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Original Contribution

Nonsteroidal Antiinflammatory Drugs and Risk of Gastric Adenocarcinoma

The Multiethnic Cohort Study

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In many epidemiologic studies, investigators have reported an inverse relation between nonsteroidal antiinflammatory drugs (NSAIDs) and colon cancer, but fewer researchers have examined the relation with gastric cancer. Cases for this study consisted of incident gastric adenocarcinomas ($n = 643$) identified between 1993 and 2004 among members of the Multiethnic Cohort (Hawaii and Los Angeles, California). Aspirin and nonaspirin NSAID use was assessed on the basis of a self-administered questionnaire. Multivariate-adjusted hazards ratios and 95% confidence intervals were calculated using Cox proportional hazards regression. Compared with no regular use, regular use of aspirin was associated with a decreased risk of distal gastric cancer (hazard ratio (HR) = 0.73, 95% confidence interval (CI): 0.61, 0.89; $P_{trend} = 0.009$), but use of nonaspirin NSAIDs was not (HR = 1.00, 95% CI: 0.81, 1.24; $P_{trend} = 0.99$). The inverse association with regular aspirin use was observed only for intestinal-type distal gastric adenocarcinoma (HR = 0.66, 95% CI: 0.47, 0.95; $P_{trend} = 0.01$), as opposed to diffuse-type distal gastric adenocarcinoma (HR = 0.92, 95% CI: 0.53, 1.60; $P_{trend} = 0.45$). In this study, the authors found aspirin use to be inversely associated with distal gastric adenocarcinoma, particularly of the intestinal type.

adenocarcinoma; anti-inflammatory agents, non-steroidal; aspirin; stomach neoplasms

Abbreviations: CI, confidence interval; COX, cyclooxygenase; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drug.

Many epidemiologic investigators have reported an inverse relation between nonsteroidal antiinflammatory drugs (NSAIDs) and risk of colon cancer and colorectal adenomatous polyps, with sustained use of NSAIDs reducing the risk of these conditions by 25%–60% (1, 2). The 2 main mechanisms by which NSAIDs are believed to act as chemopreventive agents are the stimulation of apoptosis and the inhibition of angiogenesis, since NSAIDs are known to suppress the production of cyclooxygenase (COX) enzymes, which are involved in prostaglandin biosynthesis (1). Because these anti-tumor-growth mechanisms could potentially be effective against other types of cancer as well, investigators have also examined the relation of NSAIDs with several other cancers. In a meta-analysis of NSAID use and cancer at sites other than the colon and rectum, González-Pérez et al. (3) found that the possible protective effect of NSAIDs, as seen for colorectal cancer, potentially applies only to other gastrointestinal cancers such as those of the stomach and esophagus.

The incidence of gastric cancer has been on the decline for the past century, but today gastric cancer is still second only to lung cancer as the most common cause of death from cancer worldwide (4). *Helicobacter pylori*, a gram-negative spiral bacterium, is the strongest known risk factor for gastric cancer, although with the majority of the world population being infected with *H. pylori*, it is by no means a sufficient cause of gastric cancer (5). It is hypothesized that NSAIDs protect against gastric cancer through both COX-dependent and independent pathways (6). Specifically, studies have found expression of higher levels of COX-2 in human gastric carcinoma as compared with adjacent, normal mucosa (7, 8); but there are also findings that

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proliferation of cells that do not express COX can be inhibited by NSAIDs, suggesting other pathways (9).

When examining the fewer than 10 studies published on NSAIDs and gastric cancer in a 2009 meta-analysis, Abnet et al. (10) found a 32%–36% reduced risk of distal gastric adenocarcinoma and an 18%–20% reduced risk of gastric cardia adenocarcinoma among regular NSAID users. In the present analysis, we took advantage of the Multiethnic Cohort, which because of its ethnically diverse membership includes the largest number of gastric cancer cases in a prospective study in the United States, to examine the associations of aspirin and nonaspirin NSAIDs with the risk of gastric adenocarcinoma by both anatomic location (cardia vs. distal) and histologic type (intestinal vs. diffuse).

