quartile group according to cumulative defined daily dose (DDD) of metformin. Cumulative DDD was calculated as the total amount of prescribed metformin for individual patients during the entire study period divided by its DDD (2000 mg). Cumulative DDD was categorized as follows: among men, low users (< 418.3), middle–low users (418.3 to < 1566.0), middle–high users (1566.0 to < 2509.0), and high users (≥ 2509.0); among women, low users (< 701.3), middle–low users (701.3 to < 1724.0), middle–high users (1724.0 to < 2653.8), and high users (≥ 2653.8).

Incidence of stomach cancer was defined as the first record of cancer diagnosis (C16 based on ICD-10 code) as a main diagnosis code during hospital admission after Jan 1st, 2005.

In metformin users and non-users, the research start date was defined as the earlier date between (1) the first date when participants received any anti-diabetic drugs and were diagnosed with diabetes (ICD-10 code E11-14), or (2) the date of health screening with a fasting glucose level ≥ 126 mg/dL. For individuals in the No DM group, the start date was defined as the first health screening between 2002 and 2003. For participants diagnosed with stomach cancer, the end date was defined as the initial diagnosis date with ICD-10 code C16. For participants who died before stomach cancer occurred or had not be diagnosed with stomach cancer, the study end date was defined as the latest day among the following: (1) the last available date of the last health screening, (2) the date of the last outpatient clinic visit, and (3) the last date on which the prescription was taken.

Definition of covariates

To account for the effects of confounding factors on stomach cancer incidence, the analysis was adjusted for age, systolic blood pressure (SBP), body mass index (BMI), blood glucose, total cholesterol, alanine aminotransferase (ALT) levels, cigarette smoking, alcohol intake, physical activity, economic status according to household income, and a personal history of hypertension between 2002 and 2003. BMI (unit, kg/m^2) was defined as body weight (kg) divided by the squared height (m). Information on cigarette smoking, alcohol intake, physical activity, household income, and history of hypertension was collected through self-reported questionnaires. Cigarette smoking comprised those classified as ever smokers (individuals who had ever smoked cigarettes) or non-smokers (individuals who had never smoked cigarettes). Alcohol intake was stratified into rare (less than twice a month), sometimes (twice a month to twice a week) and regular (more than three times a week). Physical activity was stratified into three groups: rare (rarely does exercise), sometimes (does exercise 1–4 days a week) and regular (does exercises at least 5 days a week). Household income was categorized into three groups: low (the 0–3rd decile), middle (the 4–7th decile), and high (the 8–10th decile).

In addition, to investigate the effect of other anti-diabetic drugs such as insulin, sulfonylurea, and thiazolidinedione on stomach cancer development, those anti-diabetic drugs were considered as covariates for Cox proportional hazard (Cox-PH) regression model. Insulin user was defined as the individuals who had been prescribed insulin for 6 months or longer. Sulfonylurea and thiazolidinedione users were defined as users who had been prescribed sulfonylurea and thiazolidinedione for at least 3 months, respectively.

Statistical analysis

In this study, the incidence of stomach cancer was compared for three groups. Therefore, the event was defined as the occurrence of stomach cancer; because some subjects were right censored, the data were analyzed as survival time. The survival function of each group was estimated using the Kaplan–Meier method. In addition, log-rank test was performed to compare survival rates among groups to figure out how survival function differs.

Next, we built Cox-PH regression models to compare the three groups after controlling for confounding covariates. In Model 1, only age was considered as a covariate. In Model 2, cigarette smoking, alcohol intake, and physical activity were considered as confounding factors in addition to the variable from Model 1. In Model 3, BMI, SBP, total cholesterol, ALT, hypertension history, and household income as well as the variables in Model 2 were additionally adjusted. Finally, blood glucose levels were adjusted in addition to the variables in Model 3 to control for hyperglycemic effect (Model 4). Further Cox-PH regression models were conducted to investigate the dose–response relationship between cumulative DDD of metformin and stomach cancer incidence after additionally adjusting for insulin, sulfonylurea and thiazolidinedione as covariates in Supplementary Table 1. All p values were based on two-sided tests and p values below 0.05 were regarded as statistically significant.

