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ORIGINAL REPORT

Timing of Aspirin and Other Nonsteroidal Anti-Inflammatory Drug Use Among Patients With Colorectal Cancer in Relation to Tumor Markers and Survival

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ABSTRACT

Purpose

Regular use of aspirin is associated with improved survival for patients with colorectal cancer (CRC). However, the timing of and the subtype of CRC that would benefit the most from using aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) in relation to survival is unclear.

Patients and Methods

In all, 2,419 patients age 18 to 74 years with incident invasive CRC who were diagnosed from 1997 to 2008 were identified from population-based cancer registries in the United States, Canada, and Australia. Detailed epidemiologic questionnaires were administered at study enrollment and at 5-year follow-up. Survival outcomes were completed through linkage to national death registries. *BRAF*- and *KRAS*-mutation status, microsatellite instability, and CpG island methylator phenotype were also evaluated. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% CIs for overall survival (OS) and CRC-specific survival.

Results

After a median of 10.8 years of follow-up since diagnosis, 381 deaths (100 as a result of CRC) were observed. Compared with nonusers, postdiagnostic aspirin-only users had more favorable OS (HR, 0.75; 95% CI, 0.59 to 0.95) and CRC-specific survival (HR, 0.44; 95% CI, 0.25 to 0.71), especially among those who initiated aspirin use (OS: HR, 0.64; 95% CI, 0.47 to 0.86; CRC-specific survival: HR, 0.40; 95% CI, 0.20 to 0.80). The association between any NSAID use after diagnosis and OS differed significantly by *KRAS*-mutation status ($P_{interaction}$ = .01). Use of any NSAID after diagnosis was associated with improved OS only among participants with *KRAS* wild-type tumors (HR, 0.60; 95% CI, 0.46 to 0.80) but not among those with *KRAS*-mutant tumors (HR, 1.24; 95% CI, 0.78 to 1.96).

Conclusion

Among long-term CRC survivors, regular use of NSAIDs after CRC diagnosis was significantly associated with improved survival in individuals with *KRAS* wild-type tumors.

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INTRODUCTION

With improvements in early detection and treatment, the number of survivors of colorectal cancer (CRC) has grown to 1.2 million.[1] Because of this large burden of CRC in the United States, identifying modifiable behaviors associated with better prognosis and long-term outcomes among CRC survivors has a major impact on public health. Several studies have demonstrated that long-term regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a lower risk of colorectal neoplasia.[2-12] However, there is limited information on whether prediagnostic[12-21] and postdiagnostic[17-24] NSAID use differentially affect CRC survival. Some studies have found no association between prediagnostic NSAID use and survival,[15-20] and others have observed more favorable survival among regular users of NSAIDs before diagnosis.[12-14] Most of the current literature on postdiagnostic NSAID use has focused exclusively on aspirin.[18-20,23,24] Information is limited on the changes in NSAID use from the pre- to postdiagnostic time periods and their associations with CRC survivorship.

We aim to investigate the association between survival and postdiagnostic use of aspirin

ASSOCIATED CONTENT

Appendix
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and other NSAIDs and to evaluate whether this relationship differs according to time of use, patient characteristics, and tumor characteristics. To accomplish this, we analyzed data from population-based sites of the Colon Cancer Family Registry (CCFR).

PATIENTS AND METHODS

Study Population

The CCFR, an international consortium, has enrolled more than 32,000 participants with CRC, their relatives, and controls from six centers in Australia, Canada, and the United States.[25,26] This analysis was restricted to patients with CRC who were identified from population-based cancer registries and were recruited through four CCFR study centers (Fred Hutchinson Cancer Research Center, Seattle, WA; Mayo Clinic, Rochester, MN; Cancer Care Ontario, Toronto, ON, Canada; and University of Melbourne, Melbourne, VIC, Australia). Eligible participants were diagnosed between 1997 and 2008 with incident cases of invasive adenocarcinoma of the colon and rectum and were age 18 to 74 years.

All participants completed a standard baseline questionnaire at enrollment (median, 9 months after diagnosis; interquartile range [IQR], 6 to 15 months after diagnosis), and those who were alive at approximately 5 years after baseline (median, 4.9 years; IQR, 4.6 to 5.5 years) were asked to complete a follow-up epidemiologic and medical history questionnaire. Additional descriptions of CCFR recruitment approaches have been published.[25] All participants provided informed consent. The institutional review board at each of the CCFR sites approved the study protocol.

