

Statins Were Associated with a Reduced Gastric Cancer Risk in Patients with Eradicated *Helicobacter Pylori* Infection: A Territory-Wide Propensity Score Matched Study



Ka Shing Cheung¹, Esther W. Chan², Angel Y.S. Wong³, Lijia Chen¹, Wai-Kay Seto¹, Ian C.K. Wong^{2,4}, and Wai K. Leung¹

ABSTRACT

Background: Individuals may still develop gastric cancer even after *Helicobacter pylori* eradication. We aimed to investigate statin effect on gastric cancer development in *H. pylori*-eradicated subjects.

Methods: All adult subjects who were prescribed clarithromycin-based triple therapy between 2003 and 2012 were identified in this retrospective cohort study utilizing a territory-wide electronic healthcare database. Patients were observed from index date of *H. pylori* therapy, and censored at gastric cancer diagnosis, death, or December 2015 (study end date). Statin use was defined as ≥ 180 -day use after index date. Exclusion criteria included gastric cancer diagnosed within the first year after index date, previous gastric cancer or gastrectomy, and *H. pylori* treatment failure. Subdistribution hazard ratio (SHR) of gastric cancer with statins was calculated by competing risk regression with propensity score (PS) analysis

matching 19 variables (age, sex, comorbidities, and other drug usage, including proton pump inhibitors, nonsteroidal anti-inflammatory drugs, aspirin, cyclooxygenase-2 inhibitors, and metformin).

Results: During a median follow-up of 7.6 years (interquartile range = 5.1–10.3), 169 (0.27%) of 63,605 patients developed gastric cancer at an incidence rate of 3.5 per 10,000 person-years. Among 22,870 PS-matched subjects, statins were associated with a lower gastric cancer risk (SHR = 0.34; 95% confidence interval, 0.19–0.61), in a duration- and dose-response manner ($P_{\text{trend}} < 0.05$).

Conclusions: Statins were associated with a lower gastric cancer risk in a duration- and dose-response manner among *H. pylori*-eradicated patients.

Impact: This study provides evidence on the additional benefits of statins as chemopreventive agents against gastric cancer among *H. pylori*-eradicated patients.

Background

Globally, gastric cancer is the fifth most common cancer and third leading cause of cancer-related death (1). *Helicobacter pylori* (*H. pylori*) is the most important etiologic agent of gastric cancer (more than three-fold increase in risk; refs. 2, 3). As eradication of *H. pylori* only reduces gastric cancer risk by 47% (4, 5), there is still an unmet need to identify chemopreventive agents against gastric cancer.

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (an enzyme involved in cholesterol synthesis), and are used for primary and secondary prevention of cardiovascular diseases (6). In addition to their lipid lowering effect, statins have potential chemopreventive effects on various solid organ tumors, which are believed to be mediated via arresting cell-cycle progression,

inducing apoptosis, inhibiting angiogenesis, and immunomodulation (7). Lovastatin has been shown to suppress genes involved in cell division, upregulate cell-cycle inhibitors, and suppress antiapoptotic proteins in human gastric cancer-derived cell lines (8). In addition, statins inhibit gastric cancer cell growth in mice models (9).

As yet, there is no randomized clinical trial (RCT) dedicated to investigate the effect of statins on gastric cancer as the primary outcome. Observational studies, on the other hand, yield conflicting results with some studies showing a lower gastric cancer risk by statins (10–13), whereas others failed to show such a benefit (14–20). Although a recent meta-analysis conclude that statins were associated with lower gastric cancer risk (21), all included studies enrolled both *H. pylori*-infected and *H. pylori*-negative subjects. In addition, few studies stratified the cancer risk according to cancer location of noncardia and cardia, as etiologic factors are different for these two cancer subtypes, with *H. pylori* infection and gastroesophageal reflux disease being the major risk factors for noncardia and cardia cancer, respectively (2, 22). However, in areas where *H. pylori* are prevalent, both noncardia and cardia gastric cancer could be associated with *H. pylori* infection (2). To date, there are no studies that specifically investigate the potential chemopreventive role of statins in gastric cancer prevention after *H. pylori* eradication. Therefore, we conducted this territory-wide study to determine the potential effect of statins on gastric cancer risk with stratification to cancer subsites after receiving *H. pylori* eradication therapy.

Material and Methods

Study design and data source

This was a retrospective cohort study based on data retrieved from the territory-wide electronic healthcare database, Clinical Data

¹Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong. ²Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong. ³Department of Non-communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom. ⁴UCL School of Pharmacy, University College London, London, United Kingdom.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

Guarantor of the article: W.K. Leung.

Corresponding Author: Wai K. Leung, University of Hong Kong, Hong Kong 852, Hong Kong. Phone: 852-22553348; E-mail: waikleung@hku.hk

Cancer Epidemiol Biomarkers Prev 2020;29:493–9

doi: 10.1158/1055-9965.EPI-19-1044

©2019 American Association for Cancer Research.

Cheung et al.

Analysis and Reporting System (CDARS), of the Hong Kong Hospital Authority. The Hospital Authority is the only public-funded health-care provider in Hong Kong with a population of around 7.3 million, covering 87% to 94% of all secondary and tertiary care in the territory during the study period (23). Essential clinical information such as patient's demographics, death, diagnoses, drug dispensing records, procedures and laboratory results, hospitalization records, attendance of outpatient clinics, and emergency departments are all recorded in CDARS. Prescription and dispensing are performed at the same time, and prescription record generally matches the dispensing record. Various studies utilizing CDARS were undertaken (24–27), demonstrating a high diagnostic coding accuracy [International Classification of Diseases, Ninth Revision (ICD-9)] with positive and negative predictive values of more than 85% to 90%.

