5-11-2021

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Recommended Citation

Chudy-Onwugaje K, Huang WY, Su LJ, Purdue MP, Johnson CC, Wang L, Katki HA, Barry KH, and Berndt SI. Aspirin, ibuprofen, and reduced risk of advanced colorectal adenoma incidence and recurrence and colorectal cancer in the PLCO Cancer Screening Trial. Cancer 2021.

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Original Article

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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BACKGROUND: Studying the differential impact of aspirin and other nonsteroidal anti-inflammatory drugs 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, the authors prospectively evaluated the association between aspirin and ibuprofen use and incident distal adenoma (1221 cases), recurrent adenoma (862 cases), and incident colorectal cancer (CRC; 2826 cases) among men and women in the population-based Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. With multivariable-adjusted models, odds ratio (ORs) and 95% confidence intervals (CIs) for adenoma incidence and recurrence and hazard ratios (HRs) and 95% CIs for incident CRC were determined. **RESULTS:** The authors observed a significantly reduced risk of incident adenoma with ibuprofen use (≥30 vs <4 pills per month: OR, 0.76 [95% CI, 0.60-0.95]; P_{trend} = .04), particularly advanced adenoma (OR, 0.48 [95% CI, 0.28-0.83]; P_{trend} = .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 per 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} <.0001) and ibuprofen use (HR, 0.81 [95% CI, 0.70-0.93); P_{trend} = 0.003) ≥30 versus <4 pills per month were significantly associated with reduced CRC risk. **CONCLUSIONS:** In this large prospective study with long-term follow-up, a beneficial role for not only aspirin, but also ibuprofen, in preventing advanced adenoma and curbing progression to recurrence and cancer among older adults was observed. ***Cancer* 2021;0:1-11**. *© 2021 American Cancer Society. This article has been contributed to by US Government employees and their work is in the public domain in the USA.*

KEYWORDS: aspirin, colorectal cancer, ibuprofen, incident adenoma, recurrent adenoma.

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 nonsteroidal anti-inflammatory drugs (NSAIDs) have been identified in preclinical 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

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We thank the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial participants, as well as the study management team at the Division of Cancer Epidemiology and Genetics and the Division of Cancer Prevention of the National Cancer Institute (National Institutes of Health, Department of Health and Human Services), staff at Information Management Services, Inc, and staff at Westat, Inc. In particular, we 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 Centers for Disease Control and Prevention, National Program for Central Registries, local states, or the National Cancer Institutes, Surveillance, Epidemiology, and End Results program. The results reported here and the conclusions derived are the sole responsibility of the authors.

The first 2 authors contributed equally to this article.

The last 2 authors contributed equally to this article.

DOI: 10.1002/cncr.33623, **Received:** December 6, 2020; **Revised:** March 23, 2021; **Accepted:** March 29, 2021, **Published online** Month 00, 2021 in Wiley Online Library (wileyonlinelibrary.com)

and COX-2, prevents the conversion of arachidonic acid to prostaglandins, which are important mediators of inflammation. COX-independent mechanisms have also been proposed for the anticarcinogenic 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 end point 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 posttrial 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 to 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 2 nonselective COX inhibitors: aspirin, which binds irreversibly to COX and ibuprofen, a reversible COX inhibitor.[27,28]

MATERIALS AND METHODS

Study Design

This is a prospective study of participants in the PLCO Cancer Screening Trial, which is a randomized, multicenter 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 between 55 and 74 years of age 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 health care providers for follow-up and 80.5% had a diagnostic intervention.[31] Trained staff reviewed all available medical records related to the ensuing workup 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; approximately 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 (ie, negative baseline trial screen), and had an adequate T3/T5 follow-up flexible sigmoidoscopy 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 1221 incident distal colorectal adenoma cases (806 men and 415 women) and 19,626 controls (10,699 men and 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 1 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 (ie, those with an 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 that were found to have an adenoma on any later surveillance screen, whereas 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 and 248 women) and 877 controls (499 men and 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, 2826 were diagnosed with colorectal cancer over the median follow-up period of 13 years.

