Research Article

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Exploring Differences in the Aspirin–Colorectal Cancer Association by Sex and Race/Ethnicity: The Multiethnic Cohort Study

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Abstract

Background: Evidence has accumulated that long-term use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) protects against colorectal cancer. We tested whether the inverse associations between NSAIDs and colorectal cancer is similarly observed across sexes and five racial/ethnic groups (Japanese, Latino, African American, Native Hawaiian, and white) in the Multiethnic Cohort (MEC) Study.

Methods: During a mean follow-up of 16.1 years, we identified 4,882 invasive incident colorectal cancer cases among 183,199 eligible participants. Cox proportional hazards models were used to calculate HRs and 95% confidence intervals (CI).

Results: Use of aspirin and other NSAIDs was associated with a lower incidence of colorectal cancer in men (HR = 0.77; 95% CI, 0.69–0.86 for current vs. never users of aspirin) but not in women ($P_{interaction} = 0.005$). Among male current users, a reduced risk was observed with ≥6 years of aspirin or total NSAID use. The inverse association with current NSAID use in men was observed in all racial/ethnic groups, except for Native Hawaiians, and was stronger in whites.

Conclusions: Our findings suggest that the benefit of NSAIDs for colorectal cancer may be strongest for white men and generalizes to African American, Japanese, and Latino, but not to Native Hawaiian men. The lack of inverse association observed in women and Native Hawaiian men in the MEC should be interpreted with caution.

Impact: As only very few ethnic/racial groups are likely to be represented in trials of NSAIDs and colorectal cancer, it is important to conduct prospective observational studies in various populations to test the generalizability of their results. *Cancer Epidemiol Biomarkers Prev; 26(2); 162–9. ©2016 AACR.*

Introduction

Evidence has accumulated that long-term use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) protects against colorectal cancer (1–3). Indeed, the United States Preventive Services Task Force (USPSTF) recently released a statement recommending low-dose aspirin to prevent both cardiovascular disease (CVD) and colorectal cancer among U.S. adults, 50–69 years old, with a >10% ten-year risk of CVD events (4). These are the first guidelines recommending aspirin to prevent any form of cancer, reversing the 2007 USPSTF recommendation against the routine use of aspirin and NSAIDs for the prevention of colorectal cancer.

The systematic evidence review conducted by the USPSTF concluded that aspirin reduces the risk of colorectal cancer incidence after an induction and latency period of approximately 10 years, on the basis of randomized clinical trials and supplementary data from cohort studies (5). Importantly, the review also stated that limited data were available to address possible differences in the effect of aspirin in subgroups, including by sex and race. Also, randomized trials suggested that aspirin decreased the risk of right colon but not left colon tumors (5), whereas findings from cohort studies are inconsistent (1, 6–9).

Using the large Multiethnic Cohort (MEC) Study, we prospectively examined the associations between NSAID use status at baseline and colorectal cancer incidence by sex and anatomic subsite among five racial/ethnic groups.

Materials and Methods

Study population

Details of the MEC have been described previously (10). In brief, more than 215,000 men and women in Hawaii and California ages 45–75 years were enrolled into the cohort between 1993 and 1996. At cohort entry, the participants, who were mostly African American, Japanese American, Native Hawaiian, Latino, or white (as a result of targeted recruitment) completed a self-administered, 26-page baseline questionnaire. The study protocol was approved by the institutional review boards of the University of Hawaii (Honolulu, HI) and the University of Southern California (Los Angeles, CA). In the current analysis, we excluded participants who did not belong to one of the five major ethnic groups ($n = 13,987$), who had a prior history of colorectal cancer based on questionnaire ($n = 2,251$) or linkage to population-based cancer registries in Hawaii and California ($n = 300$), whose

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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dietary records were invalid based on total energy intake or its components ($n = 8,137$; ref. 11), or who had missing information on aspirin use ($n = 7,750$). Therefore, the analysis included 183,199 participants. In multivariate models, we further excluded participants with missing information on history of intestinal polyps, smoking, body mass index, physical activity, and multivitamin use ($n = 17,406$), resulting in 165,793 participants remaining.

Data collection

The following question was asked in the baseline questionnaire to assess NSAID use: "Have you ever taken any of the following medications at least two times per week (for one month or longer)?" The question was posed for aspirin and other NSAIDs (ibuprofen, naproxen, indomethacin, or other) separately, and examples of brand names were provided. Participants chose "no," "yes, but not at this time," or "yes, currently." If participants answered "yes," they were asked to provide the duration of NSAID use as "1 year or less," "2–3 years," "4–5 years," "6–10 years," or "11 years or more."

Ascertainment of outcomes

Incident cases of invasive colorectal cancer were identified by linkage to the Surveillance, Epidemiology, and End Results (SEER) Program cancer registries for the states of Hawaii and California. Deaths and causes of death were identified by linkage to death certificate files in both states and to the National Death Index. Case and death ascertainment was complete through December 31, 2012. During a mean follow-up of 16.1 years, 4,882 cases with incident invasive colorectal cancer were identified.