MATERIALS AND METHODS

Study population

As described previously (11), the Multiethnic Cohort comprises over 215,000 persons from Hawaii and Los Angeles, California, targeting the ethnic groups of African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites. Cohort participants were recruited from 1993 to 1996 and were required to be aged 45–75 years in 1993. For this analysis, we excluded persons who: 1) did not belong to one of the 5 major ethnic groups listed above ($n = 13{,}991$); 2) had invalid dietary data ($n = 8{,}264$), a marker of quality for the questionnaire; 3) had received a previous diagnosis of gastric cancer ($n = 558$); or 4) were diagnosed with gastric cancer of a histologic type other than adenocarinoma ($n = 75$). Thus, this analysis included data on approximately 193,000 persons.

Data collection

At baseline, participants completed a 26-page questionnaire that included questions on medication history and lifestyle factors and a detailed food frequency questionnaire. Medication history was assessed by means of the question, ''Have you ever taken any of the following medications at least 2 times a week (for 1 month or longer)?'' If the participant responded yes, he or she was asked to classify the duration of use as 1 year or less, 2–3 years, 4–5 years, 6–10 years, or 11 years or more. Specific medications asked about in the questionnaire included ''aspirin,'' ''acetaminophen,'' and ''other pain relief medication'' (such as ibuprofen).

Case identification

Incident cases of gastric cancer were identified through the Hawaii and California tumor registries, which are part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Information was available on the anatomic location of the tumor in the stomach (cardia vs. distal) for all adenocarcinomas. Only 44% of distal gastric adenocarcinomas had a histologic type that could be categorized on the basis of Laurén's classification (12); of these tumors, 161 were of the intestinal type, 65 were of the diffuse type, and 15 were of mixed subtypes. Cohort members were linked to the National Death Index and the vital statistics offices of Hawaii and California for information on deaths. Case ascertainment was complete through December 31, 2004.

Statistical analysis

For the primary analyses, we created 4 categories to classify the use of aspirin, nonaspirin NSAIDs, and acetaminophen: no use (of any pain medication) and use for $\leq$1 year, 2–5 years, or $\geq$6 years. For total NSAID use, we summed years of aspirin use and years of nonaspirin NSAID use and classified it in 5 categories: no use and use for $\leq$1 year, 2–5 years, 6–10 years, or $\geq$11 years. Excluded from all analyses were cohort members who did not answer the questions about use of aspirin, nonaspirin NSAIDs, or acetaminophen ($n = 17{,}523$). Also excluded were cohort members who were missing information on any of the identified confounders ($n = 1{,}721$ for education, $n = 1{,}071$ for smoking status, and $n = 3{,}323$ for smoking duration). Thus, the data set for these analyses included 169,292 members of the Multiethnic Cohort.

Follow-up time for each cohort member was started at the date of completion of the baseline questionnaire and ended at the first of the following outcomes: 1) diagnosis of gastric cancer; 2) death; or 3) the last date of follow-up.

We used multivariate Cox proportional hazards regression to compute hazard ratios and 95% confidence intervals, with age as the time metric. Indicator variables were entered into the model representing duration categories, using no use as the reference category. We performed trend tests for medications by creating a variable that was assigned the median value of duration of use for each category of use, for each medication. We assessed Schoenfeld residuals to test the proportional hazards assumption. We fitted separate models by anatomic location, since the likelihood ratio test determined that the difference in the effects of the exposures and confounding variables by cancer site (cardia vs. distal) was highly significant ($P < 0.00001$) in a competing-risks analysis.

We used 2 models for each analysis: a base model and a fully adjusted model, confounding variables for which were chosen because they were associated with both the exposure and the outcome in the data. Base models for risk of distal gastric cancer were adjusted for age at cohort entry (as a continuous variable) and sex as independent variables and for ethnicity (white, African American, Native Hawaiian, Japanese American (first generation), Japanese American (second generation), Japanese American (third generation or later), Latino (first generation), or Latino (second generation or later)) as a strata variable. Japanese Americans who had 1 parent born in the United States and 1 parent born in Asia were categorized as third-generation Japanese American. The 148 Japanese Americans who were missing data on place of birth or who had been born outside of the United States, Canada, or Northeast Asia were excluded from the analyses of distal gastric cancer. Japanese Americans and Latinos were separated into groups based on place of birth because of the association between foreign birthplace and gastric cancer incidence (which is

potentially reflective of *H. pylori* prevalence) in our population. Fully adjusted models for distal gastric cancer included age, sex, and ethnicity (as defined above), in addition to smoking status (never, former, or current), pack-years of smoking (as a continuous variable), education (less than high school/high school or more), processed meat intake in terms of density (g/kcal/day; continuous variable), and family history of gastric cancer (yes/no).

