



ACID-SUPPRESSIVE THERAPY AFTER HELICOBACTER PYLORI ERADICATION AND SUBSEQUENT GASTRIC CANCER RISK: A SYSTEMATIC REVIEW

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ABSTRACT

Acid-suppressive therapy is frequently used after *Helicobacter pylori* (*H. pylori*) eradication, but its association with subsequent gastric cancer remains uncertain. This systematic review evaluated the relationship between post-eradication acid-suppressive therapy and gastric cancer risk, including associations according to treatment duration, frequency, and dose. This systematic review was conducted according to PRISMA 2020. PubMed/MEDLINE, Cochrane Library, Web of Science, and Scopus were searched from inception to September 25, 2026. Studies published between 2018 and 2026 were included if they evaluated adults who underwent *Helicobacter pylori* eradication and subsequently received acid-suppressive therapy, including proton pump inhibitors (PPIs), potassium-competitive acid blockers (P-CABs), or histamine-2 receptor antagonists (H2RAs). The primary outcome was subsequent gastric cancer, including incident and metachronous cancer. Risk of bias was assessed using ROBINS-I V2. Findings were synthesized narratively. Seven retrospective cohort studies involving 571 to 288,182 participants were included. Five studies evaluated PPI exposure and two evaluated P-CABs. Four of five PPI studies reported statistically significant associations with gastric cancer, with effect estimates ranging from aHR 1.15 to 3.61, whereas one study comparing PPI with H2RA use found no significant association (aHR 1.30, 95% CI 0.75–2.27). Both P-CAB studies reported increased risk, including HR 1.92 (95% CI 1.13–3.25) for vonoprazan versus H2RA and aHR 3.89 (95% CI 2.45–5.74) for P-CAB versus non-use. Longer treatment duration, higher frequency, and greater dose or cumulative exposure were generally associated with higher risk estimates. Overall risk of bias was moderate in two studies and serious in five. Post-eradication PPI and P-CAB use was associated with increased gastric cancer risk in several observational cohorts, with higher risk estimates generally observed with more prolonged or intensive exposure.

Keywords: gastric neoplasms; *helicobacter pylori*; histamine h2 antagonists; proton pump inhibitors; risk factors

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INTRODUCTION

Gastric cancer remains a major global health burden, with more than 968,000 new cases and nearly 660,000 deaths estimated worldwide in 2022, ranking fifth for both incidence and mortality among cancers globally (Bray et al., 2024; Thrift et al., 2023). *Helicobacter pylori* (*H. pylori*) infection is the principal established cause of non-cardia gastric cancer and plays a central role in gastric carcinogenesis (Bray et al., 2024; Wu et al., 2025). Eradication of *H. pylori* reduces the subsequent risk of gastric cancer (Ford et al., 2015; Wu et al., 2025), including metachronous gastric cancer after endoscopic treatment (Choi et al., 2020). However, eradication does not eliminate the risk of gastric cancer, particularly once gastric atrophy or intestinal metaplasia has developed (Choi et al., 2020; Hooi et al., 2017). Acid-suppressive therapy remains widely used in the management of acid-related conditions, including dyspepsia, gastroesophageal reflux disease, and peptic ulcer disease (Hooi et al., 2017). Given the widespread use of these medications, whether acid suppression after *H. pylori* eradication is associated with subsequent gastric cancer risk warrants further investigation (Cheung et al., 2018; Seo et al., 2021).

Proton pump inhibitors (PPIs) are widely used acid-suppressive agents, and prolonged acid suppression has been proposed to influence the gastric environment through sustained hypochlorhydria, hypergastrinemia, and alterations in gastric mucosal and microbial conditions (Brusselaers et al., 2017; Cheung et al., 2018). Several observational studies have reported an association between PPI use and gastric cancer, including studies demonstrating higher risks with longer duration or greater cumulative exposure (Brusselaers et al., 2017; Cheung et al., 2018; Kim et al., 2023). However, other studies have reported weaker or non-significant associations, particularly when longer lag periods or alternative comparator designs were applied (Gong et al., 2022; Liu et al., 2020; Poulsen et al., 2009). Differences in comparator selection, exposure definitions, lag periods, and the potential for confounding by indication and reverse causation may contribute to these inconsistent findings (Abrahami et al., 2022; Gong et al., 2022; Liu et al., 2020). More recently, potassium-competitive acid blockers (P-CABs), including vonoprazan, have emerged as potent acid-suppressive agents (Arai et al., 2024). Evidence regarding their association with gastric cancer after *H. pylori* eradication is more recent and remains limited (Arai et al., 2024; Shiratori et al., 2026). Thus, the available evidence differs across drug classes, comparators, exposure duration and dose, and gastric cancer outcomes (Arai et al., 2024; Cheung et al., 2018; Seo et al., 2021; Shiratori et al., 2026).

