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Use of Nonsteroidal Antiinflammatory Drugs and Risk of Colon Cancer in a Population-based, Case-Control Study of African Americans and Whites

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African Americans have the highest colon cancer incidence and mortality rates among all US ethnic groups. Epidemiologic studies suggest that use of nonsteroidal antiinflammatory drugs (NSAIDs) is associated with a reduced risk of colon cancer, but no study to date with adequate sample size has reported on the association among African Americans. The authors examined the association between NSAID use and risk of colon cancer in a population-based, case-control study in North Carolina that enrolled 731 African-American (294 cases, 437 controls) and 960 White (349 cases, 611 controls) participants between 1996 and 2000. Odds ratios were calculated using unconditional logistic regression for categories of NSAIDs and colon cancer risk. Inverse associations between regular NSAID use and colon cancer were similar for African Americans (odds ratio = 0.41, 95% confidence interval: 0.22, 0.77) and Whites (odds ratio = 0.48, 95% confidence interval: 0.28, 0.83) but stronger for women than men. Inverse associations were slightly weaker for occasional versus regular NSAID use, but they were similar for aspirin and nonaspirin NSAID use. These results add new knowledge suggesting that the protective effect of NSAIDs against colon cancer is similar among African Americans and Whites.

African Americans; anti-inflammatory agents, non-steroidal; case-control studies; colonic neoplasms; European Continental Ancestry Group

Abbreviations: CI, confidence interval; COX-2, cyclooxygenase-2; MET, metabolic equivalent task; NSAID, nonsteroidal antiinflammatory drug.

There is a large discrepancy in the incidence and mortality rates of colon cancer between ethnic groups in the United States. African Americans have the highest incidence rates, whereas Hispanics, Asians/Pacific Islanders, and American Indians/Alaskan Natives have the lowest, with the incidence in Whites falling in the middle (1). Between 1996 and 2000, the incidence and mortality rates for colon cancer among African Americans were 48.4 and 28.5, respectively, compared with 38.9 and 20.7 among Whites (2). Differences in colorectal cancer screening rates between African Americans and Whites do not completely explain the differences in incidence and mortality (1, 3). To date, the majority of epidemiologic studies have not included sufficient numbers of African Americans in order to appropriately conclude whether risk factors for colon cancer are similar in Whites and African Americans. Integrating genetic and environmental risk factor information from large, racially diverse populations offers the potential for uncovering new clues to the etiology of colon cancer that may contribute to the future prevention of the disease.

To date, almost two dozen observational studies have consistently reported a 40–50 percent reduction in the risk

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for colon cancer among users of nonsteroidal antiinflammatory drugs (NSAIDs) (4–21). The most well-supported chemopreventive mechanism of NSAIDs is their inhibition of cyclooxygenase-2 (COX-2) in the inducible pathway of the arachidonic acid cascade, the rate-limiting step in the synthesis of prostaglandins (5, 18, 22–24). Controversy remains over the cellular mechanisms by which NSAIDs exert their chemopreventive effects; however, evidence strongly supports their capacity to restore apoptosis and inhibit angiogenesis (19, 23). Rosenberg et al. (16) were among the first to report an inverse association between NSAID use and risk of colorectal cancer, sparking what is now over a decade of research on this hypothesis (6–9, 14, 15, 20). Reported data on dose, duration, and frequency of NSAID use necessary for prevention of colon cancer are inconsistent. Epidemiologic evidence supports that duration of NSAID use is important for this association, in that increased duration of NSAID use is associated with a larger reduction in the risk of colorectal cancer (6, 7, 14–16, 25). However, the minimum duration required for an observed protective effect is still unknown. Data on the optimal frequency and dose associated with a decreased risk of colon cancer are less clear but suggest that more frequent NSAID use is associated with a further reduction in risk. Some epidemiologic studies report that inverse associations were comparable regardless of the dose of NSAIDs, while others report that larger doses of aspirin and aspirin-based NSAIDs were more strongly associated with reduced risk than were smaller ones (5, 9, 17, 20, 26–28). Only a handful of the observational studies conducted to date were population based, and to our knowledge, no epidemiologic study has reported on the association between NSAID use and risk of colon cancer among African Americans (4, 5, 11, 17, 21, 27, 29).

There is evidence of racial differences in the prevalence of drug metabolism phenotypes and allelic frequencies of polymorphisms in drug metabolism genes (30–33). In addition, allelic frequencies of polymorphisms in the *COX-2* gene—the proposed target for chemoprevention by NSAIDs—appear to vary by race (34). It is possible that variants in drug metabolism genes or in the *COX-2* gene may modify or inhibit the association between NSAIDs and colon cancer, thus explaining some of the observed differences in incidence and mortality and deserving further research. Furthermore, it is important to identify risk or preventive factors that are modifiable and that, in turn, may decrease the risk of colon cancer in African Americans and Whites. Thus, investigation of the association between NSAIDs and colon cancer among African Americans is vital in order to make accurate population-wide recommendations for their use for colon cancer prevention. This population-based, case-control study of African Americans and Whites was designed to examine whether the protective effect of NSAIDs associated with colon cancer risk is comparable for African Americans and White Americans.

