Nonsteroidal Anti-inflammatory Drugs and Subsite-Specific Colorectal Cancer Incidence in the Iowa Women's Health Study

Amit Mahipal,[1] Kristin E. Anderson,[1] Paul J. Limburg,[2] and Aaron R. Folsom[1]

[1]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota and
[2]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, Minnesota

Abstract

Background: **Previous epidemiologic studies have shown that regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with decreased colorectal cancer risk. However, few studies have examined associations between NSAID use and subsite-specific colorectal cancer risks. Because tumors of the proximal and distal colon differ with respect to their genetic alterations, clinicopathologic features, and demographic distribution, further investigation of subsite-specific colorectal cancer risks may be rewarding.**

Methods: **Data about aspirin and nonaspirin-NSAID use were recorded by self-report in 1992 among the initially cancer-free cohort of postmenopausal women in the Iowa Women's Health Study (n = 27,160). In total, 637 women developed colorectal cancer during the 11 years of follow-up, including 365 proximal colon, 132 distal colon, and 120 rectal cancer cases (11 overlapping and 9 not specified).**

Results: **For colon cancer, the multivariable-adjusted hazard ratios (HR) for women reporting use of aspirin two to five times and six or more times weekly (compared with nonusers of aspirin) were 0.79 [95% confidence interval (95% CI), 0.59-1.04] and 0.76 (95% CI, 0.58-1.00), respectively. The corresponding HRs for nonaspirin NSAIDs were 0.63 (95% CI, 0.41-0.96) and 0.85 (95% CI, 0.63-1.15), respectively. For proximal colon cancer, the multivariable-adjusted HRs for women reporting use of aspirin or nonaspirin NSAIDs two or more times weekly (compared with nonusers of each) were 0.67 (95% CI, 0.51-0.87) and 0.71 (95% CI, 0.52-0.97), respectively. No statistically significant association was found between either distal colon or rectal cancer and aspirin or nonaspirin NSAID use.**

Discussion: **Our study is consistent with a limited number of prior reports that have observed stronger associations between NSAID use and proximal versus distal colorectal cancer.** (Cancer Epidemiol Biomarkers Prev 2006;15(10):1785–90)

Introduction

Colorectal cancer is the second leading cause of cancer death in the United States with 55,170 deaths and 148,610 incident cases estimated in 2006 (1). Despite the recent advances in diagnostic methods and therapeutic interventions, the 5-year relative survival rate for this relatively common disease remains ~60% (1). Thus, more effective preventive strategies would have important public health implications.

Except for a cohort study in the elderly (2), previous observational studies, both cohort and case-control studies, have shown that use of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAID) are associated with reduced colorectal cancer risks (3-17). In contrast, the Physicians' Health Study and the Women's Health Study, the only randomized controlled trials that reported on associations between regular use of aspirin and colorectal cancer incidence, did not find any statistically significant reduction in colorectal cancer incidence with low dose aspirin use (18, 19). Chemoprevention of sporadic colorectal adenomas with aspirin has been reported in three randomized, controlled clinical trials (20-22). Few observational studies have evaluated associations between NSAID use and colorectal cancer risks by anatomic subsite within the colorectum (10, 13, 17). It has been suggested that proximal and distal colon cancers may progress through distinct carcinogenic pathways because these tumors differ with respect to their genetic alterations, clinicopathologic features, and demographic distribution (23-30). Thus, further investigation of proximal, distal, and rectal cancer risks among NSAID users may be rewarding. In this study, we examined associations between self-reported use of aspirin or nonaspirin NSAIDs and subsite-specific colorectal cancer risks (proximal colon, distal colon, and rectum) among postmenopausal women in the Iowa Women's Health Study (IWHS).

Materials and Methods

Detailed descriptions of the IWHS cohort have been published previously (31-33). In 1986, a 16-page questionnaire was mailed out to 99,826 randomly selected women, between the ages of 55 and 69 years, who resided in Iowa and held a valid driver's license. The baseline questionnaire was completed by 41,836 women (42%) and they constituted the IWHS cohort. Nonresponders to the initial questionnaire had similar demographic characteristics and colorectal cancer incidence rates as initial responders (33). Information about potential colorectal cancer risk factors, place of residence, and vital status was updated among cohort subjects using follow-up mail surveys in 1987 (91% response rate), 1989 (89% response rate), 1992 (83% response rate), and 1997 (79% response rate).

