HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2022 September 01.

Published in final edited form as:

Cancer. 2021 September 01; 127(17): 3145–3155. doi:10.1002/cncr.33623.

Aspirin, Ibuprofen and Reduced Risk of Advanced Colorectal Adenoma Incidence and Recurrence and Colorectal Cancer in the PLCO Cancer Screening Trial

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Abstract

Background: Studying the differential impact of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) across the stages of colorectal neoplasia from early adenoma to cancer is critical for understanding the benefits of these widely used drugs.

Methods: With 13 years of follow-up, we prospectively evaluated the association between aspirin and ibuprofen use and incident distal adenoma (1,221 cases), recurrent adenoma (862 cases), and

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Conflict of Interest:

The authors disclose no conflicts.

incident colorectal cancer (CRC, 2,826 cases) among men and women in the population-based Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Using multivariable-adjusted models, we determined odds ratios (ORs) and 95% confidence intervals (CI) for adenoma incidence and recurrence, and hazard ratios (HR) and 95% CI for incident CRC.

Results: We observed a significantly reduced risk of incident adenoma with ibuprofen use [≥30 vs. <4 pills/month: OR, 0.76 (95% CI 0.60 – 0.95); P_{trend}= 0.04], particularly advanced adenoma [OR, 0.48 (95% CI 0.28 – 0.83); P_{trend}= 0.005]. Among those with a previous adenoma detected through screening, aspirin use was associated with a decreased risk of advanced recurrent adenoma [≥30 vs. <4 pills/month: OR, 0.56 (95% CI 0.36 – 0.87); P_{trend}= 0.006]. Both aspirin [HR, 0.88 (95% CI 0.81 – 0.96); P_{trend}= <0.0001] and ibuprofen use [HR, 0.81 (95% CI 0.70 – 0.93); P_{trend}= 0.003] ≥30 vs. <4 pills/month were significantly associated with reduced CRC risk.

Conclusion: In this large prospective study with long-term follow-up, we observed a beneficial role for not only aspirin, but also ibuprofen, in preventing advanced adenoma and curbing progression to recurrence and cancer among older adults.

Precis:

This large, population-based, prospective study with long-term follow-up demonstrates a beneficial role for not only aspirin, but also ibuprofen, in preventing advanced adenoma and curbing progression to recurrence and cancer among older adults. The protection offered by these widely used NSAIDs was notably significant against the development of advanced adenoma, an important target for intervention.

Keywords

aspirin; ibuprofen; incident adenoma; recurrent adenoma; colorectal cancer

Introduction

Colorectal cancer (CRC), the second leading cause of cancer-related deaths in the United States, exerts a significant human and financial burden and is poised to remain a major health challenge in the new decade.[1-3] With the rising costs of health care and known barriers to screening[4], there is growing interest in the use of appropriate chemoprevention strategies to reduce the burden of CRC in the general population.[5,6] Chronic inflammation has been implicated in the process of colorectal tumorigenesis, and non-steroidal anti-inflammatory drugs (NSAIDs) have been identified in pre-clinical and clinical studies to have a protective effect against colorectal tumors.[7-11] The mechanism of NSAID chemoprevention against tumor proliferation is not completely understood, but is thought to partly be related to its inhibition of the cyclooxygenase (COX) enzyme.[12,13] NSAID-induced antagonism of the COX isoforms, COX-1 and COX-2, prevents the conversion of arachidonic acid to prostaglandins, which are important mediators of inflammation. Cyclooxygenase-independent mechanisms have also been proposed for the anti-carcinogenic effects of NSAIDs.[14-16] Although CRC is thought to develop over time from precursor lesions along the adenoma-carcinoma pathway[17], it is unclear whether NSAIDs act preferentially in the early stages of this sequence to prevent tumor initiation or in the later stages to delay progression. A better understanding of the differential impact of NSAIDs on

the clinical stages of colorectal tumorigenesis will help inform the benefits of these widely used drugs and guide the development of an appropriate framework for chemoprevention in a general population.

Prospective observational studies have shown a consistent reduction in colorectal cancer risk with aspirin use.[18,19] Although the ASPirin in Reducing Events in the Elderly (ASPREE) trial showed no benefit after a few years of follow-up[20] raising new questions about aspirin's efficacy, especially in the elderly population, evidence from earlier randomized controlled trials with colorectal cancer as a secondary endpoint and longer follow-up has shown a reduction in risk with aspirin use.[11] Fewer studies have evaluated non-aspirin NSAIDs, such as ibuprofen, one of the most commonly used non-aspirin NSAIDs, and most have grouped all non-aspirin NSAIDs together without regard for pharmacological differences.[21] Randomized trials of aspirin and other NSAIDs among those with a history of adenoma have also largely reported a decreased incidence of recurrent adenoma,[22,23] but the long-term benefit is unclear with some studies reporting an increased risk of recurrence during the post-trial follow-up.[9,24,25] Few population-based studies have prospectively evaluated the risk of incident and recurrent adenoma,[26] and many retrospective case-control studies have had methodological challenges related to selection and recall bias.

