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ARTICLE

Aspirin and risk of gastric cancer after *Helicobacter pylori* eradication: a territory-wide study

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ABSTRACT

Background: Despite successful *H. pylori* (HP) eradication, some individuals remain at risk of developing gastric cancer (GC). Previous studies showed that aspirin was associated with a reduced GC risk. However, whether aspirin can reduce GC risk in HP-eradicated subjects remains unknown. We aimed to determine the chemopreventive effect of aspirin in HP-eradicated subjects.

Methods: We identified subjects who had received a prescription of clarithromycin-based triple therapy for HP between 2003 and 2012 from a territory-wide healthcare database. The observation period started from commencement of HP therapy (index date), and the follow-up was censored at the end of the study (December 2015), death or GC diagnosis. Aspirin use was defined as ≥once weekly use. Subjects who failed HP eradication or diagnosed with GC within 12 months of HP therapy were excluded. The hazard ratio (HR) of GC with aspirin use was calculated by Cox model with propensity score adjustment for age, sex, comorbidities and concurrent medications. All statistical tests were two-sided.

Results: The median follow-up was 7.6 years (IQR: 5.1-10.3 years), and 169 (0.27%) out of 63,605 patients developed GC. The incidence rate of GC was 3.5 per 10,000 person-years. Aspirin use was associated with a reduced GC risk (HR 0.30, 95% CI: 0.15-0.61). The risk of GC decreased with increasing frequency, duration and dose of aspirin (all p-trend <0.001).

Conclusions: Aspirin use was associated with a frequency-, dose- and duration-dependent reduction in GC risk after HP eradication. The effect was most prominent in those who used aspirin daily or for ≥ 5 years.

INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer related

mortality in the world (1). *Helicobacter pylori (H. pylori)* infection is a major gastric

carcinogen, which triggers and promotes the Correa's gastric carcinogenesis cascade (2).

Individuals infected with *H. pylori* have more than 3-fold increase in risk of gastric cancer (3),

and previous meta-analyses have shown that the risk of gastric cancer development was

reduced by 33%-47% after *H. pylori* eradication (4, 5). However, the role of other modifiable

risk factors, particularly the role of medications on subsequent risk of gastric cancer

development has not been thoroughly examined.

Meta-analyses of observational studies suggest that aspirin reduces gastric cancer risk,

while long-term follow-up of randomized trials of aspirin in preventing cardiovascular events

shows a statistically non-significant trend favouring reduction in gastric cancer risk (6, 7).

With low dose aspirin, the chemopreventive effect is unlikely to be mediated solely through

cyclooxygenase (COX)-2 inhibition. Other non-COX related pathways have been proposed,

such as phosphatidylinositol 3-kinase (PI3K) (8, 9), nuclear factor (NF)-κB (10), Wnt-ß-

catenin, extracellular signal-regulated kinase (ERK) and activated protein1 (AP-1) (11),

which increases the complexity underlying the chemopreventive effects of low dose aspirin.

To date, most published studies on the role of aspirin in gastric chemoprevention

included both *H. pylori*-infected and *H. pylori*-negative subjects. Only a few studies with

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limited sample size performing stratified analysis according to *H. pylori* statuses which showed that the protective effect of aspirin was <u>larger</u> in *H. pylori*-infected subjects (12-14). No study has attempted to determine the role of aspirin in gastric cancer development after *H. pylori* eradication. In addition, the dose- and duration-benefit relationships remain largely elusive (15). As aspirin is also associated with an increased risk of gastrointestinal bleeding, particularly in *H. pylori-infected* subjects, the actual beneficial effects of aspirin as chemoprevention remains to be determined (16).

We aimed to determine the role of aspirin in gastric cancer development in a large cohort of *H. pylori*-infected subjects who had received *H. pylori* eradication therapy.

