International Journal of Clinical Oncology (2023) 28:99–109
https://doi.org/10.1007/s10147-022-02253-2

ORIGINAL ARTICLE

Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review and meta-analysis

Tzu-Rong Peng[1] · Ta-Wei Wu[1] · Chung-Hsien Li[2,3]

Received: 7 March 2022 / Accepted: 4 October 2022 / Published online: 12 October 2022

Abstract

Background Proton pump inhibitors (PPIs) may be associated with gastric cancer, but studies in recent years have proven still inconsistent results. We conducted a systematic review and meta-analysis to investigate the association between PPI use and gastric cancer.

Methods Pubmed, EMBASE, and Cochrane library were searched for studies published up to 15th February 2022. Studies on the association between PPI and the risk of gastric cancer, pooled the odds ratios (ORs) using a random-effects model. The subgroup analysis for study design, site of gastric cancer, and the duration of PPI use was performed. Heterogeneity was assessed using the I^2 and Cochran's Q statistics.

Results Sixteen cohorts and case–control studies were included. PPI use was significantly associated with gastric cancer (OR: 1.75, 95% CI: 1.28–2.40). The subgroup analysis found a significant risk increase in non-cardia gastric cancer (OR: 2.14, 95%CI: 1.50–3.07). There was no duration-dependent effect of PPI use and gastric cancer risk (< 1 year: OR: 2.56, 95% CI: 1.41–4.64, $I^2 = 98\%$; 1–3 years: OR: 1.47, 95% CI: 1.26–1.71, $I^2 = 41\%$; > 3 years: OR: 1.58, 95% CI: 1.16–2.14, $I^2 = 74\%$).

Conclusions PPIs were significantly associated with an increased risk of gastric cancer. However, this association does not confirm causation. Several well-design studies are needed to confirm the findings in the future.

Keywords Proton pump inhibitors · Gastric cancer · Meta-analysis

Background

Proton pump inhibitors (PPIs) have been extensively prescribed for excessive gastric acid [1]. PPIs were clinically prescribed for peptic ulcer, gastroesophageal reflux disease, dyspepsia, and *Helicobacter pylori* (*H. Pylori*) eradication [2–4]. In addition, patients exposed to some drugs (aspirin, non-steroidal anti-inflammatory drugs, etc.) consider taking PPI to prevent ulcers. PPIs have been considered to be safe for clinical use [5]. However, an increasing number of observational studies on the risk of gastric cancer in patients taking long-term PPI therapy.

Gastric cancer is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide [6]. There are many risk factors for stomach cancer, such as *Helicobacter pylori* infections, dietary habits, smoking, obesity, and atrophic gastritis. An association between gastric cancer and PPI use has been found for many years. The previous meta-analysis pooled large observational studies and found a 2.5-fold increased gastric cancer risk [7, 8]. The mechanisms of PPI therapy with the risk of gastric cancer are not well understood and have drawn attention. Due to three new shreds of evidence from the United Kingdom [9] and Korea [10, 11], we performed an updated systematic review and meta-analysis. This study aims to evaluate the available data on the suggested association between PPIs and gastric cancer through a meta-analysis.

✉ Chung-Hsien Li
top920819@gmail.com

[1] Department of Pharmacy, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan

[2] Division of Gastroenterology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, #289, Jianguo Road, Xindian Dist., New Taipei City 23142, Taiwan, Republic of China

[3] School of Medicine, Tzu Chi University, Hualien, Taiwan

Methods

Ethical statement

Ethical approval and informed consent are not required, as the study will be a literature review and will not involve direct contact with patients or alterations to patient care.

Literature search strategy

We performed literature searches in PubMed, Cochrane Library, Embase, and ClinicalTrials.gov through 15th February 2022, limiting to human patients and publications in English. The following search terms were included in the search: "proton pump inhibitor", "omeprazole", "esomeprazole", pantoprazole", "lansoprazole", "dexlansoprazole", "rabeprazole", "gastric cancer", "gastric carcinoma", "gastric adenocarcinoma", "gastric neoplasm", "gastric neoplasia", "stomach cancer", "stomach carcinoma", "stomach adenocarcinoma", "stomach neoplasm" and "stomach neoplasia". All retrieved abstracts, studies, and citations were reviewed. The details of the search strategy for eligible studies are given in the flowchart provided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses [12]. Two reviewers (T. W. W. and T. R. P.) screened all titles and abstracts independently and evaluated relevant articles.

Inclusion and exclusion criteria

We included trials that met the following criteria: (1) observational studies (case–control studies or cohort studies); (2) defined use of PPIs (users and non-users); (3) defined outcomes of gastric or stomach cancers; (4) data were reported with standardized incidence ratio (SIR), relative risk (RR), hazard ratio (HR) or odds ratio (OR) for risk of gastric or stomach cancers and with the 95% confidence interval (CI). We excluded studies with any of the following features (1) literature review or case reports; (2) no related data in the study; (3) studies on other malignant gastric tumors.

Data extraction

This study was performed by Cochrane Collaboration guidelines [13]. Two reviewers (T. W. W. and T. R. P.) extracted data independently. The following information was extracted, including first author, year of publication, study design, country, number, and mean age of the included population, period, and lag time.