In this prospective study, we examined the association of aspirin and ibuprofen with colorectal adenoma incidence, adenoma recurrence, and colorectal cancer in a large cohort of men and women followed in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial to gain a better understanding of the population impact of NSAIDs on the different stages of colorectal tumorigenesis. Participants randomized to the screening arm of the trial were assigned to be endoscopically evaluated at baseline and after 3-5 years, allowing for a robust prospective assessment of the association of NSAID use and incident adenoma without selection or recall bias, and recurrence was evaluated using follow-up data collected on endoscopies over 10 years. We evaluated study outcomes with respect to the use of two nonselective COX inhibitors: aspirin, which binds irreversibly to COX and ibuprofen, a reversible COX inhibitor.[27,28]

Methods

Study design

This is a prospective study of participants in the PLCO Cancer Screening Trial, which is a randomized, multi-center trial designed to evaluate the impact of screening on cancer-related mortality for malignancies arising in the prostate, lungs, ovaries, colon and rectum.[29] As described previously[30], a total of 154,952 men and women aged between 55 and 74 years were enrolled at 10 sites across the United States between 1993 and 2001 and were randomized to either the intervention arm and underwent cancer screening, or to the control arm and received usual medical care. Participants completed a self-administered risk factor questionnaire at baseline, and information was collected on demographics, medical history, and medication use, including NSAIDs. The study was approved by the human subjects review boards at the National Cancer Institute and at the 10 study centers, and all participants provided written informed consent.

Screening examinations and outcome data collection

Of 77,447 participants randomized to the intervention arm of the PLCO trial, 64,655 (96.4%) underwent CRC screening with flexible sigmoidoscopy at baseline and 39,443 of those with a baseline screen had a second sigmoidoscopy at either the third (T3) or fifth (T5) year after enrollment.[31] Those with a positive screen were sent to their usual healthcare providers for follow-up and 80.5% had a diagnostic intervention.[31] Trained staff reviewed all available medical records related to the ensuing work-up and outcomes were recorded based on pathology reports. Participants in both arms of the trial were actively followed for cancer incidence by each of the 10 study sites through 2011. In 2011, data collection transitioned to follow-up at a centralized data center through medical record review (2012-2013) and cancer registry linkage; about 19,000 participants declined further follow-up during the re-consent process. All colorectal cancer cases were histologically-confirmed through medical record review and/or via linkage to cancer registries. The present study included data on cancer incidence through 2014.

Study population

Similar to what we reported previously[32], participants who completed the baseline questionnaire, had data on NSAID use, and no history of Crohn's disease, ulcerative colitis, familial polyposis, or Gardner's syndrome were included in these analyses. Further exclusions for each specific outcome of interest are briefly described below.

Incident distal colorectal adenoma: To examine the association with incident adenoma, we conducted a nested case-control study. This analysis was restricted to participants in the intervention arm with an adequate flexible sigmoidoscopy (insertion ≥ 50 cm with ≥ 90% of mucosa visualized) at baseline that did not reveal any abnormalities or suspicious findings in the distal colon and rectum (i.e. negative baseline trial screen), and an adequate T3/T5 follow-up flexible sigmoidscopy screen. We further excluded participants who had a diagnosis of CRC before the T3/T5 screening or a self-reported history of colorectal polyps at baseline. Cases were those who had a negative baseline trial screen and discovered to have adenoma in the distal colon or rectum at T3/T5. Controls were those with negative trial screens for adenoma at both baseline and T3/T5. In total, there were 1,221 incident distal colorectal adenoma cases (806 men; 415 women) and 19,626 controls (10,699 men; 8927 women).

Recurrent colorectal adenoma: For recurrent adenoma, we conducted a case-control study. This analysis included participants in the intervention arm who had an adenoma at baseline and at least one follow-up endoscopy within the 10-year period after baseline. The majority of subjects were part of a study nested within the PLCO Trial known as the Study of Colonoscopy Utilization (SCU)[33], and we also included recurrent adenoma cases diagnosed as part of the trial (i.e. those with a adenoma on both the baseline and T3/T5 trial endoscopy screens). We excluded participants who had a history of colorectal cancer before diagnosis of a recurrent adenoma or a self-reported history of colorectal polyps at baseline. We defined cases as those with a baseline adenoma who were found to have an adenoma on any later surveillance screen, while controls were those with an adenoma diagnosis at baseline but no evidence of adenoma on any surveillance colonoscopy during the following

10 years. After exclusions, there were 862 recurrent adenoma cases (614 men; 248 women) and 877 controls (499 men; 378 women).

Incident colorectal cancer: To evaluate the association with colorectal cancer, we conducted a cohort study. This analysis included participants randomized to either the intervention or control arm of the trial. Participants were followed from the time of completion of the baseline questionnaire to the date of CRC diagnosis, death, loss to follow-up, or December 31, 2014, whichever occurred first. Of the 127,454 included participants, 2,826 were diagnosed with colorectal cancer over the median follow-up period of 13 years.

Exposure assessment

NSAID use was evaluated based on participant response to four NSAID-related questions on the baseline questionnaire. Two questions asked if participants had regularly used aspirin or aspirin-containing products and/or ibuprofen or ibuprofen-containing products in the 12 months prior to screening. Those who reported regular use of either product were asked two additional questions about the usual number of pills taken in the preceding 12 months, and response options were as follows: 1/day, ≥2/day, 1/week, 2/week, 3-4/week, <2/month, and 2-3/month. For the present analysis, we converted responses into the number of pills taken per month as described previously[34] and created separate variables for aspirin and ibuprofen use as follows: <4/month (including those reporting irregular use), 4-29/month, and ≥30/month. We also created a variable for the combined use of aspirin and ibuprofen and categorized this as follows: <4/month (including irregular use), 4-29/month, 30 – 59/month, and ≥60/month. We collapsed the two most frequent use groups (30 – 59/month & ≥60/month) into one (≥30/month) for aspirin use and ibuprofen use individually due to small sample sizes.

