VOLUME 28 · NUMBER 18 · JUNE 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Effective Reduction of Gastric Cancer Risk With Regular Use of Nonsteroidal Anti-Inflammatory Drugs in *Helicobacter Pylori*–Infected Patients

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Submitted September 8, 2009; accepted March 11, 2010; published online ahead of print at www.jco.org on May 17, 2010.

Supported by Grant No. PH-098-PP-26 from Taiwan's National Health Research Institutes.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2818-2952/$20.00

DOI: 10.1200/JCO.2009.26.0695

ABSTRACT

Purpose
Nonsteroidal anti-inflammatory drugs (NSAIDs) play protective roles in gastric carcinogenesis. However, the interaction between NSAIDs and *Helicobacter pylori* (*H pylori*) infection and the number needed to treat to prevent gastric cancer remains unclear.

Patients and Methods
We conducted a nationwide retrospective cohort study based on data from the Taiwan National Health Insurance Database. Hospitalized patients with a primary diagnosis of peptic ulcer disease were selected. Overall, 52,161 patients were divided into non-NSAID user and regular NSAID user cohorts. Standardized incidence ratios (SIRs), cumulative incidences, and hazard ratios (HRs) were calculated.

Results
Patients with peptic ulcers who never used NSAIDs had higher risk of gastric cancer compared with the general population (SIR, 2.11; 95% CI, 2.07 to 2.15), but regular NSAID use conferred lower risk (SIR, 0.79; 95% CI, 0.77 to 0.81). The protective role of NSAID use was observed in patients with gastric ulcer, but not in patients with non–*H pylori*-associated duodenal ulcer. On multivariate analysis, regular NSAID use was an independent protective factor for gastric cancer development (HR, 0.79 for each incremental year; $P < .001$), especially in *H pylori*-associated patients (HR, 0.52 for each incremental year; $P < .001$). Among patients with *H pylori*-infected gastric ulcers, the NNT to prevent a gastric cancer was 50.

Conclusion
Regular NSAID use may be a feasible way to prevent gastric cancer, at least in patients with gastric ulcers, and especially in *H pylori*-infected subjects.

J Clin Oncol 28:2952-2957. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Despite the declining trend in both incidence and mortality worldwide, gastric cancer remains the fourth most common cancer and the second leading cause of cancer mortality.[1] Gastric carcinogenesis is a multifactorial process, involving complex interactions between host and environmental factors. Among these factors, chronic inflammation plays an important role in the development of gastric cancer.[2,3] Inflammation-induced injury may compromise tissue integrity and drive the multistage process of carcinogenesis by altering targets and pathways crucial to normal tissue homeostasis.[4] In addition, inflammatory conditions stimulate the formation and expansion of blood and lymphatic vessels within tumor, thus promoting tumor growth and invasion.[5] A prime example is *Helicobacter pylori* (*H pylori*) infection, which has been known to induce chronic gastric inflammation that leads to atrophy, metaplasia, dysplasia, and gastric cancer.[2,6] After eradicating *H pylori*, precancerous lesions may regress.[7,8] Testing and treating for the *H pylori* infection earlier rather than later in life is suggested to be the more beneficial approach.[9] In our recent population-based study, early *H pylori* eradication was found to be associated with decreased risk of gastric cancer.[10]

Elucidation of inflammation-based carcinogenesis offers new opportunities for gastric cancer chemoprevention.[11] Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have been suggested to prevent gastric cancer by inhibiting production of cyclooxygenase (COX) -1 and COX-2 through both prostaglandin-dependent and -independent pathways.[12] In a meta-analysis pooling of the results of clinical studies, NSAID use was found to be associated with a reduced risk of gastric cancer, with

similar magnitudes of risk reduction for aspirin and nonaspirin NSAID users. Regular users of NSAIDs were found to have a lower risk of gastric cancer compared with nonusers and irregular users.[13] Another meta-analysis also reported similar protective effect of NSAIDs in gastric cancer.[14]

