Research Article

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Association of Nonsteroidal Anti-Inflammatory Drugs with Colorectal Cancer by Subgroups in the VITamins and Lifestyle (VITAL) Study

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Abstract

Background: There is substantial evidence that use of NSAIDs reduces the risk of colorectal cancer, but no subgroup has been identified for which the chemoprevention effect outweighs the risk of side effects.

Methods: We tested the interaction between NSAID use and multiple risk factors on colorectal cancer risk in the VITAL cohort. A total of 73,458 individuals ages 50 to 76 years completed a questionnaire between 2000 and 2002, and 674 incidental colorectal cancer cases were identified through 2010.

Results: In stratified analysis, high use of any type of NSAIDs (4+ days/week for 4+ years) was statistically significantly associated with a lower risk of colorectal cancer across all subgroups stratified by sex, body mass index, physical activity, smoking, alcohol intake, screening, and dietary factors. There was a suggestion of stronger associations among men, obese individuals, and heavier drinkers; however, none of these tests for interaction reached statistical significance. The associations were almost identical for subjects with higher overall colorectal cancer risk scores [HR, 0.62; 95% confidence interval (CI), 0.49–0.79] and those with lower risk scores (HR, 0.61; 95% CI, 0.42–0.88). Differential effects by cancer subsites and stages were tested. NSAID use was associated with a greater risk reduction of proximal colon cancer versus distal (P for difference = 0.06) and distant stage versus local (P for difference = 0.04).

Conclusion: The association between high use of NSAIDs and colorectal cancer risk does not differ significantly among subgroups.

Impact: Our results suggest that NSAIDs have a generally beneficial role in colorectal cancer prevention, largely unmodified by other exposures. *Cancer Epidemiol Biomarkers Prev; 24(4); 727–35.* ©2015 AACR.

Introduction

Chronic inflammation has been established as a risk factor for colorectal cancer, and there is substantial experimental and epidemiologic evidence that long-term use of aspirin and other NSAIDs is protective for this disease (1–4). A meta-analysis of randomized trials with 20 years of follow-up found that long-term aspirin use reduced the incidence of and mortality due to colorectal cancer, and the benefit increased with scheduled duration of treatment (2). The effect was reported to be greatest 10 to 14 years after randomization in patients who had scheduled trial treatment of 5 years or more (1). The likely mechanism of NSAIDs is that they reduce inflammatory mediators, such as high-sensitivity C-reactive protein (5, 6) and IL6 (7), through the inhibition of cyclooxygenase-2 (COX-2; ref. 8), which is responsible for producing various inflammatory prostaglandins (9). Cox-independent pathways have also been observed to be modified by aspirin exposure, including the oncogenic Wnt/β-catenin pathway (10) and the NF-κB pathway (11, 12).

Several other risk factors for colorectal cancer have also been identified, including obesity, high consumption of red and/or processed meat, physical inactivity, smoking, moderate-to-heavy alcohol consumption (13), and family history (14). It is suspected that some of these risk factors may also affect colorectal cancer risk by increasing inflammation, but their interactions with NSAID use are unclear. A population-based case–control study found significant interaction between smoking duration and use of any NSAIDs (15); however, the result was not confirmed in a later cohort study (16). Among nonaspirin NSAID users, a statistically significant lower risk of colorectal cancer in association with body mass index (BMI) above 25, but not with BMI of 25 or below, was reported in a Danish cohort study (17), but results from other large cohort studies did not reach statistical significance (16, 18, 19). Meta-analyses did not find the effect of NSAID use significantly different between men and women (1, 20). Randomized trials also reported synergistic effects of calcium and any NSAID use in lowering the risk of advanced colorectal neoplastic polyps (21). However, these results are not consistent with other studies that did not find significant interactions between aspirin/NSAID use and other risk factors of colorectal cancer (3, 16). Similarly, evidence for differential associations by anatomic site or cancer stage is not consistent across single studies (3, 16, 22–24). A systematic review from randomized and observational studies reported no differences in the associations of aspirin and other NSAIDs by colorectal cancer site or aggressiveness (1). A meta-analysis of cohort studies found a stronger but statistically nonsignificant effect of aspirin on the risk of rectal cancer

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compared with colon cancer (20), whereas the follow-up meta-analysis of randomized trials found that long-term aspirin use was associated with significant reduction of proximal colon cancer and rectal cancer, but not with distal colon cancer (2). In addition, meta-analyses have reported that regular use of aspirin was associated with reduced risk of distant metastasis (25, 26).

Despite their potential for chemoprevention, NSAIDs are currently not recommended for colorectal cancer prevention among the general population due to the potential side effect of gastrointestinal bleeding. Furthermore, due to the inconsistent results among prior studies of interaction effects between NSAID use and other risk factors, no subgroup of the population has been identified for which the benefits clearly outweigh the risks. In this study, we aimed to identify potential effect modifiers of the association between long-term NSAID use and colorectal cancer risk to explore differences in the effect of NSAIDs among subgroups of the population. We also examined differential effects of NSAIDs by stage and anatomic site of colorectal cancer.