Results

Of total 347,895 individuals (186,295 men and 161,600 women), 5621 stomach cancers (4158 in men and 1463 in women) occurred during the entire study period with a median follow-up of 12.70 years.

Table 1 shows the baseline characteristics of the study population according to the presence of DM (metformin non-users, users, and No DM). The mean age of metformin non-users, users and No DM was 54.4, 56.7, and 51.7 years, respectively, in men and 59.8, 60.4, and 53.3 years, respectively, in women. Individuals with DM, regardless of metformin usage, tended to have higher BMI, glucose levels, ALT levels, hypertension history, and rate of lower household income, for both sexes (all $p < 0.05$). BMI, blood glucose levels, ALT levels, and percentage of subjects with hypertension, and percentage of subjects participating in regular physical activity were highest in metformin users for both sexes. The status of ever smoker was most common in metformin non-users in both sexes.

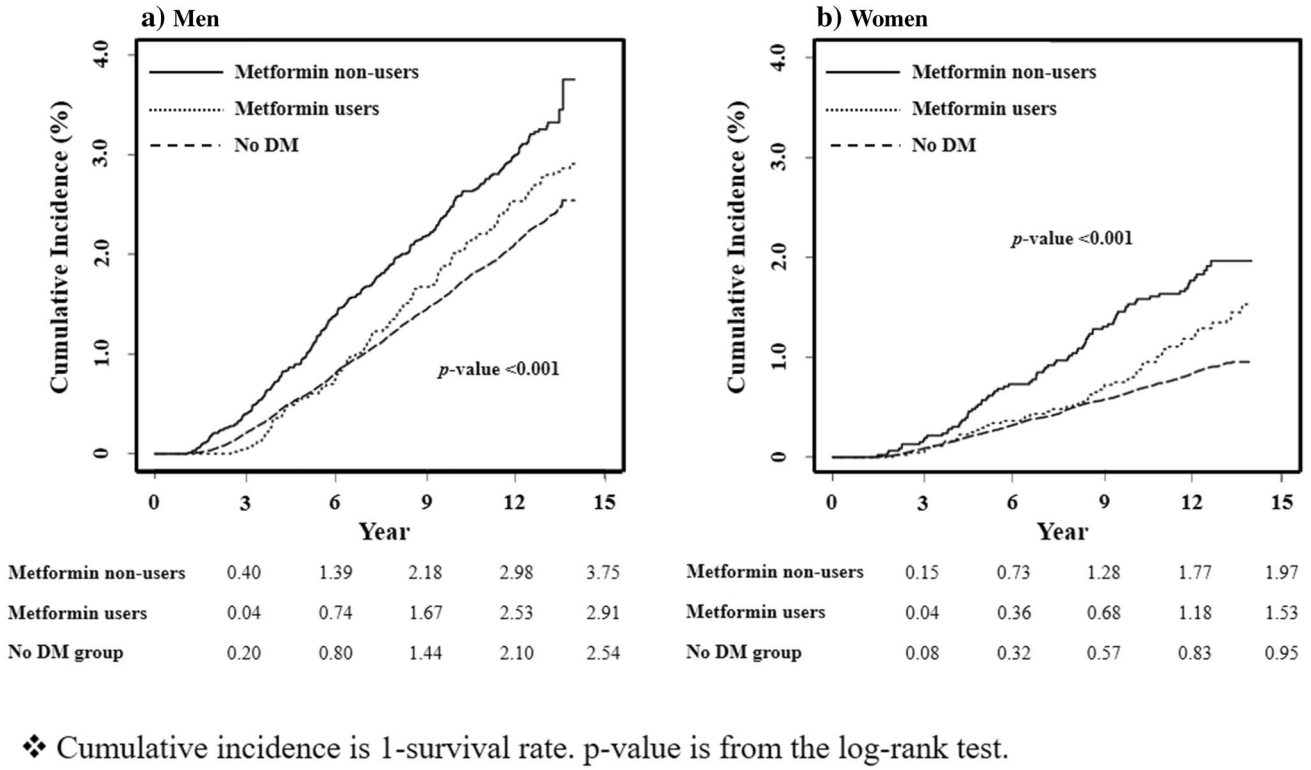
Figure 2 shows the Kaplan–Meier's survival curves of the association between metformin use and stomach cancer incidence. The estimated cumulative incidence of stomach cancer was highest in metformin non-users with DM and