Risk of bias of included studies

Two reviewers (T. W. W. and T. R. P.) independently assessed the quality of the included studies. The Newcastle–Ottawa scale was used to assess the quality of observational studies [14]. This scale evaluated the quality from the following 3 aspects: reporting of participant selection, comparability, and outcome assessment. The total quality scale was 9 points. The outcome was considered high quality for studies with ≥ 6 points.

Statistical analyses

Statistical analysis was performed according to the Cochrane Handbook for Statistical Review of Interventions (version 6.2) [13]. The statistical analyses were performed using RevMan software (Cochrane Review Manager Version 5.4, Oxford, UK) and Comprehensive Meta-Analysis software. The odds ratios (ORs) were used as the common measure of association across studies. As the incidence of cancer is rare, SIRs, HR, OR, and RR were treated as equivalent measures of risk estimates [15–17]. The pooled adjusted ORs were calculated by DerSimonian–Laird random-effects meta-analysis [18]. We assessed heterogeneity using a χ^2 test with $p < 0.10$ considered statistically significant. Heterogeneity was considered low, moderate, or high for I^2 values of < 25, 25–50, and $> 50\%$, respectively. Results were considered statistically significant with a p-value of < 0.1. Subgroup analysis was performed according to different study designs, different sites of gastric cancer, duration of PPIs use, and *H. pylori* infection status. We used a funnel plot to assess the publication bias. Egger's and Begg's tests were also used. A p-value of > 0.05 based on the results of Egger's and Begg's tests indicated the absence of publication bias.

Ethics approval

Ethics approval was not required for this study since the analyzed data had been published previously.

Results

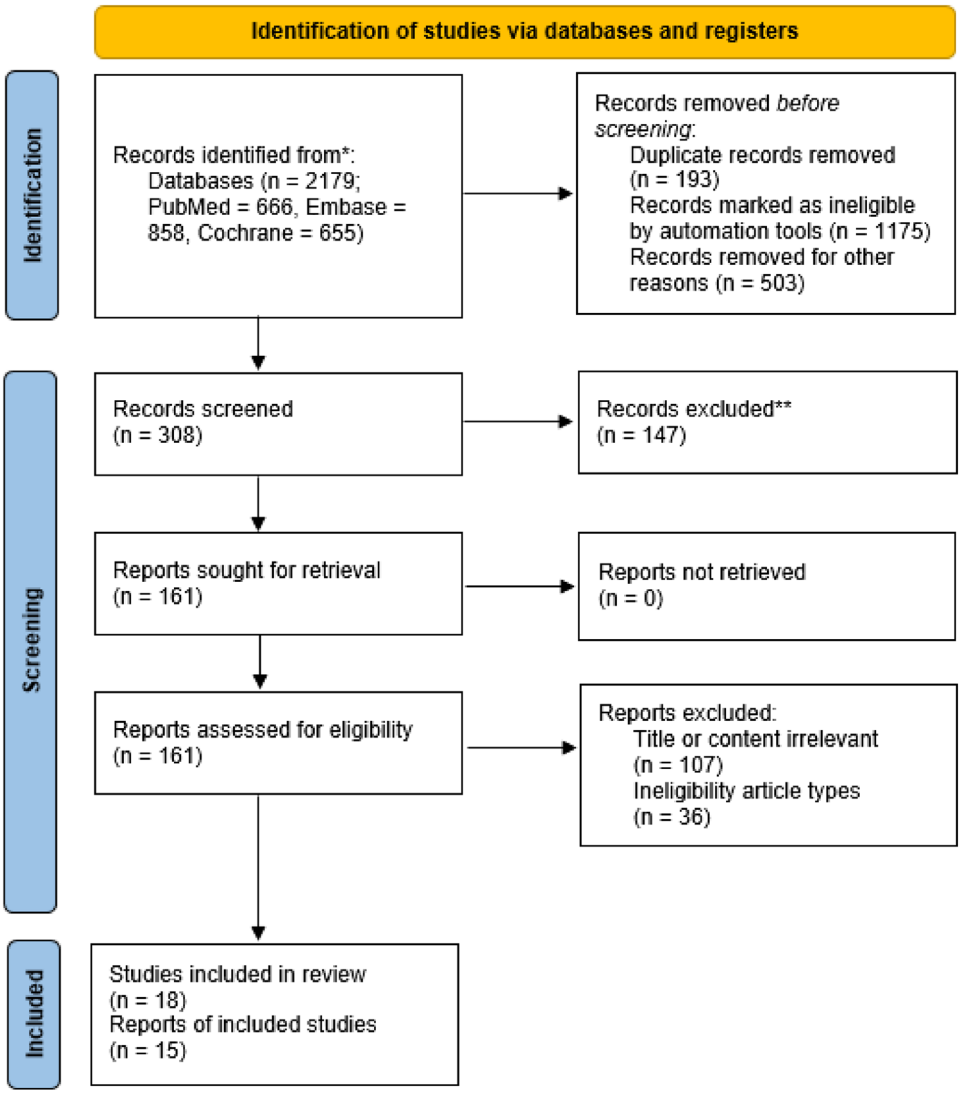
Studies retrieved

The initial search using electronic databases and manual searching retrieved 2,179 peer-reviewed articles and abstracts. After Records were removed before screening and removing duplicates, 308 records remained. Preliminary screening of titles and abstracts resulted in 54 remaining articles, and a further 36 review articles, case

reports, and studies not meeting the inclusion and exclusion criteria were rejected upon detailed evaluation. Of the 18 remaining records, 3 were excluded due to a lack of sufficient relevant data. The remaining 15 contained data relating to the prevalence of gastric cancer in PPI users or PPI use in subjects with gastric cancer. Figure 1 is a detailed flow diagram of the selection process described.