Statistical methods

Descriptive analyses were performed to evaluate the association between characteristics at baseline, exposure and outcomes. For the risk of incident and recurrent adenoma, logistic regression was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). For the colorectal cancer analysis, we created inverse propensity score weights to improve the representativeness of the analytic cohort for incident CRC and account for potential bias from the loss of some participants to follow-up during the re-consent process while transitioning to a central data collection system.[35] Using Cox proportional hazards regression models, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of incident CRC with NSAID use. With <4 pills/month as the reference category for all analyses, we constructed overall and sex-stratified models for the respective outcomes of interest. The impact of multiple potential confounders of the relationship between colorectal tumorigenesis and NSAID use were evaluated (e.g., physical activity) and only those that changed the beta coefficient for NSAID use by ≥10% were included in final multivariable regression models.[36] All regression models included the following covariates: sex, age at baseline or screening (for CRC analyses, age was the underlying time metric, and we adjusted for calendar year at baseline), study center at enrollment, race, family history of CRC, smoking status and body mass index (BMI) at baseline. We additionally adjusted for study year of screening (T3 or T5) in the incident

adenoma analyses, number of follow-up colonoscopies and follow-up time from baseline endoscopy in the recurrent adenoma analyses, and trial arm in the colorectal cancer analyses. Separate analyses were performed for aspirin (controlling for ibuprofen use), ibuprofen (controlling for aspirin use), and the combined use of both medications. Additional analyses were conducted evaluating aspirin use only and ibuprofen use only; findings were similar to the results with mutual adjustment and therefore not presented.

To evaluate the association with increasing frequency of NSAID use, we estimated *P* values for trend assuming an ordinal variable (i.e. 0, 1, 2) for the multi-level frequency categories of use. We also performed separate analyses by anatomic site (proximal colon, distal colon or rectum), adenoma subtype (advanced, non-advanced), CRC stage (IV vs. I to III), and participant's age at enrollment (55-64 vs. >65 or 55-69 vs. >70). An adenoma was considered to be advanced if it had one of the following features: ≥1 cm in size, villous histology, or high-grade dysplasia.[37] A 2-tailed *P* value of < 0.05 was considered to be statistically significant for all analyses.

Results

Characteristics of the study population

Among the 127,454 eligible subjects with NSAID data in the PLCO Cancer Screening Trial, the mean age at baseline was 63 years, 50.8% were male and the mean BMI was 27.3kg/m^2. The majority of participants (88%) were non-Hispanic white. Ten percent of the study population had a family history of CRC and 10.9% were current smokers. No regular use of NSAIDs was reported in 39% of the population, while regular use of aspirin (only) and ibuprofen (only) was recorded in 32% and 12% of them, respectively, and regular use of both aspirin and ibuprofen in 17% of the population (Table 1). Among the PLCO Trial participants with a negative baseline screen and adequate T3/T5 screen, incident adenoma cases were more likely to be male, have a family history of CRC, and be current or former smokers compared to controls, and were less likely to receive > 3 hours of physical activity per week compared to controls (Table 2). Among PLCO Trial participants with adenoma at baseline and information on follow-up surveillance endoscopies, recurrent adenoma cases were more likely to be male and non-white when compared to those without a recurrence (Table 2).

Incident distal colorectal adenoma

Regular use of ibuprofen was associated with a significant reduction in the risk of incident distal colorectal adenoma overall [≥30 vs <4 pills/month: OR, 0.76 (95% CI 0.60 – 0.95); P_{trend}= 0.04] (Table 3). The protective association was stronger for advanced adenoma [≥30 vs <4 pills/month: OR, 0.48 (95% CI 0.28 – 0.83); P_{trend}= 0.005] with no significant risk observed for non-advanced adenoma [≥30 vs <4 pills/month: OR, 0.87 (95% CI 0.64 – 1.18); P_{trend}= 0.29] ($P_{\text{heterogeneity for advanced vs. non-advanced}}$ = 0.06). Similarly, combined use of aspirin and ibuprofen was associated with a significantly lower risk of incident distal adenoma overall [≥60 vs <4 pills/month: OR, 0.79 (95% CI 0.64 – 0.97); P_{trend}= 0.01], with greater benefit for advanced adenoma [≥60 vs <4 pills/month: OR, 0.53 (95% CI 0.33 – 0.84); P_{trend}= 0.008] and no significant protection against non-

advanced adenoma [≥60 vs <4 pills/month: OR, 0.82 (95% CI 0.62 – 1.09); P_{trend}= 0.13] ($P_{heterogeneity\ for\ advanced\ vs.\ non\text{-}advanced}$ = 0.18). Although there was no evidence of an association between aspirin use and the risk of incident distal colorectal adenoma overall [≥30 vs <4 pills/month: OR, 0.92 (95% CI 0.80 – 1.06); P_{trend}= 0.12], we observed some evidence of a trend between increased aspirin use and reduced risk of advanced adenoma [≥30 vs <4 pills/month: OR, 0.86 (95% CI 0.65 – 1.13); P_{trend}= 0.07]. No significant differences in risk were observed by anatomic site (i.e. distal colon vs. rectum) with the use of aspirin, ibuprofen, or both combined ($P_{heterogeneity}$ > 0.10 for all).