MATERIALS AND METHODS

Study population

Data were collected from participants in the North Carolina Colon Cancer Study, a population-based, case-control study of colon cancer in North Carolina. A randomized recruitment approach was used to ascertain potential participants, in which race-, sex-, and age-specific incidence rates from 1991 to 1993 were used to select cases and controls from 33 counties in central North Carolina. This approach was used to obtain approximately equal numbers of African-American and White cases and to approximately frequency match controls to cases by race, sex, and 5-year age groups. The study was approved by the institutional review board at the University of North Carolina, School of Medicine, and by equivalent committees at collaborating hospitals. All participants provided written, informed consent.

Study cases were identified through a rapid ascertainment system (35) in conjunction with the North Carolina Central Cancer Registry. Eligible cases were noninstitutionalized study area residents aged 40–84 years with a first diagnosis of invasive adenocarcinoma of the colon between July 1, 1996, and June 30, 2000. Cases aged less than 65 years were required to have a North Carolina driver's license or identification card since controls of the same age were sampled from driver's license rosters. In addition, cases were recruited only if their primary physician gave the study coordinators permission to do so. Participants were asked to provide written consent to obtain pathology slides, which were reviewed by a study pathologist to confirm diagnoses.

Study controls were selected from Division of Motor Vehicle records if they were aged less than 65 years or from a list of Medicare-eligible beneficiaries obtained from the Health Care Financing Administration if they were aged 65 or more years. Eligible controls were noninstitutionalized study area residents sampled from these listings with sampling probabilities based on the expected distribution of cases (within 5 years), gender, and ethnic group.

Completed interviews were obtained from 1,691 participants, of whom 731 were self-described as African American (294 cases, 437 controls) and 960 as White (349 cases, 611 controls). Among cases, the contact rate was 78 percent, the cooperation rate (interviewed/(interviewed + refused)) was 84 percent, and the overall response rate (interviewed/eligible) was 66 percent. For controls, these rates were 90 percent, 62 percent, and 56 percent, respectively. Response rates were 62 percent for cases and 49 percent for controls among African Americans and 69 percent for cases and 61 percent for controls among Whites.

Data collection

Data were collected in person by trained nurse interviewers at the participant's home or other convenient location. The questionnaire collected information on family history of colon cancer, demographic characteristics, and lifestyle factors such as diet, physical activity, tobacco use, use of medications, and medical history. A modified version of a previously validated 100-item semiquantitative Block food frequency questionnaire (36) was used to measure the usual frequency of specific food intakes 1 year prior to diagnosis for cases or interview date for controls.

TABLE 1. Characteristics of cases and controls, by race, North Carolina Colon Cancer Study, 1996–2000*

	African Americans					Whites				
	Cases		Controls		Chi-square *p* value†	Cases		Controls		Chi-square *p* value†
	No.	%	No.	%		No.	%	No.	%	
Total	293		437			345		611		
Age (years)										
40–49	38	13.0	28	6.4		27	7.8	35	5.7	
50–59	76	25.9	82	18.8		67	19.4	110	18.0	
60–69	95	32.4	136	31.1		116	33.6	206	33.7	
≥70	84	28.7	191	43.7	<0.01	135	39.1	260	42.6	0.85
Median age	64		68			67		68		
Sex										
Male	138	47.1	186	42.6		193	55.9	330	54.0	
Female	155	52.9	251	57.4	0.23	152	44.1	281	46.0	0.56
Smoking status										
Never smoker	135	46.7	200	46.0		116	33.9	246	40.3	
Former smoker	97	33.6	144	33.1		180	52.6	268	43.9	
Current smoker: <35 years	26	9.0	40	9.2		18	5.3	28	4.6	
Current smoker: ≥35 years	31	10.7	51	11.7	0.98	28	8.2	68	11.2	0.05
Annual household income ($)										
≤15,000	102	40.6	162	44.1		62	19.7	66	12.0	
>15,000–25,000	52	20.7	84	22.9		60	19.0	100	18.2	
>25,000–50,000	64	25.5	74	20.2		98	31.1	183	33.3	
>50,000	33	13.2	47	12.8	0.45	95	30.2	200	36.4	0.01
Education										
Less than high school graduate	126	43.3	192	44.2		96	28.0	121	19.8	
High school graduate/some college	137	47.1	186	42.9		171	49.8	325	53.4	
College graduate	28	9.6	56	12.9	0.31	76	22.2	163	26.7	0.01
Family history of colon cancer										
Yes	51	17.4	45	10.3		74	21.6	57	9.4	
No	242	82.6	391	89.7	<0.01	268	78.4	548	89.6	<0.01
Regular vitamin use‡										
Yes	94	32.9	166	39.2		154	45.4	328	55.4	
No	192	67.1	258	60.8	0.09	185	54.6	264	44.6	<0.01

