Associations of aspirin, statins, and metformin with lung cancer risk and related mortality: time-dependent analysis of population-based nationally representative data

Jihun Kang, MD;, Su-Min Jeong, MD, Dong Wook Shin, MD, DrPH, MBA, Mihee Cho, MD, PhD;, Jong Ho Cho, MD, PhD, Jehun Kim, MD

PII: S1556-0864(20)30712-7

DOI: https://doi.org/10.1016/j.jtho.2020.08.021

Reference: JTHO 1909

To appear in: *Journal of Thoracic Oncology*

Received Date: 19 March 2020

Revised Date: 24 August 2020

Accepted Date: 31 August 2020

Please cite this article as: Kang J, Jeong S-M, Shin DW, Cho M, Cho JH, Kim J, Associations of aspirin, statins, and metformin with lung cancer risk and related mortality: time-dependent analysis of population-based nationally representative data, *Journal of Thoracic Oncology* (2020), doi: https://doi.org/10.1016/j.jtho.2020.08.021.

Associations of aspirin, statins, and metformin with lung cancer risk and related mortality: time-dependent analysis of population-based nationally representative data

Running Title: **aspirin, statins, metformin, and lung cancer**

Jihun Kang, MD; [1*] Su-Min Jeong, MD [2,3*]; Dong Wook Shin, MD, DrPH, MBA[4,5,6]; Mihee Cho, MD, PhD;[7] Jong Ho Cho, MD, PhD[8]; Jehun Kim, MD[9]

[1]Department of Family Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Republic of Korea

[2] Department of Family Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Republic of Korea.

[3] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[4]Supportive Care Center, Samsung Comprehensive Cancer Center/Department of Family Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[5]Department of Digital Health, SAIHST, Sungkyunkwan University, Seoul, Korea

[6]Center for Clinical Epidemiology, SAIHST, Sungkyunkwan University, Seoul, Korea

[7] Samsung C&T Medical Clinic, Kangbuk Samsung Hospital, Seoul, Republic of Korea

[8] Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine Seoul, Korea

[9] Division of Pulmonology, Department of Internal Medicine, Kosin University Gospel Hospital, Busan, South Korea

*Contributed equally as first author

Acknowledgements: This study used National Health Insurance Service (NHIS) data (NHIS-2019-1-359) generated by the NHIS. The authors declare no conflict of interest with the NHIS.

Conflict of interest: none

Corresponding Author: Dong Wook Shin, MD, DrPH, MBA

Department of Family Medicine / Supportive Care Center, Samsung Medical Center, , Sungkyunkwan University School of Medicine

Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Science and Technology (SAIHST), Sungkyunkwan University

81 Irwon-Ro, Gangnam-gu, Seoul, Korea

Tel: +82.2-6190- 5252, Fax: +82.2-3410- 2459

E-mail: dwshin.md@gmail.com

ABSTRACT

OBJECTIVES: 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 had undergone a national health check-up in 2002–2003. Lung cancer incidence and mortality were identified using a registered lung cancer diagnosis code (ICD-10 code C34) and the Korean National Death Registry. The study participants were followed from January 1, 2004 to 31 December 2013. Medication exposure was defined by cumulative duration of use and cumulative defined daily dose (cDDD) 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 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 cDDD of metformin ≥ 547.5, compared with non-diabetic patients. 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]). Combined use of aspirin, statins and metformin showed more prominent protective associations with lung cancer risk and mortality.

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

Keyword: lung cancer, aspirin, statins, metformin, anticancer

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide[1]. Although lung cancer mortality and incidence has steadily decreased over the last 15 years, lung cancer still accounts for more than 20% of cancer-related deaths and its incidence rate ranks 4th 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 commonly 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 decreased risk of lung cancer, while other reports showed differing results[20-22]. Furthermore, other studies focused on lung cancer mortality showed that these medications have beneficial effects on lung cancer mortality as well as lung cancer incidence[23-25].

However, the 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 due to their close inter-relationship among 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 examined the use of aspirin, statins, and metformin as a dichotomous variable (yes or no) and did not examine the dose-response relationship[20, 25], while 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 due to 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 multiple other confounders, concomitant use, and combination of these cardiovascular drugs in our analyses.