Recurrent colorectal adenoma

There was no significant association between the use of aspirin and the risk of recurrent adenoma overall [≥30 vs <4 pills/month: OR, 0.90 (95% CI 0.69 – 1.17); P_{trend}= 0.47], but aspirin use was significantly associated with a reduced risk of advanced recurrent adenoma [≥30 vs <4 pills/month: OR, 0.56 (95% CI 0.36 – 0.87); P_{trend}= 0.006] (Table 4). This beneficial association was not observed for non-advanced recurrent adenoma [≥30 vs <4 pills/month: OR, 1.05 (95% CI 0.79 – 1.38); P_{trend}= 0.63], and the difference in risk between advanced and non-advanced adenoma was statistically significant ($P_{heterogeneity}$ = 0.001). Although there was no significant association for the highest category, combined use of both aspirin and ibuprofen was also associated with a decreased risk of advanced recurrent adenoma for most use categories [i.e., 4 to <30 [OR, 0.49 (95% CI 0.29, 0.82)] and 30 to <60 pills/months [OR, 0.50 (95% CI 0.31, 0.80)]]. No protective associations were observed for combined use with regard to non-advanced recurrent adenoma (P_{trend} = 0.69), and the difference between advanced and non-advanced adenoma was significant ($P_{heterogeneity}$ = 0.047). There were no significant associations between ibuprofen use and the risk of recurrent adenoma (Table 4). No significant risk differences was observed by anatomic site (i.e. proximal colon, distal colon, rectum).

Colorectal Cancer Incidence

We observed a decrease in the risk of colorectal cancer overall with increased use of aspirin [≥30 vs <4 pills/month: HR, 0.88 (95% CI 0.81 – 0.96); P_{trend}= <0.0001], ibuprofen [≥30 vs <4 pills/month: HR, 0.81 (95% CI 0.70 – 0.93); P_{trend}= 0.003] and the combined use of both medications [≥60 vs <4 pills/month: HR, 0.79 (95% CI 0.69 – 0.89); P_{trend}= <0.0001] (Table 5). Overall, there were no significant differences by anatomic location between NSAID use and cancer risk ($P_{heterogeneity}$ > 0.10). With aspirin use, we observed a significant inverse association for cancers in the proximal [≥30 vs <4 pills/month: HR, 0.89 (95% CI 0.79 – 1.00); P_{trend}= 0.008] and distal colon [≥30 vs <4 pills/month: HR, 0.82 (95% CI 0.69 – 0.98); P_{trend}= 0.003]. Similarly, there was a significant protective effect observed with the combined use of both medications for cancers in the proximal [≥60 vs <4 pills/month: HR, 0.77 (95% CI 0.65 – 0.92); P_{trend}= 0.0003] and distal colon [≥60 vs <4: HR, 0.81 (95% CI 0.64 – 1.04); P_{trend}= 0.02]. Ibuprofen use was also associated with a decreased cancer risk in the proximal colon [≥30 vs <4: HR, 0.75 (95% CI 0.62 – 0.91); P_{trend}= 0.0091], but not in the distal colon [≥30 vs <4: HR, 0.87 (95% CI 0.66 – 1.13); P_{trend}= 0.23]. No significant associations were observed with rectal cancer for either aspirin or ibuprofen, but the sample size was smaller. We observed no significant differences in the relative risk of CRC with NSAID use when stratifying by stage of CRC, participant's age at enrollment, or trial arm.

Discussion

In this large prospective study of participants in a cancer screening trial followed for cancer incidence over a median duration of 13 years, we identified beneficial protective associations between NSAIDs and the risk of incident distal colorectal adenoma, recurrent colorectal adenoma, and CRC. First, we found that ibuprofen and combined use of aspirin and ibuprofen were significantly associated with a decreased risk of incident distal adenoma overall, and we observed a more pronounced protective effect for advanced than non-advanced incident distal adenoma. Second, we observed that although there was no association between NSAID use and the risk of recurrent adenoma overall, aspirin and the combined use of both medications were significantly associated with a decreased risk of advanced recurrent adenoma, whereas there was no significant protection against non-advanced recurrent adenoma. Finally, we observed significant inverse associations between the use of aspirin, ibuprofen and the combined use of both medications and the risk of incident CRC. Taken together, these findings show the chemopreventive benefits of NSAIDs against the development and recurrence of colorectal adenoma, particularly advanced adenoma, and the progression to colorectal cancer. To our knowledge, this is one of the first studies to prospectively evaluate the impact of NSAIDs across the stages of colorectal tumorigenesis in the context of a colorectal cancer screening trial with long-term follow-up. Although the numbers of advanced adenoma cases were relatively small in some categories and replication is needed to confirm that our findings are not due to chance, our study is one of the first prospective studies to report a beneficial role of ibuprofen in reducing the risk of advanced incident adenoma and CRC in a general population.

Data from experimental and clinical studies have shown that NSAIDs suppress colorectal tumor formation.[7,8] However, evidence for the role of NSAIDs in preventing the initiation of colorectal adenoma in a population with no history of adenoma is sparse with many studies reporting the association with prevalent adenoma[38], where it is difficult to assess how long the adenoma was present prior to endoscopy and whether NSAID use occurred before or after development of adenoma. In the present study, participants without a history of polyps at baseline who had a negative baseline endoscopy were prospectively followed to see if they developed adenoma after 3 or 5 years, allowing us to capture incident cases. We found that use of ibuprofen and the combined use of ibuprofen and aspirin were associated with a significantly reduced risk of incident distal adenoma overall, particularly advanced adenoma, suggesting that they may curb progression more than prevent initiation. Consistent with our findings for ibuprofen, we observed a trend towards a reduced risk of advanced incident distal adenoma with increased aspirin use (P_{trend} = 0.07). Among adenomas, the advanced ones are of utmost clinical concern due to their greater likelihood of progression to CRC. Analyses of participants in the Nurses' Health Study and Health Professional Follow-up Study provide support for the protective role of aspirin against incident adenoma, as regular aspirin use was associated with a reduced risk of incident distal colorectal adenoma among women with a previous negative endoscopy (OR 0.73, 95% CI 0.60 – 0.89),[26] while a borderline association was observed for men (OR 0.65, 95% CI 0.42 – 1.02).[39] Few studies have specifically evaluated advanced adenoma. Consistent with ours, a study among participants in the Nurses' Health Study and Health Professional Follow-up Study reported a

