Original Study

Diabetes, Metformin, and Lung Cancer: Retrospective Study of the Korean NHIS-HEALS Database

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Abstract

Metformin therapy provides pleotropic effects in addition to glycemic control. We studied lung cancer incidence in a retrospective study including 336,168 individuals and with a median study duration of 12.86 years. Metformin receipt did not reduce lung cancer incidence. However, individuals without diabetes were at a lower risk of lung cancer, especially in male ever smokers and female nonsmokers.

Background: Metformin is the first option in managing type 2 diabetes mellitus (DM) and has pleotropic effects. We studied the incidence of lung cancer in patients who received metformin therapy. **Patients and Methods:** This study was retrospectively designed and based on the Korean National Health Insurance Service–National Health Screening Cohort to determine whether metformin reduces lung cancer risk in the diabetic population. At baseline, all participants were 40 to 69 years old and were categorized into 3 groups: metformin nonrecipients with DM, metformin recipients with DM, and the nondiabetic group. **Results:** A total of 336,168 individuals were included in the final analysis (314,291 nondiabetic individuals, 8806 metformin recipients, and 13,071 metformin nonrecipients). The study median follow-up period was 12.86 years. The estimated cumulative lung cancer incidence of metformin nonrecipients, metformin recipients, and the nondiabetic group was 1.80%, 1.97%, and 1.24% in men and 1.87%, 0.61%, and 0.41% in women, respectively ($P < .05$). Compared to metformin nonrecipients, the hazard ratios (95% confidence intervals) for lung cancer incidence of metformin recipients and the nondiabetic group were 1.287 (0.979-1.691) and 0.835 (0.684-1.019) in men and 0.664 (0.374-1.177) and 0.553 (0.359-0.890) in women, respectively. The hazard ratios (95% confidence intervals) were statistically significant in male ever smokers (0.784 [0.627-0.979]) and female nonsmokers (0.498 [0.320-0.774]) after stratification according to smoking status. **Conclusion:** Metformin therapy did not reduce lung cancer incidence in the diabetic population. However, individuals without DM were at a lower risk of lung cancer, especially in male ever smokers and female nonsmokers.

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Introduction

Metformin, a drug that belongs to a biguanide class, is most commonly prescribed as the first-line treatment option for managing type 2 diabetes mellitus (DM). DM increases progression and risk of atherosclerotic cardiovascular complications, and it imposes a socioeconomic burden on public health. The UK Prospective Diabetes Study (UKPDS) reported that thorough glycemic control with metformin from early diabetes diagnosis could reduce further diabetes-related complications and mortality in the future.[1] Clinical practice guidelines from the American Diabetes Association and the European Association for the Study of Diabetes recommend that metformin and healthy lifestyle changes such as regular exercise should be adopted in the earlier phase of DM.[2,3] Metformin lowers blood glycemic levels by inhibiting hepatic gluconeogenesis and promoting peripheral insulin sensitivity.[4] In addition to glucose-lowering action, metformin activates adenosine monophosphate (AMP)-activated protein kinase (AMPK), which mediates metformin's pleiotropic effects such as cancer prevention and immune modulation.[4-7]

In Korea, more than 229,000 cancer cases are newly diagnosed (298.0 cases per 100,000 persons when age standardized), and more than 78,000 individuals die from various cancers (27.8% of total death).[8] Cancer is the number one cause of death in Korea.[8] Cancer mortality is higher than that of cardiovascular or cerebrovascular diseases. Of total cancers, lung cancer is still the leading cause of cancer death even though its 5-year relative survival rate increased from 11.3% in 1993-1995 to 28.2% in 2012-2106.[8] Prevention and vigilant surveillance of lung cancer are essential to reduce lung cancer mortality and its associated public health burden. The Korean Ministry of Health and Welfare (MOHW) has provided a lung cancer screening program for the high-risk population since July 2019. Prevention of lung cancer is more important than earlier detection. Smoking cessation may be the most effective method for prevention of lung cancer. If the commonly prescribed drugs like metformin are chemopreventive for lung cancer, then we expect there to be dual effects on glycemic control and cancer prevention.

We hypothesized that metformin increases insulin sensitivity and activates AMPK, resulting in reduction of lung cancer incidence. Thus, whether or not metformin prevents lung cancer was investigated on the basis of data extracted from the Korean National Health Insurance Service (NHIS)-National Health Screening Cohort (HEALS) data.

Patients and Methods

Study Population

The Korean NHIS-HEALS cohort is a database including individuals participating in national health examination programs that the Korean NHIS provides biennially. These health examinations are available to adults aged 40 years or older. A total of 514,794 individuals were selected among health examination participants in 2002 or 2003 who underwent follow-up evaluations until 2015. The Korean NHIS primarily collected information for reimbursement of claims; this information included diagnosis code, examination, and prescription data. In addition, the NHIS-HEALS contains information collected during health examination such as laboratory data, responses to self-reported questionnaires, and death records. Seong et al[9] described the cohort profile in more detail.