In 1992, NSAID use was ascertained. First, women were asked how often they took aspirin. The question included examples of aspirin-containing products: Bufferin, Anacin, enteric-coated aspirin, Ecotrin, and Excedrin. Second, they were asked how often they took NSAIDs or arthritis medicines and the question included examples of ibuprofen, Advil, Nuprin, Motrin, Naprosyn, Feldene, and Clinoril. The

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Requests for reprints: Kristin E. Anderson, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 South Second Street, Suite 300, Minneapolis MN 55454. Phone: 612-626-8568; Fax: 612-624-0315.
E-mail: anderson_k@epi.umn.edu

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respondents were specifically directed to exclude acetaminophen and Tylenol use in both questions. Response options for both questions on frequency of use were as follows: (*a*) never, (*b*) less than one per week, (*c*) one per week, (*d*) two to five per week, and (e) six or more per week. Current use of estrogen replacement, family history of colon cancer in a first-degree relative, and personal diagnosis of osteoarthritis, rheumatoid arthritis, and migraine were also self-reported in 1992. Data about demographics, weight, height, waist circumference, hip circumference, physical activity, multivitamin use, and dietary intake were self-reported on the 1986 questionnaire, whereas smoking status and alcohol intake were obtained using both 1986 and 1992 questionnaires. The 127-item Willet semiquantitative food-frequency questionnaire (34) was used to assess dietary intake. Body mass index (BMI) was calculated as follows: weight (kg) / height $(m)^2$. In 1986, a paper tape measure and written instructions to have a friend measure waist (1 inch above the umbilicus) and hip (maximal protrusion) were included with the questionnaire. The waist-to-hip circumference ratio (WHR) was calculated. Physical activity was assessed from several questions that asked about the frequency of moderate- and heavy-intensity leisure time activities. These responses were combined to create a three-level activity index (low, medium, and high), which has been associated inversely with coronary heart disease mortality rate among IWHS participants (35).

Incident colorectal cancer cases (n = 637) were ascertained from time of completion of the questionnaire in 1992 until December 31, 2002 through annual linkage with the Iowa Cancer Registry, which is a part of the National Cancer Institute Surveillance, Epidemiology, and End Results program (36). WHO *International Classification of Diseases for Oncology, Second Edition* codes (18.0-18.9, 18.0-19.9, and 18.0-20.9) were used to define cases. Name, address, maiden name, birth date, and social security number were used for linkage. For subsite-specific analysis, *International Classification of Diseases for Oncology* codes 18.0 to 18.5 and 18.6 to 18.7 defined proximal and distal colon cancers cases, respectively. Rectal cancer cases were defined by codes 19.9 and 20.9. Deaths among nonrespondents to follow-up surveys and emigrants from Iowa were determined by linkage with the National Death Index of the National Center for Health Statistics.

We excluded women who reported in 1986 that they had a cancer other than skin cancer (n = 2,293) and those with incident cancer from 1986 to 1992 (n = 2,512). There were 27,160 women left for analysis after further excluding women who did not complete the 1992 questions about aspirin and NSAID use. For subsite-specific analyses, we excluded cases with synchronous tumors in more than one colorectal subsite and cases for whom tumor subsite could not be definitively localized (n = 20). Follow-up time was calculated from the date of completion of the 1992 questionnaire to one of the following: (*a*) the date of incident colorectal cancer diagnosis; (*b*) the date of death (if occurred in Iowa); (*c*) the date of emigration from Iowa (if known); (*d*) the midpoint of interval between the last follow-up contact and December 31, 2002 (if the date of emigration from Iowa was unknown); or (*e*) the midpoint of the interval between the date of last contact and the date of death (for deaths in women who had emigrated from Iowa). Women who did not meet any of the above criteria were assumed to be living in Iowa and contributed follow-up time until December 31, 2002. Emigration from Iowa was identified by the follow-up questionnaires and by identifying location of deaths for decedents.

