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Non-Steroidal Anti-Inflammatory Drug Use and Colorectal Polyps in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

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Abstract

OBJECTIVES—Non-steroidal anti-inflammatory drugs (NSAIDs) have been documented in animal and human studies to reduce risk for colorectal cancer and adenomatous polyps, but risk modification for subgroups of the population and effects on hyperplastic polyps have been less studied.

METHODS—Data on recent use of two frequently ingested NSAIDs, aspirin and ibuprofen, were collected at baseline from participants aged 55–74 years in the 10 centers of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). Participants randomized to the intervention arm of the trial received a flexible sigmoidoscopy during a baseline examination. Follow-up of detected polyps was accomplished outside the Trial setting and relevant records were sought and abstracted. Cases ($n = 4,017$) included subjects with a biopsy-proven polyp in the left side of the colon (descending colon, sigmoid, and rectum) detected as a consequence of PLCO screening; controls ($n = 38,396$) were subjects with no left-sided colon polyp.

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CONFLICT OF INTEREST

Guarantor of the article: Christine Cole Johnson, PhD, MPH.

Specific author contributions: Planned the study as a steering committee member, oversaw data collection at one PLCO site, interpreted the analyses, and wrote the manuscript: Christine Cole Johnson; conducted the analyses, interpreted the analyses, and wrote the manuscript: Wen-Yi Huang; planned the study, interpreted the analyses, and wrote the manuscript: Richard B. Hayes; planned the study as a steering committee member, oversaw data collection at one PLCO site, and edited the manuscript: Robert E. Schoen; edited the manuscript: Marc J. Gunter. All authors approved the final draft.

Potential competing interests: None.

RESULTS—Regular use of aspirin (≥ 4 times/month) in the past year was inversely associated with hyperplastic polyps (odds ratios (OR) = 0.8, 95% confidence interval (CI) = 0.7–0.9), adenomatous polyps (OR = 0.8, 95% CI = 0.8–0.9), and advanced adenomas (OR = 0.8, 95% CI = 0.7–0.9). As frequency of aspirin use increased, the prevalence of polyps decreased significantly for each histological classification (*P* for trend = 0.0004). Similar patterns were found for adenomas and ibuprofen. Overall protection was consistent in both the descending colon or sigmoid and the rectum, but more evident in males. In males, the OR for heavy use of combined aspirin and ibuprofen (≥ 2 times/day) was 0.6 (95% CI = 0.5–0.8), as opposed to 0.9 (95% CI = 0.8–1.1) in females. The protective effects of NSAIDs for females were apparent only among those with body mass index (BMI) < 25 (OR = 0.8, 95% CI = 0.7–1.0 for regular use of NSAIDs; *P* interaction = 0.04). We also found a slightly stronger protection of NSAIDs in the 70–74 years age group compared with those aged 55–69 years.

CONCLUSIONS—This study of a large general risk population supports previous work that recent use of aspirin and ibuprofen is associated with a decreased risk of colorectal adenomas and demonstrates that this protective effect may be stronger in certain population subgroups and is also evident for aspirin and hyperplastic polyps.

INTRODUCTION

Laboratory, epidemiologic, and clinical trial research support the premise that non-selective non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen have a chemo-preventive effect against colorectal cancer (1–15). NSAIDs have also been shown to be inversely related with the incidence and recurrence of colorectal polyps, established precursors of colorectal cancer (2–4,9,13,16–19). Non-selective NSAIDs inhibit the activity of both cyclooxygenase-1 (COX-1) and COX-2, with aspirin preferentially inhibiting COX-1 activity at normal doses (6) and ibuprofen targeting both COX enzymes (20). The most widely recognized mechanism to explain the chemopreventative effects of NSAIDs on colorectal polyp development relates to the anti-inflammatory properties of NSAIDs. Specifically, the inhibition of COX activity leads to downregulation of the synthesis of prostaglandins, lipids that have a pivotal role in the development of the inflammatory response (5,8,21,22). However, there is also evidence to suggest that NSAIDs have pro-apoptotic properties, suppress angiogenesis, and operate through additional mechanisms that are cyclooxygenase independent (1,5–9,22–26).

As NSAIDs also have adverse affects, such as increased risk of gastric ulcer perforation and upper gastrointestinal bleeding, it is recognized that any chemopreventative recommendations associated with NSAID use will need to be tailored by individual cost-benefit assessment (3,24). However, few studies of the association of NSAID use and colorectal polyps in a general risk population undergoing colonic examination under highly controlled circumstances have been large enough to allow for the consideration of risk subgroups such as sex, age (especially older age), and body mass index (BMI) characteristics. Further, less data have been available concerning the association of NSAIDs with risk of hyperplastic polyps, lesions that have been generally thought not to have malignant potential, but have been hypothesized to be related to one subtype of colorectal cancer (27). The analyses presented here use data generated by the 56,175 men and women

undergoing flexible sigmoidoscopy screening examinations between September 1993 and September 2000 as part of the baseline intervention in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). Using a cross-sectional design, we investigated the relationship between recent use of the most commonly ingested NSAIDs, aspirin and ibuprofen, among population subgroups of the PLCO screened participants, and risk for polyp prevalence by histotype.