Statistical analysis

We created a "total NSAID use" variable, which summed years of use for aspirin and other NSAIDs, assuming that the two were not taken concomitantly (12). The results of a sensitivity analysis assigning the maximum duration of use were similar. We estimated HRs and 95% confidence intervals (CI) using Cox proportional hazards models with age as the time metric. Basic models were adjusted for race/ethnicity as a strata variable and age at cohort entry as a covariate. Multivariate models were further adjusted for family history of colorectal cancer (yes/no), history of colorectal polyp (yes/no), body mass index (<25, 25–<30, ≥30 kg/m^2), pack-years of cigarette smoking (continuous), multivitamin use (yes/no), physical activity (hours spent in vigorous work or sports per day), menopausal hormone therapy use (never, past, current) for women only, alcohol consumption (g/day), total energy (log transformed kcal/day), red meat (g/1,000 kcal/day), dietary fiber (g/1,000 kcal/day), calcium (mg/day from food and supplements), folate (μg/day from food and supplements), and vitamin D (IU/day from food and supplements). Aspirin use and other NSAID use were adjusted for each other. Participants who had never used any NSAIDs (including aspirin) as defined in the questionnaire were the reference group for all models. Tests for linear trends were obtained by including an ordinal variable with equally spaced scores in models (i.e., 1, 2, 3, ...). We tested whether the association of NSAIDs with colorectal cancer risk varied by sex and ethnicity using tests for interaction, which were based on the Wald statistics for cross-product terms. We also tested whether the associations varied across subsites of cancer based on the Wald statistics using competing risk methodology (13). The results of a sensitivity analysis of adenocarcinomas (4,583 cases) were similar. We considered the use of colorectal cancer screening tests (colonoscopy or sigmoidoscopy) using data from a follow-up survey conducted in 1999–2002, when the information was first collected in the cohort. We repeated our analysis stratified by ever use of screening tests among the 145,011 (79%) participants who completed the follow-up survey using only follow-up after that time. *P* values were two-sided and were considered statistically significant at <0.05. All analyses were conducted using SAS statistical software, version 9.4.

Results

At the time of cohort entry, 24% of male and 19% of female participants were current users of aspirin, and approximately 11% of all participants had used aspirin for 11 years or longer. Nine percent of men and 15% of women were current users of NSAIDs other than aspirin at cohort entry. Three percent of men and 2% of women reported currently taking both aspirin and non-aspirin NSAIDs. Among men, incidence rates of colorectal cancer in the MEC, left truncated at the age of 45 years and age standardized to the US 2000 standard, were highest in Japanese Americans (170.8 per 100,000), followed by Native Hawaiians (157.1), African Americans (152.7), and were lower in Latinos (112.4) and whites (109.8). In women, the rates were highest in African Americans (129.2), followed by Japanese Americans (108.9) and Native Hawaiians (108.2), and were lower in whites (80.2) and Latinas (71.5).

Compared with the entire cohort, participants who were diagnosed with colorectal cancer during follow-up were more likely to be older, have higher pack-years of cigarette smoking, be less physically active, consume more alcohol, and have a family history of colorectal cancer. They were also less likely to use multivitamin supplements both in men and women (Table 1). In postmenopausal women, cases were less likely to use menopausal hormone therapy. Among colorectal cancer cases, Native Hawaiians tended to be younger, have higher body mass index, and be more physically active, and were less likely to use multivitamin supplements and colorectal cancer screening tests both in men and women, compared with the other racial/ethnic groups.

Current use of aspirin (HR = 0.77; 95% CI, 0.69–0.86), other NSAIDs (HR = 0.72; 95% CI, 0.59–0.88), and total NSAIDs (HR = 0.79; 95% CI, 0.71–0.87) was associated with a lower risk of colorectal cancer among men in the multivariate models (Table 2). The association was not as marked for past users of aspirin and total NSAIDs in men, and was not observed in women, for whom HRs ranged from 0.93 to 1.03 ($P_{\text{interaction by sex}} = 0.005$ for aspirin and 0.002 for total NSAIDs). The multivariate-adjusted HRs were similar to those from the base models adjusting for age at cohort entry and race/ethnicity only. Among current users, longer years of aspirin use was related to a further decrease in risk of colorectal cancer in men ($P_{\text{trend}} = 0.02$); HRs were 0.74 (95% CI, 0.58–0.95) for 6–10 years and 0.61 (95% CI, 0.49–0.75) for 11+ years of use (Table 2). Duration of aspirin use was not associated with risk in women ($P_{\text{trend}} = 0.58$). Similar trends were found for total NSAIDs. Among past users, duration of NSAID use was not associated with colorectal cancer risk either in men or in women ($P_{\text{trend}} > 0.15$).

