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Prediagnostic Non-steroidal anti-inflammatory drug use and survival after diagnosis of colorectal cancer

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Abstract

Objective—Nonsteroidal anti-inflammatory drug (NSAID) use decreases both the incidence of colorectal cancer and recurrence of adenomas among patients with prior colorectal neoplasia. However, few studies have investigated the association between NSAID use and colorectal cancer-specific survival. We therefore examined the role of pre-diagnostic NSAID use in relation to colorectal cancer-specific survival among cases from the Seattle Colon Cancer Family Registry (Seattle Colon CFR).

Design—This was a follow up study that included incident cases of colorectal cancer from the Seattle Colon CFR. Cases were ages 20–74, diagnosed from 1997–2002, and were identified using the population-based Puget Sound SEER registry. Detailed information on history of NSAID use, including type, recency, and duration, was collected through an interviewer-administered questionnaire. Follow-up for mortality was completed through linkages to the National Death Index (NDI). The main outcome measure was death due to colorectal cancer after diagnosis. Cox proportional hazards regression was used to investigate the relationship between pre-diagnostic NSAID use and colorectal cancer-specific mortality among cases.

Results—NSAID use prior to colorectal cancer diagnosis was associated with an approximately 20% lower rate of colorectal cancer mortality after diagnosis compared to never use (HR: 0.79; 95% CI 0.65–0.97). This relationship appeared to be duration-dependent, with longer reported use prior to diagnosis associated with lower rates of colorectal cancer mortality among cases. The most pronounced reductions in mortality were observed among cases diagnosed with proximal disease (HR: 0.55; 95% CI 0.37–0.82), whereas we observed no association between NSAID use prior to diagnosis and colorectal cancer-specific mortality among cases diagnosed with distal or rectal disease.

Conclusions—Our findings suggest that regular use of NSAIDs prior to diagnosis is associated with improved colorectal cancer survival, particularly among cases diagnosed with proximal disease and in longer-term NSAID users.

Keywords

colorectal cancer mortality; inflammation; COX-2; epidemiology

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INTRODUCTION

The National Cancer Institute reported a five-year survival rate for colorectal cancer of 67.3% in 2002, representing an improvement of only approximately 5% over the previous decade. [1] Evidence-based recommendations are needed to identify factors that can improve survival among colorectal cancer cases. NSAIDs (nonsteroidal anti-inflammatory drugs) are commonly used medications in the United States for treating pain and reducing inflammation and are available without a prescription. [2] NSAID use has been associated with decreased incidence of colorectal cancer [3–8] and lower risk of developing fatal colorectal tumors. [9–12] Use among individuals previously diagnosed with colorectal cancer is associated with a decreased risk of adenoma recurrence. [13,14] However, only three observational studies to date have reported on the association between NSAID use and survival among colorectal cancer cases. [15–17] Only one investigated non-aspirin NSAID use, and that study was only able to include women. [17] Of the remaining two studies, one was restricted to stage III colorectal cancer patients concurrently enrolled in a randomized chemotherapy trial. [16] The other included both male and female stage I–III colorectal cancer patients. [15] Although findings regarding the importance of the timing of use were not consistent across these studies, all three provided evidence that use of NSAIDs was inversely associated with mortality among colorectal cancer cases.

We investigated the association between pre-diagnostic aspirin and ibuprofen use (individually and combined) and colorectal cancer survival after diagnosis in a population-based sample of cases identified through the Seattle Colon Cancer Family Registry (Seattle Colon CFR). This study was the largest to date addressing this question, enrolled cases representing all stages of disease as well as both men and women, and collected data on tumor characteristics not investigated in previous studies, including microsatellite instability (MSI) status and tumor sub-site. It was hypothesized that NSAID use prior to diagnosis would be inversely associated with the rate of colorectal cancer-specific mortality among cases.

METHODS

Study Population

We investigated our hypothesis using colorectal cancer cases ascertained from the Seattle Colon CFR. Details of case recruitment have been presented elsewhere. [18] Incident, invasive colorectal cancer cases were identified from the Puget Sound Surveillance, Epidemiology and End Results (SEER) Registry. All cases ages 20–74 diagnosed between 1997–2002 in the Puget Sound SEER counties were eligible for study participation (n=2,551). Permission to contact cases from physicians and patient consent to be interviewed was obtained for 90% of the eligible cohort (n=2,290). A total of 553 cases were excluded due to: death prior to interview (n=169), withdrawal from study (n=77), completion of only a partial interview (n=21), or loss to follow-up prior to interview (n=286). Therefore, 1,737 colorectal cancer cases were eligible and completed the interview. Cases were enrolled an average of 8 (95% CI: 3–13) months after diagnosis. Informed consent was obtained from all participants, and the study was approved by the Institutional Review Board at the Seattle Colon CFR study site, the Fred Hutchinson Cancer Research Center.