This study was conducted in accordance with Declaration of Helsinki. Each patient was assigned an anonymous identifier (reference key) in CDARS to protect confidentiality. Therefore, written informed consent was not required with ethics approval obtained from the Institutional Review Board of the University of Hong Kong and the Hong Kong West Cluster of the Hospital Authority.

Study subjects

All *H. pylori*-infected adults ages ≥ 18 years who had received a course of clarithromycin-based triple therapy for *H. pylori* between January 1, 2003 and December 31, 2012 (i.e., index date) were

identified from CDARS. The use of triple therapy was identified by co-prescription of one of the proton pump inhibitors (PPI) with clarithromycin and either amoxicillin or metronidazole with the correct doses, same prescription start date, and a treatment duration of 7 to 14 days as described previously (25, 26). Clarithromycin-based triple therapy was the first-line treatment for *H. pylori* due to the low clarithromycin resistance rate (8%; ref. 28) and high eradication rate ($>90\%$) in Hong Kong during the study period (29). Endoscopy-based tests (including histology and rapid urease test) as well as urea breath test are the only diagnostic tests for *H. pylori* infection available in local public hospitals.

Exclusion criteria were: (i) gastric cancer development within the first year of index date (to exclude prevalent cases due to possibly missed/delayed diagnosis); (ii) history of gastric cancer or gastrectomy before index date; and (iii) triple therapy failure. Because of unavailability of direct ICD-9 code, triple therapy failure was inferred by repeated clarithromycin-based triple therapy, or requirement of a second-line therapy (either PPI–levofloxacin–amoxicillin or bismuth-based quadruple therapy), or a third-line therapy (rifabutin-based therapy). Subject recruitment process is depicted in Fig. 1.

Study outcome and data validation

The outcome of interest was gastric adenocarcinoma. We observed the patients from index date, and they were censored at cancer diagnosis, death or study end date (December 31, 2015).

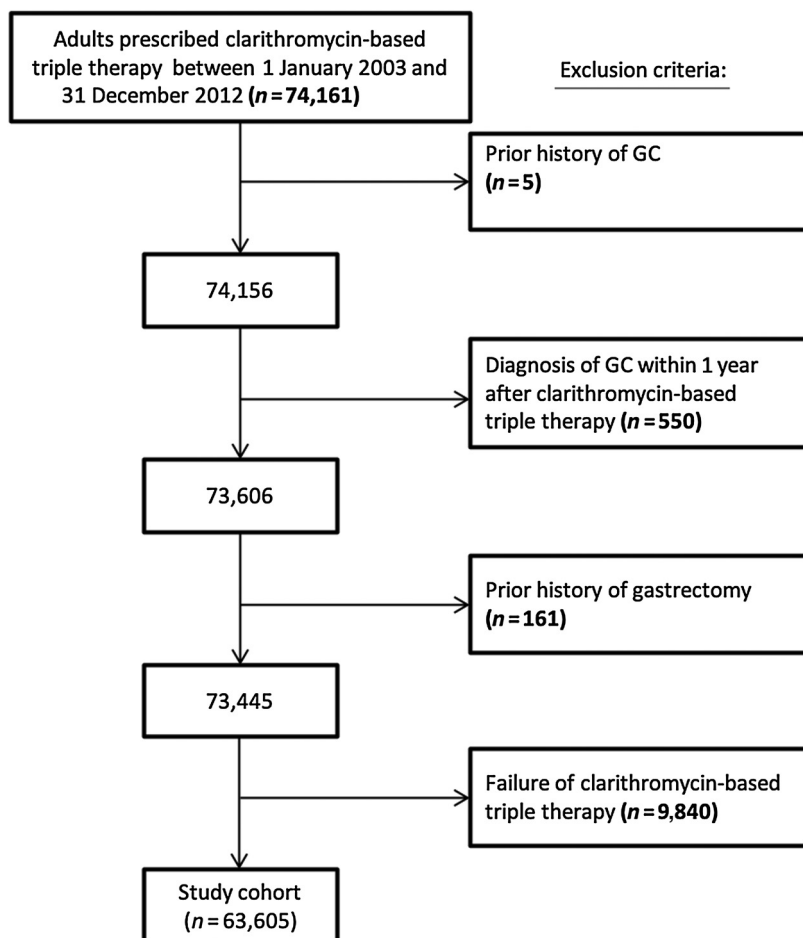


Figure 1. Patient selection flow diagram. GC, gastric cancer.

Table 1. Baseline characteristics of study cohort before and after propensity score matching.

