Published in final edited form as:
Am J Gastroenterol. 2011 July ; 106(7): 1340–1350. doi:10.1038/ajg.2011.38.

Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort

Elizabeth H. Ruder[1,2], **Adeyinka O. Laiyemo**[3], **Barry I. Graubard**[1], **Albert R. Hollenbeck**[4], **Arthur Schatzkin**[1], and **Amanda J. Cross**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD

[2]Cancer Prevention Fellowship Program, Center for Cancer Training, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD

[3]Department of Medicine, Howard University, Washington DC

[4]AARP, Washington, DC

Abstract

Objectives—Use of non-steroidal anti-inflammatory drugs (NSAIDs) has been inversely associated with colorectal cancer; however, the association within colorectal subsites or among higher risk individuals is understudied. We investigated NSAID use and colorectal adenocarcinoma by subsite, and among individuals with a family history of colon cancer in the National Institutes of Health-AARP Diet and Health Study.

Methods—Using Cox proportional hazards regression, we estimated hazard ratios (HR) and 95% confidence intervals (CI) for colorectal cancer incidence among 301,240 men and women (mean age 62.8 y); including 26,994 individuals with a first degree relative with a history of colon cancer. We accrued 3,894 colorectal cancer cases during 10 years of follow-up; 372 cases had a first degree relative with colon cancer.

Results—Both aspirin and non-aspirin NSAID use reduced colorectal cancer risk (HR for users compared to non-users=0.91, 95% CI: 0.85, 0.98; HR=0.82, 95% CI: 0.77, 0.87, respectively). Daily aspirin use reduced the risk of cancer in the distal colon (HR=0.84, 95% CI: 0.71, 0.99) and rectum (HR=0.76, 95% CI: 0.64, 0.90); daily non-aspirin NSAID use reduced the risk of both proximal (HR=0.65, 95% CI: 0.54, 0.78) and distal colon cancer (HR=0.69, 95% CI: 0.55, 0.87), but not rectal cancer. Among participants with a first degree relative with colon cancer, daily use of aspirin was associated with a decreased risk of rectal cancer (HR= 0.38, 95% CI: 0.19, 0.78), and daily use of non-aspirin NSAIDs was associated with a decreased risk of colon cancer (HR= 0.49, 95% CI: 0.29, 0.82). No protective benefit for daily aspirin use and colon cancer or daily non-aspirin NSAID use and rectal cancer was observed in this higher risk subgroup, although power was limited by small case numbers.

Conclusions—NSAID use was associated with a reduced colorectal cancer risk; the magnitude of this association differed between aspirin and non-aspirin NSAIDs. Daily aspirin and non-aspirin

Corresponding author: Elizabeth H. Ruder, 6120 Executive Blvd, Rockville, MD, 20852. Tel: +1-301-496-5700; Fax: +1-301-496-6829; rudereh@mail.nih.gov.

Author contributions: Drs. Ruder, Laiyemo and Cross contributed to the analysis and drafting of the manuscript, Dr. Graubard contributed to the statistical analysis and drafting of the manuscript, Drs. Hollenbeck and Schatzkin contributed to the study design and concept.

Disclosures: The authors have nothing to disclose.

NSAID use by individuals with a family history of colon cancer significantly reduced the risk of rectal and colon cancer, respectively.

Keywords

Non-steroidal anti-inflammatory drugs; colorectal cancer; cohort study

Introduction

Inflammation is thought to play a critical role in the development of cancer, particularly colorectal cancer. Intrinsic inflammation (via inflammatory cells and mediators within the tumor microenvironment), as well as extrinsic inflammation related to chronic inflammatory conditions, are contributors to tumor progression (1). Epidemiologic evidence indicates that pro-inflammatory conditions, such as inflammatory bowel disease increase the risk of colorectal cancer (2), whereas chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) may decrease risk (3–4). NSAIDs inhibit the cyclooxygenase (COX)-1 and COX-2 enzymes, which are involved in the synthesis of prostaglandins, leading to decreased activation of the inflammatory response (2), decreased epithelial proliferation and angiogenesis and increased apoptosis (5–6).

There are limited data investigating whether use of NSAIDs, including the specific classes of NSAIDs (aspirin versus non-aspirin), have differential effects within anatomic subsites of the colorectum. Some evidence from cohort studies suggests a stronger association between NSAID use and proximal versus distal colon cancer (7–8), but the evidence regarding rectal cancer is mixed, likely attributable to small case numbers in the existing literature (7, 9). Anatomic subsites within the colorectum derive from different embryonic origins (10–11), and different risk factors for colon versus rectal cancer have been documented (12). Furthermore, there are very little data on whether NSAIDs provide a chemoprotective benefit among individuals at increased risk of developing colorectal cancer due to the presence of a family history of the disease. Given that colorectal cancer is the third most commonly diagnosed cancer in the U.S. (13), the potential population attributable benefit for chemoprevention is substantial in this subgroup of people.

In this investigation, we examined the association between aspirin and non-aspirin NSAID use and risk of adenocarcinoma of the colorectum by subsite in a large prospective study conducted in the United States. In addition, we conducted subanalyses of individuals with a family history of colon cancer in a first degree relative.

Methods

Study population

The National Institutes of Health (NIH)-AARP Diet and Health Study is a large prospective cohort of men and women, ages 50 to 71 y at recruitment, from six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan) and has been described in detail elsewhere (14). A self-administered baseline questionnaire regarding demographic and lifestyle characteristics was completed in 1995–1996. In total, 617,119 individuals returned the baseline questionnaire. A second questionnaire, hereafter called the risk factor questionnaire, was mailed approximately six months after completion of the baseline questionnaire to collect additional information, including use of NSAIDs, and was returned by 334,908 individuals. For our analyses, we excluded individuals for whom either the baseline (n=6,959) or the risk factor questionnaire (n=3,424) was completed by proxies, those with prevalent cancer at the administration of the baseline (n=14,565) or risk factor questionnaire

(n=4,297), those who had a death only report for any cancer (n= 983), those with zero person years of follow-up (n=18), and those with missing data on use of both aspirin and non-aspirin NSAIDs (n=3,422). The resulting analytic cohort for our primary analysis included 301,240 participants (175,807 men and 125,433 women). The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute.

