Short Communication

Nonsteroidal Anti-Inflammatory Drugs and Risk of Digestive Cancers at Sites Other Than the Large Bowel[1]

Patricia F. Coogan,[2] Lynn Rosenberg, Julie R. Palmer, Brian L. Strom, Ann G. Zauber, Paul D. Stolley, and Samuel Shapiro

Slone Epidemiology Unit, Boston University School of Medicine, Brookline, Massachusetts 02446 [P. F. C., L. R., J. R. P., S. S.]; Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, and Division of General Internal Medicine of the Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania [B.L.S.]; Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York [A. G. Z.]; and Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, Maryland [P. D. S.]

Abstract

Regular continuing nonsteroidal anti-inflammatory drug (NSAID) use has been associated with a reduction in risk of large bowel cancer in many studies, including our Case-Control Surveillance Study of medication use and cancer risk. We assessed the relation of NSAID use to the risk of digestive cancers at sites other than the large bowel in this database. Nurse-interviewers administered questionnaires to patients admitted to hospitals in four centers from 1977 to 1998. Cases comprised 1149 patients with cancers of the pancreas ($n = 504$), stomach ($n = 254$), esophagus ($n = 215$), gallbladder ($n = 125$), or liver ($n = 51$). Controls were 5952 patients admitted for trauma or acute infection. History of NSAID use was elicited by questions about indications for use. Multiple logistic regression models were used to calculate odds ratios (ORs) for categories of regular NSAID use (at least 4 days/week for at least 3 months) relative to never use. The OR for regular use initiated at least 1 year before admission and continuing into that year was reduced for stomach cancer (OR = 0.3; 95% confidence interval, 0.1–0.6) and was compatible with 1.0 for other sites. The ORs for regular continuing use of at least 5 years duration were <1.0 for cancers of the stomach, pancreas, esophagus, and gallbladder but were statistically significant only for stomach cancer. These data suggest that regular continuing NSAID use may be associated with reduced risk of stomach cancer. For the other sites, the data are consistent with no effect of NSAID use.

Introduction

Epidemiological (1–7) and experimental (8–13) studies have consistently found that the use of NSAIDs[3] is associated with a reduced risk of large bowel cancer. Some data suggest that NSAIDs may reduce the incidence of tumors of the esophagus (14, 15), pancreas (16), liver (17), and stomach (18) in rodents. Four epidemiological studies have reported a reduced risk of digestive tract cancers at sites other than the large bowel associated with NSAID use (19–22). The most recent study found that use of aspirin at least once per week for 6 or more months was associated with a halving in risk of esophageal cancer and noncardia gastric adenocarcinoma (22). In this study, we assessed the relation of NSAID use to the risk of digestive cancers at sites other than the large bowel. The data were derived from our hospital-based Case-Control Surveillance Study (23). We have previously reported a 50% reduction in risk of large bowel cancer among regular, sustained users of NSAIDs compared with nonusers based on these data (1).

Materials and Methods

Data Collection. The data were collected from 1977 to 1998 from English-speaking patients <70 years of age in hospitals in Baltimore, Boston, New York, and Philadelphia. Nurse-interviewers administered standard questionnaires to patients admitted for recently diagnosed malignant and nonmalignant disorders; 95% of patients approached for an interview participated (including cases and controls). Information was obtained on demographic factors, medical history, history of cancer in parents and siblings, cigarette smoking, and alcohol consumption. Histories of medication use were elicited by questions about 42 indications for use, which included arthritis and other conditions for which NSAIDs are used. For each episode of use, the drug name, the date started, and the duration and frequency of use were recorded. Details of the diagnosis were abstracted from the discharge summaries and pathology reports. The study was approved by the institutional review board of each participating institution.

Cases. The case group comprised 1149 patients with primary cancers of the digestive tract at sites other than the large bowel diagnosed no more than 1 year before admission and who had no other cancer. The numbers of patients studied with cancer at respective sites are as follows: pancreas, 504; stomach, 254; esophagus, 215; gallbladder, 125; and liver, 51. Cases were confirmed by review of pathology reports.

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[2] To whom requests for reprints should be addressed, at Slone Epidemiology Unit, Boston University School of Medicine, 1371 Beacon Street, Brookline, MA 02446; Phone: (617) 734-6006; Fax: (617) 738-5119; E-mail: pcoogan@slone.bu.edu.

[3] The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; CI, confidence interval.

