Early *Helicobacter pylori* Eradication Decreases Risk of Gastric Cancer in Patients With Peptic Ulcer Disease

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This article has an accompanying continuing medical education activity on page 1837. Learning Objective: Upon completion of differentiating the following questions, successful learners will be able to increase their ability in accessing the risk of gastric cancer development and eradicating *Helicobacter pylori* in patients with peptic ulcer diseases.

BACKGROUND & AIMS: *Helicobacter pylori* (*H pylori*) is a risk factor for gastric cancer. We investigated whether early *H pylori* eradication is associated with gastric cancer risk in patients with peptic ulcer diseases. **METHODS:** This nationwide cohort study was based on the Taiwan National Health Insurance Database (NHID), which provided data on 80,255 patients who were hospitalized for the first time between 1997 and 2004 with a primary diagnosis of peptic ulcer diseases and received *H pylori* eradication therapy. The patient population was divided into early (within 1 year) and late (after 1 year) eradication cohorts; standardized incidence ratios (SIRs) and hazards ratios (HRs) were determined. **RESULTS:** There was no significant difference in gastric cancer risk between patients who received early *H pylori* eradication and the general population (SIR, 1.05; 95% confidence interval [CI]: 0.96–1.14), but late eradication was associated with an increased risk (SIR, 1.36; 95% CI: 1.24–1.49). In gastric ulcer patients who received early eradication, SIRs of gastric cancer decreased from 1.60 at 3–4 years to 1.05 at 7–10 years after hospitalization; the SIRs decreased from 0.57 to 0.33 for duodenal ulcer patients over the same period. Among patients who received late eradication, SIRs decreased from 2.14 to 1.32 for those with gastric ulcers and from 0.90 to 0.66 for those with duodenal ulcers. Early *H pylori* eradication (HR, 0.77) and frequent aspirin or nonsteroidal anti-inflammatory drug use (HR, 0.65) were independent protective factors for gastric cancer. **CONCLUSIONS: Early *H pylori* eradication is associated with decreased risk of gastric cancer in patients with peptic ulcer diseases.**

Gastric carcinogenesis is a multifactorial process, involving complex interactions between host and environmental factors.[1,2] In addition to diet, smoking, and other environmental factors, *Helicobacter pylori* (*H pylori*) is associated with gastric cancer development, especially for noncardia cancer.[3–5] In animal models, *H pylori* infection has been shown to induce gastric cancer through the development of atrophic gastritis, intestinal metaplasia, and dysplasia.[6–8] Early eradication of *H pylori* in Mongolian gerbils leads to significantly lower incidence of gastric cancer.[9] In hypergastrinemic mice, early *H pylori* eradication completely prevents gastric cancer development, but late eradication delays the development of severe dysplasia.[10]

In contrast to the clear causal link between *H pylori* and gastric cancer in animal experiments, results of clinical studies remain conflicting. Uemura et al demonstrated the protective effect of *H pylori* eradication in a nonrandomized trial by reporting that gastric cancer develops in patients infected with *H pylori* but not in uninfected subjects.[11] However, in a randomized controlled trial conducted in China, *H pylori* eradication therapy did not significantly reduce the incidence of gastric cancer.[12] Eradication of *H pylori* was found to prevent progression of precancerous lesions, ie, atrophic gastritis and intestinal metaplasia, in 4 other randomized control studies.[13–16] However, the incidence of gastric cancer was not significantly reduced by *H pylori* eradication after pooling the results of these 4 intervention trials.[17] In a recent meta-analysis study, *H pylori* infection was found to be strongly associated with early gastric cancer.[18]

Previous studies provide important evidence for the potential roles of *H pylori* in gastric carcinogenesis; however, there is still no clear answer as to whether *H pylori* eradication therapy prevents future gastric cancer development. Based on the hypothesis that *H pylori* eradication may be a feasible method for gastric cancer prevention, we conducted a population-based retrospective cohort study of hospitalized patients with peptic ulcer

Abbreviations used in this paper: NHID, National Health Insurance Database; SIRs, standardized incidence ratios.

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diseases who received *H pylori* eradication therapy over a 10–year period. The primary outcome of interest was whether early *H pylori* eradication is associated with decreased risk of gastric cancer in patients with peptic ulcer disease.

Patients and Methods

Study Population

This nationwide cohort study was based on patient data obtained from the National Health Insurance Database (NHID), managed by the Taiwan National Health Research Institutes. The NHID contains health care data from > 99% of the entire population of 23.74 million. The NHID comprises comprehensive information, such as demographic data, dates of clinical visits, diagnostic codes, details of prescriptions, and expenditure amounts, and others, as detailed previously.[19] International Classifications of Diseases-9 codes were used to define diseases during the study period. Gastric cancer diagnosis was defined according to the Registry for Catastrophic Illness Patient Database, which is a separate subpart of the NHID. The diagnosis of gastric cancer in NHID needs histologic confirmation to be reported in the Registry for Catastrophic Illness Patient Database. This study has been approved by the National Health Research Institutes.