	All (n = 63,605)	Before PS matching			After PS matching ^a		
		Statin (n = 15,990)	Nonstatin (n = 47,615)	ASD ^b	Statin (n = 11,678)	Nonstatin (n = 11,192)	ASD ^b
Age at triple therapy (years)	55.6 (±14.6)	62.6 (±11.1)	53.5 (±14.9)	0.66	61.7 (±11.0)	63.6 (±13.8)	0.18
Male sex (n, %)	29,629 (46.6%)	8,041 (50.3%)	21,588 (45.3%)	0.09	5,714 (48.9%)	5,313 (47.5%)	0.01
Duration of follow-up (years)	7.6 (5.1–10.3)	8.0 (5.5–10.5)	7.4 (4.9–10.2)	—	7.9 (5.5–10.3)	7.1 (4.7–9.8)	—
Smoking (n, %)	1,647 (2.6%)	561 (3.5%)	1,086 (2.3%)	0.08	394 (3.4%)	327 (2.9%)	0.02
Alcohol (n, %)	556 (0.9%)	78 (0.5%)	478 (1.0%)	0.01	51 (0.4%)	45 (0.4%)	0.01
History of GU (n, %)	1,463 (2.3%)	448 (2.8%)	1,015 (2.1%)	0.05	322 (2.8%)	286 (2.6%)	0.03
History of DU (n, %)	1,913 (3.0%)	444 (2.8%)	1,469 (3.1%)	0.02	318 (2.7%)	270 (2.4%)	0.01
DM (n, %)	7,436 (11.7%)	4,652 (29.0%)	2,784 (5.8%)	0.44	2,827 (24.2%)	1,821 (16.3%)	0.07
Dyslipidemia (n, %)	5,082 (8.0%)	3,974 (24.9%)	1,108 (2.3%)	0.39	1,897 (16.2%)	851 (7.6%)	0.08
Hypertension (n, %)	13,173 (20.7%)	6,776 (42.4%)	6,397 (13.4%)	0.47	4,271 (36.6%)	3,221 (28.8%)	0.06
IHD (n, %)	5,756 (9.0%)	4,189 (26.2%)	1,567 (3.3%)	0.37	2,054 (17.6%)	1,092 (9.8%)	0.05
AF (n, %)	2,439 (3.8%)	1,107 (6.9%)	1,332 (2.8%)	0.16	770 (6.6%)	653 (5.8%)	0.04
CHF (n, %)	2,554 (4.0%)	1,300 (8.1%)	1,254 (2.6%)	0.18	831 (7.2%)	612 (5.5%)	0.02
Stroke (n, %)	4,005 (6.3%)	2,422 (15.1%)	1,583 (3.3%)	0.28	1,485 (12.7%)	929 (8.3%)	0.01
CRF (n, %)	1,416 (2.2%)	764 (4.8%)	652 (1.4%)	0.14	487 (4.2%)	362 (3.3%)	0.40
Cirrhosis (n, %)	1,049 (1.6%)	115 (0.7%)	934 (2.0%)	0.02	75 (0.6%)	86 (0.8%)	0.03
Aspirin (n, %)	11,116 (17.5%)	7,684 (48.1%)	3,432 (7.2%)	0.63	4,215 (36.1%)	2,287 (20.4%)	0.01
Metformin (n, %)	8,993 (14.1%)	6,200 (38.8%)	2,793 (5.9%)	0.57	3,772 (32.3%)	2,253 (20.1%)	0.06
NSAIDs/COX-2 inhibitors (n, %)	14,692 (23.1%)	4,435 (27.7%)	10,257 (21.5%)	0.10	1,418 (12.1%)	1,383 (12.4%)	0.01
PPIs (n, %)	7,715 (12.1%)	2,955 (18.5%)	4,760 (10.0%)	0.18	1,224 (10.5%)	1,020 (9.1%)	0.02

Note: Age of receiving triple therapy was expressed as mean (years) ± 1 SD. Duration of follow-up was expressed as median (years) with IQR. Categorical variables were expressed as number (%). Drug use was defined as use for more than 180 days, and expressed as number (%).

Abbreviations: AF, atrial fibrillation; ASD, absolute standardized difference; CHF, congestive heart failure; CRF, chronic renal failure; DM, diabetes mellitus; DU, duodenal ulcer; GU, gastric ulcer; IHD, ischemic heart disease; PS, propensity score.

^aPS matching was performed after trimming of the extreme PS strata (5th and 95th percentiles). Nonstatin users were matched to statin users on PS within a caliper width of 0.1. All variables were included in the model for PS estimation.

^bVariables with an ASD >0.20 are considered to be imbalanced.

Supplementary Table S1 shows the ICD-9 codes for gastric adenocarcinoma. The date of cancer diagnosis was the earliest date of hospitalization for treatment and/or workup.

As individuals are anonymized in CDARS, we could only validate the outcome of subjects in our institution (Queen Mary Hospital), which is an acute hospital and a tertiary referral center. The clinical details of 14 (8.3%) patients with gastric cancer were reviewed, with all fulfilling the selection criteria. Histology reports revealed all cases being adenocarcinoma without *H. pylori* infection.

Exposure of interest and covariates

The exposure of interest was statin usage after index date. Simvastatin, atorvastatin, and rosuvastatin were the only statins available in the public hospitals. Covariates used for propensity score (PS) matching (described in details in later section) included the age of receiving triple therapy, sex, alcohol use, smoking, prior peptic ulcer disease, diabetes mellitus (30), and other comorbidities (hypertension, dyslipidemia, ischemic heart disease, atrial fibrillation, congestive heart failure, stroke, cirrhosis, and chronic renal failure) as well as usage of other drugs [NSAIDs, aspirin (25), COX-2 inhibitors, metformin (26), and PPIs (31); **Table 1**]. As the true prevalence of smoking and alcoholism may be underestimated by diagnosis coding only, a large set of comorbidities were included to serve as surrogate markers of these two imperfectly measured confounders. The diagnosis codes of these variables are shown in Supplementary Table S1.

We defined statin exposure (as well as other medications) as ≥180-day use after index date during the observation period according to Lee and colleagues (11). The date of prescription, daily dose, and duration of each prescription were collected. To investigate dose–response

relationship, we quantified statin use based on the defined daily doses (DDD) to unify the dose for different statins (one DDD is equivalent to simvastatin 30 mg, atorvastatin 20 mg, and rosuvastatin 10 mg; ref. 32). With this approach, the cDDD would take both the potency and quantity of statins into consideration, which is a common proxy for both duration and dose effect of different statins. Cumulative DDD (cDDD) was then derived by summing the DDDs of any statins during observation period. To investigate the duration–response relationship, statin use was categorized into three groups: (i) nonstatin use, (ii) <5 years, and (iii) ≥5 years.

