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Influence of NSAID Use among Colorectal Cancer Survivors on Cancer Outcomes

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Abstract

Purpose—Colorectal cancer (CRC) is the third most common cancer diagnosed in men and women in the United States. Given the availability of effective screening, most tumors are found early enough to offer patients substantial long-term survival. Thus there is a resulting significant population of colorectal cancer survivors for whom modifiable risk factors for recurrence and survival would be of interest.

Methods—We conducted a population-based retrospective cohort study among patients enrolled in two large Midwestern health plans for which claims data, including pharmacy fill data, and medical record data were available. Men and women who were 40 years of age or older at the time of CRC diagnosis with disease less than Stage IV and no history of Crohn's disease, ulcerative colitis, and irritable bowel syndrome. CRC cases diagnosed between January 1, 1990 and December 31, 2000 were included if they met the inclusion criteria. Adjusted Cox proportional hazard models were used with exposure modeled as a time-dependent covariate. We assessed progression free survival, defined as an aggressive polyp or invasive disease, and overall survival.

Results—After adjustment for age at diagnosis, sex, race, body mass index, stage, side of initial tumor, and tumor histology, we found that current users of non-steroidal anti-inflammatory had a 3-fold decreased risk of recurrence and a greater than 7-fold decreased risk of death. Our results are statistically significant with p-values < 0.05.

Conclusions—Our results suggest that current use of non-steroidal anti-inflammatory drugs provides significant improvements in colorectal cancer outcomes.

Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed in men and women in the United States.¹ It is estimated that nearly 140 000 new cases of CRC will be diagnosed in the United States in 2014. Moreover, the relative survival rate for CRC is quite favorable

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with 5-year estimates for local and regional disease of 90% and 70%,² respectively, contributing to one of the largest populations of cancer survivors in the United States. Therefore, modifiable risk factors for CRC recurrence and survival would have a large target audience.

Non-selective non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, have been shown to be inversely related with the incidence and recurrence of colorectal polyps, established precursors of CRC. Laboratory, epidemiologic, and clinical trial research support the premise that NSAIDs have a chemopreventive effect against CRC incidence.³⁻¹⁸ However, to date, few studies have investigated the relationship between NSAID use and CRC outcomes among survivors.¹⁹⁻²⁴ These studies vary in the period of exposure (pre-diagnosis and post-diagnosis) and the drugs (NSAIDs only, aspirin only, both) captured in self-reported questionnaires and some use a single self-report of drug use behavior to estimate long-term effects. We are not aware of a single study that has used prescription fill data, an objective measure of exposure, to assess the relationship of NSAIDs with CRC progression free survival (PFS) and overall survival (OS). Only two studies have assessed post-diagnosis exposure, which unlike pre-diagnosis is when medical intervention is more feasible. In addition, these two studies only assessed aspirin use.^{19,20} In the current study, we use a cohort of health maintenance organization enrollees who have drug coverage. Using electronic data sources and medical record review, we examine the association of NSAID use as a time-dependent exposure on PFS and OS in a cohort of CRC survivors.

Methods

We conducted a retrospective cohort study in two Midwestern health maintenance organizations (HMOs) using electronic data and medical record review. The two HMOs included were HealthPartners, in Minneapolis and St. Paul, Minnesota, and Health Alliance Plan, part of Henry Ford Health System (HFHS), in Detroit, Michigan. Both HMOs are affiliated with the National Cancer Institute-sponsored HMO Cancer Research Network, a population-based research program comprised of enrollees, research centers and data systems of, at the time of the study, 11 United States HMOs.²⁵ This protocol was approved by the institutional review boards at both health plans.

Cohort subjects were identified by using the automated data resources at each health plan. Tumor registry data at HFHS was used to identify all primary cases of CRC that fit the age and stage criteria. HFHS is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) tumor registry so case identification and reporting are conducted to these standards. At HealthPartners, where an onsite tumor registry was not available, cases were identified using a claims algorithm. The algorithm was first developed at HFHS using the tumor registry as a "gold standard" and then applied to databases at HealthPartners. The final case ascertainment algorithm identified cases that had received a pathology read less than 7 days after a colon procedure and had a subsequent International Classification of Diseases, Ninth Revision (ICD-9) coded encounter for CRC. Medical chart review confirmed CRC diagnosis. Comparing the algorithm against the gold standard in the Michigan databases, we estimated 87% sensitivity in identifying potential cohort subjects.

