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Colorectal Cancer After Start of Nonsteroidal Anti-Inflammatory Drug Use

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Abstract

Purpose—Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, have been consistently shown to reduce the risk of colorectal cancer (CRC) in non-experimental studies, but little is known of the factors associated with starting and continuing regular NSAID use and their effect on the NSAID - CRC association.

Subjects and Methods—Prospective cohort study of 22,071 healthy male physicians aged 40–84 years without indications or contraindications to regular NSAID use at baseline. Annual questionnaires assessed quantity of NSAID use, occurrence of cancer, and risk factors for CRC. Propensity for regular NSAID use (> 60 days/year) was estimated using generalized estimating equations. We used a time-varying Cox proportional hazards model to estimate the association between duration since initiation of regular NSAID use and risk for CRC.

Results—Regular non-aspirin and any NSAID use increased from 0 to 12% and 1 to 56% over time, respectively, and was predicted by age, body mass index, alcohol consumption, medication use, coronary artery disease, gastrointestinal diseases, arthritis, hypertension, and headaches. Over a median follow-up of 18 years, 495 physicians were diagnosed with CRC. There was no trend of CRC risk with increased duration of regular NSAID use. Five or more years of regular use of any NSAID were associated with a relative risk for CRC of 1.0 (95% confidence interval: 0.7 – 1.5), after adjustment for predictors of regular NSAID use.

Conclusion—Regular NSAID use was not associated with a substantial risk reduction of CRC after controlling for time-varying predictors of both NSAID use and CRC.

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Keywords

colorectal neoplasms; anti-inflammatory agents; non-steroidal; selection bias; confounding factors (epidemiology); pharmacoepidemiology; epidemiology; chemoprevention

Overwhelming evidence from non-experimental studies supports an association between long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, and a substantially reduced risk for colorectal cancer (1,2). An approximately 40 percent reduction in colorectal cancer incidence or mortality was observed in both case-control and cohort studies (2,3). NSAIDs could influence carcinogenesis through their cyclooxygenase inhibition which seems to play an important role in cell transformation, tumor growth, and metastasis (4), but other mechanisms have been proposed (5). Several, but not all, randomized trials of NSAID treatment showed regression of adenomatous polyps in patients with familial adenomatous polyposis and other young high-risk populations (e.g. 6–8). In contrast, randomized trials of 325mg and 100mg of aspirin every other day showed no effect on colorectal cancer in apparently healthy men (9,10) and women (11), respectively, raising some doubts on the potential for primary chemoprevention of colorectal cancer by NSAIDs in average risk populations.

Conflicting evidence from randomized trials and observational studies (12) increased awareness regarding the role of selection bias and confounding in non-experimental research of the effects of long-term medication use. Selection bias and confounding may arise due to factors influencing the propensity to start medication use, including indications and contraindications, but also due to factors influencing the propensity for regular, long-term medication use. To better address both forms of biases, new-user designs have been advocated (13) that may conceptually be compared to ‘intention-to-treat’ analyses in randomized trials.

Apart from the results on randomized and post-randomized study aspirin, the Physicians’ Health Study offers the unique opportunity to apply a new-user design to study the possible chemoprevention of colorectal cancer by non-aspirin NSAIDs and any NSAIDs (including aspirin). First, regular users of NSAIDs and those not tolerating regular use of NSAIDs were excluded from participation. And second, NSAID use and non-study aspirin use and factors possibly affecting the propensity for any NSAID use were prospectively assessed annually for up to 20 years. Application of the new-user design is likely to reduce selection biases and confounding that could previously not be addressed in non-experimental studies.