Study Subjects

From the NHID, hospitalized patients who were admitted for the first time between January 1, 1997, and December 31, 2004, with a primary diagnosis of peptic ulcer (Classifications of Diseases-9 codes: 531, 532, and 533 for gastric ulcer, duodenal ulcer, and nonspecific peptic ulcer, respectively) and received *H pylori* eradication therapy after the index hospitalization were recruited. Patients less than 20 years of age and those with previous gastric cancer or a diagnosis of gastric cancer registered within the first 2 years of the index admission were excluded. Patients who underwent gastric resection or vagotomy before index hospitalization discharge were also excluded. Admissions for uncomplicated and complicated (bleeding and/or perforated) peptic ulcers were analyzed separately. The numbers of endoscopic examinations after *H pylori* eradication were also analyzed. Aspirin or nonsteroidal anti-inflammatory agents (NSAIDs) included high-dose aspirin (>100 mg/day), low-dose aspirin (50–100 mg/day), cyclooxygenase (COX)-2 specific inhibitors (COXIBs), and traditional NSAIDs (excluding COXIBs). Patients who used aspirin or NSAIDs for more than 30 days within 3 months prior to the index hospitalization were defined as frequent aspirin or NSAIDs users. Comorbidities were defined as diseases diagnosed on previous admission before the index hospitalization.

H pylori *Eradication Cohorts*

H pylori eradication with triple or quadruple therapy was defined as proton pump inhibitor or H_2 receptor blocker, plus clarithromycin or metronidazole, plus amoxicillin or tetracycline, with or without Bismuth (details for all eligible *H pylori* eradication regimens are shown in Supplementary Table 1). These drug combinations were prescribed within the same prescription order, and the duration of therapy was between 7 and 14 days. One year was chosen as the cut-off value based on the distribution of *H pylori* eradication date after index hospitalization (Supplementary Figure 1). Patients who received *H pylori* eradication therapy within the first year of the index admission were included in the "early eradication cohort." Patients included in the "late eradication cohort" were given *H pylori* eradication therapy 1 year or more after the index hospitalization.

Gastric Cancer Risk Analysis

These 2 cohorts were followed up until the development of gastric cancer, death, or the end of 2006. Because gastric cancer developing in the first 2 years of the index hospitalization is difficult to differentiate from gastric cancer mimicking gastric ulcer, we excluded patients with a diagnosis of gastric cancer registered within the first 2 years of the index hospitalization. Each subject was followed up for a minimum of 2 years and a maximum of 10 years. Standardized incidence ratios (SIRs), cumulative incidences, and hazards ratios (HRs) of gastric cancer were analyzed. Stratified analyses according to age, sex, ulcer characteristics, endoscopic examination number, frequent aspirin or NSAIDs use, and year of follow-up were conducted.

Statistical Analysis

The demographic data, ulcer characteristics, aspirin or NSAIDs use, and comorbidities of these 2 cohorts were first analyzed. The SIR was defined as the ratio of the observed to the expected gastric cancer incidences in the cohorts. The expected incidence of cancer was calculated by adding up all person-time experienced in the cohort divided into strata by age (in 10-year gradient intervals) and sex and then multiplying the stratum-specific person-time by the corresponding stratum-specific incidence rates of the entire Taiwan population. The population of each age and sex strata and the corresponding stratum-specific incidence rates of gastric cancer for the entire Taiwan population were based on the population census in 2001 and cancer registry data in 2001, respectively. The 95% confidence intervals (CIs) for the SIRs were calculated on the assumption that the observed events followed Poisson distribution. Because the SIRs of early and late cohorts could not be compared directly, log-

rank test was used to compare the risk of gastric cancer between the 2 cohorts.

Cumulative incidence analyses were performed using Kaplan–Meier method, and the differences between the curves were tested with the 2-tailed log-rank test. To determine whether early *H pylori* eradication is an independent prognostic factor for gastric cancer development, HRs were calculated using the Cox proportional hazards model. Variables in the model included age, sex, peptic ulcer site, peptic ulcer complications, aspirin or NSAID use, *H pylori* eradication, and number of endoscopic examinations. Assessment of goodness-of-fit of the models with step-down method was used to analyze the independent prognostic factors. All data management and SIR analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC). Cumulative incidence and HRs were analyzed via the SPSS program for Windows 11.0 (SPSS Inc, Chicago, IL). Role of the funding source: National Health Research Institutes provided NHID for the present study.

Results

Demographic Data

Between 1997 and 2004, 80,255 hospitalized patients who were admitted for the first time with a primary diagnosis of peptic ulcer diseases and received *H pylori* eradication therapy after the index hospitalization were recruited. Among these subjects, 54,576 received *H pylori* eradication therapy within the first year of the index admission and were defined as "early eradication cohort," and 25,679 received eradication therapy 1 year or more after the index admission and were defined as "late eradication cohort." The median index hospitalization years of early and late cohorts were 2001 and 1999, respectively. The median intervals between the index admission date and *H pylori* eradication date were 14 and 1053 days for early and late eradication cohorts, respectively. The average numbers of years of follow-up for early and late eradication cohorts were 5.92 and 7.22 years, respectively. Because only 3929 patients (4.9%) were diagnosed as