All individuals deemed eligible from the administrative databases at both sites were subject to medical record review to confirm eligibility. Cases were excluded if there was a history of CRC prior to the study period. For HealthPartners, cases were reviewed per the AJCC (American Joint Commission on Cancer) criteria for staging. Cases greater than stage III were excluded at both sites. For data quality and consistency purposes, data on tumor stage was reviewed by a certified tumor registrar to confirm the stage captured at each site.

All patients aged 40 years or older at diagnosis, with incident AJCC Stage 0, I, II, or III CRC identified between January 1, 1990 and December 31, 2000 were identified (n = 956). Patients with Crohn's disease, ulcerative colitis, and irritable bowel syndrome identified using chart review were excluded (n = 49) from the study because these comorbidities may affect screening behaviors, recurrence, and survival. The resulting study cohort included 907 patients.

Because subjects at both sites were health plan members with prescription drug coverage, we were able to capture all NSAID prescription fill information. Exposure to NSAIDs was determined using pharmacy claims (prescription fills) data, which included data elements for National Drug Code, brand name, generic name, class, quantity, dose, route, date of dispensing, and number of days supplied. For each subject data on prescription fills from the time of CRC diagnosis to death, disenrollment from the plan, or end of study period (June 30, 2009) was captured. All formulations of available NSAIDs were included in the data capture. For the univariate analysis, we defined "ever" use as having at least 1 NSAID prescription fill. "Never" users were those without any prescription fill. For the multivariate analysis, we calculated exposure as a time dependent variable so that each person contributed time to the exposed category (referred to in the analysis as "current") from the fill date until the end of the calculated days supply. Continuous exposure was defined by sequential prescription fills with no more than a 30 day gap between last day supplied and a new fill. All prescription fills were included regardless of whether they were sequential in order or sporadic during the observation time. Because pain is a symptom of cancer recurrence, we did not include any new prescriptions within 3 months of a recurrence, death, end of enrollment, or end of study.

Covariates

Potential confounders examined in the analysis included year of diagnosis, age at diagnosis, race, sex, body mass index (BMI) at diagnosis, stage at diagnosis, and location of initial tumor. Age was included as a categorical variable (40-49, 50-59, 60-69, 70+). Because the racial distribution at either site included very few races other than white or black, race was dichotomized as either white or non-white. BMI was analyzed using the accepted categories of underweight (BMI < 18.5), normal (BMI ≥ 18.5 and < 25), overweight (BMI ≥ 25 and < 30), and obese (BMI ≥ 30). BMI categories were analyzed as an ordinal variable (1 = underweight, 2 = normal weight, 3 = overweight, and 4 = obese) so risk estimates are for a 1 unit change in BMI category. Tumors that occurred in the cecum, appendix, ascending colon, or the hepatic flexure were considered right sided. Tumors that occurred in the transverse, descending, sigmoid or rectum were considered left sided tumors.

Outcomes

Patients were followed up from CRC diagnosis until date of death, last encounter, and end of study or disenrollment from the health plan, whichever occurred first. Surveillance examinations were captured from the medical record review. Whenever possible, the colonoscopy report was reviewed; however, if this was not available then a doctor's visit note was used. Pathology reports for all tissue removed for any colorectal procedures, including surveillance, were reviewed and the specimen pathology was recorded. Polyps found during colonoscopies that were defined as aggressive by histology, number, or size were included as a recurrence event for the PFS analysis. An aggressive polyp was defined as having a tubulovillous or villous only histology, 2 polyps of any histology, or a polyp 10mm in largest dimension regardless of histology. Deaths were abstracted from the medical record. In addition, we used the National Death Index for the identification of death events.