Cohort follow-up and case ascertainment

Cohort members were followed for change of address using the U.S. Postal Service. Annual linkage of the cohort to the U.S. Social Security Administration Death Master File, follow-up searches of the National Death Index, cancer registry linkage, questionnaire responses, and responses to other mailings were employed to obtain vital status. We identified cancer cases through probabilistic linkage with state cancer registries. In addition to the eight original states from which the cohort recruited, our cancer registry ascertainment area was expanded to include Texas and Arizona, wherein participants have most commonly moved during follow-up. Approximately 4% of participants were lost to follow-up as a result of moving out of the 10 states. Our case ascertainment method has been described in a previous study, which demonstrated that approximately 90% of cancers were identified through the cancer registries (15).

Colorectal cancer end points were defined by anatomic site and histologic code of the International Classification of Diseases for Oncology (16) and included codes C180–C189, C199, C209, and C260. We further classified cases as those in the proximal colon (C180–184), distal colon (C185–187), and rectum (C199, C209). We only included first primary diagnoses of adenocarcinoma; we excluded cases with unspecified histologies (n=26), neuroendocrine tumors/carcinoids (n=87), lymphomas (n=25), sarcomas (n=9), squamous cell carcinomas (n=8), large cell carcinoma with rhabdoid phenotype (n=1), cloacogenic carcinoma (n=1), gastrinoma (n=1), cribriform carcinoma (n=1), and pigmented nevus (n=2). Follow-up for these analyses began on the date the risk factor questionnaire was received until censoring at the end of 2006 or when the participant moved out of the 10 state cancer registry areas, had a cancer diagnosis, or died, whichever came first.

Assessment of NSAID use

The risk factor questionnaire assessed NSAID use (yes/ no) during the previous 12 months and ascertained aspirin (generic aspirin and trade names) use and non-aspirin NSAID use separately. COX-2 inhibitors were not on the market at the time of questionnaire administration. Assessment of non-aspirin NSAID use was assessed in one question that listed examples of 19 non-aspirin NSAIDs (e.g., ibuprofen, sulindac, using both generic and trade names) and specifically excluded Tylenol, acetaminophen, and other pain relievers not listed. Our analyses examined aspirin use, non-aspirin NSAID use, and any NSAID use (defined as use of either of the previous two categories of drugs) separately. Participants were asked to mark how frequently they took each category of aspirin and non-aspirin NSAIDs individually: less than two times per month, two to three times per month, one to two times per week, three to four times per week, five to six times per week, one time per day, or two or more times per day. Due to small numbers in some of the categories, we collapsed these into monthly (≤ 2–3 times/month), weekly (1–2 times per week to 5–6 times per week), or daily use (1 or more times / day). Frequency of any NSAID use among individuals who reported use of both aspirin and non-aspirin NSAIDs was defaulted to the higher frequency (for example, an individual reporting daily aspirin use and weekly non-aspirin NSAIDs use was categorized as a daily user of any NSAIDs).

Statistical analysis

Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression with person-years as the underlying time metric; analyses using age as the underlying time metric yielded nearly identical HRs. Moreover, modeling the baseline hazard stratified by age group and sex also yielded similar estimates to those using person-years as the underlying time metric. The proportional hazard assumption was verified using a time interaction model. Tests for trend were calculated by assigning a categorical value to frequency of use where 0 = never use, 1 = monthly use, 2 = weekly use, and 3= daily use.

To assess the relationship between NSAIDs use and colorectal cancer risk, we examined three separate models: (1) any use of aspirin or non-aspirin NSAIDs (2) use of aspirin, and (3) use of non-aspirin NSAIDs. We assessed the relationship between frequency of use of NSAIDs (monthly, weekly, daily) in the three models described above with never users as the referent group. Combining the monthly and never users in one referent group did not materially alter our results. Furthermore, we investigated use of NSAIDs among a subcohort of individuals who reported having a first degree relative with a history of colon cancer at the time of the baseline questionnaire (n=26,994).

The final multivariate models only contained variables that changed the HR by 10% or more or were established risk factors for colorectal cancer, and they included sex, body mass index (BMI), smoking, race, education, physical activity, alcohol consumption, and use of hormone replacement therapy. Variables that were investigated but did not alter the HR by 10% or more included: personal history of diabetes or colorectal polyps, colorectal cancer screening practices, stage at diagnosis, and intake of calcium, iron, folate (including dietary and supplementary), whole grains, fiber, total fat, saturated fat, red meat, processed meat, and total energy. Interactions for sex, BMI, smoking status, presence of a first degree relative with a history of colon cancer with NSAID use (any use, aspirin use, and non-aspirin NSAID use) were evaluated by including cross-product terms in multivariate models. Stratified analyses by sex, BMI, smoking status, and presence of a first degree relative with history of colon cancer were also investigated. In addition, we conducted a lag analysis excluding the first 2 y of follow-up. In attempt to establish a surrogate marker of longer-term NSAIDs use, we conducted a separate analysis of NSAID users who self-reported a history of heart disease in the baseline questionnaire relative to non-users with a history of heart disease, since these people were likely to have been advised to take aspirin for heart disease prevention.

To test for heterogeneity between the anatomic subsites (colon versus rectum and proximal colon versus distal colon), we calculated the weighted average of the two β coefficients from the Cox model, with weights being proportional to the inverse of the variances. We then calculated the following χ^2 statistic with one degree of freedom: $T=\sum_{i=1}^{2}(\widehat{\beta_i}-\overline{\beta})^2/\sigma_i^2$ wherein $\hat{\beta}_i$ and σ_i^2 are the coefficient and its variance for each subsite, and $\overline{\beta}$ is the weighted average of the β coefficients. All statistical analyses were carried out using Statistical Analytic Systems software version 9.1 (SAS Institute Inc., Cary, NC).

Results

Among the 301,240 eligible participants, we ascertained 3,894 incident colorectal cases (2,551 males and 1,343 females), of which 2,889 were colon (1,684 proximal, 1,118 distal, 87 lacked definite site information) and 1,005 were rectal cancers over 2,605,365 person years. The study cohort was predominately white with a mean age of 62.8 years. The incidence rate of colorectal cancer among cohort members was similar to the rate in a

similarly aged Surveillance Epidemiology and End Results (SEER) reference population (17). A total of 13.4% did not use aspirin or non-aspirin NSAIDs in the 12 months prior to administration of the risk factor questionnaire. Non-users were less likely to be male, married, a college graduate, and to be white (Table 1). Aspirin use in the previous 12 months was reported by 73.3% of the study population, and 56.5% reported use of non-aspirin NSAIDs. Among aspirin users, 42.6% reported monthly use, 23.0% reported weekly use, and 34.4% reported daily use. Monthly use was most common among the non-aspirin NSAIDs users (58.2%), followed by weekly (23.6%) and daily (18.1%) use, data not shown.

