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 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, during 2005 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).

Results: Out of 1,008,101 people, 21,454 incident cancers and 4,031 cancer deaths occurred. The aHRs for the association between the risk of cancers and statin use were 0.71 (95% CI 0.67-0.75) for gastric cancer, 0.73 (95% CI 0.69-0.78) for colorectal cancer, and 0.56 (95% CI 0.44-0.71) for esophageal cancer. There were associations between statin use and decreased gastric cancer mortality (HR 0.73, 95% CI 0.62-0.85), and colorectal cancer mortality (HR 0.67, 95% CI 0.57-0.80), whereas no significant association for esophageal cancer mortality.

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

Introduction

Statins are 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 [1]. Statins decrease cholesterol levels by inhibiting 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase, which converts HMG-CoA to mevalonate and lowers blood cholesterol levels. 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. Disruptions caused by statins in the mevalonate synthesis pathway inhibit cancer growth and lead to apoptotic cell death [1]. Statins have been shown to induce apoptosis (programmed cell death) and reduce cell invasiveness, therefore, also have pleiotropic effects to prevent multiple sclerosis and rheumatoid arthritis [2–5].

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 [6–17]. In South Korea (hereafter, Korea), cancer incidence has increased over time and has been the leading cause of death since 1983 [18]. 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 [19].

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 [20–27]. 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 [28–35]. Studies have yielded conflicting results regarding the effect of statins on the risk of gastric cancer [36–39], the risk of colorectal cancer and colorectal cancer survival [30, 35, 40–46], and the risk of esophageal cancer [29, 47]. 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. In order to determine patient mortality, the claims data of deceased patients were compared against Statistics Korea data. 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 to 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. In order to prevent other underlying diseases from affecting the outcomes at the initial index date, the exclusion criteria were as follows: (1) patients with a history of any cancer within the previous year, (2) patients whose deaths occurred within 1 year during the follow-up period, (3) and patients who were newly diagnosed with cancer within 1 year during the follow-up period (Fig. 1, Fig. 2).

We calculated the cumulative exposure to statins between the first index date in 2005 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, 730-1,459 cDDDs, or 1,460 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 (i.e., 1 year after the index date) and June 30, 2013. The follow-up period began 1 year after the index date, 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 angiotensin-converting enzyme (ACE) inhibitors and 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. In addition, the annual intake of ACE inhibitors was 1.2 cDDDs and 3.4 cDDDs for statin users and non-statin users, respectively. 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 730-1,459 cDDDs, 36.5% took more than 1,460 cDDDs (Table 1).

Table 1
Baseline characteristics of the study cohort, number of patients (%)

Variable	Non-statin users (n=802,521)		Statin users (n=205,580)		*p*-value
Sex					
Men	335,178	(41.8)	85,218	(41.5)	0.01
Women	467,343	(58.2)	120,362	(58.5)	
Age, years (mean ± SD)	58.8 ±	7	58.1 ±	7	<.0001
Age (years)					
<55	254,479	(31.7)	69,248	(33.7)	<.0001
55-64	344,781	(43.0)	90,322	(43.9)	
≥65	203,261	(25.3)	46,010	(22.4)	
Charlson comorbidity index					
0	495,572	(61.8)	48,999	(23.8)	<.0001
1	11,538	(1.4)	4,599	(2.2)	
2	153,532	(19.1)	51,353	(25.0)	
≥3	141,879	(17.7)	100,629	(48.9)	
Comorbidity					
Congestive heart failure	14,804	(1.8)	15,156	(7.4)	<.0001
Hemorrhagic stroke	4,321	(0.5)	2,077	(1.0)	<.0001
Hypertension	197,365	(24.6)	153,212	(74.5)	<.0001
Diabetes	77,206	(9.6)	81,667	(39.7)	<.0001
Hyperlipidemia	31,617	(3.9)	147,783	(71.9)	
Liver dysfunction	41,315	(5.1)	23,528	(11.4)	<.0001
Renal failure	4,560	(0.6)	5,321	(2.6)	<.0001
Duration of statin use					
Non-statin user	802,521	(100.0)			<.0001
<4 years			72,477	(35.3)	