Exposure Assessment

NSAID use was evaluated based on participant responses to 4 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 before screening. Those who reported regular use of either product were asked 2 additional questions about the usual number of pills taken in the preceding 12 months, and response options were as follows: 1 per day, ≥2 per day, 1 per week, 2 per week, 3 to 4 per week, <2 per month, and 2 to 3 per 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 per month (including those reporting irregular use), 4 to 29 per month, and ≥30 per month. We also created a variable for the combined use of aspirin and ibuprofen and categorized this as follows: <4 per month (including irregular use), 4 to 29 per month, 30 to 59 per month, and ≥60 per month. We collapsed the 2 most frequent use groups (30-59 per month and ≥60 per month) into 1 (≥30 per month) for aspirin use and ibuprofen use individually because of 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

TABLE 1. Characteristics of 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, mean (IQR), y	63.1 (8.7)	63.8 (8.8)	62.0 (8.3)	62.5 (8.6)
Male, No. (%)	24,178 (49.1)	24,493 (60.0)	5539 (35.5)	10,528 (48.4)
White, No. (%)	42,029 (85.3)	36,576 (89.5)	13,900 (89.0)	19,370 (89.1)
Intervention arm, No. (%)	25,430 (51.6)	21,096 (51.6)	8121 (52.0)	11,053 (50.8)
Family history of colorectal cancer, No. (%)	4890 (9.9)	3907 (9.6)	1552 (9.9)	2155 (9.9)
BMI, mean (IQR), kg/m^2	27.0 (5.6)	27.3 (5.5)	27.8 (6.3)	27.8 (5.9)
Physical activity >3 h/wk, No. (%)	5054 (10.3)	4267 (10.4)	1449 (9.3)	2083 (9.6)
Cigarette smoking, No. (%)				
Current	5204 (10.6)	4457 (10.9)	1766 (11.3)	2447 (11.3)
Former	19,432 (39.5)	18, 966 (46.4)	6523 (41.8)	10,605 (48.8)
History of, No. (%)				
Cardiovascular diseases[a]	15,646 (31.8)	19,933 (48.8)	5162 (33.1)	9110 (41.9)
Arthritis	15,706 (31.9)	13,929 (34.1)	7937 (50.8)	9873 (45.4)
Osteoporosis	2538 (5.2)	1660 (4.1)	1016 (6.5)	1161 (5.3)
Diabetes mellitus	3399 (6.9)	3848 (9.4)	1032 (6.6)	1801 (8.3)

Abbreviations: BMI, body mass index; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drugs; PLCO, Prostate, Lung, Colorectal, and Ovarian.
[a]Coronary artery disease, heart attack, hypertension, and stroke.

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% CIs for the risk of incident CRC with NSAID use. With <4 pills per 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 (eg, physical activity) and only those that changed the β 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 (ie, 0, 1, 2) for the multilevel frequency categories of use. We also performed separate analyses by anatomic site (proximal colon, distal colon, or rectum), adenoma subtype (advanced or nonadvanced), 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 <.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% of the subjects were male, and the mean BMI was 27.3 kg/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, whereas 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 was recorded in 17% of the population (Table 1). Among the PLCO Trial participants with a negative baseline screen and adequate T3/T5 screen, incident adenoma

TABLE 2. Characteristics of PLCO Trial Participants in the Incident and Recurrent Adenoma Analyses by Case and Control Status