METHODS

Data source

This study used the data from the electronic database of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority (17). This electronic database system has been previously established for both audit and research purposes (18-22). The CDARS used the International Classification of Diseases, Ninth Revision (ICD-9) for disease coding. High accuracy of the coding with positive and negative predictive values of more than 90% have been demonstrated in previous studies (19, 23). An anonymous patient identifier is generated by the system to protect patient confidentiality. Owing to the

retrospective nature of this study, written informed consent could not be obtained, and the study protocol was approved by the Institutional Review Board of the University of Hong Kong and the West Cluster of Hospital Authority, Hong Kong (reference no: UW 16-545).

Study Subjects

We recruited all *H. pylori*-infected adult patients aged 18 years or above who had received a course of clarithromycin-based triple therapy between 1 January 2003 and 31 December 2012. This was identified by the co-prescription of one of the proton pump inhibitors (PPIs) with clarithromycin and either amoxicillin or metronidazole with the correct doses, same prescription start dates and a treatment duration of 7-14 days (24). Because of the low clarithromycin resistance rate (8%) (25) and high eradication rate (> 90%) in Hong Kong (26), clarithromycin-based triple therapy remained the first-line anti-*H. pylori* treatment in this study period. *H. pylori* infection was diagnosed by either histology or urea breath test because *H. pylori* serology and stool antigen tests were unavailable in the public hospitals.

As the diagnosis of gastric cancer may be delayed, we excluded patients with gastric cancer diagnosed within the first year of receiving *H. pylori* therapy. Patients who had prior history of gastric cancer, prior gastrectomy or failed *H. pylori* eradication were also considered ineligible. Failure of *H. pylori* eradication was identified by the subsequent prescriptions of (a) another course of clarithromycin-based triple therapy, (b) a second-line

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therapy (either PPI-levofloxacin-amoxycillin or bismuth-based qudadruple therapy), or (c) a

third-line therapy (rifabutin-based therapy). The patient disposition is illustrated in **Figure 1**,

and the time frame is depicted in **Supplementary Figure 1**.

Outcomes

The primary outcome of this study was the development of gastric adenocarcinoma after *H.*

pylori eradication therapy. The observation period started from the date of *H. pylori*

eradication therapy (i.e. index date), and patients were censored at gastric cancer diagnosis,

death, their last clinic visit, or the end of study (31 December 2015) if they had at least one

follow-up in 2016. Patients diagnosed with gastric adenocarcinoma were identified using the

ICD-9 (International Classification of Diseases, ninth revisions) (**Supplementary Table 1**),

and those diagnosed with gastric lymphoma were excluded. The earliest date of

hospitalization for the workup or treatment of gastric cancer was used to define the date of

gastric cancer diagnosis.

Study variables

The primary exposure of interest was aspirin use after receiving *H. pylori* eradication therapy.

Potential confounders included the age of receiving triple therapy, gender, smoking and

alcohol use, past history of peptic ulcer disease and other comorbidities (diabetes mellitus,

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dyslipidemia, hypertension, obesity, congestive heart failure, atrial fibrillation, ischemic heart

disease, chronic renal failure, cirrhosis and stroke) as well as use of other medications (non-

steroidal anti-inflammatory drugs [NSAIDs], cyclooxygenase-2 [COX-2] inhibitors,

clopidogrel, metformin, statin and PPIs). As smoking and alcohol use were not included in

the CDARS, we identified smoking- and alcohol-related diseases as in the study by Poulsen

et al (27). We defined patients who smoked either directly by the ICD-9 code of V15.82 or

indirectly by the presence of chronic obstructive pulmonary disease (COPD) (ICD-9 codes:

491, 492, 496). Alcohol use was indicated by alcohol-associated diseases, which included

gastrointestinal, hepatic, psychiatric and neurological diseases (ICD-9: 291, 303, 305.0, 571,

980). **Supplementary Table 1** shows the diagnostic codes of other variables.