Table 1. Baseline Characteristics of Patients in Early and Late *H pylori* Eradication Cohorts

	Early eradication cohort (n = 54,576)		Late eradication cohort (n = 25,679)		
Characteristics	Number	%	Number	%	*P* value
Age (mean ± SD), *y*	55.66 ± 0.07		55.98 ± 0.10		.009
20–39	9226	16.9	4078	15.9	<.0001
40–49	10,435	19.1	4715	18.4	
50–59	10,405	19.1	4900	19.1	
60–69	11,376	20.8	5972	23.3	
≥70	13,134	24.1	6014	23.4	
Sex					<.0001
Male	38,782	71.1	17,859	69.5	
Female	15,794	28.9	7820	30.5	
Index hospitalization year (median)	2001		1999		
Days of *H pylori* eradication after index hospitalization					<.0001
Mean ± SE	53.7 ± 0.4		1236.2 ± 4.4		
Median	14		1053		
Follow-up years (mean ± SD)	5.92 ± 0.01		7.22 ± 0.01		<.0001
Peptic ulcer site					<.0001
Gastric ulcer	23,005	42.2	11,419	44.5	
Duodenal ulcer	29,731	54.5	12,171	47.4	
Nonspecific peptic ulcer	1840	3.4	2089	8.1	
Ulcer complication					<.0001
Complicated peptic ulcer	41,812	76.6	17,981	70.0	
Uncomplicated peptic ulcer	12,764	23.4	7698	30.0	
Endoscopic examination (mean ± SD)	1.0 ± 1.8		1.0 ± 1.9		.0051
Annual endoscopic examination	0.16		0.15		
Aspirin or NSAID use					
High-dose aspirin	237	0.4	157	0.6	.0010
Low-dose aspirin	3903	7.2	1341	5.2	<.0001
NSAIDs	2790	5.1	1408	5.5	.0280
COXIBs	1328	2.4	573	2.2	.0390
Comorbidity					
Ischemic heart disease	8378	15.4	3174	12.4	<.0001
Cerebral vascular disease	5696	10.4	2088	8.1	<.0001
Chronic obstructive lung disease	10,186	18.7	3853	15.0	<.0001
Diabetes	7956	14.6	2869	11.2	<.0001
Cirrhosis	8875	16.3	3479	13.6	<.0001

nonspecified peptic ulcer diseases, they were analyzed together with gastric ulcer patients. Other demographic data, including age, sex, peptic ulcer site with or without complication, number of endoscopic examinations, use of aspirin or NSAIDs, and comorbidities, are shown in Table 1. For all comparisons of the 2 cohorts, differences were statistically significant.

Standardized Incidence Rates of Gastric Cancer

Early *H pylori* eradication conferred no significant difference in gastric cancer risk compared with the general population (SIR, 1.05; 95% CI: 0.96–1.14), but late eradication cohort was associated with an increased risk compared with the general population (SIR, 1.36, 95% CI: 1.24–1.49). On stratified analysis, in the early eradication cohort, there were higher risks of gastric cancer associated with age younger than 60, female sex, gastric ulcer, ulcer with complications, and nonfrequent aspirin or NSAIDs use compared with the general population. In the late eradication cohort, higher risk of gastric cancer was associated with age younger than 70 years, male and female sex, gastric ulcer, ulcers with or without complications, and nonfrequent aspirin or NSAIDs use (Table 2). Because unevenness of the eradication time in the late eradication groups was large, we also analyzed SIRs of late eradication group by limiting the time of eradication to within 2 years following the first year of index hospitalization. Compared with the general population, late eradication cohort was still found to have higher risk of gastric cancer (SIR, 1.40; 95% CI: 1.37–1.44). Similar results were found on the stratified analysis after limiting the time of eradication to within 2 years after the first year of index hospitalization (Supplementary Table 2).

The youngest patients (20–39 years of age) had the highest SIRs compared with other age groups. In early eradication cohort, patients with gastric ulcer had significantly higher risk of gastric cancer (SIR, 1.49; 95% CI: 1.35–1.64), whereas patients with duodenal ulcer had significantly lower risk (SIR, 0.56; 95% CI: 0.47–0.66). The inverse relation was also found in late eradication cohort but with 22% and 30% increased risks of gastric cancer compared with early eradication cohort for gastric and duodenal ulcer, respectively (Table 2). Late eradication cohort had significantly higher risk of gastric cancer compared with early eradication cohort in patients 50–70 years of age, male sex, patients with ulcer complications, receiving less than 2 endoscopic examinations, and nonfrequent aspirin or NSAIDs user (Table 2).