Statistical analyses

We used R version 3.2.3 (R Foundation for Statistical Computing) statistical software to perform the statistical analyses. We expressed continuous variables as median and interquartile range (IQR). PS analysis was used to control for confounding due to imbalance in treatment allocation. PS was derived by multivariable logistic regression taking various covariates (age, sex, comorbidities, and concurrent medications) into consideration. As such, any difference in cancer risk would be theoretically ascribed to statin effect solely. Furthermore, we excluded individuals in the extreme ends of PS distribution to reduce the effect of unmeasured confounding (33). Twenty categories of 5% each for the PS distribution were created, followed by trimming of the first and 20th PS categories (i.e., PS trimming).

We used PS matching as the primary analysis to calculate gastric cancer risk with statin usage with reference to nonstatin usage. Statin users were matched to nonstatin users in a 1:1 ratio with replacement using a greedy distance-based matching algorithm with the logit of the PS within 0.1 standard deviation. Because of the strict matching

Table 2. Association between statin use and gastric cancer risk (whole cohort and stratified analysis according to noncardia and cardia regions).

Statin use	Univariate analysis (n = 63,605, GC = 169)		PS matching ^a (n = 22,870, GC = 62)		PS adjustment ^a (n = 57,243, GC = 150)		Multivariable analysis (n = 63,605, GC = 169)	
	SHR (95% CI)	P value	SHR (95% CI)	P value	SHR (95% CI)	P value	SHR (95% CI)	P value
Nonstatin use	Ref	—	Ref	—	Ref	—	Ref	—
Statin use	0.61 (0.41–0.92)	0.020	0.34 (0.19–0.61)	<0.001	0.33 (0.18–0.59)	<0.001	0.44 (0.28–0.68)	<0.001
Noncardia GC	(n = 63,571, GC = 135)		(n = 22,865, GC = 36)		(n = 57,123, GC = 120)		(n = 63,571, GC = 135)	
	SHR (95% CI)	P value	SHR (95% CI)	P value	SHR (95% CI)	P value	SHR (95% CI)	P value
Nonstatin use	Ref	—	Ref	—	Ref	—	Ref	—
Statin use	0.56 (0.35–0.90)	0.017	0.48 (0.24–0.98)	0.044	0.33 (0.17–0.65)	0.001	0.46 (0.27–0.74)	0.002
Cardia GC	(n = 63,470, GC = 34)		(n = 22,865, GC = 15)		(n = 57,123, GC = 30)		(n = 63,470, GC = 34)	
	SHR (95% CI)	P value	SHR (95% CI)	P value	SHR (95% CI)	P value	SHR (95% CI)	P value
Nonstatin use	Ref	—	Ref	—	Ref	—	Ref	—
Statin use	0.83 (0.39–1.90)	0.660	n.a. ^b (n.a. ^b)	n.a. ^b	0.31 (0.09–1.03)	0.055	n.a. ^b (n.a. ^b)	n.a. ^b

Note: Statin use was defined as use for more than 180 days.

Abbreviations: GC, gastric cancer; SHR, subdistribution hazard ratio.

^aPS analysis was performed after trimming of the extreme PS strata (5th and 95th percentiles).

^bSHR could not be calculated as the estimation procedure for fitting the subdistribution hazard model failed to converge.

criteria, the final patient number was 11,678 and 11,192 in statin and nonstatin groups. The balance of covariates between the two groups was assessed by absolute standardized difference (ASD), which was derived from the absolute difference in means or proportions divided by the pooled standard deviation. An ASD of <0.20 indicates good balance for a particular covariate. Imbalance covariates with ASD >0.20 after matching were adjusted for in the competing regression risk model (34).

Competing risk regression model was used to estimate the subdistribution hazard ratio (SHR; ref. 35), as death was a competing risk for gastric cancer with statin users having higher cardiovascular risk (Table 1) and thus mortality. Stratified analysis was performed according to the location of gastric cancer (cardia and noncardia regions), as the underlying carcinogenic mechanisms differ (22). The PS adjusted absolute difference in cancer risk between the two groups was derived by (adjusted HR – 1) × (crude incidence rate of gastric cancer in nonstatin users). The duration- and dose-response relationship between statins and gastric cancer was derived by the competing risk regression model using PS adjustment after trimming. The trend for duration-response of statins was assessed by Cochran-Armitage test. The survival difference between the statin and nonstatin users was illustrated in terms of Kaplan-Meier curve and log-rank P value.

Sensitivity analyses were conducted by (i) changing the days of exposure to define statin use (≥30 and ≥90 days), (ii) not including other comorbidities except for peptic ulcer disease and diabetes mellitus, (iii) PS regression adjustment with trimming (with all covariates included into the competing risk regression model), (iv) multivariable analysis as well as (v) Cox proportional hazards model (effect estimate expressed as adjusted HR). “Complementary log-log”-scaled Kaplan-Meier plot and Schoenfeld residuals for statin use (P-value > 0.05) confirmed nonviolation of the Cox proportional-hazard assumption. Prior statin users (defined as individuals with any statin prescription within 2 years before the index date) were excluded in further sensitivity analysis.

To address potential immortal time bias that may spuriously augment the beneficial effect of a drug (36), further sensitivity analysis was performed by treating all medications including statins as time-varying covariates in the multivariable Cox model (37), in which the

observation period was disintegrated into yearly intervals and medication usage was defined as ≥90-day use in each interval. Statistical significance was defined by a two-sided P value of <0.05.