Characteristic	Incident Adenoma		Recurrent Adenoma	
	Cases (n = 1221)	Controls (n = 19,626)	Cases (n = 862)	Controls (n = 877)
Age, mean (IQR), y	62.4 (8.6)	62.7 (8.3)	63.3 (7.7)	63.1 (8.4)
Male, No. (%)	806 (66.0)	10,699 (54.5)	614 (71.2)	499 (56.9)
White, No. (%)	1095 (89.7)	17,187 (87.6)	786 (91.2)	836 (95.3)
Family history of colorectal cancer, No. (%)	125 (10.2)	1691 (8.6)	106 (12.3)	105 (12.0)
BMI 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 h/wk, No. (%)	261 (21.4)	4587 (23.4)	192 (22.3)	192 (21.9)
Cigarette smoking, No. (%)				
Current	136 (11.1)	1053 (5.4)	129 (15.0)	125 (14.3)
Former	566 (46.4)	8076 (41.1)	437 (50.7)	415 (47.3)
History of, No. (%)				
Cardiovascular diseases[a]	440 (36.0)	6859 (34.9)	314 (36.4)	310 (35.3)
Arthritis	363 (29.7)	6630 (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)	1204 (6.1)	59 (6.8)	68 (7.8)

Abbreviations: BMI, body mass index; IQR, interquartile range; PLCO, Prostate, Lung, Colorectal, and Ovarian.
[a]Coronary artery disease, heart attack, hypertension, and stroke.

TABLE 3. Aspirin/Ibuprofen Use and the Risk of Incident Colorectal Adenoma in the PLCO Cancer Screening Trial

NSAID Use (Times/mo)	Controls	Incident Adenoma Overall		Advanced		Nonadvanced	
		Cases	OR (95% CI)[a]	Cases	OR (95% CI)[a]	Cases	OR (95% CI)[a]
Aspirin[b]							
<4	11,979	743	1.00	181	1.00	370	1.00
4 to <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}			.12		.07		.48
Ibuprofen[b]							
<4	16,172	1027	1.00	253	1.00	511	1.00
4 to <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}			.04		.005		.29
Combined use							
<4	9934	623	1.00	157	1.00	312	1.00
4 to <30	3488	225	0.97 (0.83-1.14)	45	0.77 (0.55-1.08)	110	0.95 (0.76-1.18)
30 to <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}			.01		.008		.13

Abbreviations: BMI, body mass index; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PLCO, Prostate, Lung, Colorectal, and Ovarian.
[a]The OR and 95% CI were calculated by using unconditional logistic regression and adjusted for study center, race, sex, family history of colorectal cancer, smoking history, BMI, age at the T3/T5 flexible sigmoidoscopy screen, and the study year of the repeat flexible sigmoidoscopy screen (T3 or T5).
[b]Aspirin use is adjusted for ibuprofen use and vice versa.

cases were more likely to be male, have a family history of CRC, 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 per month: OR, 0.76 [95% CI, 0.60-0.95]; P_{trend} = .04; Table 3). The protective association was stronger for advanced adenoma (≥30 vs <4 pills per month: OR, 0.48 [95% CI, 0.28-0.83]; P_{trend} = .005) with no significant risk observed for nonadvanced adenoma (≥30 vs <4 pills per month: OR, 0.87 [95% CI,

TABLE 4. Aspirin/Ibuprofen Use and the Risk of Recurrent Colorectal Adenoma in the PLCO Cancer Screening Trial

NSAID Use (Times/mo)	Controls	Recurrent Adenoma Overall		Advanced		Nonadvanced	
		Cases	OR (95% CI)[a]	Cases	OR (95% CI)[a]	Cases	OR (95% CI)[a]
Aspirin[b]							
<4	553	544	1.00	154	1.00	390	1.00
4 to <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}			.47		.006		.63
Ibuprofen[b]							
<4	736	737	1.00	185	1.00	552	1.00
4 to <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}			.75		.52		.79
Combined use							
<4	462	478	1.00	136	1.00	342	1.00
4 to <30	166	139	0.81 (0.61-1.08)	24	0.49 (0.29-0.82)	115	0.92 (0.68- 1.26)
30 to <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}			.29		.06		.69

Abbreviations: BMI, body mass index; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PLCO, Prostate, Lung, Colorectal, and Ovarian.

[a]The OR and 95% CI were calculated by using unconditional logistic regression and adjusted for study center, race, sex, family history of colorectal cancer, smoking history, BMI, age at baseline, number of follow-up colonoscopies, and follow-up time from baseline endoscopy.

[b]Aspirin use is adjusted for ibuprofen use and vice versa.