Materials and Methods

Study population

Subjects were participants in the VITamins And Lifestyle (VITAL) study, a prospective cohort of persons ages 50 to 76 years residing in the 13-county western Washington catchment area of the Surveillance, Epidemiology, and End Results (SEER) cancer registry. Details of the VITAL study have been published previously (27). Briefly, potential participants were identified through a purchased commercial mailing list. Between October 2000 and December 2002, 77,719 of the 364,418 people contacted returned the 24-page questionnaire and met the eligibility and quality-control checks. The study procedures were approved by Fred Hutchinson Cancer Research Center Institutional Review Board.

We excluded participants who reported a history of colorectal cancer at baseline or missing history ($n = 1{,}184$), those with a history of ulcerative colitis or Crohn's disease ($n = 1{,}030$) or intestinal polyposis ($n = 272$), *in situ* colorectal cancer diagnosed during follow-up ($n = 13$), colorectal cancer noted on death certificate or autopsy only ($n = 3$), and diagnosis with colorectal cancer of certain rare morphologies, including malignant carcinoid tumors, neuroendocrine carcinomas, and lymphomas ($n = 38$). We also excluded participants with missing information on use of any type of NSAIDs ($n = 1{,}787$), leaving 73,458 individuals for analyses (the above-listed exclusions are not mutually exclusive).

Exposure assessment

Participants completed a self-administered, sex-specific, 24-page questionnaire on medication use, medical history, personal characteristics, cancer risk factors, supplement use, and diet.

Use of NSAIDs, including low-dose "baby" aspirin (81 mg), regular or extra-strength aspirin, ibuprofen, naproxen, celecoxib, rofecoxib, and other pain relievers (e.g., piroxicam or indomethacin), over the previous 10 years was ascertained. For each category of NSAID, participants were asked to report years taken in the previous 10 years and frequency (days per week) of use in those years. NSAID use was defined as use at least once per week for at least 1 year during the prior 10 years. Ten-year average use of each drug was categorized into three groups based on frequency and duration: nonuse, low use (<4 days/week or <4 years), and high use ($\geq$4 days/week and $\geq$4 years). NSAID use was analyzed as four types: low-dose aspirin, regular/extra strength aspirin, nonaspirin NSAIDs, and any type of NSAID.

Covariate assessment

Information on potential confounders of the NSAID–colorectal cancer association was ascertained on the baseline questionnaire. Potential confounders were selected *a priori* and included known or suspected risk factors for colorectal cancer. We controlled for age, sex, race/ethnicity, education, BMI, physical activity, smoking, alcohol intake, fruit and vegetable intake excluding potatoes, red/processed meat intake, energy intake, dietary fiber intake, dietary plus supplemental calcium intake, family history of colorectal cancer, history of sigmoidoscopy/colonoscopy in the 10 years before baseline, and hormone therapy use for females. We also controlled for indications for NSAID use, including history of frequent headaches, arthritis or joint pain, coronary heart disease, diabetes, and use of cholesterol-lowing medicine.

BMI was calculated based on self-reported height and baseline weight (kg/m^2). One thousand two hundred eighty-nine participants were missing baseline weight, but reported weight at age 45. For these participants, we estimated baseline BMI by calculating the average BMI change per year within sex-age-race groups among those with complete data, and then applying this to the number of years elapsed since age 45 for those missing BMI at baseline.

Dietary information was ascertained by a food-frequency questionnaire (FFQ) adapted from the Women's Health Initiative (28), which captured frequency and serving size of 120 foods and beverages consumed over the year before baseline. Red/processed meat intake was computed as intake of beef, pork, and lamb, including mixed dishes and processed meat. We excluded participants from dietary variable calculations if they did not complete all pages of the FFQ or if they reported abnormally high or low energy intake (men: <800 kcal/day or >5,000 kcal/day; women: <600 kcal/day or >4,000 kcal/day).

Physical activity was categorized based on the participants' 10-year average metabolic equivalent of task (MET) hours per week of moderate/vigorous physical activities (activities with MET $\geq$ 4.0), which was derived from a one-page questionnaire covering years, days per week, and minutes per day of 16 activities over the prior 10 years (29).

Case and censoring ascertainment

Incident cases of invasive colorectal cancer (ICD-O-3: 18.0–20.9) were identified during follow-up by linkage to the western Washington SEER cancer registry. As noted above, those with rare histologies were excluded. Between baseline and December 2010, there were 674 eligible invasive colorectal cancer cases diagnosed. Cancer stage was based on SEER stage, which defines localized cancer as cancer that is limited to the organ of origin, regional cancer as beyond the original site to nearby lymph nodes or organs and tissues, and distant cancer as cancer that has spread to distant organs or distant lymph nodes. Subsites of cancer cases were defined based on ICD-O-3 codes and categorized into proximal colon cancer (ICD-O-3: 18.0–18.5), distal colon cancer (ICD-O-3: 18.6–18.9), and rectal cancer (ICD-O-3: 19.9 and 20.9).

Cases were followed to the date of colorectal cancer diagnosis, and noncases were censored at whichever occurred earliest: date of death (9.1%), date of emigration out of the areas covered by SEER

(7.5%), date of withdrawal from the study (0.03%), or end of follow-up period (December 31, 2010; 83.4%). Deaths were ascertained by linkage to the Washington State death file, and emigrations out of area were identified primarily by linkage to the US Post Office National Change of Address System.

