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Original Contribution

Use of Nonsteroidal Antiinflammatory Drugs and Distal Large Bowel Cancer in Whites and African Americans

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Despite the belief that the etiology of and risk factors for rectal cancer might differ from those for colon cancer, relatively few studies have examined rectal cancer in relation to use of nonsteroidal antiinflammatory drugs (NSAIDs). The authors evaluated the association between NSAIDs and distal large bowel cancer in African Americans and whites, using data from a population-based case-control study of 1,057 incident cases of adenocarcinoma of the sigmoid colon, rectosigmoid junction, and rectum and 1,019 controls from North Carolina (2001–2006). NSAID use was inversely associated with distal large bowel cancer in whites (odds ratio (OR) = 0.60, 95% confidence interval (CI): 0.46, 0.79). The inverse association was evident for all types of NSAIDs but was slightly stronger with prescription NSAIDs, particularly selective cyclooxygenase 2 inhibitors (OR = 0.38, 95% CI: 0.25, 0.56). Compared with whites, a relatively weak inverse association was found in African Americans (OR = 0.87, 95% CI: 0.55, 1.40), although odds ratio heterogeneity by race could not be confirmed ($P = 0.21$). In addition, the strength of the association with NSAIDs varied by tumor location, suggesting more potent effects for rectal and rectosigmoid cancers than for sigmoid cancer. The chemopreventive potential of NSAIDs might differ by population and by tumor characteristics.

anti-inflammatory agents, non-steroidal; colonic neoplasms; colorectal neoplasms; intestine, large; population groups; rectal neoplasms

Abbreviations: CI, confidence interval; COX-2, cyclooxygenase 2; NSAID, nonsteroidal antiinflammatory drug; OR, odds ratio.

The inverse association between nonsteroidal antiinflammatory drugs (NSAIDs) and colorectal cancer has been well documented (1–13); however, relatively few studies have focused specifically on rectal cancer, despite the belief that the etiology of and risk factors for rectal cancer might differ from those for colon cancer. The proximal and distal parts of the large bowel have different embryonic origins, as well as physiologic differences in bile salt concentration and bacterial populations (14). Different genetic aberrations have been associated with cancers arising at different subsites of the large bowel (15). Moreover, although the anatomic distribution of colorectal cancer has been shown to differ between African Americans and whites (16, 17), there have been few studies of risk factors for colorectal cancer in African Americans. We therefore examined the association between NSAIDs and adenocarcinoma of the distal large bowel (i.e., sigmoid colon, rectosigmoid junction, and rectum) in African Americans and whites.

MATERIALS AND METHODS

We used data from phase 2 of the North Carolina Colon Cancer Study. North Carolina Colon Cancer Study II is a population-based case-control study in 33 counties in the central and eastern part of North Carolina. Between October 1, 2001, and May 31, 2006, patients with a first diagnosis of invasive adenocarcinoma of the sigmoid colon, rectosigmoid junction, or rectum were identified through the rapid ascertainment system of the North Carolina Central Cancer Registry. The procedure for case ascertainment and its

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effectiveness has been described in detail elsewhere (18). Cases were eligible for the study if they were residents of the selected counties, aged 40–80 years, and African American or white; if they had a North Carolina driver's license or identification card; and if they were able to complete an interview in English. A total of 1,831 potentially eligible cases were identified; of these, 57 (3%) were excluded for physician refusal and 357 (19%) were subsequently found to be ineligible. Of the remaining 1,417 eligible cases, 118 (8%) could not be contacted, 242 (17%) refused to participate, and 1,057 (75%) completed an in-person interview.

Controls were randomly selected from North Carolina Division of Motor Vehicle records, based on sampling probabilities within blocks defined by 5-year age group, sex, and race, using the technique of randomized recruitment (19). Initially, 2,345 subjects who were free of cancer were identified as potentially eligible controls, but 518 (22%) were later determined to be ineligible. Of the 1,827 eligible controls, 325 (18%) could not be contacted and 483 (26%) refused to participate. A total of 1,019 (56% of eligible controls) completed an interview. The final data set for analysis included 1,057 cases and 1,019 controls.

The study was approved by the institutional review board at the University of North Carolina School of Medicine, and all subjects provided written informed consent.