Table 1 Baseline characteristics of the study population

Men	Metformin non-users	Metformin users	No DM	*p* value
N	10,196	5,407	170,692	N.A
Age (years)	54.4 ± 9.8	56.7 ± 9.1	51.7 ± 9.2	< 0.001
BMI (kg/m^2)	24.0 ± 3.1	24.6 ± 2.8	23.8 ± 2.8	< 0.001
SBP (mmHg)	133.9 ± 18.8	132.7 ± 17.6	127.1 ± 17.0	< 0.001
Glucose (mg/dL)	150.0 ± 77.4	160.4 ± 70.1	90.5 ± 12.3	< 0.001
Total cholesterol (mg/dL)	199.3 ± 47.3	196.7 ± 40.9	197.1 ± 36.1	< 0.001
ALT (IU/L)	32.1 ± 28.1	33.5 ± 25.0	27.9 ± 20.3	< 0.001
Hypertension *N* (%)	929 (9.1)	850 (15.7)	9,668 (5.7)	< 0.001
Ever smoker, *N* (%)	6,066 (59.5)	2,900 (53.6)	97,303 (57.0)	< 0.001
Drinking status, *N* (%)				< 0.001
Rare	3,522 (34.5)	2,385 (44.1)	60,303 (35.3)	
Sometimes	4,323 (42.4)	2,111 (39.0)	78,726 (46.1)	
Regular	2,351 (23.1)	911 (16.9)	31,663 (18.6)	
Physical activity, N (%)				< 0.001
Rare	5,304 (52.0)	2,362 (43.7)	84,123 (49.3)	
Sometimes	3,824 (37.5)	2,204 (40.8)	70,636 (41.4)	
Regular	1,068 (10.5)	841(15.6)	15,933 (9.3)	
Household income, *N* (%)				< 0.001
Low	2,582 (25.3)	1,116 (20.6)	28,010 (16.4)	
Middle	3,660 (35.9)	1,724 (31.9)	54,568 (32.0)	
High	3,954 (38.8)	2,567 (47.5)	88,114 (51.6)	
Women	Metformin non-users	Metformin users	No DM	*p* value
N	4,726	4,484	152,390	N.A
Age (years)	59.8 ± 10.6	60.4 ± 8.7	53.3 ± 9.7	< 0.001
BMI (kg/m^2)	24.4 ± 3.4	25.1 ± 3.2	23.7 ± 3.0	< 0.001
SBP (mmHg)	132.8 ± 20.5	133.0 ± 19.3	123.7 ± 18.5	< 0.001
Glucose (mg/dL)	158.5 ± 107.4	160.2 ± 73.3	89.1 ± 11.7	< 0.001
Total cholesterol (mg/dL)	210.9 ± 59.2	207.1 ± 42.0	200.6 ± 37.7	< 0.001
ALT (IU/L)	23.0 ± 16.6	27.8 ± 19.0	20.1 ± 15.7	< 0.001
Hypertension, *N* (%)	751 (15.9)	1,098 (24.5)	12,182 (8.0)	< 0.001
Ever smoker, *N* (%)	247 (5.2)	197 (4.4)	5,513 (3.6)	< 0.001
Drinking status, *N* (%)				< 0.001
Rare	4,059 (85.9)	4,099 (91.4)	124,855 (81.9)	
Sometimes	575 (12.2)	336 (7.5)	24,672 (16.2)	
Regular	92 (2.0)	49 (1.1)	2,863 (1.9)	
Physical activity, *N* (%)				< 0.001
Rare	3 530 (74.7)	2,836 (63.2)	101,830 (66.8)	
Sometimes	794 (16.8)	990 (22.1)	37,082 (24.3)	
Regular	402 (8.5)	658 (14.7)	13,478 (8.8)	
Household income, *N* (%)				< 0.001
Low	1,616 (34.2)	1,243 (27.7)	41,895 (27.5)	
Middle	1,533 (32.4)	1,521 (33.9)	49,604 (32.6)	
High	1,577 (33.4)	1,720 (38.4)	60,891 (40.0)	

BMI body mass index, *SBP* systolic blood pressure, *ALT* alanine aminotransferase

lowest in the No DM group for both sexes (Log-rank test $p < 0.001$). The estimated cumulative incidence of stomach cancer was 3.75 and 1.97% in metformin non-users, 2.91 and 1.53% in metformin users, and 2.54 and 0.83% in No DM for men and women, respectively. Please note that the last follow-up was about 14 years.



