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Association of Non-steroidal Anti-inflammatory Drugs with Colorectal Cancer by Subgroups in the VITamins And Lifestyle (VITAL) Study

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Abstract

Background—There is substantial evidence that use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk of colorectal cancer (CRC), but no subgroup has been identified for which the chemoprevention effect outweighs the risk of side effects.

Methods—We tested the interaction between NSAID use and multiple risk factors on CRC risk in the VITAL cohort. A total of 73,458 individuals aged 50-76 completed a questionnaire between 2000 and 2002, and 674 incidental colorectal cancer cases were identified through 2010.

Results—In stratified analysis, high use of any type of NSAIDs (4+days/week for 4+ years) was statistically significantly associated with a lower risk of CRC across all subgroups stratified by sex, BMI, physical activity, smoking, alcohol intake, screening and dietary factors. There was a suggestion of stronger associations among men, obese individuals, and heavier drinkers; however, none of these tests for interaction reached statistical significance. The associations were almost identical for subjects with higher overall CRC risk scores (HR: 0.62; 95% CI: 0.49-0.79) and those with lower risk scores (HR: 0.61; 95% CI: 0.42-0.88). Differential effects by cancer subsites and stages were tested. NSAID use was associated with a greater risk reduction of proximal colon cancer vs. distal (p for difference = 0.06) and distant stage vs. local (p for difference = 0.04).

Conclusion—The association between high use of NSAIDs and CRC risk does not differ significantly among subgroups. Impact: Our results suggest that NSAIDs have a generally beneficial role in colorectal cancer prevention, largely unmodified by other exposures.

Keywords

Non-steroidal anti-inflammatory drugs; aspirin; colorectal cancer; effect modification; cohort study

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Conflicts of Interest

None of the authors had a conflict of interest.

Introduction

Chronic inflammation has been established as a risk factor for colorectal cancer, and there is substantial experimental and epidemiologic evidence that long-term use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are protective for this disease (1-4). A meta-analysis of randomized trials with 20-years of follow-up found that long-term aspirin use reduced the incidence of and mortality due to colorectal cancer, and the benefit increased with scheduled duration of treatment (2). The effect was reported to be greatest 10-14 years after randomization in patients who had scheduled trial treatment of 5 years or more (1). The likely mechanism of NSAIDs is that they reduce inflammatory mediators, such as high-sensitivity C-reactive protein (CRP) (5, 6) and interleukin (IL)-6 (7), through the inhibition of cyclooxygenase-2 (COX-2) (8), which is responsible for producing various inflammatory prostaglandins (9). Cox-independent pathways have also been observed to be modified by aspirin exposure, including the oncogenic Wnt/β-catenin pathway (10) and the NF-κB pathway (11, 12).

Several other risk factors for colorectal cancer have also been identified, including obesity, high consumption of red and/or processed meat, physical inactivity, smoking, moderate-to-heavy alcohol consumption (13) and family history (14). It is suspected that some of these risk factors may also affect colorectal cancer risk by increasing inflammation, but their interactions with NSAID use are unclear. A population-based case-control study found significant interaction between smoking duration and use of any NSAIDs (15); however, the result was not confirmed in a later cohort study (16). Among non-aspirin NSAID users, a statistically significant lower risk of colorectal cancer in association with body mass index (BMI) above 25, but not with BMI of 25 or below, was reported in a Danish cohort study (17), but results from other large cohort studies did not reach statistical significance (16, 18, 19). Meta-analyses did not find the effect of NSAID use significantly different between men and women (1, 20). Randomized trials also reported synergistic effects of calcium and any NSAID use in lowering the risk of advanced colorectal neoplastic polyps (21). However, these results are not consistent with other studies that did not find significant interactions between aspirin/NSAID use and other risk factors of CRC (3, 16). Similarly, evidence for differential associations by anatomic site or cancer stage is not consistent across single studies (3, 16, 22-24). A systematic review from randomized and observational studies reported no differences in the associations of aspirin and other NSAIDs by colorectal cancer site or aggressiveness (1). A meta-analysis of cohort studies found a stronger but statistically non-significant effect of aspirin on the risk of rectal cancer compared to colon cancer (20), whereas the follow-up meta-analysis of randomized trials found that long-term aspirin use was associated with significant reduction of proximal colon cancer and rectal cancer, but not with distal colon cancer (2). In addition, meta-analyses have reported that regular use of aspirin was associated with reduced risk of distant metastasis (25, 26).

Despite their potential for chemoprevention, NSAIDs are currently not recommended for colorectal cancer prevention among the general population due to the potential side effect of gastrointestinal bleeding. Furthermore, due to the inconsistent results among prior studies of interaction effects between NSAID use and other risk factors, no subgroup of the population has been identified for which the benefits clearly outweigh the risks. In this study, we aimed

to identify potential effect modifiers of the association between long-term NSAID use and colorectal cancer risk to explore differences in the effect of NSAIDs among subgroups of the population. We also examined differential effects of NSAIDs by stage and anatomic site of colorectal cancer.