reduced prevalence of high-risk adenoma, including both advanced adenoma and those with >3 adenomas on their initial screen, with both non-aspirin NSAID use and aspirin use.[40]

In our study, we observed that aspirin use was associated with a significantly decreased risk of recurrence of advanced adenoma, but not non-advanced recurrent adenoma or recurrent adenoma overall. Our finding for advanced recurrent adenoma is consistent with the findings of a meta-analysis of five published randomized controlled-trials (RCTs), where subjects with previously-resected adenomas who received daily aspirin were observed to have a decreased risk of advanced adenoma (RR, 0.70; 95% CI 0.55 – 0.88) and adenoma overall (RR, 0.83; 95% CI 0.73 – 0.94).[22] Although we did not observe a significant reduction in overall adenoma risk, this may be explained by our use of irregular aspirin use (<4 pills/month) as the reference category. The baseline PLCO survey did not have response options on NSAID use that would have allowed for the creation of a purely null category as a reference group and the inclusion of irregular users with never users may have attenuated our results. Nonetheless, we posit that our use of the 'irregular use' category as the referent may be more reflective of real-world use of NSAIDs as there are relatively few never-users. In a survey of adults aged between 45 – 75 years in the United States, approximately three-quarters reported regular or previous aspirin use.[41]

In this analysis, there was no association between ibuprofen use and the risk of recurrent adenoma overall or advanced recurrent adenoma over a 10-year period. While there are no comparable ibuprofen studies that have evaluated this association, three RCTs have evaluated the effect of other non-aspirin NSAIDs – celecoxib and rofecoxib, on recurrent colorectal adenoma in the general population.[9,42,43] Compared to placebo, daily use of these COX-2 inhibitors reduced the risk of recurrent adenoma overall and advanced recurrent adenoma over a 3-year follow-up period in subjects drawn from a general population who had histologically-confirmed adenomas removed before the start of the study; however, increased risks of adenoma were observed for the treatment groups in the post-trial follow-up period[9,24,25], suggesting the benefit may not be long-lasting. In contrast to aspirin where the inhibition of COX is irreversible due to covalent binding, the binding of ibuprofen and other non-aspirin NSAIDs to COX is reversible.[27] Over an extended period, some individuals may give up taking non-aspirin NSAIDs, such as ibuprofen or selective COX-2 inhibitors due to their adverse effects, especially at higher doses, leading to reduced benefit. Notably, COX-2 selective inhibitors have been found to be associated with a greater risk of cardiovascular adverse effects, and rofecoxib has since been withdrawn from the market for this reason.[44]

Consistent with findings from multiple observational studies[18,19,21,45], we found an inverse association between the use of aspirin, ibuprofen and combined use of both medications, and the risk of CRC. In a meta-analysis of 30 observational studies (15 case-control and 15 cohort), a 27% reduction in CRC risk was reported with regular use of aspirin (RR = 0.73, 95% CI 0.67 – 0.79).[45] Similarly, a 20% reduction in CRC risk was observed with non-aspirin NSAIDs in a meta-analysis of ten prospective studies (RR, 0.80; 95% CI 0.72 – 0.88), although ibuprofen was not evaluated specifically.[21] While we observed greater benefit for CRC with increasing frequency of use for analyses of ibuprofen, for aspirin, we observed a similar protective effect regardless of frequency. It is possible that for aspirin,

which binds irreversibly to COX, an increased frequency of use does not provide greater benefit, whereas for ibuprofen, which binds reversibly to COX and acts as a competitive inhibitor of arachidonic acid oxygenation, may provide greater protection when taken more frequently.

Randomized clinical trials with CRC as a secondary endpoint have yielded more mixed results on the association between aspirin and CRC. In the ASPREE trial among elderly populations in Australia and the US (100 mg of aspirin daily)[20] and the US Physicians' Health Study (325 mg of aspirin on alternate days)[46], administration of aspirin did not reduce the risk of colorectal cancer over a treatment and follow-up period of 4.7 and 5 years, respectively. However, analyses of the Women's Health Study (100 mg of aspirin on alternate days)[47]and two smaller trials in the United Kingdom of a higher daily dose of aspirin (300 – 1,200 mg) administered over a period of 1 – 9 years[48,49] found an inverse association between allocation to aspirin and the risk of CRC, consistent with findings from review articles[50,51]. Notably, these protective effects were observed only after a follow-up period of 10 years, as further confirmed in a meta-analysis of four RCTs with a mean duration of scheduled aspirin treatment of approximately 6 years and a median follow-up period of 18 years.[11] This is close to the median follow-up period of 13 years in our study and may account for the time needed for the completion of the multistep process of tumorigenesis in the natural history of CRC development.[52]

