

ORIGINAL ARTICLE OPEN ACCESS

Long-Term Risk of Gastric Cancer After *Helicobacter pylori* Eradication in Gastric Ulcer Patients: A Nationwide Cohort Study in Korea

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Received: 3 May 2025 | **Revised:** 18 June 2025 | **Accepted:** 27 June 2025

Funding: This research was supported by the Korean Ministry of Education, Science, and Technology (NRF- RS-2019-NR040058 and 2022R1A2C2008281) and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (HA23C0266).

Keywords: gastric cancer | gastric ulcer | *Helicobacter pylori* | long-term follow-up | standardized incidence ratio

ABSTRACT

Background: *Helicobacter pylori* eradication reduces gastric cancer risk, but the long-term impact in peptic ulcer patients, particularly those with gastric ulcers (GU), remains unclear.

Aims: To assess the long-term incidence of gastric cancer in patients with *H. pylori*-treated gastric ulcers compared to the general population and to patients with duodenal ulcers (DU).

Methods: Using Korea's National Health Insurance Service database, we identified patients aged ≥ 40 years with endoscopically and histologically confirmed peptic ulcers treated for *H. pylori* between 2005 and 2008. Follow-up continued until 2019. Standardized incidence ratios (SIRs) for gastric cancer were calculated by comparing incidence in the study cohorts with the age- and sex-matched general population.

Results: Among 166,260 eligible patients (median follow-up 9.2 years), 2630 (1.58%) developed gastric cancer (SIR, 1.20; 95% CI, 1.15–1.24; $p < 0.001$), with consistently elevated risks across all age groups. Although cancer incidence remained elevated up to 12 years, patients followed for ≥ 13 years exhibited a significantly reduced risk compared to the general population (SIR, 0.78; 95% CI, 0.60–0.99; $p = 0.049$). In a sensitivity analysis, duodenal ulcer patients ($n = 46,602$) showed a lower overall risk (SIR, 0.86; 95% CI, 0.78–0.94; $p < 0.001$), with significant reductions even before 13 years of follow-up.

Conclusions: Gastric ulcer patients remain at increased risk for gastric cancer following *H. pylori* treatment. However, this risk declines over time and may fall below that of the general population after 13 years. These findings support the need for long-term surveillance in this high-risk group.

1 | Introduction

Gastric cancer ranks among the most common and lethal malignancies worldwide, standing fifth in incidence and fourth in cancer-related mortality [1]. An estimated 4.4 billion people

globally are infected with *Helicobacter pylori* (*H. pylori*), which remains the most important risk factor for gastric carcinogenesis [2]. Numerous studies have demonstrated that *H. pylori* eradication reduces the risk of gastric cancer in the general population as well as in patients already at high risk [3–6].

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Accordingly, guidelines in high-prevalence regions such as East Asia recommend screening and eradication of *H. pylori* to curb gastric cancer risk [7, 8].

Gastric ulcer has long been associated with an increased likelihood of malignancy, partly because it shares many of the same *H. pylori*-related pathogenic pathways [9]. While *H. pylori* therapy is effective in reducing peptic ulcer recurrence, it is not unequivocally clear whether such treatment lowers the risk of gastric cancer in gastric ulcer patients to levels comparable with the general population [10]. Prior investigations have been either insufficiently powered or limited by short follow-up durations [11, 12]. Additionally, the virulence of certain *H. pylori* strains and the potential for precancerous histological changes may further complicate risk reduction in this subgroup [13, 14].

In Korea, a country with one of the highest gastric cancer burdens worldwide [15], the National Health Insurance Service (NHIS) provides a unique opportunity to screen gastric cancer. Although previous research has addressed *H. pylori* eradication efficacy and gastric cancer incidence in broader populations [11, 12], data focusing specifically on gastric ulcer patients and their long-term risk remain sparse. Understanding these outcomes carries significant implications for clinical surveillance strategies and health policy.

Therefore, in this nationwide cohort study, we aimed to determine whether *H. pylori* treatment in gastric ulcer patients effectively reduces their risk of developing gastric cancer over an extended follow-up period. We additionally sought to characterize how the incidence of gastric cancer in this cohort compares to that of the age- and sex-matched general population and to identify subgroups that may benefit from prolonged endoscopic surveillance.

2 | Methods

2.1 | Data Sources

We analyzed data from the Korean National Health Insurance Service (NHIS) and the Korean Statistical Information Service (KOSIS), covering the period from January 1, 2003 to December 31, 2019. The NHIS serves as the primary government insurer in Korea, providing health coverage to nearly the entire population, while KOSIS compiles a broad range of national statistics, including data on gastric cancer progression, death certification, and underlying causes of mortality. The Korean NHIS claims database does not store pathology reports or endoscopic findings. As such, we were unable to directly assess the presence or severity of precancerous lesions (e.g., atrophic gastritis, intestinal metaplasia, dysplasia) at baseline or during follow-up. Further methodological details regarding these databases have been published previously [16].

2.2 | Study Design

We designed a retrospective cohort study to evaluate the incidence of gastric cancer among patients who underwent *H. pylori*

treatment following a diagnosis of gastric ulcer, compared with the general population. The overall study schema is depicted in Figure S1. The date on which the *H. pylori* eradication regimen was prescribed served as the index date. Follow-up continued from the index date until a diagnosis of gastric cancer, a competing event (death from nongastric cancer causes or gastric surgery), termination of health insurance coverage, or the end of the study period, whichever occurred first. Follow-up duration was defined from the date of first *H. pylori* eradication prescription to the earliest occurrence of gastric cancer diagnosis, death, disenrollment from insurance, or December 31, 2019, whichever came first. The study protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea (IRB No. KC21ZISI0308). As all data were managed in an anonymized format, the requirement for informed consent was waived.