Exposure and Covariate Assessment

Information on known and potential colorectal cancer risk factors was collected through an interviewer-administered questionnaire at study enrollment. Interviewer-collected data

included family history of colorectal cancer, lifetime smoking and alcohol consumption history, height and weight two years prior to diagnosis, colorectal cancer screening history, existence of prior inflammatory or co-morbid conditions, and demographic characteristics such as age, race, and sex. The questionnaire collected information on type of NSAID (aspirin or ibuprofen) used, recency of use relative to a reference date (current, former, never), and amount used (average daily dose, duration of use in years).

For exposure definitions, a reference date approximately two years before the case's diagnosis of colorectal cancer was selected. Regular use was defined as use at least twice per week for one month or greater. `Ever use' was defined as regular use at any point prior to the selected reference date. For cases who reported ever using NSAIDs regularly, each patient was asked whether he/she was taking NSAIDs at the time two years prior to his/her colorectal cancer diagnosis. If yes, the case was recorded as using NSAIDs at the time 2 years before diagnosis (current user); if no, the case was considered to only have used NSAIDs at a point in time greater than two years prior to diagnosis (former user). `Never users' reported no use or use below the `regular use' threshold prior to the reference date. Information on average daily dose (measured in `times pills taken daily') among regular users and the duration of regular use in years was also collected. The duration of regular NSAID use was divided into quartiles (1^{st}: 0–6 months; 2^{nd}: 6 months-2.5 years; 3^{rd}: 2.5–7 years; 4^{th}: ≥7 years).

First-course treatment and tumor characteristics at the time of diagnosis, including stage, sub-site, and MSI status, were obtained from SEER reports. Advanced disease was defined as colorectal cancer with distant metastasis (n=202); non-advanced disease included localized and regional stage disease (n=1,526). Sub-site of disease was categorized using ICD10 codes: proximal disease (C18.0–C18.5); distal disease (C18.6–18.7); and rectal disease (C19.9, C20.9, and C21.8). MSI status was assessed using ten separate markers. Based upon established guidelines [19], cases were classified as MSI-stable if 0% of loci were unstable, MSI-low if 0–40% of loci (less than 3 markers) were unstable, and MSI-high if >40% of loci (4 or more markers) were unstable, with unequivocal results for at least four markers required to characterize MSI status.

Outcome Assessment

Vital status was ascertained through linkage to the National Death Index (NDI) records to obtain date and cause of death; causes of death were classified using ICD10 codes. [20] The National Death Index identifies known deaths with a high degree of sensitivity, validity, and completeness. [21] The primary outcome of interest was mortality from colorectal cancer, assessed from underlying cause of death obtained from the NDI. Time to colorectal cancer mortality was evaluated from Seattle Colon CFR records of date of colorectal cancer diagnosis and NDI-recorded date of death. Patients alive and free of endpoint at the time of their last known vital assessment were administratively censored at that date, with the most recent vital status linkage occurring in January 2010. Patients dying of causes other than colorectal cancer were administratively censored at their recorded date of death.

Statistical Analysis

Kaplan-Meier survival curves were generated comparing NSAID `ever use' to `never use.' Differences between survival curves were evaluated using the log-rank test. The proportional hazards assumption was evaluated both graphically and statistically, using Schoenfeld residuals. [22] Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals for the association between pre-diagnostic NSAID use and colorectal cancer-specific mortality after diagnosis. To account for lag time between

diagnosis and study enrollment, staggered entry was used such that cases did not contribute follow-up time to the analysis until completion of the baseline interview.

Cox regression models were restricted to Caucasian cases (n=1,549) only due to sparse numbers of events among persons of other races that led to a lack of positivity in adjusted models. To increase comparability to previous studies that excluded metastatic disease, [15] we also reported hazard ratio estimates restricted to cases diagnosed with non-advanced disease (n=1,379). Cox regression models included covariates from the following list of potential confounders: age, sex, body mass index (BMI), smoking status, history of diabetes, prior inflammatory conditions (ulcerative colitis, Crohn's disease), receipt of preventive colorectal screening (sigmoidoscopy or colonoscopy received at least 2 years prior to diagnosis of colorectal cancer), first-course treatment, and stage of disease at diagnosis. Models without stage at diagnosis and first-course treatment are presented due to the potential for stage to be in the causal pathway between NSAID use prior to diagnosis and mortality after diagnosis. Results from models including both stage and treatment are also presented. The multivariable adjusted Cox regression models were evaluated across strata of tumor sub-site, MSI status, and BMI; potential interactions between NSAID use and stratification variables were investigated by inclusion of interaction terms in the model. Additionally, exploratory analyses were run among non-Caucasian cases. All statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC); all p-values reported are two-sided.

