Nonsteroidal Anti-inflammatory Drugs and Risk of Esophageal and Gastric Adenocarcinomas in Los Angeles County

Lei Duan,[1,2] Anna H. Wu,[2] Jane Sullivan-Halley,[2] and Leslie Bernstein[2]

[1]Institute for Health Promotion and Disease Prevention Research, University of Southern California and
[2]Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California

Abstract

Background: **Nonsteroidal anti-inflammatory drug (NSAID) use has been associated with a reduced risk of colon cancer; further epidemiologic data appear consistent for stomach and esophageal adenocarcinomas. Yet, data on potential confounding effects by upper gastrointestinal tract (UGI) disorders on adenocarcinomas of the UGI are limited.**

Methods: **This study recruited newly diagnosed patients with esophageal adenocarcinoma (n = 220), gastric cardia adenocarcinoma (n = 277), or distal gastric adenocarcinoma (n = 441) as well as 1,356 control subjects in Los Angeles County. Unconditional multivariable logistic regression analyses were done to evaluate the association between regular NSAID use, at least two pills per week for 1 month, and these cancers.**

Results: **Duration of regular use of aspirin and nonaspirin NSAIDs was associated with reduced relative odds of distal gastric adenocarcinoma [>5 years use versus no regular use: odds ratio (OR), 0.61; 95% confidence interval, 0.40-0.92; P_{trend} = 0.009] and esophageal adenocarcinoma (OR, 0.60; 95% confidence interval, 0.38-0.95; P_{trend} = 0.04) in multivariable models that included history of UGI disorders and other potential confounding factors. Daily regular use was also associated with statistically significant reduced ORs of these two tumor types. No significant heterogeneity in risk estimates was noted after stratification by history of UGI disorders for any of the sites studied. However, irregular users of NSAIDs also had reduced risk of these cancers when compared with nonusers.**

Conclusions: **Results from this study support an inverse association between regular NSAID use and risk of esophageal and distal gastric adenocarcinomas in individuals with and without a history of UGI disorders with long duration and daily use, providing the greatest risk reduction. Reduced risk in irregular users suggests that factors other than an effect on cyclooxygenase may also be important.** (Cancer Epidemiol Biomarkers Prev 2008;17(1):126–34)

Introduction

Since the late 1980s, evidence has accumulated to suggest that aspirin and other nonsteroidal anti-inflammatory drug (NSAID) use reduces cancer risk (1-5). The hypothesized mechanism is that NSAIDs are able to inhibit the enzyme cyclooxygenase (COX), which is key in prostaglandin synthesis. One subtype of this enzyme, COX-2, is usually absent from normal intestinal mucosa but is overexpressed in premalignant (6, 7) and malignant gastrointestinal cancers. High concentrations of prostaglandins have been shown to promote cellular proliferation and tumor growth, suppress the immune system, and induce angiogenesis (8). Thus, NSAIDs may protect against gastrointestinal tract cancers by inhibiting COX-2, which in turn suppresses prostaglandin synthesis (8).

NSAID use has been associated with reduced risks for several cancers, although results are considered to be most consistent for colon cancer (1, 2, 9, 10). Recent studies have shown that NSAID use reduces the risk of esophageal adenocarcinoma (11-16). Three recent meta-analyses that included both case-control studies and cohort studies indicated that aspirin and other NSAID users were at reduced risk of esophageal squamous cell carcinoma, esophageal adenocarcinoma, and noncardia gastric adenocarcinoma but not at reduced risk of gastric cardia cancers (17-19). In considering the effect of NSAIDs on risk of upper gastrointestinal tract (UGI) cancers, it is important to consider how use of NSAIDs might be influenced by history of UGI disorders, which are related to risk of these tumor types. However, few studies have adequately controlled for UGI conditions and results are conflicting (15, 20-22).

We investigated the association between use of aspirin and other NSAIDs and the risk of adenocarcinomas of the esophagus and stomach using data from a large population-based case-control study conducted in Los

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Requests for reprints: Leslie Bernstein, Division of Population Sciences, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010. Phone: 626-471-7315; Fax: 626-471-7308. E-mail: lbernstein@coh.org

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Angeles County. We sought to clarify the nature of the association between these drugs and risk of adenocarcinoma of the esophagus, gastric cardia, or distal stomach and whether the risk patterns differ depending on history of nonmalignant UGI disorders.

Materials and Methods

The study population and study design have been described previously (23-27). Briefly, patients included in this analysis are men and women ages 30 to 74 years with histologically confirmed adenocarcinomas of the esophagus, gastric cardia, or distal stomach, who had no prior history of a cancer at any of these sites. These patients were identified by the Los Angeles County Cancer Surveillance Program, the population-based cancer registry covering Los Angeles County. We included patients who were newly diagnosed with first incident esophageal adenocarcinoma (*International Classification of Diseases for Oncology* code C15.0-C15.9) or gastric cardia adenocarcinoma (code C16.0) between 1992 and 1997 and patients newly diagnosed with distal gastric cancer (codes C16.1-C16.6 and C16.8-C16.9) between 1992 and 1994.

