Statins and the risk of gastric, colorectal, and esophageal cancer incidence and mortality: a cohort study based on data from the Korean national health insurance claims database

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Abstract
Background This study investigated the association between the use of statins, the incidence of gastric, colorectal, and esophageal cancers, and mortality between January 2005 and June 2013 in South Korea.

Methods We compared patients aged 45–70 years statin users for at least 6 months to non-statin users matched by age and sex, from 2004 to June 2013 using the National Health Insurance database. Main outcomes were gastric, colorectal, and esophageal cancer incidence and mortality. Cox proportional hazard regression was used to calculate the adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) among overall cohort and matched cohort after propensity score matching with a 1:1 ratio.

Results Out of 1,008,101 people, 20,473 incident cancers, 3938 cancer deaths occurred and 7669 incident cancer, 1438 cancer death in matched cohort. The aHRs for the association between the risk of cancers and statin use were 0.7 (95% CI 0.65–0.74) for gastric cancer, 0.73 (95% CI 0.69–0.78) for colorectal cancer, and 0.55 (95% CI 0.43–0.71) for esophageal cancer. There were associations between statin use and decreased gastric cancer mortality (HR 0.46, 95% CI 0.52–0.57), colorectal cancer mortality (HR 0.43, 95% CI 0.36–0.51), and esophageal cancer mortality (HR 0.41, 95% CI 0.27–0.50) in the overall cohort and this pattern was similar in the matched cohort.

Discussion Statin use for at least 6 months was significantly associated with a lower risk of stomach, colorectal, and esophageal cancer incidence as well as cancer mortality after a diagnosis.

Keywords Statin · Gastric cancer · Colorectal cancer · Esophageal cancer · Incidence · Mortality

Introduction
Statin is an antihyperlipidemic drug that prevents cardiovascular disease by controlling blood cholesterol concentrations, which are a significant cardiovascular risk, by reducing low-density lipoprotein (LDL) cholesterol and triglyceride levels and increasing high-density lipoprotein (HDL) cholesterol levels (Konstantinopoulos et al. 2007). Statins decrease cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase, which converts HMG-CoA to mevalonate and lowers blood cholesterol levels.

However, by inhibiting HMG-CoA reductase, statins can also inhibit the synthesis of isoprenoids, which are important lipid attachments for intracellular signaling molecules, such as Rho, Rac, and Cdc42 (Wang et al. 2007). Also, disruptions caused by statins in the mevalonate synthesis pathway inhibit cancer growth and lead to apoptotic cell death (Konstantinopoulos et al. 2007). Therefore, statins might exert 'pleiotropic' effects to prevent multiple sclerosis and rheumatoid arthritis through direct inhibition of these small GTP-binding proteins (Wang et al. 2007), induced apoptosis (programmed cell death) and reduction of cell invasiveness (Bocan 2002; Osmak 2012; Shaw et al. 2009; Sleijfer et al. 2005; Blum and Shamburek 2008). In addition, there is evidence demonstrating the effect of statins on endothelial and smooth muscle cells through anti-inflammatory (inflammatory response control),
immunomodulatory, and anti-thrombotic/antiplatelet actions (Blum and Shamburek 2008).

Cancer incidence and mortality are rapidly increasing worldwide, and an estimated 4.8 million of the 18.1 million new cancer cases in 2018 were gastrointestinal (GI) cancers, which also caused an estimated 3.4 million of the 9.5 million cancer-related deaths in the same year. GI cancers account for 26% of global cancer incidence and 35% of all cancer-related deaths (Cabasag et al. 2021; Sung et al. 2020; Araghi et al. 2019a, b, 2021; Ferlay et al. 2019; Siegel et al. 2019; Pilleron et al. 2021; Morgan et al. 2021; Arnold et al. 2020; Bray et al. 2018; Steliarova-Foucher et al. 2018). In South Korea (hereafter, Korea), cancer incidence has increased over time and has been the leading cause of death since 1983 (Jung et al. 2019). In 2017, cancers of the stomach; the colon and rectum (colorectal); the trachea, bronchus, and lung (lung); thyroid; liver; breast; and prostate posed a substantial overall burden in Korea (Center 2017).