Table 1 Characteristics of cases and controls (%)[a]

	Esophagus (n = 215)	Stomach (n = 254)	Pancreas (n = 504)	Gallbladder (n = 125)	Liver (n = 51)	Controls (n = 595)
Male	73.5	48.0	53.6	45.6	51.0	47.8
Female	26.5	52.0	46.4	54.4	49.0	52.2
Age						
<50	23.8	25.2	20.3	23.2	25.5	61.6
50–59	34.0	31.9	34.1	35.2	35.3	20.9
60–69	42.3	42.9	45.6	41.6	39.2	17.6
Race						
White	73.0	75.6	87.3	89.6	78.4	74.3
Black	24.2	20.9	11.5	7.2	17.6	22.6
Other	2.8	3.5	1.2	3.2	3.9	3.2
Education						
<12	34.4	22.8	17.5	15.2	19.6	18.4
12	28.4	39.0	36.2	40.8	43.1	32.4
≥13	36.7	37.8	46.1	44.0	37.3	48.6
Religion						
Jewish	3.3	13.0	14.7	8.0	7.8	9.8
Catholic	37.2	44.5	39.9	47.2	37.3	42.6
Protestant	47.0	29.1	35.3	36.0	33.3	37.4
Other	2.3	3.9	1.6	2.4	0	4.7
Alcohol consumption						
Current drinker	68.4	63.4	68.3	60.0	56.9	74.7
Ex-drinker	15.8	11.0	11.9	6.4	17.6	7.2
Never drank	10.7	24.0	18.5	31.2	21.6	17.1
Cigarette smoking						
Current smoker	44.2	34.4	33.0	27.2	35.2	39.7
Ex-smoker	37.7	26.0	34.5	34.4	41.2	23.2
Never smoked	18.1	38.6	31.5	38.4	21.6	36.1

[a] May not sum to 100% because of exclusion of subjects with missing values.

Controls. The controls were 5952 patients admitted for the following conditions with no history of cancer: traumatic injury, 3486; appendicitis, 575; or other acute infections, 1891. The age- and sex-adjusted prevalence of regular NSAID use initiated at least 1 year before admission and continuing into that year was 7.2% in trauma patients and 6.1% in patients with appendicitis or other acute infections. The prevalence of use varied by study center (highest in Philadelphia and lowest in New York), year of interview (higher in later years), age (higher in older patients), race (higher among white patients), alcohol consumption (higher among ex-drinkers), and cigarette smoking (higher among heavy smokers).

Analysis. NSAID use was defined as use of salicylates (*e.g.*, aspirin), indoles (*e.g.*, indomethacin), propionic acids (*e.g.*, ibuprofen), fenamates (*e.g.*, mefenamic acid), and/or oxicams (*e.g.*, piroxicam). We focused on regular use, defined as use for at least 4 days/week for at least 3 months, that had been initiated at least 1 year before admission. Because our work and that of others indicate that recent use affects risk of colorectal cancer, we divided regular use initiated at least 1 year before admission into continuing use (continued into the year before admission) and discontinued use (last use at least 1 year before admission).

We used multivariate logistic regression to calculate ORs for categories of NSAID use relative to never use (24). All models included terms for age, sex, race, religion, family history of digestive cancer in a parent or sibling, years of education, geographic area, cigarette smoking, alcohol consumption, and interview year. For pancreatic cancer, we also included terms for drug-treated diabetes and body mass index [wt(kg)/ht^2(m)]. A continuous term was used to test for trend across the duration of use among regular continuing NSAID users.

Results

The study population was evenly distributed among men and women with the exception of esophageal cancer (Table 1). Most cases were >50 years of age. The study population was predominantly white, had at least a high school education, and was Catholic or Protestant. Most patients currently drank alcohol and were current or ex-smokers.

The ORs for NSAID use initiated at least 1 year before admission and continuing into that year (continuing use) were compatible with 1.0 for cancers of the pancreas, esophagus, gallbladder, and liver (Table 2). The OR for stomach cancer was significantly reduced (OR = 0.3; 95% CI, 0.1–0.6). Some NSAID use among the cases of stomach cancer may have been initiated in response to long-standing symptoms. Therefore, we assessed regular continuing use that had been initiated at least 3 years before admission; based on 6 case users and 269 control users, the OR was 0.3 (95% CI, 0.1–0.8). Aspirin accounted for most NSAID use: 7 of 8 users among the cases of stomach cancer and 267 of 403 users among the controls used aspirin, yielding an OR of 0.4 (95% CI, 0.2–0.8). The adjusted ORs for stomach cancer for regular continuing NSAID use were reduced in both sexes (0.3 in men and 0.2 in women) and in all geographic areas (0.2 in New York, 0.2 in Philadelphia, 0.5 in Baltimore, and no exposed cases occurred in Boston).

