Aspirin, Nonsteroidal Anti-inflammatory Drugs, and the Risks of Cancers of the Esophagus

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Abstract

Background: **Frequent consumption of aspirin and nonsteroidal anti-inflammatory drugs (NSAID) has been associated with reduced occurrence of cancers of the esophagus, although potential modifying effects of other causal factors remain relatively unexplored.**

Methods: **We compared nationwide samples of Australian patients with adenocarcinomas of the esophagus (EAC; *n* = 367) or esophagogastric junction (EGJAC; *n* = 426) or esophageal squamous cell carcinoma (ESCC; *n* = 309) with control participants sampled from a population register (*n* = 1,580). Intakes of aspirin, other NSAIDs, and acetaminophen (paracetamol) were assessed from self-reports. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) using multivariable logistic regression.**

Results: **Compared with never-users of aspirin, those who used aspirin at least weekly had significantly lower risks of EAC (OR, 0.48; 95% CI, 0.32-0.72), EGJAC (OR, 0.71; 95% CI, 0.49-1.01), and ESCC (OR, 0.63; 95% CI, 0.40-0.98). At least weekly use of other NSAIDs was also associated with reduced risks of EAC (OR, 0.74; 95% CI, 0.51-1.08), EGJAC (OR, 0.53; 95% CI, 0.37-0.77), and ESCC (OR, 0.46; 95% CI, 0.30-0.73). No association was observed between frequent use of acetaminophen and esophageal cancer. Risk reductions for EAC among users of aspirin and NSAIDs were greater among those who experienced at least weekly symptoms of reflux (OR, 0.26; 95% CI, 0.12-0.55 and OR, 0.41; 95% CI, 0.21-0.77, respectively) than those who did not experience reflux (OR, 0.96; 95% CI, 0.46-2.00 and OR, 0.78; 95% CI, 0.35-1.72, respectively). Recent use of NSAIDs in the past 5 years was associated with greater risk reductions.**

Conclusions: **Frequent use of aspirin and NSAIDs is associated with reduced occurrence of esophageal cancers, particularly among those with frequent symptoms of gastroesophageal reflux.** (Cancer Epidemiol Biomarkers Prev 2008;17(5):1169–78)

Introduction

Worldwide, cancers of the esophagus are the fourth leading cause of death from cancer (1). The two main histologic types of esophageal cancer, namely squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), are characterized by different patterns of occurrence and different causal mechanisms. Until recently, almost all esophageal cancers were of the squamous subtype; however, during the past three decades, the incidence of esophageal adenocarcinomas has increased rapidly, especially in Western countries. Indeed, in some populations, the rates of esophageal adenocarcinoma are increasing faster than for any other major cancer (2). Despite efforts to improve methods for detection and to develop better treatments, the overall 5-year survival for both types of esophageal cancer remains around 5% to 23% (3-5).

For ESCC, the major causal factors in Western popuations are high levels of smoking and alcohol consumption (6-10). Other factors such as poor diet, chronic mucosal irritation, infection with human papilloma virus, and, to a lesser extent, genetic predisposition, have also been implicated (11-16). The principal risk factors for EAC include gastroesophageal acid reflux (17), smoking (8, 18), and obesity (9, 19-23).

Because of the increasing incidence of esophageal adenocarcinoma and the very high mortality associated with the disease, strategies to control this cancer through chemoprevention are being urgently explored. One focus of attention has been aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) as possible chemopreventives of a range of epithelial cancers, including cancers of the esophagus (24). This class of medications inhibits the activity of the cyclooxygenase (COX) enzymes (both constitutional COX-1 and inducible COX-2 isoenzymes). COX-2 is overexpressed in many epithelial cancers, including esophageal cancers (25-37). With regard to tumor growth, COX-2 enzyme functions to reduce cellular adhesion and apoptosis and increase angiogenesis (38-40). There is evidence from animal studies that inhibiting the COX-2 enzyme reduces the growth of early esophageal cancers (41-43).

Received 12/4/07; revised 2/8/08; accepted 2/20/08.

Grant support: Queensland Cancer Fund and the National Health and Medical Research Council of Australia (program no. 199600). David Whiteman and Penelope Webb are supported by Senior Research Fellowships from the National Health and Medical Research Council of Australia. Shahram Sadeghi and Nirmala Pandeya are supported by Ph.D. scholarships from the Ministry of Health and Medical Education of IR Iran and the National Health and Medical Research Council of Australia, respectively. The funding bodies played no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

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doi:10.1158/1055-9965.EPI-07-2852

Epidemiologic studies have reported significantly lower risks of esophageal cancer among those who frequently consume aspirin or NSAIDs (10, 44-47) compared with never users; however, it is not known whether the inverse relationship is modified by other causal factors or whether the duration or timing of NSAID intake is important in determining risk reduction. To address these issues, we analyzed data from a population-based case-control study conducted in Australia.

Materials and Methods

Approval to undertake the study was obtained from the research ethics committees of the Queensland Institute of Medical Research and participating hospitals. We obtained written informed consent from all participants.

