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Research Article

Cancer Prevention Research

Nonsteroidal Anti-inflammatory Drug Use and Risk of Adenomatous and Hyperplastic Polyps

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Abstract

Adenomatous polyps are known precursor lesions for colorectal cancer and some hyperplastic polyps also have malignant potential. The use of aspirin and nonsteroidal anti-inflammatory drugs (NSAID) is associated with a reduced risk of adenomatous polyps; however, less evidence exists with regard to NSAID use and hyperplastic polyp risk. We conducted a colonoscopy-based case–control study including 2,028 polyp cases (1,529 adenomatous and 499 hyperplastic) and 3,431 polyp-free controls. Multivariate logistic regression models were constructed to derived adjusted ORs and 95% CIs as the measure of the association between NSAID use and polyp risk. Use of baby aspirin, regular aspirin, and nonaspirin NSAIDs, were associated with a reduced risk of adenomatous polyps (OR = 0.79, 95% CI: 0.66–0.93, OR = 0.73, 95% CI: 0.58–0.90, and OR = 0.67, 95% CI: 0.53–0.86, respectively). Baby aspirin was also associated with a reduced risk of hyperplastic polyps (OR = 0.74, 0.56–0.97). Although a dose response was seen with adenoma risk and regular use of any NSAIDs (less than 7 doses per week, 7 doses per week, and greater than 7 doses per week), a dose response was not seen with hyperplastic polyps. We found no evidence of interaction between NSAID dose and duration and polyp risk. The use of any NSAID regardless of type was associated with a reduced risk of adenomatous polyps; however, regular aspirin and COX-2 inhibitors use was not associated with hyperplastic polyp risk. *Cancer Prev Res; 4(11); 1799–807. ©2011 AACR.*

Introduction

Colorectal cancer is the second leading cause of cancer-related mortality within the United States (1), and adenomatous polyps are established precursors for colorectal cancer (2). Although colorectal cancer screening tests are effective at reducing cancer-related mortality through the removal of cancer precursor lesions, the uptake rates for these procedures are low (3–5). Therefore, there is considerable interest in potential chemopreventive strategies for reducing colorectal tumors. To date, the most rigorously studied agents have been the nonsteroidal anti-inflammatory drugs (NSAID; refs. 6–8).

In randomized clinical trials, NSAIDs and selective COX-2 inhibitors reduced the risk of recurrent adenomas by as much as 45% (9–14). Emerging evidence suggests that some colorectal cancers may arise from certain hyperplastic polyps along the serrated neoplastic pathway. This pathway has several key differences to the classical adenoma–carcinoma pathway, including early mutations in *BRAF* and CpG island methylation (15). As such, it is important to determine whether NSAIDs may also reduce the risk of hyperplastic polyps. Only a few studies have evaluated this hypothesis, and the sample sizes for these studies were small (16, 17).

In the general population, it is estimated that approximately 5% to 27% of regular aspirin users concomitantly use nonaspirin NSAIDS (18–20). These numbers could be significantly greater as both aspirin and nonaspirin NSAIDs are available over-the-counter without requiring a prescription. Limited data exists examining the influence of both agents simultaneously on colorectal neoplasms. Although one might assume a synergistic effect, an earlier cohort study found that the addition of nonaspirin NSAIDs to regular aspirin use in women did not offer additional protection from proximal colorectal cancers (21). Herein, we report results from a large colonoscopy-based study involving 5,459 patients that evaluated the association of regular use of aspirin, nonaspirin NSAID, or a combination of the two on adenomatous and hyperplastic polyp risk.

Materials and Methods

Study participants

Participants were part of the Tennessee Colorectal Polyp Study (TCPS), an on-going colonoscopy-based case–control study conducted in Nashville, Tennessee. Study

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Table 1. Age-adjusted characteristics of adenomatous and hyperplastic polyp cases and controls

