ORIGINAL ARTICLE

The Associations of Aspirin, Statins, and Metformin With Lung Cancer Risk and Related Mortality: A Time-Dependent Analysis of Population-Based Nationally Representative Data

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ABSTRACT

Introduction: The aim of this study was to investigate the associations of aspirin, metformin, and statins with lung cancer risk and mortality using population-based nationwide cohort data.

Methods: This study included a total of 732,199 participants who underwent a national health check-up from 2002 to 2003. Lung cancer incidence and mortality were identified using a registered lung cancer diagnosis code (International Classification of Diseases, 10th revision, code C34) and the Korean National Death Registry. The study participants were followed up from January 1, 2004 to December 31, 2013. Medication exposure was defined by the cumulative duration of use and cumulative defined daily dose per 2-year interval. To avoid immortal-time bias, drug exposure was inserted as a time-dependent variable in Cox analysis, which evaluated the associations of these medications with lung cancer.

Results: Metformin use had a protective association with lung cancer incidence (p's for trend 0.008) and mortality (p's for trend < 0.001) in a dose-response fashion, and these associations were prominent among participants with a metformin cumulative defined daily dose of 547.5 and above compared with patients without diabetes. Lung cancer mortality was dose-dependently reduced with the use of aspirin (p's for trends 0.046) and statin (p's for trends < 0.001). The combined use of aspirin, statins, and metformin exhibited more prominent protective associations with lung cancer risk and mortality.

Conclusions: The use of aspirin, metformin, and statins had independent protective associations with lung cancer mortality, and metformin had an inverse association with lung cancer risk. Further studies are necessary to develop clinically applicable anticancer strategies using these drugs for the reduction of lung cancer and related mortality.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide.[1] Although lung cancer mortality and incidence have steadily decreased over the past 15 years, it still accounts for more than 20% of cancer-related deaths, and its incidence rate ranks fourth among all cancers in Korea.[2] The risk of lung cancer is mainly associated with tobacco consumption[3]; however, other factors such as aging,[4] genetic susceptibility,[5] air pollution,[6] and occupational exposure[7] are also linked to the development of lung cancer.

Aspirin, statins, and metformin are frequently used cardiovascular and diabetic medications in the clinical field. In addition to their therapeutic purposes in cardiovascular disease and diabetes, accumulating evidence indicates that aspirin,[8,9] statins,[10] and metformin[11] could have potential protective effects against multiple cancers. Some previous epidemiologic studies revealed that aspirin,[12–14] statins,[15,16] and metformin[11,17–19] were associated with a decreased risk of lung cancer, whereas other reports found differing results.[20–22] Furthermore, other studies, focusing on lung cancer mortality, reported that these medications have beneficial effects on lung cancer mortality and lung cancer incidence.[23–25]

However, previous studies have several methodological limitations. First, many studies separately investigated the impact of aspirin,[12–14,20] statins,[15] or metformin[11,17,18] on lung cancer incidence and mortality, although these drugs are concomitantly prescribed in the clinical field owing to their close interrelationship with cardiovascular disease, diabetes, and dyslipidemia.[26] If this concomitant use was not taken into account, the effect of those drugs could have overestimated the anticancer effects of these cardiovascular drugs. Second, many studies evaluated the use of aspirin, statins, and metformin as a dichotomous variable (yes or no) and did not evaluate the dose-response relationship,[20,25] whereas other studies did not use standard methods of drug exposure assessment.[12,13] Third, many studies did not appropriately reflect the time-dependent exposure of these drugs in the anticancer effects on lung cancer.[13,16,19,25] Fourth, some case-control studies also have selection or recall bias because of their study design.[15,16] Finally, to our knowledge, no study has evaluated aspirin, statins, and metformin use and their combined impact on lung incidence and mortality.

In this context, we investigated the association of aspirin, metformin, and statins with lung cancer risk and mortality using nationally representative, population-based cohort data. We also considered other confounders, and also the concomitant use and combination of these cardiovascular drugs in our analyses.

Materials and Methods

Data Source

The Korean National Health Insurance Services (NHIS) (KNHIS) database was used in this study. The KNHIS is a universal health care system that covers the entire Korean population (approximately 50 million). For this cohort study, three cohort data sets derived from KNHIS were pooled to increase statistical power: (1) the NHIS-Senior cohort, which comprised randomly selected Korean participants aged 60 years and older in 2002 (n = 558,147); (2) the NHIS–Health Screening Cohort, which comprised randomly selected Korean participants aged 40 to 79 years in 2002 who participated in a national health screening program between 2002 and 2003 (n = 514,866); and (3) the NHIS-National Sample Cohort (NHIS-NSC), which was composed of 2.2% of the total Korean population covered by the Korean national health insurance program in 2002 (n = 1,125,692). Detailed information on the cohort design and features of these databases are described in previous studies.[27,28]

Because a 2-year time interval was used to define medication exposure for time-dependent analysis, patients who died of any cause (n = 23,823) or had recorded for any cancer diagnosis (n = 55,529) before January 1, 2004 were excluded. In addition, individuals aged younger than 40 years and those 80 years and older from 2002 to 2003 (N = 522,945), and those who did not participate in the national health screening examination between 2002 and 2003 (N = 864,172) were excluded, leaving a total of 732,199 participants from the NHIS-Senior cohort, NHIS–Health Screening cohort, and NHIS-NSC data sets (Fig. 1).

Follow-Up and Cases

Lung cancer incidence and mortality were considered as primary outcomes. Lung cancer incidence was identified with the use of the registered lung cancer diagnosis code from the 10th revision of the International Classification of Diseases (ICD)-10 (code C34) and matched lung cancer treatments (surgical operation, radiation therapy, or use of chemotherapeutic or targeted agents) claimed in the KNHIS data. Data on lung cancer mortality were drawn from the Korean National Death Registry. The study participants were followed up from January 1, 2004 (the index date) to the date of lung cancer