Sensitivity Analysis

Mortality occurring in the lag time between diagnosis and interview for enrolled cases did not contribute to our regression models. Therefore, we conducted a sensitivity analysis to see if the association between NSAID use prior to diagnosis and colorectal cancer survival varied by time between diagnosis and interview. A series of analyses was performed to simulate failure to enroll cases in a timely manner by restriction of case groups to patients enrolled after 6 months, 8 months, and one year, respectively. Results were used to determine if inclusion in our analyses of only cases that survived long enough after diagnosis to be interviewed could have resulted in enough lost information to introduce longevity bias. It is possible that cases who were not enrolled in a timely manner, possibly due to death from severe disease, were distinct from cases who survived long enough to be interviewed and that the effect of pre-diagnostic NSAID use therefore differed according to enrollment lag time.

RESULTS

Approximately 50% of cases reported ever using NSAIDs regularly prior to colorectal cancer diagnosis (Table 1). `Ever-users', compared to `never-users', were more likely to be older, report ever smoking, have received preventive colorectal screening, have diabetes, and be obese. A larger proportion of `ever users' compared to `never users' were also more likely to be diagnosed with localized colorectal tumors.

After an average of 8 years of follow-up after colorectal cancer diagnosis, 707 deaths from any cause, including 462 deaths due to colorectal cancer, were ascertained among eligible and enrolled cases. Colorectal cancer survival curves based on NSAID use are presented for all enrolled cases in Figure 1. `Ever users' experienced improved colorectal cancer survival compared to `never users.' This association of NSAID use with improved survival was observed among cases with proximal disease (log rank p-value=0.04) but not cases with distal or rectal disease (log rank p-value=0.41). The proportional hazards assumption was not significantly violated.

Among all colorectal cancer cases, `ever use' of NSAIDs prior to diagnosis was associated with a 21% (95% CI: 3–35%) lower rate of colorectal cancer mortality after diagnosis compared to `never use.' (Table 2). Regular use at the time 2 years prior to diagnosis (current use) was associated with a similar decrease in the hazard of colorectal cancer mortality among all cases (HR: 0.79; 95% CI 0.62–0.99). The effect estimate for former use (use more than 2 years prior to diagnosis) was also consistent with an inverse association, although the 95% confidence interval included the null value (HR: 0.78; 95% CI 0.60–1.01). Inclusion of stage in regression models or restriction to cases with non-advanced disease did not the change interpretation of results, with reductions in colorectal cancer mortality after diagnosis associated with NSAID use prior to diagnosis of approximately 20–30% reported consistently. However, hazard ratio estimates were attenuated after stage adjustment, and confidence intervals for cases with non-advanced disease included the null value.

Investigation of duration of pre-diagnostic NSAID use in years (using quartiles of duration) suggested a duration-dependent relationship Table 3, with lower colorectal cancer-specific mortality observed among cases reporting longer durations of use (p-trend=0.03), although very long term users (> 7 years) did not follow the trend and may instead represent very sick colorectal cancer patients. In an exploratory model investigating `NSAID use in years' and `average number of times pills taken daily' as distinct exposures, with each centered around its mean, each additional year of NSAID use prior to diagnosis was associated with a significantly lower hazard of colorectal cancer mortality; however, after accounting for duration of use, the average daily dose taken did not appear to be associated with colorectal cancer survival (data now shown).

Estimates for aspirin use were remarkably similar to those reported for overall NSAID use across all stages of disease, with observed reductions in colorectal cancer mortality risk after diagnosis of 20–30%. In contrast, estimates for ibuprofen use were not consistent with an improvement in colorectal cancer survival. When each medication type was examined independently of the other, aspirin was observed to significantly decrease colorectal cancer mortality risk among all cases (HR: 0.74; 95% CI 0.60–0.92), while ibuprofen use results were null (Table 2). The patterns of regular use for aspirin and ibuprofen also differed substantially. Among cases using aspirin, approximately 85% reported taking pills no more than once per day; over 50% reported at least 2 years of regular use, with an average duration of 5.8 years. In contrast, only 30% of cases using ibuprofen reported use for more than 2 years, with an average duration of 2.8 years. Additionally, approximately 60% of ibuprofen users reported taking pills at least twice per day.