Pre- and Postdiagnostic NSAID use

Data on the use of aspirin and other NSAIDs were collected at the baseline and follow-up interviews. Non-aspirin NSAIDs included ibuprofen- and naproxen-based medications. We defined prediagnostic use as the reported use approximately 1 year before diagnosis of CRC assessed at the baseline interview and postdiagnostic use as being between baseline and the 5-year follow-up interview. At each time point, use of aspirin or other NSAIDs, the frequency of use, and the duration of use were assessed. Regular use of NSAIDs was defined as using the medications at least twice per week for more than 1 month. Ever users were persons who regularly used the medications, and nonusers were defined as those who used the medications other than regularly or never used such medications. Ever users were further divided into aspirin-only, other NSAID–only, and any-NSAID groups. The duration of postdiagnostic NSAID use was calculated as total years of using these mediations between baseline and 5-year follow-up. Change in use of aspirin or NSAIDs was categorized according to regular use of these medications during the pre- and postdiagnostic time periods: nonuse/nonuse as nonusers, any use/nonuse as discontinued users, nonuse/any use as initiated users, and any use/any use as continued users.

Tumor Characteristics

Tumor location was determined on the basis of International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes[27] abstracted from cancer registry entries, pathology records, or medical records. Proximal colon cancer was defined as cancers in the cecum through transverse colon (C180, C182-184), distal colon cancers included cancers arising from the splenic flexure to sigmoid colon (C185-187), and rectal cancers consisted of cancers of the rectosigmoid junction or rectum (C199, C209). Patients with an unknown CRC primary site were classified as unknown. For tumor stage at diagnosis, the majority of patients had staging (I, II, III, or IV) according to the American Joint Committee on Cancer (AJCC, 7th edition) available. For a subset of individuals whose AJCC staging was missing, imputation from SEER summary staging and TNM staging was performed for each AJCC stage: I (SEER 1 and T1/T2), II (SEER 1 and T3; SEER 3/7 and N0, M0), III (SEER 3/4/7, and N1/N2, M0), and IV (SEER 7 and M1).

For tumor marker testing, DNA was extracted from paraffin-embedded formalin-fixed tumor tissues. Microsatellite instability (MSI) status was evaluated as previously described.[25,28] For the majority of patients with available tumor samples (73%), MSI status was determined by using a 10-marker panel. Tumors were classified as MSI-high (MSI-H) if instability was observed in $\geq$ 30% of markers, and as microsatellite stable (MSS) or MSI-low (MSI-L) if otherwise. For the remaining patients, MSI status was determined on the basis of immunohistochemistry testing to evaluate the expression of the MLH1, MSH2, MSH6, and PMS2 proteins.[29,30] Patients with positive staining for all markers were considered MSS/MSI-L; those who were negative on one or more markers were classified as MSI-H. Previous studies demonstrated a high concordance (97%) between these two methods.[30,31] Our data showed a similar level of agreement (98.4%). Extracted tumor DNA was also tested for p.V600E *BRAF* mutation by using a fluorescent allele-specific polymerase chain reaction assay.[32] For a subset of patients, coding sequence in *KRAS* exon 2 was amplified, and mutations were tested by using forward and reverse sequencing.[33,34] Testing of the CpG island methylator phenotype (CIMP) was based on a validated five-marker DNA methylation assay (*CACNA1G*, *IGF2*, *NEUROG1*, *RUNX3*, and *SOCS1*).[35-37] Tumors were classified as CIMP-positive if three or more of five markers had a percentage of methylated reference ratio $\geq$ 10 and as CIMP-negative otherwise.

Deaths

Follow-up for vital status, date of death, and cause of death was completed through linkage to population-based cancer registries, national death indices, and death certificates, with the most recent linkage occurring in January 2014. We used the ICD-9 or ICD-10 (depending on study site and year of linkage) to classify cause of death into CRC-specific deaths (ICD-9: 153.0-153.4, 153.6-153.9, or 154.0-154.1; ICD-10: C18.0-20.0 or C26.0), cardiovascular disease (CVD)–specific deaths (ICD-9: 390-459; ICD-10: I00-I99), or other causes.

Statistical Analysis

Of the 4,796 eligible population-based patients with CRC enrolled in CCFR, 3,430 were alive 5 years after diagnosis; 3,001 (88%) responded to the follow-up questionnaires. In addition, we excluded 295 individuals who had missing data on either pre- or postdiagnostic aspirin or non-aspirin NSAID use, 170 patients who were diagnosed more than 2 years before baseline, 114 who had follow-up interviews more than 6.5 years after baseline, and three participants who did not have a date of death recorded. A total of 2,419 patients with CRC were included in this analysis.

Delayed-entry Cox proportional hazards regression was used to estimate adjusted hazard ratios (HRs) and 95% CIs for the association of postdiagnostic NSAID use and duration and change in NSAID use with CRC-specific survival (CSS), CVD-specific survival, and overall survival (OS). Person time accrued from the date of follow-up interview to the date of death or the end of follow-up. Proportional hazards assumptions were examined by testing for a nonzero slope of the scaled Schoenfeld residuals as a function of survival time. Multivariable regression models were stratified on age at diagnosis and study center, in light of violation of the proportional hazards assumption, and adjusted for potential confounders selected a priori, including sex, body mass index, and smoking status at baseline, stage at diagnosis (as categorized in Table 1), and number of years between baseline and follow-up interviews (as a continuous variable). Analyses restricted to patients with stage I, II, or III CRC were also conducted.