Study characteristics

A summary of the study characteristics is provided in Table 1. A total of 2,936,935 subjects from 15 studies were included and one study included 2 different study designs (population-based, and case–control studies). Eight were cohort studies, eight were case–control studies. The sixteen studies were from different regions: seven from Asia, six from Europe, and three from America. PPI is used after *H. pylori* eradication among three of the included studies [10,



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Study design	Country	Observation period	Age; min–max (years)	Follow-up	Overall population	Case (*n*)	Control (*n*)	Lag time
García Rodríguez [19]	2006	Case–control	United Kingdom	1994–2001	N/A; 40–84	N/A	10,293	507	9786	1 year
Tamim [20]	2008	Case–control	Canada	1995–2003	75.5 (mean); N/A	N/A	8,229	1071	7158	6 months
Poulsen [21]	2009	Retrospective cohort	Denmark	1990–2003	N/A; 40–84	N/A	36,268	18,790	17,478	1 year
Brusselaers [22, 23]	2017, 2019	Retrospective cohort	Sweden	2005–2012	N/A; ⩾ 18	4.9 (mean)	815,700	795,490	20,210	1 year
Cheung [24]	2018	Retrospective cohort	Hong Kong	2003–2012	54.7 (median); ⩾ 18	7.6 (median)	63,397	3271	60,126	6 months
Niikura [25]	2017	Retrospective cohort	Japan	1998–2017	N/A; N/A	6.9 (mean)	533	118	415	N/A
Lai [26]	2019	Case–control	Taiwan	2000–2013	65.6 (mean); 20–84	N/A	1298	649	649	1 year
Peng [27]	2019	Case–control	Taiwan	1996–2011	N/A; ⩾ 20	N/A	2,122	1061	1061	1 year
Chien [28]	2016	Case–control	Taiwan	2000–2010	69 (mean); N/A	6.6 (mean)	241,144	21,956	219,188	3 year
Lee [29]	2019	Case–control	United States	1996–2016	N/A; ⩾ 18	N/A	11,776	1233	10,543	2 year
Liu_PCCU [30]	2020	Case–control	Scotland	1999–2011	N/A; All age	5.1 years (median)	8,055	1448	6607	1 year
Liu_UK [30]	2020	Retrospective cohort	United Kingdom	1999–2014	N/A; All age	4.6 years (median)	471,779	46,146	425,633	1 year
Abrahami [9]	2021	Retrospective cohort	United Kingdom	1990–2018	60.4 (mean); ⩾ 40	5.1 years (median)	1,171,587	973,281	198,306	1 year
Shin [11]	2021	Retrospective cohort	Korean	2002–2017	62 (median); ⩾ 40	4.2 years (median)	78,706	39,799	38,907	N/A
Seo [10]	2021	Retrospective cohort	Korean	2002–2013	N/A; ⩾ 19	4.4 years (median)	13,754	6877	6877	2 year
Duan [31]	2009	Case–control	United States	1992–1997	60 (mean); N/A	N/A	2,294	1356	938	1 year

24, 25]. Most studies did not report on the age distribution of participants and the type or dose of PPIs. The risk-of-bias assessment results of the 16 included trials are summarized in Table 2.

Association between PPI use and gastric cancer

All of the 16 studies contained information on PPIs and gastric cancer risk. This meta-analysis of all 16 studies revealed that PPIs users was associated with an increased risk of gastric cancer than PPIs non-users (OR: 1.75, 95% CI: 1.28–2.40, $I^2 = 97\%$; $p < 0.001$; Fig. 2). We also performed analyses of different study designs (cohort studies vs. case–control studies). Compared to PPI users in the case–control studies (OR: 1.54, 95% CI: 1.30–1.84, $I^2 = 73\%$; Fig. 3), PPI users in the cohort studies (OR: 2.00, 95% CI: 1.17–3.41, $I^2 = 98\%$) had a higher risk of gastric cancer.

Association between PPI use and gastric cancer according to the gastric cancer site

Seven out of 16 studies contributed to a stratified meta-analysis according to the gastric cancer site. There was a significant increase risk in non-cardia gastric cancer (OR: 2.14, 95% CI: 1.50–3.07, $I^2 = 77\%$) with a non-significant trend towards an increased risk in the cardia (OR: 1.45, 95% CI: 0.77–2.74, $I^2 = 90\%$; Fig. 4).

Association between PPI use and gastric cancer according to PPI duration

Eleven out of 16 studies contributed to a stratified meta-analysis according to the PPI duration. There was no duration-dependent effect of PPI use and risk of gastric cancer (< 1 year: OR: 2.56, 95% CI: 1.41–4.64, $I^2 = 98\%$; 1–3 years: OR: 1.47, 95% CI: 1.26–1.71, $I^2 = 41\%$; > 3 years: OR: 1.58, 95% CI: 1.16–2.14, $I^2 = 74\%$; Fig. 5).