Statistical analysis

Cox regression, with age as the time variable, was used to estimate HRs and corresponding 95% confidence intervals (CI) for each NSAID variable by comparing colorectal cancer risk among nonusers, low users, and high users after adjustment for covariates. A missing indicator term was included for those missing education, race, the FFQ, BMI, and physical activity variables. At-risk time was defined as age at the completion of baseline questionnaire through age at last follow-up. A test for trend was performed for each NSAID variable by treating the categorical variable as a linear variable (codes as 1 = no use, 2 = low use, 3 = high use). Proportional hazards assumption was tested for each NSAID variable.

We tested for effect modification of the association between NSAID use and colorectal cancer risk by factors associated with inflammation (30–32), including sex, BMI (normal, overweight, and obese/severely obese), moderate/vigorous physical activity (yes/no), smoking (never/10+ year quitter, and current/recent quitter), alcohol intake (≤4 drinks/week and >4 drinks/week), fruit and vegetable intake (lower and upper halves), and red/processed meat intake (lower and upper halves). Other factors that may have modified the association between NSAID use and colorectal cancer risk were also tested, including family history of colorectal cancer (yes/no), history of sigmoidoscopy/colonoscopy (yes/no), history of coronary artery disease (yes/no), history of arthritis or joint pain (yes/no), dietary and supplemental calcium intake (lower and upper halves), and overall colorectal cancer risk scores (lower and upper halves). Effect modification by colorectal cancer overall risk was included to understand whether those at higher risk of colorectal cancer based on multiple factors might have a greater or lesser relative benefit from use of NSAIDs. The risk score was derived from sex-specific Cox models of colorectal cancer risk based on all risk factors listed as potential confounders above, except sex and hormone therapy in the model for men, and all except sex for women. The resulting betas were then applied to each participant's set of risk factors to yield their overall risk score. Interaction was tested as the significance of the cross product of the linear (trend) NSAID variable and the effect modifier in the multivariate model that included the main effects of the NSAID variable and the potential effect modifier. Stratified analyses were also performed by cancer subsites and stages. Logistic regression limited to cases was used to determine the statistical significance of subsite- and stage-specific heterogeneity, by comparing NSAID use of proximal colon cancer or rectal cancer with distal colon cancer cases, and of regional or distant cancer with local cancer cases.

All analyses were performed in Stata v.13 (StataCorp).

Results

Subjects were followed for a total of 618,289 person-years (mean follow-up, 8.4 years), among which colorectal cancer cases contributed 3,034 person-years. Cases were older, reported having a lower education level, higher BMI, and higher red/processed meat intake than the overall cohort (Table 1). They also had lower fruit and vegetable intake and were less likely to have had sigmoidoscopy/colonoscopy in the 10 years before baseline.

NSAID use was examined for its association with colorectal cancer in the entire cohort (Table 2). For each type of NSAID use (low-dose aspirin, regular aspirin, nonaspirin NSAIDs, and any type of NSAIDs), there was a statistically significant trend of lower colorectal cancer with increasing use (all P for trend <0.01). The strongest association was with any type of NSAID use: persons reporting high use of any NSAID (>4 days/week for >4 years in the 10-year period prior to baseline) had a 42% lower risk of colorectal cancer than persons reporting no use of NSAIDS (multivariate adjusted HR, 0.58; 95% CI, 0.46–0.71; P for trend < 0.001).

Table 3 presents the association of any NSAID use with colorectal cancer risk for subgroups of the cohort defined by colorectal cancer risk factors and by indications for NSAID use. High use of any type of NSAID was consistently associated with a lower risk of colorectal cancer across all subgroups, with risk reductions of 32% to 56%, and P for trends <0.05 within each subgroup, except for

Table 1. Distribution of colorectal cancer risk factors among VITAL cohort participants and cases

