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Metformin use in cancer survivors with diabetes reduces all-cause mortality, based on the Korean National Health Insurance Service between 2002 and 2015

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Abstract

Malignant neoplasms are the leading cause of death in Korea. We aimed to examine if metformin use in cancer survivors reduces all-cause mortality. This study was retrospectively designed based on data from the Korean National Health Insurance Service-National Health Screening Cohort (HEALS) between 2002 and 2015. The Kaplan–Meier estimator and log-rank test was performed to estimate the survival function according to metformin usage (3721 metformin non-users with diabetes, 5580 metformin users with diabetes, and 24,483 non-diabetic individuals). Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality were calculated using Cox proportional hazards regression models.

The median follow-up duration was 4.2 years. The HRs (95% CIs) for all-cause mortality of metformin users and the non-diabetic group were 0.762 (0.683–0.850) and 1.055 (0.966–1.152) in men and 0.805 (0.649–0.999), and 1.049 (0.873–1.260) in women, respectively, compared with metformin non-users among diabetic cancer survivors, in a fully adjusted model. After stratifying metformin users into pre- and post-diagnosis of cancers, adjusted HRs (95% CIs) of pre- and post-diagnosis metformin users for all-cause mortality were 0.948 (0.839–1.071) and 0.530 (0.452–0.621) in men and 1.163 (0.921–1.469) and 0.439 (0.323–0.596) in women, respectively.

Metformin use in cancer survivors with diabetes reduced overall mortality rates. In particular, metformin use after cancer diagnosis, not before cancer diagnosis, was inversely associated with overall mortality.

Active treatment with metformin for diabetic cancer survivors after cancer diagnosis can improve their survival rates.

Abbreviations: ALT = alanine aminotransferase, AMP = adenosine monophosphate, AMPK = adenosine monophosphate kinase, ATP = adenosine triphosphate, BMI = body mass index, CI = confidence interval, Cox-PH = Cox-proportional hazard, CVD = cardiovascular disease, DM = diabetes mellitus, HEALS = national health screening cohort, HR = hazard ratio, ICD = international classification of disease, NHIS = national health insurance service, SBP = systolic blood pressure.

Keywords: cancer survivorship, malignant neoplasm, metformin, mortality, non-insulin treated type 2 diabetes

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1. Introduction

Malignant neoplasms are the number 1 cause of death in Korea.[1] The age-standardized rate of cancer incidence in Korea was 282.8 per 100,000 persons in 2017.[2] The cancer incidence and mortality rates have been decreasing (annual percent change, −3.1% for incidence and −2.7% for mortality), while the 5-year relative survival rate for cancer patients has increased.[3] As cancer survival rates have gradually improved, the number of cancer survivors also increased by approximately 1.87 million in 2018.[2] The main concerns for cancer survivors are fear of recurrence or metastasis of the primary cancer and premature death. To reduce recurrence, metastasis, and premature death, strict management of chronic diseases such as diabetes mellitus (DM) and vigilant surveillance and prevention of cancer have become very important, especially in long-term cancer survivors.

DM is prevailing in the world and has become a threat to public health. DM is the 6th most common cause of death in Korea in 2018 and its prevalence was 14.4% in adults aged 30 years and older in 2016.[1,4] The prevalence of DM in cancer survivors is higher and its control rate in cancer survivors is lower than in individuals who have not been diagnosed with cancer.[5] DM is closely related to cancer development and poor clinical outcomes, in addition to atherosclerotic cardiovascular diseases (CVDs).[6] Intensive treatment of early phase diabetes with lifestyle modification and metformin medication can reduce diabetes-related events such as atherosclerotic CVDs and death.[7]

Metformin is a biguanide drug that is used as the first treatment option in managing diabetes.[8] Although the exact mechanism underlying how metformin controls blood glucose levels has not been elucidated, inhibition of hepatic gluconeogenesis, and enhancement of peripheral insulin sensitivity such as in muscle seem to be the main mechanisms for glycemic control.[9] Metformin has pleiotropic effects beyond glucose-lowering activity. Metformin has been shown to prevent carcinogenesis and modulate the immune response, and these activities may be mediated by adenosine monophosphate (AMP)-activated protein kinase (AMPK).[9,10] These beneficial health effects of metformin could improve the health and longevity of cancer survivors with DM.