Data collection

In-person interviews were conducted in each subject's home or at another convenient location by trained nurse interviewers using a standard questionnaire. The questionnaire included information regarding demographic characteristics, socioeconomic indicators (such as years of education, income level, and occupation history), medication use, medical history, family history of cancer, smoking habits, and weight 1 year prior to diagnosis (for cases) or interview (for controls). Current weight and height at the time of interview were also measured. Subjects were asked about type and duration of various activities engaged in on typical week/working and weekend/nonworking days. Then the energy expenditure involved in each activity was retrieved from the Compendium of Physical Activities (20). Metabolic equivalents were calculated by multiplying the number of hours spent in these activities, the number of metabolic equivalents for the category, and body weight (20). Dietary intake was assessed with the Diet History Questionnaire, which was developed and evaluated at the National Cancer Institute (21). Cancer stage (local, regional, distant, or unknown), tumor location (sigmoid colon, rectosigmoid junction, or rectum), and other diagnosis-related data were available from the Central Cancer Registry.

Assessment of NSAID use

We assessed use of NSAIDs during the past 5 years (for controls) and for the 5 years prior to diagnosis (for cases). For the purpose of data collection, NSAIDs were classified into 4 categories: 1) over-the-counter aspirin (e.g, Bufferin, Anacin, Excedrin, BC Powder or Goody's Powder, Alka-Seltzer, or generic equivalents); 2) over-the-counter nonaspirin NSAID pain medications (e.g., Advil, Motrin, Aleve, or generic equivalents); 3) prescription selective cyclooxygenase 2 (COX-2) inhibitors (e.g., Vioxx, Celebrex, or generic equivalents); and 4) prescription nonselective NSAID pain medications (e.g., Motrin, Daypro, Naprosyn, Feldene, or generic equivalents). For each NSAID category, respondents who reported ever use of NSAIDs were asked about frequency of use, duration of use, and use 1 year prior to diagnosis (for cases) or interview (for controls). Participants were queried separately about their use of acetaminophen or Tylenol, which is an antipyretic and analgesic with very weak antiinflammatory activity (22). Acetaminophen was not classified as an NSAID in these analyses. (The names and locations of the manufacturers of all brand-name products in this paper are given in the Appendix Table.)

Statistical analysis

We stratified study participants by race to compare distributions of selected characteristics between cases and controls. Odds ratios and 95% confidence intervals for the association between NSAID use and distal large bowel cancer were estimated from unconditional logistic regression models in all subjects and in race-specific models. For all analyses, the referent group consisted of subjects who reported never use of any NSAIDs in the past 5 years. Subjects who had used any of the NSAIDs queried about in the past 5 years were defined as ever users. We also examined recent use (defined as use of any NSAIDs in the past year or none) and average monthly dose in the past 5 years (categorized as use <15 times per month or ≥ 15 times per month over the past 5 years). In addition, we assessed use of different types of NSAIDs (over-the-counter aspirin only, over-the-counter nonaspirin NSAIDs only, prescription selective COX-2 inhibitors, or other prescription nonselective NSAIDs) in relation to distal large bowel cancer, with participants classified as regular users of specific types of NSAIDs if they had taken them at least 3 times per week for 3 months or more.

All logistic regression models included age (continuous), sex, race, and an offset term to adjust for sampling probability. Other potential covariates assessed for inclusion in multivariable models were: years of education (<12, 12–15, or ≥ 16 years), annual household income ($<$\$15,000, \$15,000–\$24,999, \$25,000–\$49,999, or $\geq$\$50,000), smoking status (current, past, or never smoker) at the time of diagnosis (for cases) or interview (for controls), family history of colorectal cancer (having had at least 1 first-degree relative with colorectal cancer or not), comorbidity (having at least 1 of the following conditions: arthritis, hypertension, heart attack, or diabetes mellitus) prior to diagnosis (for cases) or at the time of interview (for controls), body mass index (weight (kg)/height $(m)^2$) 1 year prior (<25 (normal or underweight), 25–29.9 (overweight), or ≥ 30 (obese)), physical activity 1 year prior (tertiles based on the distribution among controls), ever use of calcium supplements during the past 5 years (yes or no), and dietary intakes of energy and fat during the past year (tertiles based on the distributions among controls). To determine which covariates should be entered into the final multivariable models, we constructed full models by race with all potential confounders and assessed the change in race-specific β coefficients for ever

Table 1. Characteristics of Distal Large Bowel Cancer Cases and Controls, by Race, North Carolina Colon Cancer Study II, 2001–2006