Association between PPI use and gastric cancer according to *H. pylori* infection status

Eight out of 16 studies contributed to a stratified meta-analysis according to PPI use and *H. pylori* infection status. A higher risk of gastric cancers was observed in individuals who received PPI therapy even after *H. pylori* eradication (OR: 2.67, 95% CI: 1.79–4.0, $I^2 = 0\%$; Fig. 6). There was no significant risk increase in PPI users with or without *H. pylor*i eradication treatment (OR: 2.14, 95% CI: 0.62–7.46, OR: 0.97, 95% CI: 0.49–1.89, respectively; Fig. 6).

Table 2 Newcastle–Ottawa scale scores and quality assessment of included studies

Case–control studies ($n = 8$)	Selection				Comparability		Exposure			Total
	Adequate	Representativeness	Selection	Definition	Main factors	Additional factors	Ascertainment	Method	Non-response	
García Rodríguez	1	1	1	1	1	1	1	1	0	8
Tamim	0	1	1	1	1	1	1	1	0	7
Chien	0	1	1	1	1	1	1	1	0	7
Lee	0	1	1	1	1	1	1	1	0	7
Lai	0	1	1	1	1	0	1	1	0	6
Peng	0	1	1	1	0	1	1	1	0	6
Liu_PCCU	0	1	1	1	1	1	1	1	0	7
Duan	0	1	1	1	1	1	1	1	0	7
Cohort studies($n = 8$)	Selection				Comparability		Outcome			Total
	Representativeness	Selection	Ascertainment	Outcome	Main factors	Additional Factor	Assessment	Follow-up	Adequacy	
Poulsen	1	1	1	1	1	1	1	0	1	8
Niikura	0	1	0	0	1	1	0	1	1	5
Cheung	0	0	1	1	1	1	1	1	1	7
Brusselaers	1	1	1	1	1	0	1	1	1	8
Liu_UK	1	1	1	1	1	1	1	0	0	7
Abrahami	1	1	1	1	1	1	1	1	1	9
Shin	1	1	1	1	1	0	1	1	1	8
Seo	1	1	1	1	1	0	1	0	1	7

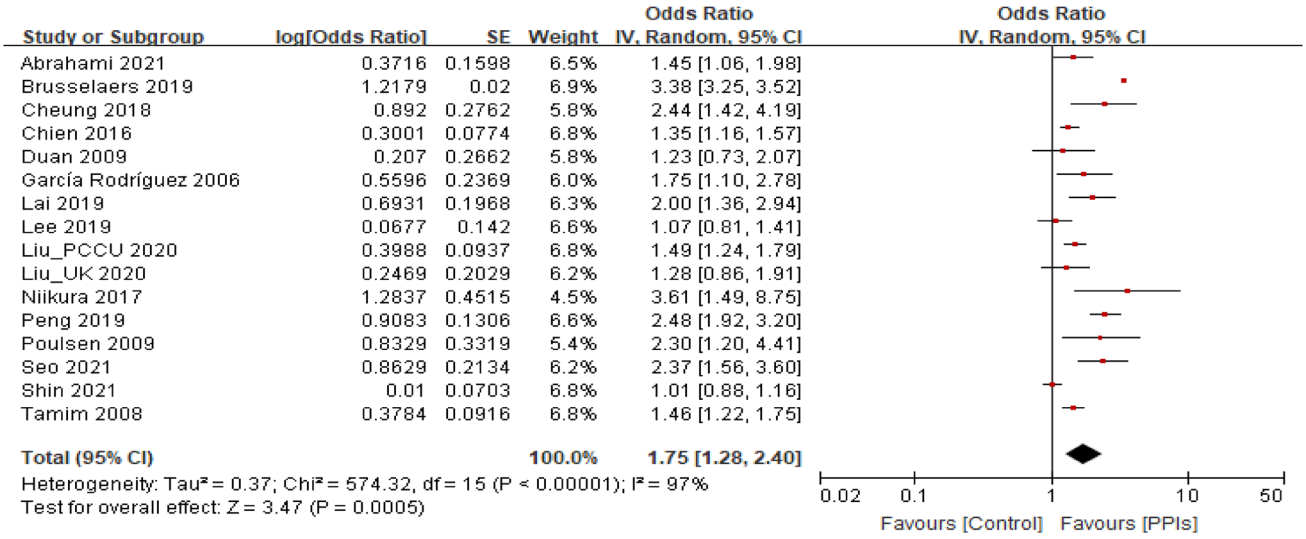


Fig. 2 Forest plot of the pooled odds ratio of gastric cancer with a 95% confidence interval for proton pump inhibitor users versus non-users