Evidence on whether metformin use in overall cancer survivors with DM reduces all-cause death is lacking. We aimed to investigate the association between metformin use and overall death among Korean cancer survivors using the Korean National Health Insurance Service (NHIS)-National Health Screening Cohort (HEALS) database.

2. Methods selection of research subjects

The NHIS-HEALS cohort data between 2002 and 2015 provided by the Korean NHIS were used. The cohort consists of 514,794 subjects, which represents a random sample out of the 5.15 million people who undertook medical check-ups between 2002 and 2003. The cohort included individuals aged 40 to 79 years as of December 2002. Age, sex, socioeconomic levels, and medical information such as medical care information, death-related information, prescription, and past medical history were included. Biennial health check-up records between 2002 and 2015 for most subjects were available in this cohort.

Figure 1 Shows a flowchart for patient selection. Subjects who were diagnosed with cancer once or more during hospitalization according to the International Classification of Diseases, Tenth Revision (ICD-10) code (C00-C97) between 2002 and 2015 were selected (n=52,499). Subjects who met any of the following conditions were excluded:

1. subjects who were 70 years or older between 2004 and 2005 (n=9777),
2. subjects who died within 1 year after being enrolled in the study in the study (n=6434),
3. subjects who had taken metformin for 30 days or less (n=486),
4. subjects with missing values in confounding variables (n=1440),
5. non-diabetic subjects who were prescribed metformin between 2002 and 2015 (n=123), or
6. subjects with a total study duration of 30 days or less (n=455).

Finally, 33,784 subjects (24,483 non-diabetic individuals, 3721 metformin non-users, and 5580 metformin users) were included in this analysis.

This study followed the 1964 Declaration of Helsinki, and the Institutional Review Board of Chungbuk National University approved this study (CBNUH 2020-03-024).

2.1. Definition of subject groups

In this study, diabetic patients were defined as 1) subjects who were diagnosed with diabetes (ICD-10 code: E11-14) and were prescribed anti-diabetic medication such as insulin, sulfonylurea, metformin, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, α-glucosidase inhibitor, sodium-glucose cotransporter-2 inhibitor, glucagon-like peptide-1 agonist and other glucose-lowering agents for 90 days or longer or 2) subjects with fasting blood glucose $\geq$ 126 mg/dl. Based on the above definition of diabetes, the study subjects were divided as follows: the non-diabetic group, subjects without DM; metformin non-users, subjects with DM who were prescribed other anti-diabetic drugs except for metformin or metformin for less than 90 days between 2002 and 2015; and metformin users, subjects with DM who were prescribed metformin for at least 90 days. Metformin users were further stratified into pre- and post-diagnosis user groups. The pre-/post-diagnosis metformin users were determined based on whether the initial prescription date for metformin was before or after the initial cancer diagnosis.

The start date of the study was the date of the initial cancer diagnosis as a main sick code when hospitalized between 2002 and 2015. Since the primary event of interest was death, the study end date was the date of death by subject. For the subjects who survived, the last date of medical records became the end of study among health check-ups, hospital visit, or metformin intake date if available.