Those who used any NSAIDs, aspirin, or non-aspirin NSAIDs had a reduced risk of colorectal cancer (any NSAIDs HR = 0.80, 95% CI: 0.73, 0.87; aspirin HR= 0.91, 95% CI: 0.85, 0.98; and non-aspirin NSAIDs HR= 0.82, 95% CI: 0.77, 0.87) compared to non users (Table 2); these risks were evident for both men and women and the sex interactions with the outcome of colorectal cancer were not statistically significant (P-interaction$_{\text{any NSAIDs*sex}}$ = 0.70, P-interaction$_{\text{aspirin*sex}}$ = 0.41, P-interaction$_{\text{non-aspirin NSAIDs*sex}}$ = 0.92), nor were tests for interaction between BMI or smoking status and NSAID use (data not shown). Furthermore, analyses stratified by sex, BMI or smoking status revealed consistent associations across strata; and thus stratified tables are not presented for these factors. For aspirin users, there was a statistically significant reduction in rectal cancer risk (HR=0.83, 95% CI: 0.72, 0.96), but not colon cancer (HR=0.94, 95% CI: 0.86, 1.02). In contrast, the use of non-aspirin NSAIDs resulted in a reduced risk for all subsites within the colorectum (Table 2). Assessment of individuals who used both aspirin and non-aspirin NSAIDs, individuals who used one type but not the other, as well as mutually adjusting for both classes of NSAIDs, did not materially alter our inferences.

Examining frequency of use of NSAIDs in relation to colorectal cancer risk revealed further decreases in risk as the frequency of use increased. Relative to no use, daily use of any NSAID was associated with a reduced risk of colorectal cancer across all subsites. Specifically, daily users of aspirin compared to nonusers had a reduced risk of distal colon (HR=0.84, 95% CI: 0.71, 0.99, P-trend <0.01) and rectal (HR=0.76, 95% CI: 0.64, 0.90, P-trend <0.001) cancers (Table 2); and daily use of non-aspirin NSAIDs compared to nonusers resulted in risk reductions for both proximal and distal colon cancers (HR=0.65, 95% CI: 0.54, 0.78, P-trend < 0.0001; HR: 0.69, 95% CI: 0.55, 0.87, P-trend <0.001, respectively, Table 2). Interestingly, decreases in risk were also evident among those who took non-aspirin NSAIDs weekly or even monthly.

We repeated our analyses after excluding individuals who developed colorectal cancer during the first 2 years of follow-up since symptoms of undiagnosed colorectal cancer could alter participants' use of NSAIDs; however, no appreciable changes were noted in the associations. No evidence of subsite heterogeneity was detected in any of the analyses. The heterogeneity test for cancer of the colon versus rectum among daily aspirin users relative to never users approached statistical significance ($P_{\text{heterogeneity}}$ =0.09); as did the test for colon versus rectal cancer among daily non-aspirin NSAIDs users relative to non-users ($P_{\text{heterogeneity}}$ =0.06), but given the number of comparisons these results may be due to chance alone. In addition, no appreciable differences in HRs were detected among n = 41,404 individuals who reported a personal history of heart disease on the baseline questionnaire; of these individuals, 81% reported taking aspirin in the past 12 months, of whom 61% reported daily use.

Unadjusted analyses indicated that having a first degree relative with history of colon cancer was positively associated with colon cancer in our cohort (HR=1.14, 95% CI: 1.01, 1.29). Tests for interaction between presence of a first degree relative with a history of colon

cancer and use of any NSAIDs, aspirin, or non-aspirin NSAIDs were statistically significant among select combinations (P-interaction$_{\text{aspirin* family history of colon cancer}}$= 0.05 (for colon cancer), P-interaction$_{\text{any NSAIDs*family history of colon cancer}}$ = 0.03, P-interaction$_{\text{aspirin * family history of colon cancer}}$ < 0.01 (for proximal colon cancer). Within the subgroup of individuals with a positive family history of colon cancer, use of any NSAIDs (yes/no) or use of non-aspirin NSAIDs specifically was not associated with colon or rectal cancer; although use of aspirin (yes/no) was associated with a reduction in rectal cancer risk (HR=0.60, 95% CI: 0.37, 0.98, Table 3). Investigating frequency of use revealed further associations, including a reduced risk for rectal cancer among daily users of aspirin compared to non-users (HR=0.38 95% CI: 0.19, 0.78, P-trend = 0.01), and a reduced risk for proximal colon cancer among weekly and daily users of non-aspirin NSAIDs (weekly use: HR= 0.54 95% CI: 0.31–0.96; daily use: HR=0.44 95% CI: 0.22, 0.88, P-trend=0.01).

Discussion

In this large prospective study with 2,605,365 person years of follow-up over 10 years, use of any NSAIDs was associated with a 20% reduced risk of colorectal cancer. Furthermore, increased frequency of use of both classes of NSAIDs was associated with lower risks across anatomic subsites of the colorectum. Within individuals with a first degree relative with a history of colon cancer, daily aspirin use (yes/no) was associated with a 40% reduction in rectal cancer risk, and weekly (defined as 1–2 times per week to 5–6 times per week) or daily use of non-aspirin NSAIDs reduced the risk of proximal colon cancer by 46% and 56%, respectively. However, the confidence intervals for the estimates among individuals with a positive family history were wide; thus, the risk reduction among the general study population and individuals with a family history of colon cancer were not statistically significantly different from each other.

A number of previously published cohort studies have assessed aspirin or non-aspirin NSAIDs use and incidence of colorectal cancer (8–9, 18–26), although only two cohort studies, the Nurses' Health Study (NHS) (18, 20) and the Health Professionals' Follow-up Study (HPFS) (21), were defined as "good" quality in the U.S. Preventive Services Task Force reports on the use of aspirin and non-aspirin NSAIDs for primary prevention of colorectal cancer (3–4). To the best of our knowledge, only one new cohort study of primary, incident colorectal cancer (7) has been published since the U.S. Preventive Services Task Force ended accruement for inclusion in its 2007 systematic reviews (3–4), although an update to the HPFS was published in 2008 (9).