Statistical Analysis

For the descriptive analysis, we used chi-square tests to determine differences between those who filled one or more prescription for an NSAID (ever user) compared to those who never filled a prescription for an NSAID (never user). For the multivariate analysis, we analyzed data by fitting Cox proportional hazards models to calculate hazard ratios (HR) with 95% confidence intervals (CI) for time-to-event analysis. Current exposure was modeled as a time-dependent covariate so that during a prescription fill period (date of fill + days supply) the person contributed time to the “current” exposed category. However, if the patient never filled a prescription for an NSAID or had gaps between fills greater than 30 days, then the time was counted in the “unexposed” category. To assess covariates as candidates for the final multivariate model, we first modeled “current” exposure alone for reference and then paired with each of the available covariates for comparison. All covariates that were significant when modeled with “current” exposure were included in the final multivariate model. This approach was used for building both the final PFS and OS models.

Results

A total of 907 patients were eligible for the study. The median follow-up for the cohort is 3.5 years with a range of < 1 year to 13 years. The mean use of NAIDs was 11.27 months (standard deviation 16 months) with a median of 5.5 months. The majority of patients were over 70 (n = 419; 46%) and male (n = 519; 57%), as well as white (n = 657; 72%). Table 1 shows the distribution of patient characteristics for the study sample by ever or never use of NSAIDs. There are statistically significant differences between ever and never users by age, race, and BMI with the highest proportions of users over 60 years of age (71%), white (64%), and above normal BMI (76%).

Table 2 shows the distribution of recurrence and death events in our cohort by ever or never exposure to NSAIDs. Recurrence events included aggressive polyps and invasive disease. Table 2 shows the mutually exclusive recurrence categories: aggressive polyp(s) only, aggressive polyp(s) and invasive disease, or invasive disease only. In total, 368 patients experienced a recurrence event and 338 deaths were recorded in the cohort. Of the recurrences, 303 (82%) were within the no NSAIDs exposure group and 65 (18%) were

within the ever NSAIDs exposed group. The chi-square comparison is not significant (p-value = 0.11). Among deaths, 255 (75%) were within the never exposed group and 83 (25%) were among those exposed. The chi-square comparison p-value is 0.24. The small number of deaths observed in the exposed category limited our analysis to overall survival.

The results in Table 3 are from the Cox proportional hazard models used for building the final multivariate model and give the HR and 95% CI. Results are presented in Table 3 for PFS and OS. The HR for current exposure to an NSAID, modeled as a time-dependent variable, and recurrence was 0.27, which is significant (95% CI, 0.10-0.73). Covariates that were significantly associated with a recurrence event included diagnosis year (HR = 1.04; 95% CI, 1.00-1.08), sex (HR = 1.34; 95% CI, 1.09-1.66), stage (HR = 1.19; 95% CI, 1.04-1.35), location (HR = 0.69; 95% CI, 0.55-0.87), and BMI (HR = 1.17; 95% CI, 1.02-1.34). These variables were retained for the full model presented in Table 4. In the full model, current NSAID exposure remains protective with a HR of 0.35 (95% CI, 0.13-0.95). Overall survival was similarly analyzed with current exposure modeled alone and with each covariate. The univariate HR for overall survival is 0.09 with 95% CI 0.02-0.39. The variables that remained significant when modeled with current exposure were year of diagnosis (HR = 1.08; 95% CI, 1.03-1.13), age at diagnosis (HR = 1.05; 95% CI, 1.04-1.92), stage (HR = 1.48; 95% CI, 1.29-1.72) and BMI (HR = 0.80; 95% CI, 0.69-1.04). After adjustment, the HR for overall survival, while currently taking an NSAID, is 0.14 (95% CI, 0.03-0.55).

Discussion

We found that current use of NSAIDs protects CRC survivors from a CRC recurrence and improves survival. To our knowledge, this is the first study to use prescription fill data to investigate the association of NSAIDs and CRC outcomes. Other studies have relied on self-reported use, which can suffer from recall bias and is limited in the details on the length of exposure, requiring investigators to assume that drug exposure behavior remained constant after questioning. Our study methods allowed us to use specifically just the time of exposure to estimate the effect of NSAIDs on our outcomes of interest. With a nearly 3 fold decrease in risk in the adjusted models for both recurrence and 7 fold for overall survival, our approach yielded the strongest effect for NSAIDs on CRC outcomes reported to date.