We identified 1,716 eligible patients [429 incident esophageal adenocarcinoma (EA)/500 gastric cardia adenocarcinoma (GCA)/787 distal gastric adenocarcinoma (DGA); numbers for the three tumor sites are shown separately]. We conducted in-person interviews with patients or with their next-of-kin when patients were unable to be interviewed due to death or illness. We were unable to obtain interviews for 769 patients: 315 (92 EA/88 GCA/135 DGA) had died or were too ill to be interviewed and did not have a next-of-kin available for interview, physicians denied permission to contact 171 (50 EA/37 GCA/84 DGA) patients largely because the patients were too ill, 144 (30 EA/51 GCA/63 DGA) patients could not be located, and 139 (34 EA/46 GCA/59 DGA) patients did not wish to participate. We completed interviews with the remaining 947 case patients: 55% (947 of 1,716) of those identified and 77% [947 of (1,716 - 315 - 171)] of those approached; 77% for esophageal adenocarcinoma, 74% for gastric cardia adenocarcinoma, and 78% for distal gastric adenocarcinoma. We excluded 9 case patients for whom information on NSAID use was incomplete. A total of 938 case patients and 1,356 control subjects are included in the analyses presented. Age, sex, and race distributions did not differ between the case patients we interviewed and those we were unable to interview.

Control subjects were matched individually to interviewed case patients on sex, race, and age ($\pm$5 years). Whenever possible, we sought two control subjects for each case patient to increase the statistical power of the study. Control subjects had no diagnosis of stomach or esophageal carcinoma. Control subjects were identified in the neighborhoods of the interviewed case patients. Each neighborhood control subject was sought using a systematic algorithm indicating the sequence of residences to be contacted based on the residential address of the case patient. This sequence eliminates the blocks immediately surrounding the residence of the case patient. If the first identified eligible matched control subject refused to participate, the second identified eligible control subject in the sequence was invited and so on. Of the 947 case patients interviewed, 528 had one control subject, 382 had two or more control subjects, and 37 had no eligible control subjects identified.

The study was approved by the Institutional Review Board of the Keck School of Medicine of the University of Southern California. Written informed consent was obtained from each study participant before interview.

Interview Method. Case patients and their matching control subjects were interviewed by the same interviewer in almost all instances. Next-of-kin interviews accounted for 269 of the 938 interviews with case patients (65 EA/85 GCA/119 DGA). Although it was not feasible to blind the interviewers to case (or next-of-kin) or control status, interviewers (and study participants) were not aware of the study hypotheses. A reference date was defined as 1 year before the date of diagnosis of the case patient. This same reference date was used for each case patient's matched control subject.

We used a structured questionnaire that we developed specifically for this study. It included questions on lifetime smoking habits, lifetime use of all types of alcoholic beverages, weight at ages 20 and 40 years and on the reference date, and height. In addition, we asked detailed questions regarding personal and family history of various nonmalignant diseases and conditions of the gastrointestinal tract and use of antacid drugs. With regard to the exposures of interest in this analysis, we explicitly listed 20 over-the-counter and 45 prescription brand-name analgesics in the questionnaire. For each of the listed medications, we first asked the subject whether they had ever used the drug. If the answer was ''no,'' the subjects was defined as a nonuser. If the answer was ''yes,'' the subject was further asked if he or she had ever taken the drug two or more times a week for 1 month or longer. If the answer was no, the subject was classified as an ''irregular user.'' Otherwise, the subject was defined as a ''regular user'' and we further asked about the ages at first and last use, duration of use, usual frequency and dosage of use, and the primary reason for each use. We also asked the subjects if they had used any analgesics that were not on our list and recorded the drug name and details of use if the subject had used the medication ''regularly.'' All of the medications in the study were categorized into the following groups based on their components: aspirin, non-aspirin NSAIDs, acetaminophen, or prescription medications not included in these categories. We focus this report on reported use of aspirin and non-aspirin NSAIDs.

Statistical Analysis. Total duration and frequency of aspirin and non-aspirin NSAID use were calculated by summing all use of the same class of medication for each person. Drugs that did not contain aspirin or other NSAIDs were excluded (46 types of drug) [All NSAID-containing drugs with any reported use are listed in Appendix 1]. We also created combined NSAID variables (duration and frequency of aspirin plus non-aspirin NSAIDs). Duration of use was categorized as no regular use, less than 5 years of regular use, and at least 5 years of regular use for aspirin, non-aspirin NSAID, and all NSAIDs combined. The no regular use category was further divided into never users and irregular users for some analyses. Frequency of regular use was grouped into three levels (0, 2 to <7, and $\geq$7 pills per week).

Because early symptoms of cancer patients might affect their NSAID use, we excluded from the calculation of total duration and frequency of use any drugs that were first taken within the interval beginning 1 year before the reference date for both case patients and control subjects, which is 2 years before diagnosis for case patients and the same date for their matched control subjects. A similar approach was used to create variables for acetaminophen use.