Participants. Detailed descriptions of the methods for this case-control study have been published previously (23). Briefly, eligible patients were those aged 18 to 79 years with a histologically confirmed primary invasive adenocarcinoma or squamous cell carcinoma of the esophagus or esophagogastric junction diagnosed from July 1, 2001, until June 30, 2005. We identified 1,610 potentially eligible patients attending treatment centers during the study period. Of these, doctors refused contact with 71 patients and 167 died before consent could be obtained. Patients who were too ill (91), were mentally incapable (23), could not read or write in English (41), or could not be contacted (26) were excluded. The remaining 1,191 patients were invited to participate, and, of these, 928 (78% of those approached) agreed to take part. A further 739 living and eligible patients were identified through population-based cancer registries in each state. Of these, treating doctors refused contact for 84; 37 were incapable of taking part; and 232 were unable to be contacted. The remaining 386 registry patients were invited to take part in the study, of whom 253 agreed. Thus, 1,181 of 2,349 patients with esophageal cancer (50.2%) consented to take part in the study. Questionnaires were returned by 1,102 patients (367 and 426 with adenocarcinomas of the esophagus and gastroesophageal junction, respectively, and 309 patients with squamous cell carcinomas).

We prospectively sampled potential controls from the Australian Electoral Roll (enrollment is compulsory) within strata of age (in 5-year age groups) and state of residence to match the distribution of the case series. We aimed for similar numbers of male cases and controls in each stratum of age and state; female controls were intentionally oversampled at all ages to accommodate their simultaneous enrollment in a parallel case-control study of ovarian cancer (48). Of 3,258 potentially eligible control participants who were contacted and invited to participate, 175 were excluded because they were deceased (16), too ill (61), or unable to read or write in English (98), and 41 were lost to follow-up in the interval between initial contact and participation. Of 3,042 remaining controls, 1,680 (55%) accepted. Completed questionnaires were returned by 1,580 controls (48% of all potentially eligible controls selected from the roll).

Details of the histologic type and anatomic site of each tumor were abstracted from diagnostic pathology reports. Anatomic sites of tumors were categorized according to the WHO classification (49) into ''esophageal'' and ''esophagogastric junction'' tumors.

Measurement of Analgesic Exposure. Our aim was to estimate separately the relative risks of EAC, EGJAC, and ESCC associated with exposure to aspirin, NSAIDs, and acetaminophen (paracetamol)—a widely used analgesic that shares similar clinical indications to NSAIDs but has no known associations with cancer. Simple measures of medication consumption were assessed through a structured, self-completed questionnaire; further details of consumption were collected at interview by trained research nurses. Thus, the self-completed questionnaire asked participants to report separately their frequency of use of aspirin, NSAIDs, and acetaminophen during the past 5 years. To aid recall, names of commonly available brands of each class of medication were listed. Frequency of use was elicited on an 8-point scale (''never,'' ''occasionally,'' ''less than once a month,'' ''2 to 3 times per month,'' ''once a week,'' ''2 to 3 times per week,'' ''4 to 7 times per week,'' ''2 or more times per day''). For analysis, these were collapsed to four categories (''never,'' ''less than monthly,'' ''less than weekly,'' ''weekly or more often''). A separate set of questions then asked participants to indicate whether they had ever taken any of 12 separately itemized NSAID medications; these questions included the generic name and all brand names licensed for use in Australia at the time. Positive responses to the latter questions prompted a series of questions during a standardized telephone interview conducted by a trained research nurse.

At interview, we asked respondents to report their ages at first and last use for each NSAID, their pattern of use (either ''regular,'' consumption of NSAIDs at least once a week for duration of 6 months or more, or ''occasional''), as well as their frequency of consumption during periods of use, duration of use, and typical dose during each of four periods (last year, 1-5 years ago, 6-10 years ago, and >10 years ago). Recency of intake was determined regardless of whether the pattern of intake was occasional or regular. Medication interviews were introduced to the data collection protocol in January 2003; participants recruited before 2003 were not interviewed. Interview data were available for 787 controls, 142 EAC cases, 147 EGJAC cases, and 93 ESCC cases. When analyzing measures of lifetime use, we excluded all exposures to NSAIDs reported in the past year.

Measurement of Potential Confounders. In addition to background information about each participant's educational history, usual occupation, and income, the questionnaire asked for details of their height and weight at various times to enable calculation of corresponding body mass index (BMI) by dividing weight in kilograms by the square of height in meters. We used standard WHO categories for analysis (''healthy weight'' <25.0 kg/m^2; ''overweight'' 25.0-29.9 kg/m^2; ''obese'' $\geq$30 kg/m^2). Participants were asked whether, over their whole life, they had ever smoked >100 cigarettes, cigars, or pipes; positive responses elicited further questions regarding consumption and duration of smoking. We derived the number of pack-years of tobacco exposure by dividing the number of cigarettes smoked on a typical day by 20 and multiplying by the total number of years smoked. We asked participants to report the frequency

with which they consumed different classes of alcohol (light beer, regular beer, white wine, red wine, port/sherry, and spirits/liqueurs) at ages 20-29, 30-49 and ≥50 years, as applicable. For these analyses, total alcohol consumption was summed across all age groups for all types of alcohol, from which we calculated a weighted average number of standard drinks (10 g ethanol) consumed per week between age 20 years and current age. We assessed the frequency of symptoms of gastroesophageal reflux 10 years before diagnosis, defined as the presence of heartburn (''a burning pain behind the breastbone after eating'') or acid reflux (''a sour taste from acid or bile rising up into the mouth or throat''). For analysis, we used the highest reported frequency for either symptom and, consistent with previous reports, defined ''frequent symptoms'' as those occurring at least weekly during the 10 years before diagnosis (50, 51).