Materials and Methods

Study Population

Subjects were participants in the VITamins And Lifestyle (VITAL) study, a prospective cohort of persons aged 50-76 years residing in the 13-county western Washington catchment area of the Surveillance, Epidemiology, and End Results (SEER) cancer registry. Details of the VITAL study have been published previously (27). Briefly, potential participants were identified through a purchased commercial mailing list. Between October 2000 and December 2002, 77,719 of the 364,418 people contacted returned the 24-page questionnaire and met the eligibility and quality-control checks. The study procedures were approved by Fred Hutchinson Cancer Research Center Institutional Review Board.

We excluded participants who reported a history of CRC at baseline or missing history (n=1,184), those with a history of ulcerative colitis or Crohn's disease (n=1,030) or intestinal polyposis (n=272), *in situ* CRC diagnosed during follow-up (n=13), CRC noted on death certificate or autopsy only (n=3), and diagnosis with CRC of certain rare morphologies including malignant carcinoid tumors, neuroendocrine carcinomas, and lymphomas (n=38). We also excluded participants with missing information on use of any type of NSAIDs (n=1,787), leaving 73,458 individuals for analyses. (The above-listed exclusions are not mutually exclusive.)

Exposure Assessment

Participants completed a self-administered, sex-specific, 24-page questionnaire on medication use, medical history, personal characteristics, cancer risk factors, supplement use, and diet.

Use of NSAIDs, including low-dose “baby” aspirin (81mg), regular or extra-strength aspirin, ibuprofen, naproxen, and celecoxib, rofecoxib, and other pain relievers (e.g. piroxicam or indomethacin), over the previous 10 years was ascertained. For each category of NSAID, participants were asked to report years taken in the previous 10 years and frequency (days per week) of use in those years. NSAID use was defined as use at least once per week for at least 1 year during the prior 10 years. Ten-year average use of each drug was categorized into three groups based on frequency and duration: non-use, low use (<4 days/week or <4 years), and high use (≥4 days/week and ≥4 years). NSAID use was analyzed as 4 types: low-dose aspirin, regular/extra strength aspirin, non-aspirin NSAIDs and any type of NSAID.

Covariate Assessment

Information on potential confounders of the NSAID-CRC association was ascertained on the baseline questionnaire. Potential confounders were selected *a priori* and included known or

suspected risk factors for colorectal cancer. We controlled for age, sex, race/ethnicity, education, body mass index (BMI), physical activity, smoking, alcohol intake, fruit and vegetable intake excluding potatoes, red/processed meat intake, energy intake, dietary-fiber intake, dietary-plus-supplemental calcium intake, family history of CRC, history of sigmoidoscopy/colonoscopy in the 10 years prior to baseline, and hormone-therapy use for females. We also controlled for indications for NSAID use, including history of frequent headaches, arthritis or joint pain, coronary heart disease, diabetes, and use of cholesterol-lowing medicine.

BMI was calculated based on self-reported height and baseline weight (kg/m^2). 1,289 participants were missing baseline weight, but reported weight at age 45. For these participants, we estimated baseline BMI by calculating the average BMI change per year within sex-age-race groups among those with complete data, and then applying this to the number of years elapsed since age 45 for those missing BMI at baseline.

Dietary information was ascertained by a food-frequency questionnaire (FFQ) adapted from the Women's Health Initiative (28), which captured frequency and serving size of 120 foods and beverages consumed over the year prior to baseline. Red/processed meat intake was computed as intake of beef, pork and lamb, including mixed dishes and processed meat. We excluded participants from dietary variable calculations if they did not complete all pages of the FFQ or if they reported abnormally high or low energy intake (men: <800 kcal/day or >5000 kcal/day; women: <600 kcal/day or >4000 kcal/day).

Physical activity was categorized based on the participants' 10-year average MET hours per week of moderate/vigorous physical activities (activities with MET≥4.0), which was derived from a one-page questionnaire covering years, days per week, and minutes per day of 16 activities over the prior 10 years (29).

Case and Censoring Ascertainment

Incident cases of invasive CRC (ICD-O-3: 18.0-20.9) were identified during follow-up by linkage to the western Washington SEER cancer registry. As noted above, those with rare histologies were excluded. Between baseline and December 2010, there were 674 eligible invasive colorectal cancer cases diagnosed. Cancer stage was based on SEER stage, which defines localized cancer as cancer that is limited to the organ of origin, regional cancer as beyond the original site to nearby lymph nodes or organs and tissues, and distant cancer as cancer that has spread to distant organs or distant lymph nodes. Subsites of cancer cases were defined based on ICD-O-3 codes and categorized into proximal colon cancer (ICDO-3: 18.0-18.5), distal colon cancer (ICD-O-3: 18.6-18.9), and rectal cancer (ICD-O-3: 19.9 and 20.9).