2.2. Definition of variables

In this study, potential confounders that might have spurious association between metformin use and all-cause mortality among cancer survivors were considered. The variables were age, body mass index (BMI), systolic blood pressure (SBP), fasting blood glucose, total cholesterol, alanine aminotransferase (ALT), hypertension history, physical activity, tobacco-smoking status, alcohol-drinking status, and economic status. BMI (unit kg/m^2) was defined as body weight (kg) divided by squared height (m). Hypertension history, tobacco-smoking, alcohol consumption, physical activity, and economic status were categorical
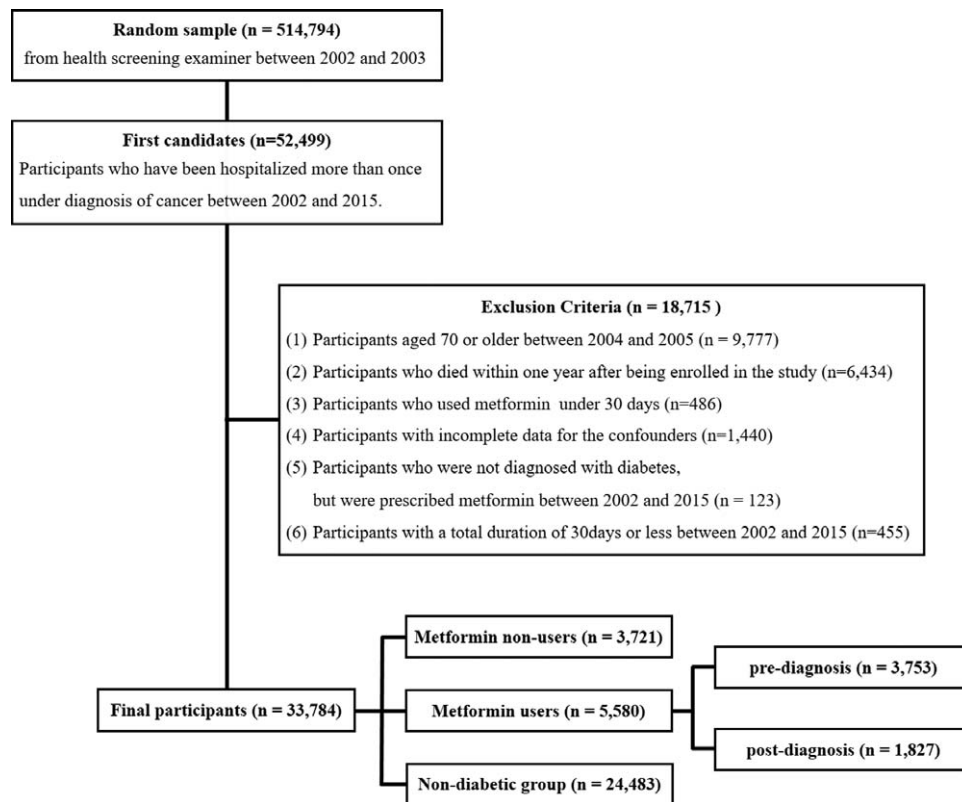
Figure 1. Flowchart of inclusion and exclusion criteria.

variables. This information was obtained from self-reported questionnaires. Tobacco-smoking status was divided into never smokers (who had never smoked tobacco) and ever smokers (who currently smoked or ever smoked tobacco). Alcohol-drinking status was categorized into rare (less than twice per month), sometimes (twice per month to twice per week), and regular (more than 3 times per week). Physical activity was classified into rare (rarely engage in exercise), sometimes (engage in exercise 1–4 days per week), and regular (engage in exercise 5 or more days per week). Economic status was stratified into low (the 0–3rd decile), middle (the 4th–7th decile), and high (the 8th–10th decile) according to monthly household income.

2.3. Statistical analysis

To compare the groups in baseline characteristics, analysis of variance (ANOVA) and Chi-Squared analysis were performed. Kaplan–Meier method and log-rank test are employed for nonparametric estimation and test of survival rates. To calculate hazard ratios (HRs) and 95% confidence intervals (CIs), Cox-proportional hazard (Cox-PH) regression models were conducted after metformin non-users were set as the reference. In this study, 3 Cox-PH regression models were considered, depending on the levels of confounders:

1. Model 1, age only;
2. Model 2, BMI, SBP, ALT, total cholesterol, and fasting blood glucose, in addition to the variable (age) in Model 1; and
3. Model 3, smoking status, drinking status, physical activity, economic status, and hypertension history, in addition to variables in Model 2.