The study subjects' inclusion and exclusion process is shown in Figure 1. Individuals who were 70 years or older were excluded (n = 38,519) (Figure 1, Exclusion of participants [1]). We excluded the individuals who were diagnosed with cancer according to International Classification of Diseases, Tenth Revision (ICD-10), code (C00-C97) (n = 19,385), who answered in the affirmative to having a history of cancer in the self-reported questionnaire (n = 3243), who died between 2002 and 2004 (n = 2526), who were prescribed insulin for 90 days or longer between 2002 and 2003 (n = 73), or who were newly diagnosed with diabetes between 2004 and 2015 (n = 74,569) (Figure 1, Exclusion of participants [2]). Because the exclusions were not applied sequentially, some participants had overlapping reasons for exclusion. In addition, the following participants were excluded: participants who were prescribed metformin before the onset of diabetes between 2002 and 2003 (n = 1049) or who did not develop diabetes but were prescribed metformin between 2002 and 2015 (n = 2752) (Figure 1, Exclusion of participants [3]). Moreover, we excluded participants who were prescribed metformin for fewer than 90 days between 2002 and 2003 but prescribed metformin for more than 90 days between 2002 and 2015 (n = 21,534) (Figure 1, Exclusion of participants [4]). Finally, individuals whose total study duration was fewer than 30 days (n = 150) and those who had missing data for confounding factors (n = 20,752) were also excluded (Figure 1, Exclusion of participants [5] and [6], respectively). After all exclusions, a total of 336,168 individuals were included in the final analysis: 314,291 nondiabetic individuals, 8806 metformin recipients, and 13,071 metformin nonrecipients.

This study was conducted in compliance with the 1964 Helsinki Declaration. The institutional review board of Chungbuk National University approved this study (CBNU-201903-BMETC-802-01).

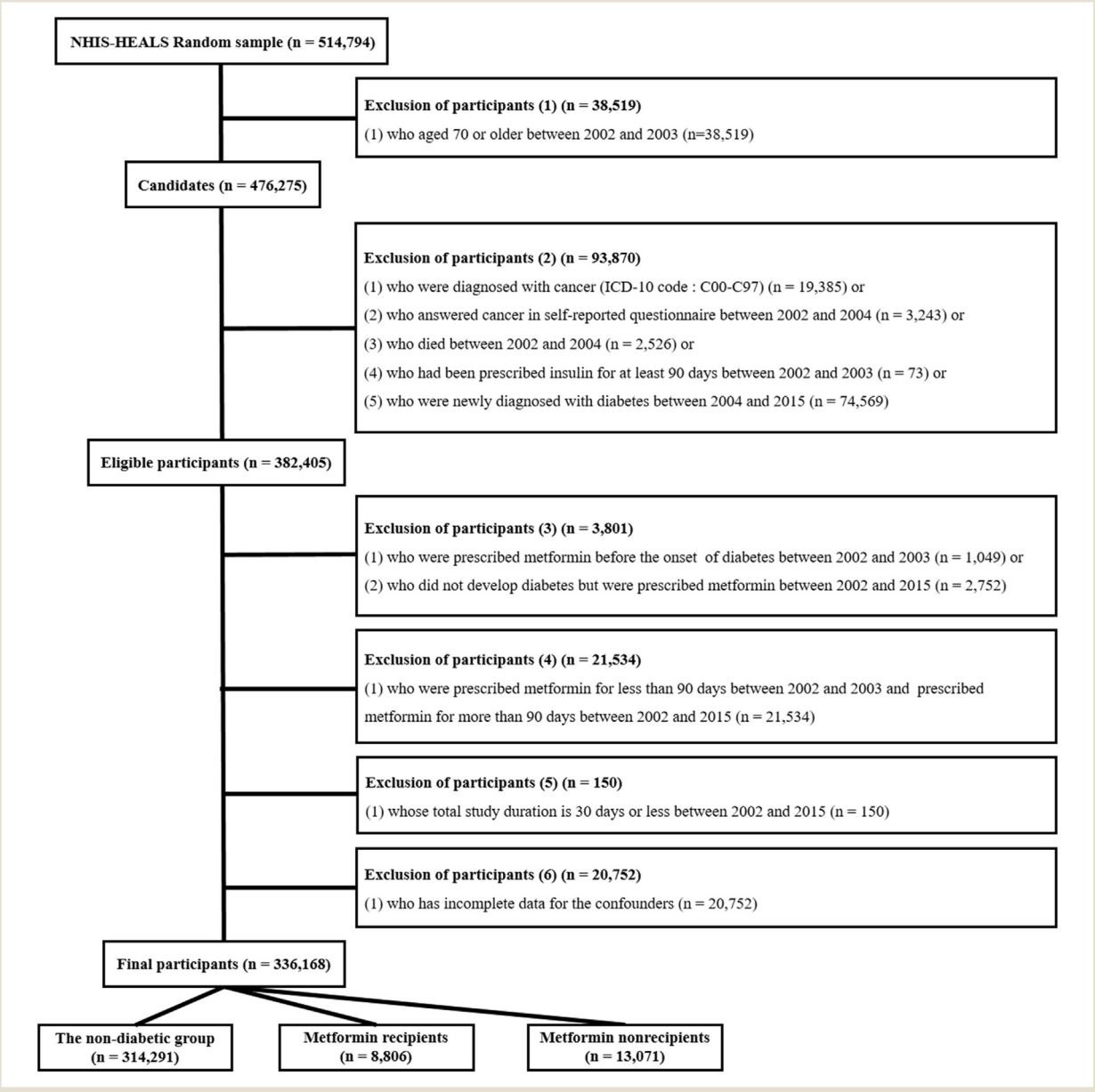
Definition of Study Groups, Lung Cancer, and Study Duration