Cases were followed to the date of CRC diagnosis, and non-cases were censored at whichever occurred earliest: date of death (9.1%), date of emigration out of the areas covered by SEER (7.5%), date of withdrawal from the study (0.03%), or end of follow-up period (December 31, 2010) (83.4%). Deaths were ascertained by linkage to the Washington State death file, and emigrations out of area were identified primarily by linkage to the US Post Office National Change of Address System.

Statistical Analysis

Cox regression, with age as the time variable, was used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for each NSAID variable by comparing colorectal cancer risk among non-users, low-users, and high-users after adjustment for covariates. A missing indicator term was included for those missing education, race, the FFQ, BMI, and physical activity variables. At-risk time was defined as age at the completion of baseline questionnaire through age at last follow-up. A test for trend was performed for each NSAID variable by treating the categorical variable as a linear variable (codes as 1=no use, 2=low use, 3=high use). Proportional hazards assumption was tested for each NSAID variable.

We tested for effect modification of the association between NSAID use and CRC risk by factors associated with inflammation (30-32), including: sex, BMI (normal, overweight and obese/severely obese), moderate/vigorous physical activity (yes/no), smoking (never/10+year quitter and current/recent quitter), alcohol intake (≤4 drinks/week and >4 drinks/week), fruit and vegetable intake (lower and upper halves), red/processed meat intake (lower and upper halves). Other factors that may have modified the association between NSAID use and CRC risk were also tested, including: family history of CRC (yes/no), history of sigmoidoscopy/colonoscopy (yes/no), history of coronary artery disease (yes/no), history of arthritis or joint pain (yes/no), dietary and supplemental calcium intake (lower and upper halves), and overall CRC risk scores (lower and upper halves). Effect modification by CRC overall risk was included to understand whether those at higher risk of CRC based on multiple factors might have a greater or lesser relative benefit from use of NSAIDs. The risk score was derived from sex-specific Cox models of CRC risk based on all risk factors listed as potential confounders above, except sex and hormone therapy in the model for men, and all except sex for women. The resulting betas were then applied to each participant's set of risk factors to yield their overall risk score. Interaction was tested as the significance of the cross product of the linear (trend) NSAID variable and the effect modifier in the multivariate model that included the main effects of the NSAID variable and the potential effect modifier. Stratified analyses were also performed by cancer subsites and stages. Logistic regression limited to cases was used to determine the statistical significance of subsite- and stage-specific heterogeneity, by comparing NSAID use of proximal colon cancer or rectal cancer to distal colon cancer cases, and of regional or distant cancer to local cancer cases.

All analyses were performed in Stata v.13 (StataCorp, College Station, TX).

Results

Subjects were followed for a total of 618,289 person-years (mean follow-up 8.4 years), among which CRC cases contributed 3,034 person-years. Cases were older, reported having a lower education level, higher body mass index, and higher red/processed meat intake than the overall cohort (Table 1). They also had lower fruit and vegetable intake and were less likely to have had sigmoidoscopy/colonoscopy in the 10 years prior to baseline.

NSAID use was examined for its association with CRC in the entire cohort (Table 2). For each type of NSAID use (low-dose aspirin, regular aspirin, non-aspirin NSAIDs and any

type of NSAIDs), there was a statistically significant trend of lower CRC with increasing use (all p for trend <0.01). The strongest association was with any type of NSAID use: persons reporting high use of any NSAID (>4 days/week for >4 years in the 10-year period prior to baseline) had a 42% lower risk of CRC than persons reporting no use of NSAIDS (multivariate adjusted HR: 0.58; 95% CI: 0.46-0.71; p for trend<0.001).

Table 3 presents the association of any NSAID use with CRC risk for subgroups of the cohort defined by CRC risk factors and by indications for NSAID use. High use of any type of NSAID was consistently associated with a lower risk of CRC across all subgroups, with risk reductions of 32% to 56%, and p for trends <0.05 within each subgroup, except for the smallest groups. There appeared to be some differential effects of NSAID use, with greater risk reduction for men, those who were obese, and regular alcohol drinkers. High NSAID use was associated with a 46% lower risk of CRC among men (HR: 0.54; 95% CI: 0.40-0.73) and 37% among women (HR: 0.63; 95% CI: 0.47-0.86) (p-interaction=0.201). High NSAID use was associated with a 56% reduction of CRC risk among the obese (HR: 0.44; 95% CI: 0.29-0.67), compared to 32% and 39% reduction in the normal and overweight groups, respectively (for BMI<25: HR: 0.68; 95% CI: 0.46-1.01; for 25≤BMI<30: HR: 0.61; 95% CI: 0.43-0.86) (p-interaction=0.379). Similarly, high NSAID use was associated with 53% reduction of CRC risk among subjects who drank more than 4 drinks per week (HR: 0.47; 95% CI: 0.32-0.69) compared to a 40% reduction among those who drank 4 or less drinks per week (HR: 0.60; 95% CI: 0.46-0.79) (p-interaction=0.186). However, the p for interaction did not reach statistical significance for these factors or for the other factors evaluated. The associations between high NSAID use and the overall risk score were almost identical between subjects with higher and lower risk scores (for lower risk score: HR: 0.61; 95% CI: 0.42-0.88; for higher risk score: HR: 0.62; 95% CI: 0.49-0.79).