Previous studies have provided important evidence of the protective roles of NSAIDs in gastric carcinogenesis. However, the interaction between NSAID use and *H pylori* infection and the subpopulation for which benefits of chemoprevention outweigh the risks gastrointestinal bleeding and the number needed to treat (NNT) remain unclear.[11,13]

PATIENTS AND METHODS

Study Population

In this population-based retrospective cohort study, data were obtained from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD has been described in detail in our previous study.[10,15] In brief, this database consists of health care data from more than 99% of the entire population of 23.72 million and comprises comprehensive health care information.[15,16] International Classification of Diseases-9 codes were used to define diseases. Gastric cancer diagnosis was defined according to the Registry for Catastrophic Illness Patient Database, which is a separate subpart of the NHIRD. Histological confirmation is required for the diagnosis of gastric cancer to be entered into this registry. This study has been approved by the National Health Research Institutes.

Study Subjects

From this database, we selected patients who were admitted to a hospital for the first time between January 1, 1998, and December 31, 2004, with a primary diagnosis of peptic ulcer disease (International Classification of Diseases-9 codes: 531, 532, and 533 for gastric ulcer, duodenal ulcer, and nonspecific peptic ulcer, respectively). Patients younger than 20 years and those with previous gastric cancer were excluded. Patients who underwent gastric resection or vagotomy before index hospitalization discharge were also excluded. Comorbidities were defined as diseases diagnosed on previous admission before the index hospitalization.

Gastric Cancer Risk Analysis

The observation period started on the discharge day of the index hospitalization until the end of 2006, death, or development of gastric cancer. The selected patients were divided into two cohorts according to their NSAID exposure status. Since 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 in this period. Each subject was observed for a minimum of 2 years and a maximum of 9 years. Standardized incidence ratios (SIRs), cumulative incidences, and hazards ratios (HRs) of gastric cancer were analyzed. To exclude the potential influence of competitive mortality, we also analyzed cumulative incidence of gastric cancer by excluding patients who died during the observation period.

Exposure to Aspirin and NSAIDs

NHIRD contains details of every prescription for nearly entire population of Taiwan between 1997 through 2006, including dose, frequency, starting and ending days, and administration routes. All information on aspirin and NSAID use for individual patients was obtained from NHIRD. NSAIDs included high-dose aspirin (> 100 mg/d), low-dose aspirin (50 to 100 mg/d), COX-2 specific inhibitors, and traditional NSAIDs (excluding COX-2 specific inhibitors). All analyzed NSAIDs are shown in Appendix Table A1 (online only). During the observation period, patients taking NSAIDs regularly (more than 28 days monthly) and continuously for more than 6 months were defined as regular NSAID users. Non-NSAID users were defined as those who had not used NSAIDs during the observation period. Because NSAID use changes after the index hospitalization, we also analyzed the results by treating NSAID use as a time-dependent covariate.[17]

H pylori-Associated Peptic Ulcer

Those who received *H pylori* eradication therapy were defined as *H pylori*-associated peptic ulcer patients. *H pylori* eradication was defined as proton pump inhibitor (PPI) or H2 receptor antagonist (H2RA), plus clarithromycin or metronidazole, plus amoxicillin or tetracycline, with or without bismuth (details of all eligible *H pylori* eradication regimens are shown in Appendix Table A2, online only). These drug combinations were prescribed within the same prescription order and the duration of therapy was between 7 and 14 days.

Statistical Analysis

To compare the risk of gastric cancer with the age- and sex-matched general population, SIR was calculated. The SIR was defined as the ratio of the observed to the expected gastric cancer incidences in the two cohorts. The expected incidence of cancer was calculated by adding up all person-time