Table continues

Assessment of NSAIDs

Information on NSAID use was ascertained in the interview by asking participants the following question: "During the five years prior to your diagnosis (for cases), or the date of selection (for controls), have you taken any prescription or over-the-counter medications, for headache, backache, arthritis, bursitis, rheumatism, joint pain, injury, accident, operation, migraine, sinus trouble, or (women) menstrual cramps or other reasons?" The specific indication(s) for NSAID use were not determined for individual participants. Information was collected on NSAIDs obtained from a physician's prescription, a hospital or neighborhood clinic, a pharmacy, supermarket, friends, neighbors, and relatives. Individuals who reported NSAID use were asked whether they took the drug "regularly (≥3 days per week), occasionally (≥1 day a month, but <3 days per week), or rarely/seldom (<1 day a month)." Individuals who reported regular use were asked, "How many times per day or week did you take the medicine?"; "in total, for how many weeks, months, or years did you take the medicine?"; and "did you use medicine in the year prior to diagnosis/selection?"

Variable coding

Participants who reported regular use of NSAIDs (as defined above) were categorized as regular users, while other NSAID users were classified as occasional users. Nonusers (the reference category) included participants who did not use any NSAIDs ($n = 55$), who used NSAIDs in cold products

TABLE 1. Continued

	African Americans					Whites				
	Cases		Controls		Chi-square *p* value†	Cases		Controls		Chi-square *p* value†
	No.	%	No.	%		No.	%	No.	%	
Physical activity (average MET§-minutes/day)										
≤1,944.0	95	34.5	193	45.1		89	26.2	174	28.8	
1,944.01–2,235.0	89	32.4	105	24.5		124	36.5	236	39.0	
>2,235.0	91	33.1	130	30.4	0.01	127	37.3	195	32.2	0.28
Median physical activity	2,055.0		1,978.9			2,096.4		2,085.0		
Body mass index, 1 year ago (kg/m^2)										
≤24.9	46	16.3	86	21.0		92	27.5	187	31.3	
25.0–29.9	113	39.9	148	36.2		140	41.8	252	42.1	
≥30.0	124	43.8	175	42.8	0.26	103	30.8	159	26.6	
Median body mass index	29.1		28.9			27.6		26.7		
Total energy (kcal/day)										
≤1,432.7	88	30.4	169	39.1		80	23.4	178	29.2	
1,432.8–1,980.0	69	23.9	128	29.6		98	28.7	219	35.9	
≥1,980.1	132	45.7	135	31.3	<0.01	164	47.9	213	34.9	<0.01
Median total energy	1,845.5		1,600.0			1,926.5		1,762.4		
Dietary fat (g/day)										
≤57.2	84	29.1	156	36.1		91	26.6	191	31.3	
57.3–83.0	71	24.6	133	30.8		77	22.5	214	35.1	
≥83.1	134	46.4	143	33.1	<0.01	174	50.9	205	33.6	<0.01
Median dietary fat	78.6		66.6			84.0		69.8		
Red meat (servings/day)										
≤0.50	68	23.5	135	31.3		116	33.9	262	42.9	
0.51–1.00	92	31.8	151	34.9		129	37.7	223	36.6	
>1.00	129	44.6	146	33.8	<0.01	97	28.4	125	20.5	<0.01

* All data are for the reference year, which is the year before diagnosis for cases and the year before interview for controls. Five cases with incomplete interview data were excluded from all analyses.

† Chi-squared test for the difference between cases and controls.

‡ Use of any vitamin or mineral supplement at least once a week over the past year.

§ MET, metabolic-equivalent task.

only ($n = 4$), and who used acetaminophen only ($n = 86$). Acetaminophen was not included with NSAIDs because it does not have the antiinflammatory or COX-2 inhibitory effects associated with NSAIDs, and because it has not been consistently associated with a decreased risk of colon cancer (5, 6, 8, 9, 17, 20, 26, 27, 37). NSAID users were also categorized according to the source of NSAIDs (nonprescription only, prescription only, or both) and the type of NSAID (aspirin only, nonaspirin NSAID only, or both). Finally, any NSAID users were subclassified as current or past users (use in the year prior to diagnosis/selection, no use in the year prior to diagnosis/selection), and regular users were also subclassified by the median duration of use among the controls (less than 2 years, 2 or more years).