The results of several studies have indicated that statin use can reduce cancer incidence and improve cancer survival. Several systematic reviews have found that statins have a preventative effect against liver and gastric cancer, but also increase the risk of lymphoma, melanoma, non-melanoma, and skin cancer (Bjerre and LeLorier 2001; Bonovas et al. 2006, 2008; Boudreau et al. 2010; Farooqi et al. 2018; Jeong et al. 2019; Kuoppala et al. 2008; Liu et al. 2016). The number of studies examining cancer-related deaths among patients taking statins has risen in recent years. Meta-analyses of epidemiological studies have found a reduced mortality risk among statin users with ovarian and prostate cancer (Cai et al. 2015; Deng et al. 2019; Gray et al. 2016; Jeong et al. 2020; Ling et al. 2015; Zhong et al. 2015; Zhou et al. 2019; Li et al. 2019). Studies have yielded conflicting results regarding the effect of statins on the risk of gastric cancer (Cho et al. 2021; Kwon et al. 2021; Lai et al. 2020; You et al. 2020), the risk of colorectal cancer and colorectal cancer survival (Gray et al. 2016; Li et al. 2019; Coogan et al. 2007; Fransgaard et al. 2018; Ibanez-Sanz et al. 2019; Lakha et al. 2012; Lash et al. 2017; Lee et al. 2019; Shao et al. 2015), and the risk of esophageal cancer (Deng et al. 2019; Chan et al. 2013). Moreover, there has been little research examining both cancer incidence and cancer mortality simultaneously. The aim of the current study was to investigate the associations of statin use with gastric, colorectal, and esophageal cancer risk as well as mortality in patients treated with statins compared to the general population.

Methods

Data source

This study used health insurance claims data and national statistics data on causes of death for analysis. Data from the Health Insurance Review and Assessment Service included information on healthcare utilization; patients’ diagnoses according to the International Classification of Disease and Related Health Problems, 10th Revision (ICD-10); and drug use history for the entire South Korean population of 50 million people (Park et al. 2021). To determine patient mortality, the claims data of deceased patients were compared against Statistics Korea data (Korea 2015). Statistics Korea data included official government records of the causes of death for all deceased persons as determined at the time of death by a physician, and all death cases were recorded according to the ICD-10.

Study population and drug exposure

The subjects of this study were individuals aged 45–70 years old who visited a medical institution between January 1 and December 31, 2005. The study included new statin users whose prescriptions for statins had been filled for at least 6 months at the first index date in 2005 and who had not been prescribed statins within the previous year. Non-statin users—consisting of 802,541 people—were extracted at a proportion of 1:4 from the general population and consisted of people who had not filled a prescription for statins with matching for age and sex. The total study population was 1,008,101 people. To prevent other underlying diseases from affecting the outcomes at the initial index date, we excluded (1) patients with a history of any cancer within the previous 2 years, (2) patients whose deaths occurred within 6 months during the follow-up period, (3) and patients who were newly diagnosed with cancer within 6 months during the follow-up period (Figs. 1, 2).

To adjust the difference in comorbidities, we estimated the propensity scores for statin use without regard to outcomes by multiple logistic regression analysis using age and Charlson comorbidity index. Matching was done between statin users and non-statin users with a 1:1 ratio using the Greedy 5→1 digit matching macro with the estimated propensity score (Institutte 2001) (Fig. 2).