METHODS

Study population

Men and women 55 to 74 years of age were recruited to the PLCO Cancer Screening Trial beginning in 1993. This large trial, designed to test the effectiveness of screening procedures for these four cancers, is being conducted at 10 centers located throughout the United States (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St Louis, MO; and Washington, DC). The study was approved by the Institutional Review Boards of the NCI and all 10 centers, initially in 1991 and continuing to date, and written informed consent was obtained from each participant.

To be eligible for the trial, subjects must have been 55–74 years of age, have the ability to sign the consent form, not be undergoing treatment for cancer (excluding non-melanoma skin), have no history of cancer of the sites involved in the trial, no history of surgical removal of the prostate, colon or one lung, no current participation in another cancer screening or primary prevention trial, no use of Finasteride in the previous 6 months, and beginning in April 1995, no PSA test, colonoscopy, sigmoidoscopy, or barium enema in the previous 3 years. After recruitment, subjects completed a baseline risk factor survey that included questions on usual use of aspirin and ibuprofen in the previous year as well as sociodemographic, lifestyle, and medical history variables. At study entry, individuals in the intervention arm received a flexible sigmoidoscopic visualization of the distal colon (left side) up to 60 cm, which did not include removal of any detected lesions, but visualized polyps (up to 4) were documented. Participants who completed a sigmoidoscopic examination with results classified as “abnormal suspicious” (evidence of possible neoplasia such as polyp or mass) were advised to obtain further medical follow-up, which often entailed a colonoscopy (28). All available clinical and pathological reports regarding lesions removed during diagnostic and related surgical procedures were reviewed and coded by trained medical record abstractors.

Data were retrieved for these analyses on 14 March 2003 for those recruited and undergoing baseline screening from September 1993 through September 2000. Among the randomized participants, 56,175 had undergone an initial successful sigmoidoscopic screening examination (insertion to at least 50 cm with > 90% of mucosa visible or a suspect lesion identified), described in detail elsewhere (28). Of these, 56,081 (99.8%) had completed the baseline risk factor questionnaire. We excluded 6,895 (12.3%) of these participants because they had a self-reported history of one or more of these selected conditions: colorectal polyps ($n = 3,997$), ulcerative colitis ($n = 722$), Crohn’s disease ($n = 220$), familial polyposis

($n = 168$), Gardner's syndrome ($n = 133$), or a history of non-PLCO cancer other than non-melanoma skin cancer ($n = 2,556$), leaving 49,186 subjects in our base population.

As the flexible sigmoidoscopy procedure only examines the left side of the colon (descending colon, sigmoid colon, and rectum), we restricted our case group to polyps (adenomas or hyperplastic polyps) confirmed by follow-up in these locations. We did not include polyps found in other locations in the colon as examination of the remainder of the colon was not done for the control group. Subjects with left-sided invasive colon cancer or benign lesions not classified as polyps diagnosed as a consequence of baseline screening were excluded from these analyses, as were subjects with no evidence of adequate follow-up of abnormal suspicious findings in the subsequent 12 months or with pending results ($n = 4,738$; 9.6%). Subjects for which a benign polyp or a polyp with high-grade dysplasia was found but the location was undetermined were also excluded ($n = 209$; 0.4%).

All cases included in this study had a positive result on the screening examination followed by histological verification of colorectal polyps in the distal colon ($n = 5,663$). The cases were subclassified into subjects with hyperplastic polyps only ($n = 1,646$) and subjects with at least one adenoma, including cases with concurrent hyperplastic polyps ($n = 4,017$). The adenoma group was further classified into those with at least one advanced adenoma ($n = 1,571$), defined as large (> 1 cm), having villous elements (including villous or tubulovillous adenoma), or having high-grade dysplasia (carcinoma *in situ*). Controls were those individuals ($n = 38,396$) who screened negative for polyps of the distal colon ($n = 36,635$) or screened positive but were found on follow-up diagnostic examination not to have polyps of the distal colon ($n = 1,761$).

Exposure ascertainment

Two separate questions on the baseline survey asked whether participants regularly used aspirin and aspirin-containing products (e.g., Bayer, Bufferin, or Anacin) and/or ibuprofen and ibuprofen-containing products (Advil, Nuprin, or Motrin) in the 12 months prior to screening. Regular users of either products were asked to report the frequency of use of aspirin and/or ibuprofen in two additional questions, with the eight following possible response categories: no regular use, < 2 /month, 2–3/month, 1/week, 2/week, 3–4/week, 1/day, and ≥ 2 /day. To categorize the frequency of medication use, we converted the responses for each drug into a frequency of pills per month, assuming 30 days and 4 weeks/month. Four frequency categories for aspirin, for ibuprofen and for the two combined, were defined based on the number of pills per month, which also reflect commonly prescribed doses: < 4 /month (irregular use), 4 to 29/month (low use), 30–59/month (moderate use), and ≥ 60 /month (heavy use). For the calculation of trend tests across the use categories, we treated the four-level NSAID dose variables as a continuous variable in the model, with each level represented by the mean value of that category (e.g., 0, 17.45, and 105).