We determined tertile cutpoints for continuous covariates (intake of total energy, total fat, total calcium, dietary fiber, dietary folate, and red meat, along with physical activity) based on the distributions among controls (38). Fat intake was highly correlated with total energy intake. Therefore, the calorie-adjusted fat variable was derived using the residual method as described by Willett and Stampfer (39) to provide a measure of fat intake independent of total energy intake.

Participants self-reported their race as African American, White, or "other." Very few participants reported their race as other ($n = 8$); therefore, the analyses were restricted to Whites and African Americans. Stage of disease (local, regional, distant, or unknown) and tumor site (proximal or distal) were reported by the Central Cancer Registry, and the diagnosis of cancer was confirmed by the study pathologist.

Additional covariates evaluated for confounding (refer to "Statistical analysis" section) included the following: regular vitamin/mineral supplement use (≥1 day per week, <1 day per week over the last year); cigarette smoking (never, former, or current, with current smokers subclassified by duration (<35 years, ≥35 years) for some analyses); annual

family income; educational level (less than high school graduate, high school graduate/some college, college graduate or higher); first-degree relative with colon cancer (yes, no); and age (continuous). Body mass index (kg/m^2) was computed on the basis of reported weight 1 year ago and height measured at the interview (40). Participants were asked about the number of work and nonwork hours they usually spent in activity the year before their diagnosis and 10 years prior to their diagnosis. Participants were asked to record hours in light, moderate, hard, and very hard activity. Physical activity was measured using a modified version of the validated Stanford 7-day recall instrument, in which metabolic equivalent task (MET)-minutes per day were computed for combined occupational, nonoccupational, and non-work/weekend activities (including duration, frequency, and intensity), where a MET of 1.5 is equivalent to 60 minutes of ''light activity,'' and a MET of 10 is equivalent to 60 minutes of ''very hard activity'' (41, 42).

Statistical analysis

We used unconditional logistic regression models to calculate adjusted odds ratios and 95 percent confidence intervals to estimate associations of NSAID use and colon cancer risk (SAS, version 8.1, software; SAS Institute, Inc., Cary, North Carolina). All models included offset terms (OFFSET) to account for randomized recruitment selection probabilities (prob) for cases and controls in each age-sex-race stratum: OFFSET = ln(prob(case)/prob(control)).

Potential confounders were identified using a directed acyclic graph (43) and were retained in models based on a 10 percent or greater change in the β coefficients for NSAID use (any vs. none) between the crude and the adjusted models. None of the potential confounders met the change in estimate criterion when evaluated individually, but we identified joint confounding by smoking history, physical activity, energy intake, fat intake, regular vitamin/mineral use, red meat intake, body mass index, and first-degree family history of colon cancer. Therefore, multivariate adjusted models included all of these covariates, in addition to age, race, and sex (which were used to define randomized recruitment probabilities).

Effect measure modification by race, sex, fat intake, body mass index, regular vitamin/mineral supplement use, location of tumor, and stage of disease was hypothesized a priori and tested using product interaction terms in the model. We evaluated significant departures from expectations for multiplicative joint effects using the log-likelihood ratio test ($p < 0.2$), comparing the logistic model containing the NSAID variable and the potential interaction exposure variable with a similar model but one containing an interaction term of the NSAID and exposure variable for the a priori-mentioned variables coded as follows: race (African American vs. White); sex (male vs. female); fat intake (greater than the median vs. less than or equal to the median); body mass index (greater than the median vs. less than or equal to the median); and regular vitamin/mineral supplement use ($\geq$1 day per week, $<$1 day per week). A log-likelihood ratio test p value of less than 0.20 was considered significant (44). We used polytomous regression to test whether the difference in the odds ratios for NSAID use was statistically significant ($p < 0.20$) for location of the tumor (right vs. left colon) and stage of disease (local, regional, or distant) (45, 46).

RESULTS

Demographic and lifestyle characteristics of the study participants, stratified by race, are presented in table 1. These analyses were based on 638 cases (294 African Americans) and 1,048 controls (437 African Americans). The mean age of the study population was 65 years. African-American cases were younger than African-American controls, but White cases and controls were similar with regard to age. In both racial groups, cases were more likely to have a first-degree family history of colon cancer than were controls, and cases were less likely to use vitamin/mineral supplements regularly. African-American and White cases also consumed more fat, red meat, and energy than did controls, while controls were more likely to be of normal weight than cases in both racial groups. Smoking was similar among African-American cases and controls, but White cases were less likely to have been nonsmokers than were White controls. African-American cases and controls were also similar with regard to calcium, dietary fiber, folate, and vitamin C and E intakes, while intakes of these nutrients were lower in White cases compared with controls (data not shown). Income and education levels were similar between African-American cases and controls, but White cases had a lower annual household income compared with White controls.