SUBJECTS AND METHODS

Population

The Physicians’ Health Study was designed to test the hypotheses that 325 mg of aspirin on alternate days reduces risk of cardiovascular disease and that 50 mg of beta-carotene on alternate days decreases the incidence of cancer. The population and methods have been described in detail in previous reports (14,15). In brief, 33,223 US male physicians aged 40 to 84 years who did not regularly use aspirin or other NSAIDs (or were willing to give up use), without a history of myocardial infarction, stroke, cancer, liver or renal disease, gout, peptic ulcer, or other contraindications to aspirin were eligible and enrolled in a 3 month run-in phase of active aspirin. During the run-in period, 22,071 (66 percent) followed the study regimen, remained willing and eligible to participate, provided written informed consent, and were randomly assigned to the treatment regimen in 1982. The aspirin arm was terminated early after an average follow-up of five years in January 1988, primarily due to a 44% reduction in risk of a first myocardial infarction in the aspirin group (15). The beta-carotene component of the trial continued to its scheduled end in December 1995. Post trial non-experimental follow-

up continued after this date (16). The trial and continued follow-up of participants were approved by the Institutional Review Board of the Brigham and Women's Hospital. For this analysis, we followed participants until death, the occurrence of cancer, or their last questionnaire returned until May 2003.

Assessment of NSAID use

Both during the randomized period as well as during the post-trial non-experimental period, participants completed annual questionnaires asking about compliance to study medication (e.g. 325mg of aspirin every other day), outside use of aspirin or aspirin containing drugs, and non-aspirin NSAIDs, possible side effects of aspirin or non-aspirin NSAID use, and the occurrence of relevant health outcomes. As of May 2003, 95 percent of surviving participants provided these data within the past two years.

In all questionnaires, participants reported their number of days of non-study aspirin or aspirin containing drug use and non-aspirin NSAID use during the preceding 12 months (i.e. since the last questionnaire) separately in several categories. Over the whole follow-up period, aspirin and non-aspirin NSAID use could be consistently categorized into none (0 days), 1 to 14 days, 15 to 60 days, and more than 60 days. First, regular non-aspirin NSAID use was defined as use on more than 60 days per year. Second, regular use of any NSAIDs was defined as either use of aspirin or of aspirin containing medications on more than 60 days per year or regular use of non-aspirin NSAIDs. Finally, study aspirin (325mg every other day) was added to the exposure definition. This was based on information on compliance to randomized study aspirin (up to the end of the aspirin arm of the trial in 1988) and self-selected study aspirin thereafter until 1995. Use of study aspirin, or non-study aspirin, or non-aspirin NSAID on more than 60 days was considered regular use. Thus, virtually all physicians randomized to aspirin had at least 5 years of regular use in this analysis. Overall, 2.2 percent of all possible information on non-study NSAID use was missing and could be imputed in 2.0 percent by carrying forward the last available category of NSAID use, including up to two missing questionnaires. If NSAID information was missing for more than two consecutive questionnaires, values were no longer imputed but assumed to reflect non-use up to the next available information on NSAID use for the analyses looking at duration of use (0.2 percent).

Assessment of Colorectal Cancer

All cancer reports (excluding non-melanoma skin cancers) were followed by a request to review medical records, including pathology reports. An endpoints committee of physicians blinded to the treatment assignment reviewed medical records. For this analysis, we used all confirmed cases of incident colorectal cancer (N=480) as well as cases reported and not yet confirmed (N=15) until May 2003. As of May 2003, 95 percent of surviving participants provided morbidity data within the past two years.

Information on Covariates

Current age was calculated at the time of every questionnaire. Body mass index (weight in kilograms divided by squared height in meters) was calculated from height information at baseline and weight assessed at baseline, at 96 months and every questionnaire thereafter. Information about the usual frequency of exercise vigorous enough to work up a sweat was assessed at baseline and updated at 36, 108, and 216 months. Smoking status (current, past, or never) was assessed at baseline and updated at 24, 60, 144, and 216 months. Usual frequency of alcohol consumption during the last 12 months was assessed at baseline and updated at 84 and 216 months. Multivitamin use was asked for at baseline and yearly starting with the 60 month questionnaire. Usual frequency of consumption of servings of vegetables and fruits was asked for at baseline and was updated at the 24, 48, 72, 96, 120, and 156 months questionnaires. Systolic and diastolic blood pressure values as well as use of antihypertensives were reported

by participating physicians at baseline and as of the 24, 84, 180, and 216 month questionnaires. Hypertension was defined as systolic or diastolic blood pressure $\geq 140/90$, respectively, or use of antihypertensives.