Polychotomous logistic regression was used to compute the odds ratios (OR), as estimates of the relative risk, and corresponding 95% confidence intervals (95% CI) for adenocarcinomas of the esophagus, gastric cardia, and distal stomach simultaneously in relation to duration and frequency of each type of drug use. We used all control subjects in this analysis to maximize statistical power and adjusted for the matching factors in our analysis. In our previous study (27), this approach provided more precise estimates of the ORs, and the magnitude of the ORs was consistent with those obtained in separate conditional logistic regression analyses that preserved the original case-control match within each cancer site.

In multivariable analyses, we adjusted for age (≤39, 40-49, 50-59, 60-69, ≥70 years), sex (male/female), race (non-Latino White, African American, Latino American, Asian American), birthplace (U.S. born, non-U.S. born), education (less than high school, high school, some college, college graduate or higher), smoking status (never smoker, ex-smoker, current smoker), body mass index (BMI) at reference age (<25, 25-29.9, ≥30 kg/m^2), history (no/yes) of UGI disorders (including gastric ulcer, duodenal ulcer, unspecified type of ulcer, gastritis, hiatal hernia, esophagitis, Barrett's esophagus, gastroesophageal reflux disease, excess acid or gastric hyperacidity, and other diseases of the stomach), and antacid use (never/ever). A test for trend across ordinal categories of duration and frequency of use was done for each type of cancer to evaluate the dose-response effects.

We constructed a 1 *df* likelihood ratio test to assess homogeneity of trends in duration of NSAID use among individuals who had a history of UGI disorders and those who did not. We conducted these analyses separately for each type of cancer using unconditional logistic regression comparing a multivariable model that

Table 1. Selected characteristics of esophageal and gastric adenocarcinoma case patients and control subjects, Los Angeles County

	Control subjects (n = 1,356)	Patients with		
		EA (n = 220)	GCA (n = 277)	DGA (n = 441)
Age				
<40	98 (7.2)	9 (4.1)	13 (4.7)	29 (6.6)
40-49	194 (14.3)	14 (6.4)	23 (8.3)	50 (11.3)
50-59	345 (25.4)	56 (25.5)	73 (26.4)	91 (20.6)
60-69	463 (34.1)	95 (43.2)	108 (39.0)	153 (34.7)
≥70	256 (18.9)	46 (20.9)	60 (21.7)	118 (26.7)
Sex				
Men	999 (73.7)	200 (90.9)	231 (83.4)	260 (59.0)
Women	357 (26.3)	20 (9.1)	46 (16.6)	181 (41.0)
Race				
Non-Latino White	841 (62.0)	171 (77.3)	210 (75.8)	133 (30.2)
African American	90 (6.6)	3 (1.4)	10 (3.6)	54 (12.2)
Latino American	308 (22.7)	39 (17.7)	40 (14.4)	169 (38.3)
Asian American	117 (8.6)	7 (3.2)	17 (6.1)	85 (19.3)
Birthplace				
U.S. born	1,011 (74.6)	184 (83.6)	211 (76.2)	217 (49.2)
Non-U.S. born	345 (25.4)	36 (16.4)	66 (23.8)	224 (50.8)
Education				
Less than high school	252 (18.6)	48 (21.8)	53 (19.1)	184 (41.7)
High school	252 (18.6)	50 (22.8)	68 (24.6)	96 (21.8)
Some college	392 (28.9)	63 (28.6)	86 (31.1)	83 (18.8)
College graduate or higher	460 (33.9)	59 (26.8)	70 (25.3)	78 (17.7)
Smoking status				
Never smoker	540 (39.8)	48 (21.8)	78 (28.2)	183 (41.5)
Ex-smoker	588 (43.4)	105 (47.7)	123 (44.4)	169 (38.3)
Current	228 (16.8)	67 (30.5)	76 (27.4)	89 (20.2)
BMI (kg/m^2)*				
Normal	558 (41.2)	66 (30.0)	88 (31.2)	189 (42.9)
Overweight	555 (40.9)	91 (41.4)	110 (39.7)	126 (28.6)
Obese	218 (16.1)	55 (25.0)	68 (24.6)	78 (17.7)
UGI disease history				
Yes	362 (26.7)	103 (46.8)	110 (39.7)	143 (32.4)
No	994 (73.3)	117 (53.2)	167 (60.3)	298 (67.6)
Antacid use				
Never	973 (71.8)	136 (61.8)	193 (69.7)	282 (64.7)
Ever	382 (28.2)	84 (38.2)	84 (30.3)	154 (35.3)

*At reference date (1 y before case patient's date of diagnosis; control subject has reference date of the case patient to whom he or she was initially matched).