The multivariable adjusted odds ratio for NSAID use was 0.49 (95 percent confidence interval (CI): 0.34, 0.72) (table 2). The inverse association was stronger for regular users (odds ratio = 0.42, 95 percent CI: 0.29, 0.65) than occasional users (odds ratio = 0.57, 95 percent CI: 0.39, 0.85) and for use of prescription-only NSAIDs or combined use of prescription and nonprescription NSAIDs than for use of nonprescription NSAIDs only. The strength of association did not vary substantially according to duration of use among regular users. The inverse association with regular NSAID use diminished when use was discontinued more than 1 year prior to the reference date (table 2) but was similar for aspirin-containing NSAIDs and nonaspirin NSAIDs (table 2).

Race did not modify the association between any NSAID use and colon cancer ($p_{\text{interaction}} = 0.96$) (table 3). Odds ratios tended to be somewhat lower in African Americans than in Whites, but overall effect estimates were similar for any use, regular use, occasional use, and current use of NSAIDs. In contrast, we did observe a significant interaction between any NSAID use and sex ($p_{\text{interaction}} = 0.07$), with stronger inverse associations for almost all categories of use for women compared with men (table 4). Finally, we found no difference in odds ratios for any NSAID use according to tumor location (right- vs. left-sided tumors) ($p_{\text{interaction}} = 0.99$). Inverse associations with NSAIDs were consistently stronger with increasing stage of disease, though estimates were imprecise because of the small numbers of cases in each category of stage, and the odds ratios were not significantly different ($p > 0.20$) (table 5). We

TABLE 2. Odds ratios and 95% confidence intervals between nonsteroidal antiinflammatory drug use and colon cancer, North Carolina Colon Cancer Study, 1996–2000*

NSAID† use	All participants							
	Cases		Controls		Odds ratio‡	95% confidence interval‡	Multivariable odds ratio§	95% confidence interval§
	No.	%	No.	%				
No use	71	11.2	74	7.1	1.0	Referent	1.0	Referent
Any use	561	88.8	971	92.9	0.54	0.38, 0.76	0.49	0.34, 0.72
Occasional use¶	313	49.5	473	45.3	0.61	0.43, 0.89	0.57	0.39, 0.85
Regular use#	248	39.2	498	47.6	0.47	0.32, 0.68	0.42	0.29, 0.65
<2 years	84	13.3	168	16.1	0.47	0.31, 0.73	0.41	0.25, 0.67
≥2 years	164	25.9	330	31.6	0.49	0.33, 0.72	0.47	0.31, 0.71
Nonprescription-only use	399	63.1	548	52.4	0.70	0.49, 1.00	0.65	0.44, 0.96
Prescription-only use	19	3.0	55	5.3	0.30	0.15, 0.57	0.28	0.14, 0.58
Nonprescription and prescription use	143	22.6	365	34.9	0.33	0.22, 0.50	0.29	0.18, 0.44
Current user**	240	38.0	556	53.2	0.40	0.28, 0.58	0.37	0.25, 0.55
Former user	321	50.8	415	39.7	0.75	0.52, 1.08	0.69	0.47, 1.03
Current regular user	201	31.8	452	43.3	0.42	0.29, 0.62	0.40	0.27, 0.60
Former regular user	47	7.4	46	4.4	0.97	0.57, 1.67	0.94	0.50, 1.76
Aspirin-containing NSAIDs only	49	7.8	103	9.9	0.48	0.29, 0.79	0.47	0.27, 0.80
Nonaspirin NSAIDs only	99	15.7	171	16.4	0.49	0.32, 0.75	0.46	0.29, 0.74

* Reference years are the 5 years prior to diagnosis for cases and 5 years before interview date for controls.
† NSAID, nonsteroidal antiinflammatory drug.
‡ Odds ratio and 95% confidence interval from unconditional logistic regression models based on data from 632 incident colon cancer cases and 1,045 population-based controls, adjusted for age, race, sex, and offsets. Six cases and three controls with missing data were excluded from models.
§ Multivariable odds ratio and 95% confidence interval adjusted for age, race, sex, smoking history, physical activity, total energy, regular vitamin/mineral use, red meat intake, body mass index, fat intake, family history, and sampling probability offsets.
¶ Occasional use includes use for less than 3 months and/or use less than 12 times per month.
# Regular use includes use 3 or more days a week for 3 or more months.
** Current users took NSAIDs in the year prior to the reference date; former users discontinued use before the reference date.

identified a significant modification of the odds ratios for any NSAID use and colon cancer by fat intake ($p_{\text{interaction}} = 0.03$) but not for body mass index ($p_{\text{interaction}} = 0.31$) or regular vitamin/mineral supplement use ($p_{\text{interaction}} = 0.72$).

DISCUSSION

Evidence for an inverse association between use of NSAIDs and the risk of colon cancer is substantial, but among the previous case-control studies that investigated this association, few were population based, and no studies to our knowledge have reported on the association among African Americans. Furthermore, many previous studies are limited by a lack of information on frequency, duration, and type of NSAID use. We collected detailed information on NSAID use to investigate the association between NSAIDs and colon cancer in a large, population-based study with adequate representation of African Americans to permit effect estimation separately among Blacks and Whites.