Table 1. Baseline Characteristics of Non-NSAID Users and Regular NSAID Users

Characteristic	Non-NSAID Users* (n = 27,016) No.	%	Regular NSAID Users† (n = 25,145) No.	%
Mean age, years	56.01		67.75	
SE	18.68		11.01	
20-39	6,145	22.75	424	1.69
40-49	5,129	18.99	1,555	6.18
50-59	3,950	14.62	3,360	13.36
60-69	4,072	15.07	7,723	30.71
≥ 70	7,720	28.58	12,083	48.05
Sex				
Male	20,617	76.31	15,206	60.47
Female	6,399	23.69	9,939	39.53
Mean index hospitalization year	2001		2000	
Mean follow-up years	5.17		5.88	
Standard deviation	1.80		1.80	
Peptic ulcer site				
Gastric ulcer	11,787	43.63	15,069	59.93
Duodenal ulcer	12,797	47.37	8,067	32.08
Non-specific peptic ulcer	2,432	9.00	2,009	7.99
Peptic ulcer complication				
Complicated peptic ulcer	20,645	76.42	16,597	66.01
Uncomplicated peptic ulcer	6,371	23.58	8,548	33.99
Mean No. of endoscopic examinations after admission	0.2		0.7	
Standard deviation	0.7		1.5	
Annual endoscopic examination	0.03		0.12	
H pylori-associated peptic ulcer				
No	19,826	73.39	17,188	68.36
Yes	7,190	26.61	7,957	31.64
Comorbidity				
Ischemic heart disease	1,688	6.25	4,264	16.96
Cerebral vascular disease	2,360	8.74	3,811	15.16
Chronic obstructive lung disease	1,965	7.27	2,971	11.82
Diabetes	2,626	9.72	4,555	18.11
Liver cirrhosis	2,114	7.82	2,035	8.09
Acute, chronic hepatic failure	131	0.48	103	0.41
Renal failure	997	3.69	746	2.97

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; *H pylori*, *Helicobacter pylori*.

*Patients who did not take NSAIDs or aspirin were defined as non-NSAID users.

†Patients who took NSAIDs or aspirin regularly (longer than 28 days monthly) and continuously for more than 6 months were defined as regular NSAID users.

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.

Since cumulative incidence by log-rank analysis may be incorrectly estimated in the presence of competing risks, we directly model the cumulative incidences by a semiparametric proportional hazards model suggested by Fine and Gray.[18,19] The cumulative incidence is estimated in a two-step process to account for the informative nature censoring due to competing risk.[20,21] HRs were calculated using the Cox proportional hazards model, adjusted by the partial likelihood principle and weighting techniques.[19] The assumption of proportional hazards was confirmed by plotting the graph of the survival function versus the survival time and the graph of the log(−log(survival)) versus log of survival time. Variables in the model included age, sex, peptic ulcer site, peptic ulcer complications, NSAID use, and *H pylori* eradication. We also fit the model with interaction term between NSAID use and *H pylori* infection. Assessment of goodness-of-fit of the models with step-down method was used to analyze the independent prognostic factors. All data management and analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Demographic Data

Among the 52,161 subjects who were admitted for the first time with a primary diagnosis of peptic ulcer disease between 1998 and 2004, 27,016 were selected into the non-NSAID users group; 25,145 patients were defined as regular NSAID users. The average durations of follow-up for non-NSAID users and regular NSAID users were 5.17 and 5.88 years, respectively. Other demographic data, including age, sex, peptic ulcer site, with or without complications, numbers of endoscopic examinations, *H pylori* eradication, and comorbidities, are presented in Table 1.

SIRs of Gastric Cancer

Patients with peptic ulcers who did not use NSAIDs had significantly higher risk of gastric cancer compared with the general population (SIR, 2.11; 95% CI, 2.07 to 2.15), but those with regular NSAID use showed significantly lower risk of gastric cancer compared with the general population (SIR, 0.79; 95% CI, 0.77 to 0.81). On stratified analysis, non-NSAID users had significantly higher risks of gastric cancer in nearly all stratified groups compared with the general population. In contrast, regular NSAID users were associated with reduced risk of gastric cancer for all stratified groups compared with the general population except for patients of female sex, with gastric ulcer and non-*H pylori*-associated gastric ulcer (Table 2).