2.3 | Study Population

We identified individuals aged ≥ 40 years who had endoscopically and histologically confirmed gastric ulcers and tested positive for *H. pylori* between January 1, 2005 and December 31, 2008. We restricted the study population to individuals aged ≥ 40 years to reflect the eligibility criteria of the Korean National Cancer Screening Program, which begins upper endoscopic screening at age 40. Additionally, gastric cancer incidence in individuals under 40 is rare ($< 3\%$ of surgical cases), and inclusion of this group would have had minimal statistical impact [17]. During that period, *H. pylori* eradication (clarithromycin-based triple or bismuth-based quadruple therapy) was reimbursed only when benign gastric ulcers had been confirmed by biopsy, in addition to histologic verification of *H. pylori* infection [18]. The initial prescription date for the *H. pylori* eradication regimen served as the index date. Drug codes are detailed in Table S1. Patients were excluded if they had (1) any prior prescription history of *H. pylori* eradication therapy, (2) a preexisting diagnosis of gastric cancer (ICD-10 code C16) or dysplasia (D131, D371), or (3) a history of gastric surgery (Table S2) before the index date. To further reduce the likelihood of including preexisting or “missed” neoplastic lesions, we also excluded patients who were diagnosed with gastric cancer or dysplasia—or who died—within 3 years of enrollment. After applying these criteria, 166,260 patients with gastric ulcers were included in the primary cohort (Figure 1). Baseline characteristics appear in Table 1.

2.4 | Comparison Groups

In addition to the primary cohort, we identified 46,602 patients with duodenal ulcers (and no concomitant gastric ulcers) who underwent *H. pylori* eradication during the same period; this served as a lower-risk comparison group. To contextualize the observed incidence of gastric cancer in both cohorts, we extracted age- and sex-specific data for the general Korean population from the Korean Statistical Information Service (KOSIS) spanning 2008–2019, as previously described [16]. We excluded any reported gastric cancer diagnoses or deaths that occurred prior to the patient's index year or within 3 years thereafter, thereby minimizing misclassification due to prevalent or sub-clinical cases.

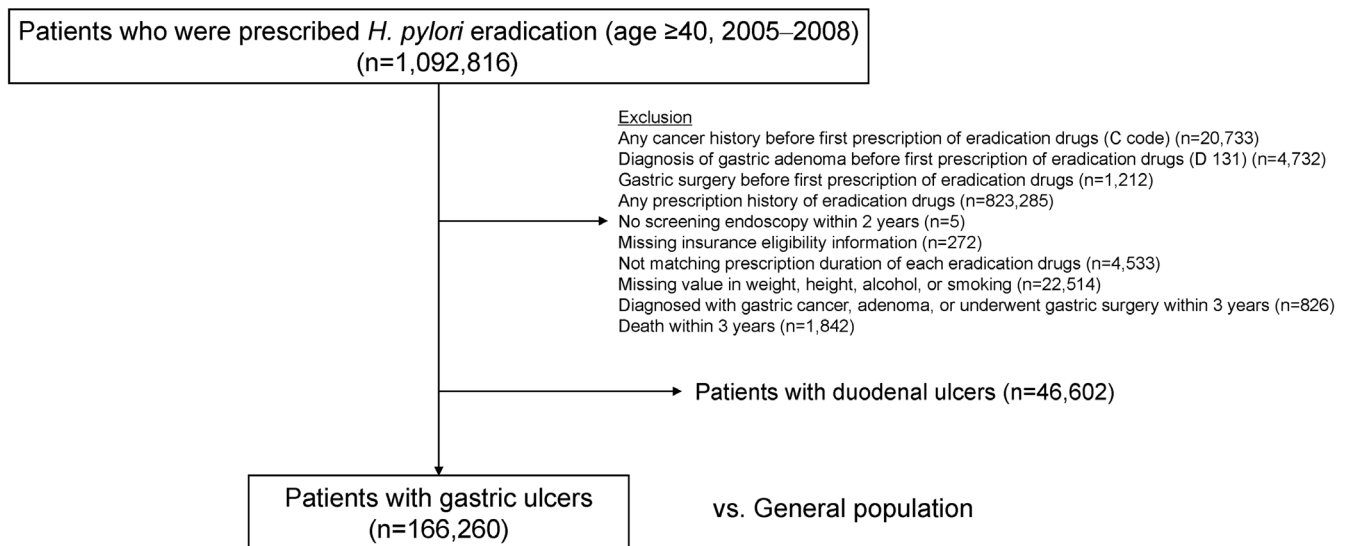


FIGURE 1 | Study design and patient selection flowchart. A flow diagram illustrating the identification of the final study cohort. Among 1,092,816 individuals prescribed *Helicobacter pylori* eradication therapy between 2005 and 2008, those with confirmed gastric ulcers ($n = 166,260$) were retained after applying exclusion criteria (cancer/dysplasia history, prior gastric surgery, incomplete data, and events within 3 years). An additional group of 46,602 patients with duodenal ulcers was used as a comparison cohort.