For all sites, the ORs for regular use that ended at least 1 year before admission (discontinued use) were compatible with 1.0, as were the ORs for nonregular use (Table 2).

For all sites, ORs for 5 or more years of use were lower than those for <5 years of use (Table 3). However, with the exception of stomach cancer, none of the estimates were statistically significant. There were too few cases of liver cancer to evaluate duration.

Table 2 NSAID use in cases of pancreatic cancer (n = 504), stomach cancer (n = 254), esophageal cancer (n = 215), gallbladder cancer (n = 125), liver cancer (n = 51), and controls (n = 5952)

Group	Total	NSAID use[a]			
		Never used	Regular use initiated ≥1 year previously		Nonregular use
			Continuing[b]	Discontinued[c]	
Controls	5833	2339	403	88	3003
Pancreas	491	207	41	7	236
OR[d]		1.0[e]	0.8	0.6	1.0
95% CI			0.5–1.1	0.3–1.5	0.8–1.3
Stomach	250	123	8	3	116
OR		1.0[e]	0.3	0.6	0.7
95% CI			0.1–0.6	0.2–1.8	0.5–0.9
Esophagus	207	93	19	8	87
OR		1.0[e]	0.8	2.1	0.9
95% CI			0.5–1.4	0.9–4.8	0.6–1.2
Gallbladder	125	57	9	1	58
OR		1.0[e]	0.5		0.9
95% CI			0.3–1.1		0.6–1.3
Liver	49	15	4	0	30
OR		1.0[e]	0.9		1.6
95% CI			0.3–2.9		0.8–3.1

[a] Analysis excludes 22 total cases and 102 controls who initiated regular use within 1 year of admission and 5 total cases and 17 controls with unknown NSAID use.
[b] Use continuing into the year before admission.
[c] Use discontinued at least 1 year before admission.
[d] Adjusted for age, sex, interview year, center, race, religion, cigarettes, family history of digestive cancer, education, and alcohol consumption.
[e] Reference category.

Table 3 Duration of regular continuing NSAID use among cases of pancreatic cancer (n = 504), stomach cancer (n = 254), esophageal cancer (n = 215), gallbladder cancer (n = 125), and controls (n = 5952)

Group	Never used	Duration of NSAID use (years)	
		<5	5+
Controls	2339	198	188
Cancers			
Pancreas	207	22	18
OR[a]	1.0[b]	0.8	0.6
95% CI		0.5–1.4	0.4–1.1
Stomach	123	5	3
OR	1.0[b]	0.4	0.2
95% CI		0.1–0.9	0.1–0.7
Esophagus	93	13	6
OR	1.0[b]	1.2	0.4
95% CI		0.7–2.4	0.2–1.1
Gallbladder	57	6	3
OR	1.0[b]	0.8	0.3
95% CI		1.3–2.0	0.1–1.1

[a] Adjusted for age, sex, interview year, center, race, religion, cigarette smoking, family history of digestive cancer, education, and alcohol consumption.
[b] Reference category.

Discussion

In an earlier study based on data from our Case-Control Surveillance Study, regular continuing NSAID use was associated with a 50% reduction in the incidence of cancer of the large bowel (1). The present report, based on data from the same study, suggests that continuing regular use may also be associated with a reduction in the incidence of stomach cancer. The odds ratios were compatible with 1.0 for cancers of the pancreas, esophagus, gallbladder, and liver. For cancers of the pancreas, stomach, esophagus, and gallbladder, ORs for ≥5 years of regular use were lower than those for <5 years of use, but numbers of exposed cases were small, and only the OR for stomach cancer was statistically significant.

The major risk factors for digestive cancers were controlled in the analyses, and multivariate estimates differed little from those adjusted only for age and sex. Selection bias is not a major concern. The controls were selected to have diagnoses that are unrelated to NSAID use and for which admission to a hospital is obligatory; there is no evidence linking the use of NSAIDs to the incidence of trauma or acute infection. Moreover, most of these drugs are obtained over-the-counter and do not require contact with the medical care system. ORs obtained with trauma controls alone or with infection controls alone did not vary materially for any site (data not shown). The possibility that the association observed for stomach cancer is accounted for by some cases having given up NSAID use because of symptoms is not supported by the data in that there was no excess of cases in the category of regular discontinued NSAID use. Because most NSAID use is sporadic, there may have been misclassification. If random, as we would expect, such misclassification would most likely have diluted any real associations. Changes in diagnostic methods over the 21 years of data collection are unlikely to have introduced a bias because methods are probably independent of NSAID use.