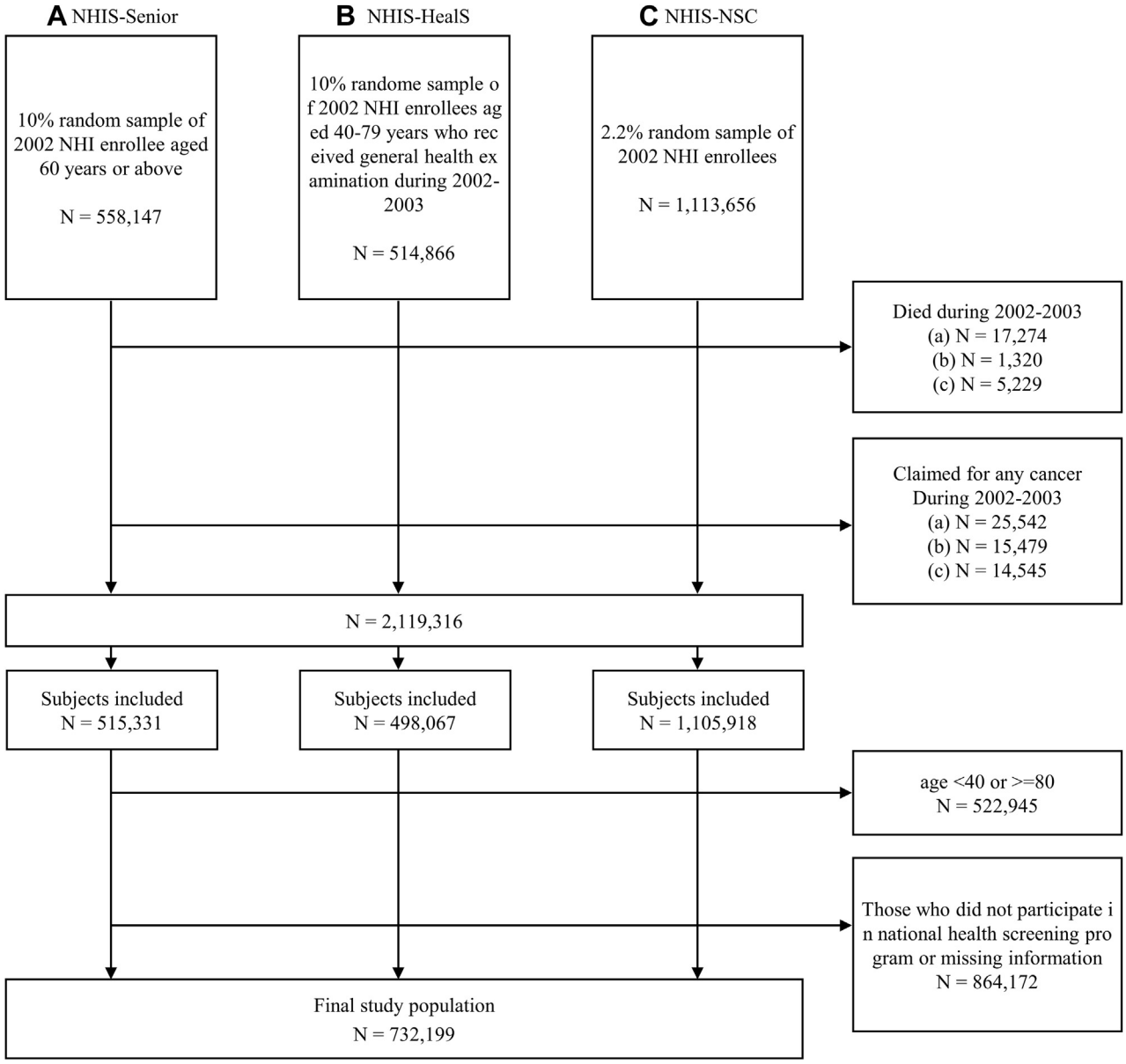

Figure 1. Flow diagram of study participants. The final pooled cohort includes the (*A*) NHIS-Senior cohort, (*B*) the NHIS-HealS cohort, and *(C)* the NHIS-NSC. HealS, Health Screening cohort; NHIS, National Health Insurance Service; NSC, National Sample Cohort.

diagnosis (incidence), lung cancer death (mortality), death from any other cause, or until December 31, 2013, whichever came first.

Exposure to Cardiovascular Drugs (Aspirin, Statin, and Metformin)

We analyzed the cumulative use of cardiovascular drugs within a 2-year latent period. To avoid immortal-time bias, cumulative use of these medications was inserted in the analysis as a time-dependent variable. We defined time-dependent exposure to aspirin, statins, and metformin as follows: (1) the cumulative duration of drug use was defined as the total number of days of drug exposure; and (2) the cumulative defined daily dose (cDDD). As a validated unit of drug use, the DDD is defined by WHO as "the assumed average maintenance dose per day for a drug used for its main indication in adults."[29] The cumulative duration and cDDD were calculated for each 2-year period, and participants were categorized into nonusers, less than 182.5, 182.5 to 365.0, 365.0 to 547.5, and 547.5 or more days or cDDD.

Covariates

Information on potential covariates was available using a datalink between the Korean national health insurance claims database and the national health

screening program data. Income was categorized into three groups on the basis of monthly insurance premiums because the premium is determined according to income levels. The comorbidity of participants was categorized into five groups on the basis of the Charlson comorbidity index (CCI).[30] Smoking status was categorized into nonsmokers, former smokers, and current smokers. Alcohol consumption was categorized into five groups on the basis of the amount of daily drinking.

Statistical Analysis

To compare the different baseline characteristics of study participants according to medication use (aspirin, statins, and metformin), the chi-square test for categorical variables (10-year age group, sex, income, smoking, and alcohol) and the Student's *t* test and analysis of variance for continuous variables (body mass index [BMI] and CCI) were used.

We used the Cox proportional hazards model, and cardiovascular drug exposure was entered in the analysis as a time-dependent variable. First, the individual effect of the cumulative dose of aspirin (by the number of days), statins, or metformin (by cDDD) on the incidence and mortality of lung cancer was evaluated in the analyses considering the concomitant use of other cardiovascular drugs. We adjusted for the following covariates to determine the independent associations of aspirin, statins, and metformin with lung cancer risk: (1) model 1 was adjusted for age and sex; and (2) model 2 was additionally adjusted for income, BMI, smoking status, alcohol consumption, CCI, age, and sex. Second, considering the important effect of smoking on lung cancer, stratified analyses by smoking status were performed to test the associations among aspirin, statins, and metformin use and lung cancer risk and mortality. The *p*'s for trend was calculated to evaluate the dose-response relationship. For metformin use, *p*'s for trend was calculated among patients with diabetes. In the additional sensitivity analysis, smoking status was inserted in the analysis as a time-dependent variable using the last observation carried forward to address change in smoking status over time.[31] Stratified analyses by sex were also performed.