In the period between 3 to 4 years and 7 to 10 years, SIRs of early and late eradication cohorts decreased persistently (from 1.13 to 0.68, 40% decrease for early eradication; and, from 1.64 to 1.03, 37% decrease for late eradication) (Table 3). In early eradication cohort, the SIRs of gastric cancer in gastric ulcer patients declined from 1.60 in the period 3 to

Table 2. Risk of Gastric Cancer for Early and Late *H pylori* Eradication Cohorts

	Early eradication cohort (n = 54,576)		Late eradication cohort (n = 25,679)		
Characteristics	GCA, n	SIR	GCA, n	SIR	*P* value[a]
Total	136	1.05 (0.96–1.14)	113	1.36 (1.24–1.49)	.0128
Age, *y*					
20–39	7	10.47 (6.52–14.42)	5	13.13 (7.25–19.02)	.5322
40–49	23	5.38 (4.26–6.51)	7	2.80 (1.75–3.86)	.4580
50–59	17	1.83 (1.38–2.27)	17	2.86 (2.17–3.56)	.0341
60–69	23	0.83 (0.66–1.00)	32	1.70 (1.40–2.00)	.0250
≥70	66	0.77 (0.68–0.87)	52	0.97 (0.84–1.11)	.0969
Sex					
Male	106	1.00 (0.90–1.10)	84	1.25 (1.12–1.39)	.0387
Female	30	1.23 (1.00–1.45)	29	1.82 (1.49–2.16)	.1394
Peptic ulcer site					
Gastric ulcer	102	1.49 (1.35–1.64)	88	1.82 (1.63–2.01)	.2115
Duodenal ulcer	34	0.56 (0.47–0.66)	25	0.73 (0.59–0.88)	.2097
Ulcer complication					
Complicated	112	1.11 (1.00–1.21)	80	1.36 (1.21–1.52)	.0417
Noncomplicated	24	0.84 (0.65–1.02)	33	1.37 (1.13–1.61)	.0681
Endoscopic examination					
≥2	85	3.07 (3.00–3.13)	54	3.13 (3.05–3.21)	.5749
<2	51	0.57 (0.55–0.58)	59	0.97 (0.95–1.00)	.0036
Aspirin or NSAID use					
Frequent user	19	0.82 (0.63–1.01)	14	1.05 (0.77–1.33)	.6780
Nonfrequent user	117	1.27 (1.15–1.39)	99	1.65 (1.48–1.82)	.0118

NOTE. Table includes the standardized incidence ratios after the second year of follow-up for early and late *H pylori* eradication cohorts according to different demographic and ulcer characteristics.

SIRs, standardized incidence ratios; GCA, gastric cancer.

[a]Log-rank test was used to compare the risk of gastric cancer between 2 cohorts.

Table 3. Risk of Gastric Cancer According to Years of Follow-up

	Early eradication cohort (n = 54,576)		Late eradication cohort (n = 25,679)		
Years of follow-up	GCA, n	SIR	GCA, n	SIR	*P* value[a]
All patients					
3–4	66	1.13 (0.99–1.27)	50	1.64 (1.41–1.87)	<.0001
5–6	45	1.01 (0.86–1.16)	31	1.08 (0.89–1.27)	.0088
7–10	25	0.68 (0.55–0.82)	32	1.03 (0.85–1.21)	.0879
Gastric ulcer					
3–4	51	1.60 (1.37–1.82)	39	2.14 (1.80–2.48)	<.0001
5–6	32	1.38 (1.13–1.62)	26	1.54 (1.24–1.84)	.0206
7–10	19	1.05 (0.81–1.30)	23	1.32 (1.04–1.60)	.5118
Duodenal ulcer					
3–4	15	0.57 (0.43–0.72)	11	0.90 (0.63–1.17)	.0001
5–6	13	0.62 (0.45–0.79)	5	0.42 (0.23–0.61)	.7171
7–10	6	0.33 (0.19–0.46)	9	0.66 (0.44–0.89)	.1589

NOTE. Table includes the standardized incidence ratios of gastric cancer for early and late *H pylori* eradication cohorts according to years of follow-up and peptic ulcer site.
SIRs, standardized incidence ratios; GCA, gastric cancer.
[a]Log-rank test was used to compare the risk of gastric cancer cases between 2 cohorts.

4 years after the index hospitalization to 1.05 in the period 7 to 10 years after admission. The SIRs of gastric cancer in duodenal ulcer patients declined from 0.57 to 0.33 over the same periods. In late eradication cohort, similar trends were observed. The SIRs decreased from 2.14 to 1.32 in patients with gastric ulcer and from 0.90 to 0.66 in patients with duodenal ulcer.

Cumulative Incidences and Relative Risks of Gastric Cancer

Kaplan–Meier estimates of cumulative incidences of gastric cancer for early and late eradication cohorts are shown in Figure 1. The cumulative incidence of gastric cancer in early eradication cohort was significantly lower than the cumulative incidence in late eradication cohort ($P = .0128$) (Figure 1).

On Cox multivariable proportional hazards analysis, older age (HR, 1.03 for each incremental year, $P < .001$), male sex (HR, 1.46; $P = .012$), gastric ulcer (HR, 2.89; $P < .001$), peptic ulcer with complications (HR, 1.35; $P = .048$), and numbers of endoscopic examinations ≥2 (HR, 3.52; $P < .001$) were independent risk factors of gastric cancer. Frequent aspirin or NSAIDs use (HR, 0.65; $P = .022$) and early *H pylori* eradication (HR, 0.77; $P = .038$) were independent protective factors for gastric cancer development (Table 4).