Despite growing interest in the potential relationship between acid-suppressive therapy and gastric cancer, the available evidence remains heterogeneous (Gong et al., 2022; Seo et al., 2021). Studies have differed in population characteristics, comparator groups, definitions of acid-suppressive exposure, follow-up duration, and clinical context, including the distinction between incident gastric cancer and metachronous gastric cancer after previous gastric cancer treatment (Arai et al., 2024; Shiratori et al., 2026). Most of the available evidence has focused on PPIs, whereas evidence concerning P-CABs has emerged more recently (Arai et al., 2024; Cheung et al., 2018; Seo et al., 2021; Shiratori et al., 2026). Furthermore, duration, frequency, dose, and cumulative exposure have not been consistently evaluated across studies (Kim et al., 2023; Seo et al., 2021). A systematic synthesis is therefore needed to integrate the available evidence and clarify the association between acid-suppressive therapy after *H. pylori* eradication and subsequent gastric cancer risk. This systematic review aimed to evaluate this association and to examine differences according to acid-suppressive drug class, treatment duration, frequency, dose, and cumulative exposure.

METHOD

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. PRISMA 2020 provides updated guidance for transparent reporting of the rationale, methods, study selection, and synthesis of evidence in systematic reviews. The review was designed to evaluate the available evidence regarding the association between acid-suppressive therapy administered after *Helicobacter pylori* (*H. pylori*) eradication and the subsequent risk of gastric cancer. The review question and eligibility criteria were formulated using the Population, Exposure, Comparator, and Outcome (PECO) framework (Table 1).

Table 1.
PECO framework

Population	Adults aged ≥ 18 years with confirmed <i>H. pylori</i> infection who underwent <i>H. pylori</i> eradication therapy
Exposure	Acid-suppressive therapy administered after <i>H. pylori</i> eradication, including PPI, P-CAB, or H2RA
Comparator	No acid-suppressive therapy or alternative acid-suppressive therapy
Outcome	Subsequent gastric cancer, including incident and metachronous gastric cancer
Primary objective	Association between post-eradication acid-suppressive therapy and subsequent gastric cancer risk
Secondary objectives	Associations according to drug class, treatment duration, frequency, dose, or cumulative exposure

Research question and eligibility criteria

The primary research question was: "Among adults who have undergone *H. pylori* eradication, is post-eradication acid-suppressive therapy associated with the subsequent risk of gastric cancer compared with no acid-suppressive therapy or alternative acid-suppressive therapy?". Eligible study designs included randomized controlled trials, prospective cohort studies, retrospective cohort studies, and cross-sectional studies. Cross-sectional studies were included when the temporal relationship between *H. pylori* eradication, post-eradication acid-suppressive exposure, and gastric cancer could be appropriately established.

Studies were excluded if they evaluated acid-suppressive therapy only as part of the initial *H. pylori* eradication regimen without assessing exposure after eradication; did not evaluate gastric cancer as an outcome; were case reports, case series, reviews, systematic reviews, meta-analyses, editorials, or other non-original publications; involved animal or in vitro experiments; or did not provide sufficient information to determine the relationship between post-eradication acid-suppressive exposure and gastric cancer. Studies in which acid-suppressive therapy was included only as a secondary covariate rather than as the exposure of interest were also excluded. When multiple publications involved overlapping populations, the report providing the most comprehensive and relevant data for the review question was retained.

Literature search strategy

A systematic literature search was conducted in four electronic databases: PubMed/MEDLINE, Cochrane Library, Web of Science, and Scopus, from database inception to September 25, 2026. The search strategy was developed around three principal concepts: *H. pylori* infection and eradication, acid-suppressive therapy, and gastric cancer. Where applicable, both controlled vocabulary terms and free-text keywords were used. Boolean operators were used to combine search terms, which were adapted to the specific indexing systems and search syntax of each database. The search strategy was intentionally designed without restricting the search according to study design in order to maximize the identification of potentially eligible observational studies. The complete search strategies for each database are provided in Table 2.

Table 2.

Search concepts and keywords

Search concept	Keywords
<i>H. pylori</i> and eradication	" <i>Helicobacter pylori</i> " OR " <i>H. pylori</i> " OR " <i>Helicobacter</i> infection" OR " <i>H. pylori</i> eradication" OR eradication OR treatment OR therapy
Acid-suppressive therapy	"proton pump inhibitor*" OR PPI* OR omeprazole OR lansoprazole OR esomeprazole OR pantoprazole OR rabeprazole OR "potassium-competitive acid blocker*" OR P-CAB* OR vonoprazan OR tegoprazan OR fexuprazan OR revaprazan OR "histamine-2 receptor antagonist*" OR H2RA* OR famotidine OR cimetidine OR nizatidine OR ranitidine OR "acid suppress*"
Gastric cancer	"gastric cancer" OR "stomach cancer" OR "gastric neoplasm*" OR "stomach neoplasm*" OR "gastric carcinoma*" OR "gastric adenocarcinoma*" OR "gastric malignancy" OR "stomach malignancy"

Study selection

All records retrieved from the electronic database searches were screened for eligibility after removal of duplicate records. Titles and abstracts were screened against the predefined inclusion and exclusion criteria, followed by full-text assessment of potentially eligible records. Full-text articles were evaluated to determine whether the population, exposure, comparator, outcome, and study design fulfilled the eligibility criteria. The reasons for exclusion at the full-text stage were documented and presented in the PRISMA 2020 flow diagram. Study selection was independently performed by two reviewers. Disagreements were resolved through discussion and consensus, with consultation with a third reviewer when necessary.