SD: standard deviation, ACE inhibitors: angiotensin-converting enzyme inhibitors, cDDD: cumulative defined daily dose

Variable	Non-statin users (n=802,521)		Statin users (n=205,580)		*p*-value
≥4 years to <6 years			47,698	(23.2)	
≥6 years			85,405	(41.5)	
Statin use, cDDDs	-				
Non-user	802,521	(100.0)			<.0001
<730 cDDDs			54,481	(26.5)	
730-1,459 cDDDs			76,121	(37.0)	
≥1,460 cDDDs			74,978	(36.5)	
Aspirin use, cDDDs (mean ± SD)	1.5 ±	20.8	6.5 ±	48.1	<.0001
Aspirin use					
<30 cDDDs	795,962	(99.2)	199,269	(96.9)	<.0001
30~179 cDDDs	3,948	(0.5)	3,700	(1.8)	
≥180 cDDDs	2,611	(0.3)	2,611	(1.3)	
ACE inhibitors, cDDDs (mean ± SD)	1.2 ±	22.7	3.4 ±	45.8	<.0001
ACE inhibitors					
<180 cDDDs	800,613	(99.8)	204,416	(99.4)	<.0001
≥180 cDDDs	1,908	(0.2)	1,164	(0.6)	
Days with visits to physicians (mean ± SD)	39.1 ±	56.8	73. 0 ±	70.6	<.0001
No. of hospitalization (mean ± SD)	0.4 ±	1.7	0.8 ±	2.1	<.0001

SD: standard deviation, ACE inhibitors: angiotensin-converting enzyme inhibitors, cDDD: cumulative defined daily dose

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, a total of 10,971 cases of gastric cancer, 9,598 cases of colorectal cancer, and 885 cases of esophageal cancer were recorded among the 1,008,101 people included in this study. A total of 17,401 all-cancer deaths, 2,096 gastric cancer deaths, 1,573 colorectal cancer deaths, and 362 esophageal cancer deaths were recorded after a cancer diagnosis.

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 0.71 (95% CI 0.67-0.75) for gastric cancer, 0.73 (95% CI 0.69-0.78) for colorectal cancer, and 0.56 (95% CI 0.44-0.71) for esophageal cancer. Statin use was significantly associated with reduced cancer mortality overall (HR=0.72, 95% CI 0.68-0.75), mortality related to gastric cancer (HR=0.73, 95% CI 0.62-0.85), and mortality related to colorectal cancer (HR=0.67, 95% CI 0.57-0.80). There was not a significant association between statin use and mortality related to esophageal cancer.

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.

Compared with non-statin users, statin use of ≥1,460 cDDDs was significantly associated with a reduced risk of gastric cancer, with an aHR of 0.24 (95% CI 0.21-0.28), whereas statin use of <1,460 cDDDs was not. Statin use of <1,460 cDDDs was significantly associated with an increased risk of colorectal cancer, with an aHR of 1.11 (95% CI 1.04-1.19), while statin use of ≥1,460 cDDDs was significantly associated with a reduced risk of colorectal cancer. Lastly, statin use of ≥1,460 cDDDs was also significantly associated with a reduced risk of esophageal cancer, with an aHR of 0.20 (95% CI 0.12-0.35), while statin use of <1,460 cDDDs was not.

There was a dose-response relationship with all-cancer, gastric cancer, and colorectal cancer mortality, though not esophageal cancer mortality. Compared to non-statin users, statin use of <1,460 cDDDs and ≥1,460 cDDDs was significantly associated with reduced all-cancer mortality, with aHRs of 0.78 (95% CI 0.74-0.83) and 0.36 (96% CI 0.31-0.43), respectively. The aHRs for gastric cancer mortality were 0.81 (95% CI 0.69-0.94) and 0.34 (96% CI 0.21-0.55), respectively, for statin use of <1,460 cDDDs and ≥1,460 cDDDs. In addition, statin use of <1,460 cDDDs and ≥1,460 cDDDs was significantly associated with reduced colorectal cancer mortality, with aHRs of 0.74 (95% CI 0.62-0.88) and 0.24 (96% CI 0.12-0.47), respectively. The association between statin use of <1,460 cDDDs and ≥1,460 cDDDs and esophageal cancer mortality was not significant.