All analyses were done using SAS statistical software (SAS Institute, Inc., Cary, NC). Descriptive statistics were initially used to characterize the cohort. Aspirin and nonaspirin-NSAID use were considered separately in the colorectal cancer risk models. Proportional hazard regression analyses (SAS: PROC PHREG) were used to estimate and compare the age-adjusted and multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI). Never users of aspirin and nonaspirin NSAIDs were used as the referent category to compare the HRs at different frequencies of aspirin and nonaspirin NSAID use, respectively. Use of aspirin and nonaspirin NSAIDs were adjusted for each other, as appropriate. When both aspirin and nonaspirin NSAID use were stratified simultaneously, never users of any NSAIDs were considered as the referent group. Potential confounding variables were evaluated by comparing the −2 log-likelihoods of proportional hazards regression models with and without the potential confounder. P values for the trends in HR for categories of increasing frequency of aspirin and NSAID use were obtained from the trend test option in the proportional hazards regression model. The analyses were done for colon and rectal tumors and subsequently for proximal and distal colon tumors separately.

Results

The analysis cohort consisted of 27,160 women contributing 264,460 person-years of observation. Twenty-eight percent of women reported no current use of aspirin, 28% reported using aspirin less than once weekly, 5% reported using aspirin once weekly, 18% reported using aspirin two to five times weekly, and 21% reported using aspirin six or more times weekly. The corresponding figures for nonaspirin-NSAID use were 60%, 15%, 3%, 8%, and 13%, respectively. Women who reported use of aspirin and nonaspirin NSAIDs tended to have higher prevalence of calcium and vitamin E intake above the median and multivitamin and postmenopausal estrogen use compared with nonusers (Table 1). Women with more frequent use of nonaspirin NSAIDs tended to have higher mean BMI and WHR. Women using more nonaspirin NSAIDs more often had a history of migraine, rheumatoid arthritis, and osteoarthritis.

During the follow-up period, 637 women developed colorectal cancer, including 510 colon (365 proximal colon and 132 distal colon) and 120 rectal cancer cases. Eleven cases had synchronous tumors in more than one colorectal subsite and nine cases had tumors for which the anatomic subsite was not specified. We also evaluated the distribution of selected subject characteristics by colorectal cancer incidence (data not shown). Women who developed incident colorectal cancer versus those who did not were older and had higher BMI and WHR. Calcium intake, vitamin E intake, multivitamin use, estrogen-replacement use, physical activity level, and history of migraine were higher among women who remained free of colorectal cancer than in those who developed colorectal cancer.

For colorectal cancer, the age- and multivariable-adjusted HRs for any NSAID (aspirin or nonaspirin-NSAID) users versus nonusers were 0.86 (95% CI, 0.71-1.04) and 0.86 (95% CI, 0.70-1.05), respectively. The corresponding HRs for colon cancer were 0.78 (95% CI, 0.63-0.97) and 0.77 (95% CI, 0.62-0.96). Table 2 presents the age- and multivariable-adjusted colon cancer risk associations for each level of aspirin use and nonaspirin NSAID use. Compared with nonusers of aspirin, the multivariable-adjusted HRs for women who reported use of aspirin two to five times and six or more times weekly were 0.79 (95% CI, 0.59-1.04) and 0.76 (95% CI, 0.58-1.00), respectively. When nonaspirin NSAIDs were considered, the corresponding HRs (use versus nonuse) were 0.63 (95% CI, 0.41-0.96) and 0.85 (95% CI, 0.63-1.15), respectively. The P_{trend} in HRs (over categories of increasing frequency of use) was statistically significant for both aspirin use (P_{trend} = 0.036) and nonaspirin NSAID use (P_{trend} = 0.032). We did not find any statistically significant changes in these associations after excluding subjects who developed colorectal cancer during the first 2 years of follow-up. The multivariable-adjusted HR between rheumatoid arthritis (as a surrogate for long-term NSAID use) and colorectal cancer was 0.74 (95% CI, 0.55-1.01).

