Diabetes Increases Risk of Gastric Cancer After *Helicobacter pylori* Eradication: A Territory-Wide Study With Propensity Score Analysis

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OBJECTIVE

Whether diabetes mellitus (DM) increases risk of gastric cancer (GC) remains controversial because of inadequate adjustments for important risk factors, including *Helicobacter pylori* (HP) infection status, concomitant medication use, and cancer site. We investigated whether type 2 DM increased risk of GC in patients after they received treatment for HP infection.

RESEARCH DESIGN AND METHODS

This was a territory-wide cohort study of patients aged ≥45 years who had received clarithromycin-based triple therapy for HP infection between 2003 and 2012 in Hong Kong. Data were retrieved from a public electronic health database. Observation started from receipt of therapy for HP infection to GC diagnosis, death, or the end of the study (December 2015). Exclusion criteria included type 1 DM, GC diagnosed within the 1st year of HP therapy, prior GC or gastrectomy, and retreatment for HP infection. The adjusted hazard ratio (aHR) of GC with type 2 DM was calculated by using a Cox model that adjusted for 20 covariates (age, sex, comorbidities, and medications) through propensity score regression.

RESULTS

During a median follow-up of 7.1 years (interquartile range 4.8–9.3 years), 153 of 46,460 patients (0.33%) developed GC at a median age of 72.4 years. Type 2 DM was associated with an increased risk of GC (aHR 1.73 [95% CI 1.08–2.79]). Stratified analysis showed an increase in risk for cardia cancer only (aHR 3.40 [95% CI 1.45–7.97]) and in those with suboptimal DM control (time-weighted mean HbA_{1c} ≥6.0% [42 mmol/mol]; aHR 1.68 [95% CI 1.07–2.63]).

CONCLUSIONS

Type 2 DM is associated with an increased risk of GC among patients in whom HP was eradicated, in particular gastric cardia cancer and in those with suboptimal DM control.

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide (1). The presence of *Helicobacter pylori* infection increases the risk of GC by at least threefold, and it remains the most important risk factor for GC (2,3) because it triggers the Correa cascade of multistage gastric

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carcinogenesis (4). Despite *H. pylori* eradication, a recent meta-analysis demonstrated that the risk of developing GC can be reduced by only 38% among asymptomatic individuals (5).

In addition to *H. pylori* infection, the presence of diabetes mellitus (DM) has also been linked to GC development. Various potential biological mechanisms for this have been proposed, including stimulation of cell proliferation via hyperinsulinemia and increased production of insulin-like growth factor (6), promotion of angiogenesis by increasing vascular endothelial growth factor level (7), and DNA damage as a direct effect of hyperglycemia (8) and an indirect effect of increased production of reactive oxygen species (9).

To date, data conflict regarding the association between GC and DM. A meta-analysis of 17 observational studies showed that DM increased the risk of GC by 19% (10), but another meta-analysis of 15 cohort studies refuted this association, showing a pooled relative risk of 1.10 (95% CI 0.94–1.29) (11). Failure to stratify patients with DM by *H. pylori* infection might be an important reason for this disparity. In addition, GC risk was higher among *H. pylori*–infected subjects with higher hemoglobin A_{1c} (HbA_{1c}) levels in a Japanese population-based cohort study. Those with HbA_{1c} $\geq$6.0% (42 mmol/mol) had a more than twofold higher GC risk than individuals with HbA_{1c} of 5.0–5.9% (31–41 mmol/mol) (12). Furthermore, none of the existing studies adjusted for concomitant medication use, which might modulate the risk of GC. These medications include aspirin (13), nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, statins (14), metformin (15), and proton pump inhibitors (PPIs) (16,17). Failure to adjust for potential chemopreventive agents could bias a positive association between DM and GC to null, as a higher proportion of patients with DM might require treatment with aspirin, a statin, and metformin. Last, GC from cardia and noncardia regions could have different tumor characteristics and risk factors, but only two of the studies reported GC risk according to the site of cancer (18,19).