Table 2. Multivariable ORs (95% CIs) for use of aspirin and non-aspirin NSAIDs in relation to esophageal, gastric cardia, and distal gastric adenocarcinomas

Exposure	Control	EA		GCA		DGA	
	n	*n*	OR* (95% CI)	*n*	OR* (95% CI)	*n*	OR* (95% CI)
Duration							
Aspirin							
No regular use	1,037	168	1.00 (Reference)	200	1.00 (Reference)	375	1.00 (Reference)
<5 y	148	26	0.98 (0.62-1.57)	40	1.30 (0.88-1.94)	39	1.00 (0.67-1.49)
≥5 y	170	25	0.77 (0.48-1.23)	35	0.95 (0.63-1.42)	25	0.58 (0.36-0.92)
P_{trend}			0.30		0.86		0.04
Non-aspirin NSAID							
No regular use	1,140	193	1.00 (Reference)	237	1.00 (Reference)	399	1.00 (Reference)
<5 y	160	20	0.69 (0.42-1.16)	26	0.74 (0.47-1.17)	32	0.63 (0.41-0.97)
≥5 y	55	5	0.37 (0.14-0.97)	12	0.86 (0.44-1.67)	8	0.54 (0.24-1.20)
P_{trend}			0.02		0.28		0.02
Any NSAID							
No regular use	927	155	1.00 (Reference)	176	1.00 (Reference)	353	1.00 (Reference)
<5 y	219	38	0.94 (0.63-1.41)	55	1.25 (0.88-1.78)	52	0.80 (0.55-1.10)
≥5 y	210	26	0.60 (0.38-0.95)	44	0.96 (0.66-1.40)	34	0.61 (0.40-0.92)
P_{trend}			0.04		0.86		0.01
Tablet/wk							
Aspirin							
No regular use	1,038	168	1.00 (Reference)	200	1.00 (Reference)	375	1.00 (Reference)
2 to <7	85	14	1.07 (0.58-1.99)	18	1.10 (0.64-1.90)	21	0.97 (0.57-1.65)
≥7	231	37	0.81 (0.54-1.21)	57	1.12 (0.80-1.58)	43	0.71 (0.49-1.04)
P_{trend}			0.35		0.49		0.09
Non-aspirin NSAID (pills/wk)							
No regular use	1,140	193	1.00 (Reference)	239	1.00 (Reference)	399	1.00 (Reference)
2 to <7	32	6	1.01 (0.40-2.55)	3	0.40 (0.12-1.34)	10	1.28 (0.58-2.85)
≥7	182	19	0.53 (0.31-0.89)	33	0.79 (0.52-1.19)	30	0.51 (0.33-0.79)
P_{trend}			0.02		0.18		0.01
Any NSAID (pills/wk)							
No regular use	929	155	1.00 (Reference)	178	1.00 (Reference)	353	1.00 (Reference)
2 to <7	96	17	1.10 (0.61-1.90)	20	1.05 (0.62-1.77)	24	0.95 (0.58-1.57)
≥7	330	47	0.70 (0.48-1.01)	77	1.10 (0.80-1.48)	62	0.63 (0.46-0.88)
P_{trend}			0.07		0.59		0.01

NOTE: Participants who used at least two pills per week for 1 mo of any of the NSAIDs were defined as a regular user of that drug.
*Adjusted for age, sex, race, birthplace, education, smoking status, BMI (at reference age), UGI history, and antacid use in a multivariable polychotomous logistic regression models.

fit two trend variables (one for each category of UGI disorder history) with a multivariable model that fit a single trend variable for all subjects. The *P* values reported for trend tests and for the test for homogeneity of trends are two sided.

For validity purposes, we repeated all statistical analyses excluding data collected from next-of-kin subjects. Risk estimates were not materially different from the results presented below based on all subjects combined (that is, self-respondents and next-of-kin subjects).

Results

Selected characteristics of each of the three groups of case patients and the control subjects are summarized in Table 1. The mean ages at diagnosis were 61.2 years (SD, 9.4) for patients with esophageal adenocarcinoma, 60.8 years (SD, 10.2) for patients with gastric cardia adenocarcinoma, and 60.4 years (SD, 11.5) for patients with distal gastric adenocarcinoma; control subjects were, on average, 59.5 years (SD, 11.2) at their assigned reference age. Among control subjects, 73.7% were male

Table 3. Multivariable ORs (95% CIs) for use of aspirin and non-aspirin NSAIDs in relation to esophageal, gastric cardia, and distal gastric adenocarcinomas using never users as the reference group

Exposure	Control	EA		GCA		DGA	
	n	*n*	OR* (95% CI)	*n*	OR* (95% CI)	*n*	OR* (95% CI)
Any NSAID							
Never use	160	36	1.00 (Reference)	50	1.00 (Reference)	145	1.00 (Reference)
No regular use	767	119	0.55 (0.35-0.87)	126	0.45 (0.30-0.67)	208	0.47 (0.35-0.64)
<5 y	219	38	0.58 (0.34-1.00)	55	0.66 (0.42-1.06)	52	0.45 (0.30-0.68)
≥5 y	210	26	0.37 (0.20-0.66)	44	0.50 (0.31-0.82)	34	0.34 (0.22-0.55)
P_{trend}			<0.01		0.24		<0.01

*Adjusted for age, sex, race, birthplace, education, smoking status, BMI (at reference age), UGI history, and antacid use in a multivariable polychotomous logistic regression models.