Heterogeneity in the role of pre-diagnostic NSAID use in relation to colorectal cancer survival was observed across strata of tumor sub-site (p-interaction=0.08). `Ever use' of NSAIDs prior to diagnosis was associated with a 45% (95% CI: 18–63%) lower rate of colorectal cancer mortality among cases with proximal tumors (Table 4). In contrast, no evidence of an association was observed among cases diagnosed with distal or rectal tumors (HR: 1.00; 95% CI 0.72–1.41). Duration of NSAID use prior to diagnosis appeared to be important for proximal disease, with longer durations associated with greater reductions in the hazard of colorectal cancer mortality after diagnosis (p-trend=0.03), Table 3. Estimates reported in Table 4 were consistent with those unadjusted for stage as well as those observed for patients diagnosed with advanced disease (data not shown).

Hazard ratio estimates were imprecise across strata of MSI status, particularly among MSI-low and MSI-high cases, due to limited sample size, but no statistical evidence of heterogeneity was observed (p- interaction=0.57). No statistical significance for the association between NSAID use prior to diagnosis and colorectal cancer mortality after diagnosis was observed in any MSI subgroup. Exploratory analyses revealed some

suggestion of heterogeneity between strata of BMI (data not shown). Reductions in colorectal cancer mortality after diagnosis appeared to be limited to non-obese cases. However, results were not consistent by type of NSAID, with this pattern only being observed among regular aspirin and not ibuprofen users.

Among non-Caucasian cases, we observed 30 total events, with a suggestion that NSAID users may actually experience elevated mortality, in contrast to results observed among the Caucasian cases (p-interaction for NSAID effect and race= 0.10). However, among African American cases, who accounted for 20 of the 30 observed events, the prevalence of obesity was 40%, high cholesterol 50%, and smoking 80%, raising the possibility that these cases used NSAIDs for other serious indications that may in fact have led to elevated mortality rates. These subgroup results need to be confirmed in future studies designed to investigate these specific hypotheses

The sensitivity analyses run with models restricted to cases with increasing lag times between diagnosis and enrollment did not reveal any evidence of substantive bias, producing effect estimates consistent with those reported here (data not shown).

DISCUSSION

Regular NSAID use prior to a diagnosis of colorectal cancer was associated with an approximately 20% lower rate of colorectal cancer-specific mortality among cases. This inverse association was most pronounced among cases with proximal tumors, with reductions in the hazard of colorectal cancer mortality of approximately 45%. Our results also suggest that the improved colorectal cancer survival associated with pre-diagnostic NSAID use may increase with longer duration of use prior to diagnosis.

Our findings are consistent with previous studies that observed an inverse association between NSAID use and colorectal cancer mortality. A study done using stage III colorectal cancer patients (n=846) observed that consistent aspirin use, measured both prior to diagnosis and after treatment initiation, was associated with a reduced risk of cancer recurrence and death. [16] A recent report from the California Teacher's Study (n=621) observed a significant decrease in the rate of colorectal cancer mortality among cases associated with NSAID use prior to diagnosis. [17] Chan and colleagues from the Nurses Health Study and Health Practitioners Follow-up Study (n=1,279) observed that aspirin use after a colorectal cancer diagnosis was associated with a reduced risk of colorectal cancer-specific mortality among cases. [15] These studies suggest that both pre- and post-diagnostic NSAID use may be important for colorectal cancer survival.

Previous studies have either not investigated the role of non-aspirin NSAIDs in relation to colorectal cancer survival [15,16] or have only reported results combined for overall NSAID use. [17] Our results by type of NSAID appeared to suggest that aspirin use may be more important than ibuprofen for colorectal cancer survival, but the limited number of cases regularly using ibuprofen precluded any meaningful inference regarding its role in colorectal cancer mortality among cases. Patterns of regular NSAID use by type observed suggest that ibuprofen users were shorter-term, higher-dose users compared to cases regularly taking aspirin, who medicated at lower doses on average albeit for substantively longer periods of time. The difference in the pattern of use and potentially not the type of NSAID may be the crucial factor in determining effectiveness against colorectal cancer mortality. The importance of considering the cumulative pattern of exposure is further supported by our observation that increasing duration of pre-diagnostic use in years was associated with greater reductions in colorectal cancer mortality after diagnosis.