Base models for risk of gastric cardia cancer included adjustment for age (as a continuous variable), sex, and ethnicity (white, African American, Native Hawaiian, Japanese American, or Latino). Place of birth was ignored here because cardia cancer is not as related to *H. pylori* infection as distal cancer; in addition, we needed a parsimonious model because of the small sample. Fully adjusted models for gastric cardia cancer included age, sex, ethnicity, smoking status, and pack-years of smoking (as defined above), in addition to body mass index (weight (kg)/height $(m)^2$; continuous variable) and alcohol consumption (g/day; continuous variable).

Variables for aspirin, nonaspirin NSAIDs, and acetaminophen use were entered into models together, so that results for these variables were jointly adjusted for use of all pain medications.

Because the results produced by the base models and the fully adjusted models were very similar for all analyses, only results from the fully adjusted models are presented.

We performed separate analyses for the association of NSAID use with intestinal-type versus diffuse-type distal gastric adenocarcinoma, as well as a joint analysis in which heterogeneity was tested using a competing-risk approach. Additionally, we examined the associations between NSAID use and risk of distal gastric adenocarcinoma separately by ethnicity, smoking status, and sex.

RESULTS

Just over half (51%) of all study subjects classified themselves as regular users of NSAIDs, either aspirin or nonaspirin NSAIDs (Table 1). Regular NSAID users were similar to nonusers in most respects, except that regular users were more likely to be white or African American (and less likely to be Japanese American), to be overweight or obese, to have ever smoked, and to have ever been a regular user of antacids or acetaminophen. Among regular NSAID users, 30% had used NSAIDs for 1 year or less, 43% had used NSAIDs for 2–10 years, and 27% had used NSAIDs for 11 or more years.

No association was observed between any regular aspirin use (hazard ratio (HR) = 1.01, 95% confidence interval (CI): 0.66, 1.57; $P_{trend} = 0.54$), nonaspirin NSAID use (HR = 1.25, 95% CI: 0.77, 2.03; $P_{trend} = 0.78$), or total NSAID use (HR = 1.23, 95% CI: 0.80, 1.90; $P_{trend} = 0.70$) and gastric cardia cancer (Table 2). Because of the difficulty at times in identifying the primary tumor site between gastric cardia adenocarcinoma and esophageal adenocarcinoma, we also analyzed the association between NSAIDs and gastric cardia and esophageal adenocarcinoma (55 additional cases) combined. Similarly, we observed no association between regular aspirin use (HR = 1.05, 95% CI: 0.75, 1.48; $P_{trend} = 0.22$), nonaspirin NSAID use (HR = 1.13, 95% CI: 0.77, 1.66; $P_{trend} = 0.44$), or total NSAID use (HR = 1.26, 95% CI: 0.89, 1.79; $P_{trend} = 0.54$) and gastric cardia *or* esophageal adenocarcinoma.

For distal gastric cancer, any regular use of NSAIDs was associated with a 20% reduction in risk (95% CI: 0.67, 0.95), and increasing duration of total NSAID use was associated with a decreasing risk of distal gastric cancer ($P_{trend} = 0.02$) (Table 2). Specifically, regular use of aspirin was associated with a 27% reduction in risk of distal gastric cancer (95% CI: 0.61, 0.89), and there was a significant trend of decreasing risk of distal gastric cancer with increasing use of aspirin ($P_{trend} = 0.009$). However, no association was observed between regular nonaspirin NSAID use and distal gastric cancer risk (HR = 1.00, 95% CI: 0.81, 1.24; $P_{trend} = 0.99$). When we excluded persons whose distal gastric cancer had been diagnosed within 2 years of study entry ($n = 87$), the results did not substantially change (data not shown).