Data extraction

Data were independently extracted from the eligible studies using a standardized data extraction form. Extracted information included study characteristics, population characteristics, exposure and comparator definitions, gastric cancer outcomes, follow-up duration, and reported effect estimates. Study-level characteristics included the first author, year of publication, country, study design, study population, sample size, and follow-up duration. Population characteristics included *H. pylori* eradication status and, where relevant, previous gastric cancer and gastric cancer treatment history. For exposure characteristics, we extracted the acid-suppressive drug class and specific agent, timing of exposure after *H. pylori* eradication, treatment duration, frequency of use, and dose or cumulative exposure when reported. Comparator definitions were also recorded.

We extracted the definition and ascertainment of gastric cancer, number of gastric cancer events, and whether the outcome represented incident or metachronous gastric cancer for outcome assessment. For quantitative results, we extracted hazard ratios (HRs), adjusted hazard ratios (aHRs), risk ratios (RRs), odds ratios (ORs), or other effect measures reported by the original studies, together with their corresponding 95% confidence intervals (CIs) and P values. Where multiple adjusted analyses were available, the estimate considered most relevant to the predefined PECO question was preferentially extracted. Dose-, frequency-, and duration-response estimates were extracted separately when reported. Any discrepancies between reviewers during data extraction were resolved through discussion and consensus.

Risk of bias assessment

The risk of bias of the included studies was assessed independently by two reviewers using the Risk of Bias In Non-randomized Studies of Interventions, Version 2 (ROBINS-I V2). The assessment followed the November 2025 version of the ROBINS-I V2 framework. ROBINS-I V2 evaluates six domains: (1) bias due to confounding; (2) bias in classification of intervention; (3) bias in selection of participants into the study; (4) bias due to missing data; (5) bias in measurement of the outcome; and (6) bias in selection of the reported result.

The assessment was based on the signalling questions and corresponding algorithms provided by the ROBINS-I V2 framework. Particular consideration was given to potential confounding, exposure classification, selection mechanisms, missing information, outcome ascertainment, and selective reporting. Potential immortal-time bias was also considered when the definition of exposure required participants to survive or remain under observation for a predefined period before being classified as exposed. Each domain was assigned a judgement of low, moderate, serious, critical, or no information according to the ROBINS-I V2 framework. An overall risk-of-bias judgement was subsequently determined for each study result. Disagreements between reviewers were resolved through discussion and consensus.

Data synthesis

Because the included studies differed substantially in their populations, exposure definitions, comparator groups, acid-suppressive agents, duration of exposure, gastric cancer outcomes, follow-up periods, and analytical approaches, the findings were synthesized using a narrative descriptive approach. First, the evidence was summarized according to study characteristics, including country, study design, population, sample size, follow-up duration, and gastric cancer outcome. The association between post-eradication acid-suppressive therapy and gastric cancer was then synthesized according to the principal exposure and comparator evaluated in each study.

Adjusted effect estimates were preferentially considered because they accounted for potential confounding factors within the individual studies. HRs and aHRs were presented as reported by the original investigators and were not converted into other effect measures. The findings were additionally organized according to acid-suppressive drug class, including PPI and P-CAB therapy, as well as according to the comparator used in each study. Duration-, frequency-, and dose-response

findings were synthesized separately to characterize whether the magnitude of the reported association varied according to the intensity or duration of acid-suppressive exposure.

Incident and metachronous gastric cancer were considered separately during synthesis because the underlying populations and clinical contexts differed. In particular, studies evaluating metachronous gastric cancer after previous gastric cancer resection were not considered directly interchangeable with studies evaluating incident gastric cancer in patients without previous gastric cancer. Where studies reported multiple exposure categories, the reported estimates were summarized descriptively rather than treated as independent study populations.

Statistical analysis

The present review used narrative synthesis rather than quantitative meta-analysis. Individual-study effect estimates were therefore presented as reported in the original publications, together with their corresponding 95% CIs and P values. For duration-, frequency-, and dose-response analyses, effect estimates across exposure categories were compared descriptively within each study. Particular attention was given to the direction and magnitude of associations, precision of estimates, and reported tests for trend. Given the observational nature of the included evidence, the findings were interpreted as associations rather than causal effects. The interpretation also considered differences in study populations, exposure definitions, outcome definitions, follow-up periods, and risk-of-bias judgements.

RESULT

The literature search identified 1,377 records from PubMed/MEDLINE, Cochrane Library, Web of Science, and Scopus. After removal of 708 duplicate records, 669 records were screened based on their titles and abstracts. Of these, 565 records were excluded, and 104 reports were sought for retrieval. Among these, 57 reports could not be retrieved, while 47 reports were assessed for eligibility. Following full-text assessment, 40 reports were excluded, comprising 19 reports with an inappropriate study design, 16 reports addressing an irrelevant research topic, and 5 reports with insufficient data. Ultimately, seven studies met the predefined eligibility criteria and were included in the systematic review. The study selection process is presented in the PRISMA flow diagram (Figure 1).

