RESEARCH ARTICLE

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Helicobacter pylori-Associated Atrophic Gastritis and Risk of Gastric and Breast Cancer: A Prospective Cohort Study in Thailand

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Abstract

Background: Chronic atrophic gastritis (CAG), primarily driven by Helicobacter pylori infection, is a well-established precursor to gastric cancer. However, its association with extragastric malignancies remains poorly understood, especially in high-prevalence, resource-limited settings. We aimed to evaluate the risk of gastric and extragastric cancers in Thai patients with CAG. **Methods:** This hospital-based prospective cohort study included 1,252 Thai adults with histologically confirmed CAG between 2012 and 2017. Participants were stratified by H. pylori status. Incident cancers were identified via linkage with the national cancer registry through 2023. Cancer risks were estimated using Kaplan–Meier survival analysis and Cox proportional hazards models, adjusting for demographic, behavioral, and familial factors. **Result:** Over a median follow-up of 7.9 years (9,679 person-years), 44 participants developed cancer, corresponding to an incidence of 455 per 100,000 person-years. Gastric cancer (n = 14) and breast cancer (n = 16) were the most frequent malignancies. H. pylori–associated atrophic gastritis (HPAG) was significantly associated with increased risks of gastric cancer (HR 2.03; 95% CI: 1.25–3.26; p = 0.012) and breast cancer (HR 7.35; 95% CI: 2.08–17.13; p < 0.001) compared with non-HPAG patients. No significant associations were observed for other cancer types. **Conclusion:** HPAG is a primary driver of gastric cancer risk and is associated with a significantly elevated risk of breast cancer in this cohort. These findings underscore the importance of early detection and eradication of H. pylori before irreversible glandular loss. While the breast cancer association is exploratory, it suggests systemic oncogenic effects of chronic infection, warranting prioritized gastric surveillance and consideration for breast cancer screening in female HPAG patients.

Keywords: Atrophic gastritis, Breast neoplasms, Helicobacter pylori, Stomach neoplasms, Thailand

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Introduction

Chronic atrophic gastritis (CAG) represents a pivotal step in the gastric precancerous cascade, marked by progressive glandular loss and sustained mucosal inflammation [1, 2]. Among its etiologies, *Helicobacter pylori* infection remains the most prevalent and clinically significant driver, particularly in endemic regions such as Southeast Asia, where infection rates exceed 60% [3–5]. The International Agency for Research on Cancer classifies *H. pylori* as a Group 1 carcinogen, with infection increasing gastric cancer risk by up to tenfold [6, 7]. Despite advances in eradication therapy, the burden of *H. pylori*–associated gastric pathology remains substantial in low-resource settings.

Beyond its established role in gastric carcinogenesis, emerging evidence suggests that *H. pylori* may exert systemic oncogenic effects through chronic inflammation, immune dysregulation, and endocrine disruption [8–10]. These mechanisms raise the possibility of extragastric malignancies linked to persistent infection, although prospective data remain limited, especially from high-prevalence regions with constrained cancer surveillance infrastructure.

Thailand faces a dual challenge of high *H. pylori* prevalence and limited access to early cancer detection [11]. Gastric cancer in Thailand is frequently diagnosed at advanced stages, resulting in poor outcomes and high mortality [12]. Characterizing the cancer risk profiles of CAG is therefore essential to guide targeted prevention

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strategies, including risk-based surveillance and timely eradication therapy. In this context, we conducted a prospective, registry-linked cohort study of Thai adults with histologically confirmed CAG, stratified by *H. pylori* status. We hypothesized that *H. pylori*–associated gastritis (HPAG) confers not only an increased risk of gastric cancer but also heightened susceptibility to extragastric malignancies. By addressing this important knowledge gap, our findings aim to improve understanding of the chronic infection–carcinogenesis paradigm and inform regionally tailored cancer prevention policies.

Materials and Methods

Study Design and Participants

This investigation was designed as a hospital-based prospective cohort study conducted at Chiang Mai University Hospital in northern Thailand between June 2012 and May 2017. Figure 1 illustrates the flowchart of participant selection. Adult patients undergoing esophagogastroduodenoscopy (EGD) for dyspeptic symptoms were consecutively screened. Eligible participants were required to have histologically confirmed CAG, no cancer diagnosis within one year of the index endoscopy, and complete follow-up data available through December 31, 2023. Exclusion criteria included a history of gastroduodenal surgery, peptic ulcer disease, prior *H. pylori* eradication therapy, or chronic systemic illnesses requiring long-term medication.