2.5 | Definition of *H. pylori* Eradication Therapy

Two main regimens were included, based on NHIS prescription claims (Table S1): (1) clarithromycin-based triple therapy—a proton pump inhibitor (PPI), clarithromycin, and amoxicillin for 7–14 days, and (2) bismuth-based quadruple therapy—a PPI, bismuth, metronidazole, and tetracycline for 7–14 days [18]. Patients whose prescriptions fell outside these duration ranges were excluded. During the study period, *H. pylori* eradication was reimbursed only for standardized regimens: 14-day clarithromycin-based triple therapy or bismuth-based quadruple therapy. Over 93% of patients received one of these, with no meaningful variation across ulcer groups. Because the NHIS database does not routinely record post-treatment test results, successful *H. pylori* clearance could not be directly confirmed.

2.6 | Ascertainment of Gastric Cancer

The primary outcome was newly diagnosed gastric cancer (ICD-10 code C16) confirmed by a V code (V193), an indicator of cancer registration in the NHIS. We defined the index date as the day of the first prescription for *H. pylori* eradication. Each patient was followed from the index date until: (1) gastric cancer diagnosis, (2) death from any cause, (3) insurance disenrollment, or (4) December 31, 2019, whichever came first.

2.7 | Covariates

We retrieved baseline demographics (age, sex, body mass index [BMI], income level), health behaviors (smoking and alcohol intake), and comorbidities (Charlson comorbidity index [CCI], diabetes mellitus, hypertension, dyslipidemia) from the NHIS database. Smoking and alcohol status were categorized using self-reported questionnaires at NHIS health check-ups, as

described previously [16]. Data on lifestyle factors (smoking, alcohol, BMI, income) and comorbidities were available only for patients who underwent national health screening at baseline. These variables were summarized descriptively but not included in regression models, as incorporating them would have excluded a substantial portion of the cohort and introduced potential selection bias.

2.8 | Statistical Analysis

We computed person-years at risk from the index date until an outcome or censoring. Gastric cancer incidence in the gastric ulcer cohort was compared with age- and sex-matched general population incidence rates derived from KOSIS data, yielding the standardized incidence ratio (SIR) [19]. Briefly, the SIR was defined as the ratio of the observed number of gastric cancer cases (O) to the expected number of cases (E), derived from age- and sex-specific incidence rates in the general population ($SIR = O/E$). The expected number was calculated by applying population-based gastric cancer incidence rates, stratified by 5-year age groups and sex, to the person-years accumulated in each subgroup of our cohort. The step-by-step procedure for calculating the SIR is outlined in Method S1. We have also noted that a chi-squared test for homogeneity was used to assess statistical differences between observed and expected counts across subgroups. A one-sample log-rank test assessed differences between observed and expected incidence. We also explored SIRs by age group (40–49, 50–59, 60–64, 65–69, ≥ 70 years) and follow-up duration (3–4, 5–6, 7–8, 9–10, 11–12, and ≥ 13 years).

Similarly, patients with duodenal ulcers were analyzed as a comparison cohort, and their incidence of gastric cancer was evaluated with the same methods: person-years, observed cases, and SIRs for each subgroup. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary,

TABLE 1 | Baseline characteristics of patients treated for *Helicobacter pylori* infection, stratified by ulcer type.

Characteristic		Total (n = 212,862)	Gastric ulcer patients (n = 166,260)	Duodenal ulcer patients (n = 46,602)
Age at treatment (years)	Mean ± SD	53.3 ± 8.6	53.7 ± 8.6	52.0 ± 8.2
	40–49	80,450 (37.8%)	60,153 (36.2%)	20,297 (43.6%)
	50–59	79,571 (37.4%)	62,471 (37.6%)	17,100 (36.7%)
	60–64	28,135 (13.2%)	22,860 (13.8%)	5275 (11.3%)
	65–69	14,786 (7.0%)	12,369 (7.4%)	2417 (5.2%)
	≥ 70	9920 (4.7%)	8407 (5.1%)	1513 (3.3%)
Sex	Male	121,494 (57.1%)	94,981 (57.1%)	26,513 (56.9%)
	Female	91,368 (42.9%)	71,279 (42.9%)	20,089 (43.1%)
Index year	2005	22,940 (10.8%)	18,130 (10.9%)	4810 (10.3%)
	2006	47,345 (22.2%)	37,053 (22.3%)	10,292 (22.1%)
	2007	60,040 (28.2%)	46,552 (28.0%)	13,488 (28.9%)
	2008	82,537 (38.8%)	64,525 (38.8%)	18,012 (38.7%)
Body mass index (kg/m ²)	< 18.5	3769 (1.8%)	2947 (1.8%)	17,753 (1.8%)
	18.5–22.9	74,281 (34.9%)	56,528 (34.0%)	12,947 (38.1%)
	23.0–24.9	59,221 (27.8%)	46,274 (27.8%)	15,080 (27.8%)
	≥ 25.0	75,591 (35.5%)	60,511 (36.4%)	17,753 (32.4%)
Smoking	Never	136,222 (64.0%)	106,389 (64.0%)	29,833 (64.0%)
	Former	22,721 (10.7%)	17,241 (10.4%)	5480 (11.8%)
	Current	53,919 (25.3%)	42,630 (25.6%)	11,289 (24.2%)
Alcohol consumption (/week)	< 1	147,272 (69.2%)	115,144 (69.3%)	32,128 (68.9%)
	1–2	38,023 (17.9%)	29,486 (17.7%)	8537 (18.3%)
	3–4	17,863 (8.4%)	13,886 (8.4%)	3977 (8.5%)
	≥ 5	9704 (4.6%)	7744 (4.7%)	1960 (4.2%)
Income (quartile)	1st	34,415 (16.2%)	27,194 (16.4%)	7221 (15.5%)
	2nd	30,320 (14.2%)	23,891 (14.4%)	6429 (13.8%)
	3rd	39,231 (18.4%)	30,825 (18.5%)	8406 (18.0%)
	4th	45,553 (21.4%)	35,561 (21.4%)	9992 (21.4%)
	5th	63,343 (29.8%)	48,789 (29.4%)	14,554 (31.2%)
Charlson comorbidity index	0	29,935 (14.1%)	19,637 (11.8%)	10,298 (22.1%)
	1–2	113,256 (53.2%)	87,496 (52.6%)	25,760 (55.3%)
	3–4	54,061 (25.4%)	45,352 (27.3%)	8709 (18.7%)
	≥ 5	15,610 (7.3%)	13,775 (8.3%)	1835 (3.9%)
Diabetes mellitus	No	180,875 (85.0%)	139,752 (84.1%)	41,123 (88.2%)
	Yes	31,987 (15%)	26,508 (15.9%)	5479 (11.8%)
Hypertension	No	148,599 (69.8%)	113,197 (68.1%)	35,402 (76.0%)
	Yes	64,263 (30.2%)	53,063 (31.9%)	11,200 (24.6%)
Dyslipidemia	No	147,895 (69.5%)	112,768 (67.8%)	35,127 (75.4%)
	Yes	64,967 (30.5%)	53,492 (32.2%)	11,475 (24.6%)