In racial/ethnic-specific analyses (Table 3), male current users of total NSAIDs were at decreased colorectal cancer risk among

Table 1. Baseline characteristics of participants by colorectal cancer status in the MEC Study, 1993–1996

	Colorectal cancer cases						
	African American	**Native Hawaiian**	**Japanese American**	**Latino**	**White**	**All**	**All participants**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Men	*n* = 375	*n* = 164	*n* = 979	*n* = 541	*n* = 514	*n* = 2,573	*n* = 83,290
Age at cohort entry, years	64.1 (8.2)	58.9 (8.4)	63.3 (8.3)	62.7 (7.0)	62.8 (8.6)	62.9 (8.2)	60.1 (8.9)
Age at diagnosis, years	72.8 (8.4)	67.7 (8.8)	72.2 (9.0)	72.4 (7.9)	71.9 (8.8)	72.0 (8.7)	—
Body mass index, kg/m^2	27.7 (4.2)	29.5 (5.6)	25.3 (3.5)	27.3 (3.7)	27.1 (4.4)	26.7 (4.2)	26.7 (4.2)
Pack-years of cigarette smoking[a]	16.9 (14.6)	22.0 (16.8)	24.4 (16.5)	14.5 (15.0)	27.5 (19.6)	21.8 (17.3)	20.7 (16.6)
Vigorous physical activity, hours/day	0.43 (0.93)	0.86 (1.34)	0.36 (0.72)	0.52 (0.97)	0.59 (1.03)	0.48 (0.93)	0.58 (1.02)
Alcohol, g/day	13.8 (35.3)	19.3 (36.0)	14.9 (30.7)	17.2 (38.9)	24.6 (41.9)	17.5 (36.1)	14.7 (32.6)
Dietary fiber, g/1,000 kcal/day	11.1 (4.2)	8.9 (3.1)	9.4 (3.6)	12.2 (4.2)	10.7 (4.0)	10.5 (4.0)	10.9 (4.1)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Family history of colorectal cancer	40 (10.7)	10 (6.1)	113 (11.5)	26 (4.8)	61 (11.9)	250 (9.7)	6,042 (7.3)
History of colorectal polyps	14 (3.7)	10 (6.1)	64 (6.5)	18 (3.3)	40 (7.8)	146 (5.7)	5,720 (6.9)
Multivitamin use	143 (39.2)	50 (31.3)	400 (41.5)	232 (43.6)	229 (44.9)	1,054 (41.7)	39,027 (47.5)
Colorectal cancer screening use[b]	118 (45.4)	43 (33.9)	344 (42.3)	167 (40.0)	212 (50.5)	884 (43.4)	24,913 (38.7)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Women	*n* = 574	*n* = 149	*n* = 743	*n* = 373	*n* = 470	*n* = 2,309	*n* = 99,909
Age at cohort entry, years	63.6 (8.4)	58.7 (8.1)	64.1 (8.1)	61.6 (7.1)	63.5 (8.0)	63.1 (8.1)	59.6 (8.8)
Age at diagnosis, years	73.1 (9.2)	68.1 (9.3)	73.9 (9.2)	71.6 (8.2)	73.5 (8.7)	72.9 (9.1)	—
Body mass index, kg/m^2	29.1 (5.8)	30.3 (6.7)	23.9 (4.4)	29.0 (6.2)	26.6 (5.9)	27.0 (6.0)	26.5 (5.8)
Pack-years of cigarette smoking[a]	14.3 (12.2)	19.1 (14.3)	15.0 (12.7)	12.0 (12.8)	22.7 (17.8)	16.8 (14.7)	15.5 (14.5)
Vigorous physical activity, hours/day	0.19 (0.57)	0.32 (0.71)	0.13 (0.39)	0.14 (0.35)	0.22 (0.55)	0.18 (0.50)	0.21 (0.55)
Alcohol, g/day	4.3 (20.2)	8.5 (32.2)	1.5 (7.2)	3.0 (16.2)	9.9 (21.5)	4.6 (18.2)	4.3 (15.0)
Dietary fiber, g/1,000 kcal/day	12.9 (4.5)	10.6 (4.1)	12.1 (4.1)	14.0 (4.3)	13.0 (4.5)	12.7 (4.4)	12.7 (4.4)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Family history of colorectal cancer	67 (11.7)	11 (7.4)	119 (16.0)	23 (6.2)	59 (12.6)	279 (12.1)	8,612 (8.6)
History of colorectal polyps	25 (4.4)	3 (2.0)	32 (4.3)	17 (4.6)	35 (7.4)	112 (4.9)	4,382 (4.4)
Multivitamin use	286 (50.8)	49 (34.3)	363 (49.7)	203 (55.2)	247 (53.5)	1,148 (50.6)	52,832 (53.9)
Ever use of MHT[c]	221 (44.1)	50 (43.9)	312 (47.1)	147 (44.5)	244 (55.6)	974 (47.6)	44,802 (54.8)
Colorectal cancer screening use[b]	190 (45.2)	43 (36.4)	244 (38.2)	109 (38.8)	192 (48.4)	778 (41.9)	27,456 (34.0)

Abbreviation: MHT, menopausal hormone therapy.