Results

Cohort characteristics

We identified 63,605 eligible subjects. Table 1 shows the baseline characteristics of the cohort. Out of 54,594 subjects with available ethnicity data, 54,219 (99.3%) were Asian. The mean age of receiving clarithromycin-based triple therapy was 55.6 (±14.6) years, and 46.6% were male. There were 15,990 (25.1%) statin users in the cohort [simvastatin:12,578 (78.7%); atorvastatin: 532 (3.3%); rosuvastatin: 275 (1.7%); use of two or more statins at different times: 2,605 (16.3%)]. Before PS matching, most of the baseline characteristics were imbalance between statin and nonstatin users. However, there was no statistically significant difference in the median number of upper endoscopies (statin users: 2, IQR: 1.5–3 vs. nonstatin users: 2, IQR: 1–3; P = 0.892). After PS matching, a balance of covariates were achieved between the two groups except for chronic renal failure (ASD > 0.2), which was adjusted for in the subsequent competing risk regression model.

Risk of gastric cancer development

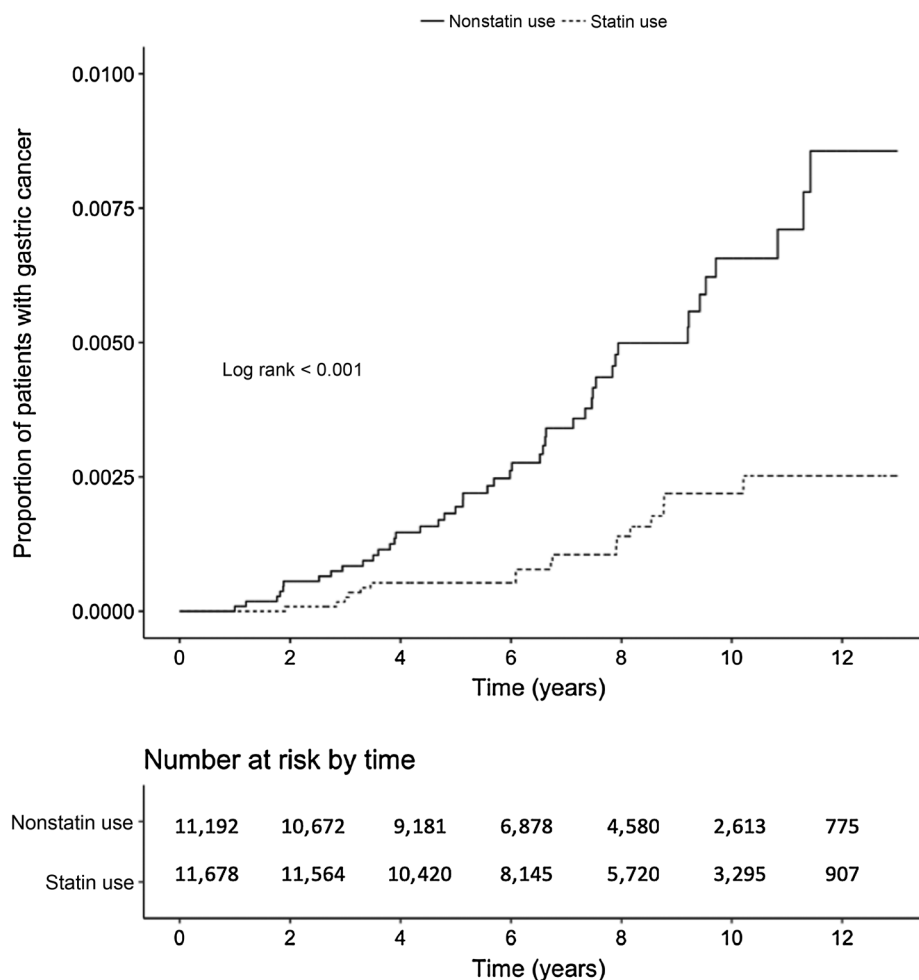
During a median follow up of 7.6 years (IQR: 5.1–10.3) with 484,680 person-years, 169 (0.27%) patients were diagnosed with gastric cancer at an incidence rate of 3.5 per 10,000 person-years. Patients with gastric cancer were diagnosed at a median of 71.1 years (IQR = 61.6–81.8), and they received eradication therapy at a median of 66.7 years (IQR = 56.6–76.5). The location of these cancers were as follows: 34 (20.1%) in cardia, 98 (58.0%) in noncardia region, and site was unspecified in 37 (21.9%) cases.

Relationship between statins and gastric cancer

The median duration of statin use was 3.6 years (IQR = 1.6–5.9), with a median cDDD of 432 (IQR = 181.6–323.2). Thirty-one (0.19%) of 15,990 statin users developed gastric cancer (crude incidence rate: 2.4 per 10,000 person-years). In contrast, 138 (0.29%) nonstatin users developed gastric cancer (crude incidence rate: 3.8 per 10,000

Figure 2.

Kaplan-Meier plot of gastric cancer incidence among propensity score matched statin and nonstatin users.



person-years). After PS matching, statins were associated with a lower gastric cancer risk [adjusted SHR = 0.34; 95% confidence interval (95% CI), 0.19–0.61; **Table 2**]. The PS adjusted absolute risk difference was 2.6 fewer gastric cancers (95% CI, 1.56–3.12) per 10,000 person-years when comparing statin with nonstatin use. **Figure 2** shows the Kaplan-Meier plot of gastric cancer incidence among statin and nonstatin users (log-rank $P < 0.001$). Stratified analysis shows statins remained protective for noncardia cancer (SHR = 0.48; 95% CI, 0.24–0.98), but borderline significance was noted for cardia cancer (SHR = 0.31; 95% CI, 0.09–1.03).