Note: Values are expressed as mean ± standard deviation (SD) or number (percentage). The Charlson comorbidity index was used to quantify overall comorbidity burden. Smoking and alcohol habits reflect self-reported questionnaires.

NC), with two-sided *p*-values <0.05 considered statistically significant.

2.9 | Ethical Considerations

The Institutional Review Board of Seoul St. Mary’s Hospital, The Catholic University of Korea, approved the study protocol (KC21ZISI0308). Informed consent was waived due to the use of anonymized, de-identified administrative data. All methods adhered to applicable guidelines and regulations.

3 | Results

3.1 | Study Population

Among 1,092,816 individuals prescribed *H. pylori* eradication therapy between 2005 and 2008, 166,260 patients with endoscopically confirmed gastric ulcers met the inclusion criteria (Figure 1). Detailed baseline characteristics, including demographic factors and comorbidities, are presented in Table 1 and Table S3. The mean age was 53.7±8.6 years, and 57.1% were male. Common comorbidities included diabetes mellitus (15.9%), hypertension (31.9%), and dyslipidemia (32.2%).

3.2 | Incidence of Gastric Cancer

During a median follow-up of 9.2 years (interquartile range: 8.4–10.2), 2630 (1.58%) of the gastric ulcer patients were diagnosed with gastric cancer, yielding an incidence rate of 173.4 per 100,000 person-years. Compared to the age- and sex-matched general population, these patients showed a significantly higher incidence of gastric cancer (SIR, 1.20; 95% CI, 1.14–1.24; *p*<0.001). Full details on observed and expected cases, person-years at risk, and SIRs are summarized in Table 2, and cumulative incidence curves for gastric ulcer versus general population are illustrated in Figure 2A.