In addition, we found high use of any NSAID was associated with a lower risk of CRC for all subsites and stages (Table 4). The association was strongest for proximal colon cancer (HR: 0.44; 95% CI: 0.27-0.70), compared to distal colon cancer (HR: 0.65; 95% CI: 0.49-0.87; p-heterogeneity = 0.062), and for distant stage (HR: 0.37; 95% CI: 0.21-0.66), compared to local colorectal cancer HR: 0.59; 95% CI: 0.42-0.82; p-heterogeneity=0.042).

We also evaluated effect modification separately for aspirin use (low dose and regular/extra strength combined) and non-aspirin NSAID use (Supplemental Tables 1-4). The suggestion of effect modification by sex also appeared for aspirin use and CRC risk (p-interaction=0.086), but not for non-aspirin NSAID use. For both types, CRC risk reduction was greatest among the obese. Family history of colorectal cancer modified the association of non-aspirin NSAID use with CRC risk (p-interaction=0.009), with the lowest risk among those without family history. The associations between aspirin use and overall risk score did not differ between the higher and lower risk score group. However, we observed a large difference in the association between non-NSAID use and overall risk score (for lower risk score: HR: 0.46; 95% CI: 0.21-0.99; for higher risk score: HR: 0.93; 95% CI: 0.63-1.38) (p-interaction=0.108). Anatomic subsite differences persisted for aspirin use only (p-heterogeneity between proximal and distal =0.051), while the lowest risk was for distant

stage CRC for both types of NSAIDs. However, the tests for interaction and for differences were not statistically significant except as noted.

Discussion

In this prospective study, we found NSAID use of any type for 4+ days per week for 4+ years was associated with a 42% lower risk of colorectal cancer (p-trend<0.001). Furthermore, there was a statistically significant risk reduction of CRC within each subgroup of the study population stratified by sex, BMI, physical activity, smoking, alcohol intake, screening and various dietary factors, suggesting that NSAID use is beneficial for most subgroups of CRC risk. The risk reduction may be greater among men, the obese and heavier alcohol drinkers; however, none of the tests for effect modification reached statistical significance. We also found NSAID use was associated with a lower risk of proximal colon cancer compared to distal colon cancer, and distant stage colorectal cancer compared to local stage.

Although prior studies of NSAID use on CRC risk generally reported on aspirin and/or non-aspirin NSAID use separately rather than combined, meta-analyses of randomized and observational studies suggested that regular use of aspirin and NSAIDs had similar association with CRC (1), and our results are consistent with most of the randomized controlled trials and observational studies that suggest a benefit for both aspirin and/or non-aspirin NSAID use (1-3, 16, 23, 33). In a meta-analysis based on the long-term effect of aspirin on colorectal cancer incidence and mortality from five randomized trials (2), assigned treatment of low-dose and regular aspirin for 5 years or more was statistically significantly associated with 38% reduction in colorectal cancer incidence. Our results of 33% and 42% lower risk associated with low-dose and regular aspirin respectively are consistent with the meta-analysis. However, some cohort studies did not observe a reduction in CRC risk in relation to dose or duration of aspirin use (18, 22), which may due to the short follow-up period and the possibility, based on follow-up reports from five randomized trials, that the effects of NSAID use may have a 10-year latency (1, 2).

The reduction of CRC risk associated with NSAID use appeared to be 10% greater among men than women. Another large prospective cohort study found the protective effect of aspirin on colon cancer was 10% greater among men than women, but the test for interaction did not reach statistical significance (34). They also found that aspirin use was associated with 52% lower risk of rectal cancer among men, but a 7% higher risk among women. However, systematic reviews of observational studies have reported that the association between regular use of aspirin or NSAIDs and CRC does not significantly differ by sex (1, 20).

We also found a suggestion of a stronger inverse association between NSAID use and CRC risk among obese individuals than overweight or normal-weight individuals, and this differential association was consistent for aspirin and non-aspirin NSAIDs. Obesity is associated with a chronic proinflammatory state with increased cytokine levels (35). A similar but smaller difference in association by BMI groups was also observed in Danish cohort study (17). In that study, non-aspirin NSAID use was associated with lower risk of

CRC only among those with BMI greater than 25 kg/m^2, although the association between aspirin use and CRC did not differ by BMI group. Analyses of other large cohort studies did not observe statistically significant interaction between BMI and aspirin on colorectal cancer risk (16, 18, 19), but in two of the cohort studies the effect of aspirin use was found to be greater among overweight or obese participants than those of normal weight (18, 19). Thus there is some consistency across studies of a greater risk reduction associated with NSAID use among overweight or obese individuals, but most studies, including ours, did not have power to detect statistically significant interaction between NSIAD use and BMI.