The NHS, which examined 962 colorectal cancer cases over 20 years of follow-up in nearly 83,000 average risk women reported a dose dependent reduction in colorectal cancer risk with years of regular aspirin use (defined as consumption of 2 or more standard tablets / week), as well as a reduction with increasing dose per week. However, the authors reported a reduced risk in colon cancer but not rectal cancer in site-specific analyses (18) whereas we noted reductions in risks for both colon and rectal cancers. Results from 47,363 males enrolled in the HPFS were comparable to those from the NHS; although aspirin use was associated with decreased rectal cancer risk, and this association was stronger than that noted for proximal or distal colon cancers (9). However, the authors cautioned that a limited number of cases were available for each subsite and confirmatory studies are needed. Tests for subsite heterogeneity were not reported in the HPFS, but the overlapping confidence intervals suggest that the difference was not statistically significant. Results from the Iowa Women's Health Study reported greater reductions in risk of proximal colon cancer compared to cancer of the distal colon and rectum among aspirin users, although that study had fewer cases than HPFS and our study (7).

Our investigation found reductions in colon and rectal cancers among individuals who reported aspirin and non-aspirin NSAIDs use, particularly at increased frequencies of use. Results from our study suggesting that monthly use of any NSAID or non-aspirin NSAIDs (defined as no greater than 2–3 times per month) was associated with protection from colorectal cancer was unexpected; but demonstrates that it is possible that use of NSAIDs just 2–3 times per month could be enough to elicit an effect. However, it is also possible that participants misclassified their exposure or that current monthly users may have used NSAIDs frequently enough in the past to confer a protective benefit. Furthermore, since the frequency of "use of any NSAID" defaulted to the higher frequency if an individual reported use of both classes of NSAIDs, these results could be biased by the individuals who were taking both aspirin and non-aspirin NSAIDs monthly; however, this is unlikely since only 1.2 % (data not shown) of the monthly users reported use of both classes of NSAIDs.

Unlike the previous cohort studies, which had fewer than 230 cases of rectal cancer; data were available for over 1,000 cases of rectal cancer in our study. Our data support the observation made in the HPFS regarding a stronger inverse association between aspirin use and rectal cancer than that observed for cancer of the proximal or distal colon. Although we noted a greater reduction in risk for rectal cancer than colon cancer with daily aspirin use, the evidence for subsite heterogeneity did not reach statistical significance, suggesting that the magnitudes of these associations are not materially different. Results from a population-based case-control study of incident distal colorectal cancer also reported more potent effects of aspirin use for rectal and rectosigmoid cancers than for sigmoid cancer among 1,057 incident cases and 1,019 controls from North Carolina (27). Although neither the NHS nor HPFS reported the relationship between non-aspirin NSAIDs use and colon subsites, Smalley and colleagues (8) noted the protective benefit of non-aspirin NSAIDs use was more pronounced for proximal colon cancer compared to distal colon cancer, as did results from the Iowa Women's Health Study (7) and our study. Proximal colon tissue has an embryonic origin different from that of tissue distal to the splenic flexure (10–11) and cancers of the proximal colon, distal colon, and rectum differ in regard to their epidemiological, clinical and histological parameters (27–30). Thus, it is possible that investigation of risk factors, such as NSAID use, by colorectal subsite could provide valuable insight in to the etiology of colorectal cancer. Specific to NSAID use, COX-2 expression may vary depending on colorectal tumor location (31–32), although it is unclear whether it is over- or under-expressed in rectal tumors compared with colon tumors. In the future, if confirmatory studies continue to show a more protective effect on the proximal colon and safer COX inhibitors are available in the marketplace, then more widespread use of this class of drugs may be warranted given that colonoscopy may be less effective in identifying right-sided neoplasia. Indeed, results from a recent pooled analysis of five randomized trials of daily aspirin use indicated that the decrease in colon cancer risk was driven by reductions in cancer of the proximal, but not distal colon. In addition, no reduction in rectal cancer risk with aspirin use was observed in the pooled analysis. The authors hypothesize that overexpression of COX-2 in the distal colon may lead to less complete COX-2 inhibition with aspirin use in the distal colon relative to the proximal colon (33). The lack of an association of distal and rectal cancer with aspirin use in the combined analyses of these trials is intriguing, although the small case numbers must be noted: in total there were only 100 cases of distal colon cancer and 119 cases of rectal cancer. Furthermore, trial participants were overwhelmingly male.

A unique feature of our study was the ability to analyze over 26,000 individuals with a higher risk of colorectal cancer due to having a first degree relative with this malignancy. Few studies have examined the association of NSAIDs use in this higher risk group. Coogan and colleagues (34) examined two case-control studies to assess whether family history of colorectal cancer in a parent or sibling modified the association of NSAIDs use with

colorectal cancer; although they reported similar risk reductions in the two risk groups, both studies had fewer than 200 cases with a family history of the disease. Our results suggest that the protective benefit of NSAIDs among individuals with a positive family history of colon cancer is similar to, if not greater than, the risk reduction experienced in the general population. However, the risk reductions among the family history subgroup were not statistically significantly lower than those of the general study population, although the small number of cases for each subsite among the positive family history group must be noted. Overall, the risk of developing colon cancer among those with a positive family history was lower than expected. We attribute this to bias given the older age of participants at study entry, as well as possible differential screening prior to study entry among individuals with a family history of the disease. The limited case numbers is an important reminder to interpret these results with caution, but if true, these results could tip the risk-benefit equation in favor of use of these drugs in high-risk groups.

Although the published evidence for a chemopreventive role of NSAIDs among individuals at an increased risk for colorectal cancer due to a family history of this disease is limited, evidence for groups with known hereditary conditions linked to colorectal cancer is available; for example, use of celecoxib or sulindac reduced the incidence of colorectal polyps in patients with familial adenomatous polyposis (35–36). However, no protective effect of 600 mg aspirin was shown in a randomized clinical trial of 1,071 carriers of Lynch syndrome (hereditary nonpolyposis colorectal cancer) (37). Although we lacked information on whether individuals in our study had been diagnosed with either of these hereditary conditions, familial adenomatous polyposis and Lynch Syndrome are thought to contribute to less than 5%–6% of all colorectal cancers in the general population (12). Furthermore, colorectal cancer related to these genetic conditions typically occurs at a young age of onset; the median age of individuals with a family history of colon cancer in our study was 62.8.years at the time the risk factor questionnaire was administered.