METHODS

Data source

The Korean National Health Insurance Services (KNHIS) database was used in the present study. The KNHIS is a universal health care system that covers the entire Korean population (~50 million). For this cohort study, three cohort datasets derived from KNHIS were pooled to increase statistical power: the National Health Insurance Service (NHIS)-Senior Cohort comprised a randomly selected Korean participants aged ≥ 60 years in 2002 (n = 558,147); the NHIS-Health Screening Cohort (NHIS-HealS) comprised a randomly selected Korean participants aged 40–79 years in 2002 who participated in a national health screening program during 2002–2003 (n = 514,866); and the NHIS-National Sample Cohort (NHIS-NSC) was composed of 2.2% of the total Korean population covered by the KNHI 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 two-year time interval was used to define medication exposure for time-dependent analysis, patients who died of any cause (n=23,823) or had record for any cancer diagnosis (n=55,529) before January 1, 2004 were excluded. In addition, individuals <40 years and those ≥80 years in 2002–2003 (N= 522,945) and those did not participate in the national health screening examination during 2002–2003 (N=864,172) were excluded, leaving 732,199 participants from the NHIS-Senior, NHIS-HealS, and NHIS-NSC datasets (Figure 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 Statistical Classification of Diseases (ICD-10) 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 from January 1, 2004 (the index date) to the date of lung cancer diagnosis (incidence), lung cancer death (mortality), death from any other cause, or until 31 December 2013, whichever came first.

Exposure to cardiovascular drugs (aspirin, statin and metformin)

We analyzed the cumulative use of cardiovascular drugs with a two-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 the World Health Organization (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 two-year period and participants were categorized into non-users, < 182.5, 182.5–365.0, 365.0–547.5, and ≥ 547.5 days or cDDD.

Covariates

Information on potential covariates was available using datalink between the KNHI claims database and the national health screening program data. Income was categorized into three groups based on monthly insurance premium, because the premium is determined according to income levels. Comorbidity of participants was categorized into five groups based on the Charlson comorbidity index (CCI)[30]. Smoking status was categorized into non-smokers, former smokers, and current smokers. Alcohol consumption was categorized into five groups based on 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 Student's t-test and analysis of variance (ANOVA) for continuous variables (body mass index 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 number of days), statins, or metformin (by cDDD) on the incidence and mortality of lung cancer was evaluated in analyses considering 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, body mass index, 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 between aspirin, statins, and metformin use and lung cancer risk and mortality. P's-for-trend were calculated to evaluate the dose-response relationship. For metformin use, P's-for-trend were calculated among patients with diabetes. In additional sensitivity analysis, smoking status was inserted in the analysis as a time-dependent variable using 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 8 groups, accounting for possible combination use of these drugs. Different cut-off values for combination use of aspirin,

statins and metformin were serially applied from 0 (use vs. non-use), 182.5 days (higher vs. lower or non-use), 365 days, and 547.5 days to examine whether the association of combined use of these medications was augmented in a dose-dependent manner. In addition, we investigated the associations of combined use of these cardiovascular medications on lung cancer risk and mortality according to smoking status.

Comparison of aspirin, statin, and metformin use and treatment types of lung cancer was conducted to examine whether treatment types of lung cancer (i.e. 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 surgery only, surgery+(radiotherapy and/or chemotherapy), radiotherapy+ chemotherapy, radiotherapy only, and chemotherapy only. While we cannot distinguish the purpose of therapy from the claims data only, 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, USA) and two-tailed P-values <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 (6.3%) patients 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 showed high cDDD (Table 2).

Cardiovascular drug use and lung cancer risk and mortality

A total 5,990 lung cancer cases and 5,938 deaths from lung cancer was observed over the follow-up years. Ever use of aspirin was not significantly associated with lung cancer incidence and mortality. When analyzed by cumulative number of days, aspirin use was not associated with lung cancer incidence, but it showed a dose-response relationship with lung cancer mortality (P's-for-trends 0.073), with significantly reduced incidence in participants who used aspirin 547.5–730.0 days (aHR 0.87, 95% CI, 0.78–0.97).

Ever statin use and cDDD of statin use were not associated with reduced lung cancer incidence. However, lung cancer mortality was reduced in a dose-dependent fashion as cDDD of statin use increased (P's-for-trends 0.004). Participants with cDDD of statin ≥ 547.5 (aHR 0.77, 95% CI, 0.59–0.99) showed decreased lung cancer mortality.

Compared with non-diabetic participants, ever metformin users showed reduced incident lung cancer (aHR 0.89, 95% CI, 0.81–0.98). Diabetes patients with cDDD of metformin ≥ 547.5 showed

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 non-diabetics participants. In the analysis only of diabetic patients, 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 stratified analyses by smoking status and sex, 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 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, Supplementary Table 1 & 2).