Small numbers of cases who were regular continuing NSAID users limited detailed assessment of the effect of duration. In addition, cancer cell type and anatomical location were not assessed. Information on cancer cell type could have affected our results, but Farrow *et al.* (22) found reductions for both esophageal squamous cell and adenocarcinoma. However, they only found a reduction for stomach adenocarcinoma occurring at sites other than the cardia. If risk differed by tumor site within the stomach in our data, the association would have been diluted.

Few epidemiological studies have evaluated NSAID use and gastrointestinal cancers at sites other than the large bowel. In a follow-up study of Swedish patients with rheumatoid arthritis, standardized incidence ratios were significantly reduced (40–60%) for cancers of the colon, stomach, and liver and were slightly but not significantly reduced for cancers of

the rectum and pancreas; the risk of cancer of the esophagus was slightly increased (20). In the American Cancer Society follow-up study, death rates from cancers of the esophagus and stomach were decreased by 50% among subjects who had used aspirin at least 16 times in the month before entry into the study compared with nonusers (19). In the National Health and Nutrition Examination Study I cohort, patients who had used aspirin in the month prior to interview had a significant 80% reduction in the risk of esophageal cancer, based on four case users of aspirin (21). Another analysis of the National Health and Nutrition Examination Study I cohort found no reduction in risk among aspirin users for stomach cancer and a slight but nonsignificant reduction for pancreatic cancer (25). In these data, there was no marked reduction for colorectal cancer. The only large study to date (in terms of numbers of exposed cases) is a population-based, case-control study of esophageal and stomach cancers (22). The ORs for subjects who had used aspirin at least once per week for at least 6 months compared with nonusers were significantly reduced by ~50% for esophageal squamous cell carcinoma, esophageal adenocarcinoma, and gastric adenocarcinoma at sites other than the cardia. Reductions in risk were confined to current users only, with the exception of esophageal squamous cell carcinoma for which the OR was also reduced among former users.

Experimental data consistently indicate that NSAIDs reduce the incidence, multiplicity, and size of chemically induced colorectal tumors in rodents (8–13). Several mechanisms have been suggested. NSAIDs inhibit the expression of cyclooxygenases and the synthesis of prostaglandins (26), which may play a role in the proliferation and metastasis of malignant cells (27–29). Cyclooxygenases and prostaglandins are expressed by various tumors, including those of the colon (30), stomach (31, 32), liver (33), and esophagus (27, 34). In addition, studies showing that NSAIDs can induce apoptosis in colon cancer cell lines that do not express cyclooxygenases or prostaglandins suggest that there is a pathway that is independent of both (29).

There are reports of reduced incidence of chemically induced cancers of the esophagus (14, 15), pancreas (16), liver (17), and stomach (18) in rodents that were administered various NSAIDs, including indomethacin, aspirin, and sulindac. The newly developed NSAIDs that specifically inhibit cyclooxygenase-2 have been reported to suppress the proliferation of gastric (35) and esophageal (34, 36) cancer cell lines and to inhibit the growth of human gastric cancer xenografts in nude mice (37). However, other data have shown an increased incidence of tumors of the upper gastrointestinal tract (38, 39), small intestine (40), and liver (40) in rats that were administered flurbiprofen or indomethacin. Thus, the animal evidence regarding gastrointestinal tumors at sites other than the large bowel is inconsistent.

Gastrointestinal cancers are among the most lethal malignancies (41). Although there is suggestive data from our study and others, particularly on stomach and esophageal cancers, there are virtually no data on cancers of the gallbladder, pancreas, and liver. Thus, additional studies of the chemopreventive potential of NSAIDs are warranted. It is unlikely that randomized trials with digestive cancers as the outcome will be conducted because the size of the population and length of follow-up required make them impractical. However, additional observational studies complemented by the elucidation of the chemopreventive mechanisms of NSAIDs will be useful in establishing whether NSAID use reduces the risk of gastrointestinal cancers at sites other than the large bowel.

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