Table 1. Prevalence (%) of baseline characteristics of subjects by frequency of aspirin or nonaspirin NSAID use in 1992, IWHS

Times weekly	Aspirin					Nonaspirin NSAIDs				
	0	<1	1	2-5	≥6	0	<1	1	2-5	≥6
	n = 627	*n* = 7,524	*n* = 492	*n* = 799	*n* = 5,718	*n* = 16,428	*n* = 4,158	*n* = 836	*n* = 2,181	*n* = 3,557
Age (y)*										
61-65	35	41	36	38	34	36	42	37	40	37
66-70	36	35	35	35	35	35	35	38	34	35
71+	29	24	29	27	31	29	23	25	26	28
BMI, ≥30 kg/m^2 †	25	19	20	21	25	20	21	24	26	34
WHR, ≥0.8278 †,‡	52	46	50	49	53	49	47	51	51	56
Energy intake, ≥1,707 kcal/d †,‡	49	50	51	52	49	50	50	51	52	50
Dietary fiber, ≥18.6 mg/d †,‡	50	50	51	52	49	50	50	53	51	49
Calcium, ≥1,036 mg/d †,‡	49	48	53	51	53	49	51	53	52	53
Vitamin E, ≥9.7 mg/d †,‡	49	48	51	52	53	49	51	54	53	53
Current multivitamin use †	31	31	35	35	37	31	34	37	37	37
Current estrogen replacement*	15	16	18	18	19	15	19	18	19	23
Current alcohol use*	73	64	64	64	69	69	61	62	66	72
Current smoker*	9	8	8	9	10	9	8	9	9	8
Physical activity †										
Low	48	46	45	44	46	46	45	47	46	49
Moderate	27	28	30	30	27	28	30	29	30	27
High	25	26	25	26	27	27	25	24	24	24
Family history of colon cancer*	3	3	3	3	3	3	3	3	3	3
History of diabetes*	5	4	4	4	7	5	4	3	5	6
History of migraines*	9	7	8	11	13	8	10	11	13	14
History of rheumatoid arthritis*	12	7	8	9	15	7	8	9	16	27
History of osteoarthritis*	19	12	13	15	23	11	13	17	24	45

*1992 questionnaire.
†1986 questionnaire.
‡Cut point is the cohort median.

Aspirin and nonaspirin-NSAID use were associated with statistically significant reductions in proximal colon cancer incidence. The multivariable-adjusted HRs for women reporting use of aspirin and nonaspirin NSAIDs more than twice weekly (compared with nonusers of each) were 0.67 (95% CI, 0.51-0.87) and 0.71 (95% CI, 0.52-0.97), respectively (Table 3). In analyses where aspirin and other NSAIDs were stratified simultaneously, the incidence of proximal colon cancer decreased with increasing frequency of aspirin use among nonusers and occasional users of nonaspirin NSAIDs, but not among heavy NSAID users, all of whom had reduced incidence (Table 4). There were no statistically significant associations between aspirin or nonaspirin NSAIDs and distal colon cancer incidence, with HRs of 1.04 (95% CI, 0.67-1.63) and 0.88 (95% CI, 0.54-1.42), respectively, for women using aspirin or nonaspirin NSAIDs two or more times weekly compared with nonusers of each. Similarly, rectal cancer incidence was not found to be statistically significantly associated with the use of either aspirin or nonaspirin NSAIDs (Table 3). Although the differences in HRs for proximal colon, distal colon, and rectal cancers were of note, they were not statistically significant.