Given the high prevalence of DM, which affects more than 12–14% of the adult population worldwide (20), the potential burden of GC attributable to DM could be substantial. Herein we describe a territory-wide cohort study that investigated the association between type 2 DM and GC, after adjusting for various confounding factors, among *H. pylori*–infected patients who had received eradication therapy in Hong Kong.

RESEARCH DESIGN AND METHODS

Study Design and Data Source

This retrospective cohort study was based on the territory-wide electronic health care database in Hong Kong, the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The Hospital Authority is the only statutory public health care provider in Hong Kong that serves the local population of 7.3 million. It covers 87–94% of secondary and tertiary health care services. Patient clinical data recorded in CDARS include demographics, diagnoses, drug prescription and dispensing records, investigation results, hospitalization details, outpatient and emergency department visits, and death. Medications are prescribed and dispensed by hospital pharmacies on the same day at a cost of US$2 per item for a 16-week prescription, and thus the prescription records usually match with the dispensing records. A number of high-quality clinical studies have been conducted using this database (13,16,21–23). We used the ICD-9 to code diagnoses in CDARS; previous studies demonstrated a high degree of accuracy (positive and negative predictive values >90%) of using ICD-9 diagnosis codes in CDARS (13,16,21).

Patient data were deidentified in CDARS and unique reference keys were assigned. Ethical approval was obtained from the institutional review board of the University of Hong Kong and the West Cluster of the Hong Kong Hospital Authority (reference no. UW 16–545).

Study Subjects

We identified all *H. pylori*–infected adults (aged $\geq$45 years) who had received a course of clarithromycin-based triple therapy for *H. pylori* infection between 1 January 2003 and 31 December 2012. During the study period, clarithromycin-based triple therapy was the first-line treatment for *H. pylori* because of the relatively low clarithromycin resistance rate (8%) (24) and the high eradication rate (>90%) (25) in Hong Kong. Prescriptions of clarithromycin-based triple therapy for *H. pylori* infection were identified on the basis of coprescription of a PPI with clarithromycin and either amoxicillin or metronidazole (in the correct dosages), with the same commencement date and a treatment duration of 7–14 days. *H. pylori* infection was diagnosed by using standard tests available in public hospitals: either endoscopy-based tests (rapid urease test or histology) or the urea breath test.

We excluded patients with *1*) type 1 DM, *2*) GC diagnosed within the 1st year of *H. pylori* eradication therapy (as this could be missed cancer), *3*) prior GC, *4*) prior gastrectomy, and *5*) retreatment for *H. pylori* (defined as the need for a repeat course of clarithromycin-based triple therapy or subsequent prescriptions of either a second-line therapy [either PPI/levofloxacin/amoxycillin or bismuth-based quadruple therapy] or a third-line therapy [rifabutin-based therapy]). The patient selection process is depicted in Supplementary Fig. 1.

Study Outcome

The outcome of interest was gastric adenocarcinoma after receiving *H. pylori* eradication therapy. We observed patients from the 1st day of *H. pylori* eradication therapy (i.e., the index date) until the date of GC diagnosis, death, or the end of the study (31 December 2015). The date of GC diagnosis was defined as the earliest date of hospitalization for workup (e.g., upper endoscopy or imaging), treatment (surgery, chemotherapy, radiotherapy, or endoscopy), or both. Supplementary Table 1 shows the ICD-9 codes for gastric adenocarcinoma.

Exposure of Interest and Covariates

The exposure of interest was type 2 DM (ICD-9 codes 250 and 250.x; hereafter simplified as "DM") when *H. pylori* eradication therapy began or after it ended. Overall glycemic control during the observation period was represented by time-weighted mean HbA_{1c}, which was calculated by using the mean HbA_{1c} weighted by time interval between successive measurements in order to avoid bias from irregular time intervals.