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, and colorectal 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 [48] and colorectal cancer [49]. 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 [34].

A meta-analysis of 11 studies on gastric cancer found a significant 32% decrease in cancer incidence among statin users.[48] Another study found that statins had a preventative effect against stomach cancer.[23] 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 [50]. Another umbrella systematic review also found evidence that suggested that statins had a preventive effect against esophageal cancer [25].

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 [34]. An umbrella meta-analysis of previous meta-analysis studies showed that statins reduced colorectal cancer mortality by 18% [31], and another meta-analysis of seven studies found a 20% reduction in cancer mortality related to statin use [32]. 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 [35]. Other studies, however, have found an association between improved cancer mortality and pre-diagnosis statin use only [28, 30, 33]. Additionally, another meta-analysis of five studies found a 16% reduction in esophageal cancer mortality related to statin use [34]

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, 730-1,459 cDDDs, or 1,460 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 28-90 cDDDs, 91-65 cDDDs, and more than 365 cDDDs and a reduced risk of hepatocellular carcinoma compared to that of non-statin users [51, 52], 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 [53]. 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 [54].

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 was 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 in order 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 1 year during the follow-up period to eliminate the effects of other potential underlying diseases on the analysis.

However, there also are several limitations to the study. This is a retrospective study, so confounding factors related to disease progression that may have occurred were not recorded. Second, 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 and colorectal 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.

Declarations

Acknowledgementution

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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.

Conflict of interest

We declare anay competing financial/or non-financial interests.

Author Contribution

D.S.K. and H.A. participated in conceptualization.

D.S.K performed data curation and formal anlaysis.

D.S.K and H.K. wrote original draft.

H.K. and H.A edited the manuscript.