Among patients with gastric ulcers, SIRs were 6.79 and 0.86 for *H pylori*-positive NSAID nonusers and regular users, respectively; 2.53 and 1.06 for *H pylori*-negative NSAID nonusers and regular users, respectively. For patients with duodenal ulcers, SIRs were 2.01 and 0.33 for *H pylori*-positive NSAID nonusers and regular

Table 2. Risk of Gastric Cancer for Non-NSAID Users and Regular NSAID Users

Variable	Non-NSAID Users (n = 27,016)				Regular NSAID Users (n = 25,145)			
	GCA* (No.)	EXP† (No.)	SIR‡	95% CI	GCA* (No.)	EXP† (No.)	SIR‡	95% CI
Total	103	48.8	2.11	2.07 to 2.15	69	87.0	0.79	0.77 to 0.81
Age, years								
< 70	60	13.8	4.36	4.25 to 4.47	21	22.8	0.92	0.88 to 0.96
≥ 70	43	33.5	1.29	1.25 to 1.32	48	60.0	0.80	0.78 to 0.82
Sex								
Male	77	40.1	1.92	1.88 to 1.96	46	67.0	0.69	0.67 to 0.71
Female	26	8.9	2.93	2.82 to 3.05	23	20.3	1.13	1.08 to 1.18
Peptic ulcer site								
Gastric	77	23.9	3.22	3.15 to 3.29	51	51.0	1.00	0.97 to 1.03
Duodenal	26	24.5	1.06	1.02 to 1.10	18	35.9	0.50	0.48 to 0.52
Ulcer complication								
Complicated	77	39.6	1.94	1.90 to 1.99	47	58.4	0.80	0.78 to 0.83
Noncomplicated	26	9.3	2.80	2.70 to 2.91	22	28.6	0.77	0.74 to 0.80
H pylori associated								
No	66	39.4	1.67	1.63 to 1.71	52	59.6	0.87	0.85 to 0.90
Yes	37	9.4	3.92	3.79 to 4.05	17	27.3	0.62	0.59 to 0.65
Gastric ulcer								
H pylori positive	26	3.8	6.79	6.53 to 7.05	13	15.2	0.86	0.81 to 0.90
H pylori negative	51	20.1	2.53	2.46 to 2.60	38	35.8	1.06	1.03 to 1.10
DU								
H pylori positive	11	5.5	2.01	1.89 to 2.12	4	12.1	0.33	0.30 to 0.36
H pylori negative	15	19.1	0.79	0.75 to 0.83	14	23.8	0.59	0.56 to 0.62

NOTE. The standardized incidence ratios after the second year of follow-up for non-NSAID users and regular NSAID users according to different demographic and ulcer characteristics.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; GCA, gastric cancer; EXP, expected; SIR, standardized incidence rate; DU, duodenal ulcer; *H pylori, Helicobacter pylori.*

*No. of patients with gastric cancer observed in each stratified group.

†No. of patients with gastric cancer expected in each stratified group according to the age- and sex-specific gastric cancer risk.

‡SIR was defined as the ratio of the observed to the expected gastric cancer incidences in the two 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.