In addition, we evaluated the effect of aspirin-only and non-aspirin NSAID use separately, and conducted stratified analysis on any NSAID use after diagnosis in relation to OS and CSS by age at diagnosis, sex, family history (at least one first-degree relative affected with CRC, yes *v* no), tumor location, stage at diagnosis, CIMP, MSI status, *KRAS*-mutation status, and *BRAF* mutation status (as grouped in Table 3). Tests for

Table 1. Baseline Characteristics of Patients with CRC, According to Post-Diagnosis NSAID Use, CCFR 1997-2008

Characteristic	Total (N = 2,419) No.	%	Postdiagnosis NSAID Use* Nonusers (n = 1,397) No.	%	Users (n = 1,022) No.	%
Study center						
Toronto, ON, Canada	621	26	417	30	204	20
Melbourne, VIC, Australia	357	15	292	21	65	6
Rochester, MN	296	12	133	10	163	16
Seattle, WA	1,145	47	555	40	590	58
Age at diagnosis, years						
< 50	941	39	653	47	288	28
50-59	634	26	360	26	274	27
60-69	581	24	263	19	318	31
≥ 70	263	11	121	9	142	14
Sex						
Male	1,190	49	648	46	542	53
Female	1,229	51	749	54	480	47
BMI, kg/m^2†						
< 25	869	36	560	41	309	30
25-29	910	38	504	37	406	40
≥ 30	614	26	314	23	300	30
Unknown	26		19		7	
Smoking status†						
Never	1,081	45	668	48	413	41
Former	979	41	509	37	470	46
Current	347	14	215	15	132	13
Unknown	12		5		7	
Family history‡						
No	1,799	74	1,049	75	750	74
Yes	617	26	347	25	270	26
Unknown	3		1		2	
MSI						
Low/MSS	1,816	83	1,047	83	769	83
High	369	17	213	17	156	17
Unknown	234		137		97	
KRAS						
Wild-type	1,244	69	696	68	548	70
Mutant	563	31	333	32	230	30
Unknown	612		368		244	
BRAF						
Wild-type	1,919	89	1,127	90	792	88
Mutant	236	11	126	10	110	12
Unknown	264		144		120	
CIMP						
Low	1,364	87	774	88	590	86
High	200	13	107	12	93	14
Unknown	855		516		339	
Stage at diagnosis§						
I	637	33	326	30	311	36
II	650	33	391	36	259	30
III	488	25	263	24	225	26
IV	167	9	106	10	61	7
Unknown	477		311		166	
Tumor location						
Proximal	810	34	462	33	348	34
Distal	770	32	449	32	321	31
Rectal	819	34	477	34	342	34
Unknown	20		9		11	

Abbreviations: BMI, body mass index; CCFR, Colon Cancer Family Registry; CIMP, CpG island methylator phenotype; CRC, colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stable; NSAID, nonsteroidal anti-inflammatory drug.

*Postdiagnosis NSAID use was assessed at 5-year follow-up interview.

†At date of reference, defined as 2 years before baseline interview (approximately 1 year before diagnosis).

‡At least one first-degree relative affected with CRC at baseline.

§For a subset of individuals lacking American Joint Committee on Cancer (AJCC) staging, imputation from SEER and TNM staging was performed for each AJCC stage: I (SEER 1 and T1/T2), II (SEER 1 and T3; SEER 3/7 and N0, M0), III (SEER 3/4/7 and N1/N2, M0), and IV (SEER 7 and M1).

interaction were performed by adding the cross-product term of postdiagnostic NSAID use and each of these factors in the regression models. *P* values were two-sided with significance level of .05. All statistical analyses were conducted by using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Participants included in analyses of postdiagnostic NSAID use were mostly white (93%) with equal numbers of men and women who had an average age at diagnosis of 54 years (standard deviation, 11.3 years). Forty-two percent of participants regularly used either aspirin or other NSAIDs after a diagnosis of CRC. They were more likely to be older, male, overweight or obese, former smokers, and diagnosed with early-stage CRC compared with nonusers. The distributions of family history, tumor markers, and tumor location were nearly identical in these two groups (Table 1).

After the follow-up interview (median, 5.9 years since diagnosis; IQR, 5.5 to 6.5 years since diagnosis), we observed participants for a median of 4.9 years and recorded 381 deaths (16%; 100 died as a result of CRC). Regular users of any NSAIDs after diagnosis were associated with more favorable OS (HR, 0.76; 95% CI, 0.62 to 0.94). This association was similar among users of aspirin only, other NSAIDs only, or both aspirin and non-aspirin NSAIDs (Table 2). Statistical significance was lost, however, for users of other NSAIDs alone or both aspirin and other NSAIDs. For CSS, there was evidence of improved CSS among aspirin-only users compared with nonusers (HR, 0.44; 95% CI, 0.25 to 0.77). However, no statistically significant associations were observed among regular users of other NSAIDs only or both aspirin and other NSAIDs. Sensitivity analysis among patients with stage I to III CRC showed similar patterns of association.