Table 4. Multivariable ORs (95% CIs) for use of aspirin and non-aspirin NSAIDs in relation to esophageal, gastric cardia, and distal gastric adenocarcinomas by history of UGI disorders

Exposure	EA				
	UGI disorders			No UGI disorders	
	Cases/controls	OR* (95% CI)		Cases/controls	OR* (95% CI)
Aspirin					
No regular use	82/262	1.0 (Reference)		86/775	1.0 (Reference)
<5 y	9/45	0.64 (0.29-1.42)		17/103	1.52 (0.85-2.74)
≥5 y	11/55	0.72 (0.34-1.49)		14/115	0.90 (0.48-1.68)
P_{trend}		0.24			0.89
P for heterogeneity of trends			0.32		
Non-aspirin NSAID					
No regular use	85/281	1.0 (Reference)		108/859	1.0 (Reference)
<5 y	12/59	0.87 (0.42-1.80)		8/101	0.60 (0.28-1.30)
≥5 y	4/21	0.51 (0.16-1.60)		1/34	0.22 (0.03-1.70)
P_{trend}		0.25			0.05*
P for heterogeneity of trends			0.38		
Any NSAID					
No regular use	73/224	1.0 (Reference)		82/703	1.0 (Reference)
<5 y	17/69	0.86 (0.46-1.62)		21/150	1.16 (0.68-1.98)
≥5 y	12/69	0.59 (0.29-1.19)		14/141	0.71 (0.38-1.33)
P_{trend}		0.14			0.44
P for heterogeneity of trends			0.53		

NOTE: UGI symptoms, including gastric ulcer, duodenal ulcer, unspecified type of ulcer, gastritis, hiatal, esophagitis, Barrett's esophagus, gastroesophageal reflux disease, excess acid or gastric hyperacidity, and other diseases of the stomach.
*Adjusted for age, sex, race, birthplace, education, smoking status, BMI (at reference age), UGI history, and antacid use in multivariable unconditional logistic regression models.

compared with 90.9% of patients with esophageal adenocarcinoma, 83.4% of patients with gastric cardia adenocarcinoma, and 59% of patients with distal gastric adenocarcinoma. Non-Latino Whites represented 62% of those with esophageal adenocarcinoma, 77.3% of those with gastric cardia adenocarcinoma, and 30.2% of those with distal gastric adenocarcinoma. For all three tumor sites, case patients tended to have lower education than control subjects. Current smoking, history of UGI disorders, and antacid use were more common among case patients than control subjects.

Table 2 summarizes the associations between regular use of aspirin, non-aspirin NSAID, and any NSAID and each tumor site. Regular use of aspirin for at least 5 years was associated with ~40% reduced risk of distal gastric adenocarcinoma (adjusted OR, 0.58; 95% CI, 0.36-0.92). Both short-term (<5 years) and longer-term (≥5 years) regular use of non-aspirin NSAIDs were associated with lower risk of distal gastric adenocarcinoma, although the 95% CI for longer-term use did not exclude 1.0 (adjusted OR, 0.63; 95% CI, 0.41-0.97 for <5 years use and OR, 0.54; 95% CI, 0.24-1.20 for ≥5 years use). The dose-response effect was strengthened when aspirin use and non-aspirin NSAID use were examined together (P_{trend} = 0.01). The OR for adenocarcinoma of the esophagus was significantly decreased for participants who took aspirin or non-aspirin NSAIDs with a greater reduction for non-aspirin NSAIDS than for aspirin (Table 2). Among those who took NSAIDs for ≥5 years, the OR was 0.60 (95% CI, 0.38-0.95) relative to individuals who did not use any NSAID regularly and the dose-response effect was statistically significant (P_{trend} = 0.04).

Table 5. Multivariable ORs (95% CIs) for use of aspirin and non-aspirin NSAIDs in relation to esophageal, gastric cardia, and distal gastric adenocarcinomas by history of UGI disorders using never users as the reference group

Exposure	EA				
	UGI disorders			No UGI disorders	
	Cases/controls	OR* (95% CI)		Cases/controls	OR* (95% CI)
Any NSAID					
Never used	18/35	1.0 (Reference)		18/125	1.0 (Reference)
No regular use	55/189	0.45 (0.23-0.90)		64/578	0.65 (0.36-1.17)
<5 y	17/69	0.40 (0.18-0.91)		21/150	0.80 (0.39-1.62)
≥5 y	12/69	0.27 (0.11-0.64)		14/141	0.47 (0.22-1.03)
P_{trend}		<0.01			0.17
P for heterogeneity of trends			0.44		

NOTE: UGI symptoms, including gastric ulcer, duodenal ulcer, unspecified type of ulcer, gastritis, hiatal, esophagitis, Barrett's esophagus, gastroesophageal reflux disease, excess acid or gastric hyperacidity, and other diseases of the stomach.
*Adjusted for age, sex, race, birthplace, education, smoking status, BMI (at reference age), UGI history, and antacid use in a multivariable polychotomous logistic regression models.