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Figures

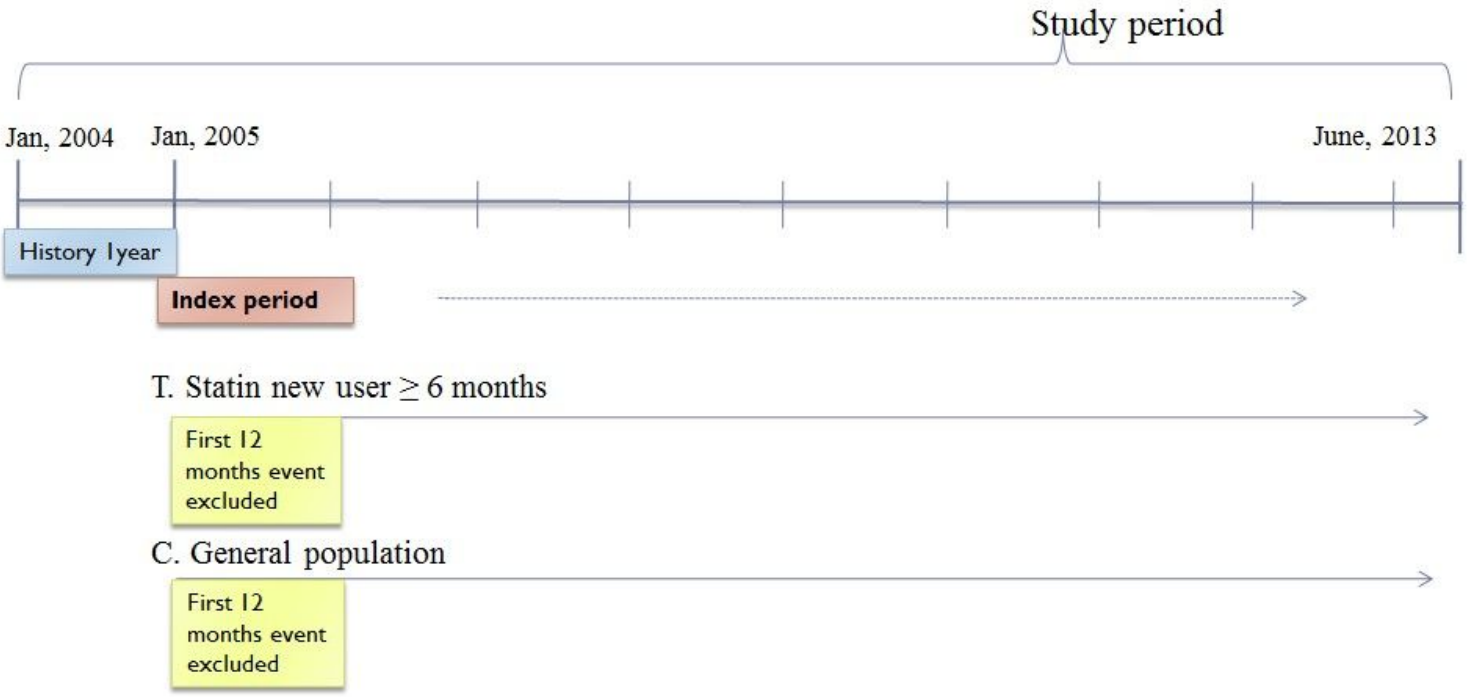


Figure 1

Study period

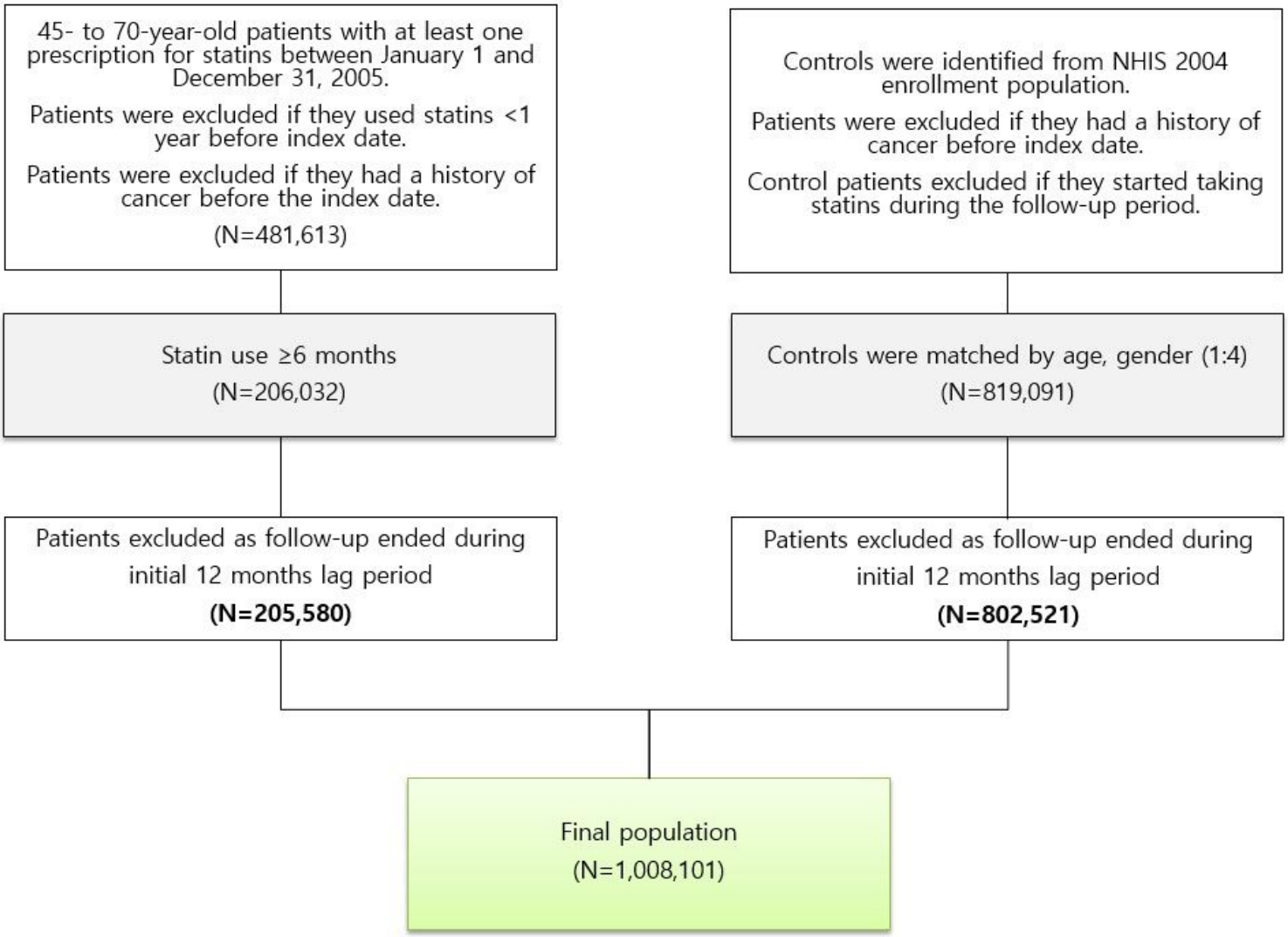


Figure 2

Inclusion and exclusion criteria of the study population

Outcome	Non-statin users (n=802,521)		Statin users (n=205,580)		aHR (95% CI)	*p*-value
	No. of events	Risk/ 1,000 people	No. of events	Risk/ 1,000 people		
Cancer incidence						
Gastric cancer (n=10,971)	9,123	11.37	1,848	8.99	**0.71 (0.67-0.75)**	<.0001
Colorectal cancer (n=9,598)	7,779	9.69	1,819	8.84	**0.73 (0.69-0.78)**	<.0001