Metformin non-users	0.40	1.39	2.18	2.98	3.75
Metformin users	0.04	0.74	1.67	2.53	2.91
No DM group	0.20	0.80	1.44	2.10	2.54

Metformin non-users	0.15	0.73	1.28	1.77	1.97
Metformin users	0.04	0.36	0.68	1.18	1.53
No DM group	0.08	0.32	0.57	0.83	0.95

❖ Cumulative incidence is 1-survival rate. p-value is from the log-rank test.

Fig. 2 The estimated cumulative incidence of stomach cancer P values are from log-rank tests

The results of the Cox-PH regression models are presented in Table 2. Compared with metformin non-users, the HRs (95% CIs) for stomach cancer incidence of metformin users and No DM were 0.690 (0.563–0.845) and 0.803 (0.713–0.905) in men and 0.696 (0.497–0.974) and 0.634 (0.505–0.797) in women, respectively, after adjusting for age (Model 1). After adjusting for age, smoking status, alcohol consumption, physical activity, BMI, SBP, past history of hypertension, total cholesterol, ALT levels, and household income, the HRs (95% CIs) for stomach cancer incidence of metformin users and No DM were 0.716 (0.584–0.877) and 0.826 (0.732–0.931) in men and 0.699 (0.498–0.980) and 0.637 (0.507–0.801) in women, respectively (Model 3). In addition to Model 3, we further adjusted for blood glucose levels to control for hyperglycemic effects (Model 4). After fully adjusted in Model 4, HRs (95% CIs) for stomach cancer incidence of metformin users and No DM were 0.710 (0.579–0.870) and 0.879 (0.767–1.006) in men and 0.700 (0.499–0.981) and 0.701 (0.544–0.903) in women, respectively.

Cox-PH regression models were performed to examine the dose–response relationship between cumulative DDD of metformin and stomach cancer risk after further adjusting for other diabetic medication such as insulin,

Table 2 Cox proportional hazard regression models for stomach cancer incidence

HRs (95% CIs)	Men			Women		
	Metformin non-users	Metformin users	No DM	Metformin non-users	Metformin users	No DM
Model 1	1	0.690 (0.563–0.845)	0.803 (0.713–0.905)	1	0.696 (0.497–0.974)	0.634 (0.505–0.797)
Model 2	1	0.712 (0.582–0.873)	0.814 (0.722–0.917)	1	0.703 (0.502–0.986)	0.637 (0.507–0.800)
Model 3	1	0.716 (0.584–0.877)	0.826 (0.732–0.931)	1	0.699 (0.498–0.980)	0.637 (0.507–0.801)
Model 4		0.710 (0.579–0.870)	0.879 (0.767–1.006)	1	0.700 (0.499–0.981)	0.701 (0.544–0.903)

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

sulfonylurea and thiazolidinedione as covariates (Supplementary Table 1). Compared with metformin non-users, HRs (95% CIs) of metformin low, middle–low, middle–high, and high users for stomach cancer were 2.175 (1.437–3.292), 1.279 (0.892–1.833), 0.378 (0.230–0.620), and 0.249 (0.139–0.447) in men and 2.211 (1.135–4.306), 1.487 (0.784–2.821), 0.862 (0.409–1.817), and 0.308 (0.110–0.864) in women, respectively, after fully adjusted. In this model, No DM group was at lower risk for stomach cancer (HR [95% CIs], 0.829 (0.728–0.944) in men and 0.604 (0.473–0.771) in women). Other anti-diabetic drugs such as insulin, sulfonylurea, and thiazolidinedione did not significantly reduce stomach cancer incidence.