Sensitivity analyses by changing days of exposure to define statin use to ≥ 30 and ≥ 90 days show similar results (≥ 30 -day use: SHR = 0.34; 95% CI, 0.20–0.59; $P < 0.001$; ≥ 90 -day use: SHR = 0.32; 95% CI, 0.18–0.56; $P < 0.001$). By not including other comorbidities except for peptic ulcer disease and diabetes mellitus, the SHR was 0.45 (95% CI, 0.27–0.77; $P = 0.003$). A total of 3,621 patients had prior statin use and were excluded for sensitivity analysis. The adjusted SHR was 0.26 (95% CI, 0.12–0.55; $P < 0.001$). Sensitivity analysis by competing risk regression model using PS regression adjustment with trimming and multivariable analysis yield similar results (**Table 2**). PS matching with Cox model also showed that adjusted HR of gastric cancer with statins was 0.29 (95% CI, 0.16–0.52). When analyzing medications as time-varying covariates in the multivariable Cox model, the adjusted HR was 0.54 (95% CI: 0.35–0.87).

Duration- and dose-response association between statins and gastric cancer

Table 3 shows that a lower gastric cancer risk was observed among patients who used statins longer [SHR = 0.46 (95% CI, 0.25–0.86) for < 5 years of use and SHR 0.43 (95% CI, 0.29–0.66) for ≥ 5 years of use; $P_{\text{trend}} < 0.001$]. In addition, the SHR of gastric cancer with every 100 increase in cDDD of statins was 0.90 (95% CI, 0.81–0.99).

Discussion

Individuals can develop gastric cancer despite successful *H. pylori* eradication. In this cohort study of more than 63,000 patients with prior *H. pylori* treatment, we demonstrate that statins were associated with a 66% decrease in gastric cancer risk in a duration- and dose-dependent manner.

To date, association between statins and gastric cancer remains elusive. Although a previous meta-analysis of 11 studies (21) conclude that statins were associated with a lower risk of gastric cancer, one of the major limitations of the included studies was the failure to acknowledge the *H. pylori* status (21). The study by Chiu and colleagues (10) was the only one that adjusted for *H. pylori* eradication, but 85% of the patients had unknown *H. pylori* status in that study. Failure to account for this causative factor likely poses a significant impact on determining the causal relationship and magnitude of beneficial effect of statins on gastric cancer. In addition, gastric cancer was the primary

Table 3. Association between duration and dose of statin use and gastric cancer risk (propensity score adjustment).

Statin use	SHR ^a (95% CI)	P value	P _{trend}
Duration			
Nonstatin use	Ref (–)	–	<0.001
<5 years	0.46 (0.25–0.86)	0.015	
≥5 years	0.43 (0.29–0.66)	<0.001	
Dose			
Nonstatin use	Ref (–)	–	
Statin use (for every 100 increase in cDDD)	0.90 (0.81–0.99)	0.037	

^aSHR was derived by PS adjustment after trimming of the extreme PS strata (5th and 95th percentiles).

outcome of interest in two studies only (10, 11). Also, inadequate adjustment for major risk factors [history of peptic ulcer diseases (38), diabetes mellitus (39), and medication usage (aspirin/NSAIDs (40, 41), metformin (42), and PPIs (43))] may either under- or overestimate the effects of statins (44). Of note, post-hoc analyses of randomized controlled trials of cardiovascular studies included a relatively short follow-up duration, with potential ascertainment bias and bias from competing risks (44).

Although being an observational study, our study had a large sample size (>63,000) with long follow-up duration (median 7.6 years), eliminated the confounding effect of *H. pylori* infection, and used PS matching to minimize bias. Importantly, few studies systematically evaluated the duration- and dose-response of statins use (44). The chemopreventive effects of statins shown in this study (SHR = 0.34) was greater than that reported by previous studies (ORs ranging from 0.68 to 0.84; refs. 10, 12, 13), except for the study by Lee and colleagues (11) which recruited patients with diabetes mellitus only (OR = 0.21). The greater risk reduction observed in this study could be due to the inclusion of subjects with prior *H. pylori* infection, therefore having a higher gastric cancer risk. We also performed stratified analysis according to cancer site, which had not been performed in any of the previous studies. We found that statins was protective against noncardia cancer, whereas the beneficial effect was of borderline significance for cardia cancer (SHR of 0.31 with $P = 0.055$). This result should be interpreted with caution due to underpower (number of cardia cancer cases = 34). Finally, our study used the territory-wide healthcare database with complete capture of diagnosis, drug prescription, and dispensing records, which could address potential selection, information, and recall biases of previous observational studies (45). Surveillance or ascertainment bias was unlikely as there existed no difference in the number of upper endoscopies between the statin and nonstatin users. The robustness of the result was further supported by various sensitivity analyses, in particular by using time-varying covariates in treating all medications to address potential immortal time bias. Furthermore, as statin users generally had more comorbidities like cardiovascular diseases and diabetes mellitus (Table 1), this negates the concern of healthy user bias (46). As such, any beneficial effect of statin would only be underestimated (i.e. biased towards null).