Characteristics	Cases (N = 674) N (%)	Cohort (N = 73,458) N (%)
Age at baseline (y)		
50–<55	59 (8.8)	17,227 (23.5)
55–<60	86 (12.8)	16,751 (22.8)
60–<65	109 (16.2)	13,412 (18.3)
65–<70	174 (25.8)	12,055 (16.4)
70+	246 (36.5)	14,013 (19.1)
Sex		
Female	343 (50.9)	38,481 (52.4)
Male	331 (49.1)	34,977 (47.6)
Education		
High school or less	210 (31.8)	14,416 (20.0)
Some college	239 (36.2)	27,665 (38.3)
College graduate or higher	211 (32.0)	30,162 (41.8)
Race/ethnicity		
White	607 (90.1)	67,403 (91.8)
Hispanic	4 (0.6)	635 (0.9)
Black	16 (2.4)	912 (1.2)
Other	47 (7.0)	4,508 (6.1)
BMI (kg^2/m)		
Normal weight (<25)	207 (32.2)	24,428 (34.3)
Overweight (≥25–<30)	248 (38.6)	29,264 (41.1)
Obese (≥30–<35)	127 (19.8)	11,790 (16.6)
Severely obese (≥35)	61 (9.5)	5,707 (8.0)
Alcohol drinks (drinks)		
None–<1 per month	252 (38.4)	26,934 (37.6)
≥1 per month–≤4 per week	174 (26.5)	21,246 (29.6)
>4 per week–<2 per day	128 (19.5)	15,422 (21.5)
≥2 per day	102 (15.6)	8,096 (11.3)
Fruit and vegetable intake (servings/day)		
0–<2.04	163 (27.4)	16,715 (25.0)
2.04–<3.16	165 (27.7)	16,715 (25.0)
3.16–<4.79	138 (23.2)	16,715 (25.0)
≥4.79	129 (21.7)	16,714 (25.0)
Red/processed meat intake (oz/week)		
0–<8.56	126 (21.2)	16,715 (25.0)
8.56–<16.55	157 (26.4)	16,715 (25.0)
16.55–<27.80	135 (22.7)	16,715 (25.0)
≥27.80	177 (29.8)	16,714 (25.0)
History of sigmoidoscopy/colonoscopy (last 10 years)		
Yes	330 (49.6)	40,957 (56.2)
No	336 (50.5)	31,890 (43.8)
Family history of colorectal cancer		
Yes	98 (14.7)	8,328 (11.4)
No	568 (85.3)	64,497 (88.6)

Table 2. Colorectal cancer risk in relation to aspirin and nonaspirin NSAID use

	Noncases *N* (%)	Cases *N* (%)	Sex and age-adjusted HR (95% CI)	Multivariate-adjusted[a,b] HR (95% CI)
Low-dose aspirin	69,119	640		
None	49,317 (71.35)	477 (74.53)	1.00 (Ref.)	1.00 (Ref.)
Low use[c]	11,301 (16.35)	93 (14.53)	0.76 (0.61–0.95)	0.73 (0.57–0.92)
High use[d]	8,501 (12.3)	70 (10.94)	0.66 (0.52–0.85)	0.67 (0.52–0.89)
P trend			<0.001	0.001
Regular aspirin	70,863	649		
None	53,377 (75.32)	519 (79.97)	1.00 (Ref.)	1.00 (Ref.)
Low use[c]	9,161 (12.93)	67 (10.32)	0.75 (0.58–0.96)	0.78 (0.59–1.02)
High use[d]	8,325 (11.75)	63 (9.71)	0.64 (0.49–0.84)	0.58 (0.44–0.78)
P trend			<0.001	<0.001
Nonaspirin NSAIDs	70,063	641		
None	47,550 (67.87)	482 (75.2)	1.00 (Ref.)	1.00 (Ref.)
Low use[c]	17,110 (24.42)	123 (19.19)	0.79 (0.64–0.96)	0.79 (0.63–0.98)
High use[d]	5,403 (7.71)	36 (5.62)	0.71 (0.51–1.00)	0.73 (0.51–1.04)
P trend			0.005	0.014
Any NSAIDs	68,044	618		
None	25,142 (36.95)	273 (44.17)	1.00 (Ref.)	1.00 (Ref.)
Low use[c]	23,327 (34.28)	188 (30.42)	0.71 (0.59–0.85)	0.70 (0.58–0.85)
High use[d]	19,575 (28.77)	157 (25.4)	0.59 (0.48–0.72)	0.58 (0.46–0.71)
P trend			<0.001	<0.001

[a]Adjusted for the following variables: age, gender, race (white, black, Hispanic, other), education (high school or less, some college/technical, college graduate or higher), BMI [normal (<25), overweight (25–<30), obese (30–<35), extremely obese (≥30)], MET hours per week of moderate/vigorous activity (none and sex-specific tertiles), smoking (never, former quit ≥10 years ago, former quit <10 years ago, current smoker), alcohol intake (0 or <1 drink per month, ≥1 drink per month and ≤4 drinks per week, >4 drinks per week and <2 drinks per day, ≥2 drinks per day), fruit and vegetable intake (servings/day; quartiles), red meat intake (ounce/week; quartiles), dietary and supplemental calcium intake (quartiles: <725.7 mg/day, ≥725.7–<1,038.16 mg/day, ≥1,038.16–<1,464.5 mg/day, and ≥1,464.5 mg/day), fiber intake (quartiles: ≤12.4 gm/day, >12.4 and ≤17.4 gm/day, >17.4 and ≤23.7 gm/day, and >23.7 gm/day), first-degree family history of colorectal cancer (none, 1, more than 1 relatives), screening history (yes or no), female hormone replacement therapy use (never, former, current), coronary artery disease (yes or no), frequent headache (yes or no), arthritis or joint pain (yes or no), diabetes (yes or no), and cholesterol-lowering drug use (yes or no). For each specific type of low-dose aspirin use, regular aspirin use, and nonaspirin NSAID use, the other two types (none, low use, or high use) were also adjusted.

[b]In multivariate-adjusted model, there are 583 cases and 63,864 noncases for low-dose aspirin use, regular aspirin use, and nonaspirin NSAID use; 600 cases and 66,248 noncases for any NSAID use.

[c]Low use defined as 1 to 3 days per week or 1 to 3 years.