0.64-1.18]; $P_{trend} = .29$; $P_{heterogeneity\ for\ advanced\ vs\ nonadvanced} = .06$). Similarly, combined use of aspirin and ibuprofen was associated with a significantly lower risk of incident distal adenoma overall (≥60 vs <4 pills per month: OR, 0.79 [95% CI, 0.64-0.97]; $P_{trend} = .01$), with greater benefit for advanced adenoma (≥60 vs <4 pills per month: OR, 0.53 [95% CI, 0.33-0.84]; $P_{trend} = .008$) and no significant protection against nonadvanced adenoma (≥60 vs <4 pills per month: OR, 0.82 [95% CI, 0.62-1.09]; $P_{trend} = .13$; $P_{heterogeneity\ for\ advanced\ vs\ nonadvanced} = .18$). Although there was no evidence of an association between aspirin use and the risk of incident distal colorectal adenoma overall (≥30 vs <4 pills per month: OR, 0.92 [95% CI, 0.80-1.06]; $P_{trend} = .12$), we observed some evidence of a trend between increased aspirin use and reduced risk of advanced adenoma (≥30 vs <4 pills per month: OR, 0.86 [95% CI, 0.65-1.13]; $P_{trend} = .07$). No significant differences in risk were observed by anatomic site (ie, distal colon vs rectum) with the use of aspirin, ibuprofen, or both combined ($P_{heterogeneity} > .10$ 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 per month: OR, 0.90 [95% CI, 0.69-1.17]; $P_{trend} = .47$), but aspirin use was significantly associated with a reduced risk of advanced recurrent adenoma (≥30 vs <4 pills per month: OR, 0.56 [95% CI, 0.36-0.87]; $P_{trend} = .006$; Table 4). This beneficial association was not observed for nonadvanced recurrent adenoma (≥30 vs <4 pills per month: OR, 1.05 [95% CI, 0.79-1.38]; $P_{trend} = .63$), and the difference in risk between advanced and nonadvanced adenoma was statistically significant ($P_{heterogeneity} = .001$). 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 (ie, 4 to <30 [OR, 0.49 (95% CI, 0.29-0.82)] and 30 to <60 pills per months [OR, 0.50 (95% CI, 0.31-0.80)]). No protective associations were observed for combined use with regard to nonadvanced recurrent adenoma ($P_{trend} = .69$), and the difference between advanced and nonadvanced adenoma was significant ($P_{heterogeneity} = .047$). There were no significant associations between ibuprofen use and the risk of recurrent adenoma (Table 4). No significant risk differences were observed by anatomic site (ie, proximal colon, distal colon, and rectum).

Colorectal Cancer Incidence

We observed a decrease in the risk of colorectal cancer overall with increased use of aspirin (≥30 vs <4 pills per month: HR, 0.88 [95% CI, 0.81-0.96]; $P_{trend} < .0001$), ibuprofen (≥30 vs <4 pills per month: HR, 0.81 [95% CI, 0.70-0.93]; $P_{trend} = .003$) and the combined use of both medications (≥60 vs <4 pills per month: HR, 0.79

TABLE 5. Aspirin/Ibuprofen Use and the Risk of Colorectal Cancer in the PLCO Cancer Screening Trial

NSAID Use (Times/mo)	Controls	Colorectal Cancer Overall		Proximal Colon		Distal Colon		Rectum	
		Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]
Aspirin[b]									
<4	75,905	1817	1.00	970	1.00	504	1.00	315	1.00
4 to <30	16,084	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	32,639	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}			<.0001		.008		.003		.39
Ibuprofen[b]									
<4	101,210	2375	1.00	1272	1.00	643	1.00	423	1.00
4 to <30	11,432	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	11,986	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}			.003		.0091		.23		.38
Combined use									
<4	61,849	1545	1.00	824	1.00	422	1.00	275	1.00
4 to <30	22,035	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 to <60	25,437	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	15,307	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}			<.0001		.0003		.02		.15

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drugs; PLCO, Prostate, Lung, Colorectal, and Ovarian.
[a]HR and 95% CI calculated by Cox proportional hazards regression adjusted for study center, race, sex, family history of colorectal cancer, smoking history, BMI, trial arm, and calendar year at baseline (age was the underlying time metric).
[b]Aspirin use is adjusted for ibuprofen use and vice.