DM was determined to be present if one of the following two conditions was met: having a diabetes ICD-10 diagnosis code (E11-14) and a prescription code for any antidiabetic agents (insulin, metformin, sulfonylurea, thiazolidinedione, α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium glucose cotransporter 2 inhibitor, glucagon-like peptide 1 analog) or having fasting glycemic levels ≥ 126 mg/dL from blood test data collected during national health examination. The use of both diagnosis code and prescription for antidiabetics as a condition was to ensure a more conservative approach to reduce misclassification.

The individuals in the final analysis were categorized into 3 groups: metformin recipients (individuals with DM who were prescribed metformin for 90 days or longer between 2002 and 2003), metformin nonrecipients (individuals with DM who were prescribed metformin for no longer than 90 days but were prescribed other oral glucose-lowering agents except metformin), and the nondiabetic group (individuals without DM).

Lung cancer occurrence was defined as two or more medical records since January 2005 in which the inpatient primary ICD-10 diagnosis code was C33 (malignant neoplasm of trachea), C34 (malignant neoplasm of bronchus and lung), or C39 (malignant neoplasm of other ill-defined sites in the respiratory system and intrathoracic organs).

Figure 1 Flowchart of Inclusion and Exclusion Criteria



Study duration was calculated differently for the 3 groups. The start date of metformin receipt (or nonreceipt) was defined as the first date that the patient met the DM definition of our study's criteria. The start date of the nondiabetic group was defined as the first health examination date between 2002 and 2003. The last research date for individuals who were diagnosed with lung cancer was defined as the first diagnosis date with C33, C34, or C39 at admission to hospitals. If participants died before lung cancer diagnosis or had not been diagnosed with lung cancer, the last research date was defined as the latest date among the following 3 days: the last day of the last health examination, the last day of the last clinic or hospital visit, or the last day on which a prescription was issued.

Definition of Other Variables

The confounding factors associated with the data collected between 2002 and 2003 were adjusted for to account for the association between metformin receipt and lung cancer incidence. Body mass index (BMI, kg/m^2) was calculated by dividing body weight (kg) by height squared (m). Additional measurement data such as systolic blood pressure, serum fasting glucose, total cholesterol, and alanine aminotransferase (ALT) levels were collected during the health examinations. On the basis of the self-reported survey, information on cigarette smoking, alcohol consumption, physical activity, monthly household income, residential area, and history of hypertension was collected. Cigarette smoking status was stratified into ever smokers (individuals who had ever smoked cigarettes) and