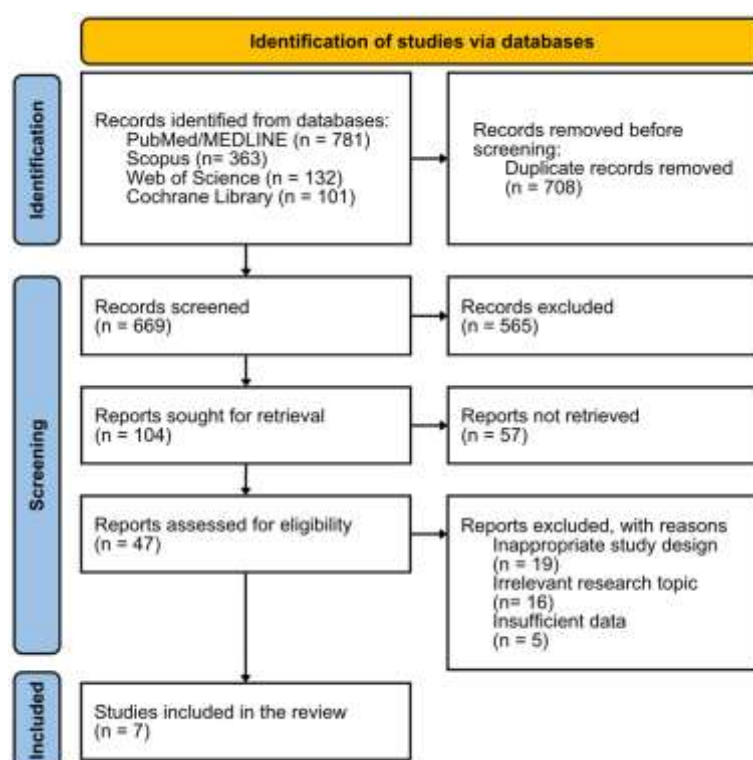


Figure 1. PRISMA flow diagram of the study selection process.

The seven included studies were published between 2018 and 2026 and were conducted in Japan, Hong Kong, and South Korea. All studies used a retrospective cohort design. The study populations consisted of adults who had undergone *Helicobacter pylori* eradication therapy, with one study specifically evaluating patients with a history of gastric cancer resection and subsequent risk of metachronous gastric cancer.

The sample sizes varied substantially across studies, ranging from 571 to 288,182 participants. Follow-up duration ranged from 3.65 to 8.3 years among studies in which follow-up was reported for the relevant post-eradication population. The included studies evaluated subsequent gastric cancer development following exposure to acid-suppressive therapy, predominantly proton pump inhibitors (PPIs), with more recent studies also evaluating potassium-competitive acid blockers (P-CABs). Overall, the studies reported incident or subsequent gastric cancer, while Shiratori et al. specifically investigated metachronous gastric cancer following previous gastric cancer resection. Detailed characteristics of the included studies are presented in Table 3.

Table 3.
Characteristics of included studies

Author, year	Country	Study design	Population	Sample size	Follow-up	Gastric cancer outcome
(Niikura et al., 2018)	Japan	Retrospective cohort study	Patients with successful <i>H. pylori</i> eradication	571	6.9 years	24 gastric cancer cases
(Cheung et al., 2018)	Hong Kong	Retrospective cohort study	Adults who received <i>H. pylori</i> eradication therapy	63,397	7.6 years	153 gastric cancer cases
(Seo et al., 2021)	South Korea	Retrospective cohort study	Patients after <i>H. pylori</i> eradication	6,877	NR	36 gastric cancer cases
(Gong et al., 2022)	South Korea	Retrospective cohort study	Patients after <i>H. pylori</i> eradication	10,012	6.56 years	51 incident gastric cancer cases
(Kim et al., 2023)	South Korea	Retrospective cohort study	Adults after <i>H. pylori</i> eradication	288,182	8.3 years	2,001 gastric cancer cases
(Arai et al., 2024)	Japan	Retrospective cohort study	Patients after <i>H. pylori</i> eradication	54,055	3.65 years	568 gastric cancer cases
(Shiratori et al., 2026)	Japan	Retrospective cohort study	Patients with previous gastric cancer resection and <i>H. pylori</i> eradication	7,172	5.8 years	342 metachronous gastric cancer cases

GC, gastric cancer; H2RA, histamine-2 receptor antagonist; *H. pylori*, *Helicobacter pylori*; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