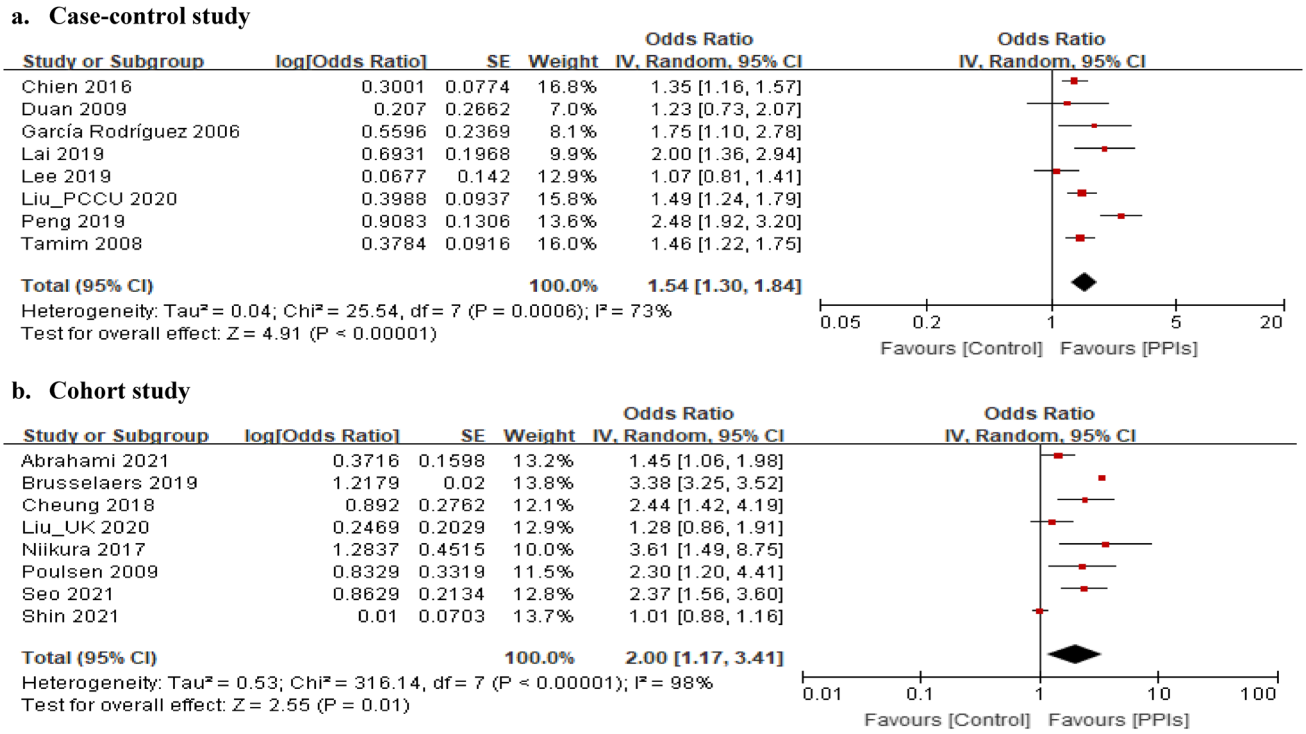


Fig. 3 Forest plot of the pooled odds ratio of gastric cancer with a 95% confidence interval for proton pump inhibitor users versus non-users by different study designs

Sensitivity analysis

Sixteen studies were included in this study. A total of 14 included studies that data were reported with HR and OR for risk of gastric cancer. Only 2 studies used incidence rate ratios (IRRs) or SIR to estimate the risk of gastric cancer [21, 23]. Therefore, we will carry out a sensitivity analysis by excluding these 2 studies. When these 2 studies were removed from this meta-analysis, similar results were shown in the risk of gastric cancer (OR: 1.57, 95% CI: 1.33–1.85, $I^2 = 80\%$).