Similarly, although not statistically different, high NSAID use was associated with 53% lower risk among those who have more than 4 drinks per week compared to 40% lower among lighter/non-drinkers. Alcohol intake is a known risk factor for colorectal cancer (36). Several studies suggest that ethanol overexposure may alter the cytokine level in a variety of tissues as well as *in vitro* (37, 38). Findings from an animal study in which chronic alcohol intake promoted intestinal tumorigenesis and tumor invasion in genetically susceptible mice, found that mast-cell-mediated inflammation could be one of the mechanisms by which alcohol promotes carcinogenesis (39). Landi et al. (40) observed that an association of CRC risk with alcohol drinking was evident in the subgroup of IL6 C-allele carriers, but the risk was halved by the use of NSAIDs among those carriers. Interaction between alcohol intake and other genes that modulate inflammation of the colorectum, including PPARγ (41), has also been found. Thus, evidence suggests the carcinogenic effect of alcohol consumption may, at least in part, result from interactions with the inflammatory response, consistent with the suggestion here, of an interaction between alcohol intake and NSAID use.

Furthermore, our data suggest that NSAID use may have differential protective effects by anatomic subsites of colorectal cancer. We found that high NSAIDs use was associated with lower risk of proximal colon cancer than of distal colon cancer. Previously reported results have differed by exposure type. Our results were consistent with studies that also analyzed all types of NSAIDs or non-aspirin NSAIDs (16, 24), whereas studies assessing aspirin use alone found a lower risk of distal than proximal colon cancer (3, 16, 22, 23). However, follow-up analysis based on five randomized trials reported the largest risk reduction to be of proximal colon cancer among long-term aspirin users (2), consistent with our study. The precise mechanisms by which NSAIDs exert differential chemoprevention effects by anatomic sites are currently unclear. Studies have suggested that different prevalence of COX expression in cancerous tissue originating from the rectum vs. colon may play a role, but results were inconsistent (42, 43). Other evidence has shown that aspirin may interact with some tumor molecular features, such as PIK3CA and BRAF mutations, to influence CRC risk and mortality and these features may differ by anatomic site (44-46). In addition, we found a statistically significantly greater protective association for CRC with distant metastasis than with local disease. This is consistent with findings from the meta-analyses of five randomized trials of aspirin (26) as well as observational studies (25), and with evidence that aspirin may reduce tumor angiogenesis and lymphangiogenesis (47).

An advantage of our study is that our measure of NSAID use may be more accurate and detailed than most prior studies. We incorporated years of use as well as frequency in our exposure variables because associations of NSAID use with colorectal cancer probably

depends on both duration and frequency (1, 2, 20, 48). In addition, by using any NSAID use as our main exposure variable, our power was strengthened as both aspirin and non-aspirin NSAIDs are associated with decreased risk of CRC. Other strengths include the prospective design, the large sample size, the inclusion of both men and women, and the near-complete follow-up using case linkage through the SEER registry. An additional advantage was the availability of detailed information on a large number of potential confounders, including risk factors for colorectal cancer as well as indications for NSAID use, specifically cardiovascular disease prevention, and arthritis and joint pain treatment.

Limitations of this study are that NSAID use was based on self-report, and additionally, we had no information on NSAID use after baseline. However, it has been suggested that the effect of NSAID use has a 10-year latency period for colorectal cancer risk (1) and the time period we assessed for NSAID use was the 10-year period before baseline, which would be 10 to 20 years prior to cancer onset. Nonetheless, we expect that the potential measurement error in NSAID use, due to both poor recall before baseline and lack of information post-baseline, would be non-differential between cases and non-cases in a prospective study. In addition, despite our control for colorectal cancer risk factors and indications for NSAID use, residual confounding may persist. Also, although we had sufficient power to detect statistically significant risk reductions associated with NSAID use within almost all subgroups examined, we did not have the power to detect effect modification of the NSAID-CRC association by other risk factors. This may be due to the limited number of cases in each subgroup and/or the relatively small differences in effect size between groups. Lastly, our findings may be due to multiple comparisons.

In conclusion, NSAID use was statistically significantly associated with lower overall risk of CRC and with a greater risk reduction of proximal colon cancer and distant-stage CRC. We did not observe statistically significant interactions between NSAID use and other risk factors or overall risk score, although the association with NSAID use appeared to be stronger among men, obese individuals, and heavier drinkers. The associations across almost all subgroups of participants suggest a generally beneficial role of NSAIDs in colorectal cancer prevention, with the relative reduction in risk largely unmodified by other exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Distribution of colorectal cancer risk factors among VITAL cohort participants and cases