Characteristic	Controls ($N = 3,431$)	Adenomatous ($n = 1,529$)	Hyperplastic ($n = 499$)	P^a
Age (y, mean ± SD)	56.8 ± 7.7	58.8 ± 7.3	56.7 ± 7.0	<0.0001
Sex (female, %)	43.9	27.5	31.0	<0.0001
Race (%)				
Caucasian	87.5	86.0	90.9	
African American	10.5	11.7	8.0	
Other	2.0	2.3	1.1	0.05
Smoking (%)				
Current	12.7	28.3	33.8	
Former	35.1	36.5	38.1	
Never	52.2	35.2	28.1	<0.0001
Alcohol consumption (%)				
Current	18.4	21.1	23.4	
Former	22.4	29.3	27.4	
Never	59.3	49.7	49.2	<0.0001
Family history of colon cancer or adenomatous polyp (yes, %)	14.6	16.6	14.7	0.17
Educational attainment (%)				
High school or less	24.3	33.2	33.7	
Some college	28.4	29.2	30.1	
College graduate	20.7	19.8	18.6	
Graduate or professional education	26.6	17.9	17.6	<0.0001
Regularly exercised (%)	57.8	49.8	54.4	<0.0001
BMI (kg/m^2, mean ± SD)	28.1 ± 5.8	28.9 ± 5.7	28.8 ± 5.9	<0.0001
Use of HRT (ever, %)[b]	59.6	62.8	60.5	0.72
Study site (%)				
Academic center	72.7	58.8	55.5	
VA	27.3	41.2	44.5	<0.0001
Indication for colonoscopy (%)				
Screening	70.5	67.6	64.6	
Diagnostic/bleeding/other	29.5	32.4	35.4	0.01

[a]ANOVA for continuous variables and χ^2 test for categorical.
[b]Women only ($n = 2,082$).

methods have been published elsewhere (22). Briefly, eligible participants, aged between 40 and 75 years, were identified from patients scheduled for either screening or diagnostic colonoscopies at the Vanderbilt Gastroenterology Clinic between February 1, 2003 and May 31, 2008 and the Veterans' Affairs Tennessee Valley Health System, Nashville campus between August 21, 2003 and May 30, 2007. Excluded from the study were patients with genetic colorectal cancer syndromes (such as hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis) or a prior history of inflammatory bowel disease, adenomatous polyps, or any cancer other than nonmelanoma skin cancers. We excluded individuals with prior histories of colorectal adenomas or cancer to ensure that colonoscopy examinations would not be surveillance endoscopies. A total of 10,467 eligible individuals were contacted with regard to study participation. Ninety-three percent ($n = 9,745$) were approached prior to colonoscopy examination and the remaining ($n = 722$) were contacted after colonoscopy. Sixty-four percent of eligible individuals agreed to participant in the study and provided written informed consent. The Vanderbilt University and the Tennessee Valley Healthcare System Institutional Review Boards approved the study.

Exposure assessment

Trained interviewers conducted a standardized telephone interview following colonoscopy to obtain information on medication use, demographics, medical history, family history, reproductive history, anthropometry, dietary, and other lifestyle factors. Interviewers were blinded to the results of the colonoscopy examination. Participants

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Table 2. Association between aspirin and NSAID dose and duration of use and adenomatous and hyperplastic polyp risk, the TCPS