[95% CI, 0.69-0.89]; P_{trend} <.0001; Table 5). Overall, there were no significant differences by anatomic location between NSAID use and cancer risk ($P_{heterogeneity}$ > .10). With aspirin use, we observed a significant inverse association for cancers in the proximal (≥30 vs <4 pills per month: HR, 0.89 [95% CI, 0.79-1.00]; P_{trend} = .008) and distal colon (≥30 vs <4 pills per month: HR, 0.82 [95% CI, 0.69-0.98]; P_{trend} = .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 per month: HR, 0.77 [95% CI, 0.65-0.92]; P_{trend} = .0003) and distal colon (≥60 vs <4: HR, 0.81 [95% CI, 0.64-1.04]; P_{trend} = .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} = .0091) but not in the distal colon (≥30 vs <4: HR, 0.87 [95% CI, 0.66-1.13]; P_{trend} = .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 nonadvanced 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 nonadvanced recurrent adenoma. Finally, we observed significant inverse associations between the use of aspirin and 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 before 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 toward a reduced risk of advanced incident distal adenoma with increased aspirin use (P_{trend} = .07). Among adenomas, the advanced ones are of utmost clinical concern because of 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, because 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] whereas 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 our study, 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 nonadvanced recurrent adenoma or recurrent adenoma overall. Our finding for advanced recurrent adenoma is consistent with the findings of a meta-analysis of 5 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 per 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 between 45 and 75 years of age 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. Although there are no comparable ibuprofen studies that have evaluated this association, 3 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 because of 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 10 prospective studies (RR, 0.80; 95% CI, 0.72-0.88), although ibuprofen was not evaluated specifically.[21] Although 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 end point have yielded more mixed results on the association between aspirin and CRC. In the ASPREE trial among elderly populations in Australia and the United States (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 2 smaller trials in the United Kingdom of a higher daily dose of aspirin (300-1200 mg) administered over a period of 1 to 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 4 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 health care coverage or indication, limiting selection bias. Regarding limitations of our study, as the PLCO used 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 because of 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. Although 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] Because information on NSAID use was obtained prospectively in this study, any misclassification of NSAID use because of inaccurate reporting is likely to be nondifferential, 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 because of 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. Because 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 use of NSAIDs for chemoprevention recommendations.

FUNDING SUPPORT

Kenechukwu 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. Kathryn Hughes Barry is supported by K07 CA230182 from the National Cancer Institute, National Institutes of Health. Wen-Yi Huang, Mark P. Purdue, Lingxiao Wang, Hormuzd A. Katki, and Sonja I. 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 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, National Institutes of Health, Department Health and Human Services.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Kenechukwu Chudy-Onwugaje: Conceptualization and writing–original draft. **Wen-Yi Huang:** Conceptualization, data curation, investigation, project administration, and writing–review and editing. **L. Joseph Su:** Formal analysis. **Mark P. Purdue:** Data curation. **Christine C. Johnson:** Data curation. **Lingxiao Wang:** Methodology. **Hormuzd A. Katki:** Methodology. **Kathryn Hughes Barry:** Conceptualization, supervision, and writing–review and editing. **Sonja I. Berndt:** Conceptualization, investigation, funding acquisition, supervision, and writing–review and editing. All authors participated in reviewing and revising the manuscript.

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).