[a]Among ever smokers.

[b]Among 64,317 men and 80,694 women who completed a follow-up questionnaire (1999–2002).

[c]Among postmenopausal women.

African Americans (HR = 0.81; 95% CI, 0.61–1.07), Japanese Americans (HR = 0.78; 95% CI, 0.66–0.91), Latinos (HR = 0.82; 95% CI, 0.66–1.03), and whites (HR = 0.68; 95% CI, 0.56–0.84), but not among Native Hawaiians (HR = 1.25; 95% CI, 0.87–1.79). Tests for interaction indicated a significant difference in the total NSAID use–colorectal cancer associations between racial/ethnic group ($P_{interaction}$ = 0.02, across all racial/ethnic groups; $P_{interaction}$ = 0.008, Native Hawaiians versus all other four racial/ethnic groups combined). The inverse association was stronger in white men than in the other three groups ($P_{interaction}$ = 0.04, whites vs. the other three racial/ethnic groups combined for total NSAIDs). When examined by duration of use, the racial/ethnic–specific associations among male current users were statistically significant or of borderline significance for 6–10 or more years of aspirin use (Supplementary Table S1). Among women, the associations did not vary by race/ethnicity ($P_{interaction}$ > 0.60), and none of the HRs for individual racial/ethnic groups showed a significant association between NSAID use and colorectal cancer risk (Table 3).

In analyses by anatomic subsite, the inverse association with current NSAID use was stronger for the rectum (HR = 0.66; 95% CI, 0.55–0.80) and left colon (HR = 0.78; 95% CI, 0.65–0.94) than for the right colon (HR = 0.91; 95% CI, 0.78–1.06) in men ($P_{interaction}$< 0.001 for all 3 NSAID categories; Table 4). Among women, no association was found for any of the subsites.

We also explored whether colorectal cancer family history, age (45–54, 55–64, 65–75 years), and menopausal hormone therapy modified the association of total NSAID use and colorectal cancer risk. All *P* values for these interaction tests were ≥0.3.

Discussion

In this large, multiethnic cohort, current use of aspirin and other NSAIDs at the time of cohort entry was associated with a decreased incidence of colorectal cancer in men but not in women. Among male current users, a statistically significant reduced risk was observed with the use of aspirin or total NSAIDs for 6–10 years or longer. This association was observed in men of all racial/ethnic groups, except Native Hawaiians. The association was found to be stronger in white men than in Japanese, African American, and Latino men, but was observed in all four groups.

In a recent systematic evidence review by the USPSTF on aspirin use for the prevention of CVD and colorectal cancer (5), six randomized clinical trials of aspirin for primary and secondary CVD prevention provided data on the effect of regular aspirin use on invasive colorectal cancer incidence in populations (1, 6, 14, 15), which were almost exclusively of European ancestry. Aspirin had no effect on colorectal cancer incidence in the first 10 years following randomization, but a reduced colorectal cancer incidence was observed after a 10-year latency (summary relative risk, RR = 0.60; 95% CI, 0.47–0.76; ref. 5). Overall, over a period of 20 years or longer, aspirin appeared to reduce the risk of colorectal cancer incidence by approximately 20% to 24% (5).

Table 2. Association between NSAID use and colorectal cancer risk in the MEC Study, 1993–2012