As expected, no association was observed between acetaminophen use and gastric cardia cancer (for any regular use, HR = 1.09, 95% CI: 0.67, 1.77) or distal gastric cancer (for any regular use, HR = 1.15, 95% CI: 0.94, 1.40).

Within the category of distal gastric adenocarcinoma, we then compared intestinal-type tumors with diffuse-type tumors, since a test of heterogeneity found that these 2 outcomes were significantly different with respect to the association with NSAID use ($P < 0.0001$). Risk of intestinal-type distal gastric adenocarcinoma was reduced by 34% for regular aspirin users (HR = 0.66, 95% CI: 0.47, 0.95; $P_{trend} = 0.01$) and reduced by 30% for regular users of any NSAID (HR = 0.70, 95% CI: 0.50, 0.97; $P_{trend} = 0.02$), although no association with intestinal-type adenocarcinoma was observed for regular use of nonaspirin NSAIDs specifically (HR = 0.97, 95% CI: 0.64, 1.47; $P_{trend} = 0.99$) (Table 3). No associations were found between regular use of aspirin (HR = 0.92, 95% CI: 0.53, 1.60), nonaspirin NSAIDs (HR = 0.71, 95% CI: 0.34, 1.46), or total NSAIDs (HR = 0.89, 95% CI: 0.54, 1.48) and risk of diffuse-type distal gastric adenocarcinoma, although the confidence intervals were wide because of the small number of cases.

No differences were observed when results were stratified by ethnicity, smoking status, or sex.

DISCUSSION

Regular use of aspirin was associated with a 27% decreased risk of distal gastric adenocarcinoma, with the relation being especially strong (34% reduction in risk) for intestinal-type adenocarcinoma, which is believed to be more environment-related (i.e., associated with salt intake and other lifestyle factors) than the more genetics-related diffuse type. No association was found between nonaspirin NSAIDs and distal gastric adenocarcinoma or between either aspirin or nonaspirin NSAIDs and gastric cardia adenocarcinoma.

The magnitude of the inverse association found in this study between aspirin and gastric cancer is very similar to that seen in previous studies, in which reductions in risk

Table 1. Distribution of Baseline Characteristics of Cohort Members According to Regularity of NSAID Use, Multiethnic Cohort Study, 1993–2004

	Regularity of NSAID Use					
	Nonregular User (n = 82,597)			Current or Former Regular User (n = 86,695)		
	No.	%	Mean (SD)	No.	%	Mean (SD)
Age at cohort entry, years						
<50	15,912	19		13,668	16	
50–59	26,146	32		26,825	31	
60–69	27,657	33		30,542	35	
≥70	12,882	16		15,660	18	
Male sex	38,926	47		38,685	45	
Ethnicity[a]						
White	18,866	23		24,724	29	
African American	9,847	12		17,489	20	
Native Hawaiian	6,579	8		5,811	7	
Japanese American (first generation)	2,798	3		1,180	1	
Japanese American (second generation)	13,031	16		8,534	10	
Japanese American (third generation or later)	16,272	20		8,488	10	
Latino (first generation)	7,045	9		9,130	11	
Latino (second generation or later)	8,062	10		11,282	13	
Less than a high school education	33,358	40		37,778	44	
First-degree family history of gastric cancer	4,700	6		3,942	5	
Body mass index[a,b]						
<25.0	43,901	54		36,047	42	
25.0–30.0	27,524	34		32,480	38	
>30.0	10,505	13		17,241	20	
Pack-years of cigarette smoking						
None	39,623	48		35,995	42	
>0–<10	15,355	19		17,728	20	
10–<20	14,280	17		16,287	19	
≥20	13,339	16		16,685	19	
Alcohol consumption, g/day						
None	42,695	52		42,797	49	
>0–<7	19,882	24		22,085	26	
≥7	20,020	24		21,813	25	
Ever regularly using antacids[a]	16,119	20		38,434	45	
Dietary intake						
Total vegetables, g/kcal/day			164 (83)			161 (80)
Cruciferous vegetables, g/kcal/day			25 (24)			24 (23)
Processed red meat, g/kcal/day			7.7 (6.5)			7.9 (6.8)
Red meat (not including processed meat), g/kcal/day			18 (13)			19 (13)
Vitamin C, mg/kcal/day			87 (52)			86 (50)
Total calories, kcal/day			2,091 (972)			2,191 (1,076)
Duration of acetaminophen use, years						
Never regular user	70,174	85		47,346	55	
≤1	3,317	4		10,522	12	
2–5	3,405	4		11,571	13	
≥6	4,003	5		12,219	14	
Regular user, but missing data on duration	1,698	2		5,037	6	
Duration of total NSAID use[a] (among regular users), years						
≤1				23,141	30	
2–5				24,886	32	
6–10				8,258	11	
≥11				21,131	27	