Statistical Analyses. We calculated the odds ratio (OR) and 95% confidence interval (95% CI) associated with each exposure using multivariable logistic regression analysis in SAS version 9.1 (SAS Institute, Inc.). Our approach was first to fit minimally adjusted models that contained terms for each exposure and the sampling variables (sex, age, and state). We then estimated relative risks associated with each class of aspirin, NSAIDs, and acetaminophen adjusted for these variables and income, smoking, alcohol consumption, and BMI. Fully adjusted models were fitted, which included the preceding variables as well as a term for frequency of gastroesophageal reflux symptoms. For each variable, the lowest category was the reference category. We also assessed the potential confounding effects of antacid medications including proton pump inhibitors, but as these terms made no material difference to the risk estimates, they were not included in the final models. We tested for trend by including categorical measures of analgesic use as ordinal variables (excluding the ''never users'') in the multivariable model and examining the Wald test.

To explore whether the inverse associations between aspirin and NSAID consumption were modified by the effects of known causal factors, we repeated the above analyses after stratifying by the frequency of symptoms of gastroesophageal reflux (never, less than weekly, at least weekly), smoking status (never, ever), and BMI (<25.0 kg/m^2, 25.0-29.9 kg/m^2, ≥30 kg/m^2). We included an interaction term in the full model to assess the statistical significance of the differences in association across strata. Statistical significance was determined at $\alpha = 0.05$, and all tests for statistical significance were two sided.

Results

Characteristics of cases and controls are presented in Table 1. Younger females were overrepresented in the control series owing to their simultaneous recruitment for parallel studies of ovarian cancer; hence, all analyses were adjusted for age in years and sex. As expected, controls differed from each of the cases groups for their distribution of acid reflux symptoms, smoking status, and BMI. Overall, mean weekly alcohol consumption differed little between controls and patients with adenocarcinoma; ESCC cases were more likely to have higher levels of alcohol consumption than controls.

Use of Aspirin, NSAIDs, and Acetaminophen in the Past 5 Years. In minimally adjusted analyses, EAC cases were less likely than controls to report using aspirin occasionally or at least weekly during the past 5 years (Table 2). After adjusting for other confounding factors, weekly users of aspirin during the past 5 years had significantly lower risks of EAC than never users (OR, 0.48; 95% CI, 0.32-0.73). Frequent use of NSAIDs during the past 5 years was also associated with reduced risks of EAC, although this was not statistically significant. When considered together, we found those who used either aspirin or NSAIDs or both more than weekly had significantly lower risks of EAC (OR, 0.55; 95% CI, 0.37-0.81). Use of acetaminophen was widespread among controls and EAC cases, and we found no association between use of this medication and EAC.

Patients with EGJAC were less likely than controls to consume aspirin or NSAIDs during the past 5 years and this was particularly evident at high frequencies of consumption (at least weekly aspirin OR, 0.70; 95% CI, 0.49-1.01; at least weekly NSAIDs OR, 0.53; 95% CI, 0.37-0.77; at least weekly aspirin or NSAIDs OR, 0.59; 95% CI, 0.41-0.84). As for EAC, we found no evidence that use of acetaminophen was associated with occurrence of EGJAC.

There was some evidence that patients with ESCC of the esophagus were less likely than controls to consume aspirin at least weekly, although lower levels of aspirin intake were similarly prevalent among ESCC cases and controls (Table 2). NSAID consumption during the past 5 years was less common among ESCC cases than controls; this was observed at all levels of intake and was statistically significant for the highest level of consumption (OR, 0.46; 95% CI, 0.30-0.73). More than weekly use of either aspirin or NSAIDs or both was associated with significantly lower risks of ESCC (OR, 0.54; 95% CI, 0.36-0.83). Again, use of acetaminophen was highly prevalent and similarly distributed among controls and ESCC cases.

The principal confounding factors differed for each of the three cancer types: For EAC, the greatest effects on risk estimates occurred after including terms for reflux and BMI, whereas for EJGAC, inclusion of terms for reflux and smoking produced the greatest changes to the estimates. For ESCC, the inclusion of terms for smoking and reflux had the greatest effects (data not shown).