On each of the follow-up questionnaires, participants were asked for a variety of diagnoses and symptoms. Since NSAID use was assessed during the 12 months prior to the questionnaire, diagnoses and symptoms assessed prior to that time were considered as determinants of NSAID use (to avoid problems about temporality). Diagnoses included diabetes, coronary artery disease (myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty), angina, arthritis, headache, migraine, peptic ulcer, and gastrointestinal bleeding. Symptoms included those suggestive of gastritis.

Statistical Analysis

Propensity for regular NSAID use—To assess variables associated with the propensity for regular non-aspirin NSAID use and regular use of any NSAID during the 12 months preceding any given questionnaire, we used logistic regression models accounting for a person's correlated use of NSAIDs in different time periods using generalized estimating equations (17). These analyses reflect predictors of initiation and persistence of regular NSAID use. Possible predictors were age, body mass index, smoking, exercise, alcohol consumption, blood pressure, multivitamin use, and hypertension, as well as a history of diabetes, coronary artery disease, angina, arthritis, headache, migraine, peptic ulcer, gastrointestinal bleeding, and gastritis. All variables were assessed as of each questionnaire, i.e. time-varying.

Risk for colorectal cancer—Patients with a diagnosis of any cancer before randomization (N=21) or no follow-up (N=7) were excluded from all analyses. As of May 2003, mortality follow-up was 97 percent complete within the past 2 years and 4314 of the participants had died. For participants with any unrefuted cancer (except non-melanoma skin cancer), person-time was censored at the time of diagnosis. For all remaining participants, person-time was censored at the date of the last returned questionnaire or death. We calculated person-time at risk and assigned colorectal cancer cases according to the duration of regular non-aspirin NSAID use and any NSAID use in 6 categories (0, 1, 2, 3, 4, and 5 or more years). The highest category of duration of use was chosen since few participants used any NSAIDs during the aspirin trial, thus limiting the information on longer term use. For the analysis of study aspirin and non-study NSAIDs, however, participants could be categorized into 0, 1 to 5, 6 to 10, and more than 10 years of regular NSAID use. In all analyses, the same person could contribute person-time in different categories with increasing duration of regular NSAID use. Once a participant had achieved a certain duration of use, he remained in that category even if he stopped using NSAIDs. We then estimated incidence rate ratios and their 95% confidence intervals (CIs) for colorectal cancer according to time-varying regular NSAID use for the total follow-up period using left and right censored Cox proportional hazards models (18). The models included updated, i.e. time-varying, covariates rather than the overall propensity score described above (19).

RESULTS

Due to the long median follow-up period of 18.1 years (inter-quartile range: 15.8 – 18.9) and to illustrate the changes of the study population over time, table 1 presents characteristics of the 22,043 male physicians as of baseline and as of the last questionnaire received. From baseline to the last questionnaire, the mean age increased from 54 to 70 years. According to the inclusion and exclusion criteria of the randomized trial, regular non-aspirin or any NSAID use were virtually nonexistent at baseline and increased to 12% and 56% over time, respectively. Whereas physicians most frequently reported exercising vigorously 1 – 4 times

per week at baseline (56%), exercising never or rarely was almost as frequently reported as of the last questionnaire. Current smoking reduced from 11% at baseline to 5% as of the last questionnaire, with former smoking increasing accordingly. With respect to alcohol consumption, both the proportion of abstainers and of those who reported drinking alcoholic beverages daily increased over time. As expected, the most pronounced differences were observed for comorbidities. The prevalence of hypertension increased from 26% to 43%. With increasing age, a history of diabetes, coronary artery disease, angina, peptic ulcer disease, gastrointestinal bleeding, gastritis, headaches, and migraine all became much more prevalent. This increase in prevalence was also observed for a history of arthritis, which increased from 3% at baseline to 28% as of the last questionnaire.