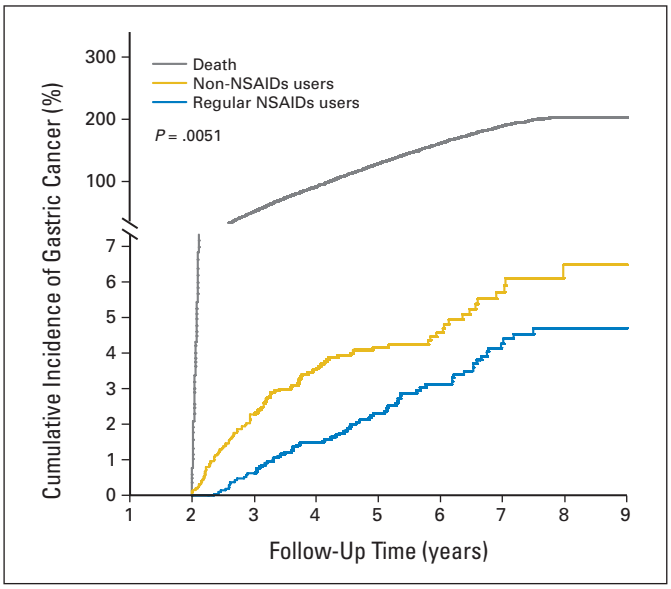

Fig 1. Cumulative incidences of gastric cancer and competing risk. The gold and blue lines show the cumulative incidences of gastric cancer for non–nonsteroidal anti-inflammatory drug (NSAID) users and regular users, respectively, after adjusting for competing risk. The gray line shows the cumulative incidence of the competing risk (ie, death as a result of causes other than gastric cancer). The cumulative incidences of gastric cancer for non-NSAID users were significantly higher than for regular NSAID users ($P < .001$).

users, respectively; 0.79 and 0.59 for *H pylori*-negative nonusers and regular users, respectively (Table 2).

Cumulative Incidences of Gastric Cancer

The cumulative incidence of gastric cancer in these 7 years for non-NSAID users was significantly higher than the cumulative incidence for regular NSAID users (6.4% *v* 4.7%; $P = .0051$; Fig 1). The NNT to prevent a gastric cancer development in peptic ulcer patients was 589. Life expectancy in Taiwan in 2006 was 74.86 and 81.41 years for male and female, respectively. Overall, 7,693 people died without developing gastric cancer.

On stratified analysis, we observed the protective role of NSAIDs in gastric cancer in patients with gastric ulcer (cumulative incidence in 7 years: 11.6% for non-NSAID users versus 6.2% for regular NSAID users; $P < .001$), but not in patients with duodenal ulcer. Among patients with gastric ulcers, the NNT to prevent a gastric cancer was 186. Also among patients with gastric ulcers, regular NSAID use had stronger prophylactic effect against gastric cancer development in *H pylori*-associated patients (cumulative incidence in 7 years: 25.2% for non-NSAID users *v* 5.0% for regular NSAID users; $P < .001$) than in non-*H pylori*-associated patients (8.7% for non-NSAID users *v* 6.7% for regular NSAID users; $P = .0169$). For *H pylori*-associated and noninfected gastric ulcer patients the NNTs to prevent a gastric cancer were 50 and 500, respectively (Appendix Fig A1, online only).

Gastrointestinal Risk of NSAID Use

During the observation period, the annual incidences of readmission due to peptic ulcer diseases were 0.09 and 0.05 for regular and non-NSAID users, respectively. For each hospitalization, the mean numbers of admission days for regular and non-NSAID users were 7.38 and 7.92, respectively. Consistent with the higher gastrointestinal risk in regular NSAID users, more PPIs and H2Rs were prescribed for regular NSAID users when compared with non-NSAID users.

Table 3. Multivariate Cox Proportional Hazards Model Analysis for Prediction of Occurrence of Gastric Cancer

Variable	Hazard Ratio	95% CI	*P*
Age			
Each incremental year	1.03	1.02 to 1.04	< .001
Peptic ulcer site			
Duodenal	1		
Gastric	2.85	2.01 to 4.03	< .001
H pylori-associated peptic ulcer			
Not	1		
Yes	1.93	1.29 to 2.88	< .001
NSAID use (each incremental year)*			
Non-NSAID user	1		
Regular NSAID user	0.79	0.69 to 0.90	< .001
NSAID use and *H pylori* interaction*			
Other	1		
Both regular NSAID use and *H pylori*	0.69	0.51 to 0.93	< .001

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; *H pylori*, *Helicobacter pylori*.
*NSAID use was treated as a time-dependent covariate.

Multivariate Analysis

On Cox multivariate proportional hazards analysis, older age (HR, 1.03 for each incremental year; $P < .001$), gastric ulcer (HR, 2.85; $P < .001$), and *H pylori*-associated peptic ulcer (HR, 1.93; $P < .001$) were independent risk factors for gastric cancer development. Regular NSAID use was independently associated with lower risk of gastric cancer (HR, 0.79 for each incremental year; $P < .005$). Patients with both regular NSAID use (each incremental year) and positive *H pylori* status were associated with even lower risk of gastric cancer (HR, 0.69; $P < .001$; Table 3). Among *H pylori*-associated patients, regular NSAID use was associated with significantly lower risk of gastric cancer (HR, 0.52 for each incremental year; $P < .001$). For those never receiving *H pylori* eradication therapy, regular NSAID use was also associated with reduced risk of gastric cancer (HR, 0.80 for each incremental year; $P < .001$; Table 4).