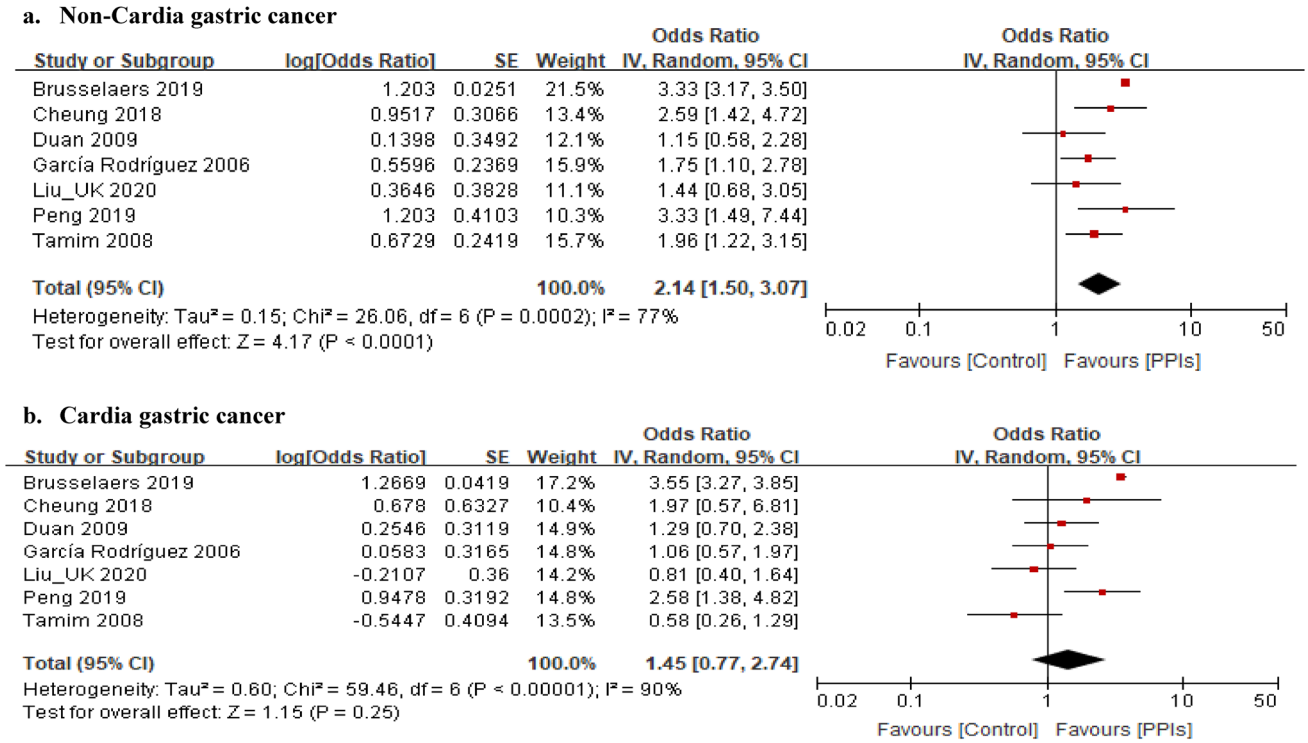


Fig. 4 Forest plot of the pooled odds ratio of total gastric cancer with a 95% confidence interval for proton pump inhibitor users versus non-users by different sites of gastric cancer

Publication bias

A visual inspection of the funnel plot of OR from these studies revealed asymmetry (Fig. 7). However, neither Egger's nor Begg's test suggested statistical evidence of publication bias, with p values of 0.101 and 0.086, respectively.

Discussion

In the previous study, data pooled from 13 studies demonstrated that PPI users are more than twice as likely to develop gastric cancer as non-PPI users [32]. The possible mechanisms of PPIs cause gastric cancer because significantly reduce gastric acid and lead to increase secretion of gastrin. An animal study found that hypergastrinemia may cause acid suppression and result from hyperplasia of enterochromaffin-like cells [33]. Hypergastrinemia commonly occurs in PPIs user, and the relation to the risk of gastric cancer is still controversial [34]. Another mechanism is to decrease gastric acidity by PPIs therapy may result in bacterial overgrowth in the gut. Studies have proven that gastric bacterial overgrowth is predictive of many clinical diseases, including lung, liver disease, and cancer [35, 36].

Many previous meta-analyses have explored the relationship between PPI and gastric cancer, but their results are inconsistent. The results of them are all based on a small number of observational studies [8, 37–39]. The latest meta-analysis conducted by Segna et al. includes thirteen studies on the association between PPI use and the risk of gastric cancer [32]. Our study was supplemented with five recent observational studies [9–11, 31], thus making the overall meta-analysis more complete and the subgroup analysis was more robust. A meta-analysis based on seven trials evaluated the effects of PPIs use and gastric mucosa changes [40]. This study shows no clear evidence that the long-term use of PPIs can cause the progression of corpus gastric atrophy or intestinal metaplasia. In addition, PPI maintenance treatment may have a higher possibility of experiencing enterochromaffin-like cell hyperplasia. However, long-term PPI therapy-induced moderate hypergastrinemia in most patients and an increased prevalence of enterochromaffin-like cell hyperplasia [41].

According to the Bradford Hill criteria, the biological gradient (dose–response) is one of the important criteria confirming a causal relationship [42]. However, there was no duration-dependent effect of PPI use and risk of gastric cancer in our study. Our study did not meet the Bradford Hill criteria, so it is difficult to confirm the causal relationship. Therefore, there are still doubts about PPIs and the risk of gastric cancer. Whether PPIs and *Helicobacter pylori* have synergistic effects to cause gastric cancer is also a highly