Combined use of cardiovascular drugs and lung cancer risk, and mortality

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 non-users. These inverse associations increased consistently as the duration of cardiovascular medication exposure increased; thus, participants who used aspirin, statin, and metformin in combination ≥ 547.5 days showed 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) was associated with slightly higher lung cancer mortality when any use was considered, these associations disappeared or even reversed when the cut-off for the duration of medication use was 182.5 days or higher (Table 5). In the analysis stratified by smoking status, 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

While age and smoking status were linearly associated with higher lung cancer risk and mortality (P-for-trends < 0.001 for both), CCI score was only associated with higher mortality from lung cancer (P-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

While participants who used all three cardiovascular drugs were most likely to receive surgery

only (66.7% vs. 66.9 - 73.1% in other groups), the difference was not that large (Supplementary Table 5)

DISCUSSION

We revealed 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, use of aspirin and statins also showed 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 increasing duration of medication use.

The major strengths of this study are as follows: 1) 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 for potential confounding factors related to lung cancer; 4) reliable prescription data gathered through a single compulsory, universal insurance system with high reliability; and 5) use of time-dependent analysis to ensure measurement of drug exposure before cancer diagnosis.

The present 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, demonstrated 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 no significant protective effect of aspirin on lung cancer incidence [32]. In contrast, our study showed that aspirin use was associated with lung cancer mortality in a dose-response manner, with an approximate 15% reduction in cases who continuously used aspirin ≥ 547.5 days within two year intervals. This is consistent with the result of the meta-analyses of data

from an individual randomized trial showing that long-term use of aspirin was associated with reduced lung cancer mortality [8]. Previous studies consistently showed improved lung cancer survival in lung-term aspirin users [8, 25]. Inhibition of COX to maintain low inflammatory states [33] and decreased risk for regional lymph nodes [34] were suggested as potential mechanisms of such survival gain. Therefore, while 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 shown conflicting results. While 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 demonstrating 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 show an increased risk for lung cancer among diabetic patients compared with non-diabetic participants. However, consistent metformin users in our study (cDDD of metformin >547.5 for two years) had a lower risk for lung cancer compared with non-diabetic participants, consistent with a recent meta-analysis that reported that metformin use reduced the risk for lung cancer by 11% [17]. Moreover, previous cohort studies revealing the protective effect of metformin against lung cancer support our study results[18, 19]. Although our study showed a statistically dose-dependent relationship between metformin use and lung cancer incidence, the protective associations of metformin were prominent in cDDD of metformin ≥ 547.5 within two years, and this result seems to support a threshold to produce 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 ≥ 365 [18].

With respect to lung cancer mortality, diabetes had a negative impact on lung cancer mortality, and this association was prominent among diabetic patients on no metformin use or low cDDD of metformin use (<182.5). However, among diabetic patients, 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 whereas the use of metformin exerts a protective impact on the survival of lung cancer patients in a dose-response manner. This result was in line with a US military study showing 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 non-smokers. 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 RCT, compared with the tyrosine-kinase inhibitor (TKI) only group, metformin plus TKI improved median progression-free survival and overall survival by 4.2 months and 14.2 months, respectively, in pulmonary adenocarcinoma with epidermal growth factor receptor (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 attributable to the additional anti-cancer 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 combined use of aspirin, statin and metformin was prominent, and the longer was the duration of combined use, the more protective was the association. This finding is in line with a study demonstrating that aspirin and metformin synergistically inhibit lung cancer cell proliferation by activating AMP activated protein kinase, which plays a critical role in

regulation of lipogenesis in cancer cells [44]. It can reasonably be hypothesized that 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 combined use of aspirin, statin, and metformin with lung cancer is sparse, a clinical study from Germany showed that participants who jointly used aspirin and statins for 5 years were at decreased risk for colorectal cancer (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 anti-cancer 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, direction of association between aspirin, statin, and metformin use and lung cancer mortality was consistent across smoking status, and protective association of metformin and lung cancer incidence was significant regardless of smoking group. In addition, combined use of these cardiovascular medications consistently showed inverse association with lung cancer risk and mortality in never smokers as well as current smokers. Considering consistent findings among never and current smokers, we assume that the association between cardiovascular medication and risk of lung cancer would not be much different due to 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 >3 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, histology, 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 mentioned 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 were 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 pack-year 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 was 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 based on disease code and reimbursement data, and cases who were very old and do not receive any treatment would have not been captured. Because such patients are also not likely to cardiovascular prevention, this will lead to underestimation of lung cancer incidence in cardiovascular drug non-users. 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 attributable to the early diagnosis of cancer, leading to the reduction in mortality. However, our supplementary analyses of treatment information as proxy of lung cancer stage showed only slight difference in treatment pattern according to cardiovascular drug use prior to 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 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 showed inverse association with the incidence of lung cancer. Furthermore, 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.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7-34.