We calculated the cumulative exposure to statins between the first index date and the event date, or study endpoint. In accordance with the Anatomic Therapeutic Chemical Classification System of drugs, the statins we selected were atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Drug exposure was calculated using the cumulative usage period from the index date until the occurrence. To calculate cumulative statin use, we used the date on which the drugs were prescribed, the daily dose of drugs, the number of pills per prescription, and the number of days of therapy to determine the defined daily dose (DDD) for each patient. The DDD, as recommended by the WHO, is the average maintenance dose per day of a drug according
to the main active ingredient and its indication for 70-kg adults. We classified patients according to statin use (users vs. non-users), the duration for which they took statins (less than 2 years, greater than or equal to 2 years and less than 4 years, or 4 years or more), and cumulative DDDs (cDDDs) of statins (less than 730 cDDDs, 730–1459 cDDDs, or 1460 or more cDDDs).
Outcome measures

The outcomes of interest considered during the follow-up period were cancer incidence and cancer-related mortality. Cancer incidence was defined as the patient’s first hospitalization for a gastric, colorectal, or esophageal cancer diagnosis (C16, C18–C20, and C15, respectively, according to the ICD-10) between January 1, 2006 and June 30, 2013.

To reduce immortal bias from methodologically wrong analysis of time-dependent events (Gleiss et al. 2017; Lev-esque et al. 2010; Suissa 2007), the follow-up period began from January 1, 2006 and data on the study population were recorded until cancer occurrence, death, or the end of the follow-up period (June 30, 2013). Causes of death as secondary outcomes were determined using information from Statistics Korea. We classified all causes of death, including deaths from cancer.

Other covariates

The confounding variables were age, sex, Charlson comorbidity index (CCI), and comorbidities (hypertension, cardiovascular disease, rheumatoid arthritis, lupus, asthma, hypothyroidism, liver disease, osteoarthritis), the number of physician visits during the baseline period, the number of hospitalizations during the baseline period, and the use of aspirin during the baseline period. The CCI was used as a summary measure. The CCI has been validated for use with hospital discharge data with diagnoses based on the ICD-10. CCI scores were classified as low (index score = 0), moderate (index score = 1–2), or high (index score > 2), based on definitions from previous studies and to increase statistical power.

Statistical analysis

We used the Chi-square test and the t test to compare the demographic and clinical characteristics of statin users and non-statin users. Categorical variables were compared using the Chi-square test and continuous variables were compared using the Student t test. We used the Cox proportional hazards regression model to calculate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incidence of cancer and cancer mortality according to statin use after adjustment for the aforementioned variables. Two-tailed p values < 0.05 were considered to indicate statistical significance. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

Results

General characteristics

Women accounted for 58.5% of the 205,580 patients who used statins and 58.2% of the 802,521 patients who were not treated with statins. The average age of both statin users and non-statin users was 58 years old. The proportion of comorbidities was higher among statin users. Using administrative data to correct for comorbidities, 23.8% of statin users received a CCI score of 0, 25% received a score of 2, and 48.9% received a score of 3, and 61.8% of non-statin users received a score of 0, 19.1% received a score of 2, and 17.7% received a score of 3. Annual aspirin intake for statin users was 6.5 cDDDs, and it was 1.50 cDDDs for non-statin users. Atorvastatin and simvastatin were the most commonly prescribed statins. In total, 14.5% of statin users had taken treatment for less than 2 years, 20.8% for greater than or equal to 2 and less than 4 years, and 64.8% for more than 4 years, and 26.5% of statin users took fewer than 730 cDDDs of statins, 37.0% took 730–1459 cDDDs, 36.5% took more than 1460 cDDDs. In the matched cohort, 24.5% of statin users received a CCI score of 0, 25.6% received a score of 2, and 47.6% received a score of 3, and 24.4% of non-statin users received a score of 0, 24.6% received a score of 2, and 48.8% received a score of 3 (Table 1).

Cancer incidence and cancer mortality according to statin use

Figure 3 shows the association between statin use and cancer incidence and mortality. During a mean follow-up time of 7.6 (SD 1.2) person-years, 20,473 incident cancers, 3938 cancer deaths occurred among 1,008,101 people and 7,669 incident cancers. 1438 cancer deaths in propensity-matched cohort. A total of 17,401 and 7173 all-cancer deaths, 2042, 743 gastric cancer deaths, 1542, 576 colorectal cancer deaths, and 354, 119 esophageal cancer deaths were recorded after a cancer diagnosis in the overall cohort and propensity-matched cohort, respectively.