Discussion

In this large prospective cohort study of postmenopausal women, self-reported use of aspirin and nonaspirin NSAIDs was found to be inversely associated with incident colon cancer, particularly proximal colon cancer. Compared with nonusers of the respective medications, users of aspirin and nonaspirin NSAIDs for six or more times weekly had 24% and 15% lower colon cancer incidence, respectively, and there were statistically significant trends in HRs for colon cancer over increasing frequency of both aspirin and nonaspirin NSAIDs. As symptoms of undiagnosed colorectal cancer could have

Table 2. Association of aspirin and nonaspirin NSAID use with colon cancer incidence, IWHS, 1992-2002

	No. cases	Total person-years	Age-adjusted HR	95% CI	Multivariable-adjusted HR*,†	95% CI
Aspirin Use						
Never	157	73,071	1.00	Referent	1.00	Referent
≤1 per week	173	88,912	0.93	0.75-1.16	0.87	0.69-1.09
2-5 per week	82	47,235	0.82	0.63-1.07	0.79	0.59-1.04
6+ per week	98	54,605	0.83	0.64-1.07	0.76	0.58-1.00
	510		P_{trend} = 0.091		P_{trend} = 0.036	
Nonaspirin NSAID use						
Never	323	159,179	1.00	Referent	1.00	Referent
≤1 per week	103	49,138	1.08	0.86-1.35	1.16	0.92-1.46
2-5 per week	29	21,424	0.69	0.47-1.00	0.63	0.41-0.96
6+ per week	55	34,083	0.81	0.61-1.08	0.85	0.63-1.15
	510		P_{trend} = 0.024		P_{trend} = 0.032	

*Adjusted for age (continuous), BMI (continuous), WHR (continuous), calcium intake (continuous), multivitamin use (yes and no), estrogen use (current and not current), family history of colon cancer (yes and no), physical activity (low, medium, and high), and smoking status (current, former, and never).
†Aspirin analyses are adjusted for nonaspirin NSAID use and nonaspirin NSAID use analyses are adjusted for aspirin use.

Table 3. Association of aspirin and nonaspirin NSAID use with proximal colon, distal colon, and rectal cancer incidence, IWHS, 1992-2002

	Proximal colon cancer			Distal colon cancer			Rectal cancer		
	No. cases	Multivariable-adjusted HR*,†	95% CI	No. cases	Multivariable-adjusted HR*,†	95% CI	No. cases	Multivariable-adjusted HR*,†	95% CI
Aspirin use									
Never	120	1.00	Referent	34	1.00	Referent	28	1.00	Referent
≤1 per week	119	0.78	0.60-1.02	49	1.06	0.67-1.68	42	1.26	0.76-2.09
≥2 per week	126	0.67	0.51-0.87	49	1.04	0.67-1.63	50	1.32	0.82-2.13
	365			132			120		
Nonaspirin NSAID use									
Never	236	1.00	Referent	80	1.00	Referent	70	1.00	Referent
≤1 per week	71	1.10	0.83-1.46	29	1.29	0.83-2.00	23	1.03	0.62-1.71
≥2 per week	58	0.71	0.52-0.97	23	0.88	0.54-1.42	27	1.26	0.80-2.00
	365			132			120		

*Adjusted for age (continuous), BMI (continuous), WHR (continuous), calcium intake (continuous), multivitamin use (yes and no), estrogen use (current and not current), family history of colon cancer (yes and no), physical activity (low, medium, and high), and smoking status (current, former, and never).
†Aspirin analyses are adjusted for nonaspirin NSAID use and nonaspirin NSAID use analyses are adjusted for aspirin use.

modified the subjects' use of aspirin or nonaspirin NSAIDs, we repeated our analyses after excluding women who developed colorectal cancer during the first 2 years of follow-up. No appreciable changes were noted in any associations.