Previous studies had used various definitions of aspirin use, which was based on

either the frequency or duration, and were summarized in a recent meta-analysis (7). For the

primary analysis in this study, we used the same approach by Thrift et al (28), in which

exposure of different medications including aspirin was grouped into two categories: non-

regular use (< weekly use; reference group) and regular use (at least weekly use) after

receiving *H. pylori* eradication. The total duration of a particular medication use was

calculated by adding up the treatment duration of each prescription within the observation

period, starting from the time of eradication. The frequency of this medication use was

derived by dividing the total treatment duration by the follow-up duration. We also further

classified aspirin use based on other definitions in subsequent analysis in order to (1) ensure consistency of the results based on different definitions, and (2) study the dose-response relationship of aspirin on gastric cancer risk. In these analyses, the frequency of aspirin use was categorized into five groups: (i) never use, (ii) < monthly use, (iii) monthly to <weekly use, (iv) weekly to <daily use, and (v) daily use. The duration of aspirin use was categorized into four groups: (i) never use, (ii) < 2 years, (iii) 2 -5 years, and (iv) ≥ 5 years (29). The dose effect of aspirin was also studied (non-use, < 100 mg and ≥ 100 mg) (7).

Data validation

Owing to the anonymity of individuals in the CDARS, only the clinical details of patients who were followed up in our center (Queen Mary Hospital), which is one of the acute hospitals and a tertiary referral center in Hong Kong, could be retrieved for data validation.

Statistical analyses

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) statistical software. Continuous variables were expressed as median and interquartile range (IQR). Continuous variables and categorical variables of two groups were compared by Mann-Whitney U-test and chi-square test or Fisher's exact test, respectively. Cox proportional hazards model was performed to evaluate the hazard ratio (HR)

of gastric cancer development with aspirin use. The Cox proportional-hazard assumption was examined by a 'complementary log-log'-scaled Kaplan-Meier plot, and was regarded to be satisfactory. Schoenfeld residuals (with a p-value > 0.05) for each covariate also confirmed that the assumption was met.

In this study, propensity score adjustment was used to control for the confounders (30, 31). The score represents the probability of assigning aspirin use to an individual that is dependent on these covariates (age of receiving *H. pylori* eradication therapy, sex, smoking, alcohol use, comorbidities and concomitant medications). The weighting of each covariate was derived from multivariable logistic regression. By adjusting for the measured confounding using propensity score, any difference in the outcome (gastric cancer development) would be possibly due to the effect of aspirin only. As unmeasured confounding could still bias the result, subjects in the extreme ends of the propensity score distribution were excluded (32). Twenty categories of 5% each for the propensity score distribution were constructed, and the first and 20th propensity score categories were subsequently trimmed. The primary analysis of this study was propensity score adjustment with trimming, in which propensity score was used as an adjustment variable in the Cox model to calculate the HR after extreme propensity score strata were trimmed. In addition, univariate and multivariable analyses (with all covariates included into the Cox model) as well as propensity score adjustment without trimming were performed as sensitivity analyses.

Subgroup analysis of aspirin effect was done by stratifying the location of the tumour (cardia and non-cardia regions).

We also estimated the propensity score adjusted absolute difference in gastric cancer risk between aspirin and non-aspirin users. This was calculated by multiplying the adjusted HR minus 1 and the crude incidence rate among non-aspirin users (33).

To determine whether a frequency-, duration- and dose-response relationship existed between aspirin use and gastric cancer developmenet, the P-trend was reported.

All statistical tests were two-sided, and the criterion to define statistical significance was a p-value of < 0.05.

RESULTS

Patient characteristics

A total of 63,605 eligible subjects were identified, and the median follow-up was 7.6 years (IQR:5.1–10.3 years), making a total of 484,680 person-years. The median age of receiving clarithromycin-based triple therapy was 54.8 years (IQR:46.0–65.5 years), and 46.6% were men. The patient characteristics are shown in **Table 1**.

Risk of gastric cancer development

One hundred and sixty-nine (0.27%) patients developed gastric cancer after *H. pylori* eradication therapy, with an incidence rate of 3.5 per 10,000 person-years. The median age of receiving *H. pylori* eradication therapy was 66.7 years (IQR:56.6–76.5 years), with a median lapse of 4.8 years (IQR:2.8–6.9 years) before gastric cancer development (median age 71.4 years, IQR:61.6–81.8 years). Thirty-four (20.1 %) cancers developed in the cardia, 98 (58.0 %) in the non-cardia regions, and the sites were unspecified in 37 (21.9%) cases (ICD-9: 151.9).