Covariates of interest included age at the time of *H. pylori* eradication therapy, sex, cigarette and alcohol use, history of gastric and duodenal ulcers, other comorbidities (atrial fibrillation, ischemic heart disease, congestive heart failure, chronic renal failure, cirrhosis, stroke,

hypertension, and obesity), and use of other medications (aspirin, NSAIDs, COX-2 inhibitors, statins, PPIs, and histamine 2 receptor antagonists). Smoking status was determined directly on the basis of the ICD-9 code V15.82 or indirectly on the basis of the presence of chronic obstructive pulmonary disease. Alcohol use was suggested by the presence of alcohol-related gastrointestinal, hepatic, psychiatric, or neurological disease. Supplementary Table 1 shows the ICD-9 codes for the covariates. Drug exposure was defined as use for more than 180 days after receiving *H. pylori* eradication therapy during the observation period.

Data Validation

Because patient information is anonymous in CDARS, we validated patients' diagnoses using the electronic medical records system only at our own center at Queen Mary Hospital. All 14 patients (9.2%) with a code for "gastric cancer" had histologically confirmed adenocarcinoma without *H. pylori* infection; two of the adenocarcinomas arose from the cardia.

Statistical Analyses

All statistical analyses were performed using R statistical software version 3.2.3 (R Foundation for Statistical Computing). Continuous variables were expressed as median and interquartile range (IQR). We performed propensity score (PS) analysis to control for confounding so that any observed difference in GC risk would likely arise from the diagnosis of DM alone. PS was estimated by using multivariable logistic regression of the aforementioned 20 covariates (age, sex, comorbidities, and medications). PS analysis is preferred over traditional outcome regression models in circumstances where relatively few outcomes exist but multiple variables are included (i.e., $<$10 events per variable) (26), as in this study.

We used PS regression adjustment as the primary PS method; DM and PS (derived from the aforementioned 20 covariates) were included in the Cox proportional hazards model in order to calculate the adjusted hazard ratio (HR) of GC with DM. We calculated PS-adjusted absolute difference in risk between patients with and patients without DM as follows: (adjusted HR − 1) × (crude incidence rate of GC in patients without DM).

Subgroup Analysis

Metformin was associated with a lower risk of GC in a previous meta-analysis (15). Thus we analyzed subgroups according to metformin use, glycemic control (i.e., time-weighted mean HbA_{1c}), and cancer site (cardia and noncardia). We adopted an HbA_{1c} cutoff of 6.0% (42 mmol/mol), given the increased risk of GC in *H. pylori*–infected subjects with higher HbA_{1c} (12).

Sensitivity Analyses

We conducted sensitivity analyses through a Cox regression model using PS matching (patients with DM were matched to those without DM at a 1:2 ratio, without replacement, by using a greedy distance-based matching algorithm, with the logit of the PS within 0.1 SD) and inverse probability of treatment weighting (27). We assessed the balance of covariates between the two groups using the absolute standardized difference, which is the absolute difference in means or proportions divided by the pooled SD. An absolute standardized difference $<$0.20 signifies a good balance for a particular covariate. We also used a competing risk regression model with PS regression adjustment to calculate the adjusted subdistribution HR (28) and thereby eliminate bias from competing risk of death due to higher risk of cardiovascular diseases among patients with DM. In order to further characterize the effect of metformin on GC risk, we used a multivariable Cox regression model that included DM, the 20 covariates, and metformin to calculate the adjusted HR.

We also performed sensitivity analyses by retaining GC cases diagnosed within 1 year after receiving *H. pylori* eradication therapy and all patients who needed retreatment for *H. pylori*, and by excluding patients with other malignant neoplasms (Supplementary Table 1). These analyses adjusted for duration of DM and complications of DM (retinopathy, nephropathy, and peripheral neuropathy).

In this study, unless otherwise specified, the comparison group refers to patients without DM (main, subgroup, and sensitivity analyses). Supplementary Table 2 summarizes the statistical methods we used in this study. For all analyses, a two-sided P value $<$0.05 defined statistical significance.

RESULTS

Patient Characteristics

The baseline characteristics of the entire cohort are shown in Table 1. A total of 46,460 patients were included, of whom 22,093 (47.6%) were men and 6,900 (14.9%) had DM. The median age at receipt of clarithromycin-based triple therapy was 58.7 years (IQR 52.0–69.2 years). Patients with DM had more cardiovascular risk factors and diseases (hypertension, dyslipidemia, obesity, ischemic heart disease, congestive heart failure, and stroke), and higher use of aspirin and statins, than did patients without DM.