African Americans currently have the highest incidence and mortality rates for colorectal cancer in North Carolina and in the United States (47–49). We observed similar patterns of reported NSAID use, as well as similar strong inverse associations between NSAIDs and colon cancer, among African Americans and Whites in our study. These results suggest that public health recommendations for colon cancer chemoprevention by NSAIDs may be equally appropriate for both racial groups. We also noted consistent inverse associations for all frequencies and types of NSAID use, including occasional users of NSAIDs and prescription and nonprescription NSAID users. The inverse association for regular NSAID use and colon cancer in this study is similar in magnitude to associations reported by a previous population-based, case-control study and by cohort studies using national prescription databases in Europe and state Medicaid databases in the United States (5, 11, 17, 27).

In our study, the strength of the association between NSAIDs and colon cancer increased with increased frequency of NSAID use (regular vs. occasional use) but not with increased duration of use (<2 years vs. ≥2 years). These findings support previous findings that increased frequency of NSAID use was associated with a further decrease in risk of colon cancer (9, 14–17); however, our results suggest that even occasional use may reduce the risk.

The strength of the inverse association between NSAIDs and colon cancer was diminished among regular users who discontinued NSAID use more than a year prior to diagnosis, consistent with previous reports (11, 12, 16). However,

TABLE 3. Associations between nonsteroidal antiinflammatory drug use and colon cancer, by race, North Carolina Colon Cancer Study, 1996–2000*

NSAID† use	African Americans						Whites					
	Cases		Controls		Multivariable odds ratio‡	95% confidence interval‡	Cases		Controls		Multivariable odds ratio	95% confidence interval
	No.	%	No.	%			No.	%	No.	%		
Total	290		435				342		610			
No use	33	11.4	31	7.1	1.0	Referent	38	11.1	43	7.0	1.0	Referent
Any use	257	88.6	404	92.9	0.48	0.28, 0.85	304	88.9	567	92.9	0.56	0.33, 0.94
Occasional use§	160	55.2	212	48.7	0.57	0.32, 1.01	153	44.7	261	42.8	0.68	0.39, 1.17
Regular use¶	97	33.4	192	44.1	0.41	0.22, 0.77	151	44.1	306	50.2	0.48	0.28, 0.83
<2 years	36	12.4	82	18.8	0.29	0.14, 0.63	48	14.0	86	14.1	0.65	0.32, 1.31
≥2 years	61	21.0	110	25.3	0.52	0.27, 0.99	103	30.1	220	36.1	0.45	0.25, 0.80
Nonprescription-only use	182	62.8	219	50.3	0.71	0.40, 1.26	217	63.4	329	53.9	0.66	0.39, 1.13
Prescription-only use	5	1.7	27	6.2	0.10	0.02, 0.39	14	4.1	28	4.6	0.50	0.19, 1.32
Nonprescription and prescription use	70	24.1	156	35.9	0.27	0.14, 0.52	73	21.3	209	34.3	0.34	0.19, 0.62
Current use	101	34.8	219	50.3	0.38	0.20, 0.70	139	40.6	337	55.2	0.41	0.24, 0.72

* Reference years are the 5 years prior to diagnosis for cases and the 5 years before interview date for controls.
† NSAID, nonsteroidal antiinflammatory drug.
‡ Multivariable odds ratio and 95% confidence interval from unconditional logistic models of data from 632 incident colon cancer cases and 1,045 population-based controls, adjusted for age, race, sex, smoking history, physical activity, total energy, regular vitamin/mineral use, red meat intake, body mass index, fat intake, family history, and sampling probability offsets. Six cases and three controls with missing data were excluded from models.
§ Occasional use includes use for less than 3 months and/or use for less than 12 times per month.
¶ Regular use includes use 3 or more days a week for 3 or more months.

these findings are imprecise because of the small number of regular users who discontinued use; therefore, these findings may be due to chance.