Histopathological Assessment and Group Classification

Gastric biopsy specimens were obtained during EGD and processed according to the Updated Sydney System. Samples were stained with hematoxylin–eosin and Giemsa and independently reviewed by two board-certified gastrointestinal pathologists blinded to clinical data. Participants were classified into *H. pylori*–associated atrophic gastritis (HPAG) and non-HPAG groups based on histological evidence of infection. Patients with confirmed *H. pylori* infection received standard eradication therapy, with treatment success verified by urea breath test or stool antigen testing 6–8 weeks post-treatment.

Baseline Data Collection

Baseline demographic and clinical variables were extracted from electronic medical records before cancer diagnosis to minimize reverse causation. Collected data included age, sex, body mass index (BMI), educational attainment, smoking and alcohol use, reproductive history (age at menarche, age at first childbirth, contraceptive use), and family history of gastric or breast cancer.

Outcome Ascertainment and Follow-Up

Incident cancer cases were identified through linkage with the Chiang Mai Cancer Registry, the National Cancer Institute database, and mortality records from the Thai Ministry of Interior. Cancer diagnoses were coded using the International Classification of Diseases, 10th Revision (ICD-10). Secondary primary cancers were excluded. Participants were followed from the date of index EGD until cancer diagnosis, death, or the study end date (31 December 2023), whichever occurred first. Registry linkage ensured high sensitivity for cancer detection and minimized loss to follow-up.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. Categorical variables were reported as frequencies and percentages, while continuous variables were expressed as medians with interquartile ranges (IQRs). Group comparisons were performed using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables.

Time-to-event outcomes were analyzed using Kaplan–Meier survival curves, with differences assessed via the log-rank test. Cancer incidence was evaluated using Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for potential confounders. Covariates with $p < 0.25$ in univariable analysis or deemed clinically relevant were included in multivariable models. Backward stepwise selection was applied to optimize model fit, and collinearity diagnostics were conducted prior to final model construction.

Missing data were minimal and addressed through complete-case analysis without imputation. All statistical analyses were performed using Stata version 15 (StataCorp LLC, College Station, TX, USA). A two-sided p-value < 0.05 was considered statistically significant.

Ethical Approval and Study Registration

This study was approved by the Institutional Review Board of the Faculty of Medicine, Chiang Mai University (Approval No. MED 2566 0571; date of approval: May 20, 2024) and conducted in accordance with the Declaration of Helsinki. The study was prospectively registered with the Thai Clinical Trials Registry (TCTR20250608006) on June 8, 2025. Written informed consent was obtained from all participants.

Results

Baseline Characteristics

A total of 1,252 patients with histologically confirmed chronic atrophic gastritis (CAG) were enrolled. Of these, 461 (36.8%) were classified as HPAG, while 791 (63.2%) were classified as non-HPAG. The median age was 55 years (IQR: 46–61). A significantly higher proportion of individuals aged ≥60 years was observed in the non-HPAG group compared with the HPAG group (68.4% vs. 31.6%; $p = 0.003$). No significant differences were noted between groups in sex distribution, BMI, smoking or alcohol use, educational attainment, reproductive history, contraceptive use, or family history of gastric or breast cancer (all $p > 0.05$). The median follow-up duration was 7.9 years (IQR: 6.8–9.1), totaling 9,679 person-years, with comparable follow-up across groups (Table 1).