		Polyp types			
		Adenomatous		Hyperplastic	
Exposures	Control	*n*	OR[a](95% CI)	*n*	OR[a](95% CI)
NSAID use					
Never	1,654	748	1.00	238	1.00
Baby aspirin only	701	333	0.79 (0.66–0.93)	92	0.74 (0.56–0.97)
Regular aspirin only	352	177	0.73 (0.58–0.90)	63	0.90 (0.65–1.25)
Nonaspirin NSAIDs only	343	125	0.67 (0.53–0.86)	49	0.73 (0.51–1.04)
COX-2 inhibitor only	77	21	0.61 (0.36–1.02)	11	0.98 (0.49–1.93)
Any combination of NSAIDS	304	125	0.60 (0.47–0.76)	46	0.69 (0.48–1.00)
Baby aspirin only, doses/wk					
Never	1,654	748	1.00	238	1.00
<7	53	27	1.03 (0.62–1.71)	6	0.75 (0.31–1.84)
≥7	648	306	0.77 (0.64–0.92)	86	0.74 (0.56–0.99)
P_{trend}			0.01		0.10
Baby aspirin only, duration (y)					
Never	1,654	748	1.00	238	1.00
<5	341	150	0.76 (0.61–0.96)	39	0.65 (0.45–0.95)
≥5	360	183	0.81 (0.65–1.01)	53	0.85 (0.60–1.21)
P_{trend}			0.02		0.07
Regular aspirin only, doses/wk					
Never	1,654	748	1.00	238	1.00
<7	58	20	0.61 (0.36–1.06)	11	1.13 (0.57–2.25)
7	229	124	0.75 (0.58–0.97)	34	0.71 (0.46–1.08)
>7	65	33	0.76 (0.48–1.20)	18	1.30 (0.73–2.32)
P_{trend}			0.04		0.22
Regular aspirin only, duration (y)					
Never	1,654	748	1.00	238	1.00
<5	117	48	0.61 (0.42–0.89)	20	0.87 (0.51–1.47)
≥5	235	129	0.78 (0.60–1.00)	43	0.89 (0.61–1.31)
P_{trend}			0.01		0.81
Single agent nonaspirin NSAID, doses/wk					
None	1,654	748	1.00	238	1.00
<7	81	27	0.81 (0.51–1.29)	13	1.00 (0.53–1.88)
7	124	45	0.72 (0.50–1.04)	21	0.94 (0.56–1.56)
>7	215	74	0.59 (0.43–0.80)	26	0.60 (0.38–0.95)
P_{trend}			0.002		0.13
Single agent nonaspirin NSAID, duration (y)					
Never	1,654	748	1.00	238	1.00
<5	176	58	0.61 (0.44–0.85)	17	0.49 (0.28–0.83)
≥5	244	88	0.71 (0.53–0.93)	43	0.97 (0.67–1.41)
P_{trend}			0.001		0.03
Any combination of NSAID, doses/wk					
None	1,654	748	1.00	238	1.00
<7	38	21	0.92 (0.52–1.64)	4	0.55 (0.19–1.63)
7	85	44	0.80 (0.53–1.19)	13	0.76 (0.40–1.44)
>7	181	60	0.45 (0.32–0.62)	29	0.67 (0.42–1.05)
P_{trend}			<0.0001		0.26
Any combination of NSAIDs, duration (y)					
Never	1,654	748	1.00	238	1.00
<5	57	22	0.56 (0.33–0.95)	9	0.63 (0.30–1.35)
≥5	247	103	0.60 (0.46–0.79)	37	0.71 (0.48–1.06)
P_{trend}			0.0002		0.15

[a]Adjusted for age, gender, race, family history, education level, BMI, energy intake, smoking status, alcohol use, physical activity, use of hormone replacement therapy, indication for colonoscopy, study site, and year of study enrollment.

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Table 3. Association between dose per week of aspirin and NSAID use and adenomatous polyp risk, the TCPS

	Aspirin, doses/wk					
	None		≤7		>7	
Nonaspirin NSAIDs, doses/wk	Case/controls	OR[a] (95% CI)	Case/controls	OR[a] (95% CI)	Case/controls	OR[a] (95% CI)
None	748/1,654	1.00	444/943	0.76 (0.65–0.89)	66/110	0.85 (0.60–1.20)
≤7	72/205	0.75 (0.56–1.01)	56/107	0.83 (0.58–1.19)	9/16	0.81 (0.34–1.92)
>7	79/232	0.58 (0.44–0.78)	39/131	0.38 (0.26–0.57)	16/33	0.65 (0.34–1.24)
						$P_{\text{-interaction}} = 0.56$

[a]Adjusted for age, gender, race, family history, education level, BMI, energy intake, smoking status, alcohol use, physical activity, use of hormone replacement therapy, indication for colonoscopy, study site, and year of study enrollment.

were asked to report whether they had ever used aspirin (regular or baby aspirin) in the past 15 years or nonaspirin NSAIDs for at least 3 days a week over a duration of at least 2 months. Individuals responding "yes" to these questions were asked to report NSAID brands, duration of use, and frequency. Participants were asked to report on both prescription and over-the-counter NSAID use. For this analysis, we defined regular users as individuals taking aspirin or NSAIDS 3 or more times a week for a minimum duration of 1 year. We categorized NSAIDs users into specific subtypes on the basis of reported use patterns. These categories included users of regular aspirin only, users of baby aspirin only, users of nonaspirin NSAIDs (such as ibuprofen, naproxen, or indomethacin), users of selective COX-2 inhibitors only, and users reporting the use of 2 or more categories of NSAID, for example, aspirin along with ibuprofen. Each NSAID subtype was then categorized into dosing groups (fewer than 7 doses a week, 7 doses a week, and greater than 7 doses a week) and duration groups (fewer than 5 years of continuous use and 5 or more years continuous use).