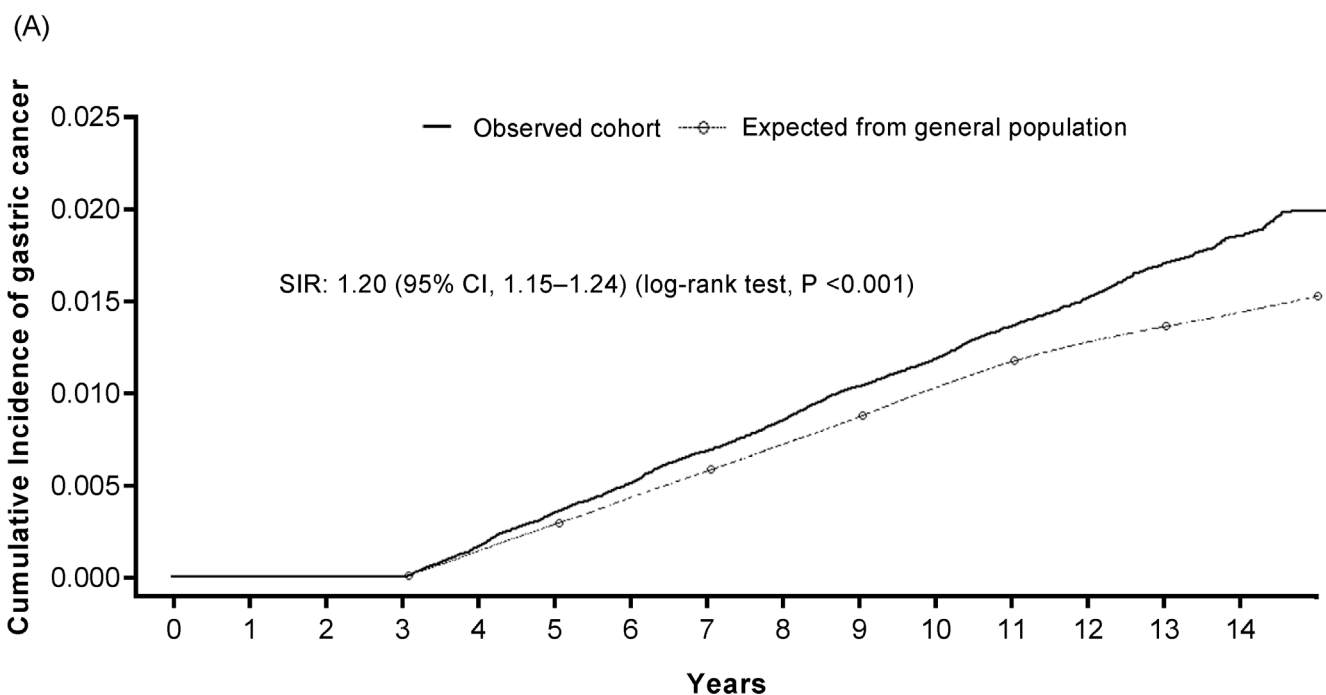
3.3 | Subgroup Analyses by Age and Sex

When stratified by age group (40–49, 50–59, 60–64, 65–69, and ≥70 years), a significant elevation in gastric cancer risk was observed across all categories (Table 2, Figure 3A). Patients aged 40–49 years showed an SIR of 1.25 (95% CI, 1.14–1.35), while those ≥70 years demonstrated an SIR of 1.18 (95% CI, 1.03–1.34). Cumulative incidence curves for gastric ulcer patients by age group in comparison with the general population are illustrated in Figure 2B. Furthermore, female patients displayed a distinctly higher incidence relative to the

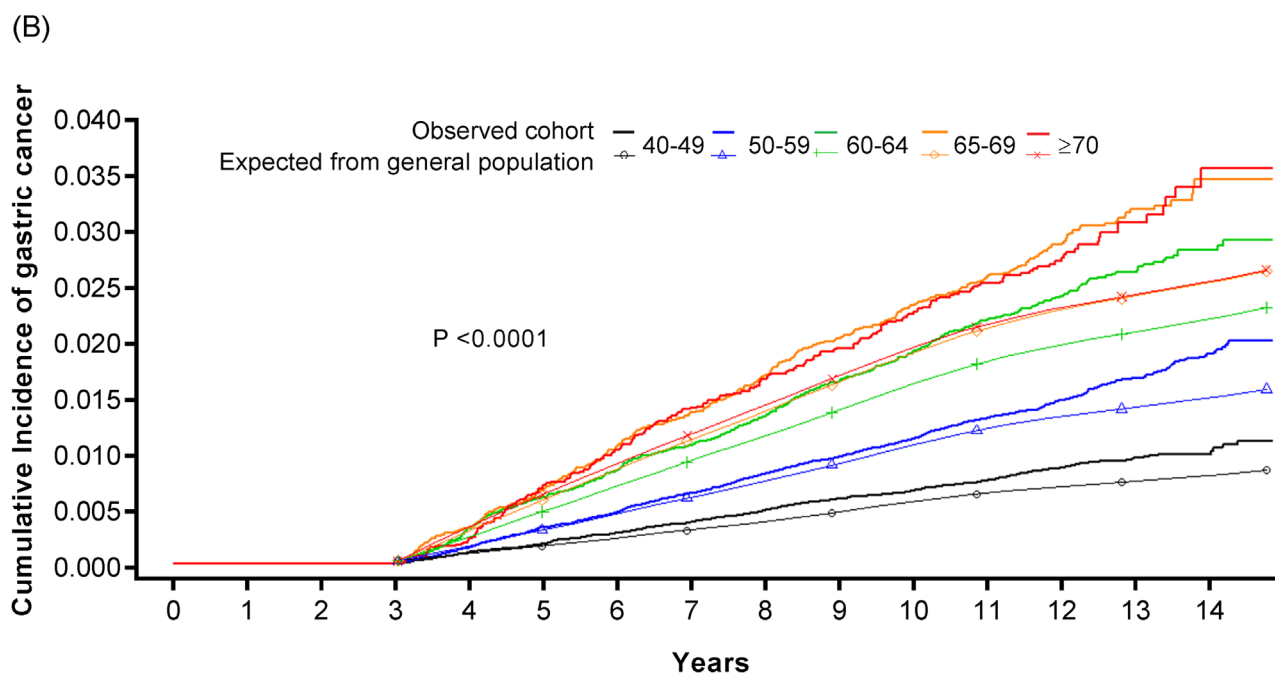
TABLE 2 | Age-, sex-, and follow-up-stratified SIR of gastric cancer in patients with gastric and duodenal ulcers following *Helicobacter pylori* treatment.

Variable		Gastric ulcer patients			Duodenal ulcer patients		
		<i>n</i> (%)	SIR (95% CI)	P	<i>n</i> (%)	SIR (95% CI)	P
Total		166,260 (100%)	1.20 (1.15–1.24)	<0.001	46,602 (100.0%)	0.86 (0.78–0.94)	<0.001
Age at treatment (years)	40–49	60,153 (36.2%)	1.25 (1.14–1.35)	<0.001	20,297 (43.6%)	0.92 (0.77–1.09)	0.378
	50–59	62,471 (37.6%)	1.14 (1.07–1.22)	<0.001	17,100 (36.7%)	0.77 (0.66–0.89)	<0.001
	60–64	22,860 (13.8%)	1.22 (1.13–1.33)	<0.001	5275 (11.3%)	0.83 (0.67–1.02)	0.089
	65–69	12,369 (7.4%)	1.26 (1.13–1.40)	<0.001	2417 (5.2%)	0.91 (0.68–1.18)	0.544
	≥70	8407 (5.1%)	1.18 (1.03–1.34)	0.017	1513 (3.2%)	1.19 (0.86–1.60)	0.262
Sex	Male	94,981 (57.1%)	1.01 (0.96–1.05)	0.730	26,513 (56.9%)	0.74 (0.67–0.82)	<0.001
	Female	71,279 (42.9%)	1.39 (1.30–1.50)	<0.001	20,089 (43.1%)	0.96 (0.80–1.14)	0.697
Follow-up duration (years)	3–4	166,260 (100.0%)	1.27 (1.17–1.37)	<0.001	46,602 (100.0%)	0.76 (0.61–0.93)	0.007
	5–6	164,233 (98.8%)	1.19 (1.09–1.29)	<0.001	46,239 (99.2%)	0.80 (0.65–0.97)	0.031
	7–8	162,036 (97.5%)	1.23 (1.13–1.33)	<0.001	45,786 (98.2%)	0.93 (0.77–1.11)	0.466
	9–10	159,519 (95.9%)	1.13 (1.03–1.22)	0.008	45,329 (97.3%)	0.92 (0.76–1.10)	0.416
	11–12	156,398 (94.1%)	1.16 (1.03–1.29)	0.011	44,738 (96.0%)	0.88 (0.69–1.11)	0.354
	≥13	50,652 (30.5%)	0.78 (0.60–0.99)	0.049	14,240 (30.6%)	0.56 (0.30–0.94)	0.040