Table 4. Multivariable ORs (95% CIs) for use of aspirin and non-aspirin NSAIDs in relation to esophageal, gastric cardia, and distal gastric adenocarcinomas by history of UGI disorders (Cont'd)

GCA				DGA			
UGI disorders		No UGI disorders		UGI disorders		No UGI disorders	
Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)
76/262	1.0 (Reference)	124/775	1.0 (Reference)	114/262	1.0 (Reference)	261/775	1.0 (Reference)
22/45	1.59 (0.87-2.90)	18/103	1.02 (0.58-1.77)	19/45	1.19 (0.64-2.24)	20/103	0.88 (0.51-1.50)
12/55	0.75 (0.37-1.51)	23/115	1.07 (0.64-1.78)	10/55	0.44 (0.20-0.96)	15/115	0.63 (0.34-1.15)
	0.84		0.80		0.10		0.13
	0.75				0.75		
88/281	1.0 (Reference)	149/859	1.0 (Reference)	127/281	1.0 (Reference)	272/859	1.0 (Reference)
14/59	0.91 (0.47-1.77)	12/101	0.61 (0.32-1.16)	12/59	0.39 (0.19-0.79)	20/101	0.81 (0.47-1.39)
8/21	1.05 (0.43-2.54)	4/34	0.66 (0.22-1.94)	4/21	0.43 (0.14-1.40)	4/34	0.58 (0.19-1.72)
	0.96		0.13		0.01*		0.22
	0.27				0.20		
64/224	1.0 (Reference)	112/703	1.0 (Reference)	106/224	1.0 (Reference)	247/703	1.0 (Reference)
29/69	1.57 (0.91-2.70)	26/150	1.02 (0.63-1.64)	22/69	0.68 (0.38-1.22)	30/150	0.81 (0.51-1.27)
17/69	0.83 (0.44-1.54)	27/141	1.03 (0.64-1.67)	15/69	0.52 (0.27-1.00)	19/141	0.62 (0.36-1.06)
	0.94		0.88		0.03*		0.06
	0.88				0.60		

Similar risk patterns were observed when we evaluated frequency of use. Statistically significant inverse relationships with increasing number of pills used per week were observed for the risk of adenocarcinomas of the esophagus and the distal stomach in relation to use of non-aspirin NSAIDs. A nearly 50% decline in the OR associated with use of at least seven pills per week of non-aspirin NSAIDs was observed for adenocarcinomas of the esophagus (OR, 0.53; 95% CI, 0.31-0.89) and distal stomach (OR, 0.51; 95% CI, 0.33-0.79; Table 2).

The observed association between any NSAID use and risk of adenocarcinomas at each site was strengthened when we restricted our reference group to never users (Table 3). The ORs for esophageal and distal gastric adenocarcinomas were significantly decreased among irregular users as well as short-term (<5 years) and longer-term NSAID users. Interestingly, we also found reduced ORs for adenocarcinoma of the gastric cardia among study participants who were irregular as well as regular NSAID users.

Because we suspected that use of aspirin or non-aspirin NSAIDs might have been affected by gastrointestinal tract disorders that are also risk factors for these cancers, we conducted analyses separately among participants with and without a history of UGI disorders (Table 4). No heterogeneity of trends was observed between individuals with and individuals without this history. Compared with persons with no regular use of any NSAID, the ORs for distal gastric adenocarcinoma among NSAID users of at least 5 years were similar for those with and those without a history of UGI disorders (OR, 0.52; 95% CI, 0.27-1.00 and OR, 0.62; 95% CI, 0.36-1.06, respectively). For esophageal adenocarcinoma, more than 5 years of NSAID use was associated with lower risk regardless whether participants had a UGI disorder history, but neither of these risk estimates nor the trend tests achieved statistical significance. In Table 5, we show risk by history of UGI disorders in logistic regression models where the reference group was restricted to participants who reported never using NSAIDs.

Table 5. Multivariable ORs (95% CIs) for use of aspirin and non-aspirin NSAIDs in relation to esophageal, gastric cardia, and distal gastric adenocarcinomas by history of UGI disorders using never users as the reference group (Cont'd)

GCA				DGA			
UGI disorders		No UGI disorders		UGI disorders		No UGI disorders	
Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)
18/35	1.0 (Reference)	32/125	1.0 (Reference)	37/35	1.0 (Reference)	108/125	1.0 (Reference)
46/189	0.40 (0.20-0.78)	80/578	0.48 (0.30-0.77)	69/189	0.52 (0.29-0.94)	139/578	0.46 (0.32-0.65)
29/69	0.73 (0.35-1.54)	26/150	0.58 (0.32-1.06)	22/69	0.43 (0.21-0.88)	30/150	0.47 (0.28-0.77)
17/69	0.40 (0.18-0.90)	27/141	0.57 (0.31-1.04)	15/69	0.35 (0.16-0.76)	19/141	0.34 (0.19-0.61)
	0.41		0.37		0.01		<0.01
	0.94				0.96		

As was observed in Table 4, we see no heterogeneity of effects by UGI disorder status, with irregular NSAID users also at lower risk for cancer at each of the three subsites than never users.