[d]High use defined as ≥4 days per week and ≥4 years.

the smallest groups. There appeared to be some differential effects of NSAID use, with greater risk reduction for men, those who were obese, and regular alcohol drinkers. High NSAID use was associated with a 46% lower risk of colorectal cancer among men (HR, 0.54; 95% CI, 0.40–0.73) and 37% among women (HR, 0.63; 95% CI, 0.47–0.86; *P* interaction = 0.201). High NSAID use was associated with a 56% reduction of colorectal cancer risk among the obese (HR, 0.44; 95% CI, 0.29–0.67), compared with 32% and 39% reduction in the normal and overweight groups, respectively (for BMI < 25: HR, 0.68; 95% CI, 0.46–1.01; for 25 ≤ BMI < 30: HR, 0.61; 95% CI, 0.43–0.86; *P* interaction = 0.379). Similarly, high NSAID use was associated with 53% reduction of colorectal cancer risk among subjects who drank more than 4 drinks per week (HR, 0.47; 95% CI, 0.32–0.69) compared with a 40% reduction among those who drank 4 or less drinks per week (HR, 0.60; 95% CI, 0.46–0.79; *P* interaction = 0.186). However, the *P* for interaction did not reach statistical significance for these factors or for the other factors evaluated. The associations between high NSAID use and the overall risk score were almost identical between subjects with higher and lower risk scores (for lower risk score: HR, 0.61; 95% CI, 0.42–0.88; for higher risk score: HR, 0.62; 95% CI, 0.49–0.79).

In addition, we found high use of any NSAID was associated with a lower risk of colorectal cancer for all subsites and stages (Table 4). The association was strongest for proximal colon cancer (HR, 0.44; 95% CI, 0.27–0.70), compared with distal colon cancer (HR, 0.65; 95% CI, 0.49–0.87; *P* heterogeneity = 0.062), and for distant stage (HR, 0.37; 95% CI, 0.21–0.66), compared with local colorectal cancer (HR, 0.59; 95% CI, 0.42–0.82; *P* heterogeneity = 0.042).

We also evaluated effect modification separately for aspirin use (low dose and regular/extra strength combined) and nonaspirin NSAID use (Supplementary Tables S1–S4). The suggestion of effect modification by sex also appeared for aspirin use and colorectal cancer risk (*P* interaction = 0.086), but not for nonaspirin NSAID use. For both types, colorectal cancer risk reduction was greatest among the obese. Family history of colorectal cancer modified the association of nonaspirin NSAID use with colorectal cancer risk (*P* interaction = 0.009), with the lowest risk among those without family history. The associations between aspirin use and overall risk score did not differ between the higher and lower risk score group. However, we observed a large difference in the association between non-NSAID use and overall risk score (for lower risk score: HR, 0.46; 95% CI, 0.21–0.99; for higher risk score: HR, 0.93; 95% CI, 0.63–1.38; *P* interaction = 0.108). Anatomic subsite differences persisted for aspirin use only (*P* heterogeneity between proximal and distal = 0.051), whereas the lowest risk was for distant stage colorectal cancer for both types of NSAIDs. However, the tests for interaction and for differences were not statistically significant except as noted.

Discussion

In this prospective study, we found NSAID use of any type for 4+ days per week for 4+ years was associated with a 42% lower risk of colorectal cancer (*P* trend < 0.001). Furthermore, there was

Table 3. Association of any NSAID use with colorectal cancer risk, stratified by risk factors for colorectal cancer and by indications for NSAID use