The included studies demonstrated varying associations between post-eradication acid-suppressive therapy and subsequent gastric cancer risk. Five studies evaluated PPI exposure, while two studies specifically evaluated P-CAB exposure. Niikura et al. reported a significantly increased risk of gastric cancer among patients receiving PPIs after *H. pylori* eradication, with an adjusted hazard ratio (aHR) of 3.61 (95% CI, 1.49–8.77; $P=0.005$) compared with PPI non-users. Similarly, Cheung et al. reported an increased risk of gastric cancer among PPI users, with an adjusted HR of 2.44 (95% CI, 1.42–4.20; $P=0.002$). In the nationwide Korean study by Seo et al., the association between PPI use and gastric cancer became more evident with longer exposure duration. PPI use for at least 30 days was not significantly associated with gastric cancer (HR, 1.35; 95% CI, 0.79–2.31; $P=0.277$), whereas exposure for at least 180 days was associated with a significantly increased risk (HR, 2.22; 95% CI, 1.05–4.67; $P=0.036$). The association was also significant among patients exposed for at least 365 days (HR, 2.54; 95% CI, 1.11–5.80; $P=0.027$).

In contrast, Gong et al. found no statistically significant association between PPI use and incident gastric cancer when PPI users were compared with H2RA users. The adjusted HR for PPI exposure was 1.30 (95% CI, 0.75–2.27; $P=0.348$). Similarly, Kim et al. reported a more modest but statistically significant association between long-term PPI use and gastric cancer, with an adjusted HR of 1.15 (95% CI, 1.06–1.25; $P<0.001$). The two studies evaluating P-CABs also reported increased gastric cancer risk. Arai et al. found that vonoprazan use was associated with a higher risk

of gastric cancer compared with H2RA use (HR, 1.92; 95% CI, 1.13–3.25; $P=0.016$). In the study by Shiratori et al., long-term P-CAB use was associated with an increased risk of metachronous gastric cancer compared with non-use (aHR, 3.89; 95% CI, 2.45–5.74; $P<0.01$). The corresponding association for PPI use was also increased, although the magnitude was lower (aHR, 1.75; 95% CI, 1.40–2.20; $P<0.01$). The individual effect estimates are summarized in Table 4.

Table 4.

Author, year	Exposure	Comparator	Outcome	Effect measure	Effect estimate (95% CI)	P value
(Niikura et al., 2018)	PPI use	No use	Gastric cancer	aHR	3.61 (1.49–8.77)	0.005
(Cheung et al., 2018)	PPI use	Non-PPI use	Gastric cancer	HR	2.44 (1.42–4.20)	0.002
(Seo et al., 2021)	PPI use ≥ 180 days	Non-PPI use	Gastric cancer after H. <i>pylori</i> eradication	HR	2.22 (1.05–4.67)	0.036
(Gong et al., 2022)	PPI use	H2RA use	Incident gastric cancer	aHR	1.30 (0.75–2.27)	0.348
(Kim et al., 2023)	PPI use	Non-PPI use	Gastric cancer after H. <i>pylori</i> eradication	aHR	1.15 (1.06–1.25)	<0.001
(Arai et al., 2024)	P-CAB (vonoprazan) use	H2RA use	Gastric cancer	HR	1.92 (1.13–3.25)	0.016
(Shiratori et al., 2026)	P-CAB use	Non-use	Metachronous gastric cancer	aHR	3.89 (2.45–5.74)	<0.01

aHR, adjusted hazard ratio; CI, confidence interval; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

Several studies assessed whether the association between acid-suppressive therapy and gastric cancer varied according to treatment duration or cumulative exposure. Cheung et al. demonstrated a dose- and duration-related pattern among PPI users. Daily PPI use was associated with a higher risk of gastric cancer than non-use (HR, 4.55; 95% CI, 1.12–18.52; $P=0.034$). Among patients with at least 1 year of exposure, daily use was associated with an HR of 5.04 (95% CI, 1.23–20.61; $P=0.024$). The corresponding estimates increased to 6.65 (95% CI, 1.62–27.26; $P=0.009$) for at least 2 years and 8.34 (95% CI, 2.02–34.41; $P=0.004$) for at least 3 years of daily use. Seo et al. similarly observed progressively higher HRs with increasing duration of PPI exposure. The HR increased from 1.35 for exposure of at least 30 days to 1.92, 2.22, and 2.54 for exposure of at least 90, 180, and 365 days, respectively.

Kim et al. evaluated annual PPI dose using tertiles. Compared with the lowest exposure tertile, the second and highest tertiles were associated with adjusted HRs of 2.40 (95% CI, 1.99–2.89) and 3.82 (95% CI, 3.20–4.56), respectively, in the 1-year lag-time analysis (both $P<0.001$). Arai et al. also demonstrated variation according to the duration and dose of vonoprazan exposure. Compared with the reference group, exposure for more than 3 years was associated with an HR of 2.36 (95% CI, 1.30–4.26; $P=0.004$), while high-dose exposure was associated with an HR of 3.01 (95% CI, 1.66–5.48; $P<0.001$). The corresponding estimates for shorter treatment durations and low-dose exposure were not statistically significant. Among patients with previous gastric cancer resection, Shiratori et al. reported increasing risks of metachronous gastric cancer with longer P-CAB and PPI exposure. For P-CABs, the adjusted HRs were 3.44 (95% CI, 1.89–6.85) for less than 1 year, 3.95 (95% CI, 2.62–7.04) for 1–3 years, and 9.36 (95% CI, 6.39–13.7) for more than 3 years of use (all $P<0.01$). For PPIs, the corresponding adjusted HRs were 1.52 (95% CI, 1.01–2.29), 1.71 (95% CI, 1.27–2.32), and 3.43 (95% CI, 2.55–4.61), respectively. These findings are summarized in Table 5.