Prior studies of NSAIDs and CRC recurrence and survival have inconsistently measured NSAID exposure. Despite this, most of the results of these studies also show a protective effect for disease-specific and overall survival. In the two studies that, like this one, assessed post-CRC diagnosis exposure to NSAIDs, both found exposure associated with a decreased risk of CRC-specific mortality with HRs of 0.71 (95% CI, 0.53-0.95) and 0.48 (95% CI, 0.24-0.99), but only one of these studies found a protective effect for overall survival (HR=0.79; 95% CI, 0.65-0.97).

Because NSAIDs are available over-the-counter (OTC) there is the possibility that regular users were counted in our study as not being exposed. In a methods study regarding the bias associated with using prescription NSAIDs to study CRC, the authors showed that as long as the proportion of those exposed to a particular drug that has OTC formulation is the same

between diseased and non-diseased persons, misclassifying the OTC users as unexposed biases the effect estimate toward the null.²⁶ Therefore, the true hazard estimate may be lower than that observed in our study.

A limitation of our study is that we did not have data on behavioral factors, such as smoking status, physical activity, or diet. Our study was limited to electronic data with no direct patient content. We were able to include BMI, which would be correlated with these variables, and would therefore have served as a partial surrogate for these factors in our analysis. Given the strong effects we observed for NSAID use, it is unlikely that having these additional variables would have reversed the association we observed. Also, we minimized the potential for reverse causality by not including any new prescriptions in the 3 months before end of follow-up, death, or disenrollment.

A challenge with observational pharmacoepidemiology studies is properly accounting for exposure. In a recent article by Suissa et al,²⁷ the authors use observational studies of metformin to show common mistakes made in this category of research. The miscounting or overcounting of the exposure can give spurious results. This often results in contradicting reports in the literature. The reader should note that when we analyzed exposure as a simple dichotomous relationship with the outcome there was no statistically significant relationship observed (Table 2) with a p-value of 0.11 for recurrence and p-value of 0.24 for survival. However, modeling exposure as a time-dependent variable gave a 3 fold decrease in risk for recurrence and a 7 fold decrease for death. In summary, we observed that current use of an NSAID was associated with a decreased risk of cancer recurrence and death by more than two-thirds in our study population. This association remained significant even after adjusting for other factors associated with our outcomes of interest suggesting that adjuvant NSAID treatment may be beneficial to CRC patients. As NSAIDs also have adverse effects, such as an increased risk of gastric ulcer perforation and upper gastrointestinal bleeding, as well as cardiovascular toxicities, it is recognized that any chemopreventive recommendations associated with NSAID use will need to be tailored by individual risk-benefit assessment.

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Table 1

Univariate analysis of patient characteristics by “never” and “ever” NSAID use.

Characteristic	Never User N = 664	Ever User N=243	X ² p-value
Age			
40-49	43 (6%)	24 (10%)	<.001
50-59	124 (19%)	46 (19%)	
60-69	166 (25%)	85 (35%)	
70+	331 (50%)	88 (36%)	
Sex			
Female	286 (43%)	102 (42%)	0.767
Male	378 (57%)	141 (58%)	
Race			
White	502 (76%)	155 (64%)	<0.001
Non-White	162 (24%)	88 (36%)	
BMI			
Underweight (< 18.5)	17 (3%)	2 (1%)	0.007
Normal (> 18.5- 25)	174 (32%)	48 (23%)	
Overweight (> 25- 30)	199 (37%)	82 (39%)	
Obese(> 30)	153 (28%)	80 (38%)	
Stage			
I	196 (30%)	71 (29%)	0.949
II	252 (38%)	95 (39%)	
III	216 (33%)	77 (32%)	
Tumor Side *			
Right	236 (36%)	89 (37%)	0.766
Left	425 (64%)	153 (63%)	
Tumor Histology			
Not Adenocarcinoma	49 (7%)	25 (10%)	0.156
Adenocarcinoma	615 (93%)	218 (90%)	

BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug.

* Right side included cecum, appendix, ascending colon, and hepatic flexure; Left side included transverse colon, descending colon, sigmoid, and rectum.