In table 2, we present independent predictors of regular non-aspirin NSAID and any NSAID use at any given time during the follow-up. Odds ratios are adjusted for all variables presented in the table and values above 1 indicate a higher propensity of regular NSAID use. They are estimated based on 336,963 individual questionnaires and an overall prevalence of regular use of non-aspirin NSAID of 6.0% and any NSAID use of 21.4%. Compared with participants younger than 50 years, all age groups were more likely to use both non-aspirin NSAIDs and any NSAIDs. This increase in use was more pronounced for any NSAID use. Use of non-aspirin NSAIDs declined after the age of 80 years. Regular use of NSAIDs increased with increasing body mass index, increasing frequency of alcohol consumption, use of multivitamins, as well as a history of coronary artery disease, gastritis, headaches, and migraine prior to the assessment of NSAID use. With an odds ratio of 4, arthritis was a very strong predictor of regular non-aspirin NSAID use but much less so for any NSAID use. Whereas regular NSAID use was less frequent in physicians exercising 1 – 3 times a month compared with those never or rarely exercising, use was more prevalent in physicians exercising more frequently. A history of coronary artery disease was a strong predictor for regular use of any NSAIDs (including aspirin), indicating a substantial proportion of aspirin use for the secondary prevention of cardiovascular disease in these participants. NSAID use decreased with increasing frequency of vegetable and fruit consumption and a history of peptic ulcer.

Over a median follow-up period of 18 years, we observed 495 incident cases of colorectal cancer in a total of 365,824 person-years. Compared with an incidence rate of 132 and 127 per 100,000 person-years in physicians never regularly using non-aspirin NSAIDs and any NSAIDs during follow-up, respectively, the rates were higher in all categories of duration of regular NSAID use. The age-adjusted incidence rate ratios for regular use of non-aspirin NSAIDs and colorectal cancer ranged from 0.9 to 1.1. There was no monotonic trend in incidence rate ratios over increasing duration, however, and the incidence rate ratio for 5 or more years of regular use was 0.9 (95% confidence interval: 0.5 – 1.6). Control for predictors of regular NSAID use except arthritis led to estimates of incidence rate ratios generally further away from the null (incidence rate ratio for 5 or more years of regular non-aspirin NSAID use: 0.8; 0.4 – 1.5). Additional control for arthritis moved this estimate closer to the null (incidence rate ratio for 5 or more years of regular use: 0.9; 0.5 – 1.7). The corresponding incidence rate ratios for regular use of any NSAID, including aspirin, were very similar with an incidence rate ratio of 1.0 (95% confidence interval: 0.7 – 1.5) for 5 or more years of regular use.

In table 4 we present the results combining randomized and self-selected study aspirin, non-study aspirin, and non-aspirin NSAIDs. The age-adjusted incidence rate ratio for 1 to 5 and 6 to 10 years of regular use compared with never users were both 1.0. After more than 10 years of regular use, the age-adjusted incidence rate ratio was 0.9 (95% confidence interval: 0.6 – 1.2). With further control for potential confounding factors, the fully adjusted incidence rate ratio was 0.8 (95% confidence interval: 0.6 – 1.2).

DISCUSSION

In contrast to virtually all previous studies on risk for colorectal cancer (1,2), we observed no substantial risk reduction of colorectal cancer in physicians initiating regular NSAID use. This finding is in accordance with our previous finding on randomized and post-randomized aspirin use in this study population (10) as well as with the recent finding after 10 years of randomized aspirin treatment in the Women's Health Study (11). Despite the wide confidence intervals around our estimates that include estimates of a substantial risk reduction, the point estimates themselves and the lack of a trend towards lower risk with increasing duration of use indicate a persisting and intriguing discrepancy between the findings from the Physicians' Health Study and virtually all other non-experimental cohort and case-control studies consistently observing risk reductions of CRC incidence or mortality around 40%.