2. Jung KW, Won YJ, Kong HJ, et al. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2016. *Cancer research and treatment : official journal of Korean Cancer Association* 2019;51:417-430.

3. Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest* 2003;123:21s-49s.

4. Malhotra J, Malvezzi M, Negri E, et al. Risk factors for lung cancer worldwide. *Eur Respir J* 2016;48:889-902.

5. Liu C, Cui H, Gu D, et al. Genetic polymorphisms and lung cancer risk: Evidence from meta-analyses and genome-wide association studies. *Lung Cancer* 2017;113:18-29.

6. Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol* 2013;14:813-822.

7. Ilar A, Plato N, Lewne M, et al. Occupational exposure to diesel motor exhaust and risk of lung cancer by histological subtype: a population-based case-control study in Swedish men. *Eur J Epidemiol* 2017;32:711-719.

8. Rothwell PM, Fowkes FGR, Belch JFF, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *The Lancet* 2011;377:31-41.

9. Cao Y, Nishihara R, Wu K, et al. Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer. *JAMA Oncol* 2016;2:762-769.

10. Graaf MR, Beiderbeck AB, Egberts AC, et al. The risk of cancer in users of statins. *J Clin Oncol* 2004;22:2388-2394.

11. Evans JM, Donnelly LA, Emslie-Smith AM, et al. Metformin and reduced risk of cancer in diabetic patients. *BMJ* 2005;330:1304-1305.

12. Ye S, Lee M, Lee D, et al. Association of Long-term Use of Low-Dose Aspirin as Chemoprevention With Risk of Lung Cancer. *JAMA Netw Open* 2019;2:e190185.

13. Lim W-Y, Chuah KL, Eng P, et al. Aspirin and non-aspirin non-steroidal anti-inflammatory drug use and risk of lung cancer. *Lung Cancer* 2012;77:246-251.

14. Van Dyke AL, Cote ML, Prysak G, et al. Regular adult aspirin use decreases the risk of non-small cell lung cancer among women. *Cancer Epidemiol Biomarkers Prev* 2008;17:148-157.

15. Yang TY, Lin WM, Lin CL, et al. Correlation between use of simvastatin and lovastatin and female lung cancer risk: a nationwide case-control study. *Int J Clin Pract* 2015;69:571-576.

16. Khurana V, Bejjanki HR, Caldito G, et al. Statins reduce the risk of lung cancer in humans: a large case-control study of US veterans. *Chest* 2007;131:1282-1288.

17. Yao L, Liu M, Huang Y, et al. Metformin Use and Lung Cancer Risk in Diabetic Patients: A Systematic Review and Meta-Analysis. *Dis Markers* 2019;2019.

18. Tsai MJ, Yang CJ, Kung YT, et al. Metformin decreases lung cancer risk in diabetic patients in a dose-dependent manner. *Lung Cancer* 2014;86:137-143.

19. Mazzone PJ, Rai H, Beukemann M, et al. The effect of metformin and thiazolidinedione use on lung cancer in diabetics. *BMC Cancer* 2012;12:410.

20. Holick C, Michaud D, Leitzmann M, et al. Aspirin use and lung cancer in men. *Br J Cancer* 2003;89:1705.

21. Cheng MH, Chiu HF, Ho SC, et al. Statin use and the risk of female lung cancer: a population-based case-control study. *Lung Cancer* 2012;75:275-279.

22. Tan M, Song X, Zhang G, et al. Statins and the risk of lung cancer: a meta-analysis. *PLoS One* 2013;8:e57349.

23. Cook NR, Lee I-M, Gaziano JM, et al. Low-Dose Aspirin in the Primary Prevention of CancerThe Women's Health Study: A Randomized Controlled Trial. *JAMA* 2005;294:47-55.

24. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. *N Engl J Med* 2013;368:576-577.