Cancer Incidence and Risk by Helicobacter pylori Status

During follow-up, 44 patients (3.5%) developed cancer, corresponding to an overall incidence of 455 per 100,000 person-years. The most frequent malignancies

Table 1. Baseline Characteristics of Participants by *Helicobacter pylori* Status

Characteristics	Participants (n=1,252)	Non-HPAG (n=791)	HPAG (n=461)	p-value
Age (years)				0.003[a]
<50 years	388 (30.99%)	257 (66.24%)	131 (33.76%)	
50-55 years	282 (22.52%)	166 (58.87%)	116 (41.13%)	
56-60 years	231 (18.45%)	128 (55.41%)	103 (44.59%)	
>60 years	351 (28.04%)	240 (68.38%)	111 (31.62%)	
Median [IQR]	55 [46-61]	55 [46-62]	55 [47-60]	0.581[b]
Gender				0.153[a]
Male	510 (40.73%)	310 (60.78%)	200 (39.22%)	
Female	742 (59.27%)	481 (64.82%)	261 (35.18%)	
Educational level				0.724[a]
Graduates	556 (44.41%)	348 (62.59%)	208 (37.41%)	
Undergraduates	696 (55.59%)	443 (63.65%)	253 (36.35%)	
Body mass index (kg/m^2)				0.825[a]
< 25 kg/m^2	840 (67.09%)	531 (63.21%)	309 (36.79%)	
≥ 25 kg/m^2	412 (32.91%)	260 (63.11%)	152 (36.89%)	
Smoking				0.181[a]
Yes	164 (13.10%)	77 (46.95%)	87 (53.05%)	
No	1,088 (86.90%)	574 (52.76%)	514 (47.24%)	
Alcohol consumption				0.634[a]
Yes	122 (9.74%)	60 (49.18%)	62 (50.82%)	
No	1,130 (90.26%)	586 (51.86%)	544 (48.14%)	
Late menarche (≥ 14 years)				0.247[a]
Yes	307 (24.52%)	185 (60.26%)	122 (39.74%)	
No	945 (75.48%)	606 (64.13%)	339 (35.87%)	
Late age at first childbirth (≥ 35 years)				0.097[a]
Yes	205 (16.37%)	119 (58.05%)	86 (41.95%)	
No	1,047 (83.63%)	672 (64.18%)	375 (35.82%)	
Contraceptive use				0.234[a]
Yes	204 (16.29%)	121 (59.31%)	83 (40.69%)	
No	1,048 (83.71%)	670 (63.93%)	378 (36.07%)	
Family history of gastric cancer				0.144[a]
Yes	298 (23.80%)	142 (47.65%)	156 (52.35%)	
No	954 (76.20%)	502 (52.62%)	452 (47.38%)	
Family history of breast cancer				0.158[a]
Yes	45 (3.60%)	24 (53.33%)	21 (46.67%)	
No	1,207 (96.40%)	767 (63.55%)	420 (36.45%)	
Duration of follow-up (years)				
Median [IQR]	7.9 [6.8-9.1]	7.8 [6.8-9.0]	7.9 [6.9-9.1]	0.274[b]

Baseline demographic, clinical, and reproductive characteristics of 1,252 Thai adults with chronic atrophic gastritis, stratified by Helicobacter pylori–associated atrophic gastritis (HPAG) versus non-HPAG. Continuous variables are presented as medians with interquartile ranges (IQR), and categorical variables as frequencies with percentages. Group comparisons were performed using Fisher's exact test (a) for categorical variables and the Mann–Whitney U test (b) for continuous variables.

were breast cancer (n = 16; crude incidence rate [CIR]: 165 per 100,000 person-years) and gastric cancer (n = 14; CIR: 144), together accounting for 68% of all cases. Less common cancers included liver cancer (n = 4; CIR: 41), cholangiocarcinoma (n = 4; CIR: 41), skin cancer (n = 4; CIR: 41), and lymphoma (n = 2; CIR: 20) (Table 2).

Breast cancer incidence was significantly higher in the HPAG group (n = 13) compared with the non-HPAG group (n = 3), with CIRs of 361.3 and 49.3 per 100,000 person-years, respectively. Kaplan–Meier analysis demonstrated a markedly increased cumulative incidence of breast cancer among HPAG patients (log-rank $p < 0.001$; Figure 2). After adjustment for demographic, behavioral, and familial confounders, *H. pylori* infection remained an independent predictor of breast cancer (adjusted HR: 7.35; 95% CI: 2.08–17.13; $p < 0.001$).