For analysis, SAS enterprise guide version 7.1 (SAS Institute Inc., Cary, NC) and R study (version 3.3.3) were used. P values were tested on both sides, and the significance level was $P < .05$.

3. Results

The median follow-up duration was 4.2 years (3.8 years in men and 4.8 years in women). Table 1 presented the baseline characteristics of participants according to metformin use and diabetes diagnosis by sex. Metformin users with DM were the oldest patient group and had the highest levels of BMI, SBP, fasting glucose, and ALT in both sexes (all P values <.001). In addition, higher percentages of patients with hypertension and regular physical activity were observed in metformin users compared with the other 2 groups in both sexes. The non-diabetic group was in higher economic status than metformin non-users and users in both sexes.

The association between metformin use and all-cause mortality incidence of cancer survivors was presented in Figure 2. An estimated cumulative incidence of mortality was calculated using Kaplan–Meier survival curve. The survival rate of cancer survivors was significantly higher in the non-diabetic group than in individuals with DM including metformin non-users and users in men (log-rank test P value <.001 in men), while the difference was not statistically significant in women.

Table 2 demonstrated the HRs (95% CIs) from Cox-PH regression models for all-cause mortality according to metformin use and the presence of diabetes. The HRs (95% CIs) of metformin users and the non-diabetic group for all-cause mortality were 0.775 (0.697–0.863) and 0.925 (0.850–1.007)

Table 1

Baseline characteristics according to metformin use and the presence of diabetes diagnosis by sex.

Men	Metformin non-users	Metformin users	Non-diabetic group	P values
Number	2726	3620	13,015	
Age, years	58.3±7.3	59.1±7.1	57.8±7.6	<.001
Body mass index, kg/m^2	23.9±3.0	24.8±3.0	23.7±2.8	<.001
Systolic blood pressure, mm Hg	130.0±16.9	130.9±17.0	127.1±16.1	<.001
Fasting Glucose, mg/dl	113.6±36.7	134.5±51.9	92.8±11.9	<.001
Total cholesterol, mg/dl	190.0±39.7	192.0±40.9	191.1±36.1	.119
ALT, μ/L	33.0±34.6	34.6±28.7	28.7±26.6	<.001
Hypertension, %	16.7	24.2	12.5	<.001
Ever smokers, %	52.9	51.9	49.6	.002
Drinking status, %				<.001
Rare	42.1	44.8	43.7	
Sometimes	36.0	35.6	38.1	
Often	22.0	19.7	18.1	
Physical activity, %				<.001
Rare	45.4	44.1	45.3	
Sometimes	41.7	42.0	43.1	
Regular	12.9	14.0	11.5	
Economic status, %				<.001
Low	22.9	20.2	17.9	
Middle	34.2	32.5	32.4	
High	42.9	47.3	49.8	
Women	**Metformin non-users**	**Metformin users**	**Non-diabetic group**	**P values**
Number	995	1,960	11,468	
Age, years	57.8±7.8	58.9±7.5	55.1±7.6	<.001
Body mass index, kg/m^2	24.4±3.2	25.7±3.5	23.8±3.0	<.001
Systolic blood pressure, mm Hg	127.9±16.7	130.2±18.0	123.0±16.6	<.001
Fasting Glucose, mg/dl	107.7±40.8	126.3±48.1	90.5±10.7	<.001
Total cholesterol, mg/dl	200.8±39.9	205.6±46.8	199.1±36.8	<.001
ALT, μ/L	24.6±17.5	28.3±19.4	22.1±18.6	<.001
Hypertension, %	21.6	33.9	13.4	<.001
Ever smokers, %	2.5	3.2	2.8	.446
Drinking status, %				<.001
Rare	85.9	88.6	84.3	
Sometimes	12.5	10.2	14.2	
Often	1.6	1.2	1.5	
Physical activity, %				<.001
Rare	56.5	55.8	54.7	
Sometimes	31.8	29.9	34.5	
Regular	11.8	14.3	10.8	
Economic status, %				<.001
Low	26.0	25.4	22.8	
Middle	36.8	34.4	33.0	
High	37.2	40.2	44.2	

Values are presented as n (%) or mean ± standard errors.