	Men ($n = 83,290$)				Women ($n = 99,909$)				
	No. of cases	HR (95% CI)[a]	No. of cases[b]	HR (95% CI)[c]	No. of cases	HR (95% CI)[a]	No. of cases[b]	HR (95% CI)[c]	$P_{interaction}$[d]
Never users[e]	1,338	1.00 (ref)	1,261	1.00 (ref)	1,061	1.00 (ref)	952	1.00 (ref)	
Aspirin[f]									
Past	469	0.99 (0.88–1.12)	420	0.98 (0.86–1.11)	433	1.06 (0.92–1.21)	359	1.03 (0.89–1.19)	0.005
Current	552	0.78 (0.70–0.88)	504	0.77 (0.69–0.86)	436	1.03 (0.90–1.17)	383	1.02 (0.89–1.17)	
Other NSAIDs[f]									
Past	372	0.76 (0.65–0.90)	334	0.77 (0.65–0.91)	461	0.97 (0.85–1.11)	370	0.94 (0.81–1.09)	0.38
Current	211	0.74 (0.62–0.89)	186	0.72 (0.59–0.88)	317	0.92 (0.79–1.08)	270	0.93 (0.79–1.09)	
Total NSAIDs									
Past	551	0.96 (0.86–1.06)	490	0.96 (0.86–1.06)	573	0.98 (0.88–1.08)	455	0.94 (0.84–1.06)	0.002
Current	680	0.81 (0.73–0.89)	612	0.79 (0.71–0.87)	676	0.96 (0.87–1.06)	586	0.97 (0.87–1.08)	
Current users									
Aspirin[f]									
≤1 y	102	0.80 (0.65–0.98)	95	0.80 (0.65–1.00)	96	1.13 (0.91–1.41)	87	1.18 (0.94–1.48)	0.01
2–3 y	140	0.86 (0.72–1.03)	129	0.86 (0.71–1.04)	87	1.02 (0.81–1.28)	73	0.96 (0.75–1.23)	
4–5 y	106	0.86 (0.70–1.05)	99	0.88 (0.71–1.08)	61	0.94 (0.72–1.22)	54	0.97 (0.73–1.29)	
6–10 y	77	0.79 (0.62–1.00)	68	0.74 (0.58–0.95)	38	0.86 (0.62–1.20)	33	0.85 (0.60–1.21)	
≥11 y	116	0.64 (0.53–0.79)	106	0.61 (0.49–0.75)	142	1.05 (0.87–1.28)	127	1.04 (0.84–1.27)	
P_{trend}[g]		0.07		0.02		0.69		0.58	
Other NSAIDs[f]									
≤1 y	60	0.79 (0.59–1.05)	51	0.73 (0.53–0.99)	88	0.95 (0.75–1.21)	72	0.90 (0.70–1.17)	0.59
2–3 y	61	0.81 (0.61–1.07)	57	0.82 (0.61–1.11)	83	0.95 (0.75–1.21)	73	1.00 (0.77–1.29)	
4–5 y	35	0.67 (0.47–0.96)	29	0.62 (0.42–0.92)	63	0.99 (0.75–1.30)	50	0.93 (0.68–1.25)	
6–10 y	23	0.75 (0.48–1.15)	22	0.80 (0.51–1.25)	24	0.66 (0.43–1.00)	21	0.66 (0.43–1.04)	
≥11 y	24	0.82 (0.54–1.26)	22	0.79 (0.51–1.24)	35	0.99 (0.69–1.41)	34	1.12 (0.78–1.61)	
P_{trend}[g]		0.76		0.98		0.66		0.81	
Total NSAIDs									
≤1 y	116	0.84 (0.69–1.01)	107	0.83 (0.68–1.01)	124	1.03 (0.86–1.25)	114	1.07 (0.88–1.30)	0.01
2–3 y	140	0.85 (0.72–1.02)	130	0.85 (0.71–1.02)	120	1.00 (0.82–1.21)	101	0.92 (0.75–1.14)	
4–5 y	111	0.85 (0.70–1.03)	103	0.86 (0.70–1.06)	87	0.90 (0.72–1.12)	81	0.95 (0.75–1.19)	
6–10 y	82	0.74 (0.59–0.93)	76	0.73 (0.58–0.93)	65	0.85 (0.66–1.09)	54	0.80 (0.60–1.05)	
≥11 y	151	0.71 (0.60–0.84)	139	0.68 (0.57–0.81)	186	0.96 (0.82–1.13)	173	0.98 (0.83–1.16)	
P_{trend}[g]		0.08		0.04		0.43		0.53	
Past users									
Aspirin[f]									
≤1 y	160	0.96 (0.81–1.15)	147	0.98 (0.81–1.18)	124	0.94 (0.76–1.15)	111	1.00 (0.81–1.24)	0.19
2–3 y	88	1.23 (0.98–1.54)	79	1.22 (0.96–1.54)	65	1.08 (0.83–1.41)	50	0.97 (0.72–1.31)	
4–5 y	32	0.71 (0.50–1.01)	28	0.68 (0.47–1.00)	41	1.06 (0.77–1.47)	34	1.04 (0.73–1.49)	
6–10 y	21	0.62 (0.40–0.96)	19	0.63 (0.40–1.00)	33	1.09 (0.76–1.56)	26	1.00 (0.67–1.50)	
≥11 y	103	0.95 (0.76–1.18)	93	0.89 (0.71–1.11)	105	1.11 (0.89–1.38)	95	1.11 (0.88–1.40)	
P_{trend}[g]		0.31		0.16		0.52		0.72	
Other NSAIDs[f]									
≤1 y	178	0.77 (0.63–0.95)	165	0.80 (0.65–0.98)	210	0.95 (0.80–1.13)	176	0.93 (0.77–1.12)	0.94
2–3 y	61	0.77 (0.57–1.02)	56	0.78 (0.58–1.06)	81	1.00 (0.78–1.28)	64	0.96 (0.73–1.26)	
4–5 y	26	0.69 (0.45–1.04)	21	0.62 (0.39–0.98)	35	0.91 (0.64–1.29)	28	0.88 (0.60–1.30)	
6–10 y	16	0.72 (0.43–1.21)	15	0.74 (0.43–1.26)	15	0.74 (0.44–1.25)	12	0.72 (0.40–1.28)	
≥11 y	17	0.79 (0.48–1.32)	17	0.89 (0.54–1.49)	21	1.04 (0.66–1.64)	19	1.09 (0.68–1.76)	
P_{trend}[g]		0.89		0.96		0.82		0.94	
Total NSAIDs									
≤1 y	192	0.91 (0.78–1.06)	181	0.94 (0.81–1.10)	190	0.92 (0.78–1.07)	169	0.93 (0.79–1.10)	0.78
2–3 y	91	1.17 (0.95–1.45)	85	1.18 (0.95–1.47)	80	1.03 (0.82–1.29)	67	0.98 (0.76–1.25)	
4–5 y	39	0.84 (0.61–1.16)	34	0.79 (0.56–1.11)	42	0.91 (0.67–1.24)	32	0.80 (0.57–1.15)	
6–10 y	21	0.62 (0.40–0.95)	21	0.68 (0.44–1.05)	32	0.98 (0.69–1.39)	27	0.93 (0.64–1.37)	
≥11 y	97	1.01 (0.82–1.24)	88	0.96 (0.77–1.19)	86	0.99 (0.80–1.24)	77	0.98 (0.77–1.24)	
P_{trend}[g]		0.89		0.82		0.21		0.91	