DISCUSSION

This study was based on patients admitted to a hospital for the first time with a primary diagnosis of peptic ulcer disease. There are several reasons for choosing patients hospitalized for peptic ulcers as the study population. First, nearly all patients received endoscopic examination during the admission, which is helpful in confirming that these patients were free from gastric cancer at the time of recruitment. Second, among patients with peptic ulcer diseases, a high proportion receive regular NSAIDs and *H pylori* eradication therapy simultaneously, which provides an excellent cohort to investigate the interaction between NSAID use and *H pylori* infection in the development of gastric cancer. Third, the relative risks of gastric cancer compared with the general population were reported to be 1.8 and 0.6 for patients with gastric and duodenal ulcers, respectively.[22] There is an opportunity to examine how NSAID use differentially alters the risk of gastric cancer among patients with gastric or duodenal ulcer.

Table 4. Multivariate Analysis for Prediction of Gastric Cancer Development According to *H pylori* Status

Variable	Hazard Ratio	95% CI	*P*
H pylori-associated peptic ulcer			
Age			
Each incremental year	1.04	1.02 to 1.06	< .001
Peptic ulcer site			
Duodenal ulcer	1		
Gastric ulcer	3.50	1.76 to 5.98	< .001
NSAID use (each incremental year)*			
Non-NSAID use	1		
Regular NSAID use	0.52	0.39 to 0.68	< .001
Non–*H pylori*-associated peptic ulcer			
Age			
Each incremental year	1.02	1.01 to 1.04	< .001
Peptic ulcer site			
Duodenal	1		
Gastric	2.62	1.72 to 4.01	< .001
Aspirin or NSAID use			
Non-NSAID use	1		
Regular NSAID use	0.80	0.70 to 0.91	< .001

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; *H pylori, Helicobacter pylori.*

*NSAID use was treated as a time-dependent covariate.

The roles of aspirin and NSAIDs in chemoprevention of gastrointestinal tumors have been widely discussed. In a meta-analysis reviewing epidemiologic studies, NSAID use was associated with a reduced risk of gastric cancer, with a summary odds ratio of 0.78.[13] In comparisons with non-NSAID users, regular NSAID users had a lower risk of gastric cancer than that of irregular NSAID users (odds ratio, 0.57 *v* 0.76 for regular and irregular users, respectively). The protective effect of NSAID use was only observed in patients with noncardia gastric cancer.[13] In Taiwan, noncardia gastric cancer comprises 86% of all gastric cancers.[23] Another meta-analysis reported similar results with relative risks of 0.73 and 0.54 for aspirin use and NSAID use, respectively.[14] In a recent study, NSAID users had a reduced risk of gastric cancer (odds ratio, 0.65).[24] These observations were compatible with our results in this study (HR, 0.79 for each incremental year).

In the cumulative incidence analysis, we found NSAIDs only decreased the risk of gastric cancer in those with gastric ulcer, but not in those with duodenal ulcer. The reason the risk of gastric cancer in those with duodenal ulcer was not significantly reduced was because the absolute risk was quite low to start with. This explanation was supported by the observation in this study that regular NSAID use actually significantly decreased the risk of gastric cancer in those infected with *H pylori*, but not in those without *H pylori* infection.