Stratified Analyses. We examined the associations between aspirin use and risks of EAC, EGJAC, and ESCC after stratifying by the frequency of symptoms of gastroesophageal acid reflux (Table 3), smoking, and BMI (not shown). We found no association between aspirin consumption and EAC among those who reported never experiencing symptoms of reflux (at least weekly aspirin OR, 0.96; 95% CI, 0.46-2.00). Among the two strata of participants with reflux symptoms, however, we found substantially lower risks of EAC associated with at least weekly use of aspirin (less than weekly reflux stratum OR, 0.52; 95% CI, 0.26-1.00; at least weekly reflux stratum OR, 0.26; 95% CI, 0.12-0.55). Inconsistent patterns across strata of reflux were observed for the association between aspirin consumption and EGJAC or ESCC. For each separate cancer (EAC, EGJAC, and

Table 1. Characteristics of control participants and patients with EAC, EGJAC, and ESCC

Variable	Controls (1,580)	EAC (367)	EGJAC (426)	ESCC (309)	All cases (1,102)
Category	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Age*	60.5 (11.7)	63.7 (9.7)	63.3 (9.3)	64.7 (9.4)	63.5 (9.4)
Gender					
Female	540 (34)	37 (10)	56 (13)	133 (43)	226 (21)
Male	1,040 (66)	330 (90)	370 (87)	176 (57)	876 (80)
Education					
Not finished high school	646 (41)	168 (46)	171 (40)	175 (56)	514 (47)
Finished high school	688 (44)	174 (47)	208 (49)	105 (34)	487 (44)
University	242 (15)	23 (6)	45 (11)	27 (9)	95 (9)
Missing	4 (0.3)	2 (0.5)	2 (0.5)	2 (0.6)	6 (1)
Reflux†					
Never	698 (44)	82 (22)	120 (28)	143 (46)	345 (31)
<Monthly	465 (29)	43 (12)	63 (15)	41 (13)	147 (13)
<Weekly	221 (14)	85 (23)	87 (20)	40 (13)	212 (19)
>Weekly	127 (8)	82 (22)	97 (23)	45 (15)	224 (20)
Daily	57 (4)	71 (19)	56 (13)	36 (12)	163 (15)
Missing	12 (1)	4 (1)	3 (1)	4 (1)	11 (1)
Smoking pack-years					
Never	710 (45)	94 (26)	97 (23)	78 (25)	269 (24)
<15	395 (25)	73 (20)	86 (20)	61 (20)	220 (20)
15-29.9	207 (13)	69 (19)	94 (20)	56 (18)	219 (20)
30+	268 (17)	131 (36)	150 (35)	112 (36)	392 (36)
Missing	0	0	0	2 (1)	2 (0)
Maximum ever BMI‡ (kg/m^2)					
<25	365 (23)	40 (11)	55 (13)	117 (38)	212 (19)
25-30	708 (45)	136 (37)	178 (42)	109 (35)	423 (38)
30.1-35	333 (21)	114 (31)	122 (29)	52 (17)	288 (26)
>35	159 (10)	67 (18)	62 (14)	20 (6)	149 (14)
Missing	15 (1)	10 (3)	9 (2)	11 (4)	30 (3)
Weekly alcohol consumption units 10 g alcohol					
Never	234 (15)	33 (9)	39 (9)	45 (15)	117 (11)
0-4.5	409 (26)	68 (19)	92 (22)	62 (20)	222 (20)
4.6-10.5	334 (21)	71 (21)	88 (21)	40 (13)	199 (18)
10.6-23.5	352 (22)	101 (28)	109 (26)	58 (19)	268 (24)
>23.5	247 (16)	93 (25)	98 (23)	102 (33)	293 (27)
Missing	0	1 (0)	0	2 (1)	3 (0.3)

*Mean age ± SD.
†History of gastroesophageal reflux symptoms 10 y before diagnosis.
‡Body mass index.

ESCC), we found consistently that the greatest risk reductions associated with NSAID consumption were observed among those who experienced frequent reflux symptoms (Table 3). When we conducted similar analyses across strata of smoking and BMI, we observed similar inverse associations with aspirin and NSAIDs among nonsmokers and smokers and across all BMI categories (data not shown). Similarly, we found no evidence that associations with either aspirin or NSAIDs differed by age or sex for any of the cancer types (data not shown).

Lifetime Use of NSAIDs. Detailed assessments of lifetime patterns and frequency of NSAID use (but not aspirin or acetaminophen) were collected at interview. Among controls, the most frequently reported classes of NSAIDs were ibuprofen (23%) followed by diclofenac (19%), celecoxib (14%), naproxen (9%), indomethacin (8%), and piroxicam (6%). Patients with esophageal cancer were significantly less likely than controls to report ever using NSAIDs during their life (Table 4), with risk estimates of similar magnitude for all three types of cancer. Both occasional and regular users of NSAIDs had lower risks of esophageal cancers than never users; however, risks were uniformly lower for those who reported regular use of NSAIDs (defined as ''at least weekly NSAID use for at least 6 months''). The greatest risk reduction was observed for ESCC among regular users of NSAIDs (OR, 0.21; 95% CI, 0.13-0.33). We found some evidence that use of NSAIDs 1 and 5 years ago was associated with lower risks of esophageal cancers than use more than 5 years ago, although for both periods of use, risks of cancer were significantly lower than for those who never used NSAIDs. There was no effect of duration of exposure to NSAIDs in our data; associations of esophageal cancers with less or more than 5 years use of NSAIDs were similar. When the pattern and duration of NSAID intake were assessed together, there was no evidence that risks of either EAC or ESCC among regular users of NSAIDs differed with duration of consumption. For EGJAC, on the other hand, there was a monotonic reduction in risk from occasional use for 5 years or less (OR, 0.70; 95% CI, 0.47-1.05) toward regular use for more than 5 years (OR, 0.25; 95% CI, 0.14-0.43; P_{trend} <0.0001).