Abbreviations: NSAID, nonsteroidal antiinflammatory drug; SD, standard deviation.

[a] Totals and percentages may vary because of missing values.

[b] Weight (kg)/height $(m)^2$.

Table 2. Association of the Use of Aspirin and Nonaspirin NSAIDs With Gastric Adenocarcinoma, by Anatomic Location, Multiethnic Cohort Study, 1993–2004[a]

Exposure	Anatomic Location					
	Cardia (n = 93 Cases)			Distal (n = 550 Cases)		
	No. of Cases	HR[b]	95% CI	No. of Cases	HR[c]	95% CI
Nonuser	35	1.00		259	1.00	
Duration of aspirin use, years						
Any regular use	40	1.01	0.66, 1.57	171	0.73	0.61, 0.89
≤1	8	0.96	0.44, 2.09	54	0.86	0.63, 1.18
2–5	13	1.11	0.59, 2.08	54	0.69	0.51, 0.93
≥6	18	1.21	0.66, 2.19	50	0.68	0.50, 0.93
P_{trend}			0.54			0.009
Duration of nonaspirin NSAID use, years						
Any regular use	28	1.25	0.77, 2.03	134	1.00	0.81, 1.24
≤1	15	1.85	1.02, 3.36	55	0.89	0.65, 1.21
2–5	4	0.53	0.19, 1.51	40	0.94	0.66, 1.34
≥6	5	1.28	0.48, 3.41	16	1.02	0.61, 1.72
P_{trend}			0.78			0.99
Duration of total NSAID use, years						
Any regular use	53	1.23	0.80, 1.90	241	0.80	0.67, 0.95
≤1	13	1.33	0.70, 2.50	78	1.00	0.78, 1.30
2–5	15	1.15	0.63, 2.11	65	0.72	0.55, 0.94
6–10	7	1.51	0.67, 3.42	22	0.73	0.47, 1.14
≥11	13	1.15	0.58, 2.28	42	0.69	0.49, 0.97
P_{trend}			0.70			0.02
Duration of acetaminophen use, years						
Any regular use	27	1.09	0.67, 1.77	161	1.15	0.94, 1.40
≤1	6	0.90	0.37, 2.19	57	1.51	1.11, 2.04
2–5	7	1.10	0.49, 2.46	39	0.95	0.66, 1.36
≥6	11	1.30	0.62, 2.71	40	1.00	0.70, 1.42
P_{trend}			0.35			0.71

Abbreviations: CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drug.
[a] All pain medications were considered in the models to adjust for use of all pain medications.
[b] Adjusted for age, sex, ethnicity, smoking, body mass index, and alcohol consumption.
[c] Adjusted for age, sex, ethnicity, smoking, education, processed meat intake, and family history of gastric cancer.