There was a significant association between statin use for at least 6 months and a reduced risk of cancer incidence and mortality. The adjusted HRs (aHRs) of statin use for the risk of cancer were 0.7 (95% CI 0.65–0.74) for gastric cancer, 0.73 (95% CI 0.69–0.78) for colorectal cancer, and 0.55 (95% CI 0.43–0.71) for esophageal cancer in the overall cohort and the pattern was similar in propensity-matched cohort. Statin use was significantly associated with reduced cancer mortality overall (HR = 0.55, 95% CI 0.52–0.71), mortality related to gastric cancer (HR = 0.46,
95% CI 0.52–0.57), mortality related to colorectal cancer (HR = 0.43, 95% CI 0.36–0.51), and mortality related to esophageal cancer (HR = 0.41, 95% CI 0.27–0.50) in the overall cohort and the pattern was similar in propensity-matched cohort.
Figure 4 shows cancer incidence and mortality according to cumulative statin use. In our analysis of the association between the classification of cDDDs and the risk of cancer and cancer mortality, a significant dose–response relationship was not found between statin use and the risk of cancer. There was a dose–response relationship with all-cancer, gastric cancer, and colorectal cancer, esophageal cancer mortality. Compared with non-statin users, statin use of ≥ 1460 cDDDs and statin use of < 1460 cDDDs were significantly associated with a reduced risk of cancer mortality, gastric cancer, colorectal cancer, esophageal cancer in overall cohort and propensity-matched cohort.

| Outcome                           | Non-statin users | Statin users | aHR (95% CI) | p-value |
|-----------------------------------|------------------|--------------|--------------|---------|
| Non-statin users                  | Statin users     |              |              |         |
| No. of events                     | Risk/1,000 people| No. of events| Risk/1,000 people|         |
| Overall cohort                    |                  |              |              |         |
| Cancer incidence                  |                  |              |              |         |
| Gastric cancer (n=10,491)         | 9,123            | 1,368        | 0.7          | (0.65-0.74) | <.0001  |
| Colorectal cancer (n=9,135)       | 7,779            | 1,356        | 0.67         | (0.69-0.78) | <.0001  |
| Esophageal cancer (n=847)         | 758              | 89           | 0.55         | (0.43-0.71) | <.0001  |
| Cancer mortality                  |                  |              |              |         |
| All-cancer mortality (n=17,401)   | 14,946           | 2,455        | 0.55         | (0.52-0.57) | <.0001  |
| Cancer death after diagnosis      |                  |              |              |         |
| Gastric cancer (n=2,042)          | 1,832            | 210          | 0.46         | (0.39-0.53) | <.0001  |
| Colorectal cancer (n=1,542)       | 1,368            | 174          | 0.43         | (0.36-0.51) | <.0001  |
| Esophageal cancer (n=354)         | 319             | 353          | 0.41         | (0.27-0.50) | <.0001  |
| Propensity based matched cohort   |                  |              |              |         |
| Cancer incidence                  |                  |              |              |         |
| Gastric cancer (n=3,863)          | 2,514            | 1,349        | 0.67         | (0.63-0.73) | <.0001  |
| Colorectal cancer (n=3,489)       | 2,149            | 1,340        | 0.73         | (0.68-0.79) | <.0001  |
| Esophageal cancer (n=847)         | 229              | 88           | 0.53         | (0.40-0.70) | <.0001  |
| Cancer mortality                  |                  |              |              |         |
| All-cancer mortality (n=7,173)    | 4,743            | 2,430        | 0.55         | (0.52-0.58) | <.0001  |
| Cancer death after diagnosis      |                  |              |              |         |
| Gastric cancer (n=743)            | 534212.41        | 209154.93    | 0.42         | (0.35-0.50) | <.0001  |
| Colorectal cancer (n=576)         | 403187.53        | 173129.10    | 0.44         | (0.36-0.53) | <.0001  |
| Esophageal cancer (n=119)         | 85371.18         | 34386.36     | 0.43         | (0.27-0.67) | <.0001  |
Discussion