P values are determined for continuous variables by ANOVA test and for categorical variables by Chi-Squared test.

in men and 0.868 (0.701–1.074) and 0.959 (0.802–1.148) in women, respectively, compared with metformin non-users, after adjusting for age only (Model 1). The HRs (95% CIs) of metformin users and the non-diabetic group were 0.762 (0.683–0.850) and 1.055 (0.966–1.152) in men and 0.805 (0.649–0.999) and 1.049 (0.873–1.260) in women, respectively, compared with metformin non-users, after adjusting for age, BMI, SBP, ALT, total cholesterol, fasting blood glucose, smoking status, drinking status, physical activity, economic status, and hypertension history (Model 3).

To determine whether metformin use before and after cancer diagnosis reduced all-cause mortality in cancer survivors, metformin users were stratified into pre- and post-diagnosis metformin users (Table 3). The HRs (95% CIs) of pre- and post-

diagnosis metformin users were 0.948 (0.839–1.071) and 0.530 (0.452–0.621) in men and 1.163 (0.921–1.469) and 0.439 (0.323–0.596) in women, respectively, compared with metformin non-users, after fully adjusting for potential confounding factors (Model 3).

4. Discussion

These findings from the current study indicated that among cancer survivors, metformin users with diabetes had a higher survival rate than metformin non-users. In particular, individuals who had taken metformin since they were diagnosed with cancer were at a lower risk of death, after fully adjusting for potential confounding factors.
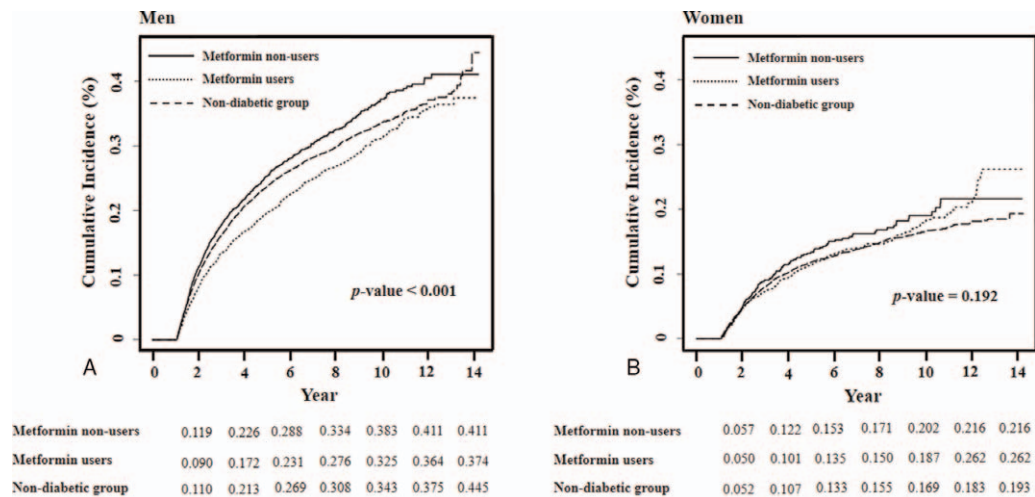
Figure 2. The estimated cumulative incidence of all-cause mortality using Kaplan–Meier estimates among cancer survivors according to metformin use and the presence of diabetes. *P* values are from log-rank tests.