Discussion

Using the NHIS–HEALS database, which is representative of the entire Korean population, this study demonstrated that metformin use was inversely associated with stomach cancer development in both sexes. This anti-carcinogenic effect of metformin appears to be dose dependent. In addition, individuals without DM (in the No DM group), were at lower risk of stomach cancer than metformin non-users with DM.

DM is prevalent and increasing [2], and it causes higher mortality rate, as well as macro-and micro-vascular complications, which threaten public health. In addition to these negative effects, DM is associated with a higher risk of some cancer due to hyperinsulinemia, metabolic alteration, and pro-inflammatory conditions [9]. If anti-diabetic medications can reduce the carcinogenic risk in diabetic patients, simultaneous control of diabetes and prevention of cancer can be achieved.

Metformin is one of the most widely prescribed drugs primarily due to the UK Prospective Diabetes Study (UKPDS) report that early intensive glycemic control with metformin lowers the risk of diabetes-related complications and death [10]. Based on UKPDS findings, several major clinical practice guidelines from ADA and EASD recommend metformin use as the first therapeutic option, along with a healthy lifestyle, in treating type 2 DM [4, 5]. The glucose-lowering action of metformin principally appears to inhibit hepatic gluconeogenesis and enhance musculoskeletal insulin sensitivity [6, 11, 12]. Although its action mechanisms are not fully understood, it appears to be mediated in part by AMPK activation and immune modulation through the mammalian target of rapamycin (mTOR) [6, 13]. Because metformin is positively charged, it can easily cross both the plasma and mitochondrial membranes, resulting in its accumulation in mitochondria [6, 14, 15]. In mitochondria, metformin inhibits Complex I protein of the respiratory chain, leading to decreased adenosine triphosphate (ATP) production [14, 15]. The reduced ATP production through the cellular respiration results in the accumulation of AMP as precursors of ATP. This increased ratio of AMP to ATP then activates energy-sensitive AMPK after metformin administration. AMPK modulates energy metabolism; increased insulin sensitivity and glycolysis in peripheral tissue and decreased gluconeogenesis in the liver and lipolysis in adipose tissue [16]. It is through these mechanisms of AMPK that deficient ATP levels decrease hepatic gluconeogenesis and lower blood glucose concentrations. Activated AMPK influences many effector proteins such as mTOR and p53, which can play important roles in carcinogenesis [17]. In addition, AMPK can inhibit pro-inflammatory processes [17]. Taken together, these results indicate that AMPK activation by metformin decreases blood glucose levels and prevents carcinogenesis.

As mentioned above, this theoretical link between metformin use and stomach cancer prevention has not been clinically proven. However, several previous studies are consistent with our results. Kim et al. reported that long-term metformin use in diabetic patients without insulin therapy were inversely associated with a lower risk of stomach cancer development, but this association was not observed in short-term users and diabetic patients on insulin therapy [18]. Ruiter et al. showed that metformin users had a lower risk for stomach cancer than sulfonylurea users [19]. However, there have also been conflicting findings that metformin use is not associated with stomach cancer incidence. In a Taiwanese study, metformin usage did not reduce stomach cancer incidence [20]. This discrepancy also appears in meta-analysis studies in that one meta-analysis demonstrated that stomach cancer risk was lower in metformin users than metformin non-users for diabetic patients [21], but the same conclusion was not reached in another meta-analysis [22]. This discrepancy could be caused by different inclusion–exclusion criteria and adjustment models. Another Taiwanese study by Tseng showed that metformin ever users were at lower risk of gastric cancer than metformin never users (HR [95% CIs], 0.577 [0.460–0.724]) [23]. However, this beneficial effect of metformin was not observed in individuals with *Helicobacter pylori (H. pylori)* infection after stratification according to *H. pylori* infection. Compared with metformin never users without *H. pylori* infection, the HR (95% CIs) of metformin ever users with *H. pylori* infection for gastric cancer was 2.465 (1.685–3.604). These findings suggest that the beneficial effect of metformin usage on stomach cancer development cannot surpass the carcinogenic effect of conventional risk factors such as *H. pylori* infection. Our study showed that metformin use reduced stomach cancer incidence in a large population over a long duration in a dose–response manner, unlike the previous studies. This is one of the several strengths which distinguish this study from the previous studies.