A limitation of our study is the absence of data on duration of NSAIDs use. Previous studies have suggested that duration of aspirin use of 10 years or more and duration of non-aspirin NSAIDs use of 2–5 years and longer is required to achieve a reduction in colorectal cancer risk (9, 18, 20–21, 38–41). Subanalysis of individuals in our cohort with self-reported history of heart disease at baseline, our rough proxy for longer duration of use, yielded HRs similar to those of the overall cohort. In addition, use of NSAIDs was only ascertained at one time point and we lacked information regarding NSAIDs use during the cohort follow-up period. There is the distinct possibility that individuals changed their pattern of NSAID use during the follow-up period; this would likely bias the results toward the null. Our study also lacked information on dose and indication for NSAIDs use. In particular, we were unable to distinguish between use of low-dose aspirin (typically 81 milligrams) versus full strength (typically 325 milligram) tablets. Two randomized trials of aspirin and colorectal cancer incidence have failed to demonstrate a benefit of low-dose aspirin therapy after 5 and 10 years of follow-up (42–43), and cohort studies suggest that dosage much greater than that achieved with daily low-dose aspirin use is necessary to derive colorectal cancer protection (9, 18, 21). Recently, however, results from 20-year follow-up of five randomized trials indicated that use of at least 75 milligrams daily was effective in the reduction of both colorectal cancer incidence and mortality (33). Thus, the possible attenuation of effect due to heterogeneity in dose among aspirin users in our study may be less than previously assumed. All data in our investigation were self-reported as part of a questionnaire; thus, misreporting of both exposure and confounding variables is possible, as well as the potential for residual confounding. Finally, our cohort was comprised of older adults (mean age = 62.8 y), and results may not be applicable to other age groups.

Our study has numerous strengths, including being the largest cohort to date to have evaluated the association of NSAIDs type and colorectal cancer by anatomic subsite as reported in state cancer registries. Our analysis of NSAIDs use and colorectal cancer risk among individuals with a first degree relative with history of the disease is one of only a few studies to examine this higher risk subgroup. Although some of the risk estimates suggest a greater risk reduction of colorectal cancer in those with a positive family history of this malignancy, some of the case numbers for daily users with a positive family history were small and the differences in the HRs with the general study population were not statistically significant. In addition, multiple interactions were tested and the possibility of chance findings cannot be eliminated. Thus, the findings for NSAID use among individuals with a family history of colon cancer should be interpreted with caution. Lastly, the risks associated with long-term NSAIDs use, including gastrointestinal and cardiovascular complications are well-documented and serious (3–4). Recommendation of chemopreventive NSAIDs use among individuals with a family history of colorectal cancer at this time is premature.

In summary, our results suggest that weekly or daily use of NSAIDs is associated with colorectal cancer protection in the general population, as well as in individuals with a first degree relative with colon cancer. The strength of the association varies by drug class, but generally a dose-response relationship is observed between increased frequency of use and cancer protection. The potential harms associated with NSAIDs use must be considered before translating these results into clinical practice.

1. WHAT IS CURRENT KNOWLEDGE
    - Use of non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with a reduction in colorectal cancer risk but the association by subsite and among those at higher risk of colorectal cancer is unknown.
2. WHAT IS NEW HERE
    - In the largest prospective study of NSAID use and colorectal cancer to date, we confirmed that NSAID use reduced the risk of this malignancy.
    - We identified variation in the protective benefits of aspirin and non-aspirin NSAIDs by colorectal subsite.
    - The reduction in risk within individuals with a positive family history of colon cancer was substantial.

Abbreviations

BMI	body mass index
CI	confidence interval
COX	cyclooxygenase
HR	hazard ratio
NSAIDs	non-steroidal anti-inflammatory drugs

Acknowledgments

This research was supported [in part] by the Intramural Research Program of the NIH, National Cancer Institute. Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (FCDC) under contract with the Florida Department of Health (FDOH). The views expressed herein are solely those of the authors and do not necessarily reflect those of the FCDC or FDOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services. We are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. We also thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Leslie Carroll at Information Management Services for data support and analysis.

Funding: This research was supported [in part] by the Intramural Research Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services

References

1. Mantovani A, et al. Cancer-related inflammation. Nature. 2008; 454(7203):436–444. [PubMed: 18650914]
2. Danese S, Mantovani A. Inflammatory bowel disease and intestinal cancer: a paradigm of the Yin-Yang interplay between inflammation and cancer. Oncogene. 2010
3. Dube C, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007; 146(5):365–375. [PubMed: 17339622]
4. Rostom A, et al. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007; 146(5):376–389. [PubMed: 17339623]
5. Barnes CJ, et al. Non-steroidol anti-inflammatory drug effect on crypt cell proliferation and apoptosis during initiation of rat colon carcinogenesis. Br J Cancer. 1998; 77(4):573–580. [PubMed: 9484814]
6. Tsujii M, et al. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. Cell. 1998; 93(5):705–716. [PubMed: 9630216]
7. Mahipal A, et al. Nonsteroidal anti-inflammatory drugs and subsite-specific colorectal cancer incidence in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev. 2006; 15(10): 1785–1790. [PubMed: 17035383]
8. Smalley W, et al. Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. Arch Intern Med. 1999; 159(2):161–166. [PubMed: 9927099]
9. Chan AT, et al. Aspirin dose and duration of use and risk of colorectal cancer in men. Gastroenterology. 2008; 134(1):21–28. [PubMed: 18005960]
10. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med. 1990; 113(10):779–788. [PubMed: 2240880]
11. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol. 2004; 88(4):261–266. [PubMed: 15565587]
12. Potter, JD.; Hunter, DJ. Colorectal Cancer, in Textbook of Cancer Epidemiology. Adami, Hea, editor. Oxford: New York: 2008. p. 279-281.
13. Jemal A, et al. Cancer Statistics, 2010. CA Cancer J Clin. 2010