Table 2. Cancer Incidence and Risk by *Helicobacter pylori* Status

Cancer Type	Cases	Crude IR (95% CI)			HR (95%CI)	p-value
		Total	non-HPAG	HPAG		
Breast Cancer	16	165.3 (101.3-269.8)	49.3 (15.9-153.0)	361.3 (209.8-622.2)	7.35 (2.08-17.13)	<0.001
Gastric Cancer	14	144.6 (85.7-244.2)	64.0 (41.7-196.2)	274.6 (88.5-305.7)	2.03 (1.25-3.26)	0.012
Liver Cancer	4	41.3 (15.5-110.1)	32.9 (8.2-131.5)	54.9 (13.9-222.2)	0.74 (0.24-2.30)	0.235
Cholangiocarcinoma	4	41.3 (15.5-110.1)	65.8 (24.7-175.3)	0	N/A	N/A
Skin Cancer	4	41.3 (15.5-110.1)	64.4 (24.2-171.6)	0	N/A	N/A
Lymphoma	2	20.7 (5.2-82.6)	32.9 (8.2-131.5)	0	N/A	N/A

Incidence rates and hazard ratios for major cancer types among patients with chronic atrophic gastritis, stratified by Helicobacter pylori–associated atrophic gastritis (HPAG) versus non-HPAG. Crude incidence rates (per 100,000 person-years) are presented with 95% confidence intervals. Hazard ratios (HRs) were estimated using Cox proportional hazards models adjusted for demographic, behavioral, and familial factors. HPAG was significantly associated with increased risks of gastric cancer (HR 2.03; 95% CI: 1.25–3.26; p = 0.012) and breast cancer (HR 7.35; 95% CI: 2.08–17.13; p < 0.001). No significant associations were observed for other cancer types.

Gastric cancer was also more frequent among HPAG patients (n = 11) compared with non-HPAG individuals (n = 3), with incidence rates of 274.6 vs. 64.0 per 100,000 person-years. The adjusted HR for gastric cancer in the HPAG group was 2.03 (95% CI: 1.25–3.26; p = 0.012), confirming the established oncogenic role of *H. pylori* (Figure 2). No significant associations were observed between *H. pylori* status and liver cancer (HR = 0.74; 95% CI: 0.24–2.30; p = 0.235). Cholangiocarcinoma, skin cancer, and lymphoma occurred exclusively in the non-HPAG group, precluding hazard ratio estimation due to limited case numbers. These findings highlight limited statistical power for rarer cancers and warrant cautious interpretation.

Risk Factors for Breast Cancer in Patients with Chronic Atrophic Gastritis

Multivariable Cox regression identified *H. pylori* infection as an independent predictor of breast cancer (adjusted HR: 6.46; 95% CI: 1.61–26.02; p = 0.009). In univariable analysis, family history of gastric cancer (HR = 45.99; p < 0.001) and breast cancer (HR = 24.54; p < 0.001) were significantly associated with increased breast cancer risk. However, these associations lost statistical significance in adjusted models, suggesting potential confounding. Other variables, including age, BMI, smoking, alcohol use, educational attainment, and contraceptive history, did not show significant associations with breast cancer risk in multivariable analysis (all p >