There are several limitations of this study. First, residual and unmeasured confounding may still exist for an observational study despite PS matching. Second, information on some risk factors were unavailable in our database, for instance, diet, body mass index, and family history. Third, the accuracy of diagnosis code could only be confirmed by validation of a small subset of gastric cancer patients who

had follow-up in our institution. There is also likely an underestimation of prevalence of smoking and alcohol use with ICD-9 codes of COPD and alcohol-related diseases only, although the inclusion of a large set of comorbidities helps to act as surrogate markers for these two imperfectly measured confounders. Fourth, identification of patients with failure of clarithromycin-based triple therapy was indirect rather than based on the actual posttreatment *H. pylori* status because this information was unavailable in the database. Nevertheless, the retreatment rate of 13% in our study was consistent with that reported in our locality during the study period (28). *H. pylori* recurrence could not be ascertained in this database. However, a past local study showed an annual recurrence rate of 3.3% only (47). Fifth, compliance to medications could not be confirmed, although non-compliance will usually underestimate the beneficial effect of statins. Although data on over-the-counter (OTC) medication usage is unavailable, this is unlikely is a major concern as medications are dispensed at a very low cost from hospital pharmacy in Hong Kong. Unlike western countries, OTC purchase of aspirin is uncommon in Hong Kong. The leading antipyretic agent is paracetamol whereas NSAIDs are more often used in pain relief. Sixth, as data on baseline gastric histology was not available, we could not determine on what stages along the Correa cascade that statins exert the strongest effect. Finally, generalizability of the study result to other statins is a concern, as the majority of patients (79%) were prescribed simvastatin. In addition, this study only focuses on the specific group of *H. pylori*-eradicated patients. Further research on the chemopreventive effects of statins in both *H. pylori*-positive and -negative subjects is mandated.

Conclusions

Long-term statin use associated a lower gastric cancer risk in a dose- and duration-response manner among *H. pylori*-eradicated patients. Our findings may help in decision making for initiating statins in patients at high gastric cancer risk.

Disclosure of Potential Conflicts of Interest

W.-K. Seto reports receiving speakers bureau honoraria from Mylan. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: K.S. Cheung, A.Y.S. Wong, W.K. Leung
Development of methodology: K.S. Cheung, I.C.K. Wong
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.Y.S. Wong, L. Chen, W.-K. Seto, I.C.K. Wong
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.S. Cheung, E.W. Chan, A.Y.S. Wong, W.-K. Seto, W.K. Leung
Writing, review, and/or revision of the manuscript: K.S. Cheung, E.W. Chan, A.Y.S. Wong, W.-K. Seto, I.C.K. Wong, W.K. Leung
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.S. Cheung, L. Chen
Study supervision: E.W. Chan, W.K. Leung

Acknowledgments

The electronic database utilized in this study is managed by the Hong Kong Hospital Authority, and researchers were granted approval to access this database without charge.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 24, 2019; revised October 8, 2019; accepted November 25, 2019; published first December 2, 2019.