To address the combined associations of these cardiovascular drugs with lung cancer risk and mortality, we also categorized exposure to aspirin, statins, and metformin into eight groups, accounting for possible combination use of these drugs. Different cutoff values for combination use of aspirin, statins, and metformin were serially applied from 0 (use versus nonuse), 182.5 days (higher versus lower or nonuse), 365 days, and 547.5 days to evaluate whether the association of combined use of these medications was augmented in a dose-dependent manner. In addition, we investigated the associations of the combined use of these cardiovascular medications on lung cancer risk and mortality according to smoking status.

A comparison of aspirin, statin, and metformin use and the treatment types of lung cancer was conducted to evaluate whether the treatment types of lung cancer (i.e., a proxy for lung cancer stage information) might affect the lung cancer mortality related to these cardiovascular drugs use. We categorized lung cancer treatment into five groups of surgical procedure only, surgical procedure plus radiotherapy or chemotherapy, radiotherapy plus chemotherapy, radiotherapy only, and chemotherapy only. Although we cannot distinguish the purpose of therapy from the claims data alone, we expect such a treatment pattern to largely reflect the extent of disease. All statistical analyses were conducted using STATA version 14.1 (StataCorp, College Station, TX), and two-tailed *p* values less than 0.05 were considered statistically significant.

Results

Baseline Characteristics and Concomitant Use of Cardiovascular Drugs

The numbers of ever-users of aspirin and statins were 66,024 (9.0%), and 37,031 (5.1%), respectively. Among the total patient group, 46,205 patients (6.3%) had type 2 diabetes, and 25,791 of these patients (55.8%) were ever-users of metformin (Table 1).

The number of cardiovascular drug users continuously increased over time, and a small proportion of aspirin, statin, and metformin users took these drugs for a long time or exhibited a high cDDD (Table 2).

Cardiovascular Drug Use and Lung Cancer Risk and Mortality

A total of 5990 lung cancer cases and 5938 deaths from lung cancer were observed over the follow-up years. The ever-use of aspirin was not substantially associated with lung cancer incidence and mortality. When analyzed by the cumulative number of days, aspirin use was not associated with lung cancer incidence, but it exhibited a dose-response relationship with lung cancer mortality (*p*'s for trends 0.073), with a significantly reduced incidence in participants who used aspirin from 547.5 to 730.0 days (adjusted hazard ratio [aHR]: 0.87, 95% confidence interval [CI]: 0.78–0.97).

The ever-use and cDDD of statins were not associated with reduced lung cancer incidence. However, lung cancer mortality was reduced in a dose-dependent fashion as the cDDD of statin use increased (p's for trends 0.004). Participants with cDDD of statin greater than or equal to 547.5 (aHR: 0.77, 95% CI: 0.59–0.99) exhibited decreased lung cancer mortality.

Table 1. Baseline Characteristics of the Study Population Classified by History of Cardiovascular Drug Use During 2002 to 2003

		Aspirin			Statins			Metformin			
Characteristic	Total	Never-User	Ever-User	*p* Value[a]	Never-User	Ever- User	*p* Value[a]	Non-DM	Never-User	Ever-User	*p* Value[a]
N	732,199 (100)	666,175 (91.0)	66,024 (9.0)		695,168 (94.9)	37,031 (5.1)		685,994 (93.7)	20,414 (2.8)	25,791 (3.5)	
Age, y, n (%)				<0.001			<0.001				<0.001
40–49	282,990 (38.6)	275,043 (41.3)	7947 (12.0)		276,206 (39.7)	6784 (18.3)		275,876 (40.2)	3144 (15.4)	3970 (15.4)	
50–59	170,780 (23.3)	157,177 (23.6)	13,603 (20.6)		161,069 (23.2)	9711 (26.2)		160,263 (23.4)	4582 (22.5)	5935 (23.0)	
60–69	213,534 (29.2)	181,802 (27.3)	31,732 (29.2)		197,274 (28.4)	16,260 (43.9)		191,845 (28.0)	9495 (46.5)	12,194 (47.3)	
70–79	54,895 (8.9)	52,153 (7.8)	64,895 (8.9)		60,619 (8.7)	4276 (11.6)		58,010 (8.4)	3193 (15.6)	3692 (14.3)	
Sex, n (%)				<0.001			<0.001				<0.001
Male	388,760 (53.1)	356,044 (53.5)	32,716 (49.6)		372,789 (53.6)	15,971 (43.1)		363,816 (53.0)	11,545 (56.6)	13,999 (51.9)	
Female	343,439 (46.9)	310,131 (46.6)	333,308 (50.5)		322,379 (46.4)	21,060 (56.9)		322,178 (47.0)	8869 (43.4)	12,392 (48.1)	
BMI, kg/m^2, mean (SD)	22.0 (6.8)	21.8 (6.9)	24.3 (4.7)	<0.001	21.9 (6.9)	24.6 (4.6)	<0.001	21.9 (6.9)	24.2 (4.7)	24.2 (4.7)	<0.001
Income, n (%)				<0.001			<0.001				<0.001
Rank 1–3 and Medicaid (low)	320,556 (43.8)	291,481 (43.8)	29,075 (44.0)		303,257 (43.6)	17,299 (46.7)		300,781 (43.8)	8939 (43.8)	10,836 (42.0)	
Rank 4–6	184,928 (25.3)	168,941 (25.4)	15,987 (24.2)		175,892 (25.3)	9036 (24.4)		173,332 (25.3)	5068 (24.8)	6538 (25.4)	
Rank 7–10 (high)	226,715 (30.9)	205,753 (30.9)	20,962 (31.8)		216,019 (31.1)	10,696 (28.9)		221,891 (20.9)	6407 (31.4)	8417 (32.6)	
CCI score, mean (SD)	0.7 (0.9)	0.6 (0.9)	1.5 (1.2)	<0.001	0.7 (0.9)	1.5 (1.2)	<0.001	0.6 (0.8)	1.7 (1.3)	1.9 (1.3)	<0.001
0	366,556 (50.1)	351,748 (52.8)	14,808 (22.4)		358,860 (51.6)	7696 (20.8)		359,115 (52.3)	3707 (18.1)	3734 (14.5)	
1–2	328,245 (44.8)	288,843 (43.4)	39,402 (59.7)		305,473 (43.9)	22,772 (61.5)		303,269 (44.2)	11,368 (55.7)	13,608 (52.8)	
3–4	34,918 (4.8)	24,274 (3.6)	10,644 (16.1)		28,970 (4.2)	5948 (16.1)		22,484 (3.3)	4794 (34.5)	7640 (29.6)	
≥ 5	2480 (0.3)	1310 (0.2)	1,170 (1.8)		1867 (0.3)	615 (1.7)		1,126 (0.2)	545 (2.7)	809 (3.1)	
Smoking status, n (%)				<0.001			<0.001				<0.001
Never	515,100 (70.3)	464,852 (69.8)	50,248 (76.1)		486,674 (70.0)	28,426 (76.8)		481,727 (70.2)	14,670 (71.9)	18,703 (72.5)	
Former	55,445 (7.6)	50,042 (7.5)	5403 (8.2)		52,540 (7.6)	2905 (7.8)		51,786 (7.6)	1735 (8.5)	1924 (7.5)	
Current	161,654 (22.1)	151,281 (22.7)	10,373 (15.7)		155,954 (22.4)	5700 (15.4)		152,481 (22.2)	4009 (19.6)	5164 (20.0)	
Alcohol, g/d, n (%)				<0.001			<0.001				<0.001
0–10	592,119 (80.9)	535,471 (80.4)	56,648 (85.8)		560,211 (80.6)	31,908 (86.2)		553,338 (80.7)	16,952 (83.0)	21,829 (84.6)	
10–20	76,703 (10.5)	71,665 (10.8)	5038 (7.6)		73,906 (10.6)	2797 (7.6)		72,920 (10.6)	1757 (8.6)	2026 (7.9)	
20–30	5648 (0.8)	5,315 (0.8)	333 (0.5)		5428 (0.8)	220 (0.6)		5286 (0.8)	156 (0.8)	206 (0.8)	
30–40	23,634 (3.2)	22,007 (3.3)	1627 (2.5)		22,785 (3.3)	849 (2.3)		22,366 (3.3)	604 (3.0)	664 (2.6)	
≥40	34,095 (4.7)	31,717 (4.8)	2378 (3.6)		32,838 (4.7)	1257 (3.4)		32,084 (4.7)	945 (4.6)	1066 (4.1)	