from aspirin ranged from 20% to 47%, even though ''regular use'' was defined somewhat differently in each study (3, 10, 13–15). In a recent study in the United Kingdom, Lindblad et al. (16) did not find an association between gastric cancer and aspirin use, but the exposure data were limited to a prescription database, which did not contain information on use of NSAIDs that are widely available over the counter. However, the null association found in the present study between nonaspirin NSAIDs and gastric cancer is not what has generally been seen in the literature. Most studies have found an inverse relation with nonaspirin NSAIDs as well (10, 13, 15, 16), although 1 other study, a large population-based case-control study in Sweden, did not find an association (17). When examining the association with nonaspirin NSAIDs, we adjusted for aspirin use, which, except for the analysis conducted within the National Institutes of Health–AARP Diet and Health Study (10), most other investigators appeared not to do. In our population, 56% of nonaspirin NSAID users also identified themselves as aspirin users. When we did not adjust for aspirin use in our models for nonaspirin NSAID use, a suggestion of an inverse relation with nonaspirin NSAIDs appeared (for ≥6 years of regular nonaspirin NSAID use, HR = 0.83, 95% CI: 0.50, 1.38).

Similarly to the present study, of the previous studies that analyzed cardia and distal gastric cancer separately, 4 studies (10, 15, 18, 19) found no association between NSAIDs and gastric cardia cancer, while 2 studies (14, 17) found similar reductions in risks of both cardia and distal gastric cancer. Note that unlike the case in the other studies, investigators in these 2 studies were not able to adjust for body mass index, one of the strongest risk factors for gastric cardia adenocarcinoma and one that was associated with NSAID use in our study. The findings of the current study also differ from those of a recent meta-analysis, which

Table 3. Association of the Use of Aspirin and Nonaspirin NSAIDs With Distal Gastric Adenocarcinoma, by Histologic Type,[a] Multiethnic Cohort Study, 1993–2004[b]

Exposure	Histologic Type					
	Intestinal (n = 161 Cases)			Diffuse (n = 65 Cases)		
	No. of Cases	HR[c]	95% CI	No. of Cases	HR[c]	95% CI
Nonuser	101	1.00		40	1.00	
Duration of aspirin use, years						
Any regular use	45	0.66	0.47, 0.95	19	0.92	0.53, 1.60
<6	27	0.65	0.42, 0.99	8	0.64	0.30, 1.36
≥6	12	0.48	0.26, 0.88	9	1.17	0.56, 2.43
P_{trend}[d]			0.01			0.45
Duration of nonaspirin NSAID use, years						
Any regular use	29	0.97	0.64, 1.47	9	0.71	0.34, 1.46
<6	22	1.05	0.67, 1.67	6	0.66	0.28, 1.55
≥6	4	1.03	0.38, 2.82	2	0.99	0.24, 4.18
P_{trend}			0.99			0.63
Duration of total NSAID use, years						
Any regular use	60	0.70	0.50, 0.97	25	0.89	0.54, 1.48
<6	35	0.69	0.47, 1.01	13	0.77	0.41, 1.44
≥6	16	0.56	0.33, 0.94	9	0.96	0.47, 1.98
P_{trend}			0.02			0.69

Abbreviations: CI, confidence interval; HR, hazard ratio; NSAIDs, nonsteroidal antiinflammatory drugs.

[a] Test for heterogeneity by histologic type: $P < 0.0001$.

[b] Hazard ratios for aspirin use were adjusted for nonaspirin NSAID use; hazard ratios for nonaspirin NSAID use were adjusted for aspirin use.

[c] Adjusted for age, sex, ethnicity, smoking, education, processed meat intake, and family history of gastric cancer.

[d] Trend tests for NSAIDs were performed by creating a variable that was assigned the median value of duration of use for each category of use, for each medication.

found significant inverse associations for NSAID use and risk of esophageal adenocarcinoma (10). Seven of the 10 observational studies of NSAID use and esophageal adenocarcinoma found significant inverse associations (14, 15, 18, 20–23), but these were all case-control studies and thus potentially susceptible to recall bias. Of the 3 studies that observed no association (10, 16, 24), 1 was a prospective cohort study (10) and 1 was a nested case-control study (16). Since the epidemiology of gastric cardia adenocarcinoma and esophageal adenocarcinoma differs greatly from that of distal gastric adenocarcinoma (25), it is plausible that the effect of NSAIDs could vary between these different anatomic sites as well.