Table 1 Baseline Characteristics of Participants

Characteristic	Nondiabetic Group	Metformin	No Metformin	*P*
Men				
N	161,604	4889	9244	
Age (y)	50.5 ± 7.8	55.0 ± 7.7	52.4 ± 8.0	<.001
BMI (kg/m^2)	23.8 ± 2.8	24.6 ± 2.8	24.1 ± 3.1	<.001
SBP (mm Hg)	126.7 ± 16.7	132.2 ± 17.3	133.4 ± 18.5	<.001
Glucose (mg/dL)	90.5 ± 12.3	160.9 ± 68.9	149.4 ± 77.8	<.001
Total cholesterol (mg/dL)	197.5 ± 36.0	197.1 ± 40.3	200.3 ± 47.9	<.001
ALT (IU/L)	28.1 ± 20.4	34.2 ± 25.6	32.8 ± 28.8	<.001
Residential area				.099
Urban	75,499 (46.7)	2210 (45.2)	4290 (46.4)	
Rural	86,105 (53.3)	2679 (54.8)	4954 (53.6)	
Ever smoker	93,295 (57.7)	2698 (55.2)	5638 (61.0)	<.001
Drinking status				<.001
Rare	55,388 (34.3)	2059 (42.1)	3033 (32.8)	
Sometimes	76,587 (47.4)	1989 (40.7)	4090 (44.2)	
Regular	29,629 (18.3)	841 (17.2)	2121 (22.9)	
Physical activity				
Rare	78,084 (48.3)	2099 (42.9)	4649 (50.3)	
Sometimes	68,952 (42.7)	2065 (42.2)	3675 (39.8)	
Regular	14,568 (9.0)	725 (14.8)	920 (10.0)	
Household income				<.001
Low	25,401 (15.7)	1001 (20.5)	2308 (25.0)	
Middle	52,056 (32.2)	1583 (32.4)	3396 (36.7)	
High	84,147 (52.1)	2305 (47.1)	3540 (38.3)	
Hypertension	8157 (5.0)	709 (14.5)	753 (8.1)	<.001
Women				
N	152,687	3917	3827	
Age (y)	51.3 ± 8.0	57.7 ± 7.4	55.5 ± 8.3	<.001
BMI (kg/m^2)	23.7 ± 2.9	25.2 ± 3.2	24.5 ± 3.3	<.001
SBP (mm Hg)	122.5 ± 17.9	131.9 ± 18.6	130.6 ± 19.7	<.001
Glucose (mg/dL)	88.9 ± 11.5	160.2 ± 73.3	160.2 ± 118.3	<.001
Total cholesterol (mg/dL)	199.5 ± 37.5	207.0 ± 42.1	210.4 ± 62.4	<.001
ALT (IU/L)	20.0 ± 15.8	28.5 ± 19.9	23.6 ± 17.6	<.001
Residential area				<.001
Urban	69,334 (45.4)	1583 (40.4)	1398 (36.5)	
Rural	83,353 (54.6)	2334 (59.6)	2429 (63.5)	
Ever smoker	5042 (3.3)	158 (4.0)	157 (4.1)	.001
Drinking status				<.001
Rare	123,701 (81.0)	3535 (90.2)	3212 (83.9)	
Sometimes	26,110 (17.1)	337 (8.6)	537 (14.0)	
Regular	2876 (1.9)	45 (1.1)	78 (2.0)	
Physical activity				<.001
Rare	99,605 (65.2)	2408 (61.5)	2747 (71.8)	
Sometimes	39,535 (25.9)	929 (23.7)	737 (19.3)	
Regular	13,547 (8.9)	580 (14.8)	343 (9.0)	
Household income				<.001
Low	40,623 (26.6)	1067 (27.2)	1322 (34.5)	
Middle	50,143 (32.8)	1392 (35.5)	1316 (34.4)	
High	61,921 (40.6)	1458 (37.2)	1189 (31.1)	
Hypertension	10,339 (6.7)	901 (23.0)	481 (12.6)	<.001

Data are presented as n (%) or mean ± standard error.
Abbreviations: ALT = alanine aminotransferase; BMI = body mass index; SBP = systolic blood pressure.

nonsmokers (individuals who had never smoked cigarettes). Alcohol consumption status was classified as rare (less than twice per month), sometimes (from twice per month to twice per week), and regular (3 times or more per week). Physical activity status was categorized as rare (rarely engaged in exercise), sometimes (engaged in exercise for 1 to 4 days per week), and regular (engaged in exercise 5 days or more per week). Economic status was classified into 3 groups as low (zero to third decile), middle (fourth to seventh decile), and high (eighth to 10th decile) according to monthly household income. For residence area, we considered urban and rural areas.

Statistical Analysis

Participants were categorized into 3 groups as metformin nonrecipients and metformin recipients with DM; and the nondiabetic individuals. All data were presented as mean ± standard errors for continuous variables and number (%) for categorical variables. To compare the differences among 3 groups, 1-way ANOVA for continuous variables and the chi-square test for categorical variables were performed. The primary outcome was the lung cancer incidence rate, which corresponded to 1-survival rate. The survival functions of the 3 groups were estimated by the Kaplan-Meier method, and log-rank tests were conducted to compare survival rates among the 3 groups.

Cox proportional-hazards regression models were built to calculate the hazard ratios (HRs) with 95% confidence intervals (CIs) to adjust for confounding factors. Statistical software (SAS Enterprise 7.1, SAS Institute, Cary, NC; RStudio 3.3.3, https://rstudio.com/) were used to perform the analyses in this study. All P values were based on 2-tailed tests, and $P < .05$ was considered statistically significant.

Results

Of a total of 336,168 participants (175,737 men and 160,431 women), 2641 cases of lung cancer (2016 in men and 625 in women) were diagnosed during the study. Median follow-up duration was 12.86 years.

Baseline characteristics of participants are shown in Table 1. Metformin recipients were older on average than the nonmetformin group and the nondiabetic group. Mean age of the nondiabetic group, metformin recipients, and metformin nonrecipients was 50.5, 55.0, and 52.4 years in men and 51.3, 57.7, and 55.5 years in women, respectively. Metformin recipients had higher BMI than other groups and had the highest glucose and ALT levels in both sexes. Nondiabetic individuals more often lived in urban areas, rarely engaged in physical activities, and had higher household income than diabetic groups. Individuals in the nondiabetic group had the lowest percentage of hypertension.