Note: SIRs (95% CI) compare observed cancer incidence in gastric and duodenal ulcer patients with that of the general population. Values >1 indicate excess risk relative to the population baseline.



Observed cohort 166260 166260 166260 166260 165298 164233 163232 162036 160787 159519 158160 156398 94566 50652 16376



40-49	60153	60153	60153	60153	60006	59864	59716	59534	59367	59202	59041	58824	36568	20556	6732
50-59	62471	62471	62471	62471	62211	61904	61627	61298	60941	60595	60254	59782	35711	18935	6203
60-64	22860	22860	22860	22860	22674	22474	22290	22094	21860	21600	21315	20973	12576	6627	2186
65-69	12369	12369	12369	12369	12206	12025	11840	11643	11438	11217	10972	10647	6377	3037	853
≥70	8407	8407	8407	8407	8201	7966	7759	7467	7171	6905	6578	6172	3334	1497	402

FIGURE 2 | Cumulative incidence of gastric cancer in *Helicobacter pylori*-treated gastric ulcer patients versus the general population. (A) Kaplan-Meier curves comparing the cumulative incidence of gastric cancer among patients with gastric ulcers (solid line) to the age- and sex-matched general population (dashed line). (B) Stratified curves by age groups (40–49, 50–59, 60–64, 65–69, and ≥70 years). Patients with gastric ulcers demonstrated a higher incidence than expected over the first 12 years, with the two curves converging or crossing after approximately 13 years.

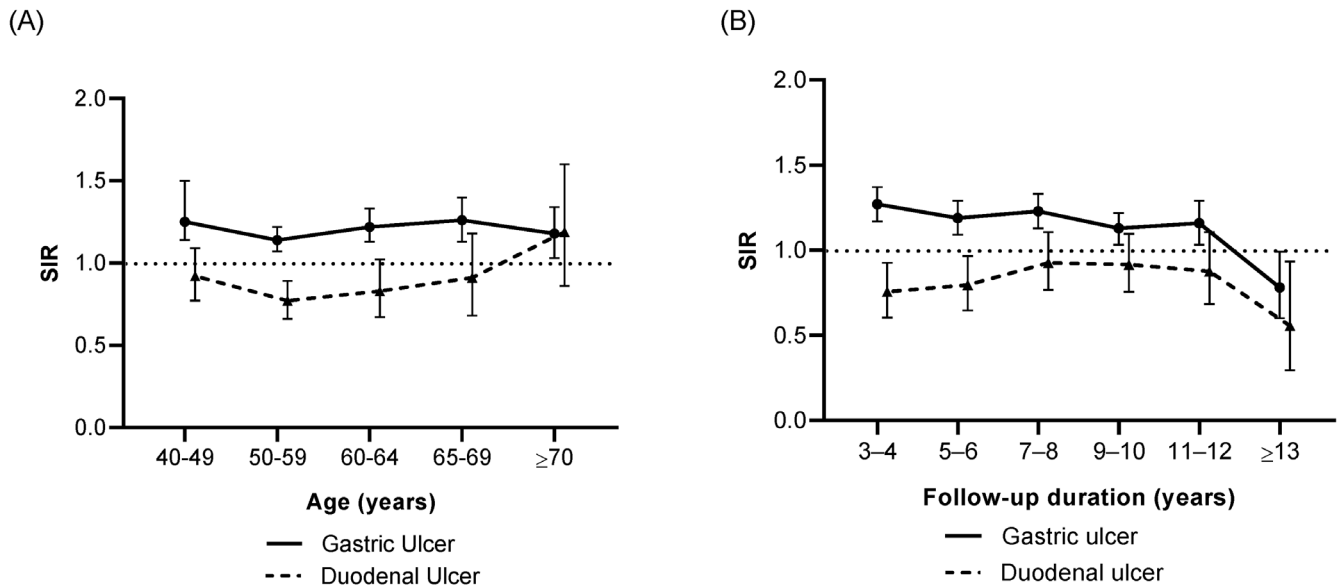


FIGURE 3 | Age-stratified standardized incidence ratios (SIRs) for gastric cancer in gastric and duodenal ulcer patients following *Helicobacter pylori* eradication. Forest plot illustrating the SIR for gastric cancer in patients with gastric ulcers and duodenal ulcers, stratified by age group (40–49, 50–59, 60–64, 65–69, and ≥70 years) and follow-up duration. SIRs were calculated by dividing observed cases by expected cases based on age- and sex-specific incidence rates in the general population. Error bars represent 95% confidence intervals. Gastric ulcer patients consistently demonstrated elevated SIRs across most age groups and time intervals, whereas duodenal ulcer patients showed no significant increase in cancer risk.

general population (SIR 1.39; 95% CI, 1.30–1.50) compared to males (SIR 1.01; 95% CI, 0.96–1.05). Detailed subgroup distributions and confidence intervals are also shown in Table 2.