During a median follow-up of 7.1 years (IQR 4.8–9.8 years), with a total of 337,313 person-years, 153 patients (0.33%) were diagnosed with GC, with an incidence of 4.5 per 10,000 person-years. The median age at GC diagnosis was 72.4 years (IQR 63.8–82.6 years) and at *H. pylori* eradication therapy was 67.9 years (IQR 57.4–77.5 years). Of the 153 GCs, 31 (20.3%) arose from the cardia and 88 (57.5%) arose from noncardia regions, whereas the remaining 34 GCs (22.2%) did not have a site specified.

Association Between DM and GC

A total of 6,900 patients had DM, of whom 36 (0.5%) were diagnosed with GC, with an incidence of 7.3 per 10,000 person-years. Of the 39,560 patients without DM, 117 (0.3%) were diagnosed with GC, with an incidence of 4.1 per 10,000 person-years. The presence of DM was associated with an increased risk of GC in both the univariate analysis (HR 1.81 [95% CI 1.25–2.64]) and the PS regression adjustment (adjusted HR 1.67 [95% CI 1.08–2.58]) (Table 2). The PS-adjusted absolute risk difference was 2.96 (95% CI 0.32–7.27) more GC cases per 10,000 person-years among patients with DM than among those without DM.

Sensitivity analyses that used a Cox model with PS matching, inverse probability of treatment weighting, and a competing risk model using PS regression adjustment yielded consistent results (Supplementary Table 3). In the PS-matched cohort, all covariates were balanced between patients with and patients without DM (absolute standardized

Table 1—Baseline characteristics of study cohort

	All patients (*n* = 46,460)	Patients with DM (*n* = 6,900)	Patients without DM (*n* = 39,560)
Age at triple therapy (years)	58.7 (52.0–69.2)	66.1 (57.5–74.7)	57.6 (51.4–67.6)
Male sex	22,093 (47.6)	3,590 (52.0)	18,503 (46.8)
Duration of follow-up (years)	7.1 (4.8–9.8)	7.0 (4.6–9.7)	7.1 (4.8–9.8)
Smoking*	1,550 (3.3)	380 (5.5)	1,170 (3.0)
Alcohol†	462 (1.0)	107 (1.6)	355 (0.9)
History of GU	1,272 (2.7)	278 (4.0)	994 (2.5)
History of DU	1,413 (3.0)	289 (4.1)	1,124 (2.8)
Hypertension	12,094 (26.0)	4,383 (63.5)	7,711 (19.5)
Dyslipidemia	4,648 (10.0)	1,908 (27.7)	2,740 (6.9)
Obesity	471 (1.0)	310 (4.5)	161 (0.4)
IHD	3,660 (7.9)	1,837 (26.6)	3,477 (8.8)
Atrial fibrillation	2,317 (5.0)	645 (9.3)	1,672 (4.2)
CHF	2,442 (5.3)	992 (14.4)	1,450 (3.7)
Stroke	3,719 (8.0)	1,317 (19.1)	2,402 (6.1)
CRF	1,368 (2.9)	757 (11.0)	611 (1.5)
Cirrhosis	942 (2.0)	262 (3.8)	680 (1.7)
Drug use‡			
Aspirin	8,885 (19.1)	2,939 (42.6)	5,946 (15.0)
NSAID/COX-2 inhibitor	4,671 (10.1)	710 (10.3)	3,961 (10.0)
Statin	11,943 (25.7)	4,181 (60.6)	7,762 (19.6)
PPI	3,664 (7.9)	930 (13.5)	2,734 (6.9)
H2RA	22,754 (49.0)	4,144 (60.1)	18,610 (47.0)