	Whites					African Americans				
	Cases		Controls		*P* Value[a]	Cases		Controls		*P* Value[a]
	No.	%	No.	%		No.	%	No.	%	
Total	790		841			267		178		
Location of tumor										
Sigmoid colon	304	38.5				100	37.5			0.014[b]
Rectosigmoid junction	143	18.1				30	11.2			
Rectum	343	43.4				137	51.3			
Age, years										
40–49	111	14.1	80	9.5	0.003	40	15.0	21	11.8	0.35
50–59	212	26.8	195	23.2		77	28.8	45	25.3	
60–69	230	29.1	268	31.9		89	33.3	59	33.2	
70–79	237	30	298	35.4		61	22.9	53	29.8	
Median age, years	60		64			59		63		
Sex										
Male	457	57.9	509	60.5	0.272	140	52.4	92	51.7	0.877
Female	333	42.2	332	39.5		127	47.6	86	48.3	
Years of education										
<12	124	16.2	81	9.8	0.000	77	30.1	40	23.1	0.28
12–15	420	55.0	403	48.9		132	51.6	97	56.1	
≥16	220	28.8	340	41.3		47	18.4	36	20.8	
Annual household income										
≤$15,000	93	12.8	79	10.1	0.158	85	37.6	60	38.7	0.976
$15,000–$24,999	123	16.9	120	15.4		42	18.6	26	16.8	
$25,000–$49,999	192	26.5	200	25.6		47	20.8	33	21.3	
≥$50,000	318	43.8	382	48.9		52	23.0	36	23.2	
Smoking status										
Never smoker	285	37.4	309	37.8	0.509	98	38.3	75	43.4	0.173
Past smoker	357	46.8	396	48.4		94	36.7	68	39.3	
Current smoker	121	15.9	113	13.8		64	25.0	30	17.3	
Family history of colorectal cancer[c]										
Yes	103	18.5	93	15.0	0.103	33	18.3	11	8.6	0.016
No	454	81.5	529	85.1		147	81.7	117	91.4	
Underwent sigmoidoscopy or colonoscopy in the past 10 years										
Yes	169	22.1	533	64.7	0.000	50	19.8	91	54.2	0.000
No	595	77.9	291	35.3		202	80.2	77	45.8	

Table continues

use versus never use of any NSAIDs in relation to distal large bowel cancer when covariates were removed. Only body mass index 1 year prior and calcium supplement use resulted in more than a 10% change in the β coefficient among whites, whereas physical activity 1 year prior, total energy intake, and dietary fat intake, as well as body mass index 1 year prior and calcium supplement use, were found to yield more than a 10% change in the β coefficient among African Americans. For consistency, we included the same set of covariates (age, sex, race, sampling probability, physical activity 1 year prior, ever use of calcium supplements, total energy intake, dietary fat intake, and body mass index 1 year prior) in the final multivariable models for all subjects and in race-specific models.

Likelihood ratio tests comparing models with and without multiplicative interaction terms between NSAID use and race were used to assess odds ratio modification (statistical interaction) in the association. We used multinomial logistic regression to simultaneously estimate odds ratios and 95% confidence intervals for sigmoid, rectosigmoid, and rectal cancers in comparison with controls. Wald statistics were used to assess statistical heterogeneity among the 3 subsite-specific effect estimates. Analyses were performed using

Table 1. Continued

	Whites					African Americans				
	Cases		Controls		*P* Value[a]	Cases		Controls		*P* Value[a]
	No.	%	No.	%		No.	%	No.	%	
Comorbid condition[d]										
Yes	525	84.4	607	85.6	0.537	198	95.2	146	94.2	0.673
No	97	15.6	102	14.4		10	4.8	9	5.8	
Body mass index[e]										
<25	177	24.1	254	31.7	0.000	49	20.3	34	20.4	0.474
25–29.9	278	37.8	325	40.5		75	31.1	61	36.5	
≥30	281	38.2	223	27.8		117	48.6	72	43.1	
Median body mass index	28.1		26.9			29.8		29.1		
Calcium supplement use										
Yes	264	34.8	375	45.7	0.000	69	27.1	55	32.0	0.272
No	495	65.2	446	54.3		186	72.9	117	68.0	
Physical activity level, average metabolic equivalent-minutes/day[f]										
First tertile (<1,882)	243	33.2	260	32.8	0.208	93	38.8	57	34.6	0.041
Second tertile (1,882–2,077)	212	29.0	260	32.8		61	25.4	61	37.0	
Third tertile (≥2,078)	277	37.8	272	34.3		86	35.8	47	28.5	
Median physical activity level	1,968.6		1,974			1,938.9		1,920.9		
Total energy intake, kcal/day[f]										
First tertile (<1,711)	220	28.3	277	33.1	0.004	72	28.2	60	34.7	0.117
Second tertile (1,711–2,413)	246	31.7	292	34.8		57	22.4	45	26.0	
Third tertile (≥2,414)	311	40.0	269	32.1		126	49.4	68	39.3	
Median energy intake	2,142.1		1,992.3			2,405.3		2,139.6		
Dietary fat intake, g/day[f]										
First tertile (<64)	203	26.1	273	32.6	0.000	70	27.5	57	33.0	0.457
Second tertile (64–97)	259	33.3	302	36.0		72	28.2	47	27.2	
Third tertile (≥98)	315	40.5	263	31.4		113	44.3	69	40.0	
Median dietary fat intake	86.7		78.9			86.7		80.0		