14. Schatzkin A, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions : the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am J Epidemiol. 2001; 154(12):1119–1125. [PubMed: 11744517]
15. Michaud DS, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. Journal of Registry Management. 2005; 32(2):70–75.
16. WHO. International Classification of Diseases for Oncology. 3rd edition. Geneva, Switzerland: 2000.
17. [cited 2010 November 2] Surveillance and End results (SEER) Fast Stats. Available from: http://seer.cancer.gov/faststats/
18. Chan AT, et al. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA. 2005; 294(8):914–923. [PubMed: 16118381]
19. Sorensen HT, et al. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. Br J Cancer. 2003; 88(11):1687–1692. [PubMed: 12771981]
20. Giovannucci E, et al. Aspirin and the risk of colorectal cancer in women. N Engl J Med. 1995; 333(10):609–614. [PubMed: 7637720]
21. Giovannucci E, et al. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. Ann Intern Med. 1994; 121(4):241–246. [PubMed: 8037405]
22. Paganini-Hill A. Aspirin and colorectal cancer: the Leisure World cohort revisited. Prev Med. 1995; 24(2):113–115. [PubMed: 7597009]
23. Sturmer T, et al. Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. Ann Intern Med. 1998; 128(9):713–720. [PubMed: 9556464]
24. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet. 2007; 369(9573):1603–1613. [PubMed: 17499602]
25. Friis S, et al. A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin. Br J Cancer. 2003; 88(5):684–688. [PubMed: 12618874]
26. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology. 1994; 5(2):138–146. [PubMed: 8172988]
27. Nelson RL, et al. The relation of age, race, and gender to the subsite location of colorectal carcinoma. Cancer. 1997; 80(2):193–197. [PubMed: 9217029]
28. Bonithon-Kopp C, Benhamiche AM. Are there several colorectal cancers? Epidemiological data. Eur J Cancer Prev. 1999; 8 Suppl 1:S3–S12. [PubMed: 10772412]
29. Gonzalez EC, et al. Predictors of proximal vs. distal colorectal cancers. Dis Colon Rectum. 2001; 44(2):251–258. [PubMed: 11227943]
30. Ward R, et al. Microsatellite instability and the clinicopathological features of sporadic colorectal cancer. Gut. 2001; 48(6):821–829. [PubMed: 11358903]
31. Dimberg J, et al. Differential expression of cyclooxygenase 2 in human colorectal cancer. Gut. 1999; 45(5):730–732. [PubMed: 10517910]
32. Wiese FW, et al. Variation in cyclooxygenase expression levels within the colorectum. Mol Carcinog. 2003; 37(1):25–31. [PubMed: 12720297]
33. Rothwell PM, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010
34. Coogan PF, et al. NSAIDs and risk of colorectal cancer according to presence or absence of family history of the disease. Cancer Causes Control. 2000; 11(3):249–255. [PubMed: 10782659]
35. Steinbach G, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med. 2000; 342(26):1946–1952. [PubMed: 10874062]
36. Giardiello FM, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med. 1993; 328(18):1313–1316. [PubMed: 8385741]
37. Burn J, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. N Engl J Med. 2008; 359(24):2567–2578. [PubMed: 19073976]
38. Collet JP, et al. Colorectal cancer prevention by non-steroidal anti-inflammatory drugs: effects of dosage and timing. Br J Cancer. 1999; 81(1):62–68. [PubMed: 10487613]

39. Garcia-Rodriguez LA, Huerta-Alvarez C. Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. Epidemiology. 2001; 12(1):88–93. [PubMed: 11138826]

40. Reeves MJ, et al. Nonsteroidal anti-inflammatory drug use and protection against colorectal cancer in women. Cancer Epidemiol Biomarkers Prev. 1996; 5(12):955–960. [PubMed: 8959316]

41. Slattery ML, et al. Aspirin, NSAIDs, and colorectal cancer: possible involvement in an insulin-related pathway. Cancer Epidemiol Biomarkers Prev. 2004; 13(4):538–545. [PubMed: 15066917]

42. Cook NR, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA. 2005; 294(1):47–55. [PubMed: 15998890]

43. Gann PH, et al. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. J Natl Cancer Inst. 1993; 85(15):1220–1224. [PubMed: 8331682]

Table 1

Distribution of covariates in NSAID users and non-users in NIH-AARP Diet and Health Study (n=301,240)

Variable	Cohort	Non-users of any NSAID in past 12 months	Users of aspirin in the past 12 months‡	Users of non-aspirin NSAIDs in past 12 months‡
Number (%)	301 240 (100)	40 210 (13.4)	220 259 (73.3)	169 326 (56.5)
Age, years, mean (SD)	62.8 (5.3)	63.6 (5.1)	62.8 (5.3)	62.2 (5.4)
Sex, male, n (%)	175 807 (58.4)	21 443 (53.3)	137 878 (62.6)	94 172 (55.6)
Married,n (%)	205 202 (68.1)	25 294 (62.9)	154 506 (70.2)	115 998 (68.5)
First degree relative diagnosed with any cancer, n (%)	148 761 (49.4)	19 496 (48.5)	108 351 (49.2)	85 122 (50.3)
First degree relative diagnosed with colon cancer, n (%)	26 994 (9.0)	3 569 (8.9)	19 629 (8.9)	15 324 (9.1)
Current BMI kg/m^2, mean (SD)	27.0 (5.0)	26.7 (5.3)	26.9 (4.9)	27.2 (5.1)
Current BMI > 35 kg/m^2, n(%)	17 550 (5.8)	2 404 (6.0)	11 840 (5.4)	11 124 (6.6)
Physically active ≥ 5x / week, n(%)	60 553 (20.1)	8218 (20.4)	44 842 (20.4)	32 649 (19.3)
Use of hormone replacement therapy, ever, n (%)*	68 328 (54.5)	8 604 (45.8)	45 428 (32.9)	44 695 (59.5)
College graduate, n (%)	123 435 (41.0)	14 511 (36.1)	93 742 (42.6)	71 664 (42.3)
Race				
White, n (%)	278 614 (92.5)	35 749 (88.9)	205 645 (93.4)	157 389 (92.9)
Black, n (%)	10 007 (3.3)	2 187 (5.4)	5 982 (2.7)	5 340 (3.2)
Other, n (%)†	12 619 (4.2)	2 274 (5.7)	8 632 (3.9)	6 597 (3.9)
Tobacco smoking				
Never	108 071 (35.9)	15 652 (38.9)	76 988 (35.0)	60 029 (35.5)
Former	144 971 (48.1)	17 974 (44.7)	108 310 (49.2)	82 920 (49.0)
Current	38 150 (12.7)	5 232 (13.0)	27 556 (12.5)	20 822 (12.3)
Total energy, kcals, mean (SD)	1 850 (917)	1 829 (986)	1 870 (911)	1 846 (914)
Alcohol, g /d, mean (SD)	13.1 (36.0)	11.7 (37.7)	13.7 (36.3)	12.8 (34.5)
Vegetables, mean, servings/1000 kcals (SD)	1.1 (0.6)	1.2 (0.7)	1.1 (0.6)	1.1 (0.6)
Fruit, mean, servings/1000 kcals (SD)	1.2 (0.8)	1.3 (0.9)	1.2 (0.8)	1.2 (0.8)

Abbreviations: BMI= body mass index, NSAID= non-steroidal anti-inflammatory drug, SD= standard deviation

*among females, only

†includes Hispanic, Asian, Pacific Islander, American Indian, Alas kan Native or unknown

‡use of one NSAID is not mutually exclusive of the other category of NSAID

Table 2

Hazard ratios (95% CI)[a] for the association between NSAID use and colorectal cancer in the NIH-AARP Diet and Health Study (n=301,240)