Observed differences in the association of NSAID use with colorectal cancer survival by tumor sub-site are consistent with literature suggesting that NSAIDs' chemopreventive effects against colorectal cancer incidence may be more pronounced for proximal disease. [23–26] This potential site-specific NSAID effect for colorectal cancer survival has not been investigated to date, and replication in future studies is needed. Although the exact reasons for a sub-site difference are not clear, proximal tumors do have a distinct molecular and genetic profile compared to distal or rectal tumors [27–29], and studies have suggested that levels of COX-2, a target for NSAIDs, may vary by location in colorectal tissue. [30–32] The question of whether NSAIDs plays a different role in colorectal cancer survival depending upon tumor sub-site is of increasing importance with recent reports of inherently poorer prognosis for proximal tumors [28,33] and ineffectiveness of colorectal screening in decreasing mortality for proximal disease. [34,35]

The stage distribution at diagnosis among NSAID users in our study included a higher proportion of localized disease compared to `never users'. NSAID users had higher screening rates than non-users, so we investigated whether the shift towards earlier stage of disease at diagnosis was due to screening practices. Among both cases who did and did not receive preventive screening, NSAID users presented with higher percentages of_localized disease compared to `never users'. This suggests that the association of NSAID use with earlier stage at diagnosis may be mediated not entirely through screening practices but in part through slowing the progression of the developing tumor. Thus, stage may be in the causal pathway between NSAID use and colorectal cancer mortality, resulting in attenuation of the association between NSAID use and colorectal cancer mortality after accounting for stage in regression models.

The anti-inflammatory and chemopreventive effects of NSAIDs are mediated through direct inhibition of COX-1 and COX-2. [36–41] Inflammation plays a well-documented role in the initiation of colorectal neoplasia [42–45] and is also important for cancer progression [46–48], and levels of inflammatory markers have been demonstrated to be prognostic for survival in patients with colorectal cancer. [43,49–51]

Some of the earliest reports of the chemopreventive effects of NSAIDs noted the association of these medications with decreased incidence not just of colorectal tumors but specifically of fatal tumors. [9–12] More recently, investigators from the NHS reported that regular pre-diagnostic aspirin use resulted in a lower than expected incidence of tumors expressing high levels of COX-2. [52] Elevated COX-2 expression in tumors has been demonstrated to be associated with tumor metastasis and to be a negative prognostic factor in colorectal cancer patients. [37,41,53–58] Use of NSAIDs prior to diagnosis may therefore lead to development of less aggressive tumors expressing lower levels of COX-2, a molecular profile that improves survival. NSAID use may not only result in the formation of inherently less aggressive tumors but may also contribute to slower disease progression for tumors of all grades through direct effects on the tumor microenvironment. COX enzyme-mediated mechanisms have been linked to the ability of tumors to initiate vascularization [55,59] and angiogenesis [60], most probably via direct effects on prostaglandin production. [38,61] The prostaglandin pathway may also regulate cellular apoptosis [62,63] and responses to growth factors such as TGF-β. [64] Ultimately, NSAID use prior to diagnosis may facilitate the development of less aggressive tumors and anti-inflammatory effects on the microenvironment of the initiating tumor that can alter colorectal tumor progression.

Our study has several important strengths. Study participants were drawn from a population-based registry, suggesting good generalizeability. Our study is the largest to date in the literature addressing NSAID use and colorectal cancer survival and includes cases diagnosed at all stages of disease. Follow up and outcome ascertainment among enrolled cases was

complete and standardized. The collection of detailed exposure information, including type, dose, and duration of use, allowed us to investigate patterns of exposure not previously addressed in the literature. In addition, our study did not suffer from long lag times between diagnosis and study enrollment that can result in patient loss and limit interpretation of study results, as we have recently suggested. [65] Finally, inclusion of data on important tumor characteristics allowed us to investigate subsite specific effects not addressed in prior studies.

This study is not without limitations. NSAID use histories were ascertained after the diagnosis of colorectal cancer, raising concerns of recall bias. However, we have no reason to believe that cases reported NSAID use differently based upon mortality status that was unknown at the time of study enrollment. This non-differential misclassification likely biased our results to the null rather than introduced a false association. Only pre-diagnostic NSAID use information was routinely collected in the study population; it was therefore not possible to examine effects of post-diagnostic use. In a sample of cases for which we had additional data at 5 years post-diagnosis, approximately one third of cases changed their NSAID exposure status (data not shown), although the pattern was not predictable and further investigation is warranted.