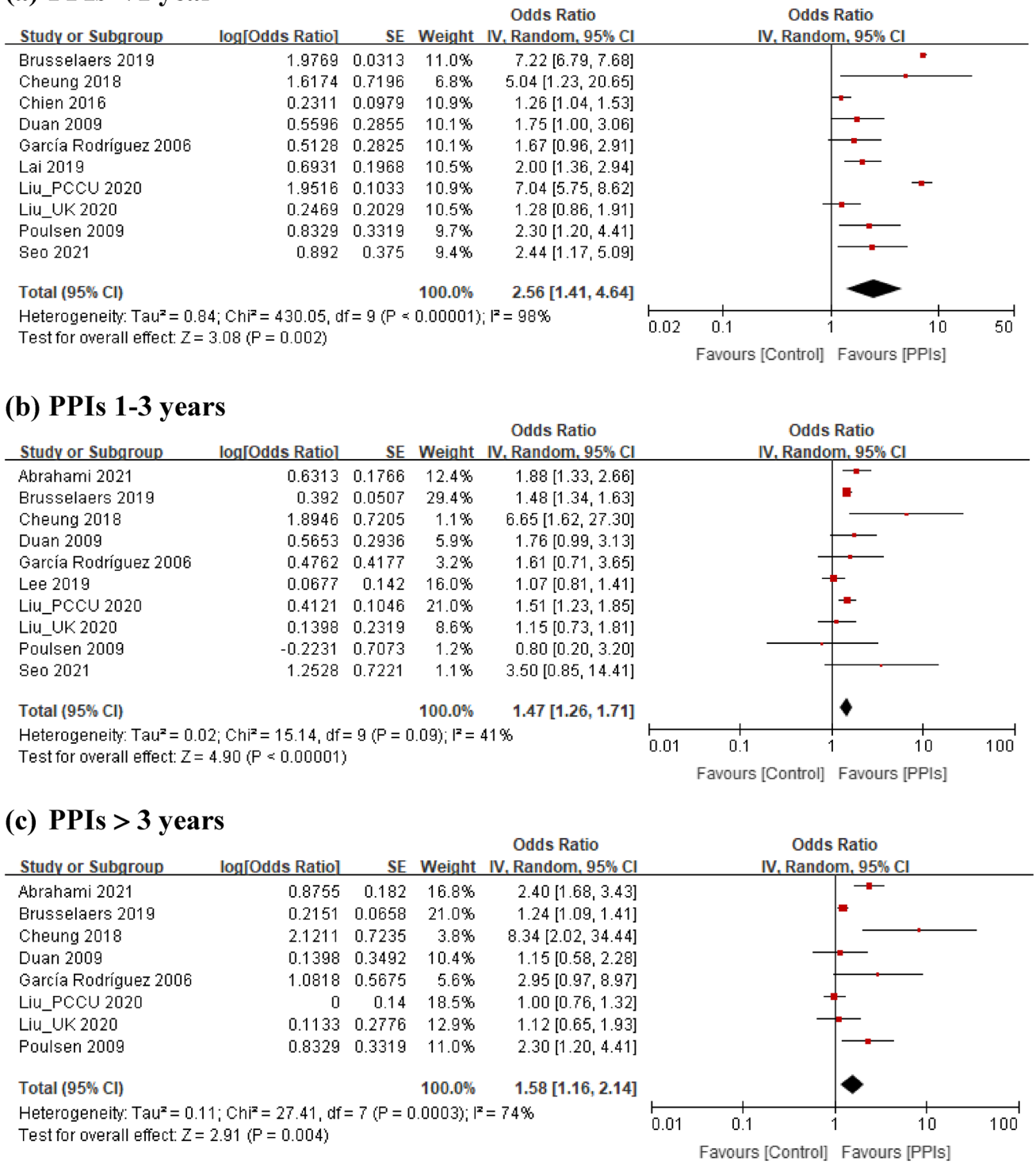


Fig. 5 Association between proton pump inhibitor use and gastric cancer risk stratified by duration of proton pump inhibitor use

concerning issue. Long-term use of PPIs may cause non-*H pylori* bacterial overgrowth; exacerbates gastritis because of the infection with *H. pylori* and non-*H. pylori* bacterial species [43]. *H. pylori*-driven gastric inflammation has been seeming to be a risk of gastric cancer [44]. Patients with *H. pylori* infection and PPIs therapy may worsen gastritis, thereby increasing the risk of atrophic gastritis. Therefore, if *H. pylori* are eradicated, long-term use of PPI may develop