Discussion

This is one of the largest studies to have examined the association between consumption of anti-inflammatory and analgesic medications and esophageal cancers. Novel features of this study were the simultaneous

Table 2. Relative risks of esophageal cancers associated with use of aspirin, NSAIDs, or acetaminophen in last 5 y, minimally and fully adjusted

	Controls	Cases	Minimally* adjusted	Fully† adjusted
	n (%)	*n* (%)	OR (95% CI)	OR (95% CI)
EAC				
Aspirin	1,580	367		
Never	638 (40)	159 (44)	1 (Reference)	1 (Reference)
Occasionally	553 (35)	101 (28)	0.65 (0.49-0.87)	0.62 (0.45-0.86)
Less than weekly	154 (10)	52 (14)	1.24 (0.86-1.88)	1.28 (0.83-1.96)
At least weekly	232 (15)	52 (14)	0.69 (0.48-0.98)	0.48 (0.32-0.73)
Missing	3 (0.2)	3 (0.1)		
P_{trend}			0.35	0.48
NSAIDs				
Never	691 (44)	174 (47)	1 (Reference)	1 (Reference)
Occasionally	488 (31)	92 (25)	0.77 (0.58-1.03)	0.76 (0.55-1.05)
Less than weekly	153 (10)	28 (8)	0.76 (0.49-1.19)	0.65 (0.39-1.07)
At least weekly	240 (15)	70 (19)	1.14 (0.83-1.59)	0.74 (0.51-1.08)
Missing	8 (1)	3 (1)		
P_{trend}			0.04	0.91
Aspirin and NSAIDs				
Never	307 (19)	83 (23)	1 (Reference)	1 (Reference)
Occasionally	599 (38)	111 (30)	0.68 (0.49-0.94)	0.68 (0.47-0.98)
Less than weekly	249 (16)	64 (17)	0.96 (0.65-1.40)	0.90 (0.58-1.39)
At least weekly	422 (27)	108 (29)	0.82 (0.58-1.14)	0.55 (0.37-0.81)
Missing	3 (0.2)	1 (0.2)		
P_{trend}			0.17	0.37
Acetaminophen				
Never	180 (12)	44 (12)	1 (Reference)	1 (Reference)
Occasionally	809 (51)	168 (46)	1.03 (0.70-1.52)	0.94 (0.61-1.45)
Less than weekly	413 (26)	96 (26)	1.33 (0.87-2.10)	1.31 (0.81-2.10)
At least weekly	177 (11)	59 (16)	1.72 (1.09-2.72)	0.85 (0.50-1.44)
Missing	1 (0.1)	0 (0)		
P_{trend}			<0.01	0.76
EJGAC				
Aspirin		426		
Never	638 (40)	171 (40)	1 (Reference)	1 (Reference)
Occasionally	553 (35)	142 (34)	0.88 (0.67-1.13)	0.89 (0.67-1.17)
Less than weekly	154 (10)	40 (10)	0.92 (0.62-1.37)	0.89 (0.58-1.38)
At least weekly	232 (15)	70 (16)	0.91 (0.65-1.26)	0.70 (0.49-1.01)
Missing	3 (0.2)	3 (0.7)		
P_{trend}			0.99	0.26
NSAIDs				
Never	691 (44)	216 (51)	1 (Reference)	1 (Reference)
Occasionally	488 (31)	114 (27)	0.80 (0.61-1.04)	0.75 (0.56-1.00)
Less than weekly	153 (10)	34 (8)	0.75 (0.50-1.13)	0.61 (0.39-0.97)
At least weekly	240 (15)	57 (13)	0.76 (0.54-1.06)	0.53 (0.37-0.77)
Missing	8 (1)	5 (1)		
P_{trend}			0.95	0.08
Aspirin and NSAIDs				
Never	307 (19)	93 (22)	1 (Reference)	1 (Reference)
Occasionally	599 (38)	160 (38)	0.89 (0.66-1.20)	0.89 (0.64-1.24)
Less than weekly	249 (16)	55 (13)	0.75 (0.51-1.10)	0.72 (0.48-1.11)
At least weekly	422 (27)	117 (27)	0.82 (0.59-1.12)	0.59 (0.41-0.84)
Missing	3 (0.2)	1 (0.2)		
P_{trend}			0.47	<0.01
Acetaminophen				
Never	180 (12)	48 (12)	1 (Reference)	1 (Reference)
Occasionally	809 (51)	214 (50)	1.14 (0.79-1.63)	1.04 (0.71-1.54)
Less than weekly	413 (26)	96 (23)	1.11 (0.75-1.66)	1.00 (0.64-1.55)
At least weekly	177 (11)	67 (16)	1.65 (1.07-2.55)	1.03 (0.64-1.70)
Missing	1 (0.1)	1 (0)		
P_{trend}			0.09	0.84
ESCC				
Aspirin	1,580	309		
Never	638 (40)	125 (41)	1 (Reference)	1 (Reference)
Occasionally	553 (35)	111 (36)	1.03 (0.81-1.43)	1.09 (0.79-1.50)
Less than weekly	154 (10)	28 (9)	1.11 (0.73-1.82)	1.32 (0.79-2.23)
At least weekly	232 (15)	39 (13)	0.69 (0.48-1.07)	0.63 (0.40-0.98)