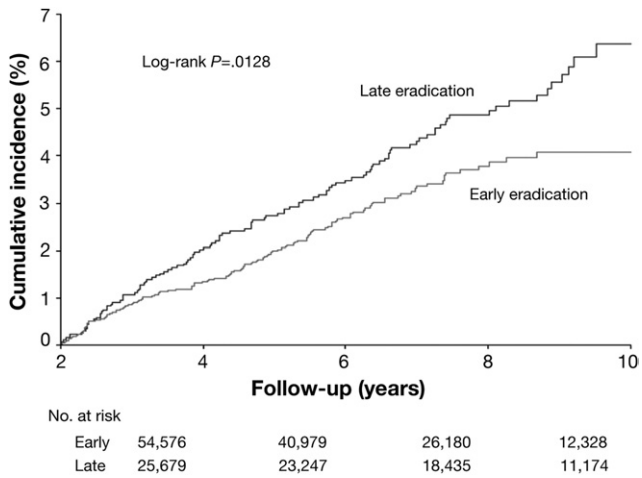

Figure 1. Cumulative incidences of gastric cancer for early and late *H pylori* eradication cohorts.

Discussion

The risk of gastric cancer among patients with peptic ulcer diseases has been investigated in a Swedish population-based study.[20] Hansson et al[20] reported that

Table 4. Multivariate Analysis for Prediction of Gastric Cancer Development

	Hazard ratios	95% CI	*P* value
Age			
Each increametal year	1.03	1.02–1.04	<.001
Sex			
Male vs female	1.46	1.08–1.95	.012
Peptic ulcer site			
Gastric ulcer vs duodenal ulcer	2.89	2.14–3.89	<.001
Peptic ulcer complications			
Complicated vs noncomplicated	1.35	1.00–1.82	.048
Numbers of endoscopic examinations			
≥2 vs <2	3.52	2.74–4.52	<.001
Aspirin or NSAID use			
Frequent user vs nonfrequent user	0.65	0.45–0.94	.022
H pylori eradication			
Early vs late eradication	0.77	0.60–0.99	.038

NOTE. Table includes multivariate Cox proportional hazards model analysis for prediction of occurrence of gastric cancer after the second year of follow-up in early and late *H pylori* eradication cohorts.
95% CI, 95% confidence interval.

the risk of gastric cancer leveled off after the first 3 years for gastric ulcer and first 2 years for duodenal ulcer. After the level-off period, the relative risks of gastric cancer remained stable. For patients with gastric ulcer, the relative risk was 1.8 throughout the follow-up period, whereas patients with duodenal ulcer showed a constant 0.6 relative risk. Compared with age- and sex-matched background population, women and younger patients (less than 50 years old) were found to be associated with higher risk of gastric cancer.[20] Based on these observations and to avoid the difficulties of differentiation from gastric cancer mimicking gastric ulcer, we excluded gastric cancer patients in the first 2 years of the index hospitalization from analysis.

The prophylactic role of *H pylori* eradication in the prevention of gastric cancer has been studied in several clinical trials. In a Chinese randomized trial with 1630 *H pylori*-infected subjects followed up for 7.5 years, *H pylori* eradication was found not to reduce incidence of gastric cancer but to prevent gastric cancer development in patients without precancerous lesions.[12] This observation is in accordance with the results of a Japanese study that revealed gastric cancer develops in persons infected with *H pylori* but not in uninfected subjects.[11] The same Japanese research group recently reported that *H pylori* eradication decreases metachronous gastric cancer after endoscopic resection of early gastric cancer at 3-year follow-up.[21] In another study based on 1342 patients with peptic ulcer diseases, gastric cancer developed in 8 of 994 patients cured of *H pylori* and 4 of 176 with persistent *H pylori* infection ($P = .04$).[22] In the 2008 Asia-Pacific Consensus Guidelines on Gastric Cancer Prevention, the estimated relative risk of gastric cancer after eradication of *H pylori* is 0.56.[3] In the present study, we found 40% and 37% decreased risks of gastric cancer in early and late *H pylori* eradication cohorts, respectively, between follow-up at 3 to 4 years and 7 to 10 years. Our results were slightly lower than the estimate of risk reduction by *H pylori* eradication in the 2008 Asia-Pacific Consensus Guidelines. However, the consistently decreasing trend of relative risk in our study may predict that the protective effect of *H pylori* eradication is even higher with longer follow-up. In the present study, early eradication cohort received *H pylori* eradication 2.84 years on average earlier than late eradication cohort. Interestingly, the SIRs of late eradication cohort were approximately equal to the SIRs of early eradication cohort 2 to 3 years earlier, which is compatible with the time lag of eradicating *H pylori* in the late eradication cohort. This observation implies that the progressively declining risk of gastric cancer with longer follow-up may be due, at least in part, to *H pylori* eradication. We also found late eradication cohort had significantly higher risk of gastric cancer compared with early eradication, especially in patients with higher risk, such as patients 50–70 years of age, male sex, patients with ulcer complications, and nonfrequent aspirin or NSAIDs users. The result infers the stronger protective roles of *H pylori* eradication in high-risk populations.