Among 6,702 participants, 5,785 (86%) completed the telephone interview. We excluded 326 participants with incomplete data about prior use of NSAIDs. Our final study included 5,459 participants categorized as 3,431 polyp-free controls and 2,028 polyp cases including 1,146 cases with adenomatous polyps, 499 cases with hyperplastic polyps, and 383 cases with synchronous adenomatous and hyperplastic polyps. Because individual effect sizes for each NSAID category stratum were similar between combined adenoma only and synchronous adenoma and hyperplastic polyp cases, we combined these 2 groups together for these analyses.

Statistical methods

We compared age-adjusted differences between cases and controls using ANOVA for continuous variables or the Cochran–Mantel–Haenszel χ^2 test for categorical variables. Unconditional logistic regression models were used to estimate the risk of colorectal polyps associated with NSAID use. All models were adjusted for age (continuous), sex (male, female), race (white, nonwhite), family history of colorectal cancer or adenomatous polyp in a first-degree relative (yes, no), educational attainment (high school or less, some college, college graduate, graduate, or professional education), body mass index (BMI, continuous), total energy intake (continuous), cigarette use (current use, former use, never use), regular alcohol use (current use, former use, never use), regular physical activity in the last 10 years (yes, no), use of hormone replacement therapy-for women only (ever, never), indication for colonoscopy (screening, diagnostic), study site (VUMC, VA), and year of colonoscopy. We calculated tests for trend by rank ordering the exposure categories and including this variable within the model as a continuous term. We stratified each NSAID category by dose and duration and adjusted these models using the same covariates used for our main effects model. Dose analyses were not adjusted for duration of use and duration analyses were not adjusted for dose used. We then constructed logistic regression models for each polyp location and polyp size (<1 cm, ≥1 cm). Polyps located from the cecum to just proximal of the splenic flexure were considered proximal, polyps located from the splenic flexure to the rectum were considered distal, and polyps found within the rectum were considered rectal polyps. For our analyses stratified by polyp location, we excluded 239 cases that had synchronous proximal and distal polyps and 89 cases with both rectal and nonrectal polyps. For hyperplastic polyps, we excluded 47 cases with polyps in multiple locations. To tests for possible interactions between aspirin use and nonaspirin NSAID use, we included the cross product of aspirin dose in pills per day (0, ≤ 7, and > 7) and nonaspirin NSAID dose in pills per day (0, ≤ 7, and > 7) as a continuous variables within our models and used the likelihood ratio test to evaluate potential multiplicative interactions of the two variables by comparing the models with and without the cross product term of these variables. We used a similar procedure to test for interaction between medication dose and duration (0, <5 years, and ≥5 years) for aspirin use and nonaspirin NSAID use. All statistical calculations were done using SAS version 9.2 (SAS Institute).

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Table 4. Association between drug dose and duration of aspirin and nonaspirin NSAID and adenomatous polyp risk, the TCPS

	Adenomatous polyp		
NSAID use	**Controls**	**Cases**	**OR[a] (95% CI)**
Never	1,654	748	1.00
Aspirin only use			
≤7 doses/wk			
<5 y of use	400	174	0.73 (0.59–0.91)
≥5 y of use	543	270	0.77 (0.64–0.94)
>7 doses/wk			
<5 y of use	32	15	0.69 (0.36–1.31)
≥5 y of use	78	51	0.92 (0.61–1.36)
$P_{\text{-interaction}}$			0.37
Single agent nonaspirin NSAID			
≤7 doses/wk			
<5 y of use	84	27	0.62 (0.39–0.99)
≥5 y of use	121	45	0.85 (0.59–1.24)
>7 doses/wk			
<5 y of use	92	31	0.60 (0.38–0.93)
≥5 y of use	123	43	0.58 (0.40–0.86)
$P_{\text{-interaction}}$			0.43
Any combination of NSAID			
≤7 doses/wk			
<5 y of use	30	15	0.68 (0.35–1.33)
≥5 y of use	93	50	0.89 (0.61–1.30)
>7 doses/wk			
<5 y of use	27	7	0.42 (0.18–0.99)
≥5 y of use	154	53	0.45 (0.32–0.64)
$P_{\text{-interaction}}$			0.83

[a]Adjusted for age, gender, race, family history, education level, BMI, energy intake, smoking status, alcohol use, physical activity, use of hormone replacement therapy, indication for colonoscopy, study site, and year of study enrollment.