Figure 2 shows the cumulative incidence rates, obtained by subtracting the Kaplan-Meier estimates from 1, for comparing the association between metformin receipt and the development of lung cancer. The log-rank test was used to compare incidence rates among 3 groups. The estimated incidence of lung cancer at the last study period was highest in metformin recipients in men and metformin nonrecipients in women. The estimated cumulative incidence of metformin nonrecipients, metformin nonrecipients, and the nondiabetic group were 1.80%, 1.97%, and 1.24% in men and 1.87%, 0.61%, and 0.41% in women, respectively (both $P < .05$) (Figure 2A and B). In order to minimize the effect of cigarette smoking, the entire population was stratified into ever smokers and nonsmokers. Among ever smokers, the estimated lung cancer incidences of metformin nonrecipients, metformin recipients, and the nondiabetic group were 2.28%, 2.70%, and 1.55% in men and 0.68%, 2.04%, and 1.20% in women, respectively ($P < .001$ in men and 0.557 in women) (Figure 2C and D). Among nonsmokers, those of metformin nonrecipients, metformin recipients, and the nondiabetic group were 1.03%, 1.06%, and 0.82% in men and 1.91%, 0.56%, and 0.38% in women, respectively ($P = .556$ in men and .001 in women) (Figure 2E and F)

Table 2 shows the findings of Cox proportional-hazards regression models. Compared to metformin nonrecipients, the HRs (95% CIs) for lung cancer in metformin recipients and the nondiabetic group were 0.850 (0.648-1.115) and 0.874 (0.733-1.043) in men and 0.614 (0.347-1.087) and 0.691 (0.469-1.018) in women, respectively, after adjusting for age (model 1). After fully adjusting for age, smoking status, residential area, alcohol consumption, physical activity, BMI, systolic blood pressure, total cholesterol, ALT, blood glucose levels, hypertension history, and household income, the HRs (95% CIs) of metformin recipients and the nondiabetic group were 1.287 (0.979-1.691) and 0.835 (0.684-1.019) in men and 0.664 (0.374-1.177) and 0.553 (0.359-0.850), respectively (model 3).

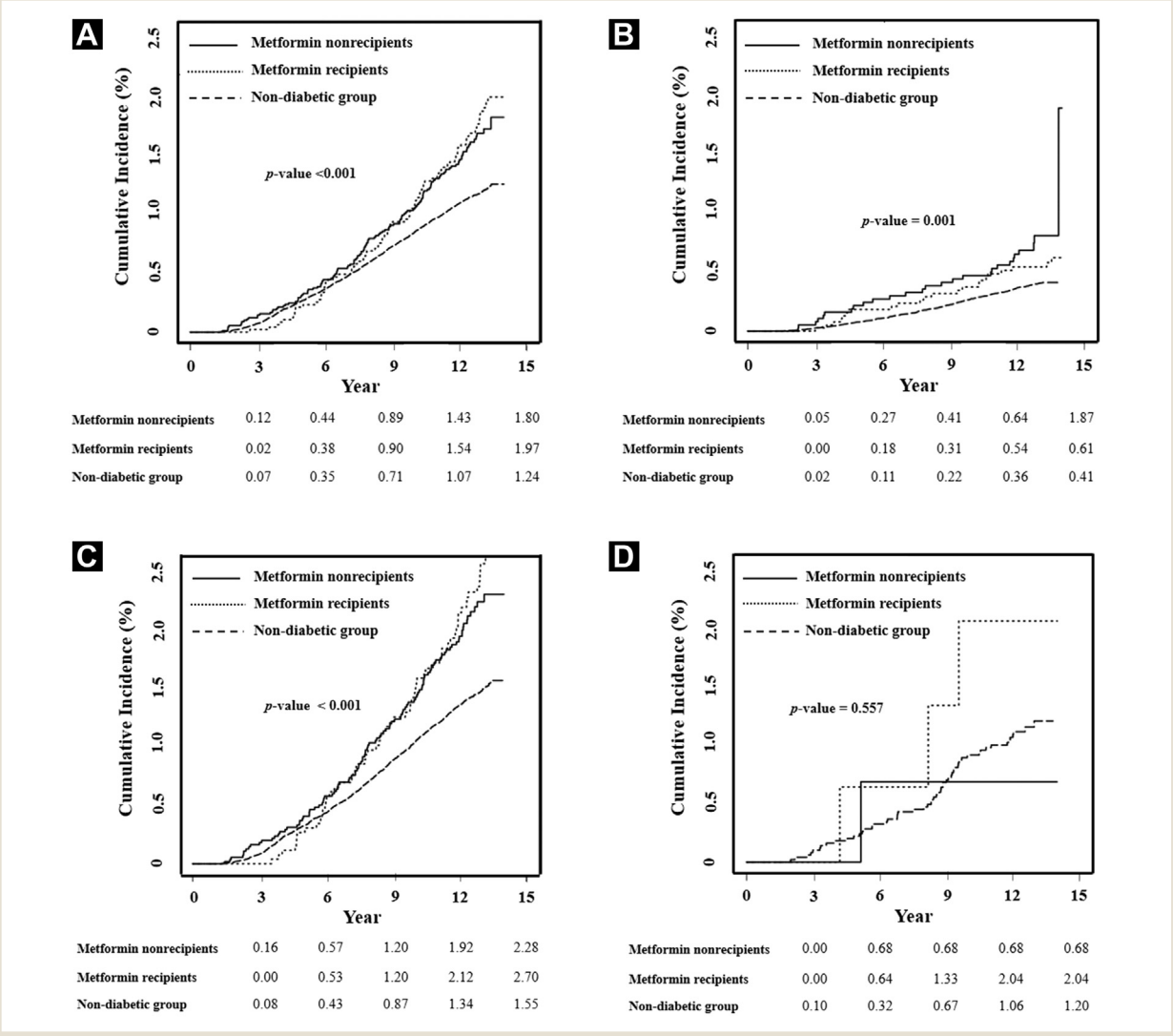
In order to minimize the effect of cigarette smoking, we reclassified the entire population into ever smokers and nonsmokers (Table 3). After full adjustment, the HRs (95% CIs) of metformin recipients and the nondiabetic group were 1.278 (0.936-1.745) and 0.784 (0.627-0.979) in male ever smokers and 2.686 (0.268-26.965) and 2.223 (0.253-19.571) in female ever smokers, respectively. Among nonsmokers, those for metformin recipients and the nondiabetic group were 1.366 (0.765-2.437) and 1.028 (0.660-1.602) in male nonsmokers and 0.590 (0.323-1.079) and 0.498 (0.320-0.774) in female nonsmokers, respectively.