For *H pylori* eradication to have a protective effect against gastric cancer, the optimal timing for eradication is an important issue. According to the results of the Chinese study, *H pylori* eradication prior to the development of precancerous lesions is ideal.[12] In terms of age, the Asia Pacific Consensus Guidelines reveal that *H pylori* eradication therapy appears to offer some protection even in older people.[4] Leung et al reported that persistent *H pylori* infection is an independent risk factor associated with intestinal metaplasia progression, after adjusting for age.[15] Mera et al found that precancerous lesions regressed in patients rendered free of *H pylori* infection after adjusting for age as confounder.[16] Consistent with these results, we found that early *H pylori* eradication provided a protective effect for nearly all age groups, not only young patients. The highest protective effect was actually found in the 60–69 age group, with the second highest protective effect in the 50–59 age group.

Another interesting observation in our study is that infrequent aspirin or NSAIDs use is associated with an increased gastric cancer risk compared with the general population in both early and late cohorts, but frequent users had similar risk compared with the general population in both early and late cohorts. Use of aspirin or NSAIDs has been reported to be associated with lower risk of gastric cancer in previous meta-analysis studies.[23,24] Gonzalez–Perez et al found that aspirin and NSAIDs use was associated with lower relative risks of gastric cancer (0.73 for aspirin and 0.54 for NSAIDs, respectively).[23] Wang et al reported similar results of NSAID and aspirin use related to lower risk of gastric cancer (odds ratio, 0.73). On stratified analysis, the reduced risk was observed only in noncardia gastric cancer.[24] In Taiwan, noncardia gastric cancer comprises 86% of all gastric cancers.[25] In concordance with the results of meta-analysis, we found that frequent aspirin and NSAIDs users were protected from gastric cancer development with a relative risk of 0.65 after controlling for other demographic data, including the timing of *H pylori* eradication. According to our observation, *H pylori* infection and aspirin/NSAIDs use seems to have an inverse relationship in the development of gastric cancer.

The median index hospitalization years of early and late cohorts were 2001 and 1999, respectively. Early eradication cohort included more patients in the later years. It was consistent with the observation that early cohort had eradication therapy about 14 days after the index hospitalization but that the late cohort had eradication therapy about 1053 days after the index admission. Some 10 or more years ago, physicians were less likely to test for and treat *H pylori* infection after hospital admission. In recent years, since the publication of many guidelines and increasing evidence for the association of *H pylori* infection and gastric cancer, physicians are more likely to

test and treat patients with peptic ulcer diseases. It is also reflected in the findings of more low-dose aspirin users (7.2%) and shorter follow-up (5.9 years) in the early eradication cohort. Therefore, other social economic or historical issues might also play a role in the difference between the early and late eradication cohorts in terms of the different gastric cancer development risks. In addition, several other hidden reasons, such as recurrent peptic ulcer diseases, and/or a complication, or continued symptoms, may contribute to the explanation of why the late cohort underwent *H pylori* eradication therapy some 3 years after recovering from a peptic ulcer disease.

There are several limitations to our study. First, our observations were a retrospective cohort study based on hospitalized patients with peptic ulcer diseases who received *H pylori* eradication therapy. Certain selection biases may exist, and caution must be taken in extrapolating our results to other characteristic populations, such as nonulcer dyspepsia patients. Second, the definitions of early and late eradication cohorts are arbitrary. However, the median intervals between the index admission and *H pylori* eradication therapy were 14 and 1053 days for early and late cohorts, respectively, which implies that these 2 cohorts actually received *H pylori* eradication at different times following the index hospitalization. Third, late eradication as defined here was long-term (1–9 years), and patients had varied follow-up periods (2–10 years), meaning that much noise and many confounders may exist. Although we have conducted multivariate analysis to examine whether early eradiation is an independent protective factor, many factors are not available for adjustment, such as precancerous lesions and others. Therefore, our study could not determine the risk reduction achieved in different subgroups of patients. Fourth, unlike the study by Uemura et al,[11] we did not analyze the relative risk of patients with peptic ulcer diseases who did not receive *H pylori* eradication. Because we did not have data regarding these patients' *H pylori* status, it would be misleading to treat all of these patients as *H pylori* negative. Fifth, we did not have data to confirm whether *H pylori* eradication was successful. Therefore, this study can only calculate and compare the SIRs in early and late eradication cohorts, not among those in whom *H pylori* was eradicated and not eradicated, which can only be carried out by a prospective study. Such a study is hard to conduct because of ethical and long-term follow-up issues. In our previous community-based study, eradication rate was 86.9% at the time this study was performed.[26] Because the failure rates of early and late eradication cohorts should be similar, the influence of the uncalculated failure rates may weaken the association but not bias the results. Sixth, several confounders may exist in the present study, such as age and peptic ulcer site, and others. Age is associated with risk of gastric cancer because age is a surrogate for frequency and severity of atrophic gastritis. Patients with duodenal ulcer or gastric ulcer had different gastric cancer risk. For controlling these confounders, stratified analysis and multivariate analysis were conducted, and early *H pylori* eradication was shown to be an independent protective factor. Seventh, the confirmation of gastric cancer development depends on the database of NIHD, and it is potentially not accurate. However, the diagnosis of gastric cancer in NHID needs histologic confirmation to be reported in the Registry for Catastrophic Illness Patient Database. Therefore, the data regarding the development of gastric cancer should be accurate. Finally, the *P* value for the effect of early vs late eradication therapy on subsequent occurrence of gastric cancer was borderline statistical significance. Further studies, especially population-based studies, will be helpful to confirm our observations.