We further assessed whether risk differed among current users, those who were NSAID users on the reference date (that is, 1 year before the case patient's date of diagnosis and a comparable date for the control subjects), and other users. We found that current users and former users both had reduced ORs for adenocarcinomas of the esophagus and distal stomach and that these results did not differ statistically (data not shown). Moving the date on which subjects were defined as current users back to 3 years before the case patients' diagnosis date did not produce different results for current users and former users.

To rule out differential reporting of NSAID use by case patients and control subjects, we also studied the association between acetaminophen use and risk of adenocarcinomas at each site. In a multivariate analysis that included NSAID use, no statistically significant association between acetaminophen use and risk of adenocarcinomas of the esophagus, gastric cardia, or distal stomach was observed (data not shown).

Discussion

Regular use of aspirin and non-aspirin NSAIDs was associated with decreased risk of distal gastric adenocarcinoma, and use of non-aspirin NSAIDs was associated with a decreased risk of esophageal adenocarcinoma in multivariable models that included adjustment for UGI disorders and other potential confounding factors. Combining the two classes of NSAIDS produced statistically significant dose-response effects for both tumor sites. Regular NSAID use was unrelated to risk of adenocarcinomas of the gastric cardia. In this study, a regular user was one who had taken at least two NSAID pills a week for 1 month. Changing the reference group from those with no regular NSAID use to never users strengthened these relationships but also uncovered lower risks among individuals who were in the irregular user category. In addition, risk of gastric cardia adenocarcinoma was significantly reduced in the analysis using nonusers as the reference group.

A history of UGI disorders did not modify these effects as none of the tests for homogeneity of trends was statistically significant. We excluded any drugs initiated in the 2 years before the patients' diagnoses or the equivalent date for control subjects as symptoms experienced by case patients before their diagnoses could have influenced their use of NSAIDs. We reanalyzed our data including drug use initiated during this time period, and our results were essentially the same as those presented here.

Our results on regular NSAID use support previous results, suggesting that NSAID use is inversely associated with risk of adenocarcinomas of the esophagus and stomach (7, 17, 18). As suggested by Anderson et al. (14), NSAIDs may affect the early stage of the inflammation-metaplasia-adenocarcinoma sequence in the esophagus. NSAID use can reduce inflammation by inhibiting COX-2 enzyme production. Overexpression of COX-2 has been found in a range of esophageal conditions, including reflux esophagitis (28), dysplasia (29), Barrett's esophagus (29, 30), and esophageal adenocarcinoma (28, 29, 31). Overexpression of COX-2 and increased prostaglandin secretion have also been found to be involved in the growth and metastasis of gastric cancer (32). Studies also suggest COX-2 inhibitors can reduce cell growth and decrease cell proliferation in Barrett's esophagus (8), in spite of the onset of COX-2 overexpression in the early stages of development of Barrett's esophagus (33, 34), and that they suppress growth of gastric cancer in a human gastric cancer cell line (35, 36).

Three previous studies suggest that current users of NSAIDs are at lower risk of esophageal or distal gastric adenocarcinoma than those who never used NSAIDs (15, 37, 38). In these three studies, current users were defined as subjects who reported taking the medications at the study's reference date (that is, that date was 1 year before interview for controls and the earlier of 1 year before interview or diagnosis date for cases); all other users were considered former users. Former NSAID use was also associated with decreased risk of esophageal or distal gastric adenocarcinoma, but the risk reductions were not statistically significant. The authors question whether their findings are artifactual because individuals with early symptoms of cancer might have stopped using NSAIDs. In our study, the associations did not differ between current and past NSAID users. Our analysis where former users ceased use at least 3 years before the diagnosis date suggests that the effect of NSAIDs, if true, may persist at least 3 years after cessation of NSAID use.

Prior studies that have evaluated frequency of use have not observed that daily use has greater effect on risk of UGI cancers (15, 38). In one prospective study, the authors found no relation between frequency of NSAID use and risk of esophageal adenocarcinoma (38). In a case-control study, the risk of esophageal and distal gastric adenocarcinomas was lower among subjects who took one aspirin pill per day, but no risk reduction was noted for users of non-aspirin NSAIDs (15). We found that risk reduction for esophageal and distal gastric adenocarcinomas was restricted to regular NSAID users who took at least seven pills per week. This suggests that daily use of an aspirin or other NSAID may be optimal for use in cancer prevention for those at high risk for esophageal or distal gastric adenocarcinoma.

However, the lack of any effect among those who were considered as regular users but had less frequent use is at odds with our finding that irregular use is associated with lower UGI cancer risk, an inconsistency we are unable to explain.