Results

Age-adjusted characteristics of the study group are presented in Table 1. Participants with adenomatous or hyperplastic polyps were more likely to be male, currently smoking, using alcohol, less educated, less physically active, and have higher BMIs when compared with polyp-free controls. There was no difference between the groups with respect to family history of colorectal cancer or use of hormone replacement therapy. Cases were more likely to have undergone colonoscopy for diagnostic purposes.

For adenomatous polyps, there was a reduction in the OR seen for all NSAID categories (Table 2). Compared with individuals who were not using NSAIDs, effect sizes ranged from 0.79 (95% CI: 0.66–0.93) for baby aspirin users to 0.60 (95% CI: 0.47–0.76) for NSAID combination users. Baby aspirin use was associated with a statistically significant reduced OR for hyperplastic polyps (0.74, 95% CI: 0.56–0.97) compared with nonusers (Table 2). A significant dose–response relationship was seen for all aspirin and nonaspirin NSAID categories and risk of adenomatous polyps. No clear dose response was seen with NSAID use and hyperplastic polyp risk. Longer duration of use of either aspirin or nonaspirin NSAID did not result in any additional reduction of polyp risk (Table 2 and 4).

There was no clear evidence of a joint effect between dose of aspirin and dose of nonaspirin NSAIDs and adenomatous polyp risk (Table 3). We found no evidence of an interaction between NSAID dose and duration of use with adenomatous polyp risk (Table 4).

When stratified by polyp location, aspirin and nonaspirin NSAID use was associated with reduced risks of both proximal and distal adenomatous polyp, although the effect sizes were slightly larger for adenomatous polyps located in the distal bowel (Table 5). Aspirin and nonaspirin NSAID use was associated with a reduction in both large (≥1 cm) and small (<1 cm) adenomatous polyp risks (Table 6). For large adenomas, regular use of aspirin and nonaspirin NSAID use was associated with an OR of 0.64 (0.43–0.95) and 0.27 (0.15–0.48), respectively.

Discussion

Consistent with prior studies, we found a reduced risk for colon adenomas in regular users of aspirin or nonaspirin NSAIDs (23–25). Although we found slightly larger effect sizes in individuals reporting regular use of both aspirin and nonaspirin NSAIDs, our test for interaction did not reach statistical significance. In addition, we found no evidence of a statistical interaction between the dose and duration of use for aspirin or nonaspirin NSAIDs. Both baby aspirin and nonaspirin NSAIDs seemed protective for hyperplastic polyps, which is consistent with previous studies of hyperplastic polyps (26–29). We found no association between use of COX-2 inhibitors and hyperplastic polyp risk; however, we had few cases and limited power to detect a true effect. The association of aspirin or nonaspirin NSAIDs with adenomatous polyp risk seems to be more prominent for distal than proximal polyps, although the difference was modest. Similar with prior studies, we found greater effect sizes associated with regular NSAID use for larger adenomas (23, 30).

Overall, we found a more pronounced effect of NSAIDS on adenomatous polyp risk as opposed to hyperplastic polyp risk. One possible mechanism for this difference in NSAID effects is likely related to the differential overexpression of COX-2 seen in adenomatous polyps as opposed to hyperplastic polyps. Although overexpression of COX-2 has been described in hyperplastic polyp specimens (31), the strength of COX-2 overexpression is less in hyperplastic polyps compared with adenomatous polyps (32, 33). Kawasaki and colleagues found that 28% of nonserrated adenomas had strong overexpression of COX-2 compared with only 4.2% of hyperplastic polyps (33). In addition, COX-2 overexpression in serrated adenomas seemed to vary on the basis of tumor location and

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Table 5. Association between aspirin and NSAID use and adenomatous and hyperplastic polyp risk stratified by polyp location, the TCPS