In this nationwide, long-term cohort study, we found that early *H pylori* eradication cohort had similar risk of gastric cancer compared with the general population but that late eradication cohort was associated with higher risk. On multivariate analysis, early *H pylori* eradication was found to be an independent protective factor for gastric cancer development. Our results provided evidence to support the viewpoint that *H pylori* eradication may be a feasible method for the prevention of gastric cancer.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi:10.1053/j.gastro.2009.07.060.

References

1. Fox JG, Wang TC. Inflammation, atrophy, and gastric cancer. J Clin Invest 2007;117:60–69.
2. Wu MS, Chen CJ, Lin JT. Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1878–1882.
3. Fock KM, Talley N, Moayyedi P, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. J Gastroenterol Hepatol 2008;23:351–365.
4. Talley NJ, Fock KM, Moayyedi P. Gastric Cancer Consensus conference recommends *Helicobacter pylori* screening and treatment in asymptomatic persons from high-risk populations to prevent gastric cancer. Am J Gastroenterol 2008;103:510–514.
5. Hunt RH. Will eradication of *Helicobacter pylori* infection influence the risk of gastric cancer? Am J Med 2004;117:S86–S91.
6. Honda S, Fujioka T, Tokieda M, et al. Development of *Helicobacter pylori*-induced gastric carcinoma in Mongolian gerbils. Cancer Res 1998;58:4255–4259.
7. Watanabe T, Tada M, Nagai H, et al. *Helicobacter pylori* infection induces gastric cancer in Mongolian gerbils. Gastroenterology 1998;115:642–648.
8. Sugiyama A, Maruta F, Ikeno T, et al. *Helicobacter pylori* infection enhances N-methyl-N-nitrosourea-induced stomach carcinogenesis in the Mongolian gerbil. Cancer Res 1998;58:2067–2069.

9. Nozaki K, Shimizu N, Ikehara Y, et al. Effect of early eradication on *Helicobacter pylori*-related gastric carcinogenesis in Mongolian gerbils. Cancer Sci 2003;94:235–239.
10. Lee CW, Rickman B, Rogers AB, et al. *Helicobacter pylori* eradication prevents progression of gastric cancer in hypergastrinemic INS-GAS mice. Cancer Res 2008;68:3540–3548.
11. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med 2001;345:784–789.
12. Wong BC, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187–194.
13. You WC, Brown LM, Zhang L, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. J Natl Cancer Inst 2006;98:974–983.
14. Zhou LY, Lin SR, Ding SG, et al. The changing trends of the incidence of gastric cancer after *Helicobacter pylori* eradication in Shandong area. Chin J Dig Dis 2005;6:114–115.
15. Leung WK, Lin SR, Ching JY, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. Gut 2004;53:1244–1249.
16. Mera R, Fontham ET, Bravo LE, et al. Long-term follow-up of patients treated for *Helicobacter pylori* infection. Gut 2005;54:1536–1540.
17. Fuccio L, Zagari RM, Minardi ME, et al. Systematic review: *Helicobacter pylori* eradication for the prevention of gastric cancer. Aliment Pharmacol Ther 2007;25:133–141.
18. Wang C, Yuan Y, Hunt RH. The association between *Helicobacter pylori* infection and early gastric cancer: a meta-analysis. Am J Gastroenterol 2007;102:1789–1798.
19. Wu C, Wu C, Wu M, et al. Decreased hospitalization for peptic ulcer disease in Taiwan after proton pump inhibitor therapy and *Helicobacter pylori* eradication. Clin Gastroenterol Hepatol 2009;7:427–431.
20. Hansson LE, Nyren O, Hsing AW, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. N Engl J Med 1996;335:242–249.
21. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008;372:392–397.
22. Take S, Mizuno M, Ishiki K, et al. The effect of eradicating *Helicobacter pylori* on the development of gastric cancer in patients with peptic ulcer disease. Am J Gastroenterol 2005;100:1037–1042.
23. Gonzalez-Perez A, Garcia Rodriguez LA, Lopez-Ridaura R. Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. BMC Cancer 2003;3:28–39.
24. Wang WH, Huang JQ, Zheng GF, et al. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2003;95:1784–1791.
25. Wu CW, Hsieh MC, Lo SS, et al. Prognostic indicators for survival after curative resection for patients with carcinoma of the stomach. Dig Dis Sci 1997;42:1265–1269.
26. Lee YC, Wu HM, Chen, et al. A community-based study of *Helicobacter pylori* therapy using the strategy of test, treat, retest, and re-treat initial treatment failures. Helicobacter 2006;11:418–424.

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Conflicts of interest

The authors disclose no conflicts.