The observed association between postdiagnostic NSAID use and OS was limited to individuals with *KRAS* wild-type tumors (HR, 0.64; 95% CI, 0.48 to 0.85; $P_{interaction}$ = .02; Table 3) but not for those with *KRAS*-mutant tumors (HR, 1.20; 95% CI, 0.75 to 1.91). Patterns of association were similar with respect to CSS, although they did not reach statistical significance ($P_{interaction}$ = .08). The interaction between *KRAS*-mutation status and postdiagnostic NSAID use in relation to survival did not differ by family history (OS: *P* for three-term interaction = .08; CSS: *P* = .50; Appendix Table A1). In addition, there were some suggestive differences, although they were not statistically significant, in the association between NSAID use and OS by *BRAF*-mutant status (for *BRAF*-mutant tumors: HR, 0.39 [95% CI, 0.19 to 0.80]; for *BRAF* wild-type tumors: HR, 0.83 [95% CI, 0.65 to 1.06]; $P_{interaction}$ = .11). We found no evidence of interaction between postdiagnostic NSAID use and other patient or tumor characteristics in relation to survival.

Duration-dependent relationships were observed for postdiagnostic NSAID use. In both any-NSAID and aspirin-only users, longer duration of use was associated with more favorable OS and CSS (P_{trend} < .05; Table 4). Use of any NSAIDs for more than 3 years significantly improved CSS compared with shorter duration of use (*P* = .02; Table 4). In exploratory analysis, we found that the observed association between the duration of postdiagnostic NSAID use and OS remained only among participants with *KRAS* wild-type tumors ($P_{interaction}$ = .02; Appendix Table A2).

Table 2. Association Between NSAID Use After Diagnosis and OS and Disease-Specific Survival, CCFR 1997-2008

Postdiagnosis NSAID Use*	Total (N = 2,419)	OS			CRC-Specific Survival			CVD-Specific Survival		
		No. of Events	HR†	95% CI	No. of Events	HR†	95% CI	No. of Events	HR†	95% CI
Nonusers	1,397	209	Ref		61	Ref		26	Ref	
Any-NSAID users	1,022	172	0.76	0.62 to 0.94	39	0.68	0.45 to 1.04	22	0.59	0.32 to 1.08
Aspirin-only users	676	122	0.74	0.59 to 0.94	17	0.44	0.25 to 0.77	19	0.68	0.36 to 1.29
Other NSAIDs–only users	181	22	0.87	0.56 to 1.36	15	1.60	0.89 to 2.85	0	—	—
Both aspirin and NSAIDs users	141	25	0.72	0.47 to 1.11	6	0.59	0.25 to 1.40	3	—	—

NOTE. (—) indicates fewer than five deaths.
Abbreviations: CCFR, Colon Cancer Family Registry; CRC, colorectal cancer; CVD, cardiovascular disease; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; OS, overall survival; Ref, reference.
*Postdiagnosis NSAID use was assessed at 5-year follow-up interview.
†HR was stratified by age at diagnosis (< 50, 50-59, 60-69, ≥ 70 years) and study center and adjusted for sex, body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), stage at diagnosis, and time between baseline and follow-up survey.

Among participants who reported any NSAID use before and after diagnosis, there were 1,315 never users (52%), 133 discontinued users (5%), 663 initiated users (26%), and 420 continued users (17%). The majority of participants who initiated or continued use of any NSAIDs were aspirin-only users (Table 5). In comparison with nonusers, initiated NSAID users experienced significantly better OS (HR, 0.71; 95% CI, 0.54 to 0.92), whereas no clear association was observed for continued and discontinued users. Similar patterns were observed for aspirin-only users. For CSS, initiated and continued aspirin-only users had improved CSS (HR, 0.39 [95% CI, 0.19 to 0.78] *v* HR, 0.45 [95% CI, 0.19 to 1.08]), although the latter did not reach statistical significance. When stratifying by *KRAS*-mutation status, we observed a similar pattern of association between pre- and postdiagnostic change in any NSAID use and OS among participants with *KRAS* wild-type tumors (Appendix Table A3).

DISCUSSION

In this population-based prospective study of long-term CRC survivors, we observed that the association between any NSAID use after diagnosis and OS seemed to be limited to individuals with *KRAS* wild-type tumors. The improved CSS may increase with longer duration of NSAID use after diagnosis. Our results also suggest that the association between aspirin use and OS was more pronounced among those who initiated aspirin use after diagnosis, whereas both initiated and continued users of aspirin after diagnosis seemed to be associated with more favorable CSS.