[a]Categorical variables were compared using the chi-square test and continuous variables were compared using Student's *t* test (aspirin or statin) or ANOVA (metformin).
ANOVA, analysis of variance; BMI, body mass index; CCI, Charlson comorbidity index; DM, diabetes mellitus.

Table 2. Use of Cardiovascular Drugs Among Study Participants

Use of Cardiovascular Drugs	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011
N	732,199	732,199	723,588	712,029	698,725
Aspirin					
Ever-use	66,024	104,852	125,704	120,441	157,900
Duration of medication use, d (per 2 y), n (%)					
<182.5	35,144 (53.2)	43,953 (41.9)	42,962 (34.2)	38,218 (31.7)	41,291 (26.2)
182.5-365.0	11,812 (17.9)	16,795 (16.0)	28,689 (22.8)	14,490 (12.0)	18,305 (11.6)
365.0-547.5	7,841 (11.9)	14,100 (13.5)	16,424 (13.1)	14,379 (11.9)	19,331 (12.2)
≥547.5	11,227 (17.0)	30,004 (28.6)	37,629 (29.9)	53,354 (44.3)	78,973 (50.0)
Statins					
Ever-use	37,031	61,347	86,485	102,275	154,949
cDDD of statin use (per 2 y), n (%)					
<182.5	31,519 (85.1)	43,842 (71.5)	52,849 (61.1)	53,163 (51.9)	66,010 (42.6)
182.5-365.0	4,566 (12.3)	12,015 (19.6)	19,889 (23.0)	23,390 (22.9)	45,773 (29.5)
365.0-547.5	830 (2.2)	3628 (5.9)	8171 (9.4)	11,956 (11.7)	18,486 (11.9)
≥547.5	116 (0.3)	1862 (3.0)	5576 (6.5)	13,766 (13.5)	24,680 (15.9)
Metformin					
Never-use among patients with DM	20,414	23,739	24,690	21,009	18,760
Ever-use	25,791	38,275	48,016	53,676	80,607
cDDD of metformin use (per 2 y), n (%)					
<182.5	17,863 (69.3)	22,982 (60.0)	28,658 (59.7)	27,328 (50.9)	37,532 (46.6)
182.5-365.0	5,826 (22.6)	10,068 (26.3)	11,968 (24.9)	12,985 (24.2)	21,849 (27.1)
365.0-547.5	1615 (6.3)	3214 (8.4)	3583 (7.5)	4473 (8.3)	7746 (9.6)
≥547.5	487 (1.9)	2011 (5.3)	3807 (7.9)	8890 (16.6)	13,480 (16.7)

cDDD, cumulative defined daily dose; DM, diabetes mellitus.

Compared with participants having no diabetes, the ever-users of metformin exhibited a reduced incidence of lung cancer (aHR: 0.89, 95% CI: 0.81–0.98). Patients with diabetes having a cDDD of metformin greater than or equal to 547.5 exhibited a decreased lung cancer incidence (aHR: 0.44, 95% CI: 0.29–0.66) and mortality (aHR: 0.76, 95% CI: 0.54–1.09), compared with participants with no diabetes. In the analysis of patients with diabetes only, the cDDD of metformin use had a dose-dependent relationship with lung cancer incidence (p's for trends 0.007) and lung cancer mortality (p's for trends < 0.001) (Table 3).

Association of Cardiovascular Drug Use and Lung Cancer Risk and Mortality Stratified by Smoking Status and Sex

In the stratified analyses by smoking status and sex, the strength of association was slightly different according to cardiovascular drugs; however, the direction of associations was similar to the overall analysis. The strength of association with metformin in relation to lung cancer mortality was more prominent in the nonsmoking group (aHR: 0.41, 95% CI: 0.22-0.77 in the group with ≥ 547.5 cDDD) and in women (aHR: 0.19, 95% CI: 0.05–0.75 in the group with ≥547.5 cDDD), compared with the analysis of the overall participants. When we considered smoking status as a time-dependent variable in the analyses, the results were consistent with those of the main analysis (Table 4 and Supplementary Tables 1 and 2).