Most of the published observational studies to date have been limited to the investigation of aspirin only, while few published studies reported on the association between colon

TABLE 4. Odds ratios and 95% confidence intervals for the association between nonsteroidal antiinflammatory drug use and colon cancer, by gender, North Carolina Colon Cancer Study, 1996–2000*

NSAID† use	Men						Women					
	Cases		Controls		Multivariable odds ratio‡	95% confidence interval‡	Cases		Controls		Multivariable odds ratio‡	95% confidence interval‡
	No.	%	No.	%			No.	%	No.	%		
Total	328		515				304		530			
No use	26	7.9	34	6.6	1.0	Referent	45	14.8	40	7.5	1.0	Referent
Any use	302	92.1	481	93.4	0.77	0.43, 1.39	259	85.2	490	92.5	0.37	0.23, 0.61
Occasional use§	155	47.3	235	45.7	0.78	0.42, 1.44	158	52.0	238	44.9	0.49	0.29, 0.82
Regular use¶	147	44.8	246	47.8	0.78	0.42, 1.46	101	33.2	252	47.5	0.28	0.16, 0.49
<2 years	44	13.4	61	11.8	0.83	0.37, 1.89	40	13.1	107	20.2	0.25	0.13, 0.49
≥2 years	103	31.4	185	35.9	0.74	0.39, 1.40	61	20.1	145	27.4	0.32	0.18, 0.58
Nonprescription-only use	225	68.6	302	58.6	0.95	0.52, 1.76	174	57.2	245	46.2	0.52	0.31, 0.87
Prescription NSAIDs only	5	1.5	19	3.7	0.16	0.03, 0.83	14	4.6	36	6.8	0.27	0.11, 0.67
Nonprescription and prescription use	72	21.9	158	30.7	0.47	0.24, 0.93	71	23.3	207	39.1	0.20	0.11, 0.36
Current use	142	43.3	275	53.4	0.67	0.36, 1.35	98	32.2	281	53.0	0.23	0.14, 0.41

* Reference years are the 5 years prior to diagnosis for cases and the 5 years before interview date for controls.
† NSAID, nonsteroidal antiinflammatory drug.
‡ Multivariable odds ratio and 95% confidence interval from unconditional logistic models of data from 632 incident colon cancer cases and 1,045 population-based controls, adjusted for age, race, sex, smoking history, physical activity, total energy, regular vitamin/mineral use, red meat intake, body mass index, fat intake, family history, and sampling probability offsets. Six cases and three controls with missing data were excluded from models.
§ Occasional use includes use for less than 3 months and/or use for less than 12 times per month.
¶ Regular use includes use 3 or more days a week for 3 or more months.

TABLE 5. Associations between nonsteroidal antiinflammatory drug use and colon cancer, by stage at diagnosis, North Carolina Colon Cancer Study, 1996–2000*

NSAID† use	Total (controls)		Local stage tumors				Regional stage tumors				Distant stage tumors			
			Cases		Multivariable odds ratio‡	95% confidence interval‡	Cases		Multivariable odds ratio‡	95% confidence interval‡	Cases		Multivariable odds ratio‡	95% confidence interval‡
	No.	%	No.	%			No.	%			No.	%		
Total	1,045		214				308				61			
No use	74	7.1	20	9.4	1.0	Referent	34	11.2	1.0	Referent	9	14.8	1.0	Referent
Any use	971	92.9	193	90.6	0.65	0.38, 1.14	270	88.8	0.48	0.30, 0.78	52	85.2	0.40	0.18, 0.87
Occasional use§	473	45.3	100	46.9	0.73	0.40, 1.32	152	50.0	0.55	0.33, 0.91	33	54.1	0.47	0.20, 1.09
Regular use¶	498	47.6	93	43.7	0.60	0.33, 1.09	118	38.8	0.43	0.26, 0.72	19	31.1	0.28	0.11, 0.70
<2 years	168	16.1	36	16.9	0.68	0.34, 1.37	43	14.1	0.43	0.26, 0.72	2	3.3	<0.01	0.01, 0.24
≥2 years	330	31.6	57	26.8	0.57	0.31, 1.06	75	24.7	0.47	0.28, 0.81	17	27.9	0.41	0.16, 1.04
Nonprescription-only use	548	52.4	135	63.4	0.84	0.48, 1.49	193	63.5	0.66	0.40, 1.07	37	60.6	0.54	0.24, 1.21
Prescription-only use	55	5.3	7	3.3	0.39	0.13, 1.16	8	2.6	0.28	0.10, 0.78	4	6.6	0.42	0.09, 1.15
Nonprescription and prescription use	365	34.9	51	23.9	0.84	0.48, 1.49	69	22.4	0.25	0.14, 0.45	11	18.0	0.15	0.05, 0.46
Current use	556	53.2	109	51.2	0.53	0.29, 0.95	116	38.2	0.36	0.22, 0.61	14	22.9	0.20	0.08, 0.51

* Reference years are the 5 years prior to diagnosis for cases and the 5 years before interview date for controls.
† NSAID, nonsteroidal antiinflammatory drug.
‡ Multivariable odds ratio and 95% confidence interval from unconditional logistic models of data from 632 incident colon cancer cases and 1,045 population-based controls, adjusted for age, race, sex, smoking history, physical activity, total energy, regular vitamin/mineral use, red meat intake, body mass index, fat intake, family history, and sampling probability offsets. Six cases and three controls with missing data were excluded from models.
§ Occasional use includes use for less than 3 months and/or use for less than 12 times per month.
¶ Regular use includes use 3 or more days a week for 3 or more months.

cancer and nonaspirin NSAIDs specifically. We found similar inverse associations for both aspirin-based NSAIDs and nonaspirin NSAIDs. Unfortunately, we did not have adequate numbers of participants to examine the association between colon cancer and specific NSAID medications other than aspirin.