Our findings on the overall association between postdiagnostic use of aspirin and improved survival are consistent with existing literature.[17-19,24,38] However, few studies had reported non-aspirin NSAID use after diagnosis in relation to survival. Our results suggest that postdiagnostic non-aspirin NSAID use may have a beneficial effect on OS, although it did not reach statistical significance. There was no evidence of a favorable association with CSS. Different patterns in use of these medications, instead of the type of NSAID, may partially explain their differential effects on CRC prognosis: non-aspirin NSAID users tended to be shorter-term and higher-dose users (on average 10.1 times per week; median duration of 1 year; IQR, 0.25 to 4 years), whereas regular users of aspirin were more likely to be medicated at a lower dose over a longer period of time (on average, 7.1 times per week; median duration of 4 years; IQR, 2 to 5 years). The importance of a cumulative pattern of NSAID use is further supported by our finding that longer duration of any NSAID use after diagnosis was associated with better CSS.

We also observed that the association between any NSAID use after diagnosis and improved survival is evident only among participants with *KRAS* wild-type tumors, but not for those with *KRAS*-mutant CRCs. An existing observational study[39] reported that patients with *PIK3CA*-mutated tumors would benefit substantially from postdiagnostic aspirin use, but not those with wild-type *PIK3CA* tumors. Although it is unclear whether the pathway underlying the effect of NSAIDs on CRC prognosis by *KRAS*-mutation status differ from that by *PIK3CA* mutations, our finding supports the hypothesis that mutation of the *KRAS* proto-oncogene by activating the downstream Ras/mitogen-activated protein kinase (MAPK) pathway may lead to pro-proliferative and/or antiapoptotic effects that cannot be inhibited by NSAIDs. The suggestive interaction between *BRAF* and NSAID use after diagnosis, showing that only participants with *BRAF*-mutant CRC tumors might benefit from any NSAID use after diagnosis, indicates that the impact of NSAIDs may not uniformly affect prognosis between *BRAF*- and *KRAS*-mutant CRC tumors. Given the enriched family history sampling from the CCFR, we performed additional analysis by family history and found that the interaction between postdiagnostic NSAID use and *KRAS* mutations in relation to OS seemed to be limited to patients without family history, although three-term interaction did not reach statistical significance ($P = .08$). This is likely the result of limited sample size in the *KRAS*-mutant and family history–positive subgroup.

Several studies evaluated some aspects of the timing of aspirin use in relation to survival after CRC diagnosis; however, the findings were inconsistent.[17,19,24] Chan et al[19] evaluated aspirin use after diagnosis according to prediagnosis use in two health professional cohorts (N = 1,279 patients with stage I to III CRC). They reported improved survival among individuals who initiated aspirin use after diagnosis compared with nonusers, similar to our findings. No association was observed in continued versus discontinued users. However, this study was not able to examine the association by additional tumor markers. In contrast, Walker et al[17] only reported an association between continued use of aspirin and

Table 3. Association Between Any NSAID Use After Diagnosis and OS and CRC-Specific Survival, According to Patient and Tumor Characteristics, CCFR 1997-2008

Characteristic	Total No. of Patients	OS				CRC-Specific Survival			
		No. of Events	HR	95% CI	$P_{interaction}$	No. of Events	HR	95% CI	$P_{interaction}$
Overall, any NSAID use after diagnosis (Yes vs No)	1,022	172	0.76	0.61 to 0.94	—	39	0.67	0.44 to 1.01	—
Age at diagnosis, years*									
<50	941	72	0.78	0.46 to 1.33	.78	38	0.77	0.38 to 1.54	.45
≥ 50	1,478	309	0.74	0.59 to 0.94		62	0.59	0.35 to 1.00	
Sex†									
Male	1,190	218	0.73	0.55 to 0.97	.97	53	0.61	0.35 to 1.08	.93
Female	1,129	163	0.77	0.56 to 1.08		47	0.77	0.42 to 1.43	
Family history‡					.82				.42
No	1,799	289	0.72	0.56 to 0.92		80	0.63	0.39 to 1.00	
Yes	617	91	0.77	0.48 to 1.27		20	0.77	0.29 to 2.05	
KRAS§									
Wild-type	1,244	225	0.64	0.48 to 0.85	.02	59	0.54	0.30 to 0.95	.08
Mutant	563	89	1.20	0.75 to 1.91		25	0.96	0.42 to 2.21	
BRAF§									
Wild-type	1,916	298	0.83	0.65 to 1.06	.11	89	0.73	0.47 to 1.14	.43
Mutant	236	47	0.39	0.19 to 0.80		4	—	—	
CIMP§									
Low	1,364	246	0.86	0.66 to 1.13	.54	71	0.80	0.49 to 1.32	.99
High	200	41	0.54	0.25 to 1.12		1	—	—	
MSI§									
Low/MSS	1,816	297	0.85	0.66 to 1.09	.16	79	0.80	0.50 to 1.29	.45
High	369	58	0.56	0.30 to 1.04		9	0.67	0.13 to 3.51	
Tumor location§									
Proximal colon	839	145	0.73	0.51 to 1.04	.93	27	0.73	0.32 to 1.63	.68
Distal colon	802	121	0.70	0.47 to 1.06		26	0.42	0.16 to 1.08	
Rectum	870	125	0.76	0.51 to 1.12		46	0.73	0.38 to 1.38	
Stage at diagnosis‖									
I	637	103	0.97	0.63 to 1.48	.34	13	0.27	0.07 to 1.03	.28
II	650	119	0.84	0.56 to 1.25		28	0.58	0.25 to 1.31	
III	488	80	0.60	0.37 to 0.99		31	1.31	0.59 to 2.91	
IV	167	35	0.37	0.14 to 0.96		18	0.23	0.05 to 1.13	

NOTE. (—) indicates fewer than five deaths.