[a] *P* values were based on chi-square tests.
[b] *P* value for comparison between race and tumor location.
[c] Having a first-degree relative diagnosed with colorectal cancer.
[d] Having at least 1 of the following conditions: arthritis, hypertension, heart attack or heart problems, or diabetes mellitus.
[e] Weight (kg)/height $(m)^2$.
[f] Tertiles were based on the distribution among controls.

Stata 9.2 (Stata Corporation, College Station, Texas), and all statistical tests were 2-sided, with an α level of 0.05.

RESULTS

The study consisted of 1,631 white participants (790 cases and 841 controls) and 445 African-American participants (267 cases and 178 controls) (Table 1). The proportion of patients with rectal cancer was higher among African-American cases than among white cases (51.3% vs. 43.4%; $P = 0.014$). In both racial groups, cases were younger, were less educated, and more often reported having a family member with colorectal cancer than controls, but far fewer had obtained colorectal cancer screening. Cases also had higher intakes of energy and dietary fat and tended to have higher body mass indexes. A greater percentage of controls than of cases reported ever use of calcium supplements in the past 5 years, whereas subjects who reported current smoking were less common among controls than among cases, particularly for African Americans (25% in cases vs. 17% in controls).

Approximately 76% of cases and 83% of controls reported ever use of any NSAIDs in the past 5 years (Table 2). Overall, compared with never use, ever use of NSAIDs was inversely associated with distal large bowel cancer (multivariable odds ratio (OR) = 0.66, 95% confidence interval (CI): 0.52, 0.83) after adjustment for age, sex, race, body mass index, level of physical activity, ever use of calcium supplements, total energy intake, dietary fat intake, and sampling probability. The strength of the association with ever use of NSAIDs was similar for recent use and did not substantially increase with a higher average monthly

use of NSAIDs in the past 5 years. All categories of NSAIDs were inversely associated with distal large bowel cancer, but the inverse associations were slightly stronger for prescription NSAIDs than for nonprescription NSAIDs, particularly selective COX-2 inhibitors (multivariable OR = 0.44, 95% CI: 0.31, 0.63).

When results were stratified by race, the association between NSAIDs and distal large bowel cancer remained strongly protective in whites, but there was less evidence of an association among African Americans (for ever use vs. never use: OR = 0.87, 95% CI: 0.55, 1.40) (Table 3). Over-the-counter aspirin and prescription COX-2 inhibitors were inversely associated with distal large bowel cancer among African Americans, but the magnitudes of the associations were weaker than those for whites (among African Americans, OR = 0.87 (95% CI: 0.50, 1.52) for aspirin and OR = 0.69 (95% CI: 0.29, 1.61) for COX-2 inhibitors). The likelihood ratio test *P* value comparing models with and without multiplicative interaction terms between race and ever use of any NSAIDs was 0.21.

We also examined the possibility that the association with NSAID use might differ by tumor location (Table 4). In general, NSAID use was inversely associated with all subsites of distal large bowel cancer; however, the inverse association for NSAID use tended to be more pronounced for rectal and rectosigmoid cancer than for sigmoid cancer. The multivariable odds ratios associated with ever use of NSAIDs were 0.60 (95% CI: 0.44, 0.81) for rectal cancer and 0.50 (95% CI: 0.33, 0.74) for rectosigmoid cancer, while the multivariable odds ratio for sigmoid cancer was 0.81 (95% CI: 0.60, 1.09) (Wald test for equality of coefficients: $P = 0.05$). A weaker association with sigmoid cancer than with rectal and rectosigmoid cancer was evident in both African Americans and whites (data not shown).