The discrepancy might be explained by chance, the relatively short duration of regular NSAID use in the Physicians' Health Study, the definition of regular NSAID use, the limited number of events with prolonged NSAID use, different control for confounding by indication and contraindication, and the very specific selection of physicians into the Physicians' Health Study.

The analysis of a cohort starting NSAID use limited the maximum duration of regular NSAID use that could be assessed. The duration of exposure necessary to prevent colorectal cancer is unclear. Giovannucci et al. observed an increasingly reduced risk of colorectal cancer with increasing duration of regular aspirin use (20). Although this reduction became significant only after 20 years of use, there was a steady decline in relative risk starting with 5 to 9 years of regular use. In their claims data study, Collet et al. observed a protective effect after 10 years of dispensed prescription of NSAIDs (21). Rosenberg et al, however, found that full protective effect with regular use started in the year before diagnosis and a rather weak effect of duration of use comparing any regular use with regular use over five and more years (22). Therefore, we should have seen an effect at least emerging in the Physicians' Health Study.

Our definition of regular use is based on availability of data and might not capture the dosing interval needed for continuous COX-2 inhibition (23), possibly needed for the reduction of colorectal cancer risk. Aspirin-treatment every other day has not been shown to prevent colorectal cancer in men (9,10) or women (11), however, and long-term NSAID use on more than 180 days per year might be rare in non-experimental settings. The every other day dosing interval in these randomized studies is nevertheless artificial and not likely to be observed in non-experimental studies. Despite the long follow-up period of up to 20 years, the new user design also limited the number of events observed with increasing duration of regular NSAID use leading to wide confidence intervals around some of our estimates, e.g. around the effect of regular non-aspirin NSAID use 5 or more years after initiation.

The discrepant finding might also be the result of different methods and variables used to control for confounding in our study. Due to the new user design, we were able to control for confounding by indication and contraindication at the time physicians started regular NSAID use. This information is usually not available in studies conducted in prevalent drug users. Not surprisingly, the single strongest predictor of regular NSAID use was a history of arthritis. In the Physicians' Health Study, a history of arthritis was independently associated with a reduced risk for colorectal cancer which explains why control for this variable strongly associated with NSAID use resulted in somewhat higher risk estimates (or less protective estimates) for NSAID use. Reduced risk for colorectal cancer in patients with arthritis has been previously reported (24,25) but was either interpreted as being due to increased physical activity leading to arthritis (24) or to NSAID use in patients with arthritis (25). Baron and Adami raised the hypothesis that chronic aspirin use is likely to be associated with a clinically significant, long-term disorder

that may in itself be related to cancer (26). Arthritis might be a candidate, albeit the change in estimate by controlling for arthritis was not large in our study and arthritis might be a surrogate for higher dose and duration of regular NSAID use.

Finally, the discrepancy might be due to the selection of participants for the original randomized trial, i.e. physicians without clear indications or contraindications for regular NSAID use. Comparisons of prevalent long-term users of medications to non-users can be substantially biased (13). This phenomenon is widely appreciated in the setting of experimental studies, where intention-to-treat analyses are applied to avoid this kind of bias. Participants adhering to study medication, including placebo, have been shown to be generally healthier than non-adhering participants (27). In the PHS, those 34% of physicians that entered the run-in phase but were unable or unwilling (for whatever reason) to regularly take low-dose aspirin and were therefore not randomized had twice the risk dying from colorectal cancer than those physicians that adhered to the treatment and were randomized (28). Dropout from regular treatment during run-in was therefore substantial and is likely to be even larger with respect to full-dose NSAIDs. Since information on factors associated with starting and continuing long-term medication use is usually not available in studies looking at prevalent users, these cannot be taken into account in the analysis. This kind of selection bias can therefore not be ruled out in previous studies on NSAIDs and CRC.