Extensive observational data support an inverse association of NSAIDs with colorectal cancer risk (3-17, 37, 38). An inverse association has also been shown between NSAIDs and colorectal adenomas (4, 14, 39-48), considered to be precursors of colorectal cancer. However, few prior studies have evaluated subsite-specific colorectal cancer risks among NSAID users. Studies that have evaluated the associations of NSAID use with colon and rectal cancers separately (3, 4, 6, 11, 14, 37, 38) have generally observed similar risk associations, although stronger associations with rectal cancer have been reported (5, 7). A limited number of previous studies have also found that NSAID use is associated with a stronger inverse association for proximal compared with distal colon cancer (10, 13, 17). In a hospital-based case-control study, Rosenberg et al. (10) reported odds ratios of 0.4 (95% CI, 0.2-0.8), 0.6 (95% CI, 0.4-1.0), and 0.6 (95% CI, 0.4-1.1) for proximal colon, distal colon, and rectal cancers, respectively, among recent NSAID users compared with nonusers. In another case-control study, Friedman et al. (17) reported that, compared with nonusers, aspirin users had odds ratios of 0.6 (95% CI, 0.5-0.8) and 0.8 (95% CI, 0.6-0.9) for proximal and distal colon cancers, respectively. Smalley et al. (13), in a cohort study, also found that associations with use of NSAIDs were more pronounced for proximal colon cancer than for distal colon or rectal cancer. The adjusted relative risks among recent users with >12 months of cumulative use for proximal colon, distal colon, and rectal cancers were 0.48 (95% CI, 0.34-0.68), 0.77 (95% CI, 0.55-1.08), and 0.81 (95% CI, 0.49-1.32), respectively.

Table 4. Joint association of aspirin and nonaspirin NSAID use with proximal colon cancer incidence, IWHS, 1992-2002

HR*	Nonaspirin NSAID Use		
	Never	≤1 weekly	≥2 weekly
Aspirin use			
Never	1.00 (referent)	1.26 (0.76-2.09)	0.62 (0.37-1.03)
≤1 per week	0.81 (0.58-1.12)	0.90 (0.59-1.37)	0.40 (0.20-0.81)
≥2 per week	0.65 (0.46-0.90)	0.59 (0.34-1.01)	0.65 (0.40-1.03)

*Adjusted for age (continuous), BMI (continuous), WHR (continuous), calcium intake (continuous), multivitamin use (yes and no), estrogen use (current and not current), family history of colon cancer (yes and no), physical activity (low, medium, and high), and smoking status (current, former, and never).

Our study is consistent with these latter studies, although we did not observe any significant reduction of risk of distal colon or rectal cancer with the current use of NSAIDs. We found the risk of proximal colon cancer was lower by approximately one third among women with aspirin or nonaspirin NSAID use of two or more times weekly compared with nonusers of each. Our data support the hypothesis that aspirin may induce differential chemopreventive effects by colorectal cancer subsite; however, because the site-specific HRs observed in our study were not statistically significant, this requires further investigation.

To date, the Physicians' Health Study and the Women's Health Study are the only randomized controlled trials that have reported on associations between regular use of aspirin and incident colorectal cancer (18, 19). In the Physician's Heath Study, no statistically significant reductions in colorectal cancer incidence were observed after either 5 or 12 years of follow-up (18, 49). However, the study was limited by analysis of colorectal cancer as a secondary end point, a relatively short duration of intervention, lack of systematic evaluation for adenomatous polyps or colorectal cancer, and a relatively low aspirin dose (325 mg every other day). The Women's Health Study also found no effect of low-dose aspirin (100 mg every other day) on colorectal cancer incidence over an average follow-up of 10.1 years (19). There was no statistically significant effect of aspirin by colorectal cancer subsite with relative risks of 0.86 (95% CI, 0.60-1.25), 0.94 (95% CI, 0.63-1.40), and 1.20 (95% CI, 0.71-1.21) for proximal colon, distal colon, and rectal cancers, respectively. In contrast, chemoprevention of sporadic colorectal adenomas with aspirin has been reported in three randomized, controlled clinical trials (20-22), each of which observed statistically significant risk reductions from the active agent in slightly different subject populations. Thus, although existing data are not entirely consistent, there appears to be an anticarcinogenic effect from NSAIDs in the colorectal mucosa.