In addition to colorectal cancer-specific survival, we attempted to explore the association between NSAID use prior to diagnosis and all-cause mortality among colorectal cancer cases. We observed hazard ratios of similar direction to those reported for colorectal cancer mortality but reduced in magnitude, with no significant associations observed. However, our ability to investigate this relationship was limited because the vast majority of deaths in our cohort were due to colorectal cancer. Finally, a proportion of eligible cases were lost prior to enrollment. We did not have covariate information for the majority of these cases; However, among a subgroup of cases who completed a baseline interview but later withdrew from the study (n=42), the NSAID use pattern appeared similar to cases included in our analyses. Cases lost from the study however were younger and had a higher BMI on average compared to cases in the study. Lost cases also had a slighter higher percentage of proximal and localized disease at diagnosis.

Our results suggest that regular, pre-diagnostic NSAID use is associated with improved colorectal cancer survival, particularly among cases diagnosed with proximal tumors. This improvement in survival could be realized through NSAIDs' altering of the profile of the developing tumor or through antiinflammatory effects on the developing tumor's microenvironment. The reductions in colorectal cancer mortality among cases appeared to be greater for cases reporting longer durations of NSAID use prior to their diagnosis. Future studies should investigate the biological changes that occur in tumors of NSAID users, including variations in COX-2 expression. The importance of the timing and dose of NSAID use should also be established so that evidence-based recommendations can be made to improve survival after diagnosis among colorectal cancer cases.

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Abbreviations Used

BMI	Body Mass Index
CTS	California Teachers Study
HPFS	Health Professionals Follow-up Study
ICD10	International Classification of Diseases Version 10
MSI	Microsatellite Instability
NDI	National Death Index
NHS	Nurses Health Study
NSAIDs	Non-steroidal anti-inflammatory drugs
Seattle Colon CFR	Seattle Colon Cancer Family Registry
SEER	Seer Epidemiology End Results
TGF-β	Transforming growth factor beta

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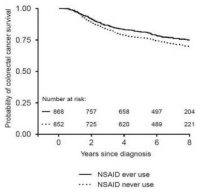

Figure 1.
Colorectal Cancer Survival According to Pre-diagnostic NSAID Use

Table 1

Characteristics of cases, stratified according to NSAID use prior to diagnosis

	Total Colorectal Cancer Cases[†] (n=1,737)		Cases who report *ever* using NSAIDs regularly (n=868)		Cases who report *never* using NSAIDs regularly (n=852)		*p-value* for association with regular NSAID use
	N	%	N	%	N	%	
Age							
<50 years	285	16.4	128	14.8	154	18.1	0.02
50–59.9 years	473	27.2	218	25.1	251	29.5	
60–69.9 years	619	35.6	328	37.8	284	33.3	
≥ 70 years	360	20.7	194	22.3	163	19.1	
Sex							
Female	791	45.5	374	43.1	406	47.6	0.06
Male	946	54.5	494	56.9	446	52.4	
Race							
White, non-Hispanic	1549	89.2	806	92.9	729	85.6	<0.01[*]
Black, non-Hispanic	54	3.1	20	2.8	33	3.9	
Hispanic	11	0.6	3	0.4	8	0.9	
Asian	72	4.2	15	1.7	57	6.7	
Body Mass Index (kg/m^2)							
Normal (<25.0)	561	32.3	252	29.0	306	35.9	<0.01
Overweight (25.0–29.9)	684	39.4	343	39.5	332	39.0	
Obese (≥30.0)	489	28.2	272	31.3	212	24.9	
Ever Smoked							
No	647	37.3	296	34.1	341	40.0	0.01
Yes	1089	62.7	572	65.9	511	60.0	
Alcohol [‡]							
No	914	56.4	432	52.9	476	59.8	<0.01
Yes	707	43.6	384	47.1	320	40.2	
Preventive Colorectal Cancer Screening							
No	1532	88.2	754	86.9	761	89.3	0.12
Yes	205	11.8	114	13.1	91	10.7	