Infection with *Helicobacter pylori*, Barrett's esophagus, hiatal hernia, and reflux symptoms are independent risk factors for esophageal and gastric adenocarcinomas in this study population (14, 23, 24). Presence of these and other UGI conditions can influence the use of NSAIDs (39); in fact, for several of these conditions, NSAID use is contraindicated. However, few epidemiologic studies have considered a history of UGI disorders when examining the relationship between NSAID use and esophageal and gastric adenocarcinomas. Case-control studies conducted in Russia and Sweden evaluated risk patterns with adjustment for a history of *H. pylori* infection; both studies found that an inverse association

with distal gastric cancer existed only among subjects who were *H. pylori* positive (20, 21). In contrast, in a U.S. population-based case-control study, Farrow et al. observed an inverse association between current non-aspirin NSAID users and risk of esophageal and gastric adenocarcinomas in analyses restricted to subjects with no history of UGI disorders (15). Another case-control study of gastric and esophageal adenocarcinomas found that long-term use (>3 years) of NSAIDs decreased the risk of all gastric cancers combined more among subjects with UGI disorders than among those with no UGI disorders, although this difference did not reach statistical significance (22). Our findings showed a clear pattern of decreasing ORs for distal gastric adenocarcinoma with increasing duration and frequency of NSAID use among persons with and without a history of UGI disorders. Similarly, no differences were observed in the risk patterns of esophageal adenocarcinoma in the two subgroups defined by presence or absence of a history of UGI disorders.

We observed greater risk reduction for distal gastric tumors and esophageal adenocarcinomas associated with non-aspirin NSAIDs than with aspirin use, but the number of exposed individuals was small. For many years, non-aspirin NSAID formulations were available only by prescription; at the time this study was conducted, many were just becoming available as over-the-counter pain relievers. One speculation is that when non-aspirin NSAIDs were used by our study subjects, they were used at the higher doses available only by prescription, yielding effective doses of non-aspirin NSAIDs that may have been greater than those for aspirin products. Further, indications for use of non-aspirin NSAIDs may have differed from those for aspirin. Aspirin and non-aspirin NSAIDs differ in that aspirin is believed to mainly inhibit the COX-1 enzyme, whereas most non-aspirin NSAIDs mainly influence COX-2 (40).

Most previous studies of the relationship between NSAID use and risk of esophageal or gastric cancer have defined the reference group as individuals whose NSAID use history falls below a certain threshold (14, 15, 20, 21, 38, 41, 42), similar to our approach where the reference group consisted of individuals whose had never used at least two NSAID pills per week for 1 month. Two studies have separated irregular users from never users (22, 37), but neither separated adenocarcinomas of the esophagus from squamous cell carcinomas nor did either study segregate gastric cancers by site. Coogan et al. (37) found that both regular use and irregular use of NSAIDs were associated with reduced risk of stomach cancers but observed no effect on esophageal cancer risk. Lindblad et al. (22) observed that long-term use of non-aspirin NSAIDs was associated with a reduced risk of gastric cancer but not esophageal cancer; further, no associations with aspirin use were noted. We found similar reductions in risk for irregular users, short-term users, and longer-term users when restricting the reference group to persons with no use. This observation calls into question whether NSAIDs are responsible for the reduction in risk of these cancers or whether nonusers differ in some heretofore undefined way from NSAID users that is predictive of risk.

Our study has several limitations. Our overall response rate was modest. Only 55% of the eligible case patients completed the interview, and they tended to have an earlier stage of disease at diagnosis than the patients who were not included (23, 24). Next-of-kin interviews accounted for 29% of the patient reports in this study. One would expect less complete reporting of NSAID use by next-of-kin. However, our results did not appear to be affected by next-of-kin interviews and were similar when next-of-kin were excluded from the analyses. In this and other studies published to date, results are based on self-reports or next-of-kin reports on NSAID use. It is not feasible to validate over-the-counter medication use and it is also difficult to validate the use of prescription analgesic medications. We did, however, ask extensive questions regarding each NSAID medication used regularly by asking about the starting and stopping dates, frequency of use, and the name of the physician who prescribed the drug (for prescription medications).

We did not ask about specific doses of the medications used but recorded the frequency of use in pills per day, week, or month over each exposure time. In addition, the number of regular NSAID users in this study was not substantial, which reduced the statistical power in our more detailed analyses that stratified by history of UGI symptoms. Similarly, the small number of regular users limited the possibility of testing for heterogeneity of effects by race.

In summary, this large, population-based case-control study indicates that regular use of aspirin and other NSAIDs is associated with reduced risk of esophageal and distal gastric adenocarcinomas and that, in analyses comparing regular with irregular or nonusers, risk declines with increasing duration of use. These relationships are evident among individuals with and without a history of upper UGI disorders or symptoms.

Appendix A. Drug List

Compounds containing aspirin
Anacin
APC tablets
APC with codeine
Arthritis pain formula
ASA compounds
Ascriptin
Aspirin enteric
Aspirin with codeine
Bayer aspirin
Buffered aspirin
Cama
Darvon compound
Ecotrin
Empirin compounds
Empirin with codeine
Equagesic
Fiorinal
Fiorinal with codeine
Momentum
Norgesic or Norgesic Forte
Percodan
Synalogos
Compounds containing non-aspirin NSAIDs
Advil
Aleve/Alleve
Anaprox
Ansaid
Aprozen
Clinoril

Datpro
Dolobidea
Feldene
Ibuprofen
Indocin
Indomethacin
Lodine
Meclomen
Midol 200
Motrin
Nalfon
Naprosyn
Nuprin
Orudis
Ponstel
Relafen
Salsalate
Tolectin
Voltaren

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