Our study has to be interpreted taking its limitations into account. We only had information on number of days of NSAID use rather than number of pills or dose. The lower limit of more than 60 days of use per year defining regular use might be too low to see an effect according to recent non-experimental studies on adenomas (29) and colorectal cancer (30). Our analyses of any NSAID use, including aspirin use, were dominated by every other day aspirin use for the prevention of myocardial infarction. Colorectal cancer was assessed by self-report and individuals using NSAIDs regularly might be more health conscious and report cancer earlier. NSAID use could also lead to bleeding and therefore earlier diagnosis, or mask early symptoms, leading to later diagnosis. In this highly screened population of physicians, however, these considerations might be less relevant and randomized aspirin did not affect overall stage of colorectal cancer at time of diagnosis (10). The possibly good participation in endoscopy screening (with removal of adenomas) might have reduced the overall incidence of CRC and thus reduced the power to detect any protective effect. Due to the time-varying analysis, we might have unduly adjusted for factors that are sequels rather than predictors of NSAID use, but we took great care in restricting the assessment of confounders to the period before we assessed NSAID use. It is furthermore implausible that our major confounder besides age, i.e. arthritis, is caused by NSAID use rather than leading to it. Finally, we were unable to address the role of specific NSAIDs or cyclooxygenase 2 (COX-2) selective NSAIDs that might have advantages with respect to possible chemoprevention of colorectal cancer (31), since we do not have information on specific drugs or drug classes, and COX-2 inhibitors have not been on the market long enough to assess their long-term effects in the Physicians' Health Study.

We conclude that, although prevalent regular NSAID users have been consistently observed to be at a reduced risk for colorectal cancer compared to non-users, initiation of regular NSAID use was not protective for colorectal cancer in the Physicians' Health Study. Different control for time-varying confounding and reduced propensity for biases due to factors associated with adherence to long-term medication use, as well as differences in the dosing regimen and duration of use, may have contributed to the apparently discrepant findings on NSAIDs in the primary prevention of colorectal cancer in average risk individuals or populations.

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Table 1
 Characteristics of 22,043 male physicians as of first (baseline) and last questionnaire

	Baseline		Last questionnaire*	
Age (years), mean (SD)	53.8	(9.5)	69.5	(8.8)
Regular NSAID use last 12 months, N (%)				
Non-aspirin NSAIDs	32	(0.2)	2,727	(12.4)
Any NSAIDs (including aspirin)	197	(0.9)	12,436	(56.4)
Body mass index (kg/m ²), mean (SD) [†]	24.8	(2.8)	25.4	(3.5)
Vigorous exercise, N (%) [‡]				
Less than once per week	6,047	(27.7)	9,103	(41.4)
1–4 times per week	12,202	(56.0)	9,283	(42.2)
5 or more times per week	3,552	(16.3)	3,621	(16.4)
Smoking, N (%)				
Never	10,906	(49.5)	10,664	(48.7)
Past	8,662	(39.4)	10,172	(46.4)
Current	2,436	(11.1)	1,069	(4.9)
Alcohol consumption, N (%)				
Never/rarely	3,255	(14.9)	4,319	(19.6)
1–3 times per month	2,440	(11.2)	2,581	(11.7)
Once per week	3,054	(14.0)	2,218	(10.1)
2–4 times per week	4,896	(22.4)	4,105	(18.7)
5–6 times per week	2,770	(12.7)	2,240	(10.2)
Daily	5,436	(24.9)	6,536	(29.7)
Multivitamin use	4,361	(19.9)	10,250	(46.5)
Vegetables (servings per day)	1.4	(0.9)	1.1	(1.0)
Fruits (servings per day)	0.8	(0.7)	0.8	(0.7)
Comorbidity				
Hypertension [§]	4,956	(25.5)	9,374	(43.1)
Diabetes	607	(2.8)	1,875	(8.5)
Coronary artery disease [¶]	103	(0.5)	2,489	(11.3)
Angina	328	(1.5)	3,084	(14.0)
Arthritis	620	(2.8)	6,061	(27.5)
Headaches ^{**}	-	-	11,103	(50.4)
Migraine ^{**}	-	-	2,704	(12.3)
Peptic ulcer	36	(0.2)	1,045	(4.7)
Gastrointestinal bleeding	47	(0.2)	2,182	(9.9)
Gastritis	4	-	10,199	(46.3)