This study examined the association between statin use and cancer risk among the Korean population. We found a significant association between statin use for a duration of at least 6 months and a reduced risk of cancer and cancer mortality. Additionally, cancer mortality according to cumulative statin use (in cDDDs) was examined, and a dose–response relationship was confirmed with regard to all-cancer deaths, gastric cancer deaths, colorectal cancer deaths, and esophageal cancer deaths.

Previous studies on statin use for cancer prevention have been mixed. Our results related to cancer incidence are similar to those of previous studies that found associations between statin use and significant decreases in the incidence of gastric cancer (Singh and Singh 2013) and colorectal cancer (Voorneveld et al. 2017). Additionally, this study’s results are consistent with those of another study that analyzed the effects of statin use on site-specific cancer risk and found that mortality was lower for colorectal cancer when statins had been prescribed before the diagnosis was made and that mortality was lower for esophageal cancer when patients took statins (Zhou et al. 2019).

A meta-analysis of 11 studies on gastric cancer found a significant 32% decrease in cancer incidence among statin users (Singh and Singh 2013). Another study found that statins had a preventative effect against stomach cancer (Boudreau et al. 2010). In addition, a recent meta-analysis of 42 studies on colorectal cancer found an association between statin use and an overall risk reduction of 10% for colorectal cancer (Liu et al. 2014). Another umbrella systematic review also found evidence that suggested that statins had a preventative effect against esophageal cancer (Jeong et al. 2019).

In addition, this study’s results are consistent with those of a study that found lower mortality for colorectal cancer after analyzing the effects of pre-diagnosis statin use and a reduction in esophageal cancer mortality related to statin use (Zhou et al. 2019). An umbrella meta-analysis of previous