	Total Colorectal Cancer Cases† (n=1,737)		Cases who report *ever* using NSAIDs regularly (n=868)		Cases who report *never* using NSAIDs regularly (n=852)		*p-value* for association with regular NSAID use
	N	%	N	%	N	%	
History of High Cholesterol							
No	1116	64.3	512	59.0	594	69.7	<0.01
Yes	616	35.5	355	40.9	255	29.9	
History of Diabetes							
No	1481	85.3	722	83.2	745	87.4	0.01
Yes	255	14.7	146	16.8	107	12.6	
Prior Inflammatory Condition							
No	1658	95.0	834	96.1	809	95.0	0.26
Yes	87	5.0	34	3.9	43	5.0	
First-Course Chemotherapy							
No	733	42.2	390	44.9	334	39.2	0.03
Single Agent	716	41.2	340	39.2	369	43.3	
Multiple Agents	132	7.6	72	8.3	60	7.0	
MSI Status **							
Stable	993	57.2	494	56.9	489	57.4	0.30
Low	137	7.9	72	8.3	65	7.6	
High	213	12.3	112	12.9	99	11.6	
Tumor Stage							
Localized	708	40.8	383	44.1	318	39.2	<0.01
Regional	818	47.1	378	43.6	432	50.7	
Distant	202	11.6	102	11.8	98	11.5	
Site of Tumor							
Proximal	673	38.7	351	40.4	314	36.9	0.31
Distal	469	27.0	222	25.6	242	28.4	
Rectal	574	33.1	287	33.1	284	33.3	

* Chi-square p-value based on less than 5 events per cell

** MSI status of tumors was available for ~77% of cases in the study population

† The values for ever and never NSAID users do not total to 1,737 due to missing exposure information for 17 cases

‡Participants classified as 'Yes' if case reported consuming at least one alcoholic beverage per week for at least six months during the age interval (20–30 years, 30–50 years, after age 50) of the relevant colorectal cancer diagnosis.

Table 2

Hazard ratios for colorectal cancer mortality after diagnosis in relation to pre-diagnostic NSAID use

	Total† Events	All Stages Combined (1549/401)				Non-Advanced Disease at Diagnosis (1379/261)			
		Model 1[1]		Model 2[2]		Model 1[1]		Model 2[2]	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
NSAID use									
Never*	729/207	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Ever‡	806/189	0.79	0.65–0.97	0.76	0.62–0.93	0.73	0.57–0.93	0.78	0.61–1.00
Current[a]	474/111	0.79	0.62–0.99	0.82	0.64–1.04	0.71	0.53–0.95	0.77	0.57–1.03
Former[b]	329/75	0.78	0.60–1.01	0.69	0.52–0.90	0.73	0.53–1.02	0.80	0.57–1.13
Aspirin use									
Never	889/252	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Ever	652/146	0.76	0.62–0.94	0.76	0.61–0.94	0.74	0.57–0.96	0.82	0.63–1.07
Current	385/82	0.71	0.55–0.92	0.77	0.59–1.00	0.71	0.52–0.97	0.77	0.56–1.07
Former	267/64	0.83	0.63–1.10	0.75	0.56–1.00	0.78	0.55–1.11	0.89	0.62–1.28
Independent**		0.74	0.60–0.92	0.76	0.61–0.95	0.72	0.55–0.94	0.83	0.63–1.09
Ibuprofen use									
Never	1234/317	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Ever	309/82	0.99	0.77–1.27	0.88	0.69–1.14	0.92	0.66–1.27	0.88	0.63–1.23
Current	124/39	1.19	0.85–1.67	1.17	0.83–1.66	0.92	0.57–1.48	0.86	0.52–1.43
Former	185/43	0.86	0.62–1.19	0.73	0.53–1.01	0.91	0.61–1.36	0.89	0.60–1.33
Independent**		1.00	0.78–1.30	0.89	0.69–1.15	0.91	0.65–1.27	0.88	0.63–1.23

†Total cases and colorectal cancer event numbers reported for each category of exposure apply to all stages combined (n=1549)

*Each line in the table represents a distinct comparison between the listed exposure category and `never users'. Comparisons are made using categorical variables, with the referent group being `never users.' For example, effect estimates for current use are generated from a model comparing only cases using NSAIDs at the point two years prior to diagnosis to cases who report `never use.'

‡Not every case who responded to the `ever versus never' NSAID use question responded to the question asking whether the case was using at the point in time two years prior to diagnosis, such that the Current and Former users do not total to the Ever users, with 3 cases missing.

[1]adjusted for age (continuous), sex, BMI (continuous), screening, smoking, diabetes, and prior inflammatory conditions

[2] adjusted for covariates in Model 1 in addition to first-course treatment and stage of disease at diagnosis

[a] Current Use was defined as use at the time two years prior to diagnosis among ever users.

[b] Former Use was defined as use greater than two years prior to diagnosis among ever users.