			Colorectal cancer[b]	Colon cancer[c,d]	Proximal colon cancer	Distal colon cancer	Rectal cancer
NSAID use in past 12 months[e]							
	No	Cases, n / person years	650/ 3160	497/ 2418	293/ 1481	189/ 742	153/742
		Reference	1.0	1.0	1.0	1.0	1.0
	Yes	Cases, n / person years	3244 / 15718	2392/ 11809	1391 / 7083	929 / 4400	852 / 3,909
		HR (95% CI)	0.80 (0.73, 0.87)	0.78 (0.71, 0.86)	0.77 (0.68, 0.88)	0.79 (0.67, 0.92)	0.87 (0.72, 1.03)
	Frequency						
	Non-user	Cases, n / person years	650/ 3160	497/ 2418	293/ 1481	189/ 882	153/ 742
		Reference	1.0	1.0	1.0	1.0	1.0
	Monthly	Cases, n / person years	1298/6533	946/ 4876	537/ 2835	380/ 1918	352/ 1657
		HR (95% CI)	0.89 (0.81, 0.98)	0.86 (0.77, 0.96)	0.83 (0.72, 0.96)	0.91 (0.76, 1.08)	1.00 (0.83, 1.21)
	Weekly	Cases, n / person years	749/ 3677	559/ 2784	320/ 1630	223/ 1063	190/ 894
		HR (95% CI)	0.76 (0.68, 0.84)	0.75 (0.66, 0.84)	0.73 (0.62, 0.85)	0.78 (0.64, 0.95)	0.79 (0.64, 0.98)
	Daily	Cases, n / person years	1197/ 5508	887/ 4149	534/ 2618	326/ 1419	310/ 1358
		HR (95% CI)	0.74 (0.67, 0.81)	0.72 (0.65, 0.81)	0.75 (0.65, 0.86)	0.69 (0.57, 0.82)	0.79 (0.65, 0.97)
		P -trend	<.0001	<.0001	0.4945	0.0089	0.0011
Aspirin use in past 12 months[e]							
	No	Cases, n / person years	1080/ 5236	790/ 3978	464/ 2418	303/ 1472	290/ 1348
		Reference	1.0	1.0	1.0	1.0	1.0
	Yes	Cases, n / person years	2800/ 13490	2088/ 10201	1211/ 6102	813/3806	712/ 3289
		HR (95% CI)	0.91 (0.85, 0.98)	0.94 (0.86, 1.02)	0.93 (0.84, 1.04)	0.94 (0.82, 1.07)	0.83 (0.72, 0.96)
	Frequency						
	Non-user	Cases, n / person years	1080/ 5236	790/ 3978	464/ 2418	303/ 1472	290/ 1348
		Reference	1.0	1.0	1.0	1.0	1.0
	Monthly	Cases, n / person years	1199/ 5959	883/ 4451	489/ 2531	365/ 1787	316/ 1508
		HR (95% CI)	0.96 (0.89, 1.05)	0.98 (0.89, 1.08)	0.93 (0.82, 1.05)	1.05 (0.90, 1.23)	0.92 (0.78, 1.08)
	Weekly	Cases, n / person years	609/ 2971	415/ 2259	269/ 1359	173/ 831	154/ 713
		HR (95% CI)	0.88 (0.80, 0.97)	0.91 (0.81, 1.02)	0.92 (0.79, 1.07)	0.89 (0.74, 1.08)	0.80 (0.66, 0.97)

		Colorectal cancer[b]	Colon cancer[c,d]	Proximal colon cancer	Distal colon cancer	Rectal cancer
NSAID use in past 12 months[e]						
Daily	Cases, n / person years	992/ 4559	715/ 3491	453/ 2212	275/ 1188	242/ 1068
	HR (95% CI)	0.86 (0.79, 0.94)	0.90 (0.81, 1.00)	0.94 (0.83, 1.08)	0.84 (0.71, 0.99)	0.76 (0.64, 0.90)
	P -trend	0.0002	0.0225	0.4945	0.0089	0.0006
Non-aspirin NSAID use in past 12 months[e]						
No	Cases, n / person years	1965/ 9509	1468/ 7156	868/4363	557/ 2604	497/ 2354
	Reference	1.0	1.0	1.0	1.0	1.0
Yes	Cases, n / person years	1908/ 9264	1404/ 6982	807/ 4154	553/ 2635	504/ 2283
	HR (95% CI)	0.82 (0.77, 0.87)	0.81 (0.75, 0.87)	0.78 (0.71, 0.86)	0.84 (0.75, 0.95)	0.85 (0.75, 0.97)
Frequency						
Non-user	Cases, n / person years	1965/ 9509	1468/ 7156	868/ 4363	557/2604	497/ 2354
	Reference	1.0	1.0	1.0	1.0	1.0
Monthly	Cases, n / person years	1186/ 5841	888/ 4481	517/ 2687	344/ 1678	298/ 1360
	HR (95% CI)	0.88 (0.82, 0.95)	0.89 (0.82, 0.97)	0.87 (0.78, 0.98)	0.90 (0.79, 1.04)	0.87 (0.75, 1.00)
Weekly	Cases, n / person years	407/ 1973	294/ 1451	161/ 840	123/ 569	113/ 522
	HR (95% CI)	0.76 (0.69, 0.85)	0.74 (0.65, 0.84)	0.68 (0.58, 0.81)	0.82 (0.67, 0.99)	0.84 (0.68, 1.03)
Daily	Cases, n / person years	315/ 1450	222/ 1050	129/ 627	86/ 388	93/ 401
	HR (95% CI)	0.71 (0.63, 0.80)	0.67 (0.58, 0.77)	0.65 (0.54, 0.78)	0.69 (0.55, 0.87)	0.86 (0.69, 1.08)
	P -trend	< 0.0001	<0.0001	<0.0001	0.0004	0.0357

Abbreviations: BMI= body mass index, CI= confidence interval, HR=hazard ratio, NSAID= non-steroidal anti-inflammatory drug.

[a] HRs and 95% CIs come from models adjusted for age at cohort entry, sex, cigarette smoking status, race, physical activity level, BMI at study baseline, alcohol, education, race, physical activity level, BMI at study baseline, use of hormone replacement therapy, and having a first degree relative with history of colorectal cancer.