This study has other strengths. First, data used in this study were based on real-world measurements in the

clinical setting. Furthermore, because the NHIS collected and provided this cohort data, it is representative of the entire Korean population. Korean public health authorities are obliged to engage medical insurance for almost all the Korean population and provide free national health check-up services for individuals aged 40 years or older. The national health check-up information, from which the NHIS-HEALS cohort is taken, includes health and lifestyle questionnaires, blood tests (including blood glucose, lipid profile and liver enzymes) and screening for the five most common types of malignant neoplasms. Because stomach cancer is the most common cancer in Korea and can be diagnosed and cured [1], a stomach cancer screening program is included in the national cancer screening program. For this reason, stomach cancer is diagnosed relatively more efficiently in this large-scale national cancer screening program and has better 5 year survival rates in Korea than in other countries [1]. The study by Kim et al. used Korean National Health Insurance claim database, which does not include blood test results [18]. Our findings, based on the NHIS-HEALS database, are consistent with Kim's study despite using a different Korean database. However, this study was able to adjust for laboratory variables, such as blood glucose levels, and the results were additionally stratified by sex, which was not controlled in Kim's study. The second major strength is the lower possibility of a false-positive diagnosis or misclassification of stomach cancer. The Ministry of Health and Welfare verifies and pays insurance claims from medical institutions. This system can minimize recall bias and misclassification. In addition, the Korean NHIS more strictly monitors special diseases, such as malignant neoplasms, and severe refractory diseases, such as end-stage renal diseases, because patients with these diseases pay less out-of-pocket for medical bills than patients with other common diseases due to insurance reimbursement. We also defined the stomach cancer diagnosis from the main diagnosis code used when patients were admitted to the hospitals to minimize misclassification. Third, the median follow-up duration (12.70 years) was relatively longer than other studies. In diseases, such as cancer, that often have a long time course from development to diagnosis, longer study durations can yield more accurate results than shorter ones. Fourth, health inequities are considered as potential risk factor for poor clinical outcomes and affect the diagnosis rate of cancer and diseases because of the disparity of accessibility to healthcare. To control these confounding effects, we adjusted for individual household income. In addition, the free national cancer screening program minimizes these disparities. Fifth, we compared the risk of stomach cancer development among metformin users with DM, non-users with DM, and individuals without DM. In addition, metformin users were further classified into four quartile groups to determine the dose-dependent anti-carcinogenic effect of metformin.

Several limitations should be considered when interpreting this study. Several risk factors for stomach cancer, such as *H. pyrolic* infection, gastric ulcer, unhealthy dietary patterns, and genetic or familial vulnerabilities, could not be controlled for because the NHIS-HEALS data does not include this information. Metformin appears not to be a potent chemopreventive agent that can completely eliminate the cancer risk of conventional carcinogenic stimuli such as *H. pylori* infection and tobacco smoking. However, in addition to avoidance of conventional risk factors, active treatment with metformin for patients with DM may help to reduce cancer risk and achieve glycemic control. Although a conservative definition of stomach cancer was used, there is still the possibility of misclassification. Because the NHIS-HEALS does not provide the pathologic findings, stomach cancer incidence was defined using the main diagnosis code at patients' admission. In addition, we could not control for the duration of diabetes or the levels of glycated hemoglobin. The cumulative effects of metformin on stomach cancer development were not assessed in this study despite the limitation of using a secondary database. Determining the cumulative effects could have shown the causal relationship more accurately.

In conclusion, metformin use reduced the incidence of stomach cancer in Korean men and women with DM in a dose–response relationship after controlling for potential confounding factors. In addition, individuals without DM were at lower risk of stomach cancer development than diabetic patients who did not take metformin.

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Compliance with ethical standards

Conflict of interest Joungyoun Kim has received research grants from Korea National Research Foundation (No. 2019R1I1A3A01059886). Hee-Taik Kang has received research grants from Ministry of Health and Welfare in Korea (No. HI19C0526).

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