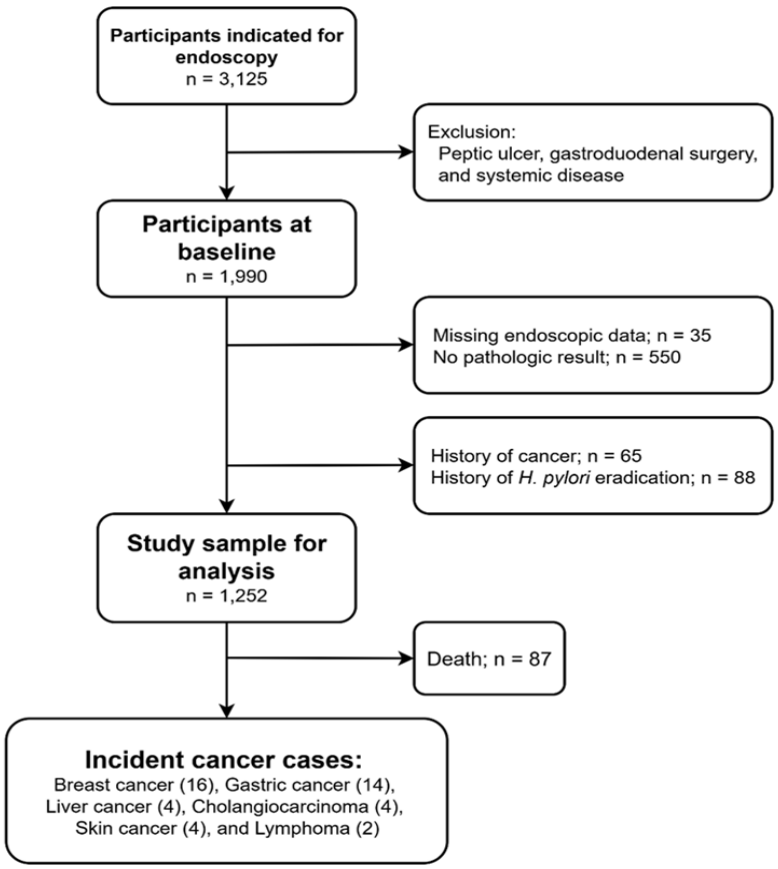


Figure 1. The Overall Design of This Study

Table 3. Risk Factors for Breast Cancer in Patients with Chronic Atrophic Gastritis

Characteristics	n/N (%)	Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	adj.HR (95% CI)	p-value
H. pylori infection					
No	3/1,029 (0.29)	1.00 [Ref.]	<0.001	1.00 [Ref.]	0.009
Yes	13/223 (5.83)	21.10 (5.96-74.76)		6.46 (1.61-26.02)	
Family history of gastric cancer					
No	4/1,158 (0.35)	1.00 [Ref.]	<0.001	1.00 [Ref.]	0.794
Yes	12/94 (12.77)	45.99 (14.68-144.05)		10.34 (0.24–24.25)	-
Family history of breast cancer					
No	9/1,193 (0.75)	1.00 [Ref.]	<0.001	1.00 [Ref.]	0.71
Yes	7/59 (11.86)	24.54 (9.15-65.81)		13.47 (0.99–35.19)	-
Age					
< 55 years	8/610 (1.31)	1.00 [Ref.]	0.914	-	-
≥ 55 years	8/642 (1.25)	1.06 (0.40-2.80)		-	-
Educational level					
Graduates	3/556 (0.54)	1.00 [Ref.]	0.048	-	-
Undergraduates	13/696 (1.87)	3.54 (1.01-12.44)		-	-
Body mass index					
≥ 25 kg/m^2	3/412 (0.73)	1.00 [Ref.]	0.235	-	-
< 25 kg/m^2	13/840 (1.55)	2.14 (0.61-7.50)		-	-
Active smoking					
No	14/1,088 (1.29)	1.00 [Ref.]	0.82	-	-
Yes	2/164 (1.22)	1.19 (0.27-5.20)		-	-
Alcohol use					
No	14/1,130 (1.24)	1.00 [Ref.]	0.761	-	-
Yes	2/122 (1.64)	1.26 (0.29-5.54)		-	-
Use of contraceptive					
No	11/1,048 (1.05)	1.00 [Ref.]	0.127	-	-
Yes	5/204 (2.45)	2.26 (0.79-6.42)		-	-

Multivariable Cox regression analysis of breast cancer risk among patients with chronic atrophic gastritis. *Helicobacter pylori* infection was an independent predictor (adjusted HR 6.46; 95% CI: 1.61–26.02; p = 0.009). Family history of gastric or breast cancer showed strong univariable associations but lost significance after adjustment. Other demographic and behavioral factors were not significantly associated.