DISCUSSION

We found that NSAID use was inversely associated with distal large bowel cancer in whites. Among whites, the inverse association was evident for all types of NSAIDs evaluated but was slightly stronger with prescription NSAIDs, particularly with selective COX-2 inhibitors, than with nonprescription NSAIDs. The strengths of the associations among whites were similar for more recent use, higher average monthly use, and ever use. On the other hand, we observed a relatively weak association with NSAID use in African Americans, although the test for odds ratio heterogeneity between racial groups was not statistically significant ($P = 0.21$). We also observed that inverse associations with NSAID use were stronger for rectal and rectosigmoid cancer than for sigmoid cancer.

The exact mechanism of the association between NSAIDs and colorectal cancer remains unclear; however, antineoplastic properties of NSAIDs are largely attributed to inhibition of cyclooxygenase enzymes, particularly COX-2 (23). COX-2 is an inducible form of cyclooxygenase that is expressed in response to proinflammatory and mitogenic stimuli (24, 25). Several investigators have reported higher expression of COX-2 in colon cancer samples than in normal colon tissue (26). NSAIDs suppress COX-2-induced angiogenesis and resistance to apoptosis in experimental studies (27), and aspirin has been associated with a reduced risk of colorectal adenoma, a precursor to colorectal cancer in randomized clinical studies (28, 29).

Our results in whites are consistent with previous epidemiologic research that has shown that persons taking aspirin/NSAIDs regularly (2–3 times per week) had a lower risk of colorectal cancer than those who were not (1–13). It has also been suggested that protection from aspirin increases with a higher dosage (30). Negative findings from 2 randomized clinical trials in which participants were treated with 325 mg (31) or 100 mg (32) of aspirin on alternate days were partly attributed to the low doses of NSAIDs used in the interventions, which were lower than the dose used to define "regular users" in most observational epidemiologic studies (31). For each category of NSAIDs, we defined regular users as those who used the corresponding NSAIDs at least 3 times per week, and we assessed different types of NSAIDs in relation to distal large bowel cancer. We observed a slightly stronger association with prescription NSAIDs relative to over-the-counter NSAIDs. Given that the dose of prescription NSAIDs is generally higher than the dose of nonprescription NSAIDs (33), our result is consistent with the previous findings that higher doses of NSAIDs may be more effective in preventing colorectal cancer.

Sansbury et al. (34) previously reported inverse associations of NSAIDs with colon cancer in both African Americans and whites in the same study counties during 1996–2000. In contrast, in the present study, we found a relatively weak inverse association between NSAIDs and distal large bowel cancer in African Americans compared with whites, although race-specific effect estimates did not provide clear evidence of odds ratio heterogeneity between the 2 racial groups.

Several explanations are possible for the weak association between NSAIDs and distal large bowel cancer in African Americans in the current study. First, there could be misclassification due to differential patterns of NSAID use between African Americans and whites. It is possible that African-American users might have taken NSAIDs less frequently than white NSAID users. To rule out this possibility, we compared the average monthly dose over the past 5 years between African-American and white NSAID users. Whereas African-American NSAID users, in fact, had a significantly lower average monthly dose (mean = 14.1 uses) compared with white NSAID users (mean = 20.5 uses; $P < 0.01$), the racial difference in average monthly dose would not fully explain a weaker association in African Americans compared with whites, since there was no inverse association even among African Americans with average monthly use of 15 or higher in the past 5 years.

We also hypothesized that the specific types of NSAIDs used and the resulting potency or dose of NSAIDs used might have differed by race. Since data on the specific types of NSAIDs taken were not collected for the current study, we indirectly tested this hypothesis using data from phase 1 of the North Carolina Colon Cancer Study, which employed 21 separate questions (12 for prescription NSAIDs and 9 for over-the-counter NSAIDs) to query about use of specific products. This additional analysis showed that certain NSAID products (BC, Goody's, or Stanback powder or tablets and Alka-Seltzer or Bromo Seltzer) or their generic equivalents were twice as

Table 2. Odds Ratios for the Association Between Use of Nonsteroidal Antiinflammatory Drugs and Distal Large Bowel Cancer, North Carolina Colon Cancer Study II, 2001–2006