The Combined Use of Cardiovascular Drugs and Lung Cancer Risk and Mortality

The combined use of aspirin, statin, and metformin was associated with decreased lung cancer incidence (aHR: 0.83, 95% CI; 0.69–0.99) and mortality (aHR: 0.83, 95% CI; 0.70–0.99) compared with nonusers. These inverse associations increased consistently as the duration of cardiovascular medication exposure increased; thus, participants who used aspirin, statin, and metformin in combination greater than or equal to 547.5 days exhibited the lowest risk for lung cancer (aHR: 0.49, 95% CI: 0.33–0.73) and associated mortality (aHR: 0.42, 95% CI: 0.22–0.81). Although the combined use of aspirin and statin (aHR: 1.12, 95% CI: 1.00–1.24), aspirin and metformin (aHR: 1.17, 95% CI: 1.00–1.37), and statin and metformin (aHR: 1.26, 95% CI: 1.01–1.58) wase associated with slightly higher lung cancer mortality when any

Table 3. Cardiovascular Drug Use and Lung Cancer Incidence and Mortality Considering the Concomitant Use of Aspirin, Metformin, or Statin

Use of Cardiovascular Drugs	Incidence			Mortality		
	Crude HR	aHR 1 (95% CI)	aHR 2 (95% CI)	Crude HR	aHR 1 (95% CI)	aHR 2 (95% CI)
Case, N (%)		5990 (0.8)			5938 (0.8)	
Incidence rates, per 1000,000 PY		0.4			0.41	
Aspirin						
Never-use	1.00	1.00	1.00	1.00	1.00	1.00
Ever-use	1.37 (1.27-1.47)	0.97 (0.90-1.04)	0.99 (0.92-1.06)	1.62 (1.52-1.73)	0.99 (0.93-1.05)	1.03 (0.97-1.10)
Duration of aspirin use, d						
<182.5	1.37 (1.24-1.52)	1.01 (0.91-1.12)	1.01 (0.91-1.12)	1.84 (1.68-2.01)	1.16 (1.06-1.27)	1.17 (1.07-1.28)
182.5-365.0	1.39 (1.20-1.62)	0.97 (0.83-1.12)	0.99 (0.86-1.15)	1.62 (1.42-1.86)	0.98 (0.85-1.12)	1.03 (0.90-1.18)
365.0-547.5	1.48 (1.26-1.73)	1.05 (0.90-1.23)	1.08 (0.92-1.27)	1.59 (1.36-1.85)	1.01 (0.86-1.17)	1.06 (0.91-1.23)
≥547.5	1.29 (1.16-1.44)	0.91 (0.82-1.02)	0.95 (0.86-1.06)	1.28 (1.15-1.43)	**0.81 (0.73-0.90)**	**0.87 (0.78-0.97)**
p trend	<0.001	0.18	0.608	<0.001	0.001	0.073
Statins						
Never-use	1.00	1.00	1.00	1.00	1.00	1.00
Ever-use	0.95 (0.87-1.02)	1.06 (0.98-1.15)	1.07 (0.98-1.16)	0.79 (0.73-0.86)	0.97 (0.89-1.05)	0.98 (0.91-1.07)
cDDD of statin use						
<182.5	0.95 (0.86-1.05)	1.08 (0.98-1.20)	1.08 (0.98-1.20)	0.90 (0.82-0.99)	1.11 (1.01-1.22)	1.12 (1.02-1.24)
182.5-365.0	0.96 (0.83-1.11)	1.08 (0.94-1.25)	1.09 (0.95-1.26)	0.66 (0.57-0.77)	**0.81 (0.70-0.95)**	**0.84 (0.72-0.98)**
365.0-547.5	0.99 (0.81-1.23)	1.00 (0.89-1.36)	1.10 (0.89-1.36)	0.70 (0.56-0.87)	0.84 (0.67-1.05)	0.86 (0.68-1.08)
≥547.5	0.96 (0.75-1.24)	1.07 (0.84-1.37)	1.06 (0.83-1.35)	0.62 (0.47-0.81)	**0.77 (0.59-0.99)**	**0.77 (0.59-0.99)**
p trend	0.041	0.348	0.44	<0.001	0.004	0.004
Metformin						
Non-DM	1.00	1.00	1.00	1.00	1.00	1.00
DM, metformin never-use (use of other hypoglycemic drugs only)	1.20 (1.04-1.38)	0.89 (0.77-1.02)	0.88 (0.77-1.02)	2.07 (1.85-2.31)	1.41 (1.26-1.57)	1.43 (1.28-1.60)
Ever-use cDDD of metformin use	1.05 (0.95-1.16)	0.92 (0.84-1.01)	0.89 (0.81-0.98)	1.27 (1.16-1.39)	1.11 (1.01-1.21)	1.07 (0.98-1.18)
<182.5	1.05 (0.93-1.20)	**0.88 (0.77-0.99)**	**0.85 (0.75-0.97)**	1.52 (1.36-1.70)	1.22 (1.09-1.36)	1.21 (1.08-1.35)
182.5-365.0	1.32 (1.12-1.55)	1.11 (0.94-1.31)	1.07 (0.90-1.26)	1.37 (1.17-1.62)	1.13 (0.96-1.33)	1.10 (0.94-1.30)
365.0-547.5	1.27 (0.96-1.68)	1.08 (0.81-1.42)	1.02 (0.77-1.35)	1.54 (1.18-2.00)	1.30 (0.99-1.69)	1.25 (0.96-1.63)
≥547.5	0.41 (0.27-0.62)	**0.46 (0.31-0.70)**	**0.44 (0.29-0.66)**	0.76 (0.53-1.10)	0.84 (0.59-1.20)[a]	0.76 (0.54-1.09)[a]
p trend[b]	0.027	0.023	0.007	<0.001	<0.001	<0.001

Note: The aHR 1 for each drug exposure was adjusted for age, sex, income, BMI, smoking, and alcohol consumption. The CCI aHR 2 for each drug was adjusted for age, sex, income, BMI, smoking, alcohol consumption, CCI, and other medication use (e.g., aspirin use was adjusted for statin use and metformin use).
[a]Significantly different compared with patients with diabetes who did not use metformin.
[b]The *p* trend was calculated among patients with diabetes only, using patients with diabetes who did not use metformin (i.e., using drugs other than metformin only) as reference.
aHR, adjusted hazard ratio; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; cDDD, cumulative defined daily dose; DM, diabetes mellitus; PY, person-year.

use was considered, these associations disappeared or even reversed when the cutoff for the duration of medication use was 182.5 days or higher (Table 5). In the analysis stratified by smoking status, the inverse association between combined use of all three medications and lung cancer risk and mortality was similar in nonsmokers and current smokers (Supplementary Table 3).