Statistical analysis

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) relating prevalence of left-sided adenomas, by histological category, to aspirin and ibuprofen use individually were calculated comparing regular use and the dose categories for each drug to the referent

category of no or irregular use. The ORs and CIs were estimated using multivariable logistic regression and included the following potential confounding variables that are either established colorectal cancer risk factors, or have been associated with use of NSAIDs: sex, age group (55–59/60–64/65–69/70–74), race/ethnicity (White/Black/Hispanic/Other), smoking (never/ever), physical activity level (none/< 1 h/week/1–2 h/week/ ≥ 3 h/week), BMI (< 25 kg/m²/25–< 30 kg/m²/ ≥ 30 kg/m²), and history of cardiovascular disease (i.e., coronary heart disease, heart attack, stroke, or hypertension) and arthritis (due to common use of NSAIDs for these conditions), as well as history of osteoporosis and screening center. A variable remained in the final model if its inclusion in models with NSAIDs and a polyp category resulted in a change in the risk estimate that was > 10%. For analyses restricted to females, we adjusted for hormone therapy (HT) (ever/never). Adjustment for history of osteoporosis and HT (for females only) resulted in a change in risk estimate that was > 10%, so we included these variables in the models. Several dietary variables that have been associated with colorectal neoplasia (fiber, calcium, and folate intake) did not materially change the risk estimates (defined as a > 10% change in the β coefficient), so they were not included in the final multivariable models.

Statistical significance of multiplicative interactions between NSAID use and selected variables (sex, age, HT use, BMI, race, smoking, history of cardiovascular disease, history of arthritis, and history of osteoporosis) in relationship to the outcomes of interest were evaluated using the Wald test for interaction in the logistic regression models. Analyses were repeated with stratification by sex, age, BMI, and HT use.

RESULTS

NSAID use among study participants

Among controls ($n = 38,396$), 50% were irregular users of NSAIDs, 31% reported regular use of aspirin (only), 10.5% used ibuprofen (only), and 8% reported regular use of both (Table 1). Slightly more men (52%) than women (48%) reported use of NSAIDs. NSAID use was most frequent in controls who were white, older, heavier, and had a history of tobacco use. Subjects with a reported history of cardiovascular disease or arthritis tended to be more frequent users of these NSAIDs, at 61% and 57%, respectively.

NSAIDs and polyp histotype

Regular use of aspirin only was inversely associated with hyperplastic polyps (OR = 0.8, 95% CI = 0.7–0.9), adenomatous polyps (OR = 0.8, 95% CI = 0.8–0.9), and advanced adenomas (OR = 0.8, 95% CI = 0.7–0.9) (Table 2). A similar and borderline statistically significant pattern was seen for regular use of ibuprofen only and advanced adenomas (OR = 0.8, 95% CI = 0.6–1.0). Regular use of both aspirin and ibuprofen was also associated with lower polyp prevalence: hyperplastic polyps (OR = 0.7, 95% CI = 0.6–0.9); adenomatous polyps (OR = 0.8, 95% CI = 0.7–0.9), and advanced adenomas (OR = 0.8, 95% CI = 0.7–1.0). Dose-response relationships were noted for hyperplastic polyps and adenomas (total and advanced), with respect to frequency of use for aspirin only and aspirin/ibuprofen combined ($P < 0.0004$ for all trends). Frequency of ibuprofen use alone showed a dose-response trend for risk of any adenomas (P for trend < 0.01). There were no statistical

differences in these risk estimates by polyp histological aggressiveness category, and no differences when considering polyp size (< 1 vs. ≥ 1 cm), or multiplicity (1 vs. 2+) (data not shown). The inverse associations between use of NSAIDs and polyp prevalence did not differ according to location of the lesion (Table 3).

NSAIDs and polyps by risk subgroups

Dose-response trends were evident for men only (Table 3; $P < 0.005$ for all trends), for whom 30–40% risk reductions were found among men using NSAIDs with the highest frequency, whereas no clear associations were noted in women (interaction by sex for aspirin use only, $P = 0.02$; for ibuprofen only, $P = 0.16$; and for combined, $P = 0.006$; data not shown).

We also evaluated NSAIDs use and risk for adenomas, stratifying by age group and BMI (Table 3). The inverse association of NSAID use with colorectal adenomas was stronger among individuals aged 70–74 years compared with those aged 55–69 years, such as an OR = 0.5 (95% CI = 0.4–0.8) for > 60 NSAIDs per month compared with an OR = 0.8 (95% CI = 0.7–0.9) in the younger group. However, the trends for stronger inverse associations with increased frequency of NSAID use were statistically significant for both age group strata.