Data are *n* (%) (categorical variables) or median (IQR) (continuous variables). CHF, congestive heart failure; CRF, chronic renal failure; DU, duodenal ulcer; GU, gastric ulcer; H2RA, histamine-2 receptor antagonist; IHD, ischemic heart disease. *Smoking status was identified either directly on the basis of ICD-9 code V15.82 or indirectly through identifying the presence of chronic obstructive pulmonary disease. †Alcohol use was suggested by the presence of alcohol-related diseases (gastrointestinal, hepatic, psychiatric, and neurological diseases). ‡Drug use was defined as use for >180 days.

difference <0.20) (Supplementary Table 4). For the multivariable Cox regression model including metformin, the adjusted HR of GC in patients with DM was 2.41 (95% CI 1.38–4.23). Subgroup analysis showed the adjusted HR of GC in patients with DM but without metformin use was 2.34 (95% CI 1.33–4.13), whereas the adjusted HR of GC in patients with DM and metformin use was 1.31 (95% CI 0.77–2.23).

The sensitivity analysis that included GC diagnosed within the 1st year of *H. pylori* therapy and patients who required retreatment for *H. pylori* but excluding all other malignant neoplasms is shown in Table 3. The adjusted HR of GC in patients with DM was 2.12 (95% CI 1.54–2.93). DM was associated with an increased risk of GC in those who received a single course of *H. pylori* treatment (adjusted HR 1.98 [95% CI 1.37–2.85]) and those who required retreatment (adjusted HR 2.54 [95% CI 1.27–5.07]).

The effects of not adjusting for certain covariates on the effect size (i.e., HR) of GC with DM and its variance are shown in Table 2. Notably, the association between DM and GC was no longer statistically significant if statins were not adjusted for (HR 1.43 [95% CI 0.93–2.19]). The HR was reduced further to 1.32 (95% CI 0.86–2.02) if both statins

Table 2—Association between DM and GC

	Patients without DM, and GC cases, *n*	Patients with DM, and GC cases, *n*	HR	95% CI	*P* value
Univariate analysis					
DM	39,560 (GC = 117)	6,900 (GC = 36)	1.81	1.25–2.64	0.002
Adjustments through PS regression					
All variables*	39,560 (GC = 117)	6,900 (GC = 36)	1.67	1.08–2.58	0.021
All variables except aspirin	39,560 (GC = 117)	6,900 (GC = 36)	1.65	1.07–2.55	0.024
All variables except NSAID/COX-2 inhibitor use	39,560 (GC = 117)	6,900 (GC = 36)	1.67	1.08–2.58	0.020
All variables except statin use	39,560 (GC = 117)	6,900 (GC = 36)	1.43	0.93–2.19	0.101
All variables except PPI use	39,560 (GC = 117)	6,900 (GC = 36)	1.67	1.08–2.58	0.020
All variables except statin and aspirin use	39,560 (GC = 117)	6,900 (GC = 36)	1.32	0.86–2.02	0.203
All variables except all drugs	39,560 (GC = 117)	6,900 (GC = 36)	1.30	0.85–1.99	0.234
All variables except comorbidities	39,560 (GC = 117)	6,900 (GC = 36)	1.92	1.28–2.90	0.002

*Variables include age at receipt of *H. pylori* eradication therapy, sex, smoking, alcohol use, history of gastric and duodenal ulcers, other comorbidities (atrial fibrillation, ischemic heart disease, congestive heart failure, chronic renal failure, cirrhosis, stroke, hypertension, and obesity), and use of other medications (aspirin, NSAIDs, COX-2 inhibitors, statins, PPIs, and histamine-2 receptor antagonists).

Table 3—Association between DM and GC (sensitivity analysis including GC cases diagnosed within 1st year and patients requiring retreatment but excluding all other malignancy)

	Patients without DM, and GC cases, *n*	Patients with DM, and GC cases, *n*	Adjusted HR*	95% CI	*P* value
Entire cohort# (*n* = 48,211; GC = 320)	40,598 (GC = 250)	7,613 (GC = 70)	2.12	1.54–2.93	<0.001
H. pylori treatment status#					
Single-treatment group (*n* = 41,932; GC = 265)	35,764 (GC = 210)	6,168 (GC = 55)	1.98	1.37–2.85	<0.001
Retreatment group (*n* = 6,279; GC = 55)	4,834 (GC = 40)	1,445 (GC = 15)	2.54	1.27–5.07	0.008