Association Between General Characteristics and Lung Cancer Risk and Mortality

Whereas age and smoking status were linearly associated with higher lung cancer risk and mortality (*p*'s for trends < 0.001 for both), the CCI score was only associated with higher mortality from lung cancer (*p*'s for trends < 0.001). Women exhibited lower lung cancer risk (aHR: 0.39, 95% CI: 0.36–0.42) and mortality (aHR:

0308, 95% CI: 0.28–0.32). BMI was inversely associated with the development of lung cancer (aHR: 0.99, 95% CI: 0.98–1.00) and mortality (aHR: 0.98, 95% CI: 0.98–0.99). Alcohol consumption was related to neither incidence nor mortality (Supplementary Table 4).

Comparison of Aspirin, Statin, and Metformin Use and Treatment Types of Lung Cancer

Whereas participants who used all three cardiovascular drugs were most likely to receive only surgergical procedure (66.7% versus 66.9, 73.1% in other groups), the difference was not that large (Supplementary Table 5).

Discussion

We reported that metformin use had protective associations with lung cancer incidence and mortality after adjustment for multiple covariates, which were more prominent among women and the nonsmoking participants. Moreover, the use of aspirin and statins also exhibited a benefit for lung cancer mortality, although the incidence of lung cancer was not affected by the use of these drugs. When these cardiovascular drugs were used in combination, their protective associations with lung cancer risk and related mortality were augmented, and the magnitude of effect increased with the increasing duration of medication use.

The major strengths of this study are as follows: (1) the evaluation of the individual and combined associations of aspirin, statin, and metformin with lung cancer incidence and mortality considering concomitant use; (2) a large sample size with sufficient statistical power and representativeness in a region where lung cancer incidence is high; (3) robust adjustment was performed for potential confounding factors related to lung cancer; (4) a reliable prescription data gathered through a single, compulsory universal insurance system with high reliability; and (5) the use of time-dependent analysis to ensure the measurement of drug exposure before cancer diagnosis.

This study suggested that aspirin use did not decrease lung cancer incidence but was associated with reduced mortality. Although a few studies reported aspirin's protective role in lung cancer incidence,[12,14] two large prospective cohort studies, the Nurses' Health Study and the Health Professionals Follow-up Study, found no association between aspirin use and the incidence of lung cancer regardless of sex, and these findings are consistent with our study results.[9,20] Recent meta-analyses also confirmed that aspirin had no significant protective effect on lung cancer incidence.[32] In contrast, our study exhibited that aspirin use was associated with lung cancer mortality in a dose-response manner, with an approximate reduction of 15% in cases who continuously used aspirin greater than or equal to 547.5 days within a 2-year interval. This is consistent with the result of meta-analyses of individually randomized trials, which reported that the long-term use of aspirin was associated with a reduced lung cancer mortality.[8] Previous studies consistently exhibited improved lung cancer survival in long-term aspirin users.[8,25] The inhibition of cyclooxygenase to maintain low inflammatory states[33] and the decreased risk for regional lymph nodes[34] were suggested as potential mechanisms of such survival gain. Therefore, although aspirin itself does not reduce lung cancer incidence, it may improve the prognosis of incident lung cancer, leading to decreased population-level mortality.

Multiple previous studies on the associations between statins and lung cancer risk have reported conflicting results. Whereas some studies reported an inverse association between statin intake and lung cancer incidence,[15,16] most studies and meta-analyses reported no significant protective effects of statin use on lung cancer risk,[10,21,22,35,36] and these results are similar with our study findings. In contrast, statin use was associated with decreasing lung cancer mortality in a dose-response manner, and this result is supported by previous studies illustrating the protective associations of statins with lung cancer prognosis.[24,37]

Although diabetes is considered as a risk factor for lung cancer,[38] our study did not find an increased risk for lung cancer among patients with diabetes compared with those without diabetes. However, consistent metformin users in our study (cDDD of metformin $>$547.5 for 2 years) had a lower risk for lung cancer compared with those without diabetes, consistent with a recent meta-analysis, which reported that metformin use reduced the risk for lung cancer by 11%.[17] Moreover, previous cohort studies reporting the protective effect of metformin against lung cancer support our study results.[18,19] Although our study exhibited a statistically prominent dose-dependent relationship between metformin use and lung cancer incidence, the protective associations of metformin were prominent in cDDD of metformin greater than or equal to 547.5 within 2 years, and this result seems to support a threshold to produce the anticancer effects of metformin. An earlier study from Taiwan also reported that the risk for lung cancer was linearly reduced as cDDD of metformin increased; however, significant protective associations were observed in participants with cDDD greater than or equal to 365.[18]

With respect to lung cancer mortality, diabetes had a negative impact on lung cancer mortality, and this association was prominent among patients with diabetes with regard to nonmetformin use or low cDDD of metformin use ($<$182.5). However, among patients with

Table 4. Cardiovascular Drug Use and Lung Cancer Risk and Mortality Stratified by Smoking Status