	Any NSAID use										
	No use			Low use (<4 days/week or <4 years)			High use (≥4 days/week and ≥4 years)				
Effect modifiers	Case (*N* = 266)	Noncases (*N* = 24,475)	HR[a]	Case (*N* = 182)	Noncases (*N* = 22,743)	HR[a] (95% CI)	Case (*N* = 152)	Noncases (*N* = 19,030)	HR[a] (95% CI)	*P* trend	*P* interaction[b]
Age (y)											
<65	68	8,997	1.00	52	7,467	0.81 (0.56–1.18)	18	4,143	0.40 (0.23–0.69)	0.001	0.222
≥65	198	15,478	1.00	130	15,276	0.66 (0.53–0.83)	134	14,887	0.62 (0.49–0.78)	0.000	
Sex											
Male	134	11,252	1.00	76	9,987	0.61 (0.46–0.82)	82	10,348	0.54 (0.40–0.73)	0.000	0.201
Female	132	13,223	1.00	106	12,756	0.79 (0.61–1.03)	70	8,682	0.63 (0.47–0.86)	0.003	
BMI (kg/m^2)											
<25	88	9,531	1.00	55	7,356	0.77 (0.55–1.09)	42	5,403	0.68 (0.46–1.01)	0.044	0.379
25–30	99	9,488	1.00	59	9,238	0.57 (0.41–0.80)	62	7,879	0.61 (0.43–0.86)	0.002	
30+	68	4,822	1.00	57	5,584	0.72 (0.50–1.04)	40	5,291	0.44 (0.29–0.67)	0.000	
Physical activity[c]											
No	162	12,147	1.00	117	11,440	0.76 (0.59–0.97)	84	9,860	0.54 (0.41–0.72)	0.000	0.427
Yes	100	12,002	1.00	63	11,044	0.62 (0.45–0.86)	65	8,934	0.60 (0.43–0.85)	0.003	
Smoking											
Never/10+ year quitter	223	21,048	1.00	144	19,243	0.67 (0.54–0.83)	126	16,008	0.58 (0.46–0.73)	0.000	0.615
Current/recent quitter	43	3,427	1.00	38	3,500	0.88 (0.56–1.39)	26	3,022	0.60 (0.35–1.11)	0.063	
Alcohol intake											
≤4 drinks/week	168	16,395	1.00	114	15,051	0.70 (0.55–0.90)	97	12,004	0.60 (0.46–0.79)	0.000	0.186
>4 drinks/week	94	7,527	1.00	64	7,249	0.68 (0.49–0.94)	47	6,627	0.47 (0.32–0.69)	0.000	
Fruit and vegetable intake											
<3.16 servings/day	132	11,061	1.00	94	10,530	0.71 (0.54–0.93)	67	8,557	0.52 (0.38–0.71)	0.000	0.614
≥3.16 servings/day	104	11,308	1.00	71	10,319	0.69 (0.50–0.94)	64	8,915	0.58 (0.41–0.81)	0.001	
Red/processed meat intake											
<16.55 oz/week	108	11,589	1.00	81	10,501	0.73 (0.54–0.98)	61	8,232	0.57 (0.41–0.80)	0.001	0.290
≥16.55 oz/week	128	10,780	1.00	84	10,348	0.67 (0.51–0.89)	70	9,240	0.52 (0.38–0.72)	0.000	
Calcium intake[d]											
<1,038 mg/day	136	12,049	1.00	75	10,209	0.62 (0.46–0.82)	59	7,638	0.54 (0.39–0.75)	0.000	0.581
≥1,038 mg/day	100	10,218	1.00	89	10,497	0.78 (0.58–1.05)	71	9,706	0.54 (0.39–0.75)	0.000	
History of sigmoidoscopy/colonoscopy (last 10 years)											
No	146	12,050	1.00	87	9,849	0.71 (0.54–0.94)	70	7,053	0.65 (0.48–0.88)	0.003	0.726
Yes	120	12,425	1.00	95	12,894	0.68 (0.54–0.90)	82	11,977	0.51 (0.38–0.69)	0.000	
Family history											
No	232	21,684	1.00	146	20,135	0.66 (0.54–0.82)	129	16,800	0.58 (0.46–0.73)	0.000	0.450
Yes	34	2,791	1.00	36	2,608	1.00 (0.62–1.62)	23	2,230	0.61 (0.34–1.08)	0.100	
History of coronary artery disease											
No	254	23,810	1.00	159	21,223	0.68 (0.56–0.83)	119	15,403	0.60 (0.48–0.76)	0.000	0.491
Yes	12	665	1.00	23	1,520	1.00 (0.49–2.05)	33	3,627	0.58 (0.29–1.16)	0.051	
Arthritis or joint pain											
No	170	15,731	1.00	74	10,537	0.61 (0.46–0.81)	66	7,846	0.58 (0.43–0.79)	0.000	0.770
Yes	96	8,744	1.00	108	12,206	0.80 (0.61–1.06)	86	11,184	0.60 (0.44–0.82)	0.001	
Risk score[e]											
Lower half	71	11,547	1.00	56	11,669	0.74 (0.52–1.05)	49	10,197	0.61 (0.42–0.88)	0.008	0.817
Upper half	195	12,928	1.00	126	11,073	0.72 (0.57–0.90)	103	8,833	0.62 (0.49–0.79)	0.000	

[a]Multivariate model adjusted for age, gender, race (white, black, Hispanic, other), education (high school or less, some college/technical, college graduate or higher), BMI (normal, overweight, obese, extremely obese), MET hours per week of moderate/vigorous activity (none and tertiles), smoking (never, former quit ≥10 years ago, former quit <10 years ago, current smoker), alcohol intake (0 or <1 drink per month, ≥1 drink per month and ≤4 drinks per week, >4 drinks per week and <2 drinks per day, ≥2 drinks per day), fruit and vegetable intake (quartiles), red meat intake (quartiles), dietary and supplemental calcium intake (quartiles), fiber intake (quartiles), first-degree family history of colorectal cancer (none, 1, more than 1 relatives), screening history (yes or no), female hormone replacement therapy use (never, former, current), coronary artery disease (yes or no), frequent headache (yes or no), arthritis or joint pain (yes or no), diabetes (yes or no), and cholesterol-lowing drug use (yes or no). Model based on 600 cases and 66,248 noncases.

[b]*P* interaction based on interaction of liner (trend) NSAID variable and effect modifier variable.

[c]Any moderate or vigorous physical activity in 10 years before baseline.

[d]Dietary plus supplemental calcium intake.

[e]The risk score is sex-specific: the median risk score for men is −0.593, and the median risk score for women is −0.391.