[**] Independent use is defined as `ever use', adjusted for use of other NSAID type. For example, results reported for `Independent use' of aspirin are generated from a model comparing `ever users' of aspirin to `never users', adjusting in the model for `ever use' of ibuprofen.

Table 3

Hazard ratios for colorectal cancer mortality after diagnosis in relation to duration of pre-diagnostic NSAID u

	All Stages Combined						Non-Advanced Disease at Diagnosis					
	All Sites		Proximal		Distal/Rectal		All Sites		Proximal[±]		Distal/Rectal	
NSAID Duration	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Never	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Quartile 1[†]	0.82	0.58–1.15	0.80	0.47–1.35	0.69	0.43–1.11	0.91	0.58–1.42	0.78	0.38–1.58	0.99	0.55–1.79
Quartile 2	0.72	0.53–0.97	0.55	0.35–0.87	1.04	0.69–1.56	0.87	0.60–1.25	0.62	0.34–1.12	1.18	0.73–1.90
Quartile 3	0.70	0.49–0.99	0.61	0.35–1.08	0.75	0.47–1.19	0.57	0.37–0.90	0.45	0.22–0.92	0.69	0.38–1.25
Quartile 4	0.83	0.59–1.16	0.76	0.44–1.30	0.88	0.56–1.38	0.79	0.52–1.22	0.46	0.22–0.95	1.12	0.65–1.92
	p-value=0.03		p-value=0.03		p-value=0.37		p-value=0.03		p-value<0.01		p-value=0.87	

All models in the table are adjusted for age (continuous), sex, BMI (continuous), smoking, screening, diabetes, prior inflammatory conditions, first-course treatment, and stage of disease at diagnosis

Models for all sites include a small number of cases without tumor site information (n=21). Hazard ratio estimates for all sites are therefore not the exact weighted average of the estimates for the proximal and distal/rectal subgroups.

[†]Quartile 1: Less than 6 months; Quartile 2: 6 months to 2.5 years; Quartile 3: 2.5–7 years; Quartile 4: More than 7 years

[*]Hazard ratio estimates are calculated from a regression model with each quartile of duration treated in an unrestricted manner as a distinct categorical variable. The p-trend is calculated from a regression model with duration treated as one ordinal variable with four levels representing each quartile.

[±]Proximal cases included cancer diagnosed in the caecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure. Distal/Rectal cases included cancer diagnosed in the descending colon, sigmoid colon, rectosigmoid junction, rectum, and anal canal.

Table 4

Hazard ratios for colorectal cancer mortality after diagnosis in relation to pre-diagnostic NSAID use, stratified by tumor sub-site among cases with non-advanced disease

	Proximal Disease (530/109)			Distal/Rectal Disease (833/148)		
	Total /Events	**HR**	**95% CI**	**Total/ Events**	**HR**	**95% CI**
NSAID use						
Never	242/64	1.00	Referent	402/73	1.00	Referent
Ever	282/43	0.55	0.37–0.82	424/74	1.00	0.72–1.41
Current	179/29	0.57	0.36–0.89	241/40	0.98	0.66–1.47
Former	100/12	0.46	0.25–0.86	180/34	1.08	0.71–1.65
Aspirin use					1.00	
Never	293/72	1.00	Referent	487/88	1.00	Referent
Ever	234/36	0.62	0.40–0.94	342/59	1.03	0.72–1.47
Current	145/23	0.58	0.38–0.96	201/33	0.97	0.63–1.50
Former	89/13	0.46	0.25–0.86	141/26	1.11	0.70–1.75
Ibuprofen use						
Never	425/93	1.00	Referent	671/116	1.00	Referent
Ever	103/15	0.55	0.31–0.99	159/32	1.16	0.77–1.74
Current	47/7	0.56	0.24–1.31	56/12	1.23	0.66–2.32
Former	56/8	0.54	0.26–1.14	103/20	1.18	0.69–1.82
p-interaction* = 0.08						

All models in the table are adjusted for age (continuous), sex, BMI (continuous), smoking, screening, diabetes, prior inflammatory conditions, first-course treatment, and stage of disease at diagnosis

All definitions for NSAID use patterns are the same as outlined for Table 2. As reported in Table 2, not every case who responded to the `ever versus never' NSAID question responded to the question asking whether the case was using at the point in time two years prior to diagnosis, such that the Current and Former users to not exactly total to the Ever users, with 3 cases missing.

*P-value calculated from a full model using an interaction term between tumor site (proximal vs. distal/rectal) and NSAID use (ever vs. never).