Use of Cardiovascular Drugs	Incidence			Mortality		
	Never	Former	Current	Never	Former	Current
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Case, N (%)	2,763 (0.5)	521 (0.9)	2,706 (1.7)	2,520 (0.5)	558 (1.0)	2,860 (1.8)
Incidence rates, per 1000,000 PY	0.3	0.5	0.9	0.3	0.5	0.9
Aspirin						
Never-use	1.00	1.00	1.00	1.00	1.00	1.00
Ever-use	0.99 (0.91-1.10)	0.93 (0.75-1.15)	1.00 (0.91-1.11)	0.98 (0.89-1.08)	1.09 (0.91-1.33)	1.07 (0.97-1.17)
Duration of aspirin use, d						
<182.5	1.00 (0.86-1.16)	1.15 (0.84-1.56)	0.98 (0.84-1.15)	1.09 (0.94-1.25)	1.37 (1.05-1.79)	1.32 (1.17-1.49)
182.5-365.0	1.15 (0.95-1.40)	0.73 (0.43-1.24)	0.85 (0.67-1.09)	1.11 (0.92-1.35)	0.89 (0.56-1.42)	1.02 (0.83-1.25)
365.0-547.5	0.97 (0.76-1.22)	1.04 (0.63-1.72)	1.25 (1.00-1.56)	1.03 (0.82-1.29)	1.39 (0.92-2.11)	1.03 (0.82-1.29)
≥547.5	0.94 (0.81-1.08)	0.79 (0.56-1.11)	0.99 (0.86-1.16)	**0.83 (0.71-0.96)**	0.85 (0.62-1.16)	**0.86 (0.74-1.00)**
p trend	0.587	0.197	0.747	0.081	0.749	0.317
Statins						
Never-use	1.00	1.00	1.00	1.00	1.00	1.00
Ever-use	1.04 (0.93-1.16)	1.01 (0.78-1.31)	1.06 (0.95-1.19)	1.03 (0.92-1.15)	0.99 (0.78-1.28)	0.99 (0.88-1.11)
cDDD of statin use						
<182.5	1.07 (0.93-1.23)	1.11 (0.80-1.54)	1.05 (0.90-1.22)	1.26 (1.10-1.44)	1.04 (0.75-1.44)	1.14 (0.99-1.32)
182.5-365.0	1.03 (0.84-1.26)	0.84 (0.50-1.41)	1.19 (0.96-1.46)	0.87 (0.70-1.08)	0.68 (0.39-1.17)	0.89 (0.71-1.11)
365.0-547.5	1.20 (0.91-1.59)	0.52 (0.19-1.40)	1.06 (0.76-1.47)	0.74 (0.52-1.06)	1.36 (0.77-2.43)	0.90 (0.64-1.25)
≥547.5	0.70 (0.49-1.01)	1.43 (0.76-2.70)	0.90 (0.65-1.25)	**0.63 (0.43-0.92)**	1.20 (0.64-2.26)	**0.64 (0.45-0.91)**
p trend	0.829	0.971	0.57	0.051	0.77	0.056
Metformin						
Non-DM	1.00	1.00	1.00	1.00	1.00	1.00
DM, metformin never-use (use of other drugs only)	0.87 (0.71-1.07)	0.53 (0.30-0.93)	1.01 (0.83-1.23)	1.37 (1.16-1.63)	1.09 (0.74-1.60)	1.55 (1.32-1.82)
Ever-use	0.86 (0.74-0.99)	0.98 (0.71-1.34)	0.93 (0.81-1.07)	1.05 (0.92-1.19)	1.17 (0.89-1.54)	1.09 (0.96-1.23)
cDDD of metformin use						
<182.5	0.89 (0.74-1.08)	0.69 (0.43-1.11)	0.88 (0.73-1.06)	1.23 (1.04-1.45)	1.22 (0.85-1.73)	1.19 (1.02-1.41)
182.5-365.0	0.96 (0.74-1.24)	1.42 (0.88-2.29)	1.15 (0.91-1.45)	1.01 (0.78-1.31)	1.23 (0.75-2.01)	1.09 (0.86-1.37)
365.0-547.5	0.81 (0.50-1.31)	1.26 (0.52-3.01)	1.21 (0.83-1.76)	1.11 (0.73-1.69)	1.21 (0.49-2.93)	1.26 (0.88-1.82)
≥547.5	**0.39 (0.21-0.73)**	0.78 (0.25-2.45)	**0.44 (0.25-0.78)**	**0.41 (0.22-0.77)**	0.71 (0.23-2.21)	**0.75 (0.49-1.14)**[a]
p trend[b]	0.014	0.063	0.581	0.009	0.57	<0.001

Note: The aHR for each drug was adjusted for age, sex, income, BMI, smoking, alcohol consumption, and CCI.
[a]Significantly different compared with patients with diabetes who did not use metformin.
[b]The *p* for trend was calculated among patient with diabetes only, using patients with diabetes who do not use metformin (i.e., using drugs other than metformin only) as reference.
aHR, adjusted hazard ratio; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; cDDD, cumulative defined daily dose; PY, person-year.

diabetes, a higher cDDD of metformin use was associated with reduced lung cancer mortality. Whether metformin has a threshold effect or dose-response effect on lung cancer risk is unclear. Even in the present study, metformin seems to have a threshold effect on lung cancer incidence, although the use of metformin exerts a protective impact on the survival of patients with lung cancer in a dose-response manner. This result was in line with a US military study, which reported that metformin use conferred beneficial effects on lung cancer survival in a dose-response manner.[39] Furthermore, although a dose-response relationship was not explored, results from multiple previous studies also, at least partly, support the anticancer associations of metformin with lung cancer survival.[40,41] More prominent protective associations of metformin use with lung cancer mortality were observed in women and nonsmokers. Although an interactive effect of sex and smoking with metformin on lung cancer risk was not apparent, the relatively prevalent adenocarcinoma among women and nonsmokers might be related to these findings. In a recent randomized control trial, compared with the

Table 5. The Combined Use of Cardiovascular Drugs and Lung Cancer Risk and Mortality

	aHR (95% CI)							
	Incidence				Mortality			
Drug Use (d)[a]	0 (Any Use)	≥182.5	≥365	≥547.5	0 (Any Use)	≥182.5	≥365	≥547.5
Nonusers	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Aspirin-only	0.99	0.96	0.97	0.96	1.04	0.96	0.92	0.93
95% CI	(0.91-1.08)	(0.87-1.06)	(0.87-1.08)	(0.85-1.08)	(0.96-1.13)	(0.87- 1.05)	(0.83-1.02)	(0.81-1.05)
Statin-only	1.12	1.01	1.12	1.16	0.98	0.82	0.70	0.78
95% CI	(0.99-1.26)	(0.87-1.19)	(0.94-1.34)	(0.95-1.42)	(0.86-1.12)	(0.69-0.97)	(0.57-0.87)	(0.54-1.12)
Metformin-only	0.92	0.91	0.98	0.98	1.19	1.16	1.17	1.08
95% CI	(0.79-1.07)	(0.78-1.07)	(0.82-1.16)	(0.81-1.19)	(1.04-1.36)	(1.01-1.33)	(1.00-1.36)	(0.87-1.35)
Aspirin + statin	1.08	1.16	1.19	1.11	1.12	0.93	0.91	0.95
95% CI	(0.96-1.21)	(1.00-1.33)	(1.01-1.41)	(0.90-1.37)	(1.00-1.24)	(0.80-1.08)	(0.76-1.09)	(0.71-1.28)
Aspirin + metformin	0.98	0.91	1.08	1.05	1.17	1.01	0.95	0.93
95% CI	(0.82-1.17)	(0.73-1.14)	(0.85-1.37)	(0.79-1.40)	(1.00-1.37)	(0.83-1.23)	(0.75-1.20)	(0.63-1.36)
Statin + metformin	0.94	0.92	1.03	0.88	1.26	1.02	1.12	0.63
95% CI	(0.73-1.21)	(0.68-1.26)	(0.72-1.47)	(0.55-1.39)	(1.01-1.58)	(0.76-1.37)	(0.80-1.56)	(0.24-1.68)
Aspirin + statin + metformin	0.83	0.75	0.57	0.49	0.83	0.53	0.46	0.42
95% CI	(0.69-0.99)	(0.58-0.96)	(0.41-0.79)	(0.32-0.73)	(0.69-0.99)	(0.40-0.70)	(0.32-0.65)	(0.22-0.81)