Table 5.

Duration-, frequency-, and dose-response associations between acid-suppressive therapy and gastric cancer risk

Author, year	Exposure	Duration/Dose category	Comparator	Effect measure	Effect estimate (95% CI)	P value
(Cheung et al., 2018)	PPI	Weekly to <daily	Non-user (<weekly)	HR	2.43 (1.37–4.31)	0.002
		Daily	Non-user (<weekly)	HR	4.55 (1.12–18.52)	0.034
		≥1 year; weekly to <daily	Non-user (<weekly)	HR	1.81 (0.90–3.64)	0.098
		≥1 year; daily	Non-user (<weekly)	HR	5.04 (1.23–20.61)	0.024
		≥2 years; weekly to <daily	Non-user (<weekly)	HR	0.98 (0.31–3.17)	0.979
		≥2 years; daily	Non-user (<weekly)	HR	6.65 (1.62–27.26)	0.009
		≥3 years; weekly to <daily	Non-user (<weekly)	HR	0.58 (0.08–4.23)	0.590
		≥3 years; daily	Non-user (<weekly)	HR	8.34 (2.02–34.41)	0.004
(Seo et al., 2021)	PPI	≥30 days	Non-PPI	HR	1.35 (0.79–2.31)	0.277
		≥90 days	Non-PPI	HR	1.92 (0.96–3.83)	0.064
		≥180 days	Non-PPI	HR	2.22 (1.05–4.67)	0.036
		≥365 days	Non-PPI	HR	2.54 (1.11–5.80)	0.027
(Kim et al., 2023)	PPI	T2 annual PPI dose vs T1	T1 annual PPI dose	aHR	2.40 (1.99–2.89)	<0.001
		T3 annual PPI dose vs T1	T1 annual PPI dose	aHR	3.82 (3.20–4.56)	<0.001
(Arai et al., 2024)	P-CAB (vonoprazan)	<1 year	H2RA	HR	0.54 (0.13–2.31)	0.542
		1–<2 years	H2RA	HR	2.13 (0.98–4.65)	0.058
		2–<3 years	H2RA	HR	1.81 (0.73–4.50)	0.199
		>3 years	H2RA	HR	2.36 (1.30–4.26)	0.004
		Low dose	H2RA	HR	1.32 (0.70–2.47)	0.395
		High dose	H2RA	HR	3.01 (1.66–5.48)	<0.001
(Shiratori et al., 2026)	P-CAB	<1 year	Non-user	aHR	3.44 (1.89–6.85)	<0.01
		1–3 years	Non-user	aHR	3.95 (2.62–7.04)	<0.01
		>3 years	Non-user	aHR	9.36 (6.39–13.7)	<0.01
	PPI	<1 year	Non-user	aHR	1.52 (1.01–2.29)	0.047
		1–3 years	Non-user	aHR	1.71 (1.27–2.32)	<0.01
		>3 years	Non-user	aHR	3.43 (2.55–4.61)	<0.01

aHR, adjusted hazard ratio; CI, confidence interval; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; NR, not reported; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

Risk of bias was assessed using the ROBINS-I V2 framework. Overall, two studies were judged to have moderate risk of bias and five studies were judged to have serious risk of bias. No study was judged to have critical risk of bias. The domain-level assessment showed that bias due to confounding was judged as moderate in all seven studies. Bias in classification of intervention was assessed as low in Niikura et al. and Gong et al., and serious in Cheung et al., Seo et al., Kim et al., Arai et al., and Shiratori et al. Bias in selection of participants was judged as low in Gong et al. and moderate in the remaining six studies. Bias due to missing data was judged as low in Cheung et al., Gong et al., and Arai et al., and moderate in the other four studies. All studies were judged to have low risk of bias in measurement of the outcome, whereas bias in selection of the reported result was judged as moderate across all studies. Overall, Niikura et al. and Gong et al. were judged to have moderate overall risk of bias, whereas Cheung et al., Seo et al., Kim et al., Arai et al., and Shiratori et al. were judged to have serious overall risk of bias. The detailed domain-level assessment is shown in Figure 2.