Similarly, we observed a slightly more pronounced protection of NSAIDs for individuals with BMI < 25 than overweight (BMI ≥ 25) individuals; for example, ORs for regular use of both aspirin and ibuprofen were 0.6 (95% CI = 0.4–0.8) for BMI < 25 and 0.9 (95% CI = 0.7–1.0) for BMI ≥ 25, although the trends for stronger inverse associations with increased frequency of NSAID use were not significantly different among the two BMI groups.

Although the estimates were imprecise, protective ORs for use of aspirin, and increasing use of aspirin and ibuprofen combined, were evident in blacks as well as whites, with no interaction between NSAID use and race (data not shown). No statistical interactions were found between NSAIDs and adenomas related to other behavioral and medical history variables.

We further investigated the associations stratifying by both gender and BMI (Table 4) and demonstrated that the inverse association between regular NSAID use and adenomas among females was observed only among the BMI < 25 group (OR = 0.8, 95% CI = 0.7–1.0) (P for interaction = 0.04), whereas a similar magnitude of protection was found for males in both BMI groups. Among the females, we also analyzed NSAID use by BMI and HT (ever vs. never), as HT has been shown to be protective for colon cancer and colon polyps in this and other populations (29–32). A protective effect for regular NSAID use and all adenomas remained only in low-normal BMI (OR = 0.8, 95% CI = 0.7–1.0) but not overweight women, and was observed across both categories of HT use (data not shown).

DISCUSSION

Our analyses confirm results from previous studies that habitual use of non-selective NSAIDs is associated with a decreased risk of adenomatous polyps. Our risk estimates fall within the same range of the previous studies (2,4,5,9–11,15,19,33–35). Consistent with

other reports, the protective association for polyps is present in the rectum and colon, as has also been found for colorectal cancer (7,12,17,19,22,36), although some studies demonstrate more protection for the colon than rectum (14,37) or the opposite (38).

Notably, we found that aspirin was protective for hyperplastic polyps in addition to adenomas, supporting suggestive findings from two other studies of hyperplastic lesions (39,40). Hyperplastic polyps have been considered of little interest for colon carcinogenesis, but there has been evidence that hyperplastic polyps may be precursors to some types of colorectal cancer, suggesting that at least a subset may be of clinical and public health interest (27).

Tangrea *et al.* (17) reported that a US study population, recruited between 1993 and 2000, were largely taking aspirin, and next, ibuprofen, supporting the premise that we captured the majority of NSAID use with our baseline survey questions directed toward the use of only these two drugs. The time period of our study predates the widespread use of COX-2 inhibitors, reducing concern that use of these drugs was not taken into account on the questionnaire (26). The protective effects in our analyses appeared to be more consistently stronger for aspirin than ibuprofen, aligned with findings related to colon malignancies reported in a review by Harris *et al.* (11), although many studies have not found differences in protection by these drugs for either colorectal adenomas or cancers (7,15,19,26,38). There are some differences in the effects of non-selective NSAIDs by dose and type; for example at lower doses, aspirin selectively inhibits COX-1 in platelets, whereas ibuprofen inhibits COX-1 and COX-2 to the same extent (6,21), and aspirin is the only NSAID that irreversibly modifies the cyclooxygenase enzyme (41). A caveat in our study is that the results for ibuprofen were less precise because fewer subjects used this drug on a consistent basis.

Similar to our findings, most studies have demonstrated stronger protective effects related to adenomas with more frequent use or higher doses of NSAIDs, including all but one (12) of recently reported randomized clinical trials (6,13,17,19,40,42). We also found the protective effects similar for all colorectal polyps including advanced adenomas, suggesting that NSAIDs could be contributing to the suppression of both early and late polyp progression. Although Garcia Rodriguez and Huerta-Alvarez (19) commented that NSAIDs appear to protect against the progression and growth of polyps rather than *de novo* formation, others believe that the greatest effects are on polyp initiation and early promotion (38,43). For colorectal cancer, there is general agreement among most long-term follow-up studies that protective effects from NSAIDs only become apparent after 6,10, or 20 years (14,15,38). Two notable long-term cohort studies, the Physician's Health Study and the Women's Health Study, did not show protective effects of aspirin use for colorectal cancer, but the doses used are not considered by many to be high enough (44,45).

Our results suggest that these associations between NSAIDs and polyps vary by sex, reflecting what has been found for aspirin use related to prevention of cardiovascular outcomes (46,47). In our data, NSAIDs were most consistently protective in men. Whether these differences, if valid, are due to a combination of variations in anatomy and physiology, hormone milieu, pharmacodynamics, or pharmacogenomics remains to be explored (48). Although most NSAIDs studies of men and women have generally not assessed effects

separately by sex, some have only included males or females. Chan *et al.*'s (49) most recent report on women in the Nurse's Health Study related to adenomas reported protection associated with aspirin use, demonstrating a clear dose-response relationship, with a decreased risk evident after 1–5 years of use. Adenomas were decreased among male regular (> 2 times/week) aspirin users in the Health Professionals Follow-up Study to the same degree, after 6 years of follow-up, with an estimated median duration of use of 9 years (50). In a clinical trial of aspirin with a follow-up at 3 years, Baron *et al.* (12) showed that protection for advanced adenomas was more evident in females. Tangrea *et al.* (17), in their analyses of data from the Polyp Prevention Trial, found that NSAIDs protected against the recurrence of polyps in both men and women. Different disease and behavior patterns for men and women in the PLCO population could have contributed to our discrepant findings; for example, if the PLCO women, on average, had not been using NSAIDs as long as the men. Perhaps a larger proportion of the women in these other studies were of normal weight compared with the women in the PLCO, which could account for some difference in findings, although one other study found, in contrast to us, that NSAIDs have stronger inverse associations with adenomas in obese individuals (51). Future work directed at clarifying these inconsistencies by sex need to consider menopausal status, HT use, BMI, and dose and duration of NSAID use in analyses.