Esophageal cancer (n=885)	758	0.94	127	0.62	**0.56 (0.44-0.71)**	<.0001
Cancer mortality						
All-cancer mortality (n=17,401)	14,946	18.62	2,455	11.95	**0.72 (0.68-0.75)**	<.0001
Cancer death after diagnosis						
Gastric cancer (n=2,096)	1,832	200.81	264	142.86	**0.73 (0.62-0.85)**	<.0001
Colorectal cancer (n=1,573)	1,368	175.86	205	112.70	**0.67 (0.57-0.80)**	<.0001
Esophageal cancer (n=362)	319	420.84	43	338.58	**0.74 (0.50-1.11)**	0.1441

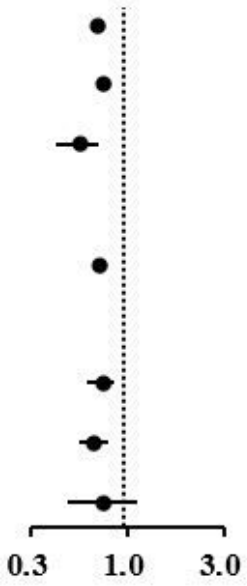
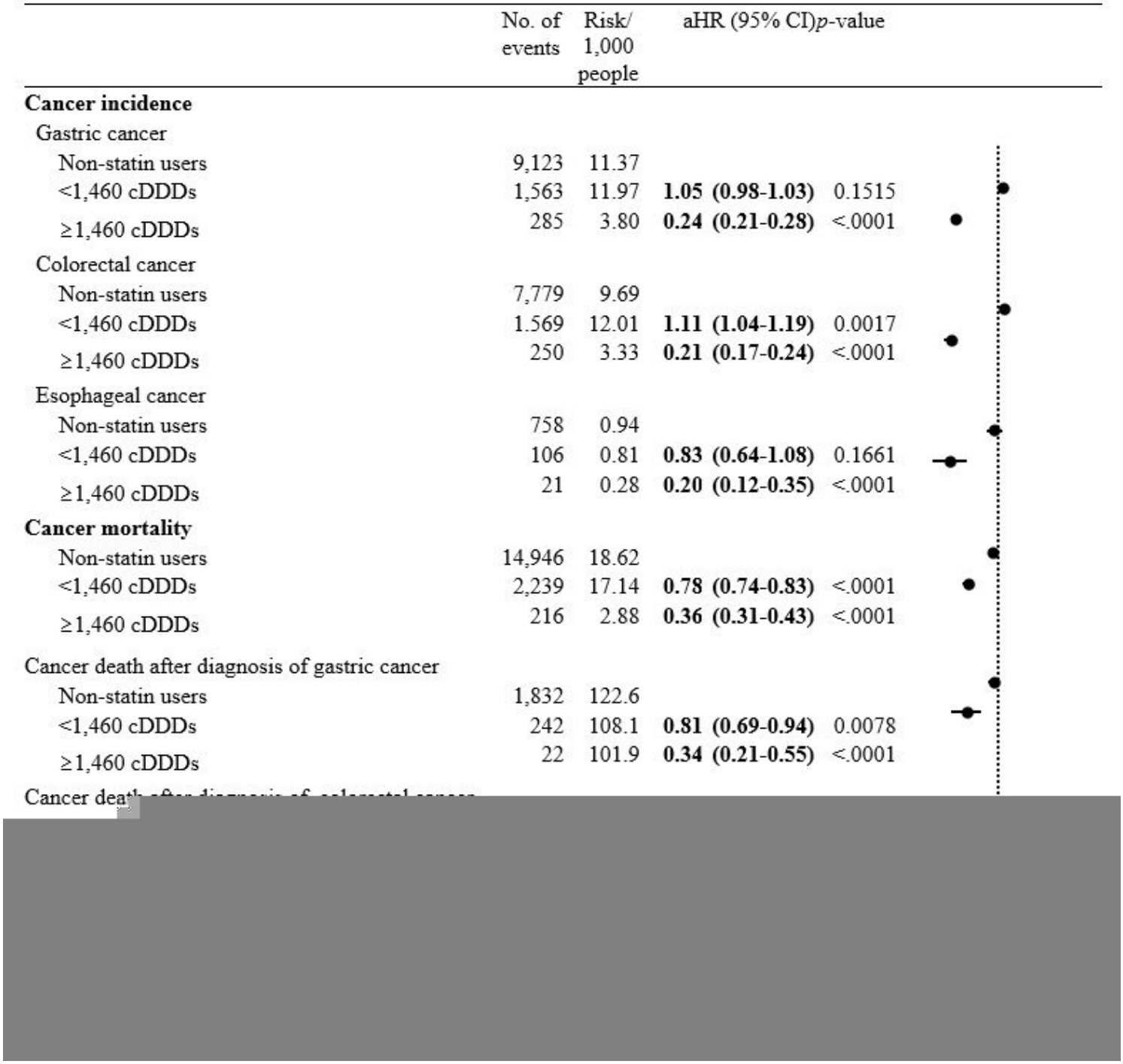