	Cases		Controls		OR[a]	95% CI	Multivariable OR[b]	95% CI
	No.	%	No.	%				
Never use (referent)	248	24.3	169	17.0	1.00		1.00	
Ever use	772	75.7	827	83.0	0.67	0.54, 0.84	0.66	0.52, 0.83
Recent use[c]	688	67.5	775	77.8	0.64	0.51, 0.80	0.62	0.49, 0.79
Average monthly use in the past 5 years, no. of times								
<15	446	43.7	415	41.7	0.73	0.57, 0.92	0.68	0.53, 0.88
≥15	326	32.0	412	41.4	0.61	0.48, 0.79	0.62	0.48, 0.81
Regular use[d] of NSAIDs, by type								
Over-the-counter aspirin	355	34.8	439	44.1	0.62	0.49, 0.80	0.62	0.48, 0.80
Over-the-counter nonaspirin NSAIDs	119	11.7	110	11.0	0.77	0.56, 1.08	0.72	0.51, 1.02
Prescription nonselective NSAIDs	66	6.5	81	8.1	0.59	0.40, 0.87	0.57	0.38, 0.85
Selective COX-2 inhibitors	87	8.5	135	13.6	0.48	0.34, 0.68	0.44	0.31, 0.63

Abbreviations: CI, confidence interval; COX-2, cyclooxygenase 2; NSAIDs, nonsteroidal antiinflammatory drugs; OR, odds ratio.

[a] Adjusted for age (continuous), sex, race (African-American or White), and sampling probability.

[b] Adjusted for age (continuous), sex, race (African-American or White), sampling probability, body mass index (weight (kg)/height (m)^2; <25, 25–29.9, or ≥30) 1 year prior, ever use of calcium supplements in the past 5 years, physical activity 1 year prior (<1,882, 1,882–2,077, or ≥2,078 metabolic equivalent-minutes/day), total energy intake (<1,711, 1,711–2,413, or ≥2,414 kcal/day), and dietary fat intake (<64, 64–97, or ≥98 g/day).

[c] Continuing use in the year before diagnosis/interview.

[d] Use at least 3 times per week for 3 months or more.

commonly used by African Americans as by whites. However, despite these differences, Sansbury et al. (34) observed an inverse association between NSAIDs and colon cancer among African Americans in North Carolina Colon Cancer Study I; consequently, it seems unlikely that differential use of these products would explain the weak association between

Table 3. Odds Ratios for the Association Between Use of Nonsteroidal Antiinflammatory Drugs and Distal Large Bowel Cancer, by Race, North Carolina Colon Cancer Study II, 2001–2006

	Whites						African Americans					
	Cases		Controls		Multivariable OR[a]	95% CI	Cases		Controls		Multivariable OR[a]	95% CI
	No.	%	No.	%			No.	%	No.	%		
Never use (referent)	174	22.8	124	15.1	1.00		74	28.9	45	26.2	1.00	
Ever use	590	77.2	700	85.0	0.60	0.46, 0.79	182	71.1	127	73.8	0.87	0.55, 1.40
Recent use[b]	530	69.4	658	79.9	0.57	0.43, 0.75	158	61.7	117	68.0	0.82	0.50, 1.32
Average monthly use in the past 5 years, no. of times												
<15	325	42.5	326	39.6	0.65	0.49, 0.88	121	47.3	89	51.7	0.78	0.47, 1.29
≥15	265	34.7	374	45.4	0.55	0.41, 0.74	61	23.8	38	22.1	1.13	0.62, 2.05
Regular use[c] of NSAIDs, by type												
Over-the-counter aspirin	280	36.7	385	46.7	0.56	0.41, 0.75	75	29.2	54	31.4	0.87	0.50, 1.52
Over-the-counter, nonaspirin NSAIDs	89	11.7	100	12.1	0.57	0.39, 0.84	30	11.7	10	5.8	1.93	0.81, 4.56
Prescription nonselective NSAIDs	48	6.3	73	8.9	0.48	0.30, 0.75	18	7.0	8	4.7	1.17	0.44, 3.07
Selective COX-2 inhibitors	69	9.0	119	14.4	0.38	0.25, 0.56	18	7.0	16	9.3	0.69	0.29, 1.61

Abbreviations: CI, confidence interval; COX-2, cyclooxygenase 2; NSAIDs, nonsteroidal antiinflammatory drugs; OR, odds ratio.

[a] Adjusted for age (continuous), sex, race (African-American or white), sampling probability, body mass index (weight (kg)/height (m)^2; <25, 25–29.9, or ≥30) 1 year prior, ever use of calcium supplements in the past 5 years, physical activity 1 year prior (<1,882, 1,882–2,077, or ≥2,078 metabolic equivalent-minutes/day), total energy intake (<1,711, 1,711–2,413, or ≥2,414 kcal/day), and dietary fat intake (<64, 64–97, or ≥98 g/day).