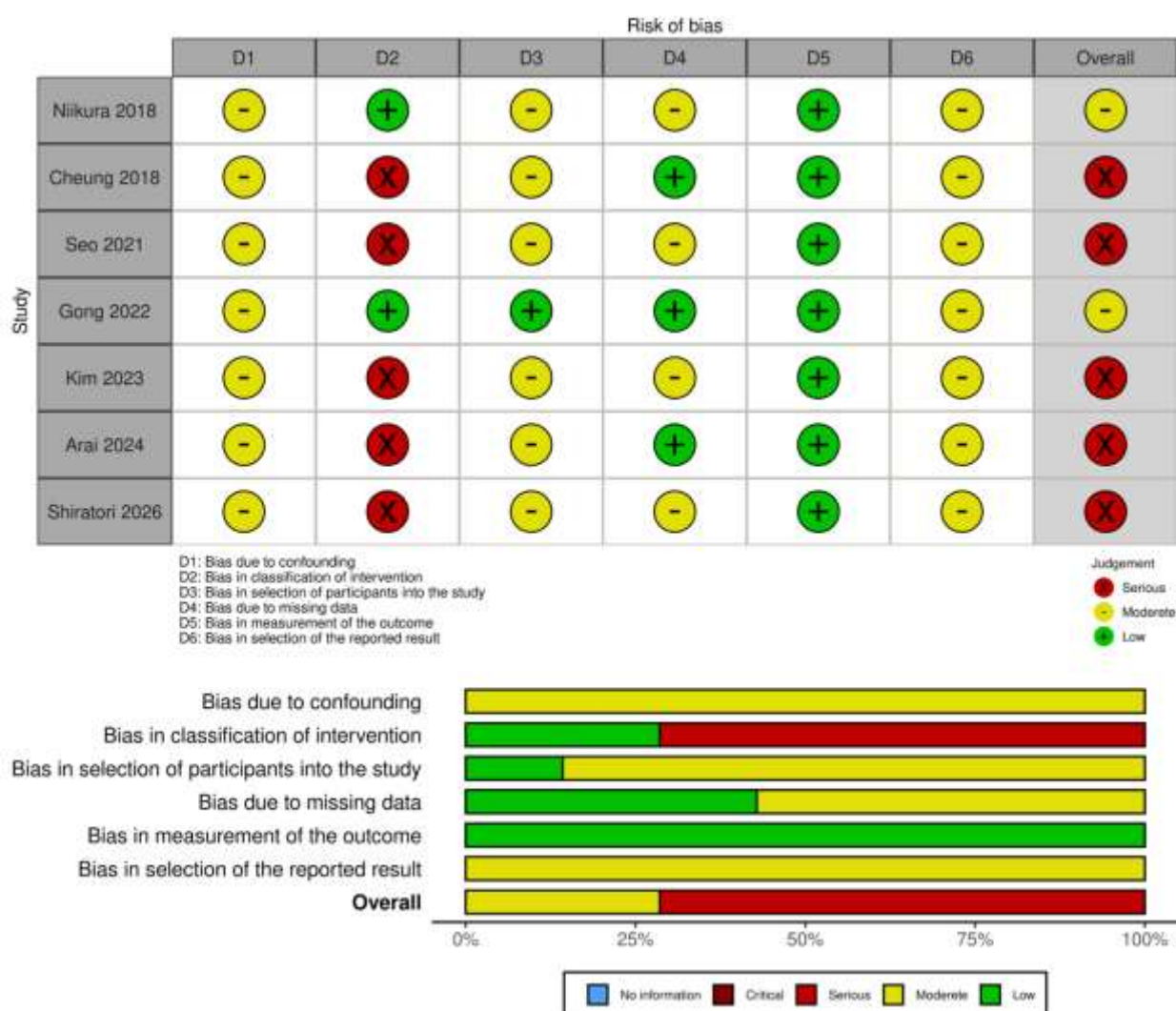


Figure 2. Risk of Bias assessment of the included studies using ROBINS-I V2.

DISCUSSION

This systematic review synthesizes evidence on the association between post-eradication acid-suppressive therapy and subsequent gastric cancer risk. Seven retrospective cohort studies published between 2018 and 2026 were identified, with most evaluating proton pump inhibitors (PPIs) and two recent studies evaluating potassium-competitive acid blockers (P-CABs). Overall, several cohorts reported increased gastric cancer risk among acid-suppressive therapy users, although findings were not uniform. Four of five PPI studies reported statistically significant associations in their primary analyses, whereas Gong et al. found no significant association when PPI users were compared with H2-receptor antagonist (H2RA) users (Cheung et al., 2018; Gong et al., 2022; Kim et al., 2023; Niikura et al., 2018; Seo et al., 2021). Both P-CAB studies also reported significant associations with gastric cancer outcomes (Arai et al., 2024; Shiratori et al., 2026). Several studies additionally showed higher risk estimates with longer duration, greater frequency, or higher dose, indicating a recurring observational signal despite substantial heterogeneity.