25. Ratnasinghe LD, Graubard BI, Kahle L, et al. Aspirin use and mortality from cancer in a prospective cohort study. *Anticancer Res* 2004;24:3177-3184.

26. Rader DJ. Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *The American journal of medicine* 2007;120:S12-S18.

27. Cheol Seong S, Kim YY, Khang YH, et al. Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol* 2017;46:799-800.

28. Seong SC, Kim YY, Park SK, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. *BMJ open* 2017;7:e016640.

29. Organization WH. The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). *Oslo: WHO* 2006.

30. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-1139.

31. Bondy SJ, Victor JC, Diemert LM, et al. Transitions in smoking status over time in a population-based panel study of smokers. *nicotine & tobacco research* 2013;15:1201-1210.

32. Jiang HY, Huang TB, Xu L, et al. Aspirin use and lung cancer risk: a possible relationship? Evidence from an updated meta-analysis. *PLoS One* 2015;10:e0122962.

33. Thun MJ, Henley SJ, Patrono C. Nonsteroidal Anti-inflammatory Drugs as Anticancer Agents: Mechanistic, Pharmacologic, and Clinical Issues. *JNCI: Journal of the National Cancer Institute* 2002;94:252-266.

34. Ogawa F, Amano H, Ito Y, et al. Aspirin reduces lung cancer metastasis to regional lymph nodes. *Biomed Pharmacother* 2014;68:79-86.

35. Haukka J, Sankila R, Klaukka T, et al. Incidence of cancer and statin usage—record linkage study. *Int J Cancer* 2010;126:279-284.

36. Taylor ML, Wells BJ, Smolak MJ. Statins and cancer: a meta-analysis of case-control studies. *Eur J Cancer Prev* 2008;17:259-268.

37. Chen Y, Li X, Zhang R, et al. Effects of statin exposure and lung cancer survival: A meta-analysis of observational studies. *Pharmacol Res* 2019;141:357-365.

38. Hsieh MC, Lee TC, Cheng SM, et al. The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. *Exp Diabetes Res* 2012;2012:413782.

39. Lin J, Gill A, Zahm SH, et al. Metformin use and survival after non-small cell lung cancer: A cohort study in the US Military health system. *Int J Cancer* 2017;141:254-263.

40. Tan BX, Yao WX, Ge J, et al. Prognostic influence of metformin as first-line chemotherapy for advanced nonsmall cell lung cancer in patients with type 2 diabetes. *Cancer* 2011;117:5103-5111.

41. Lin JJ, Gallagher EJ, Sigel K, et al. Survival of patients with stage IV lung cancer with diabetes treated with metformin. *Am J Respir Crit Care Med* 2015;191:448-454.

42. Arrieta O, Barron F, Padilla MS, et al. Effect of Metformin Plus Tyrosine Kinase Inhibitors Compared With Tyrosine Kinase Inhibitors Alone in Patients With Epidermal Growth Factor Receptor-Mutated Lung Adenocarcinoma: A Phase 2 Randomized Clinical Trial. *JAMA Oncol* 2019:e192553.

43. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013;8:823-859.

44. O'Brien AJ, Villani LA, Broadfield LA, et al. Salicylate activates AMPK and synergizes with metformin to reduce the survival of prostate and lung cancer cells ex vivo through inhibition of de novo lipogenesis. *Biochem J* 2015;469:177-187.

45. Hanai Ji, Doro N, Sasaki AT, et al. Inhibition of lung cancer growth: ATP citrate lyase knockdown and statin treatment leads to dual blockade of mitogen- activated protein Kinase (MAPK) and Phosphatidylinositol- 3- kinase (PI3K)/AKT pathways. *J Cell Physiol* 2012;227:1709-1720.

46. Hoffmeister M, Chang-Claude J, Brenner H. Individual and joint use of statins and low-dose aspirin and risk of colorectal cancer: a population-based case-control study. *Int J Cancer* 2007;121:1325-1330.

47. Gorber SC, Schofield-Hurwitz S, Hardt J, et al. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine & tobacco research* 2009;11:12-24.