There has been speculation that the inverse association of NSAIDs with adenomas wanes as age increases (7). One study of the UK General Practice Research Database suggested a trend toward a stronger preventive association among persons < 70 years old (19), and a clinical trial of aspirin and recurrent adenomas demonstrated a stronger inverse relationship for people less than the median age (57 years) (12). When we stratified by age, we found that in the oldest group of 70–74 year olds, NSAID use imposed a higher relative decrease of risk in both males and females. Hoffmeister *et al.* (52) concluded in their review that few studies have specifically considered NSAIDs and colorectal cancer in the elderly, and two of four studies that did include older people showed a risk reduction similar to that of other age groups; the review by Flossman and Rothwell *et al.* (15) concluded no difference of effect by age group. However, in a trial of a selective COX-2 inhibitor, the greatest suppression of adenomas and colorectal cancers was detected among subjects > 70 years old (53,54). Whether and how lifestyle and biologic changes related to aging (e.g., increased gene hypermethylation, decreased calcium absorption) contribute to age-related modification of NSAIDs protective action remains to be studied. Similar to our findings, Sansbury *et al.* (55) found that the relationship between NSAIDs and in their case, colon cancer, was similar between African Americans and whites.

The strength of these results lies in the large, geographically, and demographically diverse sample with a substantial number of cases and in the use of a standardized survey and screening protocol in which the entire population underwent a systematic examination of the left colon, allowing us to avoid detection bias, adjust for and consider effect modification for many variables, and reduce the misclassification of our outcome variables. We also used a more general risk population, rather than one at high risk due to a previous history of polyps or cancer, or having a genetic condition such as familial adenomatosis polyposis.

The study population consisted of people willing to participate in a prolonged and fairly demanding cancer screening trial, who are not representative of the general population (56,57). Therefore, any characteristics of this volunteer population that might affect the relationship between NSAID use and polyps would reduce the generalizability of our findings. Although our outcome variable of polyp prevalence was measured in a standardized manner, our independent variables, aspirin and ibuprofen use, relied on self-report using relatively crude questions that only queried about recent use. Our most severe limitation was that we did not collect data to assess duration of use or specific doses of medications used. An advantage to using this survey approach is that it captured the use of both prescription and over-the-counter use of these drugs.

Another limitation of our data is that we could only analyze polyps occurring on the left side of the colon as the screening study used flexible sigmoidoscopy, not colonoscopy. Further, the study was cross-sectional and the outcome was prevalent rather than incident polyps; therefore, we cannot distinguish whether NSAIDs are related to the occurrence of new polyps or the progression of polyps or both. However, we will have opportunities in the PLCO to study incident adenomas, recurrent adenoma, and colon cancer. Blood DNA samples are also available to replicate findings from others on polymorphisms that may modify the action of NSAIDs on colorectal adenomas (58–62).

NSAIDs as potential chemopreventive agents for colorectal polyps and cancer continue to be a source of both hope and controversy (25,26,53,63,64). Although these drugs are effective, their deleterious side effects among some people are well described (54,65–68). Better characterization of individuals at high risk of sporadic colorectal cancer and for whom NSAIDs help reduce their risk without a high probability of serious medical consequences, and improved understanding of NSAIDs effects for other health outcomes, would help evaluate the cost benefits of NSAIDs on a public health scale.

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Study Highlights**WHAT IS CURRENT KNOWLEDGE**

- ✓ Non-steroidal anti-inflammatory drugs: (NSAIDs) decrease the risk for colorectal adenomas.
- ✓ Decreased risk is related to longer duration of NSAIDs use.
- ✓ Decreased risk is related to increased dosage of NSAIDs use.

WHAT IS NEW HERE

- ✓ Aspirin decreases the risk for hyperplastic polyps.
- ✓ Decreased risk is more evident in males and persons over 70 years of age.
- ✓ Decreased risk is more evident in normal weight men and women.