Discussion

After controlling for confounding factors affecting lung cancer development, the risk for lung cancer was not significantly lower in metformin recipients with DM but was statistically lower in women without DM (nondiabetic group) compared to metformin nonrecipients with DM. After stratifying according to smoking status, the risk for lung cancer was statistically significant in the nondiabetic men among ever smokers and in the nondiabetic women among nonsmokers.

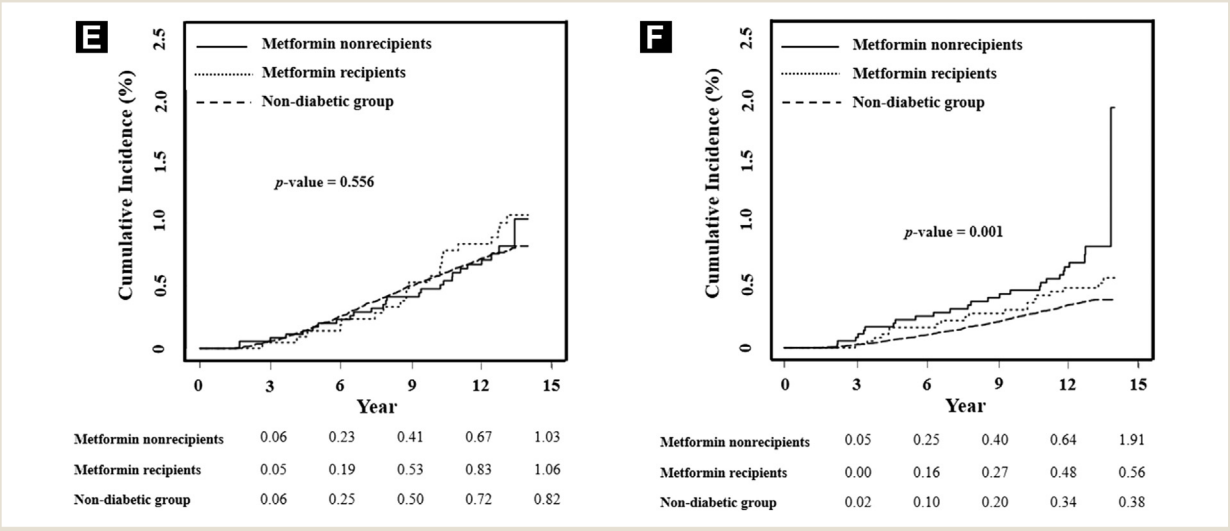
The prevalence of diabetes is increasing globally and is burdensome to public health. DM is not only a threat to public health but also increases atherosclerotic cardiovascular diseases and mortality. In addition, hyperglycemia, hyperinsulinemia, metabolic abnormalities, proinflammatory states, obesity, and unhealthier lifestyles, all of which accompany diabetes, are associated with higher risk of carcinogenesis.[10,11] However, more evidence to determine the association between DM and cancer development is required. In addition, whether or not antidiabetic medication such as metformin reverses cancer risk is unknown even though diabetes is thought to be procarcinogenic.