3.4 | Follow-Up Duration After *H. pylori* Treatment

We next categorized patients by follow-up time intervals—3–4, 5–6, 7–8, 9–10, 11–12, and ≥13 years (Table 2, Figure 3B). The excess risk remained significantly elevated during the first 12 years post-*H. pylori* treatment. However, in those who were followed for ≥13 years, the incidence of gastric cancer fell below that of the general population (SIR 0.78; 95% CI, 0.60–0.99; $p=0.049$). Stratified analyses of gastric cancer incidence by age and follow-up duration are presented in Table S3, with corresponding SIR illustrated in Figure S2.

3.5 | Sensitivity Analysis in Duodenal Ulcer Patients

To evaluate a lower-risk comparison group, 46,602 patients with duodenal ulcers who had received *H. pylori* treatment were analyzed in parallel. The median follow-up in this cohort was 9.1 years, during which 487 (1.1%) developed gastric cancer (SIR 0.86; 95% CI, 0.78–0.94; $p<0.001$). Unlike the gastric ulcer cohort, none of the duodenal ulcer subgroups showed a higher than expected incidence of gastric cancer (Table 2). A breakdown of SIRs by follow-up duration demonstrated that risk remained below or close to the general population across all intervals (Table 2). Cumulative incidence curves comparing gastric and duodenal ulcer patients are presented in Figure S3,

and additional stratified analyses by age (Figure 3) and by both age and follow-up duration (Figure S4) are also shown.

4 | Discussion

This nationwide cohort study demonstrates that patients with endoscopically confirmed gastric ulcers remain at a heightened risk of gastric cancer following *H. pylori* treatment, compared with the age- and sex-matched general population. Despite receiving standard eradication regimens, the SIR was 1.20 over a median follow-up of 9.2 years, indicating a 20% excess risk. Furthermore, subgroup analyses revealed that this elevated risk persisted across all age categories. Notably, the excess risk fell below population levels only after 13 or more years of follow-up, underscoring the protracted timeline necessary to significantly reduce malignancy risk in this population.

In comparison with prior investigations, our study uniquely leverages a large nationwide cohort focusing specifically on endoscopically confirmed gastric ulcers. Previous large-scale research often pooled patients with gastric and duodenal ulcers or predominantly evaluated *H. pylori* eradication in general populations without differentiating ulcer subtypes [4–6]. Indeed, while the overall efficacy of *H. pylori* therapy in preventing peptic ulcer recurrence and reducing gastric cancer was demonstrated in previous studies, they did not clarify the extended timeline in which gastric cancer risk in gastric ulcer patients might normalize compared to the general population [11, 12]. Moreover, certain cohorts from Hong Kong mostly included a minority of gastric ulcer patients, limiting the power to detect a distinct long-term risk pattern for this subgroup [20]. By

contrast, we employed a stringent inclusion and exclusion process to capture a more homogeneous cohort of gastric ulcer patients, allowing us to delineate the prolonged (≥ 13 years) period required for risk reduction.

Interestingly, our sensitivity analysis in duodenal ulcer patients revealed a significantly lower SIR than the general population (0.86; 95% CI, 0.78–0.94). Although the number of cancer cases appeared similar to the gastric ulcer cohort, this group had substantially more person-years of follow-up and an older age distribution. These differences explain the higher SIR despite overlapping crude case counts. This finding concurs with prior work indicating that duodenal ulcer disease may be associated with a comparatively lower long-term risk of gastric malignancy, possibly due to differences in the anatomic location of acid hypersecretion or the pathological pathways involved [9, 10]. These contrasting outcomes underscore the importance of tailoring surveillance strategies to ulcer location and baseline histopathological status.

Based on our extended analyses (Table S3), we observed a persistently elevated risk in most stratified subgroups until the follow-up period reached 13 years or more, underscoring the durable carcinogenic potential even after *H. pylori* eradication. Moreover, as illustrated in Figure S3, SIRs were significantly elevated in the 3–4 and 5–9 year follow-up periods in most age groups, except those aged ≥ 70 . In contrast, in the ≥ 10 -year follow-up group, SIRs were not significantly different from 1.0 in the majority of age groups. These findings emphasize the importance of long-term, sustained surveillance: a patient who underwent *H. pylori* eradication therapy a decade ago should not be presumed to have reverted to a “normal” risk of gastric cancer. Clinically, these results suggest that patients with gastric ulcers require closer and more sustained surveillance than previously assumed, possibly up to or beyond 13 years to achieve risk levels comparable to—or even lower than—the general population. *H. pylori* eradication alone appears insufficient to immediately normalize their gastric cancer risk, highlighting a need for vigilant endoscopic follow-up.

Information on smoking, alcohol use, BMI, income, and comorbidities was available only for a subset of patients who underwent national health screening. Although these variables were not included in our multivariable models, their distributions were broadly comparable between gastric and duodenal ulcer groups (Table 1). Moreover, prior Asian cohort studies have shown that smoking, high-salt diet, and obesity each confer modest risk elevations (approximately 1.2-fold) [21, 22], which are insufficient to explain the 1.6-fold incidence-rate difference we observed unless heavily imbalanced—something not supported by our descriptive data. These suggest that lifestyle-related confounding is unlikely to materially affect the relative risk contrast between ulcer groups.