[a]Adjusted for age at cohort entry and ethnicity.
[b]Excluding participants with missing values on covariates.
[c]Adjusted for age at cohort entry, ethnicity, family history of colorectal cancer, history of colorectal polyp, body mass index, pack-years of cigarette smoking, multivitamin use, vigorous physical activity, menopausal hormone therapy use for women only, alcohol consumption, total energy, red meat, dietary fiber, calcium, folate, and vitamin D.
[d]$P_{interaction}$ between sex and NSAID use based on the multivariate model.
[e]Participants who had never used any NSAIDs.
[f]Aspirin and other NSAID use were adjusted for each other.
[g]Among NSAID users.

Although no sex-specific estimate was provided, there was no evidence that sex modified the effect of aspirin on colorectal cancer incidence in the randomized trials (5).

The results of cohort studies also support the preventive effect of aspirin against colorectal cancer (8, 9, 16–21). A meta-analysis of 11 cohorts found that aspirin use was associated with a

Table 3. Association between NSAID use and colorectal cancer risk by race/ethnicity in the MEC Study, 1993–2012

	African American		Native Hawaiian		Japanese American		Latino		White		
	No. of cases[a]	HR (95% CI)[b]	No. of cases[a]	HR (95% CI)[b]	No. of cases[a]	HR (95% CI)[b]	No. of cases[a]	HR (95% CI)[b]	No. of cases[a]	HR (95% CI)[b]	$P_{interaction}$[c]
Men											
Never users[d]	127	1.00 (ref)	80	1.00 (ref)	587	1.00 (ref)	233	1.00 (ref)	234	1.00 (ref)	
Aspirin[e]											
Past	99	1.27 (0.93–1.74)	22	0.80 (0.47–1.36)	105	0.92 (0.73–1.16)	116	1.14 (0.88–1.48)	78	0.74 (0.55–0.99)	0.08
Current	58	0.71 (0.50–1.01)	35	1.13 (0.72–1.76)	178	0.77 (0.64–0.92)	94	0.88 (0.68–1.15)	139	0.65 (0.51–0.82)	
Other NSAIDs[e]											
Past	84	1.10 (0.75–1.60)	19	0.87 (0.47–1.59)	76	0.66 (0.47–0.92)	84	0.61 (0.43–0.88)	71	0.82 (0.55–1.22)	0.13
Current	32	0.95 (0.60–1.50)	19	1.44 (0.79–2.64)	46	0.66 (0.46–0.97)	45	0.62 (0.41–0.94)	44	0.61 (0.39–0.93)	
Total NSAIDs											
Past	117	1.27 (0.98–1.63)	26	0.76 (0.49–1.19)	127	0.88 (0.73–1.07)	132	0.97 (0.78–1.20)	88	0.87 (0.68–1.11)	0.02
Current	81	0.81 (0.61–1.07)	49	1.25 (0.87–1.79)	203	0.78 (0.66–0.91)	118	0.82 (0.66–1.03)	161	0.68 (0.56–0.84)	
Women											
Never users[d]	162	1.00 (ref)	63	1.00 (ref)	442	1.00 (ref)	114	1.00 (ref)	171	1.00 (ref)	
Aspirin[e]											
Past	119	0.98 (0.73–1.32)	23	1.04 (0.59–1.85)	67	0.94 (0.70–1.26)	61	1.00 (0.69–1.45)	89	1.20 (0.89–1.62)	0.61
Current	94	0.90 (0.67–1.22)	27	1.33 (0.78–2.25)	90	0.94 (0.73–1.20)	64	1.21 (0.85–1.72)	108	1.06 (0.81–1.39)	
Other NSAIDs[e]											
Past	130	0.91 (0.69–1.20)	24	0.83 (0.44–1.56)	69	0.97 (0.72–1.31)	72	0.95 (0.68–1.34)	75	0.92 (0.65–1.31)	0.98
Current	88	0.91 (0.67–1.24)	13	0.61 (0.29–1.26)	43	0.89 (0.62–1.26)	59	1.09 (0.76–1.56)	67	0.90 (0.63–1.28)	
Total NSAIDs											
Past	146	0.89 (0.71–1.11)	30	1.01 (0.65–1.56)	98	0.93 (0.74–1.16)	86	0.88 (0.66–1.16)	95	1.04 (0.81–1.34)	0.93
Current	162	0.90 (0.72–1.12)	34	1.06 (0.69–1.62)	125	0.93 (0.76–1.14)	109	1.04 (0.80–1.36)	156	0.99 (0.79–1.24)	