### Table 1

| Outcomes                  | Overall cohort | Propensity based matched cohort |
|---------------------------|----------------|---------------------------------|
|                           | No. of events  | Risk/1,000 people aHR (95% CI) | p-value | No. of events  | Risk/1,000 people aHR (95% CI) | p-value |
| Cancer incidence          |                |                                 |         |                |                                 |         |
| Gastric cancer            |                |                                 |         |                |                                 |         |
| Non-statin users          | 9,123          | 11.37                           |          | 2,514          | 12.54                           |          |
| <1,460 cDDDs             | 1,172          | 5.70 1.02 (0.96-1.10)           | 0.5002  | 1,156          | 5.77 0.98 (0.91-1.06)           | 0.6368  |
| ≥1,460 cDDDs             | 196            | 0.95 0.23 (0.20-0.26)           | <.0001  | 193            | 0.96 0.22 (0.19-0.26)           | <.0001  |
| Colorectal cancer         |                |                                 |         |                |                                 |         |
| Non-statin users          | 7,779          | 9.69                            |          | 2,149          | 10.72                           |          |
| <1,460 cDDDs             | 1196           | 5.82 1.1 (1.02-1.17)           | 0.0082  | 1184           | 5.91 1.09 (1.01-1.18)           | 0.0307  |
| ≥1,460 cDDDs             | 160            | 0.78 0.2 (0.17-0.23)           | <.0001  | 156            | 0.78 0.2 (0.17-0.23)           | <.0001  |
| Esophageal cancer         |                |                                 |         |                |                                 |         |
| Non-statin users          | 758            | 0.94                            |          | 229            | 1.14                            |          |
| <1,460 cDDDs             | 75             | 0.36 0.81 (0.63-1.05)           | 0.1179  | 74             | 0.37 0.76 (0.57-1.02)           | 0.0666  |
| ≥1,460 cDDDs             | 14             | 0.07 0.19 (0.11-0.33)           | <.0001  | 14             | 0.07 0.18 (0.11-0.34)           | <.0001  |
| Cancer mortality          |                |                                 |         |                |                                 |         |
| Non-statin users          | 14,946         | 18.62                           |          | 4,743          | 23.67                           |          |
| <1,460 cDDDs             | 2,239          | 10.89 0.55 (0.52-0.58)          | <.0001  | 2,215          | 11.05 0.81 (0.77-0.86)          | 0.0666  |
| ≥1,460 cDDDs             | 216            | 1.05 0.42 (0.40-0.44)           | <.0001  | 215            | 1.07 0.12 (0.10-0.13)           | <.0001  |
| Cancer death of gastric cancer |            |                                 |         |                |                                 |         |
| Non-statin users          | 1,832          | 2.28                            |          | 534            | 212.4                           |          |
| <1,460 cDDDs             | 194            | 0.94 0.7 (0.59-0.82)           | <.0001  | 193            | 167.0 0.64 (0.57-0.77)          | <.0001  |
| ≥1,460 cDDDs             | 16             | 0.08 0.08 (0.05-0.14)           | <.0001  | 16             | 82.9 0.08 (0.05-0.13)           | <.0001  |
| Cancer death of colorectal cancer |            |                                 |         |                |                                 |         |
| Non-statin users          | 1,368          | 1.70                            |          | 403            | 187.5                           |          |
| <1,460 cDDDs             | 166            | 0.81 0.67 (0.56-0.80)           | <.0001  | 165            | 139.4 0.69 (0.56-0.84)          | 0.0002  |
| ≥1,460 cDDDs             | 8              | 0.04 0.05 (0.02-0.10)           | <.0001  | 8              | 51.3 0.05 (0.02-0.10)           | <.0001  |
| Cancer death of esophageal cancer |            |                                 |         |                |                                 |         |
| Non-statin users          | 319            | 0.40                            |          | 85             | 371.2                           |          |
| <1,460 cDDDs             | 31             | 0.15 0.62 (0.41-0.93)           | 0.0201  | 30             | 405.4 0.63 (0.40-1.00)          | 0.049   |
| ≥1,460 cDDDs             | 4              | 0.02 0.1 (0.04-0.28)           | <.0001  | 4              | 285.7 0.11 (0.04-0.31)          | <.0001  |

Fig. 4 Associations of cumulative statin use with the risk of cancer and cancer mortality. aHR: adjusted hazard ratio. Adjusted for age, sex, Charlson comorbidity index (CCI), comorbidities (congestive heart failure, hemorrhagic stroke, hypertension, diabetes mellitus, renal failure, liver dysfunction), and aspirin use.
meta-analysis studies showed that statins reduced colorectal cancer mortality by 18% (Jeong et al. 2020), and another meta-analysis of seven studies found a 20% reduction in cancer mortality related to statin use (Ling et al. 2015). Other studies distinguished between pre-diagnosis statin use and post-diagnosis statin use. A meta-analysis of 14 studies on colorectal cancer found an 18% reduction in mortality related to pre-diagnosis statin use and a 14% reduction in mortality related to post-diagnosis statin use (Li et al. 2019). Other studies, however, have found an association between improved cancer mortality and pre-diagnosis statin use only (Cai et al. 2015; Gray et al. 2016; Zhong et al. 2015). Additionally, another meta-analysis of five studies found a 16% reduction in esophageal cancer mortality related to statin use (Zhou et al. 2019).

One notable distinction in our study is our examination of potential dose–response relationships. In this study, we collected data on statin dosages and stratified subjects according to statin dosage. Despite the large number of studies that have examined the association between cancer incidence and statin use, relatively few studies have examined the effects of cumulative statin use on cancer incidence and mortality related to gastric, colorectal, and esophageal cancer. We classified cumulative statin use into the following three categories: less than 730 cDDDs, 730–1459 cDDDs, or 1460 cDDDs or more. Our results showed an association between cumulative statin use (in cDDDs) and a decreased risk of cancer and cancer mortality.