Data Validation

The clinical details of 14 (out of 169; 8.3%) gastric cancer patients who were followed up in our center and fulfilled the inclusion and exclusion criteria were reviewed. All patients had negative *H. pylori* status by histological examination.

Association of aspirin use and risk of gastric cancer

Twenty five (0.3%) out of 9,045 aspirin users developed gastric cancer (3.7 per 10,000 person-years). The median duration of aspirin use was 4.9 years (IQR:2.8–7.6 years). Aspirin use (at least weekly use) was associated with a lower risk of gastric cancer (HR 0.30, 95% CI:0.15–0.61) after propensity score adjustment with trimming (**Table 2**). The propensity score adjusted absolute risk difference between aspirin and non-aspirin use was 2.52 fewer

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gastric cancers (95% CI:1.40–3.06) per 10,000 person-years. On stratifying the tumour site, a reduced risk of gastric cancer was only observed for non-cardia (HR 0.28, 95%:CI 0.12 – 0.64) but not cardia regions (HR 0.36, 95% CI:0.10–1.33). Similar results were observed in sensitivity analyses using either multivariable analysis or propensity score adjustment without trimming (**Table 2**).

Frequency, duration, and dose of aspirin use on risk of gastric cancer

The frequency-, duration-, and dose-response of aspirin use with gastric cancer development were also determined. When compared with the reference group (never use), more frequent aspirin use showed a statistically significant decreasing trend of gastric cancer risk (p-trend<0.001) (**Table 3**). Daily aspirin use was associated with the lowest cancer risk (HR 0.21, 95% CI:0.05–0.94) when compared to non-use. A longer duration of aspirin use was also associated with a lower risk of gastric cancer versus non-use (HR 0.92 [95% CI:0.51–1.64] for < 2 years of use, HR 0.27 [95% CI:0.09–0.80] for 2 -5 years of use, and HR 0.07 [95% CI:0.02–0.31] for ≥ 5 years of use; p-trend<0.001). In addition, a lower risk was observed with a higher aspirin dose (HR 0.38 [95% CI:0.18–0.79] for dose of < 100 mg, and HR 0.15 [95% CI:0.03–0.65] for dose of ≥ 100 mg versus non-use; p-trend<0.001).

DISCUSSION

The risk of gastric cancer remains high even after successful *H. pylori* eradication, particularly among those with pre-existing pre-neoplastic gastric lesions like intestinal metaplasia and dysplasia (34, 35). In this territory-wide study of a large cohort of *H. pylori*-infected individuals who had received eradication treatment, we found that users of low dose aspirin had a 70% reduction in gastric cancer risk when compared to non-users, with a statistically significant trend of frequency-, duration-, and dose-dependent effect demonstrated.

The current study has several strengths over previous studies in investigating the chemopreventive effects of aspirin on gastric cancer. First, this is the first study that focuses on the role of aspirin in *H. pylori*-eradicated subjects only. The magnitude of risk reduction in this study (HR 0.30 **[95%CI:0.15–0.61]**) was greater than that reported in the meta-analysis by Wang et al (pooled odds ratio [OR] 0.78 **[95%CI:0.69–0.87]**) including studies on both *H. pylori*-infected and *H. pylori*-negative subjects (6). One intriguing observation about these studies was that the risk reduction of gastric cancer by aspirin was greater among *H. pylori*-infected subjects. In a previous case-control study, the OR of gastric cancer with aspirin use was 0.60 in the whole cohort and 0.39 in *H. pylori*-infected subjects, while the chemopreventive effect was not statistically significant in non-infected patients (13). In a Swedish study, the ORs were 0.70 **[95%CI:0.6–1.0]** in the whole cohort and 0.60

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[95%CI:0.4 -1.0] in *H. pylori*-infected subjects, but again not statistically significant in non-infected patients (14). In a nationwide retrospective cohort study from Taiwan, the HR of gastric cancer with regular NSAID use was also lower among *H. pylori*-infected (0.52 **[95%CI:0.39–0.68]**) than non-infected subjects (0.80 **[95%CI:0.70–0.91]**) (36). In addition, previous studies failed to consider the role of other concurrent medications that may modulate the cancer risk such as statin (37), metformin (38) and PPIs (39). Nevertheless, the apparently larger chemopreventive effects of aspirin in *H. pylori*-eradicated subjects in this study should be interpreted with caution. As the HR of the upper limit of 95% CI was 0.61, the effect is compatible with a modest effect as reported in previous studies.