NSAIDs inhibit the replication and proliferation of *H pylori* and potentially increase *H pylori* clearance.[25] NSAIDs also attenuate COX-2 expression and prostaglandin synthesis stimulated by *H pylori*, thus reducing the risk of *H pylori*-related gastric cancer.[26,27] But how *H pylori* infection impacts the chemopreventive effect of NSAID use remains unclear.[28,29] In a case-control study, NSAID use was found to be associated with a reduced risk of gastric cancer, but this prophylactic effect was not found in noninfected subjects.[28] In a Swedish study, NSAID use was associated with 40% and 20% gastric cancer risk reductions among *H pylori*-positive and *H pylori*-negative subjects, respectively.[29] In this study, regular NSAID use for each incremental year was found to be associated with 48% and 20% gastric risk reduction among *H pylori*-positive and *H pylori*-negative patients with peptic ulcer.

In this study, we defined the time frame for assessing NSAID exposure starting on the discharge day of the index hospitalization until the end of 2006, death, or development of gastric cancer. We also analyzed the relative risk of gastric cancer by limiting the time frame in the first 2 years after the index hospitalization. Patients taking NSAIDs regularly (more than 28 days monthly) and continuously for more than 6 months in the first 2 years after the index hospitalization were defined as regular NSAID users. Since patients tended to avoid NSAIDs after the index hospitalization and the shorter observation period, the number of regular NSAID users decreased from 25,145 to 8,749 after limiting the time frame to 2 years after the index hospitalization. However, regular NSAID use was still associated with decreased risk of gastric cancer after adjusting age, peptic ulcer site, and *H pylori* status (HR, 0.49; $P = .021$; Appendix Table A3, online only).

The gastrointestinal safety of NSAIDs in patients with peptic ulcer history is a major concern. In a meta-analysis of 24 randomized controlled trials, gastrointestinal bleeding was found to occur in 2.47% patients taking aspirin regularly compared with 1.42% taking placebo based on an average of 28 months' therapy.[30] In another meta-analysis regarding the risk of endoscopic ulcers on treatment with NSAIDs, increasing age was found to be associated with both more frequent and more serious NSAIDs gastropathy.[31] In this study, the annual incidences of readmission due to peptic ulcer diseases were 9% and 5% for regular and non-NSAID users, respectively. Whether the chemopreventive effect of NSAIDs is offset by the increased gastrointestinal complications depends on the risk of gastric cancer of the target populations.

Even if the risk-benefit profile for gastric cancer prevention can be justified, the role of NSAIDs as a measure to prevent gastric cancer development may be challenged by the large number of subjects needing treatment. A better approach is to apply the chemoprevention only to patients highly susceptible to gastric cancer. Age, lifestyle, diet, environment, family history, and genetic factors all contribute to identifying individuals with high risk of gastric cancer. In this study, gastric ulcer and *H pylori* were identified as independent risk factors. The enhanced prophylactic effect of NSAIDs in high-risk population was reflected by the decreasing NNT from 589 for all peptic ulcer patients to 50 for patients with *H pylori*-associated gastric ulcer. Further studies are needed to improve the identification of individuals highly susceptible to gastric cancer for implementation of chemopreventive strategies.

There are several limitations to this study. First, our results were based on hospitalized patients with peptic ulcer diseases. Selection biases may exist, and caution must be taken in extrapolating our results. Second, we defined patients who received *H pylori* eradication therapy as patients with *H pylori*-associated peptic ulcer. Some patients may be *H pylori* infected, but not given anti–*H pylori* therapy and thus may be inappropriately classified into the non–*H pylori*-associated group. Since *H pylori* infection increases the risk of gastric cancer, this misclassification would not bias the results. Third, regular NSAID users were significantly older with more comorbidities than non-NSAID users. However, older age in the regular NSAID user group should contribute to a higher incidence of gastric cancer, and to

a less significant difference between regular and non-NSAID users. Fourth, although we have conducted multivariate analysis to examine whether NSAID use is an independent protective factor, many factors are not available for adjustment, such as precancerous lesions, and environmental factors, and so on.

In conclusion, our observations provide further support that NSAID use may be a feasible way to prevent gastric cancer, at least in patients with gastric ulcers, and especially in *H pylori*-infected subjects.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Final approval of manuscript: Chun-Ying Wu, Ming-Shiang Wu, Ken N. Kuo, Chang-Bi Wang, Yi-Ju Chen, Jaw-Town Lin

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