Note: HRs were adjusted for age, sex, income, BMI, smoking, alcohol consumption, and CCI.
[a]Cumulative duration of drug exposure per 2 years.
aHR, adjusted hazard ratio; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval.

tyrosine kinase inhibitor (TKI)–only group, metformin plus TKI improved the median progression-free survival and overall survival by 4.2 months and 14.2 months, respectively, in pulmonary adenocarcinoma with *EGFR* gene mutation.[42] Because *EGFR* gene mutation is prevalent in Asian patients with pulmonary adenocarcinoma (30%–60%),[43] the favorable prognosis of the metformin plus TKI group could be attributed to the additional anticancer effects of metformin with tyrosine kinase inhibition of lung adenocarcinoma with *EGFR* mutation. However, further research is warranted to determine whether any interactive effects between metformin and smoking status and sex exist.

Interestingly, the inverse association of the combined use of aspirin, statin, and metformin was prominent, and the longer the duration of combined use, the more protective the association was. This finding is in line with a study exhibiting that aspirin and metformin synergistically inhibit lung cancer cell proliferation by activating adenosine monophosphate–activated protein kinase, which plays a critical role in the regulation of lipogenesis in cancer cells.[44] It can reasonably be hypothesized that the concomitant use of aspirin, statin, and metformin concurrently inhibit multiple pathways related to lung cancer cell growth and proliferation,[42,44,45] resulting in favorable associations with lung cancer risk and mortality. Although literature regarding the association of the combined use of aspirin, statin, and metformin with lung cancer is sparse, a clinical study from Germany exhibited that participants who jointly used aspirin and statins for 5 years were at a decreased risk for colorectal cancer (adjusted OR [aOR]: 0.38, 95% CI: 0.15–0.97), and had more favorable outcomes than the aspirin-only (aOR: 0.63, 95% CI: 0.37–1.07) or statin-only (aOR: 0.87, 95% CI: 0.40–1.87) groups.[46] These findings, at least in part, support the synergistic anticancer effects of aspirin and statin combination use. The stronger protective associations observed among users of all three drugs need to be replicated and confirmed in independent prospective cohorts or randomized control trials.

In our stratified analyses by smoking status, the direction of the association between aspirin, statin, and metformin use and lung cancer mortality was consistent across smoking status, and the protective association of metformin and lung cancer incidence was statistically significant regardless of smoking group (all $p < 0.05$). In addition, the combined use of these cardiovascular medications consistently exhibited an inverse association with lung cancer risk and mortality in never smokers and current smokers. Considering consistent findings among never smokers and current smokers, we assume that the association between cardiovascular medication and the risk of lung cancer would not be much different because of the confounding effect of

smoking status. However, our study should not be interpreted to say that smokers can protect themselves by taking these drugs, as smoking itself is associated with greater than three times higher lung cancer incidence and mortality in our study.

Several limitations of this study should be noted. First, because this study used administrative data, detailed clinical information on the lung cancer stage, histological feature, *EGFR* mutation, cancer treatments, and other lung cancer risk factors such as family history and environmental toxins (asbestos, etc.) were unable to be included in the analysis. Therefore, caution is necessary when interpreting the study findings because the abovementioned factors that might affect lung cancer incidence and mortality were not included in the analyses. Second, although we adjusted for smoking status as a confounding factor in the analyses, residual confounding effects of smoking on lung cancer risk and mortality might exist because the dose of cigarettes, second-hand smoke, and misclassification of smoking status was not fully addressed.[47] A stronger association of aspirin, statin, and metformin use with lung cancer risk and mortality might have been observed if we analyzed more detailed information on the pack-years of ex- and current smokers, which was not available in our study. Nevertheless, the consistent protective associations of these cardiovascular medications and lung cancer risk and mortality found in our analyses stratified by smoking status implied that observed associations were robust, and confounding effects of smoking were not likely to affect the study results. Third, lung cancer incidence might have been underestimated because we identified lung cancer on the basis of disease code and reimbursement data, and cases that were very old and did not receive any treatment would not have been captured. Because such patients are also not likely to have cardiovascular prevention, this will lead to an underestimation of lung cancer incidence in cardiovascular drug nonusers. Systemic bias is then likely to happen toward a null association rather than producing a false-positive association. Fourth, because low-dose aspirin can be sold as an over-the-counter drug in Korea, underestimation of aspirin use in this study might have occurred. Fifth, with respect to lung cancer mortality, the protective association of cardiovascular drugs might have been overestimated owing to healthy-user effects. Patients who received cardiovascular drugs are likely to be in contact with health care professionals more frequently, so other preventive measures such as cancer screening might be attributed to the early diagnosis of cancer, leading to the reduction in mortality. However, our supplementary analyses of treatment information as a proxy of lung cancer stage exhibited only a slight difference in treatment pattern according to cardiovascular drug use before lung cancer diagnosis, suggesting that early detection does not fully account for reduced mortality in cardiovascular drug users. Finally, the current study was conducted in a single country, limiting the applicability and generalizability of observed associations.

In conclusion, the present study suggests that individual uses of aspirin, metformin, and statins have independent protective associations with lung cancer mortality, and metformin exhibited an inverse association with the incidence of lung cancer. Furthermore, the combined use of aspirin, metformin, and statins had protective associations with lung cancer and related mortality in a dose-dependent fashion. Further research is necessary to develop clinically applicable anticancer strategies of these cardiovascular drugs for the reduction of lung cancer and related mortality.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology at* www.jto.org and at https://doi.org/10.1016/j.jtho.2020.08.021.

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