(*Continued on the following page*)

Table 2. Relative risks of esophageal cancers associated with use of aspirin, NSAIDs, or acetaminophen in last 5 y, minimally and fully adjusted (Cont'd)

	Controls	Cases	Minimally* adjusted	Fully† adjusted
	n (%)	*n* (%)	OR (95% CI)	OR (95% CI)
Missing	3 (0.2)	6 (2)		
P_{trend}			0.06	0.04
NSAIDs				
Never	691 (44)	159 (52)	1 (Reference)	1 (Reference)
Occasionally	488 (31)	83 (27)	0.82 (0.61-1.10)	0.89 (0.64-1.23)
Less than weekly	153 (10)	19 (6)	0.64 (0.38-1.07)	0.62 (0.34-1.11)
At least weekly	240 (15)	38 (12)	0.62 (0.42-0.91)	0.46 (0.30-0.73)
Missing	8 (1)	10 (3)		
P_{trend}			0.14	0.01
Aspirin and NSAIDs				
Never	307 (19)	71 (23)	1 (Reference)	1 (Reference)
Occasionally	599 (38)	123 (40)	0.99 (0.71-1.38)	1.03 (0.71-1.49)
Less than weekly	249 (16)	37 (12)	0.82 (0.53-1.28)	0.96 (0.59-1.59)
At least weekly	422 (27)	72 (23)	0.66 (0.45-0.95)	0.54 (0.36-0.83)
Missing	3 (0.2)	6 (2)		
P_{trend}			0.01	<0.01
Acetaminophen				
Never	180 (12)	26 (8)	1 (Reference)	1 (Reference)
Occasionally	809 (51)	176 (57)	1.57 (1.01-2.46)	1.67 (1.01-2.75)
Less than weekly	413 (26)	52 (17)	1.02 (0.61-1. 70)	1.15 (0.65-2.03)
At least weekly	177 (11)	50 (16)	1.73 (1.02-2.92)	1.26 (0.69-2.29)
Missing	1 (0.1)	5 (2)		
P_{trend}			0.57	0.10

*Adjusted for age (in years) and sex.
†Adjusted for age (in years), sex, state of residence, household income, cumulative smoking history, mean alcohol consumption, BMI and frequency of gastroesophageal reflux symptoms 10 y before diagnosis.

analysis of cancers of the esophagus and esophagogastric junction of different histologic types; the collection of detailed information about duration, recency, and patterns of intake of aspirin and NSAIDs; and the collection of information about exposure to acetaminophen (a widely used analgesic that shares many of the same clinical indications as aspirin and NSAIDs). Overall, we found that people who reported regular use of aspirin or NSAIDs had lower risks of all types of esophageal cancer than people who reported never using these medications, whereas people who regularly used acetaminophen had similar risks to people who did not use the medication.

Our study had several strengths. First, our population-based sample was large, enhancing precision of risk estimates and allowing us to perform stratified analyses to assess effect modification. Second, we had detailed measures of exposure based on personal interviews, including measures of different aspects of consumption such as pattern, duration, and recency of intake. Third, neither participants nor interviewers were informed of the study hypotheses, minimizing the possibility of biased recall. The lack of effect with acetaminophen for any of the cancers accords with earlier findings (45) and underscores our confidence that biased recall is unlikely to account for the observed effects.

A weakness of our study was the low rates of participation, raising concerns about possibly biased selection of cases and controls. The age and sex distribution of the cases who took part was similar to the annual distribution of cases notified to the Australian National Cancer Statistics Clearing House (2002); however, we have no further details about the characteristics of nonparticipating cases due to privacy laws. For selection bias to account for these findings, nonparticipating cases would need to have used aspirin and NSAIDs ~4-fold more often than participating cases, an unlikely explanation. A more likely source of bias might arise if the participating controls differed from the source population with respect to their prevalence of aspirin or NSAID use. Directly comparable data arising from the Australian population are scant; however, the prevalence of aspirin and NSAID use in our sample was similar to that reported in other Australian studies (52, 53). Other factors known to be associated with risks of EAC, notably symptoms of reflux and BMI, were similarly prevalent in our control series to other studies in the Australian population (54, 55). We therefore consider the likelihood of biased selection to be no greater than for previous studies.