The meta-analysis[11] also found that aspirin preferentially reduced the risk of cancer in the colon – especially proximal colon, but not in the rectum. Although we observed a significant inverse association between NSAIDs and the risk of cancer in the colon, but not in the rectum, we did not detect statistically significant heterogeneity in the associations by anatomic subsite. Similar to our findings, heterogeneity of CRC risk was not observed by anatomic site with NSAID use in a recent study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.[53] Other published studies, however, have been inconsistent in their observed differences in cancer risk based on tumor location.[26,50,54-56] The association of ibuprofen with CRC risk has not been previously explored in a general population, but many observational studies have evaluated the risk of CRC with use of other non-aspirin NSAIDs, and they have largely observed a protective association.[21] In a nested case-control study using a government insurance database of patients 65 years and older, nonselective NSAIDs, as well as rofecoxib and celecoxib, were both found to be protective against the development of CRC.[57]

In this large, population-based, prospective study with long-term follow-up, we were able to comprehensively evaluate the risks associated with not only aspirin, but also ibuprofen, across the stages of colorectal tumorigenesis. Our incident adenoma analyses also benefited from drawing participants from the screening arm of the trial, such that subjects were screened regardless of healthcare coverage or indication, limiting selection bias. Regarding limitations of our study, as the PLCO utilized flexible sigmoidoscopy for screening, we were unable to evaluate the association of NSAID use with proximal adenoma. Additionally, some controls in the incident adenoma analysis may have had undetected proximal adenoma. Assuming that NSAIDs are protective for proximal adenoma, this could have led to an underestimate of the magnitude of the association between NSAIDs and incident

adenoma. There are also several limitations of the NSAIDs data. We had only limited self-reported data on frequency of aspirin and ibuprofen use. We did not collect information on the use of other, less commonly used, NSAIDs, such as naproxen or selective COX-2 inhibitors, which may have provided a fuller assessment of risk. Information on drug dose was not collected, so we were unable to explore differences between low-dose and high-dose aspirin use. Additionally, we only evaluated NSAID use at baseline, limiting our ability to conclude if the observed benefits were due to NSAID use at baseline or during follow-up. Although aspirin and ibuprofen data were available in follow-up questionnaires in the PLCO trial, when we evaluated the correlation of NSAID use patterns over time, we found that 77% of those who were regular aspirin users at baseline reported continued regular use in a follow-up questionnaire approximately 9.2 years later. Given the strong correlation with the baseline data and limited follow-up time after the questionnaire, the potential contribution to the analysis seemed small; as such, we did not incorporate the follow-up data into the present analysis. While some underreporting of NSAID use by self-report has been noted in other studies, reporting accuracy tends to improve with more frequent and regular use.[58] As information on NSAID use was obtained prospectively in this study, any misclassification of NSAID use due to inaccurate reporting is likely to be non-differential, leading most likely to an attenuation of the protective effects of aspirin and ibuprofen.

In conclusion, in this large cancer screening trial cohort, we observed a protective effect of aspirin and ibuprofen on the risk of incident distal advanced colorectal adenoma, recurrent advanced colorectal adenoma, and colorectal cancer, suggesting that these widely used NSAIDs play a role among older adults in preventing the progression of colorectal adenoma to cancer, interrupting the transformation to malignant disease. Although we cannot be certain if the benefits observed for NSAIDs are due to baseline use, ongoing use or both, our prospective, population-based study supports and extends the findings from randomized trials, providing evidence for a long-term benefit of aspirin and ibuprofen among individuals of average risk. The protection offered by these medications was shown not only for colorectal cancer, but also adenoma and advanced adenoma, which are important precursor lesions and targets for prevention. As our sample size for advanced adenoma was limited, replication of these findings is needed. Future studies should also balance the potential for medication-related adverse effects as well as life expectancy when assessing the utility of NSAIDs for chemoprevention recommendations.

Acknlowledgement:

The authors thank the PLCO participants, as well as the study management team at the Division of Cancer Epidemiology and Genetics and the Division of Cancer Prevention, National Cancer Institute (NCI), NIH, DHHS, staff at the Information Management Services, Inc., and staff at Westat, Inc. In particular, the authors thank Mr. Tom Riley, Mr. Tom Hickey, and colleagues at the Information Management Services, Inc. for their excellent support in the data analysis. Cancer incidence data have been provided by the Alabama Statewide Cancer Registry, Arizona Cancer Registry, Colorado Central Cancer Registry, District of Columbia Cancer Registry, Georgia Cancer Registry, Hawaii Cancer Registry, Cancer Data Registry of Idaho, Maryland Cancer Registry, Michigan Cancer Surveillance Program, Minnesota Cancer Surveillance System, Missouri Cancer Registry, Nevada Central Cancer Registry, Ohio Cancer Incidence Surveillance System, Pennsylvania Cancer Registry, Texas Cancer Registry, Utah Cancer Registry, Virginia Cancer Registry, and Wisconsin Cancer Reporting System. All are supported in part by funds from the Center for Disease Control and Prevention, National Program for Central Registries, local states or by the National Cancer Institute, Surveillance, Epidemiology, and End Results program. The results reported here and the conclusions derived are the sole responsibility of the authors.

Funding:

Dr. Chudy-Onwugaje was supported by a T32 Research Grant (DK067872-11) from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Dr. Barry is supported by K07 CA230182 from the National Cancer Institute, National Institutes of Health. Drs. Huang, Purdue, Wang, Katki, and Berndt are supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, and contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS.

Data availability:

Investigators may apply to access the study data through the PLCO Cancer Data Access System website (https://biometry.nci.nih.gov/cdas/learn/plco/instructions/?subtype=Data-Only).