Figure Legends

Figure 1: Flow diagram of study participants. The final pooled cohort includes the (a) NHIS-Senior cohort, (b) NHIS-HealS cohort, and (c) NHIS-NSC. NHIS, National Health Insurance Service; HealS, Health Screening Cohort; NSC, National Sample Cohort

Table 1. Baseline characteristics of the study population classified by history of cardiovascular drug use during 2002–2003

	Total	Aspirin			Statins			Metformin			
		Never user	Ever user	*p* value *	Never user	Ever user	*p* value *	Non-DM	Never user	Ever user	*p* value *
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, years, n (%)				<0.001			<0.001				<0.001
40–49	282,990 (38.6)	275,043 (41.3)	7,947 (12.0)		276,206 (39.7)	6,784 (18.3)		275,876 (40.2)	3,144 (15.4)	3,970 (15.4)	
50–59	170,780 (23.3)	157,177 (23.6)	13,603(20.6)		161,069 (23.2)	9,711 (26.2)		160,263 (23.4)	4,582 (22.5)	5,935 (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)	9,495 (46.5)	12,194 (47.3)	
70–79	54,895 (8.9)	52,153 (7.8)	64,895 (8.9)		60,619 (8.7)	4,276 (11.6)		58,010 (8.4)	3,193 (15.6)	3,692 (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)	8,869 (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 & 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)	8,939 (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)	9,036 (24.4)		173,332 (25.3)	5,068 (24.8)	6,538 (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)	6,407 (31.4)	8,417 (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)	7,696 (20.8)		359,115 (52.3)	3,707 (18.1)	3,734 (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)	5,948 (16.1)		22,484 (3.3)	4,794 (34.5)	7,640 (29.6)	
≥ 5	2,480 (0.3)	1,310 (0.2)	1,170 (1.8)		1,867 (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)	5,403 (8.2)		52,540 (7.6)	2,905 (7.8)		51,786 (7.6)	1,735 (8.5)	1,924 (7.5)	
Current	161,654 (22.1)	151,281 (22.7)	10,373 (15.7)		155,954 (22.4)	5,700 (15.4)		152,481 (22.2)	4,009 (19.6)	5,164 (20.0)	
Alcohol, g/day, 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)	5,038 (7.6)		73,906 (10.6)	2,797 (7.6)		72,920 (10.6)	1,757 (8.6)	2,026 (7.9)	
20–30	5,648 (0.8)	5,315 (0.8)	333 (0.5)		5,428 (0.8)	220 (0.6)		5,286 (0.8)	156 (0.8)	206 (0.8)	
30–40	23,634 (3.2)	22,007 (3.3)	1,627 (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)	2,378 (3.6)		32,838 (4.7)	1,257 (3.4)		32,084 (4.7)	945 (4.6)	1,066 (4.1)	

DM, diabetes mellitus; BMI, body mass index; CCI, Charlson comorbidity index; SD, standard deviation

*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) .

Table 2. Use of cardiovascular drugs among study participants

	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, days (per 2 years), 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 years), 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)	3,628 (5.9)	8,171 (9.4)	11,956 (11.7)	18,486 (11.9)
≥ 547.5	116 (0.3)	1,862 (3.0)	5,576 (6.5)	13,766 (13.5)	24,680 (15.9)
Metformin					
Never use among DM patients	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 years), 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	1,615 (6.3)	3,214 (8.4)	3,583 (7.5)	4,473 (8.3)	7,746 (9.6)
≥ 547.5	487 (1.9)	2,011 (5.3)	3,807 (7.9)	8,890 (16.6)	13,480 (16.7)

cDDD, cumulative defined daily dose

Table 3. Cardiovascular drug use and lung cancer incidence and mortality considering concomitant use of aspirin, metformin, or statin

	Incidence			Mortality		
	crude HR	aHR 1 (95% CI)	aHR 2 (95% CI)	crude HR	aHR 1 (95% CI)	aHR 2 (95% CI)
Case, N (%)	5,990 (0.8)			5,938 (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, day						
< 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	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)
cDDD of metformin use						
< 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) [§]	0.76 (0.54–1.09)[§]
P-trend*	0.027	0.023	0.007	<0.001	<0.001	<0.001

aHR, adjusted hazard ratio; CI, confidence interval; cDDD, cumulative defined daily dose

aHR 1 for each drug exposure was adjusted for age, sex, income, BMI, smoking, and alcohol consumption; and 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)**

*P trend was calculated among diabetic patients only, using diabetic patients who did not use metformin (i.e., using drugs other than metformin only) as reference

[§] significantly different compared to diabetic patients who did not use metformin

Table 4. Cardiovascular drug use and lung cancer risk and mortality stratified by smoking status*

	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, day						
< 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)**