		Adenomatous polyp					
		Proximal		Distal		Rectal	
Exposures	Control	*n*	OR[a](95% CI)	*n*	OR[a](95% CI)	*n*	OR[a](95% CI)
NSAID use							
Never	1,654	268	1.00	253	1.00	59	1.00
Baby aspirin only	701	139	0.90 (0.71–1.15)	100	0.72 (0.55–0.94)	33	0.99 (0.62–1.57)
Regular aspirin only	352	66	0.79 (0.58–1.08)	51	0.61 (0.43–0.87)	17	0.92 (0.51–1.67)
Nonaspirin NSAIDs only	343	60	0.90 (0.65–1.24)	38	0.57 (0.39–0.84)	10	0.73 (0.36–1.50)
Any combination of NSAIDs	304	53	0.69 (0.49–0.98)	33	0.46 (0.30–0.69)	13	1.00 (0.52–1.91)
		Hyperplastic polyps					
		Proximal		Distal		Rectal	
	Control	*n*	OR[a](95% CI)	*n*	OR[a](95% CI)	*n*	OR[a](95% CI)
NSAID use							
Never	1,654	36	1.00	82	1.00	86	1.00
Baby aspirin only	701	16	0.81 (0.43–1.51)	41	0.93 (0.61–1.42)	22	0.56 (0.34–0.93)
Regular aspirin only	352	5	0.52 (0.98–1.07)	29	1.13 (0.70–1.83)	19	0.84 (0.49–1.45)
Nonaspirin NSAIDs only	343	7	0.77 (0.33–1.79)	24	1.01 (0.61–1.65)	13	0.58 (0.31–1.09)
Any combination of NSAIDs	304	6	0.73 (0.29–1.84)	12	0.54 (0.28–1.04)	19	0.91 (0.52–1.58)

[a]Adjusted for age, gender, race, family history, education level, BMI, energy intake, smoking status, alcohol use, physical activity, use of hormone replacement therapy, indication for colonoscopy, study site, and year of study enrollment.

polyp histopathology. For hyperplastic and sessile serrated polyps, distally located polyps tended to have stronger COX-2 overexpression although these sample sizes were small and this difference was not statistically significant. Other studies have also found that serrated adenomas have higher levels of COX-2 overexpression compared with hyperplastic polyps (32, 34). When stratified by location, we found stronger effects for most NSAID categories on hyperplastic polyps located distally or in the rectum, but these findings should be interpreted with caution as our numbers were very small and our estimates unstable.

In our primary analysis, we found a protective effect of nonaspirin NSAIDs on hyperplastic polyp risk. Two prior studies have found a significant reduction in OR for hyperplastic polyps in NSAID users compared with non-NSAID users (16, 17). In a large cross-sectional study including 391 cases, Lieberman found that daily NSAID use was associated with an adjusted OR of 0.75 (0.56–0.99) for hyperplastic polyp risk compared with nonusers (16). In a small case–control study of 81 subjects with hyperplastic polyps and 480 controls, Martinez found an adjusted OR of 0.34 (0.14–0.83) in daily nonaspirin NSAID users (17). In both of these studies, aspirin and nonaspirin NSAID users were combined into a single regular NSAID user category. In a third case–control study which included 219 hyperplastic polyp cases and 708 controls and evaluated aspirin and nonaspirin NSAIDs separately found a nonsignificant effect in nonaspirin NSAID users (OR = 0.60; 0.3–1.11) and no effect of aspirin use (OR = 1.0; 0.6–1.6) on hyperplastic polyp risk (35); however, it was not reported whether the aspirin being used was baby aspirin versus regular aspirin. Wallace and colleagues pooled 3 large chemoprevention trials together with a total of 237 left-sided and 90 right-sided serrated polyps and found a protective effect of aspirin (both 81 mg and 325 mg) for right-sided serrated polyps that was not seen for left-sided lesions (36). It is not entirely clear why we found stronger effects with baby aspirin use than regular aspirin use in our study. Wallace and colleagues found a slight increased effect size for 81 mg of aspirin as opposed to 325 mg aspirin on serrated polyp risk which was more pronounced in distal polyps (36). Of note, when the analysis included only advanced serrated adenomas, 325 mg of aspirin had larger effect sizes than 81 mg of aspirin. This might suggest that in less advanced serrated adenomas, and presumably those with lower COX-2 overexpression, baby aspirin may have a more pronounced effect than regular aspirin; however,

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Table 6. Association between NSAID use and adenomatous polyp size