Figure 2 Estimated Cumulative Incidence of Lung Cancer. *P* Values Were Determined by Log-Rank Tests. Last Follow-Up Duration of Metformin Nonrecipients (Non-users), Recipients (Users), and Nondiabetic Individuals Was 14.00, 14.01, and 14.01 Years in Men and 14.01, 14.01, and 13.92 years in Women



Lung cancer is the leading cause of cancer death in Korea.[8] Through advances in therapeutic modalities, the lung cancer survival rate has increased from 11.3% in 1993-1995 to 28.2% in 2012-2106.[8] Compared to other cancers such as those of the stomach, colorectum, breast, and prostate, the 5-year relative survival rate from lung cancer is still low. To improve the survival rate, development of cost-effective detection modalities such as low-dose computed tomography (LDCT) has been helpful. The Korean MOHW assessed effectiveness of lung cancer screening using LDCT. The analysis of the data revealed that the lung cancer screening program using LDCT was effective in detecting early-stage lung cancer and efficient in reducing the public health burden.[12] This lung cancer screening program has been provided to high-risk individuals who had smoked more than 30 pack-years and had ceased smoking for fewer than 15 years since 2019. For quality control of this program, multidetector LDCT with at least 16 channels and the maximal radiation dose of 3 mGy for standard-size subjects were recommended.[13] Certified diagnostic radiologists should report the computed tomographic (CT) findings using the validated Lung CT screening reporting and data system.[13] However, cancer prevention is more important in reducing death from lung cancer than early detection and good therapeutic methods. Because cigarettes are the most potent carcinogen, smoking cessation is the best way to prevent lung cancer. Cigarette smoking is estimated to account for approximately 90% of lung cancer.[14] However, avoidance of other carcinogens, including asbestos and polycyclic aromatic hydrocarbon, and receiving chemotherapeutic agents such as statins are other options to prevent cancer.[14,15] While several researchers reported that metformin therapy prevented lung cancer development,[10,16,17] there is a lack of large population-based

Figure 2 continued



evidence to determine whether metformin receipt in a diabetic population can reduce lung cancer.

Metformin and lifestyle modification are the first treatment options in managing type 2 DM.[2,3] Metformin inhibits gluconeogenesis in the liver and increases insulin sensitivity in muscular tissues, resulting in blood glucose lowering.[4-6] Metformin can easily cross the plasma and mitochondrial membranes, leading to cell-cycle and energy metabolism changes.[18,19] In addition, metformin activates AMPK through altered adenosine triphosphate production. AMPK activation affects a number of effector proteins such as mammalian target of rapamycin and p53, which are closely associated with carcinogenesis.[20] We hypothesized that these actions of metformin reduce lung cancer incidence. However, contrary to our hypothesis, this study revealed that metformin receipt in a diabetic population was not associated with lung cancer development. In addition, unlike men, women without DM were at a lower risk of lung cancer than metformin nonrecipients with DM. These findings suggest that diabetes in women is a risk factor for lung cancer and that metformin does not reverse lung cancer risk in the female diabetic population. We stratified the entire population into ever smokers and nonsmokers because cigarette smoking is the most potent risk factor for lung cancer and can interact with diabetes in lung cancer development. Among ever smokers, unlike women, men without DM had a lower risk of lung cancer, and metformin did not prevent lung cancer. Results from nonsmokers were consistent with those from the entire population. The reason for the null association between DM and lung cancer in women may be that the number of female ever smokers was small. In addition, our findings suggest that men with DM who smoke should cease smoking to reduce the risk of lung cancer.

There are several strengths that distinguish this study from previous studies. First, our study was based on a data set collected in the clinical setting. In addition, the Korean NHIS cohort was representative of the entire Korean population. Second, this study was based on a large population over long duration (median follow-up was 12.86 years). The relatively large number of subjects allowed the identification of statistical differences in case of relatively rare diseases such as lung cancer. In addition, the long duration allowed for identification of lung cancer cases despite the prolonged carcinogenic process. Third, our study had a lower possibility of lung cancer misclassification or false-positive diagnosis. The Korean MOHW strictly controls the entire national health care system; the Korean insurance system is obligatory, and the Korean NHIS pays insurance claims. In addition, to minimize misdiagnosis, we defined

Table 2 Cox Proportional Hazard Regression Models for Lung Cancer Incidence

	Men			Women		
Model[a]	Metformin	No Metformin	Nondiabetic Group	No Metformin	Metformin	Nondiabetic Group
1	1	0.850 (0.648-1.115)	0.874 (0.733-1.043)	1	0.614 (0.347-1.087)	0.691 (0.469-1.018)
2	1	1.153 (0.878-1.513)	0.752 (0.630-0.897)	1	0.693 (0.391-1.227)	0.529 (0.360-0.779)
3	1	1.287 (0.979-1.691)	0.835 (0.684-1.019)	1	0.664 (0.374-1.177)	0.553 (0.359-0.850)

Data are presented as hazard ratio (95% confidence interval).
[a]Model 1 is adjusted for age; model 2, adjusted for smoking status, residential area, alcohol consumption, and physical activity in addition to model 1; and model 3, adjusted for body mass index, systolic blood pressure, serum total cholesterol levels, serum alanine aminotransferase levels, blood glucose levels, hypertension history, and household income in addition to model 2.