Another likely source of error is random misclassification of aspirin, NSAID, or acetaminophen exposure. To assess this, we measured the repeatability of our questionnaire instrument among 85 participants after a mean interval of 4.4 months (56). Good to very good agreement was observed for frequency of intake of aspirin (weighed κ statistic, Kw = 0.53), NSAIDs (Kw = 0.72), and acetaminophen (Kw = 0.58), suggesting that random misclassification is unlikely to be a major source of error.

Our findings are in agreement with the majority of earlier studies. Among those studies that have examined the association between aspirin or NSAID and risk of esophageal cancer, all but two (7, 57) have reported 30% to 50% lower risks of esophageal cancers among people who used NSAIDs compared with never users (44, 45, 58-62). We are aware of only one previous study that has separately measured associations for adenocarcinomas of the esophagus and esophagogastric junction (45). That study reported an inverse association between NSAID

Table 3. Relative risks of esophageal cancers associated with use of aspirin and NSAIDs in the last 5 y, stratified by frequency of reflux symptoms

Frequency of reflux symptoms	Frequency of aspirin	EAC	EGJAC	ESCC
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Never	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	1.24 (0.70-2.20)	1.22 (0.76-1.94)	1.29 (0.81-2.05)
	<Weekly	1.19 (0.45-3.12)	1.28 (0.62-2.68)	1.29 (0.55-3.03)
	Weekly+	0.96 (0.46-2.00)	0.81 (0.41-1.59)	0.70 (0.36-1.35)
P_{trend}		0.66	0.45	0.12
<Weekly	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	0.50 (0.39-0.84)	0.85 (0.55-1.33)	0.81 (0.46-1.45)
	<Weekly	1.86 (1.04-3.13)	0.74 (0.37-1.49)	1.07 (0.46-2.46)
	Weekly+	0.52 (0.26-1.00)	0.76 (0.42-1.35)	0.58 (0.25-1.37)
P_{trend}		0.31	0.49	0.56
Weekly+	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	0.40 (0.21-0.73)	0.59 (0.33-1.06)	0.87 (0.41-1.85)
	<Weekly	0.44 (0.18-1.06)	0.72 (0.30-1.69)	1.90 (0.56-6.42)
	Weekly+	0.26 (0.12-0.55)	0.64 (0.33-1.25)	0.72 (0.29-1.78)
P_{trend}		0.32	0.49	0.82
$P_{interaction}$		0.01	0.50	0.91
Frequency of reflux symptoms	Frequency of NSAIDs	EAC	EGJAC	ESCC
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Never	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	1.43 (0.81-2.52)	1.10 (0.67-1.79)	0.99 (0.61-1.59)
	<Weekly	0.87 (0.28-2.67)	1.01 (0.45-2.27)	0.37 (0.11-1.31)
	Weekly+	0.78 (0.35-1.72)	0.78 (0.40-1.51)	0.53 (0.26-1.08)
P_{trend}		0.19	0.32	0.07
<Weekly	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	0.63 (0.38-1.04)	0.66 (0.42-1.05)	0.94 (0.53-1.68)
	<Weekly	0.63 (0.31-1.29)	0.40 (0.19-0.87)	0.65 (0.26-1.68)
	Weekly+	1.05 (0.59-1.87)	0.64 (0.36-1.16)	1.06 (0.51-2.21)
P_{trend}		0.11	0.93	0.77
Weekly+	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	0.45 (0.24-0.84)	0.46 (0.25-0.84)	0.60 (0.26-1.40)
	<Weekly	0.47 (0.18-1.26)	0.65 (0.27-1.59)	0.67 (0.20-2.23)
	Weekly+	0.41 (0.21-0.77)	0.32 (0.16-0.62)	0.18 (0.07-0.46)
P_{trend}		0.60	0.36	0.04
$P_{interaction}$		0.10	0.06	0.12

NOTE: Adjusted for age (in years), sex, state of residence, household income, cumulative smoking history, mean alcohol consumption, and BMI.

use and risk of both cancers, with slightly greater effects observed for EAC, similar to our study.

We found no evidence that longer durations of exposure to NSAIDs altered the risk of EAC, EGJAC, or ESCC. Of two studies that have assessed the duration of NSAIDs intake and risk of esophageal adenocarcinoma (10, 45), neither observed any association between duration and risk of adenocarcinoma. From five studies that evaluated association between exposure to NSAIDs and risk for any type of esophageal cancer (10, 45, 47, 58-61, 63), three reported lower risks among people with longer exposure to NSAIDs (59, 60, 63). The remaining studies had smaller numbers of participants with wide confidence intervals in the longer duration categories, masking possible associations. We found some evidence that recent use of NSAIDs conferred lower risks of EAC, EGJAC, and ESCC than distant use. Four studies have examined the effects of recency of exposure (10, 44, 45, 61), of which two observed greater reductions in risk associated with more recent use of NSAIDs.

In regard to the specificity of anti-inflammatory medications on EAC risk, all previous studies but one (62) have reported stronger associations with aspirin than NSAIDs. We also found larger reductions in EAC risk associated with aspirin than for other NSAIDs. One possible explanation for this difference in effect could be the stage of involvement of these medications in suppression of the COX pathway, as aspirin blocks this pathway upstream by irreversibly inactivating COX-1 enzyme, whereas other NSAIDs compete with arachidonic acid in binding to COX-1 enzyme. Thus, it is possible that the earlier blockade of the COX pathway may result in stronger risk reduction for cancer.