*Adjustment for age at receipt of *H. pylori* eradication therapy, sex, smoking, alcohol use, history of gastric and duodenal ulcers, other comorbidities (atrial fibrillation, ischemic heart disease, congestive heart failure, chronic renal failure, cirrhosis, stroke, hypertension, and obesity), use of other medications (aspirin, NSAIDs, COX-2 inhibitors, statins, PPIs, and histamine-2 receptor antagonists), duration of DM, and DM complications. #Retreatment groups and patients with GC diagnosed within the 1st year of receiving *H. pylori* eradication therapy were included, whereas those with other cancers were excluded.

and aspirin were not considered, and to 1.30 (95% CI 0.85–1.99) if all drugs were not considered. However, HR did not change significantly if aspirin, NSAIDs/COX-2 inhibitors, or PPIs alone were not adjusted for. On the other hand, HR increased to 1.92 (95% CI 1.28–2.90) without adjusting for comorbidities.

Subgroup Analysis

Among 6,900 patients with DM, 6,379 (92.4%) had a time-weighted mean HbA_{1c} ≥6.0% (≥42 mmol/mol), and 5,083 (73.7%) used metformin. Table 4 shows the subgroup analysis according to time-weighted mean HbA_{1c} level, cancer site, and metformin use. Suboptimal DM control (time-weighted mean HbA_{1c} ≥6.0% [≥42 mmol/mol]) was associated with a higher risk of GC (HR 1.68 [95% CI 1.07–2.63]) than that in those without DM. This increased risk was not statistically significant in those with HbA_{1c} <6.0% (<42 mmol/mol) (HR 1.99 [95% CI 0.71–5.54]). The association between DM and GC was only significant for cardia cancer (HR 3.4 [95% CI 1.45–7.97], DM vs. no DM), whereas it was not significant for noncardia cancer (HR 1.53 [95% CI 0.84–2.78], DM vs. no DM). In addition, the increased risk of GC was observed only among those who did not use metformin (HR 2.59 [95% CI 1.42–4.74], DM vs. no DM) and not among those who did use metformin (HR 1.28 [95% CI 0.74–2.20], DM vs. no DM).

CONCLUSIONS

In this territory-wide cohort study of more than 46,000 patients who had received *H. pylori* eradication therapy, we showed that DM was associated with a 67% increase in GC risk. The subgroup analysis further showed that the increase in GC risk seems to be associated with cardia cancer, suboptimal glycemic control, and no metformin use. Moreover, we demonstrated a potential source of bias, whereby the association between DM and GC decreased toward null if the use of certain medications was not properly adjusted for and cancer risk was inflated if comorbidities were not considered.

Despite a reported 19% increase in GC risk attributed to DM in a meta-analysis by Yoon et al. (10), 9 of the 17 observational studies included did not demonstrate an association (29–37). In a subsequent meta-analysis of 22 observational studies, Miao et al. (11) concluded that DM did not increase GC risk. Inadequate adjustment for various risk factors—with *H. pylori* status being the most important—probably contributed to this conflicting result. Another reason for this discrepancy could be the significantly different inclusion criteria of these two meta-analyses with respect to study design and patient ethnicity. The meta-analysis by Yoon et al. included 11 cohort studies, 5 case-control studies, and 1 nested case-control study. Six studies were conducted in Asia, five in Europe, five in North America, and one in Israel. Two of the studies adjusted for *H. pylori* status. On the other hand, the meta-analysis by Miao et al. included cohort studies only. Seven studies were conducted in Asia, nine in Europe, and six in the U.S. None of the studies

Table 4—Subgroup analysis of the association between DM and GC (adjustment through PS regression)