Table 2
Univariate analysis of mutually exclusive outcome events by “never” and “ever” NSAID use

Outcome Event	Never User N=728	Ever User N=179	X ² p-value
Progression Free Survival			
No Aggressive polyp or invasive disease	425 (58%)	114 (64%)	0.111
Aggressive polyp only	156 (21%)	26 (15%)	
Aggressive polyp followed by invasive disease	28 (4%)	4 (2%)	
Invasive disease only	119 (16%)	35 (20%)	
Overall Survival			
No deaths	409 (62%)	160 (66%)	0.241
All Cause deaths	255 (38%)	83 (34%)	

NSAID, non-steroidal anti-inflammatory drug.

Table 3

Multivariate Cox Proportional Hazards Models of current exposure as a time-dependent variable modeled alone and paired with each covariate for progression free survival (PFS) and overall survival (OS).

Models	PFS HR (95% CI)	OS HR (95% CI)
Current Exposure *	0.27 (0.10-0.73)	0.09 (0.02-0.39)
Current Exposure	0.28 (0.10-0.74)	0.10 (0.02-0.39)
Diagnosis Year	1.04 (1.00-1.08)	1.08 (1.03-1.13)
Current Exposure	0.27 (0.10-0.73)	0.10 (0.03-0.39)
Sex (Male vs Female)	1.34 (1.09-1.66)	1.04 (0.84-1.30)
Current Exposure	0.27 (0.10-0.73)	0.10 (0.03-0.40)
Age (continuous)	0.99 (0.99-1.00)	1.05 (1.04-1.06)
Current Exposure	0.28 (0.10-0.74)	0.10 (0.03-0.41)
Stage (continuous)	1.19 (1.04-1.35)	1.49 (1.29-1.72)
Current Exposure	0.27 (0.10-0.72)	0.10 (0.02-0.38)
Race (Non-white referent)	0.89 (0.71-1.11)	0.80 (0.64-1.00)
Current Exposure	0.28 (0.10-0.74)	0.10 (0.02-0.39)
Location (Right vs Left)	0.69 (0.55-0.87)	1.20 (0.96-1.49)
Current Exposure	0.27 (0.10-0.73)	0.10 (0.02-0.39)
Histology (Adenocarcinoma vs. Other)	1.09 (0.73-1.61)	0.86 (0.59-1.26)
Current Exposure	0.34 (0.14-0.91)	0.13 (0.03-0.51)
BMI †	1.17 (1.02-1.34)	0.80 (0.69-0.92)

HR, hazard ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.

* Current exposure modeled as a time-dependent covariate

† BMI is modeled as a continuous variable with 1= underweight (BMI < 18.5); 2= normal weight (BMI > 18.5 and < 25); 3 = overweight (BMI > 25 and < 30); 4 = obese (BMI > 30)

Table 4
Final Multivariate Cox Proportional Hazards Model of current exposure as a time-dependent variable for progression free survival (PFS) and overall survival (OS)

Variable	PFS HR (95% CI)	OS HR (95% CI)
Current Exposure	0.35 (0.13-0.95)	0.14 (0.03-0.55)
Diagnosis Year	1.07 (1.02-1.12)	1.09 (1.03-1.15)
Age at Diagnosis (continuous)	--- *	1.05 (1.03-1.06)
Sex (Male vs. Female)	1.48 (1.17-1.87)	---
Stage (continuous)	1.22 (1.05-1.40)	1.48 (1.25-1.75)
Location (Right vs Left) ‡	0.65 (0.50-0.84)	---
BMI (continuous) §	1.17 (1.02-1.34)	0.90 (0.78-1.04)

HR, hazard ratio; CI, confidence interval

* Variables not significant in bivariate analyses (See Table 3) were not maintained for the full multivariate model

‡ Right side included cecum, appendix, ascending colon, and hepatic flexure; Left side included transverse colon, descending colon, sigmoid, and rectum

§ BMI, body mass index; BMI is modeled as a continuous variable with 1 = underweight (BMI < 18.5); 2 = normal weight (BMI > 18.5 and < 25); 3 = overweight (BMI > 25 and < 30); 4 = obese (BMI > 30)