Characteristics	Cases (N=674)		Cohort (N=73,458)	
	N	%	N	%
Age at Baseline (yrs)				
50-<55	59	8. 8	17,227	23 .5
55-<60	86	12.8	16,751	22.8
60-<65	109	16.2	13,412	18.3
65-<70	174	25.8	12,055	16.4
70+	246	36.5	14,013	19.1
Sex				
Female	343	50 .9	38,481	52 .4
Male	331	49.1	34,977	47.6
Education				
High school or less	210	31 .8	14,416	20 .0
Some college	239	36.2	27,665	38.3
College graduate or higher	211	32.0	30,162	41.8
Race/Ethnicity				
White	607	90 .1	67,403	91 .8
Hispanic	4	0.6	635	0.9
Black	16	2.4	912	1.2
Other	47	7.0	4,508	6.1
Body Mass Index(kg^2/m)				
Normal Weight(<25)	207	32 .2	24,428	34 .3
Overweight(≥25-<30)	248	38.6	29,264	41.1
Obese(>30-<35)	127	19.8	11,790	16.6
Severely Obese(>35)	61	9.5	5,707	8.0
Alcohol Drinks (drinks)				
None - <1 per month	252	38 .4	26,934	37 .6
≥1 per month - ≤4 per week	174	26.5	21,246	29.6
>4 per week - <2 per day	128	19.5	15,422	21.5
≥2 per day	102	15.6	8,096	11.3
Fruit and Vegetable Intake (servings/day)				
0-<2.04	163	27.4	16,715	25 .0
2.04-<3.16	165	27.7	16,715	25.0
3.16-<4.79	138	23.2	16,715	25.0
≥4.79	129	21.7	16,714	25.0
Red/Processed Meat Intake (oz/week)				
0-<8.56	126	21.2	16,715	25.0
8.56-<16.55	157	26.4	16,715	25.0
16.55-<27.80	135	22.7	16,715	25.0
≥27.80	177	29.8	16,714	25.0

Characteristics	Cases (N=674)		Cohort (N=73,458)	
	N	%	N	%
History of Sigmoidoscopy/Colonoscopy (last 10 yrs)				
Yes	330	49.6	40,957	56.2
No	336	50.5	31,890	43.8
Family History of CRC				
Yes	98	14.7	8,328	11.4
No	568	85.3	64,497	88.6

Table 2

Colorectal cancer risk in relation to aspirin and non-aspirin NSAID use

	Non-cases		Cases		Sex and age-adjusted			Multivariate-adjusted[a b]		
	N	%	N	%	HR		95% CI	HR		95% CI
Low-dose Aspirin	**69,119**		**640**							
None	49,317	71.35	477	74.53	1.00		Referent	1.00		Referent
Low use[c]	11,301	16.35	93	14.53	0.76	0.61	0.95	0.73	0.57	0.92
High use[d]	8,501	12.3	70	10.94	0.66	0.52	0.85	0.67	0.52	0.89
P trend							<0.001			0.001
Regular Aspirin	**70,863**		**649**							
None	53,377	75.32	519	79.97	1.00		Referent	1.00		Referent
Low use[c]	9,161	12.93	67	10.32	0.75	0.58	0.96	0.78	0.59	1.02
High use[d]	8,325	11.75	63	9.71	0.64	0.49	0.84	0.58	0.44	0.78
P trend							<0.001			<0.001
Non-aspirin NSAIDs	**70,063**		**641**							
None	47,550	67.87	482	75.2	1.00		Referent	1.00		Referent
Low use[c]	17,110	24.42	123	19.19	0.79	0.64	0.96	0.79	0.63	0.98
High use[d]	5,403	7.71	36	5.62	0.71	0.51	1.00	0.73	0.51	1.04
P trend							0.005			0.014
Any NSAIDs	**68,044**		**618**							
None	25,142	36.95	273	44.17	1.00		Referent	1.00		Referent
Low use[c]	23,327	34.28	188	30.42	0.71	0.59	0.85	0.70	0.58	0.85
High use[d]	19,575	28.77	157	25.4	0.59	0.48	0.72	0.58	0.46	0.71
P trend							<0.001			<0.001

Abbreviation: HR, haz ard ratio; CI, confidence interval.

[a] Adjusted for the following variables: age, gender, race (White, Black, Hispanic, other), education (high school or less, some college/technical, college graduate or higher), body mass index (normal[<25], overweight[25-<30], obese[30-<35], extremely obese[≥30]), MET-hours per week of moderate/vigorous activity (none and sex-specific textiles), smoking (never, former quit≥10 years ago, former quit<10 years ago, current smoker), alcohol intake (0 or ≥1 drink per month and ≤4 drinks per week; >4 drinks per week and <2 drinks per day), fruit and vegetable intake (servings/day; quartiles), red meat intake (ounce/week; quartiles), dietary and supplemental calcium intake (quartiles: <725.7mg/day, ≥725.7 and <1038.16 mg/day, ≥1038.16 and <1464.5 mg/day, and ≥1464.5mg/day), fiber intake (quartiles: ≤12.4gm/day, >12.4 and ≤17.4 gm/day, >17.4 and ≤23.7 gm/day, and >23.7gm/day), first degree family history of colorectal cancer (none, 1, more than 1 relatives), screening history (yes or no), female hormone replacement therapy use (never, former, current), coronary artery disease (yes or no), frequent headache (yes or no), arthritis or joint pain (yes or no), diabetes (yes or no), and cholesterol lowing drug use (yes or no). For each specific type of low-dose aspirin use, regular aspirin use and non-aspirin NSAID use, the other two types (none, low use or high use) were also adjusted.