Table 4. Association of any NSAID use with colorectal cancer risk by anatomic site and stage

	Any NSAID use										
		No use		Low use (<4 days/week or <4 years)			High use (≥4 days/week and ≥4 years)				
	Case (N = 266)	Noncases (N = 24,475)	HR[a]	Case (N = 182)	Noncases (N = 22,743)	HR[a] (95% CI)	Case (N = 152)	Noncases (N = 19,030)	HR[a] (95% CI)	P trend	P heterogeneity[b]
Subsite											
Distal	132	24,475	1.00	97	22,743	0.73 (0.56–0.96)	89	19,030	0.65 (0.49–0.87)	0.003	Ref.
Proximal	66	24,475	1.00	43	22,743	0.65 (0.44–0.97)	30	19,030	0.44 (0.27–0.70)	0.000	0.062
Rectal	68	24,475	1.00	42	22,743	0.68 (0.46–1.01)	33	19,030	0.56 (0.36–0.88)	0.009	0.163
Stage											
Local	106	24,475	1.00	83	22,743	0.79 (0.59–1.07)	64	19,030	0.59 (0.42–0.82)	0.002	Ref.
Regional	113	24,475	1.00	65	22,743	0.58 (0.43–0.80)	64	19,030	0.60 (0.43–0.84)	0.001	0.857
Distant	47	24,475	1.00	34	22,743	0.74 (0.47–1.16)	19	19,030	0.37 (0.21–0.66)	0.001	0.042

[a]Multivariate model adjusted for age, gender, race (white, black, Hispanic, other), education (high school or less, some college/technical, college graduate or higher), BMI (normal, overweight, obese, extremely obese), MET hours per week of moderate/vigorous activity (none and tertiles), smoking (never, former quit ≥10 years ago, former quit <10 years ago, current smoker), alcohol intake (0 or <1 drink per month, ≥1 drink per month and ≤4 drinks per week, >4 drinks per week and <2 drinks per day, ≥2 drinks per day), fruit and vegetable intake (quartiles), red meat intake (quartiles), dietary and supplemental calcium intake (quartiles), fiber intake (quartiles), first-degree family history of colorectal cancer (none, 1, more than 1 relatives), screening history (yes or no), female hormone replacement therapy use (never, former, current), coronary artery disease (yes or no), frequent headache (yes or no), arthritis or joint pain (yes or no), diabetes (yes or no), and cholesterol-lowing drug use (yes or no). Model based on 600 cases and 66,248 noncases.

[b]P heterogeneity used to test for differences across cancer subsite and stage: for cancer subsites, proximal colon cancer and rectal cancer were both compared with distal colon cancer; for cancer stage, regional and distant cancers were compared with local cancer.

a statistically significant risk reduction of colorectal cancer within each subgroup of the study population stratified by sex, BMI, physical activity, smoking, alcohol intake, screening, and various dietary factors, suggesting that NSAID use is beneficial for most subgroups of colorectal cancer risk. The risk reduction may be greater among men, the obese, and heavier alcohol drinkers; however, none of the tests for effect modification reached statistical significance. We also found that NSAID use was associated with a lower risk of proximal colon cancer compared with distal colon cancer, and distant stage colorectal cancer compared with local stage.

Although prior studies of NSAID use on colorectal cancer risk generally reported on aspirin and/or nonaspirin NSAID use separately rather than combined, meta-analyses of randomized and observational studies suggested that regular use of aspirin and NSAIDs had similar association with colorectal cancer (1), and our results are consistent with most of the randomized controlled trials and observational studies that suggest a benefit for both aspirin and/or nonaspirin NSAID use (1–3, 16, 23, 33). In a meta-analysis based on the long-term effect of aspirin on colorectal cancer incidence and mortality from five randomized trials (2), assigned treatment of low-dose and regular aspirin for 5 years or more was statistically significantly associated with 38% reduction in colorectal cancer incidence. Our results of 33% and 42% lower risk associated with low-dose and regular aspirin respectively are consistent with the meta-analysis. However, some cohort studies did not observe a reduction in colorectal cancer risk in relation to dose or duration of aspirin use (18, 22), which may be due to the short follow-up period and the possibility, based on follow-up reports from five randomized trials, that the effects of NSAID use may have a 10-year latency (1, 2).

The reduction of colorectal cancer risk associated with NSAID use appeared to be 10% greater among men than women. Another large prospective cohort study found that the protective effect of aspirin on colon cancer was 10% greater among men than women, but the test for interaction did not reach statistical significance (34). They also found that aspirin use was associated with 52% lower risk of rectal cancer among men, but a 7% higher risk among women. However, systematic reviews of observational studies have reported that the association between regular use of aspirin or NSAIDs and colorectal cancer does not significantly differ by sex (1, 20).