We identified gastroesophageal reflux disease using ICD-10 code K21 and defined chronic PPI exposure as ≥ 90 consecutive days of PPI prescriptions after the index eradication date. Although we performed a sensitivity analysis in this subgroup ($< 1\%$ of patients, evenly distributed across gastric- and duodenal-ulcer cohorts), estimates were unstable and thus excluded from the primary models.

A major strength of this work is the large sample size derived from a nationwide database, which minimizes selection bias and enhances the generalizability of our findings. Furthermore, the relatively long median follow-up provides robust insight into the temporal trends of carcinogenesis. Nonetheless, several limitations warrant consideration.

Despite the strengths conferred by a nationwide database, several limitations persist. One of the limitations of this study is that individual-level confirmation of *H. pylori* eradication was not possible using claims data. However, national registry studies report 71%–81% first-line success rates and $> 85\%$ eradication after two courses of therapy [23–25]. Any misclassification from persistent infection would have biased our results toward the null, reinforcing the robustness of our main findings. We did not have histopathological data on precancerous lesions like atrophic gastritis and intestinal metaplasia. Nevertheless, duodenal ulcer patients, who rarely develop corpus-predominant atrophy or IM, exhibited substantially lower gastric cancer incidence than gastric ulcer patients under the same treatment and follow-up conditions. Furthermore, the SIR in gastric ulcer patients declined over time, approaching that of the general population after 13 years, suggesting a gradual attenuation of cancer risk following *H. pylori* eradication. These internal patterns are consistent with prior histology-based studies showing that *H. pylori* eradication does not significantly reduce cancer risk once intestinal metaplasia is established [6]. Taken together, although the absence of histologic confirmation is a limitation, our real-world findings align with the natural history of gastric carcinogenesis and reinforce the need for continued endoscopic surveillance in selected high-risk patients. We acknowledge that the relative contribution of gastric ulcer versus precancerous lesions to cancer risk could not be distinguished in this study, and future research incorporating biopsy-confirmed histology is needed to resolve this question. Furthermore, lifestyle factors such as diet or family history of gastric malignancies were not fully captured in the claims database. While it would be ideal to include a comparator group of *H. pylori*-treated patients with duodenal ulcer, such individuals cannot be reliably identified in the NHIS claims database. Reimbursement for eradication therapy requires diagnosis-specific codes, and patients treated empirically or for functional indications are inconsistently captured. As a result, constructing a clean nonulcer cohort is not feasible. However, diagnostic accuracy within the ulcer-coded population is generally high, as endoscopic confirmation is routine in Korea prior to initiating eradication therapy. Future prospective registries that integrate clinical, endoscopic, and histologic data will be needed to evaluate long-term cancer risk in *H. pylori*-treated patients without structural lesions.

Multiple factors can influence gastric cancer risk; the structure of our nationwide dataset imposes certain constraints. Although we could not include family history or detailed dietary factors, their confounding impact is likely limited. Gastric cancer risk associated with family history is typically modest [26] and would not account for the observed difference between ulcer groups unless markedly imbalanced—something not supported by our data. Ulcer treatment regimens were largely uniform during the study period, with nearly all

patients receiving either clarithromycin triple or bismuth quadruple therapy. Moreover, the use of the general population as a reference for standardized incidence ratios aligns with prior studies and allows our results to be interpreted in the context of national background risk.

We limited the analysis to individuals aged 40 and older, reflecting national screening policies and the extremely low incidence of gastric cancer in younger adults. While this may limit generalizability to younger populations, the clinical and epidemiologic relevance of this age threshold supports its use in risk stratification. Last, although applying a 3-year washout period helps avoid missed lesions [27], it may exclude early cases that develop within this interval.

In summary, the main and supplementary results collectively indicate that the risk of gastric cancer in *H. pylori*-treated gastric ulcer patients remains elevated for more than a decade. Only after 13 years of follow-up did this excess risk fall below that of the general population, in sharp contrast to duodenal ulcer patients who generally exhibited a reduced or near-baseline risk. These findings underscore the importance of long-term surveillance protocols and targeted interventions for high-risk ulcer populations, offering valuable guidance for clinicians and policymakers aiming to reduce the burden of gastric cancer worldwide.

Author Contributions

Concept and design: Jae Myung Park, Hyeon Woo Yim. Acquisition, analysis, or interpretation of data: Seokho Myeong, Jae Myung Park, Hyeon Woo Yim. Drafting of the manuscript: Jae Myung Park, Seokho Myeong. Critical revision of the manuscript for important intellectual content: Jae Myung Park, Hyeon Woo Yim. Statistical analysis: Seokho Myeong, Jae Myung Park. Obtained funding: Jae Myung Park. Administrative, technical, or material support: Jae Myung Park, Donghoon Kang, Joon Sung Kim, Yu Kyung Cho. Supervision: Jae Myung Park, Hyeon Woo Yim.

Acknowledgments

We thank Yunhee Lee and Professor Jun-Pyo Myong for statistical assistance.

Ethics Statement

This study protocol was reviewed and approved by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital, the Catholic University of Korea, Seoul, Korea (IRB number: KC21ZISI0308).

Consent

The requirement for informed consent was waived by the IRB because the study utilized de-identified administrative data from a national database.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the Korean National Health Insurance Service (NHIS) and the Korean Statistical Information Service (KOSIS). Restrictions apply to the availability of these data, which were used under license for the current

study and are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the NHIS and KOSIS.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.