[b] In multivariate-adjusted model, there are 583 cases and 63,864 non-cases for low-dose aspirin use, regular aspirin use and non-aspirin NSAID use; 600 cases and 66,248 non-cases for any NSAID use.

[c] Low use defined as 1-3 days per week or 1-3 years.

[d] High use defined as ≥4 days per week and ≥4 years.

Table 3

Association of any NSAID use with CRC risk, stratified by risk factors for CRC and by indications for NSAID use

Effect modifiers	Any NSAID use													
	No Use			Low Use (<4 days/week or <4 years)				High Use (≥4 days/weeks and ≥4 years)						
	Case N=266	Non-cases N=24,475	HR[a]	Case N=182	Non-cases N=22,743	HR[a]	95% CI		Case N=152	Non-cases N=19,030	HR[a]	95% CI		p-trend	p-interaction[b]
Age (yrs)															
<65	68	8,997	1.00	52	7,4 67	0.81	0.56	1.18	18	4,1 43	0.40	0.23	0.69	0.001	0.222
≥65	198	15,478	1.00	130	15,276	0.66	0.53	0.83	134	14,887	0.62	0.49	0.78	0.000	
Sex															
Male	134	11,252	1.00	76	9,9 87	0.61	0.46	0.82	82	10,348	0.54	0.40	0.73	0.000	0.201
Female	132	13,223	1.00	106	12,756	0.79	0.61	1.03	70	8,682	0.63	0.47	0.86	0.003	
BMI (kg/m^2)															
<25	88	9,531	1.00	55	7,356	0.77	0.55	1.09	42	5,403	0.68	0.46	1.01	0.044	0.379
25-30	99	9,488	1.00	59	9,238	0.57	0.41	0.80	62	7,879	0.61	0.43	0.86	0.002	
30+	68	4,822	1.00	57	5,584	0.72	0.50	1.04	40	5,291	0.44	0.29	0.67	0.000	
Physical Activity[d]															
No	162	12,147	1.00	117	11,440	0.76	0.59	0.97	84	9,860	0.54	0.41	0.72	0.000	0.427
Yes	100	12,002	1.00	63	11,044	0.62	0.45	0.86	65	8,934	0.60	0.43	0.85	0.003	
Smoking															
Never/10+ yr quitter	223	21,048	1.00	144	19,243	0.67	0.54	0.83	126	16,008	0.58	0.46	0.73	0.000	0.615
Current/recent quitter	43	3,427	1.00	38	3,500	0.88	0.56	1.39	26	3,022	0.60	0.35	1.11	0.063	
Alcohol Intake															
≤4 drinks/week	168	16,395	1.00	114	15,051	0.70	0.55	0.90	97	12,004	0.60	0.46	0.79	0.000	0.186
>4 drinks/week	94	7,527	1.00	64	7,249	0.68	0.49	0.94	47	6,627	0.47	0.32	0.69	0.000	
Fruit and Vegetable Intake															
<3.16 servings/day	132	11,061	1.00	94	10,530	0.71	0.54	0.93	67	8,557	0.52	0.38	0.71	0.000	0.614
≥3.16 servings/day	104	11,308	1.00	71	10,319	0.69	0.50	0.94	64	8,915	0.58	0.41	0.81	0.001	
Red/Processed Meat Intake															
<16.55 oz/week	108	11,589	1.00	81	10,501	0.73	0.54	0.98	61	8,232	0.57	0.41	0.80	0.001	0.290
≥16.55 oz/week	128	10,780	1.00	84	10,348	0.67	0.51	0.89	70	9,240	0.52	0.38	0.72	0.000	

Effect modifiers	Any NSAID use														
	No Use			Low Use (<4 days/week or <4 years)					High Use (≥4 days/weeks and ≥4 years)						
	Case N=266	Non-cases N=24,475	HR[a]	Case N=182	Non-cases N=22,743	HR[a]	95% CI		Case N=152	Non-cases N=19,030	HR[a]	95% CI		p-trend	p-interaction[b]
Calcium Intake[c]															
<1038 mg/day	136	12,049	1.00	75	10,209	0.62	0.46	0.82	59	7,638	0.54	0.39	0.75	0.000	0.581
≥1038 mg/day	100	10,218	1.00	89	10,497	0.78	0.58	1.05	71	9,706	0.54	0.39	0.75	0.000	
History of Sigmoidoscopy/Colonoscopy (last 10 yrs)															
No	146	12,050	1.00	87	9,849	0.71	0.54	0.94	70	7,053	0.65	0.48	0.88	0.003	0.726
Yes	120	12,425	1.00	95	12,894	0.68	0.54	0.90	82	11,977	0.51	0.38	0.69	0.000	
Family History															
No	232	21,684	1.00	146	20,135	0.66	0.54	0.82	129	16,800	0.58	0.46	0.73	0.000	0.450
Yes	34	2,791	1.00	36	2,608	1.00	0.62	1.62	23	2,230	0.61	0.34	1.08	0.100	
History of Coronary Artery Disease															
No	254	23,810	1.00	159	21,223	0.68	0.56	0.83	119	15,403	0.60	0.48	0.76	0.000	0.491
Yes	12	665	1.00	23	1,520	1.00	0.49	2.05	33	3,627	0.58	0.29	1.16	0.051	
Arthritis or Joint Pain															
No	170	15,731	1.00	74	10,537	0.61	0.46	0.81	66	7,846	0.58	0.43	0.79	0.000	0.770
Yes	96	8,744	1.00	108	12,206	0.80	0.61	1.06	86	11,184	0.60	0.44	0.82	0.001	
Risk Score[e]															
Lower half	71	11,547	1.00	56	11,669	0.74	0.52	1.05	49	10,197	0.61	0.42	0.88	0.008	0.817
Upper half	195	12,928	1.00	126	11,073	0.72	0.57	0.90	103	8,833	0.62	0.49	0.79	0.000	