[b] all adenomcarcinomas of the colon or rectum,

[c] includes adenocarcinomas of the proximal and distal colon,

[d] proximal or distal location is not known for all colon cancers

[e] as reported at the time of completing the questionnaire

Table 3

Hazard ratios (95% CI)[a] for the association between NSAID use and colorectal cancer among individuals with a first degree relative with a history of colon cancer in the NIH-AARP Diet and Health Study (n= 26,994)

		Colorectal cancer[b]	Colon cancer[c, d]	Proximal colon cancer	Distal colon cancer	Rectal cancer
NSAID use in past 12 months[e]						
No	Cases, n/ person years	56/ 251	41/ 182	21/ 94	19/ 86	15/ 69
	Reference	1.0	1.0	1.0	1.0	1
Yes	Cases, n/ person years	316/ 1479	258/ 1228	161/ 770	88/ 421	58/ 251
	HR (95% CI)	0.87 (0.65, 1.16)	0.97 (0.69, 1.35)	1.16 (0.73, 1.83)	0.73 (0.44, 1.20)	0.61 (0.34, 1.09)
Frequency						
Non-user	Cases, n/ person years	56/ 251	41/ 182	21/ 94	19/ 86	15/ 69
	Reference	1.0	1.0	1.0	1.0	1
Monthly	Cases, n/ person years	132/ 644	108/ 536	65/ 1344	37/ 164	24/ 107
	HR (95% CI)	1.03 (0.75, 1.42)	1.15 (0.80, 1.65)	1.33 (0.81, 2.18)	0.86 (0.49, 1.50)	0.72 (0.38, 1.38)
Weekly	Cases, n/ person years	80/ 335	66/ 290	44/ 189	21/ 97	14/ 45
	HR (95% CI)	0.89 (0.63, 1.26)	1.00(0.67, 1.48)	1.27 (0.75, 2.14)	0.70 (0.37, 1.31)	0.60 (0.29, 1.24)
Daily	Cases, n/ person years	104/ 501	84/ 402	52/ 237	30/ 160	20/ 99
	HR (95% CI)	0.72 (0.52, 0.99)	0.79 (0.54, 1.14)	0.93 (0.56, 1.55)	0.62 (0.35, 1.11)	0.52 (0.27, 1.03)
	P-trend	0.0072	0.0378	0.3011	0.0756	0.0623
Aspirin use in past 12 months[e]						
No	Cases, n/ person years	95/ 435	68/ 315	35/ 165	31/165	27/ 120
	Reference	1.0	1.0	1.0	1.0	1
Yes	Cases,n/ person years	276/ 1287	230/ 1087	146/ 691	76/ 367	46/ 199
	HR (95% CI)	1.00 (0.79, 1.27)	1.16 (0.88, 1.53)	1.41 (0.97, 2.05)	0.85 (0.56, 1.30)	0.60 (0.37, 0.98)
Frequency						
Non-user	Cases, n/ person years	95/ 435	68/ 315	35/ 165	31/165	27/ 120
	Reference	1.0	1.0	1.0	1.0	1
Monthly	Cases, n/ person years	120/ 557	99/ 474	61/ 1304	33/ 150	21/ 83
	HR (95% CI)	1.09 (0.83, 1.43)	1.24 (0.91, 1.70)	1.45 (0.96, 2.19)	0.93 (0.57, 1.53)	0.71 (0.40, 1.25)
Weekly	Cases, n/ person years	70/ 303	56/ 253	39/ 174	16/ 75	14/ 49

		Colorectal cancer[b]	Colon cancer[c, d]	Proximal colon cancer	Distal colon cancer	Rectal cancer
NSAID use in past 12 months[e]						
	HR (95% CI)	1.10 (0.81, 1.50)	1.22 (0.85, 1.74)	1.59 (1.01, 2.52)	0.79 (0.43, 1.45)	0.81 (0.42, 1.55)
Daily	Cases, n/ person years	86/ 427	75/ 360	46/ 213	27/141	11/67
	HR (95% CI)	0.83 (0.62, 1.12)	1.00 (0.72, 1.40)	1.16 (0.74, 1.81)	0.83 (0.49, 1.40)	0.38 (0.19, 0.78)
	P- trend	0.2192	0.8963	0.5466	0.3883	0.0133
Non-aspirin NSAID use in past 12 months[e]						
No	Cases, n/ person years	182/ 848	147/ 687	92/ 437	50/ 235	35/ 161
	Reference	1.0	1.0	1.0	1.0	1
Yes	Cases, n/ person years	189/ 878	151/ 720	89/ 424	57/ 272	38/158
	HR (95% CI)	0.87 (0.71, 1.07)	0.86 (0.68, 1.09)	0.81 (0.60, 1.09)	0.96 (0.65, 1.41)	0.88 (0.56, 1.41)
Frequency						
Non-user	Cases, n/ person years	182/ 848	147/ 687	92/ 437	50/ 235	35/ 161
	HR (95% CI)	1.0	1.0	1.0	1.0	1
Monthly	Cases, n/ person years	134/ 639	110/ 530	66/ 330	40/180	24/ 109
	HR (95% CI)	1.07 (0.85, 1.34)	1.08 (0.84, 1.39)	1.03 (0.75, 1.41)	1.17 (0.77, 1.79)	1.21 (0.86, 1.71)
Weekly	Cases, n/ person years	30/126	25/ 108	14/ 53	Oct-52	18-May
	HR (95% CI)	0.59 (0.40, 0.87)	0.61 (0.40, 0.94)	0.54 (0.31, 0.96)	0.73 (0.37, 1.45)	1.07 (0.74, 1.56)
Daily	Cases, n/ person years	25/ 113	16/ 81	Sep-41	7/ 40	9/ 32
	HR (95% CI)	0.61 (0.40, 0.93)	0.49 (0.29, 0.82)	0.44 (0.22, 0.88)	0.63 (0.28, 1.39)	0.97 (0.67, 1.40)
	P - trend	0.0033	0.0023	0.0059	0.2171	0.6211

Abbreviations: BMI= body mass index, CI= confidence interval, HR=hazard ratio, NSAID= non-steroidal anti-inflammatory drug.

[a] HRs and 95% CIs come from models adjusted for age at cohort entry, sex, cigarette smoking status, race, physical activity level, BMI at study baseline, alcohol, education, race, physical activity level, BMI at study baseline, and use of hormone replacement therapy.

[b] all adenomcarcinomas of the colon or rectum,

[c] includes adenocarcinomas of the proximal and distal colon,

[d] proximal or distal location not known for all colon cancers

[e] as reported at the time of completing the questionnaire

Am J Gastroenterol. Author manuscript; available in PMC 2011 September 30.