Several studies have demonstrated the association between metformin use and overall survival among survivors who experienced individual cancer such as colorectal, breast, and pancreatic cancer[11–13]; however, there are still conflicting findings to show null association. [14,15] In addition, only a few studies reported the association between metformin and overall cancer types, rather than individual type of cancer.[16] The significant relationship between metformin use and lower mortality was observed among cancer survivors who were diagnosed with individual type of cancer (colorectum, breast, pancreas, and so on).[11–13] However, Lega et al observed that metformin use did not show a benefit for overall and breast cancer-specific survival.[14] Cossor et al demonstrated that colorectal cancer survivors with metformin medication did not show better survival.[15] Yin et al conducted a systematic review and meta-analysis, showing an overall survival benefit of metformin for cancer survivors.[17] In the meta-analysis, a reduction in all-cause mortality was seen in survivors of lung, breast, prostate, pancreatic, and colorectal cancer.[17] Currie et al reported that compared with other anti-diabetic drugs, metformin had a beneficial impact on survival among mixed type cancer survivors.[16] Besides Currie research, there is lack of evidence examining the beneficial effects of metformin use on all-cause mortality among mixed type cancer survivors. The findings of the current study are consistent with Currie findings and provide

more evidence that metformin medication after cancer diagnosis works better to reduce overall cancer mortality than metformin use before cancer diagnosis.

Metformin is the initial therapeutic option to manage type 2 DM with lifestyle modifications.[8] Metformin also seems to be associated with anti-aging mechanisms. The main action mechanisms to lower blood glucose appear to inhibit gluconeogenesis in liver and enhance insulin sensitivity in peripheral tissues such as muscle.[9,18,19] However, understanding how metformin improves survival rates among cancer survivors has been difficult. AMPK activation and immune modulation appear to mediate the impact of metformin on survival rate through mammalian target of rapamycin signaling.[9,20] Inhibition of respiratory complex protein by metformin results in reduced adenosine triphosphate (ATP) and reactive oxygen species.[21,22] Reduced ATP production increases the AMP:ATP ratio, which activates AMPK that modulates energy metabolism. In addition, metformin influences many effector proteins including mammalian target of rapamycin and p53 and inhibits pro-inflammatory processes.[23,24] These molecular and cellular mechanisms of metformin could underlie the positive effect on improved survival rates for cancer survivors.

In long-term cancer survivors, the fraction of primary cancer that contributes to mortality decreases over time; however, the incidence of death attributable to second primary cancers and

Table 2

Cox proportional hazards regression results for all-cause mortality according to metformin usage and the presence of diabetes.

	Men			Women		
HRs (95% CIs)	Metformin non-users	Metformin users	Non-diabetic group	Metformin non-users	Metformin users	Non-diabetic group
Model 1	1	0.775 (0.697–0.863)	0.925 (0.850–1.007)	1	0.868 (0.701–1.074)	0.959 (0.802–1.148)
Model 2	1	0.741 (0.665–0.827)	1.030 (0.943–1.125)	1	0.790 (0.637–0.980)	1.058 (0.880–1.271)
Model 3	1	0.762 (0.683–0.850)	1.055 (0.966–1.152)	1	0.805 (0.649–0.999)	1.049 (0.873–1.260)

Model 1: Adjusted for age.
Model 2: Adjusted for body mass index, systolic blood pressure, alanine aminotransferase, total cholesterol, and fasting blood glucose, in addition to age in Model 1.
Model 3: Adjusted for smoking status, drinking status, physical activity, economic status, and hypertension history, in addition to variables in Model 2.

Cox proportional hazards regression results for all-cause mortality according to metformin usage and diabetes after stratification into pre- and post-diagnosis metformin usage.

HRs (95% CIs)	Men				Women			
	Metformin non-users	Prediagnosis metformin users	Postdiagnosis metformin users	Nondiabetic group	Metformin non-users	Prediagnosis metformin users	Post-diagnosis metformin users	Non-diabetic group
Model 1	1	0.969 (0.863–1.089)	0.519 (0.443–0.607)	0.925 (0.850–1.007)	1	1.275 (1.017–1.598)	0.448 (0.330–0.607)	0.959 (0.799–1.145)
Model 2	1	0.913 (0.809–1.032)	0.522 (0.445–0.612)	1.018 (0.932–1.111)	1	1.128 (0.893–1.423)	0.434 (0.320–0.590)	1.033 (0.860–1.240)
Model 3	1	0.948 (0.839–1.071)	0.530 (0.452–0.621)	1.041 (0.953–1.137)	1	1.163 (0.921–1.469)	0.439 (0.323–0.596)	1.023 (0.852–1.228)