Table 1

Characteristics^a of the control population by use^b of aspirin and ibuprofen

Variable	Total subjects, <i>n</i> (column %) <i>n</i> = 38,396	No regular use of aspirin or ibuprofen, <i>n</i> (row %) <i>n</i> = 19,228	Regular use of aspirin only, <i>n</i> (row %) <i>n</i> = 11,961	Regular use of ibuprofen only, <i>n</i> (row %) <i>n</i> = 4,046	Regular use of aspirin and ibuprofen, <i>n</i> (row %) <i>n</i> = 3,147
<i>Gender</i>					
Male	19,756 (51)	9,503 (48)	7,252 (37)	1,488 (7)	1,508 (8)
Female	18,640 (49)	9,725 (52)	4,709 (25)	2,558 (14)	1,639 (9)
<i>Race/ethnicity</i>					
White	34,086 (89)	16,487 (48)	10,936 (32)	3,715 (11)	2,943 (9)
Black	1,524 (4)	885 (58)	386 (25)	144 (10)	107 (7)
Hispanic	663 (2)	360 (54)	187 (28)	73 (11)	43 (7)
Other	2,107 (5)	1,494 (71)	448 (21)	110 (5)	53 (3)
<i>Age group years</i>					
55–59	13,648 (36)	7,003 (51)	3,700 (27)	1,706 (13)	1,236 (9)
60–64	12,023 (31)	6,102 (51)	3,667 (30)	1,271 (11)	981 (8)
65–69	8,185 (21)	3,975 (49)	2,896 (35)	722 (9)	586 (7)
70–74	4,540 (12)	2,148 (47)	1,698 (37)	347 (8)	344 (8)
<i>Body mass index</i>					
Low-normal (< 25 kg/m ²)	13,139 (34)	7,166 (54)	3,810 (29)	1,276 (10)	886 (7)
Overweight (25–< 30 kg/m ²)	16,202 (43)	7,933 (49)	5,308 (33)	1,636 (10)	1,324 (8)
Obese (≥ 30 kg/m ²)	8,672 (23)	3,934 (46)	2,733 (31)	1,094 (12)	909 (10)
<i>Tobacco use history</i>					
Never	17,739 (46)	9,568 (54)	5,029 (28)	1,850 (11)	1,288 (7)
Ever	20,641 (54)	9,652 (47)	6,930 (33)	2,196 (11)	1,858 (9)
<i>Hours current physical activity</i>					
None	4,879 (14)	2,468 (51)	1,433 (29)	550 (11)	427 (9)
< 1 h/week	6,005 (17)	2,996 (50)	1,739 (29)	750 (12)	516 (9)
1–2 h/week	9,757 (28)	4,842 (50)	3,064 (31)	1,043 (11)	806 (8)
3 h/week	14,087 (41)	6,972 (49)	4,631 (33)	1,358 (10)	1,122 (8)

Variable	Total subjects, <i>n</i> (column %) <i>n</i> = 38,396	No regular use of aspirin or ibuprofen, <i>n</i> (row %) <i>n</i> = 19,228	Regular use of aspirin only, <i>n</i> (row %) <i>n</i> = 11,961	Regular use of ibuprofen only, <i>n</i> (row %) <i>n</i> = 4,046	Regular use of aspirin and ibuprofen, <i>n</i> (row %) <i>n</i> = 3,147
<i>History of:</i>					
Cardiovascular: disease ^c	104,050 (37)	5,459 (39)	5,905 (42)	1,273 (9)	1,371 (10)
Arthritis	13,671 (36)	5,843 (43)	3,978 (29)	2,212 (16)	1,636 (12)
Diabetes	2,673 (7)	1,145 (43)	1,067 (40)	225 (8)	235 (9)
Osteoporosis	1,726 (5)	863 (50)	454 (26)	238 (14)	170 (10)

^aMissing data for race/ethnicity (16 subjects), body mass index (383 subjects), smoking history (16 subjects), physical activity (3,668 subjects), disease history (cardiovascular disease 393 subjects, osteoporosis 1,213 subjects, arthritis 690 subjects, diabetes 1,037 subjects), and regular use of aspirin and ibuprofen (14 subjects).

^b"No regular use" was defined by subjects' responses to a question about whether they regularly used aspirin, ibuprofen, or products containing these compounds.

^cHypertension, coronary heart disease/heart attack, and stroke.

Table 2

Associations^a (ORs, 95% CIs) of NSAID use with prevalence of left-sided colorectal polyps, by histological type