We also found a suggestion of a stronger inverse association between NSAID use and colorectal cancer risk among obese individuals than overweight or normal-weight individuals, and this differential association was consistent for aspirin and nonaspirin NSAIDs. Obesity is associated with a chronic proinflammatory state with increased cytokine levels (35). A similar but smaller difference in association by BMI groups was also observed in the Danish cohort study (17). In that study, nonaspirin NSAID use was associated with lower risk of colorectal cancer only among those with BMI greater than 25 kg/m^2, although the association between aspirin use and colorectal cancer did not differ by the BMI group. Analyses of other large cohort studies did not observe statistically significant interaction between BMI and aspirin on colorectal cancer risk (16, 18, 19), but in two of the cohort studies, the effect of aspirin use was found to be greater among overweight or obese participants than those of normal weight (18, 19). Thus, there is some consistency across studies of a greater risk reduction associated with NSAID use among overweight or obese individuals, but most studies, including ours, did not have power to

detect statistically significant interaction between NSIAD use and BMI.

Similarly, although not statistically different, high NSAID use was associated with 53% lower risk among those who have more than 4 drinks per week compared with 40% lower among lighter/nondrinkers. Alcohol intake is a known risk factor for colorectal cancer (36). Several studies suggest that ethanol overexposure may alter the cytokine level in a variety of tissues as well as *in vitro* (37, 38). Findings from an animal study, in which chronic alcohol intake promoted intestinal tumorigenesis and tumor invasion in genetically susceptible mice, found that mast cell–mediated inflammation could be one of the mechanisms by which alcohol promotes carcinogenesis (39). Landi and colleagues (40) observed that an association of colorectal cancer risk with alcohol drinking was evident in the subgroup of IL6 C-allele carriers, but the risk was halved by the use of NSAIDs among those carriers. Interaction between alcohol intake and other genes that modulate inflammation of the colorectum, including PPARγ (41), has also been found. Thus, evidence suggests that the carcinogenic effect of alcohol consumption may, at least in part, result from interactions with the inflammatory response, consistent with the suggestion here, of an interaction between alcohol intake and NSAID use.

Furthermore, our data suggest that NSAID use may have differential protective effects by anatomic subsites of colorectal cancer. We found that high NSAIDs use was associated with lower risk of proximal colon cancer than of distal colon cancer. Previously reported results have differed by exposure type. Our results were consistent with studies that also analyzed all types of NSAIDs or nonaspirin NSAIDs (16, 24), whereas studies assessing aspirin use alone found a lower risk of distal than proximal colon cancer (3, 16, 22, 23). However, follow-up analysis based on five randomized trials reported the largest risk reduction to be of proximal colon cancer among long-term aspirin users (2), consistent with our study. The precise mechanisms by which NSAIDs exert differential chemoprevention effects by anatomic sites are currently unclear. Studies have suggested that different prevalence of COX expression in cancerous tissue originating from the rectum versus colon may play a role, but results were inconsistent (42, 43). Other evidence has shown that aspirin may interact with some tumor molecular features, such as PIK3CA and BRAF mutations, to influence colorectal cancer risk and mortality, and these features may differ by anatomic site (44–46). In addition, we found a statistically significantly greater protective association for colorectal cancer with distant metastasis than with local disease. This is consistent with findings from the meta-analyses of five randomized trials of aspirin (26) as well as observational studies (25), and with evidence that aspirin may reduce tumor angiogenesis and lymphangiogenesis (47).

An advantage of our study is that our measure of NSAID use may be more accurate and detailed than most prior studies. We incorporated years of use as well as frequency in our exposure variables because associations of NSAID use with colorectal cancer probably depend on both duration and frequency (1, 2, 20, 48). In addition, by using any NSAID use as our main exposure variable, our power was strengthened as both aspirin and nonaspirin NSAIDs are associated with decreased risk of colorectal cancer. Other strengths include the prospective design, the large sample size, the inclusion of both men and women, and the near-complete follow-up using case linkage through the SEER registry. An additional advantage was the availability of detailed information on a large number of potential confounders, including risk factors for colorectal cancer as well as indications for NSAID use, specifically cardiovascular disease prevention, and arthritis and joint pain treatment.

Limitations of this study are that NSAID use was based on self-report, and additionally, we had no information on NSAID use after baseline. However, it has been suggested that the effect of NSAID use has a 10-year latency period for colorectal cancer risk (1), and the time period we assessed for NSAID use was the 10-year period before baseline, which would be 10 to 20 years before cancer onset. Nonetheless, we expect that the potential measurement error in NSAID use, due to both poor recall before baseline and lack of information after baseline, would be nondifferential between cases and noncases in a prospective study. In addition, despite our control for colorectal cancer risk factors and indications for NSAID use, residual confounding may persist. Also, although we had sufficient power to detect statistically significant risk reductions associated with NSAID use within almost all subgroups examined, we did not have the power to detect effect modification of the NSAID–colorectal cancer association by other risk factors. This may be due to the limited number of cases in each subgroup and/or the relatively small differences in effect size between groups. Lastly, our findings may be due to multiple comparisons.

In conclusion, NSAID use was statistically significantly associated with lower overall risk of colorectal cancer and with a greater risk reduction of proximal colon cancer and distant-stage colorectal cancer. We did not observe statistically significant interactions between NSAID use and other risk factors or overall risk score, although the association with NSAID use appeared to be stronger among men, obese individuals, and heavier drinkers. The associations across almost all subgroups of participants suggest a generally beneficial role of NSAIDs in colorectal cancer prevention, with the relative reduction in risk largely unmodified by other exposures.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. White

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. White

Study supervision: E. White

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