There are some limitations to the present study. Foremost is the absence of information on the *H. pylori* status of study participants. Of the 2 studies on NSAIDs and gastric cancer in which investigators were able to stratify results by *H. pylori* status, a significant reduction in risk of gastric cancer associated with NSAID use was seen only for *H. pylori*-positive persons—although evidence for effect modification was found in only 1 of the 2 studies, probably because of the small numbers in the second study (17, 19). Because we were not able to separate our analyses by *H. pylori* status, our findings are probably attenuated toward the null hypothesis of no association, indicating that the true inverse association with distal gastric cancer is potentially even stronger that what we found. This misclassification, though, is tempered by the fact that 4 of the 5 ethnic groups in our population (Japanese American, Native Hawaiian, African American, and Latino) have a 2- to 3-fold higher prevalence of *H. pylori* than the general white population in the United States (26, 27); thus, most of the patients in our study were probably *H. pylori*-positive.

An additional concern about aspirin as the exposure of interest is that regular use could lead to chronic upper gastrointestinal tract symptoms (especially in those more susceptible to development of cancer), which would then account for the inverse association found between aspirin use and gastric cancer. However, our findings that regular use of aspirin does not reduce risk of gastric cardia cancer or esophageal cancer and that acetaminophen use does not reduce risk of distal gastric, gastric cardia, or esophageal adenocarcinoma suggest that the potential side effects of regular pain medication use do not necessarily lead to an earlier, precancerous diagnosis. Additionally, exclusion of cases diagnosed within 2 years of study entry from the analyses did not substantially change our findings.

Alternatively, persons who develop early symptoms may change their NSAID use as a result, confounding the association with gastric cancer. Of the 3 recent studies that have examined a history of upper gastrointestinal tract disorders in relation to the NSAID–gastric cancer association, 2 found no substantive change when stratifying by history of upper gastrointestinal disorders (15, 18). The third study found

a stronger protective effect of NSAIDs among persons with a history of upper gastrointestinal disorders, although the difference in the risk reduction was not significant between persons with and without a history of such disorders (16). Using lag times of 2–5 years prior to the date of case diagnosis for collection of exposure information in the 3 studies did not change the findings reported above when persons with and without a history of upper gastrointestinal disorders were compared.

Another limitation of the present study is the lack of detailed data on NSAID use. We did not have information on dose, which has been important in randomized trials for colon cancer and/or adenoma (2, 28, 29), but this has not been a key factor in observational studies of gastric cancer. The information we did have on NSAID use came from self-reports, which, while not as precise as pharmacy records, was the only feasible way we could obtain information on over-the-counter medications. Because we collected our exposure information through questions about duration, not specific timing, we were unable to assess the latency period for an effect on risk.

To our knowledge, the present study included the largest number of gastric cancer cases in a prospective cohort study ever examined in relation to NSAID use. The nature of the Multiethnic Cohort, with its extensive baseline questionnaire, allowed for the exploration of many potential confounders. Additionally, the relatively large number of gastric cancer cases allowed us to look for interactions by ethnicity, smoking status, and sex. Furthermore, we were able to examine the associations of NSAID use with intestinal-type and diffuse-type distal gastric adenocarcinoma separately, as only 1 previous study of NSAIDs and gastric cancer had done (17), and we found a similar result of an even stronger protective effect when limiting the outcome to intestinal-type adenocarcinoma.

In summary, our analyses suggest that regular use of NSAIDs (especially aspirin), defined as use at least 2 times per week for 1 month or longer, is inversely associated with risk of distal gastric adenocarcinoma, particularly of the intestinal type. This finding of at least a 30% reduction in risk is strongly consistent with previous observational studies of NSAID use and gastric cancer. In the only randomized controlled trial to examine NSAID chemoprevention—the COX-2 inhibitor rofecoxib—of which we are aware, Leung et al. (30) found no protective effect of the drug in reducing gastric intestinal metaplasia after a 2-year period. However, it is possible that NSAID chemoprevention could be effective at a different stage in the development of gastric cancer, possibly closer to the actual endpoint of adenocarcinoma. We believe that the strength of the association consistently seen in observational studies, along with the high mortality rate associated with gastric cancer, supports the need for further research on the potential of NSAID chemoprevention trials among select high-risk populations.

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