A particular aim of this investigation was to examine for the possibility that exposure to acid reflux, tobacco smoke, or excess body mass might modify the association between NSAIDs and esophageal cancer. We found consistently stronger risk reductions among those with frequent reflux symptoms, but no difference in associations according to smoking status or BMI. The only other study to have stratified by reflux history did not find stronger effects (45). Our finding might be explained by ''confounding by indication,'' which would occur if people with reflux symptoms avoided using aspirin or NSAIDs out of concern that these medications might exacerbate their symptoms. We found no evidence to support this explanation; indeed, control participants with regular symptoms of reflux were significantly more

Table 4. Relative risks of esophageal cancers associated with measures of NSAID use during the lifetime (interview data)

Measure	EAC	EGJAC	ESCC
Category	OR (95% CI)	OR (95% CI)	OR (95% CI)
Lifetime use of NSAIDs			
Never	1 (Reference)	1 (Reference)	1 (Reference)
Ever	0.40 (0.30-0.54)	0.47 (0.36-0.62)	0.35 (0.25-0.49)
Pattern of intake of NSAIDs			
Never	1 (Reference)	1 (Reference)	1 (Reference)
Occasional	0.49 (0.33-0.71)	0.64 (0.46-0.88)	0.53 (0.36-0.78)
Regular	0.34 (0.23-0.49)	0.35 (0.25-0.49)	0.21 (0.13-0.33)
P	<0.01	<0.01	<0.01
Recency of intake of NSAIDs			
Never	1 (Reference)	1 (Reference)	1 (Reference)
>5 y ago	0.54 (0.31-0.91)	0.62 (0.38-1.01)	0.48 (0.26-0.89)
1-5 y ago	0.37 (0.27-0.51)	0.45 (0.33-0.59)	0.33 (0.23-0.47)
P	<0.01	<0.01	<0.01
Duration of intake of NSAIDs			
Never	1 (Reference)	1 (Reference)	1 (Reference)
≤5 y	0.38 (0.27-0.55)	0.53 (0.39-0.72)	0.38 (0.26-0.55)
>5 y	0.42 (0.29-0.61)	0.40 (0.28-0.58)	0.32 (0.21-0.49)
P	<0.01	<0.01	<0.01
Regularity and duration			
Never	1 (Reference)	1 (Reference)	1 (Reference)
Occasional <5 y	0.47 (0.29-0.77)	0.70 (0.47-1.05)	0.66 (0.41-1.05)
Occasional ≥5 y	0.47 (0.30-0.74)	0.50 (0.33-0.76)	0.36 (0.21-0.61)
Regular <5 y	0.29 (0.18-0.48)	0.44 (0.29-0.66)	0.20 (0.11-0.36)
Regular ≥5 y	0.38 (0.23-0.62)	0.25 (0.14-0.43)	0.26 (0.14-0.47)
P_{trend}	<0.01	<0.01	<0.01

NOTE: Adjusted for age (in years), sex, state of residence, household income, cumulative smoking history, mean alcohol consumption, BMI, and frequency of gastroesophageal reflux symptoms 10 y before diagnosis.

likely to use aspirin or NSAIDs than controls who did not experience reflux. Similar findings have been observed elsewhere (10, 45). Alternatively, the stronger effect observed among people with reflux could reflect a biological mechanism. Gastroesophageal acid reflux is held to increase the risk of esophageal adenocarcinoma through a pathway of chronic inflammation and repair. Aspirin and NSAIDs suppress the COX and lipoxygenase pathways, which, in turn, leads to inhibition of prostaglandin synthesis, reducing prostaglandin and 15-lipoxygenase–induced immunosuppression and apoptosis (64-66). Thus, a plausible explanation for the association might be that people with the greatest ''inflammatory burden'' in the distal esophagus (that is, those with frequent symptoms of acid reflux) experience greater reductions in risks of EAC than people without inflammation because of the specificity of aspirin and NSAIDs for inhibiting the inflammatory pathways. Although our findings for aspirin support this explanation, the associations with NSAIDs among the frequent reflux group were not specific for EAC, being also observed for EGJAC and ESCC.

In summary, we have found significant reductions in risk of EAC, EGJAC, and ESCC associated with frequent use of aspirin and NSAIDs, but not acetaminophen. Use of aspirin and NSAIDs was associated with substantially lower risks of esophageal adenocarcinoma among people with frequent symptoms of reflux, but not among people who did not experience reflux symptoms. Although these findings are consistent with, and extend, previous reports from observational studies about the role of NSAIDs in inhibiting esophageal carcinogenesis, definitive evidence of benefit from these medications awaits the findings of randomized trials (24).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Appendix A. The Australian Cancer Study: Esophageal Cancer

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Acknowledgments

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We thank Harish Babu, M.D., for his assistance with pathology abstractions.

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