[a]Excluding participants with missing values on covariates.

[b]Adjusted for age at cohort entry, family history of colorectal cancer, history of colorectal polyp, body mass index, pack-years of cigarette smoking, multivitamin use, vigorous physical activity, menopausal hormone therapy use for women only, alcohol consumption, total energy, red meat, dietary fiber, calcium, folate, and vitamin D.

[c]$P_{interaction}$ between race/ethnicity and NSAID use.

[d]Participants who had never used any NSAIDs.

[e]Aspirin and other NSAID use were adjusted for each other.

Table 4. Association between NSAID use and colorectal cancer risk by subsite in the MEC Study, 1993–2012

	Right colon		Left colon		Rectum		
	No of cases[a]	HR (95% CI)[b]	No of cases[a]	HR (95% CI)[b]	No of cases[a]	HR (95% CI)[b]	$P_{interaction}$[c]
Men							
Never users[d]	458	1.00 (ref)	371	1.00 (ref)	397	1.00 (ref)	
Aspirin[e]							
Past	200	1.19 (0.98–1.44)	99	0.81 (0.63–1.04)	111	0.88 (0.69–1.13)	<0.001
Current	216	0.84 (0.70–1.01)	150	0.78 (0.63–0.97)	126	0.68 (0.55–0.85)	
Other NSAIDs[e]							
Past	162	1.01 (0.79–1.30)	81	0.61 (0.43–0.86)	86	0.65 (0.46–0.92)	<0.001
Current	87	0.95 (0.72–1.26)	54	0.65 (0.45–0.95)	42	0.52 (0.35–0.78)	
Total NSAIDs							
Past	235	1.19 (1.02–1.40)	114	0.77 (0.63–0.96)	131	0.86 (0.71–1.06)	<0.001
Current	270	0.91 (0.78–1.06)	178	0.78 (0.65–0.94)	149	0.66 (0.55–0.80)	
Women							
Never users[d]	483	1.00 (ref)	250	1.00 (ref)	198	1.00 (ref)	
Aspirin[e]							
Past	174	0.89 (0.72–1.09)	99	1.30 (0.98–1.72)	77	1.12 (0.81–1.54)	0.66
Current	205	0.96 (0.80–1.17)	89	1.08 (0.82–1.42)	75	1.02 (0.75–1.38)	
Other NSAIDs[e]							
Past	190	0.89 (0.72–1.09)	86	0.84 (0.61–1.15)	78	1.11 (0.81–1.53)	0.91
Current	145	0.91 (0.73–1.14)	62	0.83 (0.59–1.18)	58	1.11 (0.78–1.57)	
Total NSAIDs							
Past	222	0.85 (0.72–1.00)	118	1.03 (0.82–1.29)	101	1.06 (0.83–1.36)	0.66
Current	313	0.95 (0.82–1.10)	134	0.95 (0.76–1.18)	120	1.01 (0.80–1.28)	

[a]Excluding participants with missing values on covariates.
[b]Adjusted for age at cohort entry, ethnicity, family history of colorectal cancer, history of colorectal polyp, body mass index, pack-years of cigarette smoking, multivitamin use, vigorous physical activity, menopausal hormone therapy use for women only, alcohol consumption, total energy, red meat, dietary fiber, calcium, folate, and vitamin D.
[c]$P_{interaction}$ between subsite and NSAID use.
[d]Participants who had never used any NSAIDs.
[e]Aspirin and other NSAID use were adjusted for each other.

decreased risk of colorectal cancer (RR for any aspirin use vs. non-use = 0.85; 95% CI, 0.82–0.89; ref. 2). In another meta-analysis of 12 cohort studies (3), an inverse association was reported for both men and women between frequency and duration of aspirin use and colorectal cancer risk. A dose–response analysis showed that there was a 20% decreased colorectal cancer risk for a 325 mg aspirin per day increment, a 18% decreased risk for aspirin in a seven times per week increment in frequency of use, and a 18% decreased risk for aspirin use in a 10-year duration increment (3). The cohorts included in the meta-analyses were also comprised largely of participants of European ancestry.