Abbreviations: CCFR, Colon Cancer Family Registry; CIMP, CpG island methylator phenotype; CRC, colorectal cancer; HR, hazard ratio; MSI, microsatellite instability; MSS, microsatellite stable; NSAID, nonsteroidal anti-inflammatory drug; OS, overall survival.

*HRs were stratified by study site and adjusted for sex, body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), stage at diagnosis, and time between baseline and follow-up survey.

†HRs were stratified by study site and age at diagnosis and adjusted for body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), stage at diagnosis, and time between baseline and follow-up survey.

‡At least one first-degree relative affected with CRC at baseline.

§HRs were stratified by study site and age at diagnosis and adjusted for sex, body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), stage at diagnosis, and time between baseline and follow-up survey.

‖HRs were stratified by study site and age at diagnosis and adjusted for sex, body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), and time between baseline and follow-up survey.

improved OS compared with discontinued users. Their study was not able to investigate disease-specific survival, and it had relatively short follow-up (3.1 years from diagnosis). More recently, a linkage study from Norway reported that continued, but not initiated, aspirin use after CRC diagnosis was associated with improved survival.[24] Data linkage with the Norwegian Prescription Database limited their ability to adjust for potential confounders such as body mass index and smoking status and to include the use of over-the-counter aspirin, which was prevalent in Norway.[40] Together, these studies suggest an association between postdiagnostic aspirin use and improved survival.[17,19,24] However, it was inconclusive whether this association was influenced by prediagnostic aspirin use.

Limitations need to be considered when interpreting our results. Because we collected self-reported NSAID use retrospectively, misclassification of NSAID use may have occurred. Participants included in this study had to survive long enough after diagnosis to complete the follow-up questionnaire. Therefore our results may not apply to short-term survivors. In addition, without longitudinal information on all risk factors, our study design limited our ability to assess risk factors associated with mortality, specifically among long-term survivors for whom traditional risk factors might not impact survival in the same manner. Our study population was representative of the underlying source population, which was overwhelmingly white. Greater diversity is needed in future studies. Finally, the limited number of patients who used non-aspirin NSAIDs regularly led to reduced power for secondary analysis by tumor characteristics.

Our study also has many strengths. Patients were identified from population-based cancer registries, and therefore our results are generalizable to other white populations of long-term CRC survivors. Long follow-up time of the CCFR allowed us to explore not only OS, but also CSS and CVD-specific survival, and to investigate the effect of long-term NSAID use on survival. Standardized questionnaires with detailed information on types

Table 4. Association Between Duration of NSAID Use After Diagnosis and OS and Disease-Specific Survival, CCFR 1997-2008

		OS					CRC-Specific Survival					CVD-Specific Survival				
Postdiagnosis Duration (years)*	Total	No. of Events	HR†	95% CI	$P_{difference}$‡	P_{trend}§	No. of Events	HR†	95% CI	$P_{difference}$‡	P_{trend}§	No. of Events	HR†	95% CI	$P_{difference}$‡	P_{trend}§
Any NSAIDs																
Nonusers	1,397	209	Ref			.03	61	Ref			.02	26	Ref			.03
≤ 3	457	69	0.81	0.61 to 1.07	.66		23	0.96	0.59 to 1.56	.02		12	0.92	0.44 to 1.92	.07	
> 3	466	90	0.75	0.58 to 0.98			13	0.42	0.23 to 0.79			9	0.40	0.18 to 0.89		
Aspirin only																
Nonusers	1,397	209	Ref			.01	61	Ref			.001	24	Ref			.09
≤ 3	280	48	0.79	0.57 to 1.10	.77		9	0.60	0.30 to 1.24	.06		10	0.97	0.43 to 2.16	.90	
> 3	340	65	0.71	0.52 to 0.94			6	0.26	0.11 to 0.61			8	0.47	0.20 to 1.09		

Abbreviations: CCFR, Colon Cancer Family Registry; CRC, colorectal cancer; CVD, cardiovascular disease; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; OS, overall survival; Ref, reference.
*Postdiagnosis duration is years of regular NSAID use between baseline and follow-up interview (postdiagnosis period).
†HR stratified by age at diagnosis (< 50, 50-59, 60-69, ≥ 70 years) and study center and adjusted for sex, body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), stage at diagnosis, and time between baseline and follow-up survey.
‡$P_{difference}$ compares use for more than 3 years with use for ≤ 3 years.
§P_{trend} assesses the linear trend of the three categories of duration (nonusers, ≤ 3 years, and > 3 years) as an ordinal variable.