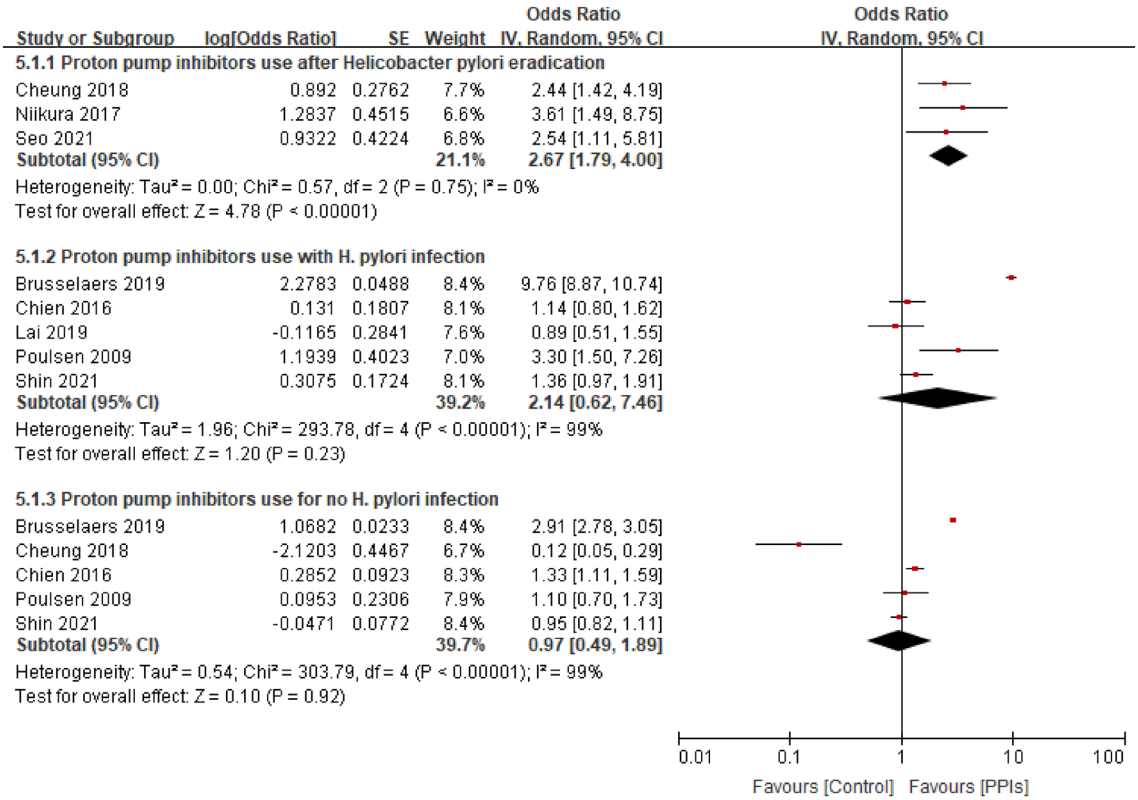
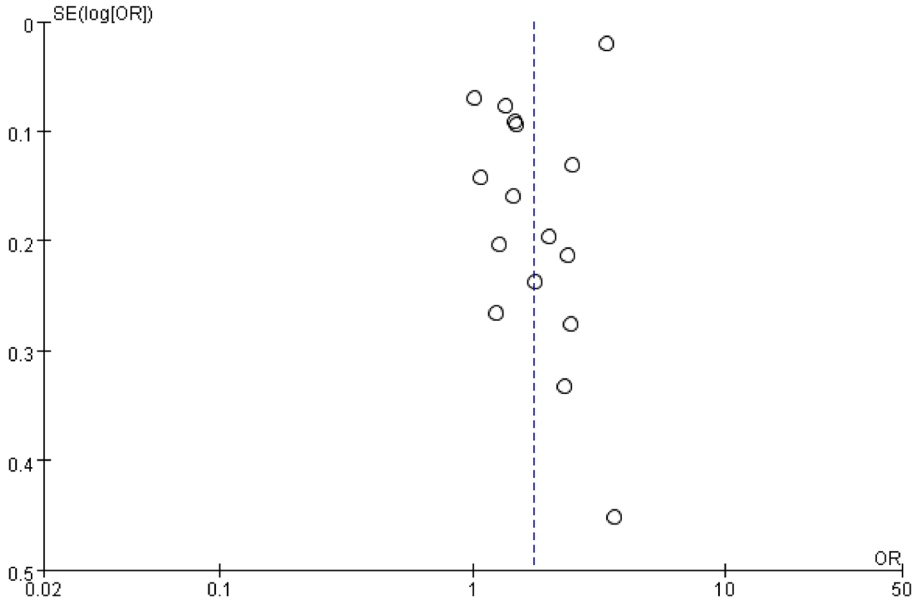


Fig. 6 Proton pump inhibitor use and *H. pylori* infection status

Fig. 7 Funnel plot



gastric cancer. In our subgroup study, we also found that long-term use of PPI after *H. pylori* were eradicated was associated with nearly three times the risk of gastric cancer.

Our subgroup analysis found that long-term use of PPI is increased the risk of non-cardia gastric cancer. The majority of non-cardia gastric cancers are related to peptic ulcers and chronic mucosal infections caused by *H. pylori* [19]. This may explain the strong relationship between the long-term use of PPIs and the development of non-cardia gastric cancer.

This study has some limitations. First, cohort and case–control studies were included in this meta-analysis. We cannot assess the causal relationship between PPIs and gastric cancer risk. Second, the results have potential confounders, such as the result from several studies and adjusted outcomes with different covariates. Third, the type and dose of PPI were not reported in the included studies. Fourth, some of the studies included in this study did not provide risk estimates or reported incomplete information. However, these unadjusted point estimates may pose a risk of confounding and are responsible for the high heterogeneity of this study. Therefore, the results should be interpreted cautiously. However, we performed a sensitivity analysis combining studies reporting OR and HR, which indicated consistent results. Fifth, information on precancerous lesions such as intestinal dysplasia and metaplasia were not provided in most included studies [19–21, 26, 28, 30], which may be prone to long-term use of PPIs and gastric cancer. Finally, overestimating the risk of occurrence is due to confounding. Sixth, there is a lack of information on many important risk factors such as smoking, drinking, eating habits, and *H. pylori* infection.

Conclusions

This meta-analysis found that PPIs were significantly associated with an increased risk of gastric cancer. However, this association does not confirm causation. Further well-design studies are needed to confirm the findings in the future.

Acknowledgements This study was supported by grants from the Taipei Tzu Chi Hospital, and Buddhist Tzu Chi Medical Foundation (TCRD-TPE-111-53 & TCRD-TPE-111-54).

Authors contribution TRP wrote the first draft of the manuscript. TWW and TRP searched databases and extracted the data. TWW and TRP evaluated the risk of bias. TWW and TRP performed the statistical analysis. CHL and TWW critically revised the manuscript. All authors contributed to the final version of the manuscript.

Funding This research received no external funding.

Data availability All data, models, and code generated or used during the study appear in the submitted article.

Declarations

Conflict of interest All authors declare no conflict to declare.

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