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Table 1.

Characteristics of Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial Participants in the Colorectal Cancer Analyses, by NSAID use

	Pattern of Aspirin and Ibuprofen use			
	No regular use (n= 49,254)	**Aspirin only (n= 40,847)**	**Ibuprofen only (n= 15,610)**	**Combined use (n= 21,743)**
Age in years, mean (IQR)	63.1 (8.7)	63.8 (8.8)	62.0 (8.3)	62.5 (8.6)
Male, n (%)	24,178 (49.1)	24,493 (60.0)	5,539 (35.5)	10,528 (48.4)
White, n (%)	42,029 (85.3)	36,576 (89.5)	13,900 (89.0)	19,370 (89.1)
Intervention arm, n (%)	25,430 (51.6)	21,096 (51.6)	8,121 (52.0)	11,053 (50.8)
Family history of colorectal cancer, n (%)	4,890 (9.9)	3,907 (9.6)	1,552 (9.9)	2,155 (9.9)
Body mass index in kg/m^2, mean (IQR)	27.0 (5.6)	27.3 (5.5)	27.8 (6.3)	27.8 (5.9)
Physical activity >3 hours/week, n (%)	5,054 (10.3)	4,267 (10.4)	1,449 (9.3)	2,083 (9.6)
Cigarette smoking, n (%)				
Current	5,204 (10.6)	4,457 (10.9)	1,766 (11.3)	2,447 (11.3)
Former	19,432 (39.5)	18, 966 (46.4)	6,523 (41.8)	10,605 (48.8)
History of, n (%)				
Cardiovascular diseases[1]	15,646 (31.8)	19,933 (48.8)	5,162 (33.1)	9,110 (41.9)
Arthritis	15,706 (31.9)	13,929 (34.1)	7,937 (50.8)	9,873 (45.4)
Osteoporosis	2,538 (5.2)	1,660 (4.1)	1,016 (6.5)	161 (5.3)
Diabetes mellitus	3,399 (6.9)	3,848 (9.4)	1,032 (6.6)	1,801 (8.3)

[1]Coronary artery disease, heart attack, hypertension, stroke

Cancer. Author manuscript; available in PMC 2022 September 01.

Table 2.

Characteristics of PLCO Trial Participants in the Incident and Recurrent Adenoma Analyses by Case and Control Status

	Incident adenoma		Recurrent adenoma	
Characteristic	**Cases (n= 1221)**	**Controls (n= 19,626)**	**Cases (n= 862)**	**Controls (n= 877)**
Age in years, mean (IQR)	62.4 (8.6)	62.7 (8.3)	63.3 (7.7)	63.1 (8.4)
Male, n (%)	806 (66.0)	10,699 (54.5)	614 (71.2)	499 (56.9)
White, n (%)	1,095 (89.7)	17,187 (87.6)	786 (91.2)	836 (95.3)
Family history of colorectal cancer, n (%)	125 (10.2)	1,691 (8.6)	106 (12.3)	105 (12.0)
Body mass index in kg/m^2, mean (IQR)	27.6 (5.7)	27.1 (5.4)	27.9 (5.6)	27.4 (5.6)
Physical activity >3 hours/week, n (%)	261 (21.4)	4,587 (23.4)	192 (22.3)	192 (21.9)
Cigarette smoking, n (%)				
Current	136 (11.1)	1,053 (5.4)	129 (15.0)	125 (14.3)
Former	566 (46.4)	8,076 (41.1)	437 (50.7)	415 (47.3)
History of, n (%)				
Cardiovascular diseases[1]	440 (36.0)	6,859 (34.9)	314 (36.4)	310 (35.3)
Arthritis	363 (29.7)	6,630 (33.8)	265 (30.7)	298 (34.0)
Osteoporosis	30 (2.5)	742 (3.8)	20 (2.3)	22 (2.5)
Diabetes mellitus	88 (7.2)	1,204 (6.1)	59 (6.8)	68 (7.8)

[1] Coronary artery disease, heart attack, hypertension, stroke

Table 3.

Aspirin/Ibuprofen Use and the Risk of Incident Colorectal Adenoma in the PLCO Cancer Screening Trial

NSAID use (times/month)	Controls	Incident Adenoma Overall		Advanced		Non-advanced	
		Cases	OR (95% CI)*	Cases	OR (95% CI)*	Cases	OR (95% CI)*
Aspirin ^							
<4	11979	743	1.00	181	1.00	370	1.00
4 - <30	2682	152	0.87 (0.72, 1.04)	29	0.69 (0.47, 1.03)	76	0.87 (0.67, 1.12)
≥30	4965	326	0.92 (0.80, 1.06)	77	0.86 (0.65, 1.13)	166	0.95 (0.78, 1.15)
P, trend			0.12		0.07		0.48
Ibuprofen ^							
<4	16172	1027	1.00	253	1.00	511	1.00
4 - <30	1664	106	0.98 (0.79, 1.21)	20	0.76 (0.48, 1.21)	52	0.97 (0.72, 1.30)
≥30	1790	88	**0.76 (0.60, 0.95)**	14	**0.48 (0.28, 0.83)**	49	0.87 (0.64, 1.18)
P, trend			**0.04**		**0.005**		0.29
Combined use							
<4	9934	623	1.00	157	1.00	312	1.00
4 - <30	3488	225	0.97 (0.83, 1.14)	45	0.77 (0.55, 1.08)	110	0.95 (0.76, 1.18)
30 - <60	3967	253	0.88 (0.75, 1.02)	64	0.84 (0.62, 1.13)	129	0.90 (0.73, 1.11)
≥60	2237	120	**0.79 (0.64, 0.97)**	21	**0.53 (0.33, 0.84)**	61	0.82 (0.62, 1.09)
P, trend			**0.01**		**0.008**		0.13

*The Odds Ratio (OR) and 95% confidence interval (CI) were calculated by using unconditional logistic regression and adjusted for study center, race, sex, family history of colorectal cancer, smoking history, body mass index, age at the T3/T5 flexible sigmoidoscopy screen, and the study year of the repeat flexible sigmoidoscopy screen (T3 orT5)

^Aspirin use is adjusted for Ibuprofen use and vice versa

Table 4.