Table 5. Association Between NSAID Use Before and After Diagnosis and OS and Disease-Specific Survival, CCFR 1997-2008

		OS			CRC-Specific Survival			CVD-Specific Survival		
Pre- and Postdiagnosis Change	Total	No. of Events	HR*	95% CI	No. of Events	HR*	95% CI	No. of Events	HR*	95% CI
Any NSAIDs†	2,419									
Nonusers	1,270	180	Ref		55	Ref		19	Ref	
Discontinued	127	29	0.94	0.62 to 1.44	6	0.79	0.33 to 1.89	5	1.12	0.37 to 3.37
Initiated	621	92	0.71	0.54 to 0.92	22	0.63	0.38 to 1.06	7	0.40	0.17 to 0.97
Continued	401	80	0.82	0.62 to 1.09	17	0.70	0.40 to 1.25	15	0.28	0.33 to 1.73
Aspirin only†	1,970									
Nonusers	1,270	180	Ref		55	Ref		19	Ref	
Discontinued	70	20	1.05	0.63 to 1.74	3	—	—	3	—	—
Initiated	416	64	0.63	0.46 to 0.85	11	0.39	0.19 to 0.78	7	0.52	0.21 to 1.28
Continued	214	49	0.89	0.63 to 1.26	6	0.45	0.19 to 1.08	9	0.98	0.41 to 2.32

NOTE. (—) indicates fewer than five deaths.
Abbreviations: CCFR, Colon Cancer Family Registry; CRC, colorectal cancer; CVD, cardiovascular disease; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; OS, overall survival; Ref, reference.
*HRs stratified by age at diagnosis (< 50, 50-59, 60-69, ≥ 70) and study center and adjusted for sex, body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), stage at diagnosis, and time between baseline and follow-up survey.
†Nonusers did not regularly use any NSAIDs during the pre- or postdiagnosis time period, discontinued users regularly used NSAIDs during the pre- but not the postdiagnosis time period, initiated users regularly used NSAIDs during the post- but not the prediagnosis time period, and continued users regularly used NSAIDs during both the pre- and postdiagnosis time periods.

and duration of NSAID use before and after diagnosis, as well as potential confounders allowed us to explore different parameterization of NSAIDs and to estimate aspirin and non-aspirin NSAID use separately. Molecular characterization of CRC tumors enhanced our ability to conduct stratified analysis by tumor characteristics that were not addressed in previous studies.

In summary, postdiagnostic NSAID use was associated with improved survival among long-term CRC survivors diagnosed with *KRAS* wild-type tumors. Patients who initiated aspirin use after diagnosis had improved OS, whereas both initiated and continued use seemed to be associated with more favorable CSS. Although both observational and randomized studies provided convincing evidence of aspirin as an effective chemopreventive agent for CRC,[8] aspirin is not generally recommended for primary prevention of CRC for people at average risk of CVD because of the potential risks. Aspirin for secondary prevention of CRC, particularly in subgroups such as those with *KRAS* wild-type tumors, is supported by our study. Future studies are needed to find the best timing, dose, and duration of aspirin use and to identify subgroups of patients with CRC for whom the benefits of aspirin outweigh its risk.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Timing of Aspirin and Other Nonsteroidal Anti-Inflammatory Drug Use Among Patients With Colorectal Cancer in Relation to Tumor Markers and Survival

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Appendix

Table A1. Association Between Any NSAID Use After Diagnosis and Overall and CRC-Specific Survival, According to *KRAS*-Mutation Status and Family History, CCFR 1997-2008.

Characteristic	Total	Overall Survival				CRC-Specific Survival			
		Events	HR*	95% CI	$P_{interaction}$†	Events	HR*	95% CI	$P_{interaction}$†
Any NSAID use after diagnosis (yes *v* no)	1,022	172	0.76	0.61 to 0.94		39	0.67	0.44 to 1.01	
Without family history‡									
KRAS wild-type	932	174	0.56	0.40 to 0.78	.003	49	0.46	0.24 to 0.89	.03
KRAS mutant	426	66	1.33	0.77 to 2.27		20	1.27	0.48 to 3.36	
With family history‡									
KRAS wild-type	311	51	0.79	0.41 to 1.53	.98	10	1.30	0.24 to 7.02	.95
KRAS mutant	137	23	0.73	0.23 to 2.34		5	—	—	

NOTE. (—) indicates fewer than five deaths.
Abbreviations: HR, hazard ratio; CRC, colorectal cancer; CCFR, Colon Cancer Family Registry.
*HRs were stratified by study site, age at diagnosis, and adjusted for sex, body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), stage at diagnosis, and time between baseline and follow-up survey.
†*P* values for two-term interaction between any NSAID use after diagnosis and *KRAS* mutation were presented in the table; *P* values for three-term interaction among any NSAID use after diagnosis, *KRAS* mutation and family history for overall survival and CRC-Specific Survival are 0.08 and 0.50 respectively.
‡At least one first-degree relative affected with CRC.