Controls, <i>n</i> = 38,396		Hyperplastic polyps only, <i>n</i> = 1,646		Any adenoma, <i>n</i> = 4,017		Any advanced adenoma, <i>n</i> = 1,571	
<i>N</i>	<i>N</i>	OR (95% CI)	<i>N</i>	OR (95% CI)	<i>N</i>	OR (95% CI)	
<i>Use of aspirin and ibuprofen</i>							
Irregular use of both	19,228	881	1.0	2,131	1.0	853	1.0
Regular use of aspirin only	11,961	469	0.8 (0.7–0.9)	1,228	0.8 (0.8–0.9)	463	0.8 (0.7–0.9)
Regular use of ibuprofen only	4,046	173	0.9 (0.7–1.0)	365	0.9 (0.8–1.0)	129	0.8 (0.6–1.0)
Regular use of both	3,147	123	0.7 (0.6–0.9)	292	0.8 (0.7–0.9)	126	0.8 (0.7–1.0)
<i>Aspirin: frequency of use^b</i>							
< 4/Month	23,274	1,054	1.0	2,496	1.0	982	1.0
4–29/Month	5,026	212	0.9 (0.7–1.0)	491	0.9 (0.8–1.0)	191	0.8 (0.7–1.0)
30–59/Month	8,065	309	0.7 (0.6–0.9)	864	0.8 (0.8–0.9)	330	0.8 (0.7–0.9)
> 60/Month	2,017	71	0.7 (0.5–0.9)	165	0.7 (0.6–0.9)	68	0.7 (0.6–1.0)
		<i>cP</i> for trend < 0.0001		<i>cP</i> for trend < 0.0001		<i>cP</i> for trend 0.0004	
<i>Ibuprofen: frequency of use^b</i>							
< 4/Month	31,189	1,350	1.0	3,359	1.0	1,316	1.0
4–29/Month	3,536	145	0.9 (0.7–1.1)	361	1.0 (0.9–1.2)	142	1.0 (0.8–1.2)
30–59/Month	945	40	1.1 (0.8–1.5)	75	0.8 (0.6–1.0)	29	0.8 (0.5–1.2)
> 60/Month	2,712	111	0.9 (0.7–1.1)	221	0.8 (0.7–1.0)	84	0.8 (0.7–1.1)
		<i>cP</i> for trend 0.3		<i>cP</i> for trend 0.01		<i>cP</i> for trend 0.1	
<i>Frequency of combined aspirin and ibuprofen use</i>							

	Controls, $n = 38,396$		Hyperplastic polyps only, $n = 1,646$		Any adenoma, $n = 4,017$		Any advanced adenoma, $n = 1,571$	
	N		N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
< 4/Month	18,961		876	1.0	2,102	1.0	835	1.0
4–29/Month	6,846		285	0.8 (0.7–0.9)	687	0.9 (0.8–1.0)	268	0.9 (0.7–1.0)
30–59/Month	7,964		302	0.7 (0.6–0.8)	846	0.8 (0.8–0.9)	318	0.8 (0.7–0.9)
> 60/Month	4,611		183	0.8 (0.6–0.9)	381	0.7 (0.6–0.8)	150	0.7 (0.6–0.9)
				cP for trend 0.0002		cP for trend < 0.0001		cP for trend < 0.0001

BMI, body mass index; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.

^aAdjusted for center, sex, age, race/ethnicity, smoking, physical activity, body mass index, cardiovascular disease, osteoporosis, and arthritis.

^bOR for aspirin use are adjusted for ibuprofen use; OR for ibuprofen use are adjusted for aspirin use.

^cTo calculate trend tests, dose categories were treated as continuous with each level represented by the mean value of each category (irregular 0, low 17, moderate 45, and heavy 105 pills/month).

Table 3

Adjusted^a risk estimates for left-sided adenomas and NSAID use, by site, sex, age, and BMI

	Site ^b		Sex		Age		BMI	
	Left colon 3,074/38,396 OR (95% CI)	Rectum 1,144/38,396 OR (95% CI)	Males 2,601/19,756 OR (95% CI)	Females 1,416/18,640 OR (95% CI)	55–69 years 3,450/33,856 OR (95% CI)	70–74 years 567/4,540 OR (95% CI)	< 25 1,161/13,139 OR (95% CI)	25 2,809/24,874 OR (95% CI)
<i>Use aspirin and ibuprofen</i>								
Irregular use of both	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Regular use of aspirin only	0.8 (0.8–0.9)	0.8 (0.7–1.0)	0.8 (0.7–0.9)	1.0 (0.8–1.1)	0.9 (0.8–0.9)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.9 (0.8–1.0)
Regular use of ibuprofen only	0.9 (0.8–1.0)	0.7 (0.6–0.9)	0.8 (0.7–1.0)	1.0 (0.8–1.2)	0.9 (0.8–1.0)	0.5 (0.3–0.8)	0.9 (0.7–1.2)	0.9 (0.7–1.0)
Regular use of both	0.8 (0.7–0.9)	0.8 (0.6–1.0)	0.8 (0.6–0.9)	0.9 (0.7–1.1)	0.8 (0.7–0.9)	0.7 (0.4–1.0)	0.6 (0.4–0.8)	0.9 (0.7–1.0)
<i>Aspirin: frequency of use^c</i>								
< 4/Month	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
> 4–29/Month	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.8 (0.7–1.0)	0.9 (0.7–1.1)	0.9 (0.8–1.0)	0.9 (0.7–1.2)	0.8 (0.7–1.0)	0.9 (0.8–1.0)
30–59/Month	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.8 (0.7–0.9)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	0.7 (0.6–1.0)	0.7 (0.6–0.9)	0.9 (0.8–1.0)
> 60/Month	0.7 (0.6–0.9)	0.6 (0.4–0.9)	0.6 (0.5–0.8)	0.8 (0.6–1.1)	0.8 (0.6–0.9)	0.5 (0.3–0.9)	0.7 (0.5–1.0)	0.8 (0.6–0.9)
	<i>dP</i> for trend 0.0004	<i>dP</i> for trend 0.01	<i>dP</i> for trend < 0.0001	<i>dP</i> for trend 0.3	<i>dP</i> for trend 0.0006	<i>dP</i> for trend 0.003	<i>dP</i> for trend 0.0002	<i>dP</i> for trend 0.003
<i>Ibuprofen: frequency of use^c</i>								
< 4/Month	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
> 4–29/Month	1.0 (0.9–1.2)	0.9 (0.7–1.1)	1.0 (0.9–1.2)	1.0 (0.8–1.2)	1.0 (0.9–1.1)	0.8 (0.5–1.3)	1.0 (0.8–1.3)	1.0 (0.9–1.2)
30–59/Month	0.8 (0.6–1.0)	0.7 (0.4–1.1)	0.8 (0.6–1.2)	0.7 (0.5–1.1)	0.8 (0.6–1.0)	0.7 (0.4–1.4)	0.6 (0.3–1.0)	0.8 (0.6–1.1)
> 60/Month	0.8 (0.7–1.0)	0.7 (0.5–1.0)	0.7 (0.6–0.9)	1.0 (0.8–1.2)	0.9 (0.7–1.0)	0.6 (0.3–0.9)	0.8 (0.6–1.1)	0.8 (0.7–1.0)