[b] Continuing use in the year before diagnosis/interview.

[c] Among ever users, use at least 3 times per week for 3 months or more.

Table 4. Odds Ratios for the Association Between Use of Nonsteroidal Antiinflammatory Drugs and Distal Large Bowel Cancer, by Tumor Location, North Carolina Colon Cancer Study II, 2001–2006

	Sigmoid Colon				Rectosigmoid Junction				Rectum			
	Cases		Multivariable OR[a]	95% CI	Cases		Multivariable OR[a]	95% CI	Cases		Multivariable OR[a]	95% CI
	No.	%			No.	%			No.	%		
Never use (referent)	97	20.7	1.00		47	28.0	1.00		104	27.2	1.00	
Ever use	371	79.3	0.81	0.60, 1.09	121	72.0	0.50	0.33, 0.74	279	72.9	0.60	0.44, 0.81
Recent use[b]	338	72.2	0.79	0.58, 1.07	107	63.7	0.47	0.32, 0.71	242	63.2	0.55	0.41, 0.75
Average monthly use in the past 5 years, no. of times												
<15	213	45.5	0.84	0.61, 1.15	76	45.2	0.55	0.36, 0.85	156	40.7	0.61	0.44, 0.85
≥15	158	33.8	0.78	0.56, 1.09	45	26.8	0.43	0.27, 0.69	123	32.1	0.58	0.41, 0.82
Regular use[c] of NSAIDs, by type												
Over-the-counter aspirin	187	39.9	0.83	0.60, 1.16	44	26.2	0.39	0.24, 0.62	124	32.4	0.54	0.38, 0.75
Over-the-counter, nonaspirin NSAIDs	53	11.3	0.81	0.52, 1.26	17	10.1	0.45	0.24, 0.86	49	12.8	0.76	0.49, 1.17
Prescription nonselective NSAIDs	33	7.1	0.71	0.43, 1.18	19	11.3	0.86	0.46, 1.60	14	3.7	0.30	0.15, 0.57
Selective COX-2 inhibitors	42	9.0	0.53	0.33, 0.83	18	10.7	0.48	0.26, 0.89	27	7.1	0.34	0.20, 0.57

Abbreviations: CI, confidence interval; COX-2, cyclooxygenase 2; NSAIDs, nonsteroidal antiinflammatory drugs; OR, odds ratio.

[a] Adjusted for age (continuous), sex, race (African-American or white), sampling probability, body mass index (weight (kg)/height (m)^2; <25, 25–29.9, or ≥30) 1 year prior, ever use of calcium supplements in the past 5 years, physical activity 1 year prior (<1,882, 1,882–2,077, or ≥2,078 metabolic equivalent-minutes/day), total energy intake (<1,711, 1,711–2,413, or ≥2,414 kcal/day), and dietary fat intake (<64, 64–97, or ≥98 g/day).

[b] Continuing use in the year before diagnosis/interview.

[c] Among ever users, use at least 3 times per week for 3 months or more.

NSAIDs and distal large bowel cancer observed among African Americans in the current study.

Alternatively, one might consider potential detection bias through NSAID-induced endoscopic screening. While it is possible that NSAIDs could cause lower gastrointestinal bleeding, most side effects of NSAIDs are localized to the upper gastrointestinal tract, such as the stomach and duodenum, where cyclooxygenase 1 is constitutively expressed (35): Upper gastrointestinal bleeding or pain alone rarely leads to a colonoscopy. Martin et al. (36) previously examined the indications for colonoscopy in cases and controls and found that the indications were similar in both races.

Lastly, the association we observed might result at least partially from differences in the biology or etiology of distal large bowel cancers between African Americans and whites. Racial differences in the anatomic location of colorectal cancer have been noted, with African Americans being more likely to develop proximal colorectal cancer than whites (16, 17). In addition, several studies have reported on polymorphisms of inflammation-related genes and their interactions with NSAID use (37–39). Interestingly, the *COX-2* V511A polymorphism, which is exclusively found in African Americans (albeit at a low allele frequency (~5%)), appears to be inversely associated with colorectal neoplasia like NSAIDs (37).