The inverse association between NSAIDs and colon cancer was stronger for women compared with men for all categories of NSAID use, although frequencies of use for most categories were similar for men and women. Furthermore, we observed a significant interaction between NSAID use and sex and risk of colon cancer in our study. To date, only one other observational study has reported a stronger inverse association in women compared with men (6), while two studies have reported a stronger inverse association in men (9, 50). The difference we observed between men and women might have been caused by bias toward the null because of exposure misclassification in men, if men misclassified NSAID use more than women did. One study investigated prescription NSAID recall accuracy in a health maintenance organization population by comparing self-reported drug use with the prescription database, and it found no difference in recall for prescription NSAIDs by sex (51); however, most of the males in our study took nonprescription NSAIDs, and it is difficult to determine whether they would accurately recall over-the-counter NSAID use similarly to prescription use. Effect estimates for women might have been biased away from the null because of confounding if NSAID use was associated with postmenopausal hormone replacement therapy, which is associated with a decreased risk for colon cancer (52–54). On the other hand, the difference between men and women might reflect biologic differences (vs. bias) if the effect of NSAIDs on colon cancer was modified by hormone replacement therapy use or by estrogen in general. We do not have data on hormone replacement therapy use among the women in our study and cannot test the joint effect of hormone replacement therapy and NSAIDs on colon cancer risk, but the odds ratios for women aged 55 or more years—a surrogate for menopausal status—were comparable with those for all women (data not shown). Future research should focus on differences in risk by sex to help elucidate whether biologic differences in the association between NSAIDs and colon cancer by sex truly exist.

Because of reports that there are molecular and genetic differences between right- and left-sided colon cancers, as well as inconsistent reports of a difference in association between NSAID use and risk of colon cancer by site, we investigated the association by the location of the cancer (55, 56). Most observational studies that have investigated the association by tumor site have not found a difference in the association between NSAID use and cancer on one side of the colon versus the other (9, 26, 57), in agreement with our findings. We also noted similar inverse associations between NSAIDs and proximal and distal colon cancers. In contrast, we did find preliminary evidence of a somewhat stronger inverse association between NSAIDs and regional and distant stage versus local stage of colon cancer that might be worthy of further investigations.

This study has several strengths; in particular, it is the first to report on the association of NSAID use and risk of colon

cancer specifically among African Americans. A second strength of this study is that we investigated the association between NSAID use and colon cancer by frequency and duration of both prescription and nonprescription NSAID use, as well as by use of aspirin-based NSAIDs and non-aspirin NSAIDs. Our findings add important knowledge to the growing body of evidence regarding the frequency and duration of NSAID use needed to effectively reduce the risk of colon cancer.

The study has some limitations; as with other case-control studies, there is a potential for selection and recall bias. The rapid ascertainment system limited losses due to death and migration and decreased the potential for recall bias by identifying and interviewing cases shortly after diagnosis (35). It is difficult to determine the potential for selection biases, since we have limited data on the characteristics of nonparticipants. A recent population-based, case-control study in North Carolina that administered a condensed version of the study questionnaire to nonrespondents reported that differences in race and educational level between respondent and nonrespondent cases and controls are unlikely to be significant sources of bias (58). However, if NSAID use was associated with comorbid or debilitating conditions that limited participation, we may have underestimated the use of NSAIDs among controls. On the other hand, if NSAID users in the base population were more likely to participate in our study than were non-NSAID users, our observed odds ratios might have underestimated the true effect.

Another potential source of error is exposure misclassification. It is possible that cases in our study recalled NSAID use differently from controls, which could result in observed odds ratios biased either toward or away from the null (59). Nondifferential misclassification due to poor recall is also a potential source of bias; thus, approaches were used during the interviews to maximize recall of NSAID use, including asking about medications the participants had obtained from various sources and by prompting responses by providing a list of indications for analgesic use. However, despite these inherent limitations, self-report is the only feasible way to collect information on both prescription and nonprescription NSAID use in a population-based study, since medical reports and pharmacy claims would miss the use of nonprescription agents.

In conclusion, this study provides evidence for a strong inverse association between NSAIDs and colon cancer that appears to be comparable for African Americans and Caucasian Americans. Our data also suggest that even occasional use of NSAIDs may reduce the risk of colon cancer along with regular use of NSAIDs. Because NSAIDs are associated with an increased risk for gastrointestinal bleeding and other side effects (60–62), public health recommendations must balance the risks and benefits of NSAID use for the prevention of colon cancer.

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