The variation among PPI studies highlights the importance of comparator selection, exposure definition, and underlying patient risk. Niikura et al., Cheung et al., Seo et al., and Kim et al. reported increased risks compared with non-users or non-PPI users, whereas Gong et al. found an attenuated, non-significant association using H2RA users as the comparator (Gong et al., 2022). Similar differences have been reported in broader pharmacoepidemiological studies, where associations between acid suppression and gastric cancer vary according to comparator and baseline risk (Abrahami et al., 2022; Brusselaers et al., 2017; Poulsen et al., 2009). Non-user comparisons may be affected by confounding by indication because patients requiring acid suppression can differ

from untreated individuals in gastrointestinal disease severity and gastric mucosal status. Atrophic gastritis and intestinal metaplasia independently increase gastric cancer risk and may also influence treatment patterns (Malfertheiner et al., 2017; Shichijo et al., 2016). Protopathic bias is another concern when lag periods are insufficient, as early symptoms of undiagnosed cancer may prompt acid-suppressive treatment before diagnosis (Poulsen et al., 2009). These considerations argue against interpreting the observed associations as direct causal effects.

Across Cheung et al., Seo et al., Kim et al., Arai et al., and Shiratori et al., longer or more intensive exposure was generally associated with higher risk estimates (Arai et al., 2024; Cheung et al., 2018; Kim et al., 2023; Seo et al., 2021; Shiratori et al., 2026). Daily administration, prolonged treatment, higher cumulative exposure, and higher dose categories were associated with stronger estimates than shorter or less intensive exposure. Sustained acid suppression may theoretically contribute through hypochlorhydria, hypergastrinemia, and alterations in the gastric microbial environment (Malfertheiner et al., 2017). However, duration and dose categories differed considerably between studies, limiting direct comparison (Brusselaers et al., 2017). Moreover, observational dose-response patterns do not establish causality because patients receiving prolonged or high-dose therapy may have more persistent gastrointestinal disease, leaving residual confounding by indication and disease severity (Abrahami et al., 2022; Poulsen et al., 2009).

The two P-CAB studies provide newer evidence but remain insufficient to establish the risk profile of this drug class. Arai et al. reported an increased risk of gastric cancer with vonoprazan compared with H2RA, while the comparison with PPI did not show a statistically significant difference (Arai et al., 2024). Shiratori et al. similarly reported increased metachronous gastric cancer risk among P-CAB users (Shiratori et al., 2026). Although P-CABs provide rapid and potent acid suppression, these findings cannot establish greater carcinogenic potential than PPIs because the evidence remains limited to retrospective cohorts with different populations and comparators. The clinical setting also differs substantially between these studies. Arai et al. evaluated incident gastric cancer after *H. pylori* eradication, whereas Shiratori et al. examined metachronous cancer in patients with previous gastric cancer resection. The latter population has a substantially different baseline risk because of previous neoplasia and persistent gastric mucosal abnormalities; therefore, incident and metachronous gastric cancer should be interpreted separately (Li et al., 2023; Shiratori et al., 2026).

These findings should be interpreted alongside the established clinical indications for acid suppression. PPIs and P-CABs remain important treatments for acid-related disorders, including peptic ulcer disease and gastroesophageal reflux disease, and may be required for ulcer prevention in selected patients receiving antiplatelet or anticoagulant therapy (Malfertheiner et al., 2017). The present findings therefore do not support routine avoidance of acid-suppressive therapy after *H. pylori* eradication. Rather, long-term treatment should continue to be guided by clinical indication, with periodic reassessment of the need and intensity of maintenance therapy, particularly in patients with established gastric premalignant lesions. Future studies should use prospective multicenter designs with clearly documented eradication status, standardized duration and cumulative-dose measures, active comparators, appropriate lag periods, and adjustment for baseline atrophy and intestinal metaplasia (Abrahami et al., 2022; Malfertheiner et al., 2017). PPI, P-CAB, and H2RA exposures should be evaluated separately, while incident and metachronous gastric cancer should remain distinct outcomes.

By focusing specifically on acid-suppressive therapy following *H. pylori* eradication, this review brings together the established PPI evidence with emerging P-CAB data while considering exposure intensity and the distinction between incident and metachronous cancer. The use of PRISMA 2020, searches across four major databases, and ROBINS-I V2 assessment provides a structured approach to interpreting the available non-randomized evidence. Nevertheless, only seven retrospective cohort studies met the eligibility criteria, and no directly relevant randomized trials were identified. The studies also differed in exposure definitions, comparators, follow-up, and baseline clinical

characteristics, with residual confounding and unmeasured gastric mucosal factors remaining important limitations. The small number of P-CAB studies further limits class-specific interpretation, while clinical and methodological heterogeneity precluded quantitative meta-analysis. Overall, the available evidence suggests an observational association between post-eradication acid suppression and gastric cancer in several cohorts, particularly with prolonged or more intensive exposure, but the extent to which this reflects a pharmacological effect rather than differences in underlying gastric cancer risk remains uncertain.

CONCLUSION

Post-eradication use of proton pump inhibitors (PPIs) and potassium-competitive acid blockers (P-CABs) was associated with an increased risk of subsequent gastric cancer in several observational cohorts. Higher risk estimates were generally observed with longer treatment duration, greater dosing frequency, and higher doses or cumulative exposure. However, the magnitude and consistency of these associations varied across comparator groups and clinical settings, particularly between incident and metachronous gastric cancer. The limited evidence on P-CABs and the observational nature of the included studies warrant cautious interpretation of these findings.

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