The precise mechanisms by which NSAIDs exert their antitumor effects are currently unclear. However, a part of their chemoprotective effect is thought to stem from their ability to inhibit prostaglandin endoperoxidase synthase [cyclooxygenase (COX)]. COX enzymes catalyze the biosynthesis of the endoperoxide intermediate prostaglandin H_2 from arachidonic acid (50). At least two different types of COX enzyme isoforms have been identified in human tissues: COX-1 and COX-2 (51-53). COX-1 is constitutively expressed in most tissues, where it synthesizes prostaglandins at low levels to maintain physiologic functions (54). COX-2 expression, on the other hand, is low or negative in most tissues, except in the central nervous system, the kidney, and the

seminal vesicles, where it is constitutively expressed in high levels (55). COX-2 expression can be induced by proinflammatory stimuli, cytokines, and mitogens resulting in increased synthesis of prostaglandins (53, 54). Several studies have reported an increase in COX-2 expression in colorectal adenomas and colorectal cancer tissue compared with normal tissue, whereas there was little or no change in COX-1 expression (56-58). A study by Oshima et al. (59), using animal models, provided direct genetic evidence that COX-2 inhibition decreases colorectal cancer growth.

COX expression has been reported to vary depending on the site of colorectal cancer. One study reported significantly lower COX-2 expression levels in rectal versus colon tumors (60). In contrast, another study reported a significantly higher prevalence of up-regulated COX-2 in cancerous tissue originating from rectum compared with that from colon (61). These studies suggest that different pathogenic mechanisms may be involved in the development of colorectal cancer at different anatomic subsites, which could influence the chemopreventive potential of NSAIDs for proximal colon, distal colon, or rectal cancers. However, further research is needed to clarify the role that differential COX-2 expression plays in subsite-specific colorectal cancer chemoprevention.

The strengths of our study were the large, population-based cohort, long follow-up, and thorough case ascertainment. The response rates to the follow-up questionnaires were excellent. Information was also collected to enable adjustment for several potential confounders. However, we had no information on the use of sigmoidoscopy or other screening procedures for colorectal cancer. The gastrointestinal symptoms associated with NSAID use could have resulted in increased diagnostic tests and thus prevention of some cases of colorectal cancer if precancerous polyps were detected and subsequently removed.

Cancer identification is nearly complete for women living in Iowa, as we used an outstanding Surveillance, Epidemiology, and End Results registry. Women known to have moved out of Iowa are censored. Because migration is low, very few women would be misclassified as living in Iowa when they had actually moved out of the state. Death ascertainment is virtually complete (99%) because we use a combination of follow-up questionnaires, linkage to Iowa death certificates, and linkage to the National Death Index to ensure completeness.

An important limitation of our study was lack of information on the duration of NSAID use. The effect of duration of NSAID use on colon cancer development is not clear. The Nurses' Health Study reported that the inverse association of aspirin with colorectal cancer was evident only after 10 years of regular use (3). In contrast, some retrospective studies have reported inverse association with shorter duration of NSAID use. The Nurses' Health study, a prospective study with repeated assessments of aspirin use, may better approximate long-term use compared with a single retrospective assessment of NSAID use. However, the Nurses' Health Study is not population based and results in nurses may not be generalizable to the population as a whole. As noted above, two randomized controlled trials (18, 19), with as much as 10 years of follow-up for some individuals, found null effects from aspirin on colorectal cancer risk. A protective effect might have emerged after longer use, but it may also be that low dose aspirin is simply not protective.

Although not ideal, we looked at rheumatoid arthritis as a surrogate measure of long-term NSAID use. Colorectal cancer risk was 26% lower among women with, versus those without, rheumatoid arthritis, which is in keeping with our risk estimates for both aspirin and nonaspirin NSAID reported use. IWHS subjects were asked to report their frequency of NSAID use, but no information on the dose of the NSAIDs was collected and this is an additional limitation of our study. Subjects using NSAIDs at higher frequencies may be taking lower doses per occasion, which could have resulted in misclassification of the subjects' exposure status. Misclassification might also occur in subjects who take the drugs sporadically, as their recall may be less accurate than regular users.

Observational data strongly support an inverse association between regular use of NSAIDs and decreased colorectal cancer risk. However, tumors originating in proximal and distal colon appear to have distinct pathogenetic mechanisms and NSAID use may differentially affect carcinogenesis in these colorectal cancer subsites. Additional clinical trials are needed to establish the role of NSAIDs in colorectal cancer chemoprevention and to further determine whether the association varies according to colorectal cancer subsite.

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