	Patients without DM, and GC cases, *n*	Patients with DM, and GC cases, *n*	Adjusted HR	95% CI	*P* value
Metformin use					
Yes	39,560 (GC = 117)	5,083 (GC = 19)	1.28	0.74–2.20	0.378
No	39,560 (GC = 117)	1,817 (GC = 17)	2.59	1.42–4.74	0.002
Time-weighted mean HbA_{1c}					
≥6.0% (≥42 mmol/mol)	39,560 (GC = 117)	6,379 (GC = 32)	1.68	1.07–2.63	0.025
<6.0% (<42 mmol/mol)	39,560 (GC = 117)	521 (GC = 4)	1.99	0.71–5.54	0.188
Cancer site*					
Cardia	39,462 (GC = 19)	6,876 (GC = 12)	3.40	1.45–7.97	0.005
Noncardia	39,513 (GC = 70)	6,882 (GC = 18)	1.53	0.84–2.78	0.161
Noncardia + unspecified site	39,541 (GC = 98)	6,888 (GC = 24)	1.33	0.80–2.23	0.271

*Total cancer cases = 153 (88 noncardia, 31 cardia, 34 unspecified site). Variables adjusted for included age at receipt of *H. pylori* eradication therapy, sex, smoking, alcohol use, history of gastric and duodenal ulcers, other comorbidities (atrial fibrillation, ischemic heart disease, congestive heart failure, chronic renal failure, cirrhosis, stroke, hypertension, and obesity), and use of other medications (aspirin, NSAIDs, COX-2 inhibitors, statins, PPIs, and histamine-2 receptor antagonists).

adjusted for *H. pylori* status. Specifically, only seven of the cohort studies were included in both meta-analyses.

The major limitation of the previous studies is a failure to stratify for the patients' *H. pylori* infection status; only two studies analyzed GC risk according to *H. pylori* infection status (12,32). Inclusion of *H. pylori*–negative subjects with a low risk of GC might bias any causal association toward null, as illustrated by Ikeda et al. (12); in their study, GC risk was increased only among patients with both *H. pylori* infection and $HbA_{1c} \geq 6.0\%$ (≥ 42 mmol/mol). In the current study, we included a large cohort of *H. pylori*–infected patients who had received eradication therapy. However, precancerous changes may have already developed before *H. pylori* was eradicated, and therefore patients infected with *H. pylori* would still have a higher risk of GC even after receiving eradication therapy (3). A sensitivity analysis including patients who required retreatment for *H. pylori* (i.e., in whom initial therapy failed) demonstrated an increase in GC risk among patients with DM in our study. More importantly, patients with DM who required retreatment had an even higher risk of GC than those who received a single course of eradication therapy (Table 3).

In addition to demonstrating the association between DM and GC, this study further illustrates the importance of adjusting for concomitant medications and comorbidities. None of the studies to date considered the effect of concomitant medications, despite increasing evidence (including from our previous studies) showing that drugs including aspirin (13), NSAIDs, COX-2 inhibitors, statins (14), metformin (15), and PPIs (16) modulate GC risk. In particular, patients with DM are more likely than those without DM to receive statins and aspirin for the associated metabolic risk factors and diseases. Both statins and aspirin have been proposed to have chemopreventive effects against GC. Statins might arrest cell cycle progression, induce apoptosis, and inhibit angiogenesis, whereas aspirin inhibits cancer development via its action on various pathways such as COX-2, phosphatidylinositol 3-kinase, nuclear factor-κB, Wnt-β-catenin, extracellular signal–regulated kinase, and activated protein 1. In this study, failure to adjust for statins alone rendered the results statistically insignificant, and the HR was further attenuated by not adjusting for aspirin (1.32) and for other drugs (1.30) (Table 2). This illustrates that aspirin and statins might negate the potential carcinogenic effect of DM on GC. Moreover, a subgroup analysis also showed that GC risk increased only for patients with DM who did not use metformin. This observation complements our previous finding that metformin reduced GC risk in patients with DM who had received *H. pylori* eradication therapy (38). On the other hand, HR would be spuriously augmented (from 1.67 to 1.92) if comorbidities were not adjusted for.