Figure 3

Associations between statin use and 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 co-medication (aspirin, ACE inhibitors).



	No. of events	Risk/ 1,000 people	aHR (95% CI)	*p*-value
Cancer incidence				
Gastric cancer				
Non-statin users	9,123	11.37		
<1,460 cDDDs	1,563	11.97	**1.05 (0.98-1.03)**	0.1515
≥1,460 cDDDs	285	3.80	**0.24 (0.21-0.28)**	<.0001
Colorectal cancer				
Non-statin users	7,779	9.69		
<1,460 cDDDs	1.569	12.01	**1.11 (1.04-1.19)**	0.0017
≥1,460 cDDDs	250	3.33	**0.21 (0.17-0.24)**	<.0001
Esophageal cancer				
Non-statin users	758	0.94		
<1,460 cDDDs	106	0.81	**0.83 (0.64-1.08)**	0.1661
≥1,460 cDDDs	21	0.28	**0.20 (0.12-0.35)**	<.0001
Cancer mortality				
Non-statin users	14,946	18.62		
<1,460 cDDDs	2,239	17.14	**0.78 (0.74-0.83)**	<.0001
≥1,460 cDDDs	216	2.88	**0.36 (0.31-0.43)**	<.0001
Cancer death after diagnosis of gastric cancer				
Non-statin users	1,832	122.6		
<1,460 cDDDs	242	108.1	**0.81 (0.69-0.94)**	0.0078
≥1,460 cDDDs	22	101.9	**0.34 (0.21-0.55)**	<.0001
Cancer death after diagnosis of colorectal cancer				

Figure 4

Associations of cumulative statin use with the risk of cancer and cancer mortality

aHR: adjusted hazard ratio, cDDD: cumulative defined daily dose

Adjusted for age, sex, Charlson comorbidity index (CCI), comorbidity (congestive heart failure, hemorrhagic stroke, hypertension, diabetes mellitus, renal failure, liver dysfunction), and co-medication (aspirin, ACE inhibitors).