Few studies have been published on the relationship of NSAID use and colorectal cancer outcomes in nonwhite populations. Consistent with results from trials in Western countries (22), a Japanese randomized clinical trial of low-dose aspirin (100 mg/day) for two years found a reduced recurrence of colorectal cancer in patients with colorectal adenomas and/or adenocarcinomas (OR = 0.60; 95% CI, 0.36–0.98; ref. 23). A small case–control study in China found a decreased risk of colon (OR = 0.13; 95% CI, 0.05–0.35) and rectal (OR = 0.15; 95% CI, 0.11–0.58) cancer with NSAID use (24). The current study is the first large prospective investigation to provide data on aspirin and colorectal cancer risk in nonwhites. In men, we observed an inverse association of aspirin and total NSAID use and colorectal cancer risk in four ethnic/racial groups (African Americans, Japanese Americans, Latinos, and whites), but not in Native Hawaiians. If confirmed with a longer follow-up and larger number of cases, this result would suggest a possible different etiology for colorectal cancer in this population which has been shown to only have a moderate risk of colorectal cancer despite a high prevalence of risk factors, such as obesity, diabetes, high fat and red meat intakes, alcohol use, and smoking (25). The association was strongest in white men, which could be due to early adoption of long-term use for CVD prevention.

Although our overall findings on NSAID use and colorectal cancer risk in men are consistent with those from previous cohort studies, we found no association in women. Unlike our results, two U.S. cohorts found an inverse association between long-term use of NSAIDs and colorectal cancer risk in both sexes (18, 20). Three female-only cohorts in the United States and Sweden also observed a lower risk of colorectal cancer with NSAID use (8, 9, 26). In the MEC, compared with men, women had a 31% lower overall risk of colorectal cancer with adjustment for age and ethnicity, and a 15% lower risk with adjustment for other risk factors. It is possible that, because women were already at a lower risk, they may not have benefited from NSAID use. It is also possible that recall of aspirin use may be less accurate in women as they are less likely to be using it long-term for CVD prevention.

One trial (27) and a pooled analysis of four trials (1), all of which were included in the USPSTF review, reported greater effects of aspirin on cancers of the right (proximal) colon versus left (distal) colon and rectum. However, observational cohort studies have found no consistent differences in associations between aspirin use and colorectal cancer risk by anatomic subsite (1, 6–9). In our data, the inverse association with current NSAID use in men was stronger for the rectum and left colon cancer than for the right colon, which is the opposite of the findings from randomized trials for anatomic subsites. Proximal colon tumors are easily missed at colonoscopy and tend to be aggressive compared with distal tumors (1). There are differences between the subsites in embryologic origins, carcinogenesis mechanisms, and molecular characteristics of the cancers (28). Thus, effects of NSAIDS on tumor prevention may vary by subsite, similar to the

way treatment effects on proximal versus distal colon tumors may be different (1).

Strengths of our study include the prospective design, the large number of colorectal cancer cases in each racial/ethnic group, except Native Hawaiians, and comprehensive information on colorectal cancer risk factors including diet and exercise. A limitation of the study is a lack of detailed data on the frequency of medication use, dosage, and age at initiation that may have resulted in some exposure misclassification. Also, information on colorectal cancer screening was not available at baseline. However, when using data from a follow-up survey and considering incident cases occurring afterward, we found no indication that use of colorectal cancer screening tests modified the associations. Despite our large sample size in most groups, the limited sample size in Native Hawaiians may have led to inaccurate results. Exclusion of participants who reported to have been diagnosed with arthritis in a sensitivity analysis did not change the findings. As data were not available on the reasons for NSAID use, we could not assess the role of other disease histories on our results.

In conclusion, our findings add to the evidence for a benefit of NSAID use against colorectal cancer by generalizing the inverse association to men of African American, Japanese, and Latino ancestry. Our data in men also suggest that this association may be stronger in whites than in these three other ethnic/racial groups. The lack of inverse association observed in women and in Native Hawaiian men in the MEC should be interpreted with caution given the possibility of differential measurement error and limited sample sizes in subgroup analyses.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.-Y. Park, L.R. Wilkens, L. Le Marchand
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.N. Kolonel, K.R. Monroe, L. Le Marchand
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.-Y. Park, L.R. Wilkens, K.R. Monroe, L. Le Marchand
Writing, review, and/or revision of the manuscript: S.-Y. Park, L.R. Wilkens, L.N. Kolonel, K.R. Monroe, C.A. Haiman, L. Le Marchand
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Le Marchand
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