References

- Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol* 2017;3:524–48.
- Helicobacter and Cancer Collaborative Group. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001;49:347–53.
- Correa P, Piazuelo MB, Camargo MC. The future of gastric cancer prevention. *Gastric Cancer* 2004;7:9–16.
- Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, et al. Association between Helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. *Gastroenterology* 2016;150:1113–24.
- Cheung KS, Leung WK. Risk of gastric cancer development after eradication of Helicobacter pylori. *World J Gastrointest Oncol* 2018;10:115–23.
- Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–78.
- Demierre MF, Higgins PD, Gruber SB. Statins and cancer prevention: statins and cancer prevention. *Nat Rev Cancer* 2005;5:930–42.
- Follet J, Corcos L, Baffet G, Ezan F, Morel F, Simon B, et al. The association of statins and taxanes: an efficient combination trigger of cancer cell apoptosis. *Br J Cancer* 2012;106:685–92.
- Cheng-Qian Y, Xin-Jing W, Wei X, Zhuang-Lei G, Hong-Peng Z, Songde X, et al. Lovastatin inhibited the growth of gastric cancer cells. *Hepatogastroenterology* 2014;61:1–4.
- Chiu HF, Ho SC, Chang CC, Wu TN, Yang CY. Statins are associated with a reduced risk of gastric cancer: a population-based case-control study. *Am J Gastroenterol* 2011;106:2098–103.
- Lee J, Lee SH, Hur KY, Woo SY, Kim SW, Kang WK. Statins and the risk of gastric cancer in diabetes patients. *BMC Cancer* 2012;12:596.
- Haukka J, Sankila R, Klaukka T, Lonnqvist J, Niskanen L, Tanskanen A, et al. Incidence of cancer and statin usage—record linkage study. *Int J Cancer* 2010;126:279–84.
- Matsushita Y, Sugihara M, Kaburagi J, Ozawa M, Iwashita M, Yoshida S, et al. Pravastatin use and cancer risk: a meta-analysis of individual patient data from long-term prospective controlled trials in Japan. *Pharmacoepidemiol Drug Saf* 2010;19:196–202.
- Kaye JA, Jick H. Statin use and cancer risk in the general practice research database. *Br J Cancer* 2004;90:635–7.
- Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to statins and risk of common cancers: a series of nested case-control studies. *BMC Cancer* 2011;11:409.
- Embersson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhalra N, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. *PLoS One* 2012;7:e29849.
- Friedman GD, Flick ED, Udaltsova N, Chan J, Quesenberry CP Jr, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. *Pharmacoepidemiol Drug Saf* 2008;17:27–36.
- Graaf MR, Beiderbeck AB, Egberts AC, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. *J Clin Oncol* 2004;22:2388–94.
- Marelli C, Gunnarsson C, Ross S, Haas S, Stroup DF, Cloyd P, et al. Statins and risk of cancer: a retrospective cohort analysis of 45,857 matched pairs from an electronic medical records database of 11 million adult Americans. *J Am Coll Cardiol* 2011;58:530–7.
- Sato S, Ajiki W, Kobayashi T, Awata N; PCS Study Group. Pravastatin use and the five-year incidence of cancer in coronary heart disease patients: from the prevention of coronary sclerosis study. *J Epidemiol* 2006;16:201–6.
- Singh PP, Singh S. Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. *Ann Oncol* 2013;24:1721–30.
- Abdi E, Latifi-Navid S, Zahri S, Yazdanbod A, Pourfarzi F. Risk factors predisposing to cardia gastric adenocarcinoma: insights and new perspectives. *Cancer Med* 2019;8:6114–26.
- The Hospital Authority. Hospital authority statistical report 2012–2013. [cited 2019 Jan 12]. Available from: http://www.ha.org.hk/haho/ho/stat/HASR1415_2.pdf.
- Cheung KS, Chen L, Seto WK, Leung WK. Epidemiology, characteristics, and survival of post-colonoscopy colorectal cancer in Asia: a population-based study. *J Gastroenterol Hepatol* 2019;34:1545–53.
- Cheung KS, Chan EW, Wong AYS, Chen L, Seto WK, Wong ICK, et al. Aspirin and risk of gastric cancer after Helicobacter pylori eradication: a territory-wide study. *J Natl Cancer Inst* 2018;110:743–9.
- Cheung KS, Chan EW, Wong AYS, Chen L, Seto WK, Wong ICK, et al. Metformin use and gastric cancer risk in diabetic patients after Helicobacter pylori eradication. *J Natl Cancer Inst* 2019;111:484–9.
- Cheung KS, Chen L, Chan EW, Seto WK, Wong ICK, Leung WK. Statins reduce the progression of non-advanced adenomas to colorectal cancer: a postcolonoscopy study in 187 897 patients. *Gut* 2019;68:1979–85.
- Gu Q, Xia HH, Wang JD, Wong WM, Chan AO, Lai KC, et al. Update on clarithromycin resistance in Helicobacter pylori in Hong Kong and its effect on clarithromycin-based triple therapy. *Digestion* 2006;73:101–6.
- Hung IF, Chan P, Leung S, Chan FS, Hsu A, But D, et al. Clarithromycin-amoxylicillin-containing triple therapy: a valid empirical first-line treatment for Helicobacter pylori eradication in Hong Kong? *Helicobacter* 2009;14:505–11.
- Cheung KS, Chan EW, Chen L, Seto WK, Wong ICK, Leung WK. Diabetes increases risk of gastric cancer after Helicobacter pylori eradication: a territory-wide study with propensity score analysis. *Diabetes Care* 2019;42:1769–75.
- Cheung KS, Leung WK. Long-term use of proton-pump inhibitors and risk of gastric cancer: a review of the current evidence. *Therap Adv Gastroenterol* 2019;12:1756284819834511.
- WHO Collaborating Center for Drugs Statistics Methodology. ATC/DDD Index 2020. [cited 2019 Jul 12]. Available from: https://www.whocc.no/atc_ddd_index/.
- Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution—a simulation study. *Am J Epidemiol* 2010;172:843–54.
- Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
- Targownik LE, Suissa S. Understanding and avoiding immortal-time bias in gastrointestinal observational research. *Am J Gastroenterol* 2015;110:1647–50.
- Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med* 2018;6:121.
- Hansson LE, Nyren O, Hsing AW, Bergström R, Josefsson S, Chow WH, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. *N Engl J Med* 1996;335:242–9.
- Yoon JM, Son KY, Eom CS, Durrance D, Park SM. Pre-existing diabetes mellitus increases the risk of gastric cancer: a meta-analysis. *World J Gastroenterol* 2013;19:936–45.
- Wu CY, Wu MS, Kuo KN, Wang CB, Chen YJ, Lin JT. Effective reduction of gastric cancer risk with regular use of nonsteroidal anti-inflammatory drugs in Helicobacter pylori-infected patients. *J Clin Oncol* 2010;28:2952–7.
- Cheung KS, Leung WK. Modification of gastric cancer risk associated with proton pump inhibitors by aspirin after Helicobacter pylori eradication. *Oncotarget* 2018;9:36891–3.
- Zhou XL, Xue WH, Ding XF, Li LF, Dou MM, Zhang WJ, et al. Association between metformin and the risk of gastric cancer in patients with type 2 diabetes mellitus: a meta-analysis of cohort studies. *Oncotarget* 2017;8:55622–31.
- Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. *Gut* 2018;67:28–35.
- Wu XD, Zeng K, Xue FQ, Chen JH, Chen YQ. Statins are associated with reduced risk of gastric cancer: a meta-analysis. *Eur J Clin Pharmacol* 2013;69:1855–60.
- Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol* 2012;13:518–27.
- Patrick AR, Shrank WH, Glynn RJ, Solomon DH, Dormuth CR, Avorn J, et al. The association between statin use and outcomes potentially attributable to an unhealthy lifestyle in older adults. *Value Health* 2011;14:513–20.
- Lai KC, Lam SK, Chu KM, Wong BC, Hui WM, Hu WH, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002;346:2033–8.

Cancer Epidemiology, Biomarkers & Prevention

Statins Were Associated with a Reduced Gastric Cancer Risk in Patients with Eradicated *Helicobacter Pylori* Infection: A Territory-Wide Propensity Score Matched Study

Ka Shing Cheung, Esther W. Chan, Angel Y.S. Wong, et al.

Cancer Epidemiol Biomarkers Prev 2020;29:493-499. Published OnlineFirst December 2, 2019.

Updated version Access the most recent version of this article at:
doi:[10.1158/1055-9965.EPI-19-1044](https://doi.org/10.1158/1055-9965.EPI-19-1044)

Supplementary Material Access the most recent supplemental material at:
<http://cebp.aacrjournals.org/content/suppl/2019/12/04/1055-9965.EPI-19-1044.DC1>

Cited articles This article cites 45 articles, 7 of which you can access for free at:
<http://cebp.aacrjournals.org/content/29/2/493.full#ref-list-1>

Citing articles This article has been cited by 1 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/29/2/493.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/29/2/493>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.