In the current study, NSAID use was more strongly associated with rectal and rectosigmoid cancers than with sigmoid cancer, which is consistent with several previous studies (6, 13). On the other hand, some authors have reported more pronounced associations between NSAIDs and colon cancer than rectal cancer (7, 40), while others have reported similarly strong associations with colon and rectal cancers (2, 4, 9, 12). Different genetic aberrations have been associated with cancers arising at different subsites of the large bowel (15), suggesting that the etiology of and risk factors for rectal cancer might differ from those for colon cancer. Emerging data show that the associations between NSAIDs and colorectal cancer might also vary depending on tumor characteristics. According to a recent study, regular use of aspirin was inversely associated with colorectal tumors characterized by modest-to-strong COX-2 expression but was not associated with tumors that had weak or absent COX-2 expression (41). Given that researchers have reported higher expression of COX-2 in tumors originating in the rectum than in those originating in the colon (42, 43), differences in COX-2 expression by tumor location might result in differences in the magnitudes of the associations with NSAIDs for rectal, rectosigmoid, and sigmoid cancers.

Several potential limitations of our study should be considered. First, we assessed NSAID exposure based on self-report. Although NSAID use may be underreported by participants (44), pharmacy records do not capture over-the-counter NSAID use, which comprises the majority of NSAID use. Second, although we evaluated and adjusted for a range of potentially confounding factors, our effect estimates for the association might have been biased by residual confounding by unknown factors related to the indication for NSAID use. However, to explain the association observed, such a factor would have had to be strongly associated with both NSAID use and distal large bowel cancer and to be common in our study population (45).

Strengths of our study relative to previous research include its exclusive focus on distal large bowel cancers. Despite anatomic and biologic differences between proximal and distal colorectal cancer (14), there are relatively few epidemiologic studies of distal colorectal cancer. The current study was specifically designed to identify risk factors for distal large bowel cancer. Our study also included relatively large numbers of African-American cases and controls. Whereas African Americans have the highest incidence of and mortality from colorectal cancer among racial groups (46), etiologic studies in this population have been few. Lastly, the prevalence of NSAID use in our study was generally comparable to that in a study that used data from a national survey (47), which enhances the potential generalizability of our results. In our study, 83% of controls (85% of white controls and 74% of African-American controls) reported ever use of NSAIDs in the past 5 years. Similarly, in the Third National Health and Nutrition Examination Survey (1988–1994), the overall prevalence of any analgesic use was approximately 73% in males and 83% in females, with a lower prevalence of nonprescription analgesic use among non-Hispanic blacks than among non-Hispanic whites (47).

In conclusion, the current study suggests that in whites, an inverse association with NSAIDs is not limited to colon cancers but also appears to be present for distal large bowel cancers, possibly with more potent effects for rectal and rectosigmoid cancer than for sigmoid cancer. On the other hand, the association between distal large bowel cancer and NSAID use was not evident in African Americans in our study. NSAIDs might not be effective in preventing all subtypes of colorectal cancer or in preventing colorectal cancer in all populations. Further studies should be directed towards identifying characteristics of subgroups that might most benefit from NSAIDs.

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Appendix Table. Names and Locations of Manufacturers of Brand-Name Products

Product	Manufacturer	Location
Advil	Wyeth Consumer HealthCare	Richmond, Virginia
Aleve	Bayer Healthcare	Morristown, New Jersey
Alka-Seltzer	Bayer Healthcare	Morristown, New Jersey
Anacin	Insight Pharmaceuticals Corporation	Langhorne, Pennsylvania
BC Powder	GlaxoSmithKline Pharmaceuticals	Memphis, Tennessee
Bromo Seltzer	Tower Laboratories Ltd.	Centerbrook, Connecticut
Bufferin	Novartis Consumer Health, Inc.	Parsippany, New Jersey
Celebrex	Pfizer Inc.	New York, New York
Daypro	Pfizer Inc.	New York, New York
Excedrin	Novartis Consumer Health, Inc.	Parsippany, New Jersey
Feldene	Pfizer Inc.	New York, New York
Goody's Powder	GlaxoSmithKline Consumer HealthCare	Pittsburgh, Pennsylvania
Motrin	McNeil Consumer Healthcare	Langhorne, Pennsylvania
Naprosyn	Hoffmann-La Roche Inc.	Nutley, New Jersey
Stanback Headache Powders	GlaxoSmithKline Consumer HealthCare	Pittsburgh, Pennsylvania
Tylenol	McNeil Consumer Healthcare	Langhorne, Pennsylvania
Vioxx	Merck & Company, Inc.	Whitehouse Station, New Jersey