REFERENCES

1. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:145-164.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74:2913-2921.
3. Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology*. 2015;149:1731-1741.
4. Honein-AbouHaidar GN, Kastner M, Vuong V, et al. Systematic review and meta-study synthesis of qualitative studies evaluating facilitators and barriers to participation in colorectal cancer screening. *Cancer Epidemiol Biomarkers Prev*. 2016;25:907-917.
5. Umezawa S, Higurashi T, Komiya Y, et al. Chemoprevention of colorectal cancer: past, present, and future. *Cancer Sci*. 2019;110:3018-3026.
6. Drew DA, Cao Y, Chan AT. Aspirin and colorectal cancer: the promise of precision chemoprevention. *Nat Rev Cancer*. 2016;16:173-186.
7. Baron JA. Epidemiology of non-steroidal anti-inflammatory drugs and cancer. *Prog Exp Tumor Res*. 2003;37:1-24.
8. Oshima M, Dinchuk JE, Kargman SL, et al. Suppression of intestinal polyposis in Apc delta716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). *Cell*. 1996;87:803-809.
9. Baron JA, Sandler RS, Bresalier RS, et al. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. *Gastroenterology*. 2006;131:1674-1682.
10. Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR, ukCAP Trial Group. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. *Gastroenterology*. 2008;134:29-38.
11. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet*. 2010;376:1741-1750.
12. Peleg II, Wilcox CM. The role of eicosanoids, cyclooxygenases, and nonsteroidal anti-inflammatory drugs in colorectal tumorigenesis and chemoprevention. *J Clin Gastroenterol*. 2002;34:117-125.
13. Taketo MM. Cyclooxygenase-2 inhibitors in tumorigenesis (part I). *J Natl Cancer Inst*. 1998;90:1529-1536.
14. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst*. 2002;94:252-266.
15. Din FV, Stark LA, Dunlop MG. Aspirin-induced nuclear translocation of NFkappaB and apoptosis in colorectal cancer is independent of p53 status and DNA mismatch repair proficiency. *Br J Cancer*. 2005;92:1137-1143.
16. Arber N. Cyclooxygenase-2 inhibitors in colorectal cancer prevention: point. *Cancer Epidemiol Biomarkers Prev*. 2008;17:1852-1857.
17. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell*. 1990;61:759-767.
18. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol*. 2012;13:518-527.
19. Ye X, Fu J, Yang Y, Chen S. Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies. *PLoS One*. 2013;8:e57578.
20. McNeil JJ, Gibbs P, Orchard SG, et al. Effect of aspirin on cancer incidence and mortality in older adults. *J Natl Cancer Inst*. 2020.
21. Tomic T, Dominguez-Lopez S, Barrios-Rodriguez R. Non-aspirin nonsteroidal anti-inflammatory drugs in prevention of colorectal cancer in people aged 40 or older: a systematic review and meta-analysis. *Cancer Epidemiol*. 2019;58:52-62.