Table A2. Association Between Duration of NSAID Use After Diagnosis and Overall and CRC-Specific Survival, According to *BRAF* and *KRAS*-Mutation Status, CCFR 1997-2008.

Postdiagnostic NSAID Use Duration, years*	Total	Overall Survival				CRC-Specific Survival			
		Events	HR†	95% CI	$P_{interaction}$‡	Events	HR†	95% CI	$P_{interaction}$
Overall					—				—
Nonusers	1,397	209	Ref			61	Ref		
≤ 3	457	69	0.81	0.61 to 1.07		23	0.96	0.59 to 1.56	
> 3	466	90	0.75	0.58 to 0.98		13	0.42	0.23 to 0.79	
BRAF wild-type					.35				.99
Nonusers	1,126	162	Ref			53	Ref		
≤ 3	364	56	0.89	0.65 to 1.22		22	1.06	0.63 to 1.76	
> 3	355	72	0.81	0.60 to 1.09		12	0.44	0.23 to 0.85	
BRAF mutant									
Nonusers	126	30	Ref			3	Ref		
≤ 3	42	5	0.36	0.11 to 1.17		0	—	—	
> 3	53	9	0.49	0.19 to 1.23		1	—	—	
KRAS wild-type					.02				.11
Nonusers	695	132	Ref			39	Ref		
≤ 3	238	32	0.66	0.44 to 1.00		11	0.64	0.32 to 1.30	
> 3	263	51	0.61	0.43 to 0.87		7	0.33	0.14 to 0.77	
KRAS mutant									
Nonusers	333	43	Ref			12	Ref		
≤ 3	105	21	1.25	0.70 to 2.21		7	1.65	0.61 to 4.47	
> 3	95	24	1.51	0.86 to 2.67		6	0.89	0.30 to 2.63	

NOTE. (—) indicates fewer than five deaths.
Abbreviations: HR, hazard ratio; CRC, colorectal cancer; CCFR, Colon Cancer Family Registry; KRAS, Kristen-Ras; Ref, reference.
*Postdiagnostic duration is years of regular NSAID use between baseline and follow-up interview (postdiagnostic period).
†HRs were stratified by study site, age at diagnosis, and adjusted for sex, body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), stage at diagnosis, and time between baseline and follow-up survey.
‡*P* values for two-term interaction between NSAID use duration after diagnosis and *KRAS*/*BRAF* mutation were presented in the table.

Table A3. Association Between NSAID Use Before and After Diagnosis and Overall Survival, According to *BRAF* and *KRAS*-Mutation Status, CCFR 1997-2008.

Pre- and Postdiagnosis Change in Any NSAID Use*	Total	Overall Survival			$P_{interaction}$‡
		Events	HR†	95% CI	
Overall					—
Nonusers	1,270	180	Ref		
Discontinued	127	29	0.94	0.62 to 1.44	
Initiated	621	92	0.71	0.54 to 0.92	
Continued	401	80	0.82	0.62 to 1.09	
BRAF wild-type					.18
Nonusers	1,025	139	Ref		
Discontinued	100	23	1.03	0.64 to 1.68	
Initiated	491	70	0.75	0.56 to 1.02	
Continued	300	66	0.96	0.70 to 1.32	
BRAF mutant					
Nonusers	112	26	Ref		
Discontinued	14	4	0.65	0.21 to 2.01	
Initiated	63	12	0.43	0.19 to 0.98	
Continued	47	5	0.27	0.09 to 0.81	
KRAS wild-type					.08
Nonusers	625	113	Ref		
Discontinued	70	19	0.81	0.48 to 1.36	
Initiated	334	51	0.59	0.42 to 0.85	
Continued	214	42	0.64	0.44 to 0.95	
KRAS mutant					
Nonusers	304	36	Ref		
Discontinued	29	7	2.02	0.75 to 5.41	
Initiated	140	22	1.06	0.59 to 1.90	
Continued	90	24	1.69	0.94 to 3.04	

NOTE. (—) indicates fewer than five deaths.

Abbreviations: HR, hazard ratio; CRC, colorectal cancer; CCFR, Colon Cancer Family Registry; Ref, reference.

*Nonusers did not regularly use any NSAIDs during the pre- or postdiagnosis time period; discontinued users regularly used NSAIDs during the pre- but not the postdiagnosis time period; initiated users regularly used NSAIDs during the post- but not the prediagnosis time period; and continued users regularly used NSAIDs during both the pre- and postdiagnosis time periods.

†HR stratified by age at diagnosis (< 50, 50-59, 60-69, ≥ 70) and study center; and adjusted for sex, body mass index (< 25, 25-29, ≥ 30), smoking status (never, former, current), stage at diagnosis, and time between baseline and follow-up survey.

‡*P* values for two-term interaction between pre- and postdiagnosis Change in any NSAID use and *KRAS*/*BRAF* mutation were presented in the table.