Prior studies of DM and GC have rarely considered such a wide array of comorbidities as comprehensively as this study. In particular, only a few studies specifically investigated GC as the only primary outcome (12,32); the majority of studies investigated the risks of cancers in multiple organs (e.g., liver, pancreas, prostate, endometrium). The subgroup analysis of HbA_{1c} level in this study showed that only patients with DM with a time-weighted mean $HbA_{1c} \geq 6.0\%$ (≥ 42 mmol/mol) had a high GC risk, implying that strict glycemic control might help to prevent the development of GC.

To date, only two studies have reported GC risk in patients with DM according to tumor location (18,19). Lin et al. (19) demonstrated a significant association between self-reported DM and risk for cardia cancer (HR 1.89 [95% CI 1.43–2.50]), whereas Kim et al. (18) refuted this association (HR 0.64 [95% CI 0.14–2.94]). The results of our subgroup analysis according to cancer subsite were more consistent with those reported by Lin et al. Although the pathogenesis and the etiological agents of cardia and noncardia cancers are believed to be different, our findings provide new insights into how DM increases GC risk, with a more prominent effect on cardia cancer development. For instance, patients with type 2 DM are often overweight or obese, increasing their risk of gastroesophageal reflux disease and hence cardia cancer. Eradicating *H. pylori* might restore gastric acid production by improving corpus inflammation, potentially worsening gastroesophageal reflux disease (39). In contrast, noncardia cancers are usually characterized by *H. pylori*–associated atrophic gastritis and hypochlorhydria, which is protective against cardia cancer development. Although it is tempting to speculate that the risk of cardia cancer might be increased by eradicating *H. pylori* in these susceptible patients with DM, further studies are needed in order to characterize the interaction between DM, *H. pylori* eradication, and cardia cancer development.

The merits of our study include the large sample size (>46,000 patients) and the long follow-up (median 7.1 years), which allow for more precise effect size estimation and subgroup analysis. In addition, the selection and recall biases common to traditional observational studies were avoided in this territory-wide cohort study that used data from electronic health records. Inclusion of *H. pylori*–infected patients who had received eradication therapy eliminated the important confounding effect of *H. pylori* infection status. Sensitivity analyses that used different PS methods and competing risk analysis further validated the robustness of our study results.

Several limitations of our study deserve attention. First, residual and unmeasured confounding is still possible in an observational study despite PS methodology. Second, data on some risk factors for GC, including family history and diet, could not be ascertained from the electronic database. Third, ICD codes alone may underestimate the true prevalence of DM, smoking, alcohol use, and obesity. It is unlikely, however, that a significant proportion of patients with DM were missed, as the proportion of DM in our cohort was 14.9%; the prevalence of DM is 10% in the general population of Hong Kong. Obesity, a risk factor for cardia GC, is more common in patients with DM, but data on BMI were not available. Nevertheless, Lin et al. (19) reported an increased risk of cardia GC among patients with DM, despite adjustment for BMI. Fourth, data on *H. pylori* infection status after treatment were unavailable in the electronic database. However, the retreatment rate of 14% in our study is similar to what was previously reported (24), and the inclusion of retreatment groups in the sensitivity analysis yielded consistent results. Fifth, as the majority of study subjects were ethnic Chinese, studies of other ethnic groups are needed in order to confirm the generalizability of our findings to other populations. Last, the inclusion and exclusion criteria and the coding accuracy could be validated only for a small subset of patients who

were followed up in our center. However, it is unlikely that coding practices deviate significantly across different hospitals under the same management system of the Hospital Authority.

Conclusion

Type 2 DM was associated with an increased GC risk in *H. pylori*–infected patients who had received eradication therapy, especially those with suboptimal glycemic control and who did not use metformin. Targeted screening should be considered after eradication therapy in high-risk *H. pylori*–infected patients with DM.

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Author Contributions. K.S.C. and W.K.S. conceived and designed the study, analyzed and interpreted data, drafted the manuscript, and approved the final version of the manuscript. E.W.C. and L.C. acquired data, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript. I.C.K.W. and W.K.L. conceived and designed the study, supervised the study, analyzed and interpreted data, drafted the manuscript, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript. W.K.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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