Second, the majority of previous studies are case-control studies, which are more prone to selection, information and recall biases (7). The use of population-based healthcare database with complete information of diagnoses and drug prescription records could help to address these concerns. In addition, our cohort study is the only study that used propensity score analysis with trimming of extreme strata to minimize the likelihood of confounding and to reduce bias when estimating the treatment effects (40). Notably, aspirin users were older and had more comorbidities (including cardiovascular diseases, hypertension, diabetes mellitus and chronic renal impairment) at baseline than the non-aspirin users (**Table 1**). This may indicate that any residual confounding from baseline health differences could only bias the association towards the null. In fact, aspirin did not appear to have a protective effect on

univariate analysis, which is likely due to the negative confounding effect of older age and concomitant comorbidities (41). Therefore, the true beneficial effects of aspirin on gastric cancer may be underestimated if these negative confounders are not properly adjusted for.

Third, previous studies used different criteria to define aspirin usage which was based on either the frequency or duration of aspirin use. In addition, some studies did not capture the information of subsequent aspirin use after baseline assessment, and did not comprehensively characterize the effect of aspirin on gastric cancer risk in terms of frequency, duration and dose (7). Our study therefore included both the baseline and subsequent use of aspirin into the analysis, and computed the magnitude of effects of aspirin by demonstrating the frequency- , duration-, and dose-response relationships.

Several limitations of the present study should be noted. First, data on some known risk factors of gastric cancer like family history, diet, physical activity and socioeconomic status were not available in the electronic database. Second, identification via coding may underestimate the true prevalence of smoking or alcohol use and obesity, as only patients with smoking- or alcohol-related diseases or who were morbidly obese would be coded. To be more precise, subjects with smoking and alcohol use in this study should be regarded as those with smoking- and alcohol-related health problems. Third, failure of triple therapy was identified indirectly by the repeated prescription of clarithromycin-based triple therapy or prescription of second and third line therapies, which accounted for 13% of this cohort. Also,

some patients might choose not to have further courses of *H. pylori* eradication therapy after failure of the clarithromycin-based triple therapy. However, the retreatment figure was similar to the reported failure rate of clarithromycin-based triple therapy in our locality with relatively low clarithromycin resistance rate during the study period (25). Fourth, information on over-the-counter (OTC) aspirin use and drug compliance could not be ascertained. In contrast to western countries, the use of over-the-counter (OTC) aspirin was very unpopular in Hong Kong to an extent that local pharmaceutical companies have stopped manufacturing generic OTC aspirin. As such, only branded OTC aspirin products are available in Hong Kong, which are far more expensive than obtaining from hospital pharmacy (£1 for 16 weeks). Moreover, medications are prescribed and dispensed in the hospital pharmacy simultaneously. Fifth, inherent to all observational studies, the possibility of residual confounding of our study cannot be excluded. However, the strong effect estimate of aspirin on gastric cancer reduction as well as the consistent frequency-, duration- and dose-effects makes this association less likely to be completely annulled due to failure to adjust for residual confounders (42). Lastly, the number of gastric cancer cases was relatively low among aspirin users (n=25). Although stratified analysis did not reveal a statistically significant protective effect of aspirin on cardia cancer development, this may be due to the relatively small number of cardia cancer cases (n=34). Further studies, particularly from western countries where cardia cancers are more prevalent, are warranted.