Aspirin/Ibuprofen Use and the Risk of Recurrent Colorectal Adenoma in the PLCO Cancer Screening Trial

NSAID use (times/month)	Controls	Recurrent Adenoma Overall		Advanced		Non-advanced	
		Cases	OR (95% CI)*	Cases	OR (95% CI)*	Cases	OR (95% CI)*
Aspirin ^							
<4	553	544	1.00	154	1.00	390	1.00
4 - <30	126	109	0.87 (0.64, 1.20)	19	**0.55 (0.31, 0.97)**	90	0.99 (0.71, 1.39)
≥30	198	209	0.90 (0.69, 1.17)	39	**0.56 (0.36, 0.87)**	170	1.05 (0.79, 1.38)
P, trend			0.47		**0.006**		0.63
Ibuprofen ^							
<4	736	737	1.00	185	1.00	552	1.00
4 - <30	77	68	0.87 (0.59, 1.27)	10	0.55 (0.26, 1.15)	58	0.94 (0.63, 1.40)
≥30	64	57	1.15 (0.75, 1.77)	17	1.31 (0.68, 2.54)	40	1.07 (0.67, 1.72)
P, trend			0.75		0.52		0.79
Combined use							
<4	462	478	1.00	136	1.00	342	1.00
4 - <30	166	139	0.81 (0.61, 1.08)	24	**0.49 (0.29, 0.82)**	115	0.92 (0.68, 1.26)
30 - <60	178	183	0.87 (0.66, 1.14)	32	**0.50 (0.31, 0.80)**	151	1.03 (0.77, 1.37)
≥60	71	62	0.91 (0.59, 1.38)	20	1.09 (0.58, 2.04)	42	0.83 (0.52, 1.33)
P, trend			0.29		0.06		0.69

*The Odds Ratio (OR) and 95% confidence interval (CI) were calculated by using unconditional logistic regression and adjusted for study center, race, sex, family history of colorectal cancer, smoking history, body mass index, age at baseline, number of follow-up colonoscopies, and follow-up time from baseline endoscopy

^Aspirin use is adjusted for Ibuprofen use and vice versa

Table 5.

Aspirin/Ibuprofen Use and the Risk of Colorectal Cancer in the PLCO Cancer Screening Trial

NSAID use (times/month)	Controls	Colorectal Cancer Overall		Proximal Colon		Distal Colon		Rectum	
		Cases	HR (95% CI)*	Cases	HR (95% CI)*	Cases	HR (95% CI)*	Cases	HR (95% CI)*
Aspirin ^									
<4	75905	1817	1.00	970	1.00	504	1.00	315	1.00
4 - <30	16084	309	**0.79 (0.70, 0.89)**	169	**0.80 (0.68, 0.94)**	78	**0.73 (0.57, 0.93)**	57	0.86 (0.64, 1.14)
≥30	32639	700	**0.88 (0.81, 0.96)**	378	0.89 (0.79, 1.00)	180	**0.82 (0.69, 0.98)**	133	0.97 (0.79, 1.19)
P, trend			**<0.0001**		**0.008**		**0.003**		0.39
Ibuprofen ^									
<4	101210	2375	1.00	1272	1.00	643	1.00	423	1.00
4 - <30	11432	231	0.92 (0.80, 1.05)	133	0.98 (0.82, 1.18)	57	0.84 (0.64, 1.11)	40	0.88 (0.63, 1.23)
≥30	11986	220	**0.81 (0.70, 0.93)**	112	**0.75 (0.62, 0.91)**	62	0.87 (0.66, 1.13)	42	0.92 (0.67, 1.27)
P, trend			**0.003**		**0.0091**		0.23		0.38
Combined use									
<4	61849	1545	1.00	824	1.00	422	1.00	275	1.00
4 - <30	22035	432	**0.79 (0.71, 0.88)**	240	**0.82 (0.71, 0.94)**	113	**0.76 (0.62, 0.94)**	73	**0.75 (0.58, 0.98)**
30 - <60	25437	550	**0.85 (0.77, 0.94)**	293	**0.84 (0.73, 0.96)**	145	0.84 (0.69, 1.02)	105	0.91 (0.73, 1.15)
≥60	15307	299	**0.79 (0.69, 0.89)**	160	**0.77 (0.65, 0.92)**	82	0.81 (0.64, 1.04)	52	0.82 (0.60, 1.10)
P, trend			**<0.0001**		**0.0003**		**0.02**		0.15

*Hazard ratio (HR) and 95% confidence interval (CI) calculated by Cox proportional hazards regression adjusted for study center, race, sex, family history of colorectal cancer, smoking history, body mass index, trial arm, and calendar year at baseline (age was the underlying time metric)

^Aspirin use is adjusted for Ibuprofen use and vice versa