* Last coded questionnaire from up to 20

[†] Weight in kilograms divided by squared height in meters

[‡] Vigorous enough to work up a sweat

[§] Systolic or diastolic blood pressure $\geq 140/90$, respectively, or use of antihypertensives

[¶] Myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty

** Any mention of headache or migraine (specific questions, not assessed at baseline)

Table 2

Independent predictors of self selected regular use of nonsteroidal antiinflammatory drugs in 22,043 male physicians

	Non-aspirin NSAIDs		Any NSAIDs	
	OR [*]	95% CI [*]	OR [*]	95% CI [*]
Age (years)				
40 – < 50	1.0	reference	1.0	reference
50 – < 60	2.1	1.9 – 2.3	2.8	2.6 – 3.0
60 – < 70	2.6	2.3 – 2.9	5.4	5.0 – 5.9
70 – < 80	2.5	2.2 – 2.9	7.0	6.4 – 7.6
80 – < 90	1.9	1.6 – 2.3	7.0	6.3 – 7.8
90 +	1.5	1.1 – 2.2	8.2	6.5 – 10
Body mass index (kg/m ²) [†]				
< 25	1.0	reference	1.0	reference
25 – < 30	1.3	1.2 – 1.4	1.2	1.2 – 1.2
30 +	1.9	1.7 – 2.1	1.6	1.5 – 1.7
Vigorous exercise [‡]				
Less than once per week	1.0	reference	1.0	reference
1–4 times per week	1.2	1.1 – 1.2	1.2	1.1 – 1.2
5 or more times per week	1.2	1.1 – 1.3	1.3	1.2 – 1.4
Smoking				
Never	1.0	reference	1.0	reference
Past	1.1	1.0 – 1.2	1.0	1.0 – 1.1
Current	0.9	0.8 – 1.1	0.8	0.7 – 0.8
Alcohol consumption				
Never/rarely	1.0	reference	1.0	reference
1–3 times per month	1.0	0.9 – 1.1	1.1	1.0 – 1.1
Once per week	1.1	1.0 – 1.3	1.1	1.0 – 1.2
2–4 times per week	1.1	1.0 – 1.3	1.2	1.1 – 1.3
5–6 times per week	1.2	1.1 – 1.3	1.2	1.1 – 1.3
Daily	1.3	1.2 – 1.4	1.1	1.1 – 1.2
Multivitamin use	1.5	1.5 – 1.6	1.7	1.7 – 1.8
Vegetables (servings per day)	0.91	0.88 – 0.94	0.80	0.78 – 0.81
Fruits (servings per day)	0.92	0.88 – 0.96	0.87	0.84 – 0.89
Comorbidity				
Hypertension [§]	1.0	1.0 – 1.1	1.1	1.1 – 1.2
Diabetes	1.0	0.8 – 1.1	1.1	1.0 – 1.2
Coronary artery disease [¶]	1.8	1.5 – 2.0	3.8	3.4 – 4.3
Angina	1.2	1.1 – 1.4	1.6	1.5 – 1.8
Arthritis	3.9	3.6 – 4.1	1.9	1.8 – 2.0
Headaches ^{**}	1.3	1.3 – 1.4	1.7	1.6 – 1.7
Migraine ^{**}	1.2	1.0 – 1.3	1.3	1.2 – 1.3
Peptic ulcer	0.7	0.6 – 0.9	0.8	0.7 – 0.9
Gastrointestinal bleeding	1.1	1.0 – 1.2	1.1	1.1 – 1.2
Gastritis	1.4	1.3 – 1.5	1.5	1.5 – 1.6

* Odds ratios and their 95% confidence intervals for use of non-aspirin NSAIDs (left columns) and non-aspirin NSAIDs or aspirin (right columns) on more than 60 days per year from generalized estimating equation model based on 324,415 individual questionnaires adjusting for intra-individual dependence of multiple (up to 20) questionnaires per person and all variables in the table