Aspirin has been demonstrated to have potent chemopreventive effect on various cancer types, particularly colorectal cancer (11). It is recently recommended by the U.S. Preventive Services Task Force to initiate low-dose aspirin for the primary prevention of cardiovascular disease and colorectal cancer in adults aged 50 to 59 years who have a more than 10% 10-year risk of cardiovascular disease and not at increased risk of bleeding (43). However, aspirin is also known to be a major cause of gastrointestinal bleeding, and the risk-benefit profile of aspirin use on gastric cancer prevention is yet to be defined. The adjusted absolute risk difference between aspirin and non-aspirin use may be considered to be modest or even low in our study (2.52 fewer gastric cancers per 10,000 person-years). Therefore, further studies are needed to characterize the potential risks of bleeding and the benefits of gastric cancer prevention by long-term low-dose aspirin use, especially after *H. pylori* eradication.

In conclusion, long-term aspirin use after *H. pylori* eradication therapy was associated with a statistically significantly lower gastric cancer risk in a frequency-, duration- and dose-response trend. This effect was most prominent in those who used aspirin daily or for at least 5 years. The magnitude of risk reduction in this study of *H. pylori*-eradicated subjects is larger than that reported in prior epidemiological studies which recruited both *H. pylori*-infected and non-infected subjects.

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FIGURE LEGEND

Figure 1: Patient recruitment flow diagram

Abbreviations: GC, gastric cancer

Table 1. Baseline characteristics of all subjects (n=63,605)

Characteristic	All (n=63,605)	Aspirin users (n=9,045)	Non-aspirin users (n=54,560)
Age at triple therapy (years)*	54.8 (46.0 – 65.5)	67.5 (58.4 – 75.9)	52.9 (44.6 – 62.4)
Male sex (n, %)	29629 (46.5%)	5184 (57.3%)	24445 (44.8%)
Duration of follow-up (years)*	7.6 (5.1 – 10.3)	7.5 (5.0 – 10.1)	7.4 (5.0 – 10.1)
Smoking (n, %) †	1647 (2.6%)	549 (6.1%)	1098 (2.0%)
Alcohol (n, %) ‡	556 (0.9%)	84 (0.9%)	472 (0.9%)
History of GU (n, %)	1463 (2.3%)	388 (4.3%)	1075 (2.0%)
History of DU (n, %)	1913 (3.0%)	251 (2.8%)	1662 (3.0%)
DM (n, %)	7436 (11.7%)	2897 (32.0%)	4539 (8.3%)
Hypertension (n, %)	13173 (20.7%)	5021 (55.5%)	8152 (14.9%)
Dyslipidemia (n, %)	5082 (8.0%)	2606 (28.8%)	2476 (4.5%)
Obesity	641 (1.0%)	174 (1.9%)	467 (0.9%)
IHD (n, %)	5756 (9.0%)	4027 (44.5%)	1729 (3.2%)
AF (n, %)	2439 (3.8%)	1427 (15.8%)	1012 (1.9%)
CHF (n, %)	2554 (4.0%)	1502 (16.6%)	1052 (1.9%)
Stroke (n, %)	4005 (6.3%)	2488 (27.5%)	1517 (2.8%)
CRF (n, %)	1416 (2.2%)	689 (7.6%)	727 (1.3%)
Cirrhosis (n, %)	1049 (1.6%)	118 (1.3%)	931 (1.7%)
Statins (n, %)	13247 (20.8%)	6130 (67.8%)	7117 (13.0%)
Metformin (n, %)	7974 (12.5%)	2599 (28.7%)	5375 (9.9%)
NSAIDs/COX-2 inhibitors (n, %)	3565 (5.6%)	580 (6.4%)	2985 (5.5%)
Clopidogrel (n, %)	990 (1.6%)	651 (7.2%)	339 (0.6%)
PPIs (n, %)	3316 (5.2%)	1380 (15.3%)	1936 (3.5%)

* Age was expressed as median (years) with interquartile range

† Smoking status was ascertained by the ICD-9 code of V15.82 or the presence of chronic obstructive pulmonary disease

‡ Alcohol use was ascertained by alcohol-associated diseases (including gastrointestinal, hepatic, psychiatric and neurological diseases)

Categorical variables were expressed as number (%)

Drug use was defined as at least weekly use, and expressed as number (%)