HR= hazard ratio; CI= confidence interval

[a] Multivariate model adjusted for age, gender, race (White, Black, Hispanic, other), education (high school or less, some college/technical, college graduate or higher), Body Mass Index (normal, overweight, obese, extremely obese), MET-hours per week of moderate/vigorous activity (none and tertiles), smoking (never, former quit≥10 years ago, former quit<10 years ago, current smoker), alcohol intake (0 or <1 drink per month, ≥1 drink per month and ≤4 drinks per week; >4 drinks per week and < 2 drinks per day, ≥2 drinks per day), fruit and vegetable intake (quartiles), red meat intake (quartiles), dietary and supplemental calcium intake (quartiles), fiber intake (quartiles), first degree family history of colorectal cancer (none, 1, more than 1 relatives), screening history (yes or no), female hormone replacement therapy use (never, former, current), coronary artery disease (yes or no), frequent headache (yes or no), arthritis or joint pain (yes or no), diabetes (yes or no), and cholesterol lowing drug use (yes or no). Model based on 600 cases and 66,248 non-cases.

[b] P-interaction based on interaction of liner (trend) NSAID variable and effect modifier variable.

[c] Dietary plus supplemental calcium intake.

[d] Any moderate or vigorous physical activity in 10 years prior to baseline.

[e] The risk score is sex-specific: the median risk score for men is −0.593, and the median risk score for women is −0.391.

Table 4

Association of any NSAID use with CRC risk by anatomic site and stage

	Any NSAID Use														
	No Use			Low Use (<4 days/week or <4 years)					High Use (≥4 days/week and ≥4 years)						
	Case N=266	Non-cases N=24,475	HR[a]	Case N=182	Non-cases N=22,743	HR[a]	95% CI		Case N=152	Non-cases N=19,030	HR[a]	95% CI		p-trend	p-heterogeneity[b]
Subsite															
Distal	132	24,475	1.00	97	22,743	0.73	0.56	0.96	89	19,030	0.65	0.49	0.87	0.003	ref
Proximal	66	24,475	1.00	43	22,743	0.65	0.44	0.97	30	19,030	0.44	0.27	0.70	0.000	0.062
Rectal	68	24,475	1.00	42	22,743	0.68	0.46	1.01	33	19,030	0.56	0.36	0.88	0.009	0.163
Stage															
Local	106	24,475	1.00	83	22,743	0.79	0.59	1.07	64	19,030	0.59	0.42	0.82	0.002	ref
Regional	113	24,475	1.00	65	22,743	0.58	0.43	0.80	64	19,030	0.60	0.43	0.84	0.001	0.857
Distant	47	24,475	1.00	34	22,743	0.74	0.47	1.16	19	19,030	0.37	0.21	0.66	0.001	0.042

[a] Multivariate model adjusted for age, gender, race (White, Black, Hispanic, other), education (high school or less, some college/technical, college graduate or higher), Body Mass Index (normal, overweight, obese, extremely obese), MET-hours per week of moderate/vigorous activity (none and tertiles), smoking (never, former qui≥10 years ago, former quit<10 years ago, current smoker), alcohol intake (0 or <1 drink per month, ≥1 drink per month and ≤4 drinks per week; >4 drinks per week and < 2 drinks per day, ≥2 drinks per day), fruit and vegetable intake (quartiles), red meat intake (quartiles), dietary and supplemental calcium intake (quartiles), fiber intake (quartiles), first degree family history of colorectal cancer (none, 1, more than 1 relatives), screening history (yes or no), female hormone replacement therapy use (never, former, current), coronary artery disease (yes or no), frequent headache (yes or no), arthritis or joint pain (yes or no), diabetes (yes or no), and cholesterol lowing drug use (yes or no). Model based on 600 cases and 66,248 non-cases.

[b] P-heterogeneity used to test for differences across cancer subsite and stage: for cancer subsites, proximal colon cancer and rectal cancer were both compared to distal colon cancer; for cancer stage, regional and distant cancer were compared to local cancer.