Previous studies have examined the dose–response relationship between statin use and other cancers. Studies have identified a dose–response relationship between 28 and 90 cDDDs, 91–65 cDDDs, and more than 365 cDDDs and a reduced risk of hepatocellular carcinoma compared to that of non-statin users (Tsan et al. 2013, 2012). However, a study in the US that surveyed participants about the duration for which they took statins—classified into less than 2 years, 3–6 years, and 6 years or more—found no statistically significant association between the duration of statin use and the risk of pancreatic cancer (Hamada et al. 2018). Another study in Scotland that distinguished between participants who had taken 1–12 prescriptions and participants who had taken 12 prescriptions or more found no evidence of an association between statin use and breast cancer death in a dose–response analysis (Mc Menamin et al. 2016).

This study compared the outcomes of interest using a quasi-experimental design to analyze health insurance claims data. Data covering the total population of South Korea were used for analysis, and the findings can be generalized to other contexts due to the large amount of real-world data used for analysis; therefore, this study has several strengths. First, our study is highly representative, since it is a cohort-based study of the entire general population of South Korea. There are few cohort studies that have covered more than 1 million people, and, to our knowledge, no study has investigated associations between statin use and the risk of cancer across the entire population. Second, our analysis of statin users among the general population is the first to assess the risk of cancer and cancer mortality simultaneously. We used data on individuals’ causes of death from Statistics Korea for our analysis of cancer mortality and its association with statin use. Third, we investigated the dose–response relationship between cancer risk and mortality and statin use, measured in cDDDs, which were calculated by multiplying daily dosages by the duration of statin use. This calculation is advantageous since it takes into account variable statin dosages and durations for which statins were taken. By classifying subjects according to the duration for which they took statins, their dosages, and their medication adherence, we quantified cancer risk by directly comparing subjects according to statin use in clinical practice. Fourth, we defined statin users as patients who took statins for at least 6 months to avoid bias resulting from short-term statin users being included in the analysis. In addition, we excluded patients who died or had new cancer diagnoses within 6 months during the follow-up period to eliminate the effects of other potential underlying diseases on the analysis. Also, to reduce immortal bias from wrong analysis of time-dependent events (Gleiss et al. 2017; Levesque et al. 2010; Suissa 2007), we began the follow-up from January 1, 2006.

However, there also are several limitations to the study. This is a retrospective study using medical claims database, so confounding factors such as patients’ lifestyles (smoking, drinking, obesity, etc.) as well as family history which might affect cancer incidence or mortality could not be recorded in medical claims data. Therefore, it is limitation that we did not adjust these factors in the analysis. Second, we did not adjust for metformin which appears to be associated with a lower risk of cancer incidence compared to other diabetic drugs in diabetes mellitus patients (Mekuria et al. 2019; Decensi et al. 2010) or angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB) (Zhao et al. 2016; Dai et al. 2015). We only adjusted co-medication drugs for cancer prevention as aspirin according to the international consensus statement (Rothwell et al. 2012; Elwood et al. 2009; Cuzick et al. 2009). Third, continued use of statins could potentially explain the reduced risk of death. For example, a poor prognosis might influence statin use, so when patients later stop taking statins as their disease progress worsens, it could potentially lead to disproportionately high mortality among statin users that is ultimately unrelated to their actual statin use. In addition, we used claims data and assumed that patients might take their prescribed medicines.

In conclusion, statin use is associated with a reduced risk of gastric, colorectal, and esophageal cancer incidence, as
well as a lower risk of death from gastric cancer, colorectal cancer, and esophageal cancer. However, further studies that are larger and multinational in scope are needed to confirm the beneficial effects of statins on survival for the three types of cancers examined in this study.

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Declarations

Conflict of interest We declare any competing financial/or non-financial interests.

Ethics approval and consent to participate The study was performed in accordance with the Declaration of Helsinki. The ethics approval and consent from the participants was waived, because this study used anonymous database.

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