GU, gastric ulcer; DU, duodenal ulcer; DM, diabetes mellitus; IHD, ischemic heart disease; AF, atrial fibrillation; CHF, congestive heart failure; CRF, chronic renal failure; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; PPIs, proton pump inhibitors

Table 2. Association between aspirin use and risk of gastric cancer for the whole cohort and according to gastric cancer sites (non-cardia and cardia regions)

Aspirin frequency	Univariate analysis			Multivariable analysis			PS adjustment without trimming			PS adjustment with trimming		
	HR	95% CI	P*	HR	95% CI	P*	HR	95% CI	P*	HR	95% CI	P*
Whole Cohort†												
Non-user (<weekly use)	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
At least weekly	1.06	0.69–1.62	0.79	0.41	0.24–0.69	<0.001	0.36	0.21–0.63	<0.001	0.30	0.15–0.61	<0.001
Non-cardia GC‡												
Non-user (<weekly use)	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
At least weekly	0.94	0.57–1.55	0.81	0.41	0.22–0.75	0.004	0.37	0.19–0.70	0.003	0.28	0.12–0.64	0.003
Cardia GC§												
Non-user (<weekly use)	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
At least weekly	1.58	0.69–3.62	0.28	0.42	0.16–1.15	0.09	0.34	0.12–1.01	0.05	0.36	0.10–1.33	0.13

*Cox proprtional hazards model was used to calculate the P values, and the test was two-sided.

HR, hazard ratio; 95% CI, 95% confidence interval; PS, propensity score; GC, gastric cancer

† For the multivariable analysis: *All patients:* n=63,605, GC=169; *Non-users:* n=54,560, GC=144; *Aspirin users:* n=9,045, GC=25. For PS adjustment with trimming: ***All patients:*** n=57,243, GC=151; ***Non-users:*** n=50,777, GC=139; ***Aspirin users:***n=6,466, GC=12.

‡ For the multivariable analysis: ***All patients:*** n=63,571, GC=135; ***Non-users:*** n=54,533, GC=117; ***Aspirin users:*** n=9,038, GC=18. For PS adjustment with trimming: ***All patients:*** n=57,214, GC=122; ***Non-users:*** n=50,756, GC=114; ***Aspirin users:*** n=6,458, GC=8.

§ For the multivariable analysis: ***All patients:***n=63,470, GC=34; ***Non-users:*** n=54,443, GC=27; ***Aspirin users:*** n=9,027, GC=7. For PS adjustment with trimming: ***All patients:***n=57,122, GC=29; ***Non-users:*** n=50,671, GC=25; ***Aspirin users:*** n=6,451, GC=4.

Table 3. HRs and 95% CIs for the association between frequency, duration and dose of aspirin use and risk of gastric cancer (propensity score adjustment)

Aspirin Use	No. of patients (n=57,243)	No. of GC (n=151)	HR	95% CI	p-value*	P_{trend}†
Frequency						
Never user	47,991	129	1.00	Reference	-	< 0.001
< Monthly use	2,204	9	0.90	0.44 – 1.84	0.77	
Monthly to < weekly use	582	1	0.35	0.05 – 2.53	0.30	
Weekly to < daily use	5,125	10	0.30	0.14 – 0.63	0.002	
Daily use	1,341	2	0.21	0.05 – 0.94	0.04	
Duration						
Never user	47,991	129	1.00	Reference	-	< 0.001
< 2 years	3,900	16	0.92	0.51 – 0.64	0.77	
2 years to < 5 years	2,464	4	0.27	0.09 – 0.80	0.02	
≥ 5 years	2,888	2	0.07	0.02 – 0.31	< 0.001	
Dose						
Non-user ‡	50,911	139	1.00	Reference	-	< 0.001
< 100 mg	4,607	10	0.38	0.18 – 0.79	0.009	
≥ 100 mg	1,725	2	0.15	0.03 – 0.65	0.01	

* Cox proprtional hazards model was used to calculate the P values, and the test was two-sided.

† Cox proprtional hazards model was used to calculate the P values, and the test was two-sided

HR, hazard ratio; 95% CI, 95% confidence interval; GC, gastric cancer

‡Non-user was defined as < weekly use of aspirin