[†] Weight in kilograms divided by squared height in meters

[‡] Vigorous enough to work up a sweat

[§] Systolic or diastolic blood pressure $\geq 140/90$, respectively, or use of antihypertensives

[¶] Myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty

^{**} Any mention of headache or migraine (specific questions, not assessed at baseline)

Incidence of colorectal cancer after initiation of regular nonsteroidal anti-inflammatory drug use in the Physician's Health Study

Table 3

Duration of regular non-aspirin NSAID use after initiation	Person-years	Events	IR per 100,000 p-y	Age-adjusted		Fully-adjusted without arthritis*		Fully-adjusted including arthritis*	
				RR	95% CI	RR	95% CI	RR	95% CI
Never	311,615	411	132	1.0	reference	1.0	reference	1.0	reference
1 year	26,235	43	164	1.1	0.8–1.5	1.1	0.8–1.5	1.1	0.8–1.6
2 years	10,411	15	144	0.9	0.5–1.5	0.9	0.5–1.5	1.0	0.6–1.7
3 years	5,814	9	155	1.0	0.5–1.8	0.9	0.5–1.8	1.1	0.5–2.1
4 years	3,802	6	158	1.0	0.4–2.1	0.9	0.4–2.0	1.0	0.5–2.3
5 or more years	7,947	11	138	0.9	0.5–1.6	0.8	0.4–1.5	0.9	0.5–1.7
Duration of regular all NSAIDs use after initiation									
Never	240,900	307	127	1.0	reference	1.0	reference	1.0	reference
1 year	42,649	57	134	0.9	0.7–1.2	0.9	0.6–1.2	0.9	0.6–1.2
2 years	24,911	36	145	0.9	0.6–1.3	0.9	0.6–1.3	0.9	0.6–1.3
3 years	17,176	22	128	0.7	0.5–1.2	0.7	0.4–1.1	0.7	0.5–1.2
4 years	12,108	23	190	1.2	0.7–1.8	1.1	0.7–1.7	1.2	0.7–1.9
5 or more years	28,079	50	178	1.0	0.7–1.4	0.9	0.7–1.4	1.0	0.7–1.5

* Rate ratios and their 95% confidence intervals from time-varying Cox proportional hazards model controlling for all variables presented in table 2: age (continuous, linear and squared), body mass index (continuous), vigorous exercise (5 categories), smoking (never, former, current), alcohol consumption (6 categories), multivitamin use, consumption of fruits and vegetables (servings per day, continuous), as well as history of hypertension, diabetes, coronary artery disease (myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty), angina, headache, migraine, peptic ulcer, gastrointestinal bleeding, and gastritis; variables are updated during follow-up whenever possible

Incidence of colorectal cancer after randomization to study aspirin or self-selected initiation of any regular nonsteroidal anti-inflammatory drug use (including study and non-study aspirin) in the Physician's Health Study

Duration of regular aspirin or NSAID use after randomization or self-selected initiation	Person-years	Events	IR per 100,000 p-y	Age-adjusted		Fully-adjusted*	
				RR	95% CI	RR	95% CI
Never	88,616	108	122	1.0	reference	1.0	reference
1 – 5 years	97,286	124	127	1.0	0.7 – 1.3	0.9	0.7 – 1.2
6 – 10 years	103,008	157	152	1.0	0.7 – 1.3	0.9	0.7 – 1.3
More than 10 years	76,915	106	138	0.9	0.6 – 1.2	0.8	0.6 – 1.2

* Rate ratios and their 95% confidence intervals from time-varying Cox proportional hazards model controlling for all variables presented in table 2: age (continuous, linear and squared), body mass index (continuous), vigorous exercise (5 categories), smoking (never, former, current), alcohol consumption (6 categories), multivitamin use, consumption of fruits and vegetables (servings per day, continuous), as well as history of hypertension, diabetes, coronary artery disease (myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty), angina, headache, migraine, peptic ulcer, gastrointestinal bleeding, and gastritis; variables are updated during follow-up whenever possible