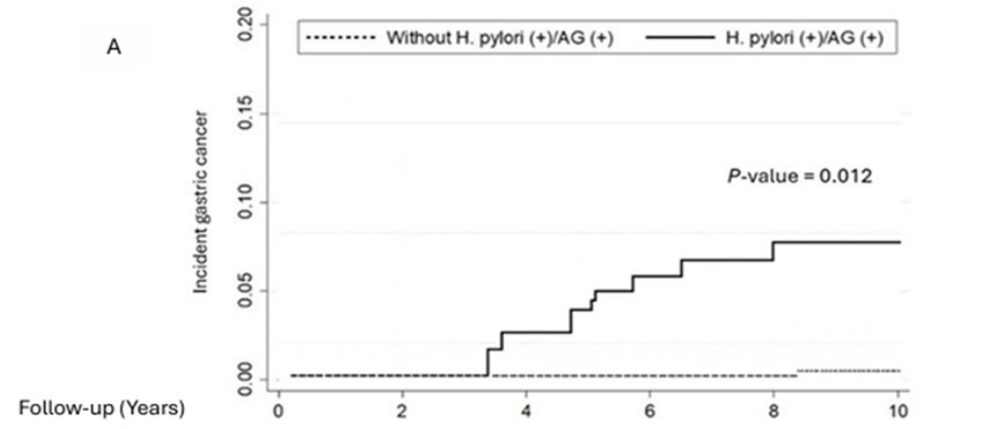
0.05; Table 3).

Discussion

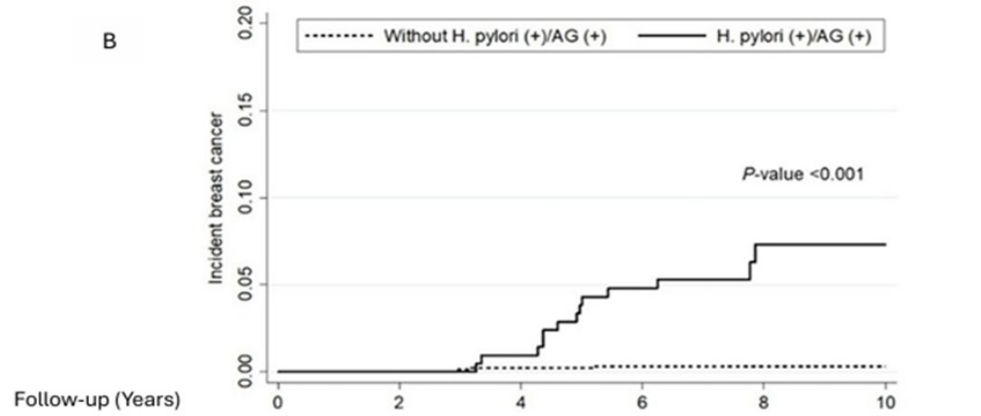
This prospective cohort study from Thailand reinforces the established oncogenic role of HPAG in gastric carcinogenesis and introduces a novel, exploratory association with breast cancer. Over a median follow-up of nearly eight years, patients with HPAG exhibited a significantly higher risk of gastric cancer (HR 2.03) and a striking seven-fold increased risk of breast cancer (HR 7.35) compared to *H. pylori*-negative individuals with atrophic gastritis. Notably, although all HPAG patients achieved successful eradication, their cancer incidence remained elevated. This finding underscores that while eradication eliminates the initiating pathogen, it does not necessarily reverse the field defects, including intestinal metaplasia and molecular alterations, that persist as fertile substrates for malignant transformation [13].

Our results identify histologically confirmed HPAG, rather than atrophy alone, as the dominant driver of gastric cancer risk. This pattern aligns with international data from the Asia-Pacific region: in Eastern Asia (Japan, Korea, China), HPAG cohorts demonstrate gastric cancer incidence rates of 300–500 per 100,000 person-years, while Southeast Asian rates (Vietnam, Thailand) are intermediate at 200–300 [14]. These findings support the classification of *H. pylori* as a Group I carcinogen and highlight the critical importance of intervention before the biological point of no return in the atrophy–carcinoma sequence [6, 7, 15]. The persistency of risk suggests that HPAG may leave a distinct epigenetic scar or cytokine profile (e.g., IL-8, TNF-α) that continues to drive carcinogenesis even after eradication [16].