22. Veettil SK, Lim KG, Ching SM, Saokaew S, Phisalprapa P, Chaiyakunapruk N. Effects of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs on the incidence of recurrent colorectal adenomas: a systematic review with meta-analysis and trial sequential analysis of randomized clinical trials. *BMC Cancer*. 2017;17:763.
23. Wang Y, Zhang FC, Wang YJ. The efficacy and safety of non-steroidal anti-inflammatory drugs in preventing the recurrence of colorectal adenoma: a meta-analysis and systematic review of randomized trials. *Colorectal Dis*. 2015;17:188-196.
24. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Five-year efficacy and safety analysis of the Adenoma Prevention with Celecoxib Trial. *Cancer Prev Res (Phila)*. 2009;2:310-321.
25. Arber N, Spicak J, Racz I, et al. Five-year analysis of the prevention of colorectal sporadic adenomatous polyps trial. *Am J Gastroenterol*. 2011;106:1135-1146.
26. Chan AT, Giovannucci EL, Schernhammer ES, et al. A prospective study of aspirin use and the risk for colorectal adenoma. *Ann Intern Med*. 2004;140:157-166.
27. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med*. 1998;104:413-421.
28. Zapolska-Downar D, Naruszewicz M. A pleiotropic antiatherogenic action of ibuprofen. *Med Sci Monit*. 2001;7:837-841.
29. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. *Control Clin Trials*. 2000;21(6 suppl):273S-309S.
30. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med*. 2012;366:2345-2357.
31. Weissfeld JL, Schoen RE, Pinsky PF, et al. Flexible sigmoidoscopy in the randomized prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial: added yield from a second screening examination. *J Natl Cancer Inst*. 2012;104:280-289.
32. Kitahara CM, Berndt SI, de Gonzalez AB, et al. Prospective investigation of body mass index, colorectal adenoma, and colorectal cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *J Clin Oncol*. 2013;31:2450-2459.
33. Pinsky PF, Schoen RE, Weissfeld JL, et al. The yield of surveillance colonoscopy by adenoma history and time to examination. *Clin Gastroenterol Hepatol*. 2009;7:86-92.
34. Johnson CC, Hayes RB, Schoen RE, Gunter MJ, Huang WY, Team PT. Non-steroidal anti-inflammatory drug use and colorectal polyps in the prostate, lung, colorectal, and ovarian cancer screening trial. *Am J Gastroenterol*. 2010;105:2646-2655.
35. Wang LG, Graubard BI, Katki HA, Li Y. Improving external validity of epidemiologic cohort analyses: a kernel weighting approach. *J R Stat Soc Ser A Stat Soc*. 2020;183:1293-1311.
36. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol*. 1993;138:923-936.
37. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2012;143:844-857.
38. Dube C, Rostom A, Lewin G, 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;146:365-375.
39. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. *Ann Intern Med*. 1994;121:241-246.
40. Cao Y, Rosner BA, Ma J, et al. Assessing individual risk for high-risk colorectal adenoma at first-time screening colonoscopy. *Int J Cancer*. 2015;137:1719-1728.
41. Williams CD, Chan AT, Elman MR, et al. Aspirin use among adults in the U.S.: results of a national survey. *Am J Prev Med*. 2015;48:501-508.
42. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med*. 2006;355:885-895.
43. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med*. 2006;355:873-884.
44. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet*. 2004;364:2021-2029.
45. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. *Ann Oncol*. 2012;23:1403-1415.
46. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. *J Natl Cancer Inst*. 1993;85:1220-1224.
47. Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. *Ann Intern Med*. 2013;159:77-85.
48. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed)*. 1988;296:313-316.
49. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54:1044-1054.
50. Flossmann E, Rothwell PM; British Doctors Aspirin Trial; UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet*. 2007;369:1603-1613.
51. Chubak J, Whitlock EP, Williams SB, et al. Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164:814-825.
52. Hisabe T, Hirai F, Matsui T. Development and progression of colorectal cancer based on follow-up analysis. *Dig Endosc*. 2014;26(2 suppl):73-77.
53. Murphy N, Ward HA, Jenab M, et al. Heterogeneity of colorectal cancer risk factors by anatomical subsite in 10 European countries: a multinational cohort study. *Clin Gastroenterol Hepatol*. 2019;17:1323-1331.
54. Larsson SC, Giovannucci E, Wolk A. Long-term aspirin use and colorectal cancer risk: a cohort study in Sweden. *Br J Cancer*. 2006;95:1277-1279.
55. Mahipal A, Anderson KE, Limburg PJ, Folsom AR. Nonsteroidal anti-inflammatory drugs and subsite-specific colorectal cancer incidence in the Iowa women's health study. *Cancer Epidemiol Biomarkers Prev*. 2006;15:1785-1790.
56. Garcia-Rodriguez LA, Huerta-Alvarez C. Reduced risk of colorectal cancer among long-term users of aspirin and non-aspirin nonsteroidal antiinflammatory drugs. *Epidemiology*. 2001;12:88-93.
57. Rahme E, Barkun AN, Toubouti Y, Bardou M. The cyclooxygenase-2-selective inhibitors rofecoxib and celecoxib prevent colorectal neoplasia occurrence and recurrence. *Gastroenterology*. 2003;125:404-412.
58. Pit S, Byles J. Older Australians' medication use: self-report by phone showed good agreement and accuracy compared with home visit. *J Clin Epidemiol*. 2010;63:428-434.