	Site ^b		Sex		Age		BMI	
	Left colon 3,074/38,396 OR (95% CI)	Rectum 1,144/38,396 OR (95% CI)	Males 2,601/19,756 OR (95% CI)	Females 1,416/18,640 OR (95% CI)	55–69 years 3,450/33,856 OR (95% CI)	70–74 years 567/4,540 OR (95% CI)	< 25 1,161/13,139 OR (95% CI)	25 2,809/24,874 OR (95% CI)
	<i>dP</i> for trend 0.02	<i>dP</i> for trend 0.01	<i>dP</i> for trend 0.005	<i>dP</i> for trend 0.6	<i>dP</i> for trend 0.06	<i>dP</i> for trend 0.02	<i>dP</i> for trend 0.1	<i>dP</i> for trend 0.06
<i>Frequency of combined aspirin/ibuprofen use</i>								
< 4/Month	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
> 4–29/Month	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.7–1.2)	0.9 (0.8–1.1)	0.9 (0.8–1.0)
30–59/Month	0.9 (0.8–0.9)	0.9 (0.7–1.0)	0.8 (0.7–0.9)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	0.7 (0.5–0.8)	0.7 (0.6–0.9)	0.9 (0.8–1.0)
> 60/Month	0.7 (0.6–0.9)	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.9 (0.8–1.1)	0.8 (0.7–0.9)	0.5 (0.4–0.8)	0.7 (0.5–0.9)	0.8 (0.7–0.9)
	<i>dP</i> for trend < 0.0001	<i>dP</i> for trend 0.0002	<i>dP</i> for trend < 0.0001	<i>dP</i> for trend 0.3	<i>dP</i> for trend < 0.0001	<i>dP</i> for trend < 0.0001	<i>dP</i> for trend 0.0003	<i>dP</i> for trend 0.0002

BMI, body mass index; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.

^a Adjusted for center, sex, age, race/ethnicity, smoking, physical activity, body mass index, cardiovascular disease, osteoporosis, and arthritis, unless used as a stratifying variable; additionally adjusted for hormone replacement therapy among females. Total n in analyses vary slightly due to missing data for included variables.

^b Including 418 cases with adenomas in both the left colon and the rectum.

^c OR for aspirin use are adjusted for ibuprofen use; OR for ibuprofen use are adjusted for aspirin use.

^d To calculate trend tests, dose categories were treated as continuous with each level represented by the mean value of each category (irregular 0, low 17, moderate 45, and heavy 105 pills/month).

Table 4Adjusted^a risk estimates for left-sided adenomas by NSAID use, BMI, and gender

NSAIDs use	BMI < 25		BMI > 25		P value for interaction
	N, cases/controls	OR (95% CI)	N, cases/controls	OR (95% CI)	
All subjects					
Irregular use	689/7,166	1.0	1,414/11,867	1.1 (1.0–1.2)	0.09
Regular use	471/5,972	0.8 (0.7–0.9)	1,395/13,004	0.9 (0.8–1.0)	
Males					
Irregular use	364/2,883	1.0	991/6,511	1.1 (1.0–1.3)	0.4
Regular use	249/2,476	0.7 (0.6–0.9)	966/7,664	0.9 (0.8–1.0)	
Females					
Irregular use	325/4,283	1.0	423/5,326	1.0 (0.8–1.2)	0.04
Regular use	222/3,496	0.8 (0.7–1.0)	429/5,340	1.0 (0.9–1.2)	

BMI, body mass index; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.

^aAdjusted for center, race/ethnicity, smoking, cardiovascular disease, osteoporosis, arthritis, physical activity, and for hormonal replacement therapy among females. Total *n* in analyses vary slightly due to missing data for included variables.