Model 1: adjusted for age.
Model 2: Adjusted for body mass index, systolic blood pressure, alanine aminotransferase, total cholesterol, and fasting blood glucose, in addition to age in Model 1.
Model 3: Adjusted for smoking status, drinking status, physical activity, economic status, and hypertension history in addition to variables in Model 2.

chronic diseases increases.[25] Metformin can play a role in preventing type 2 DM incidence and improving CVD-related outcomes and their risk factors.[7,26,27] In some observational studies, metformin was related to lower cancer incidence and mortality.[28,29] Based on the previous indirect evidence, we speculate that metformin reduced death from chronic diseases such as DM and CVDs and development of second primary cancer. These consequences may positively affect survival for cancer survivors, especially who those took metformin after cancer diagnosis.

This study has several advantages. First, the NHIS-HEALS data were obtained from real-world measurements in the clinical setting. Second, the Korean NHIS aims to maintain the representativeness of the general Korean population. In addition, almost the entire Korean population is engaged in obligatory insurance and the Korean Ministry of Health and Welfare provides free national health check-up services for adults aged 40 years or older. For these reasons, the NHIS-HEALS data are reliable to represent the entire Korean population aged over 40 years. Third, the NHIS-HEALS data contain some laboratory and socioeconomic information that were obtained from national health check-up services. Laboratory findings may reflect health status and socioeconomic status can indicate health inequity. Both can affect medical accessibility and overall mortality. Because these important confounding factors were available, we could more adequately make Cox-PH regression model after adjusting for these potential confounding factors. Fourth, metformin users were further stratified into pre- and post-diagnosis groups according to timing when the metformin medication was started. Our results suggest that metformin as a standard drug to treat diabetes might result in better mortality outcomes than other anti-diabetic medications in diabetic patients who are diagnosed with cancer. This is consistent with clinical practice guidelines of diabetes from the American Diabetes Association and European Association for the Study of Diabetes.[8,30] Fifth, the possibility of a false-positive diagnosis or misclassification of cancers is low. The Korean NHIS strictly monitors malignant neoplasms because cancer patients pay less out-of-pocket for medical costs than patients with common diseases due to the insurance reimbursement system. Finally, the median follow-up period is relatively longer than other studies (4.2 years). Because of the long study duration, we can assess metformin's long-term effect on cancer survivors.

Despite the above strengths, several limitations should be considered when interpreting these findings. First, the level of glycemic control was not fully controlled in individuals with diabetes even though fasting blood glucose levels were adjusted

for. Uncontrolled diabetes, by itself, is an important cause of death. Thus, to improve model accuracy and reflect the effects of diabetes severity, other markers should be adjusted. Although fasting blood glucose level is a second option to control for the effect of diabetes severity, glycated hemoglobin and fasting insulin level are better indicators. If these confounders were available in this cohort and adjusted, the Cox-PH regression models could be more accurate in determining the association between metformin use and overall mortality in cancer survivors with diabetes. Second, the NHIS-HEALS data did not contain information regarding pathologies and stages of cancers. In addition, the NHIS does not provide all data that could be used to identify individuals. The Korean NHIS combined sex-specific cancers (such as prostate, breast, uterine cervix, and endometrial cancer) and other rare cancers into 1 class, "Other," without their original ICD codes for de-identification. Third, detailed information including how each cancer was treated (such as surgery, chemotherapy, and radiotherapy), whether the primary treatment was effective, and whether recurrence and relapse occurred was not controlled.

In conclusion, metformin medication in cancer survivors with diabetes was associated with survival benefit. In particular, postdiagnosis metformin users were at a lower risk of all-cause mortality, after fully adjusting for potential confounding factors.

Acknowledgments

Author contributions

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Writing – original draft: Joungyoun Kim, Yoon-Jong Bae, Hee-Taik Kang.

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