		Adenomatous polyp[a]			
NSAID use	**Controls**	***n***	**≥1 cm**	***n***	**<1 cm**
Never	1,654	174	1.00	571	1.00
Baby aspirin only	701	80	0.71 (0.52–0.97)	253	0.81 (0.67–0.98)
Regular aspirin only	352	39	0.64 (0.43–0.95)	137	0.75 (0.59–0.95)
Nonaspirin NSAIDs only	343	13	0.27 (0.15–0.48)	112	0.80 (0.63–1.03)
COX-2 inhibitor only	77	3	0.34 (0.10–1.13)	18	0.70 (0.41–1.22)
Any combination of NSAIDs	304	20	0.37 (0.22–0.62)	105	0.66 (0.51–0.86)
Aspirin only, doses/wk					
Never	1,654	174	1.00	571	1.00
<7	119	8	0.60 (0.28–1.27)	44	0.96 (0.65–1.40)
7	824	88	0.65 (0.48–0.87)	303	0.77 (0.65–0.93)
>7	110	23	1.13 (0.68–1.90)	43	0.78 (0.53–1.14)
P_{trend}			0.006		0.02
Single agent nonaspirin NSAID, doses/wk					
None	1,654	174	1.00	571	1.00
<7	81	2	0.27 (0.07–1.13)	25	0.95 (0.59–1.54)
7	124	7	0.42 (0.19–0.94)	38	0.83 (0.56–1.22)
>7	215	7	0.21 (0.09–0.46)	67	0.72 (0.52–0.98)
P_{trend}			<0.0001		0.18
Any combination of NSAID, doses/wk					
Never	1,654	174	1.00	571	1.00
<7	38	7	1.25 (0.52–3.04)	14	0.79 (0.41–1.51)
7	85	5	0.32 (0.12–0.83)	39	0.95 (0.63–1.45)
>7	181	8	0.23 (0.11–0.50)	52	0.51 (0.36–0.72)
P_{trend}			0.0003		0.002

[a]Adjusted for age, gender, race, family history, education level, BMI, energy intake, smoking status, alcohol use, physical activity, use of hormone replacement therapy, indication for colonoscopy, study site, and year of study enrollment.

this is speculative and there is no clear mechanism to explain these findings.

We found a possible suggestion of a weak joint effect between the simultaneous use of aspirin and nonaspirin NSAIDs, although our interaction term was not statistically significant. In the Iowa Women's Health Study, participants who occasionally used aspirin and regularly used nonaspirin NSAIDs seem to have the most benefit, however, women who were regular users of both medications did not seem to derive additional benefit (21). Intriguingly, this is a similar pattern that we found in our study. Our data would suggest that the addition of aspirin to regular nonaspirin NSAID usage is unlikely to result in a synergistic reduction of adenoma risk.

Only a limited number of studies have evaluated subsite-specific NSAID effects with respect to colorectal adenomas. A randomized controlled trial by Baron and colleagues on adenoma recurrence noted no difference in effect by adenoma site; however, this was a trial of aspirin use and did not include nonaspirin NSAIDs (9). In observational studies, Chan and colleagues noted no association of aspirin use and the risk of adenoma by location; however, the effect size for distal adenomas (RR = 0.75, 0.66–0.84) was slightly lower than those for proximal adenomas (RR = 0.81, 0.65–1.01; ref. 28). We found stronger evidence of subsite differences with nonaspirin NSAIDs as opposed to aspirin use, but these differences were not statistically significant and would be of little clinical importance.

Our study has several strengths. The TCPS is one of the largest colonoscopy-based case–control studies of colorectal polyps conducted, providing adequate power even for some analyses that were not possible in previous studies. Only patients with complete colonoscopies were included within the study ensuring an uncontaminated control groups. There are several weaknesses to the study. First, the TCPS is a case–control study and may be subject to recall bias. This bias, however, might be mitigated using an intermediate outcome such as adenomatous polyps. A second limitation is our ascertainment of nonaspirin NSAID use was based on retrospective recall of the participants of drug use patterns and thus might result in misclassification bias. This could result in an attenuation of our effect sizes. Finally, as part of the initial pathologic review, all polyps of the serrated pathway were classified as hyperplastic polyps. Thus, this

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category could represent a diverse group of clinically and pathologically distinct lesions with varying degrees of neoplastic potential.

In summary, baby aspirin, regular aspirin, nonaspirin NSAIDs, and COX-2 inhibitor use is associated with a reduced risk of adenomatous polyps, whereas baby aspirin and nonaspirin NSAIDs use is associated with a reduced risk for hyperplastic polyp. Concomitant use of both aspirin and nonaspirin NSAIDs may offer a slight reduction in polyp risk compared with either agent by itself; however, this effect is modest and not likely to offset any possible increase in NSAID-related adverse effects. We found no clear evidence of subsite-specific effects of NSAIDs for either adenomatous or hyperplastic polyps.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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