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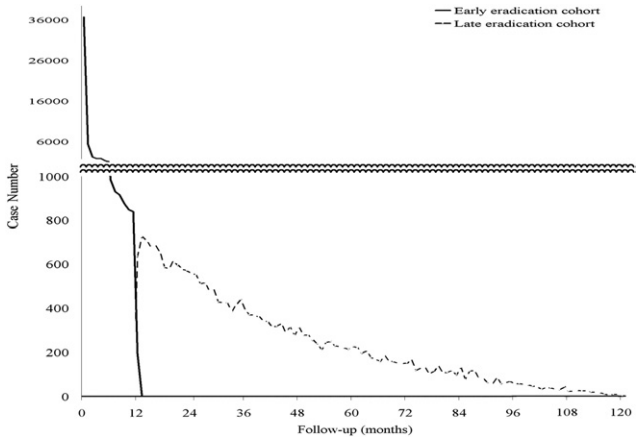
Supplementary Table 1. *Helicobacter pylori* Eradication Regimens

Type	*H pylori* eradication regimens
1	PPI + clarithromycin + amoxicillin
2	PPI + clarithromycin + metronidazole
3	PPI + amoxicillin + metronidazole
4	PPI + tetracyclin + amoxicillin
5	PPI + tetracyclin + metronidazole
6	PPI + clarithromycin + tetracyclin
7	PPI + bismuth + tetracyclin + metronidazole
8	PPI + bismuth + amoxicillin + metronidazole
9	PPI + levofloxacin + amoxicillin
10	PPI + bismuth + tetracyclin + levofloxacin
11	PPI + bismuth + amoxicillin + levofloxacin
12	H2RA + clarithromycin + amoxicillin
13	H2RA + clarithromycin + metronidazole
14	H2RA + amoxicillin + metronidazole
15	H2RA + tetracyclin + amoxicillin
16	H2RA + tetracyclin + metronidazole
17	H2RA + clarithromycin + tetracyclin
18	H2RA + bismuth + tetracyclin + metronidazole
19	H2RA + bismuth + amoxicillin + metronidazole
20	H2RA + levofloxacin + amoxicillin
21	H2RA + bismuth + tetracyclin + levofloxacin
22	H2RA + bismuth + amoxicillin + levofloxacin
23	PPI + clarithromycin + bismuth
24	PPI + amoxicillin + bismuth
25	PPI + metronidazole + bismuth
26	PPI + tetracyclin + bismuth
27	H2RA + clarithromycin + bismuth
28	H2RA + amoxicillin + bismuth
29	H2RA + metronidazole + bismuth
30	H2RA + tetracyclin + bismuth

NOTE. These drug combinations were prescribed within the same prescription order and the duration of therapy was between 7 and 14 days.
PPI, proton pump inhibitor.



Supplementary Figure 1. The distribution of *H pylori* eradication date after index hospitalization. The case numbers (*y-axis*) of *H pylori* eradication in each month vs months of *H pylori* eradication after the index hospitalization (*x-axis*) for early and late eradication cohorts.

Supplementary Table 2. Risk of Gastric Cancer for Early and Late *H pylori* Eradication Cohorts by Limiting the Time of Eradication to Within 2 Years After the First Year of Index Hospitalization

	Early eradication cohort (n = 54,576)		Late eradication cohort[b] (n = 13,448)		
	CASE, n	SIR	CASE	SIR	*P* value[+]
Total	136	1.05 (0.96–1.14)	51	1.40 (1.37–1.44)	.0379
Age, *y*					
20–39	7	10.47 (6.52–14.42)	2	9.42 (8.25–10.94)	.5703
40–49	23	5.38 (4.26–6.51)	7	5.87 (5.45–6.33)	.8713
50–59	17	1.83 (1.38–2.27)	9	3.46 (3.24–3.70)	.0209
60–69	23	0.83 (0.66–1.00)	12	1.33 (1.26–1.41)	.2600
≤70	66	0.77 (0.68–0.87)	21	0.94 (0.90–0.98)	.5644
Sex					
Male	106	1.00 (0.90–1.10)	39	1.31 (1.27–1.35)	.1424
Female	30	1.23 (1.00–1.45)	12	1.79 (1.69–1.90)	.3129
Peptic ulcer site					
Gastric ulcer	102	1.49 (1.35–1.64)	41	1.97 (1.91–2.03)	.2597
Duodenal ulcer	34	0.56 (0.47–0.66)	10	0.66 (0.62–0.70)	.6419
Ulcer complication					
Complicated	112	1.11 (1.00–1.21)	34	1.30 (1.25–1.34)	.6141
Noncomplicated	24	0.84 (0.65–1.02)	17	1.68 (1.60–1.76)	.0235
Endoscopic examination					
≥2	85	3.07 (3.00–3.13)	30	2.74 (2.65–2.84)	.9782
<2	51	0.57 (0.55–0.58)	21	0.82 (0.79–0.86)	.0797
Aspirin or NSAIDs use					
Frequent user	19	0.82 (0.63–1.01)	5	0.64 (0.58–0.70)	.6827
Nonfrequent user	117	1.27 (1.15–1.39)	46	1.66 (1.61–1.71)	.0385

[a]Log-rank test was used to compare the risk of gastric cancer between 2 cohorts.
[b]Limitimg the time of eradication to within 2 years after the first year of index hospitalization.