The observed association with breast cancer suggests that the chronic infection–carcinogenesis paradigm may extend beyond the gastrointestinal tract. Potential systemic drivers include persistent systemic inflammation, immune dysregulation, and modulation of the estrobolome [17–21]. Emerging evidence indicates that *H. pylori* outer membrane vesicles and exosomes can influence systemic cytokine profiles and estrogen metabolism [21–24]. In our



HPAG Group (n/N)	0/461	0/455	2/410	5/375	3/310	1/240
Non-HPAG Group (n/N)	0/791	0/785	0/740	1/690	2/620	0/510



HPAG Group (n/N)	0/223	0/216	2/210	8/817	3/80	0/8
Non-HPAG Group (n/N)	0/1,029	0/1,001	2/975	1/919	0/509	0/108

Figure 2. Kaplan–Meier Curves for Cancer Incidence by *Helicobacter pylori* Status

cohort, breast cancer incidence was higher than expected, but given the limited number of cases, this finding should be interpreted with caution and regarded as hypothesis generating.

Geographic variation provides important context. Thailand's relatively low background incidence of gastric and breast cancers may amplify the relative risks observed. Strain virulence and host genetic susceptibility likely contribute: Thai studies report a predominance of CagA-positive strains with Western-type ABC or East Asian-type ABD motifs, both of which are strongly pro-inflammatory [25, 26]. The vacA s1/m1 genotype, also common in Thai patients, is associated with severe atrophy and progression along the Correa cascade [27]. Systemic inflammation from these high-virulence strains may extend to extragastric tissues, including the breast. The synergy between pathogen virulence and host genetics likely explains the persistent field defects observed in our HPAG group despite eradication. The absence of associations with other malignancies suggests a selective oncogenic effect, though limited extragastric cases preclude firm conclusions.

Overall, our findings position *H. pylori* infection as a major modifiable risk factor for gastric cancer in the Thai population, reinforcing the need for risk based gastric surveillance and aggressive eradication therapy in HPAG patients. The preliminary breast cancer signal raises important questions about the systemic consequences of chronic infection, but this association remains exploratory. Rather than recommending immediate screening changes, our results highlight the need for further large scale studies to clarify whether this link reflects a true systemic oncogenic effect or a population specific phenomenon.

Strengths of this study include its long-term prospective design, histological confirmation of chronic atrophic gastritis, and robust outcome ascertainment through national cancer registry linkage, minimizing selection and detection biases. Limitations include the single-center design, a modest sample size, and the lack of microbial strain or host genomic analysis, which limited mechanistic insights. Future research should prioritize large-scale, multi-ethnic validation studies integrating multi-omics

profiling to determine whether the breast cancer link reflects a universal systemic effect or a population-specific phenomenon.

In conclusion, this study identifies HPAG as a primary driver of gastric carcinogenesis that persists even after successful *H. pylori* eradication, underscoring the need for early intervention before irreversible glandular loss. Although exploratory, the observed association between HPAG and breast cancer should be interpreted with caution. It suggests a possible systemic oncogenic effect of chronic infection, but the limited number of cases means this finding is hypothesis generating rather than definitive. Clinically, our results reinforce the importance of risk based gastric surveillance, while the potential link to breast cancer highlights an area for future investigation rather than immediate screening recommendations. Future multi ethnic, multi omic studies are warranted to validate these associations and elucidate the underlying systemic pathways.

Author Contribution Statement

TC: Conceptualization, methodology, formal analysis, data curation, investigation, writing original draft, review and editing, supervision, validation, funding acquisition. PT, PS: Formal analysis, data curation, review, and editing. NH: Data curation, review, and editing. IC: Investigation, review and editing, project administration. All the authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Funding Statement

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Ethical Approval and Declaration

This study was approved by the Institutional Review Board of the Faculty of Medicine, Chiang Mai University (Approval No. MED-2566-0571; date of approval: 20 May 2024) as part of an approved academic research project. The study was conducted in accordance with the principles of the Declaration of Helsinki. All ethical issues were overseen by the Institutional Review Board, and patient confidentiality was strictly maintained throughout the study.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to privacy and ethical restrictions, the data are not publicly accessible.

Study Registration

This study was prospectively registered with the Thai Clinical Trials Registry (TCTR20250608006) on 8 June 2025.

Conflict of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study, the collection, analysis, or interpretation of data, the writing of the manuscript, or the decision to publish the results.

List of Abbreviations

CAG, Chronic atrophic gastritis; CIR, Crude incidence rate; *H. pylori*, *Helicobacter pylori*; HPAG, *Helicobacter pylori*-associated atrophic gastritis; non-HPAG, Non-*Helicobacter pylori*-associated atrophic

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