Table 3 Cox Proportional Hazard Regression Models for Lung Cancer Incidence After Stratification According to Smoking Status

Model[a]	Men			Women		
	No Metformin	Metformin	Nondiabetic Group	No Metformin	Metformin	Nondiabetic Group
Ever smokers						
1	1	0.885 (0.650-1.205)	0.810 (0.665-0.987)	1	2.325 (0.242-22.359)	2.236 (0.309-16.204)
2	1	1.150 (0.844-1.566)	0.694 (0.570-0.845)	1	2.419 (0.250-23.477)	1.685 (0.233-12.206)
3	1	1.278 (0.936-1.745)	0.784 (0.627-0.979)	1	2.686 (0.268-26.965)	2.223 (0.253-19.571)
Nonsmokers						
1	1	0.945 (0.531-1.681)	1.227 (0.827-1.821)	1	0.547 (0.300-0.998)	0.640 (0.431-0.951)
2	1	1.222 (0.687-2.173)	0.987 (0.666-1.465)	1	0.620 (0.340-1.132)	0.484 (0.326-0.718)
3	1	1.366 (0.765-2.437)	1.028 (0.660-1.602)	1	0.590 (0.323-1.079)	0.498 (0.320-0.774)

Data are presented as hazard ratio (95% confidence interval).
[a]Model 1 is adjusted for age; model 2, adjusted for smoking status, residential area, alcohol consumption, and physical activity in addition to model 1; and model 3, adjusted for body mass index, systolic blood pressure, serum total cholesterol levels, serum alanine aminotransferase levels, blood glucose levels, hypertension history, and household income in addition to model 2.

lung cancer as two or more hospitalization primary diagnosis codes of lung cancer. This accounted for cases in which a single diagnostic code entry only reflected an exclusionary diagnosis. If the lung cancer code as a primary diagnosis has been recorded twice or more during hospital admission, it is more likely a lung cancer confirmed by biopsy or radiography. Fourth, we adjusted for socioeconomic status using residential area and monthly household income in the final Cox proportional-hazards model. Socioeconomic inequality is a potential risk factor for poor health outcomes and affects accessibility to health care. Fifth, further analyses were conducted after the entire population was stratified into ever smokers and nonsmokers because cigarette smoking is the most important risk factor of lung cancer. To minimize the carcinogenic effect of cigarette smoking, smoking status should be stratified.

Our study had some limitations. Several risk factors for lung cancer such as exposure to environmental carcinogens (eg, asbestos, radon, polycyclic aromatic hydrocarbons), radiation, secondhand smoke, and genetic/familial vulnerabilities could not be controlled for because the Korean NHIS-HEALS cohort does not include this information. Although we conservatively defined lung cancer as mentioned, misclassification was still possible. In addition, we could not reclassify lung cancer according to pathologic type. Further research is necessary to examine the relationship among metformin receipt, the presence of DM, and lung cancer incidence based on pathologic types and the stages of lung cancer through matching with the national cancer registry information of National Cancer Center.

Conclusion

Metformin did not reduce the incidence of lung cancer in the Korean diabetic population. However, women without DM was at a lower risk of lung cancer among the entire study population. Male ever smokers and female nonsmokers were at lower risk of lung cancer than diabetic subjects not receiving metformin.

Clinical Practice Points

- We investigated the association between metformin receipt and lung cancer risk using the Korean National Health Insurance Service data set.
- This study was retrospectively designed and included 336,168 individuals who were classified into metformin recipients with diabetes, metformin nonrecipients with diabetes, and individuals without diabetes (the nondiabetic group).
- The HRs (95% CIs) for lung cancer of metformin recipients and the nondiabetic group were 1.287 (0.979-1.691) and 0.835 (0.684-1.019) in men and 0.664 (0.374-1.177) and 0.553 (0.359-0.890) in women, respectively.
- The HRs (95% CIs) for lung cancer were 0.784 (0.627-0.979) for male ever smokers and 0.498 (0.320-0.774) for female nonsmokers.
- Individuals without diabetes were at a lower risk of lung cancer compared to diabetic patients who did not receive metformin; however, metformin therapy did not reduce the lung cancer risk in the diabetic population.

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Disclosure

The authors have stated that they have no conflict of interest.

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