

Original Contribution

Aspirin Use, Body Mass Index, Physical Activity, Plasma C-Peptide, and Colon Cancer Risk in US Health Professionals

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Aspirin use decreases colon cancer risk, but this association may vary among population subgroups. The aspirin-colon cancer association was evaluated according to body mass index and physical activity in 1,701 incident colon cancer cases diagnosed during follow-up of 139,310 participants for up to 26 years in 2 US prospective cohort studies that began in 1980 and 1992, respectively. Whether plasma C-peptide levels modified the association was examined by using a nested case-control design ($n = 384$ cases, 749 controls). Multiplicative and additive interactions were tested. Body mass index did not modify the association; pooled multivariable relative risks for regular aspirin use versus nonuse ranged from 0.74 to 0.75 in the normal weight and obese groups (test for multiplicative interaction, $P = 0.75$; test for additive interaction, $P = 0.66$). Pooled multivariable relative risks for regular aspirin use were 0.86 (95% confidence interval (CI): 0.66, 1.11) in the low and 0.67 (95% CI: 0.58, 0.77) in the high physical activity groups with no interaction evident on either the multiplicative or additive scale ($P > 0.10$). Plasma C-peptide levels also did not modify the aspirin-colon cancer association, with multivariable relative risks of 0.74 (95% CI: 0.50, 1.10) for the low and 0.65 (95% CI: 0.46, 0.92) for the high group. Reductions in colon cancer risk associated with aspirin use were not significantly modified by body mass index, physical activity, or plasma C-peptide level in this study.

additive model; aspirin; body mass index; cohort studies; colonic neoplasms; C-peptide; motor activity; multiplicative model

Abbreviations: BMI, body mass index; CI, confidence interval; COX-2, cyclooxygenase-2; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; NHS, Nurses' Health Study; PGE₂, prostaglandin E₂.

Colorectal cancer is the third most commonly occurring cancer in both men and women in the United States (1). Randomized controlled trials, cohort studies, and case-control studies each have shown that aspirin use reduces the incidence of colorectal cancer, particularly for high doses used for a long duration (2–9). Despite this beneficial effect, aspirin use has associated side effects including peptic ulcers and gastrointestinal bleeding (8, 10), and widespread use is not recommended for preventing colorectal cancer for individuals at average risk for colorectal cancer (10). However, the benefits of aspirin use may outweigh the potential risks among individuals at increased risk of developing colorectal cancer.

Obese or physically inactive individuals are at higher risk of developing colorectal cancer compared with normal weight and physically active individuals (11, 12), possibly because the former have higher prostaglandin E₂ (PGE₂) concentrations (13). Elevated PGE₂ levels result in activation of cell proliferation, angiogenesis, invasion, and inhibition of apoptosis (14). Aspirin has been hypothesized to decrease colorectal cancer risk through the inhibition of cyclooxygenase-2 (COX-2)-mediated synthesis of PGE₂ (15, 16). Overweight individuals are at higher risk of colon cancer (17) and also have been shown to have an increased level of COX-2 expression in normal colon mucosa compared with normal weight individuals (18). Furthermore, aspirin use

has been observed to be effective in preventing the recurrence of colorectal adenomas, precursor lesions of colorectal cancer (19), in obese individuals only (20). We thus hypothesized that the inverse association between aspirin use and colon cancer risk would be stronger among obese or physically inactive individuals compared with normal weight and physically active individuals. We examined this hypothesis in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) in which participants provided detailed and updated data on aspirin use every 2 years. Given that approximately 70%–80% of colorectal cancer in developed countries is colon cancer (21) and that the associations with aspirin use, body mass index, and physical activity are stronger for risk of colon cancer than rectal cancer (21, 22), we focus on colon cancer in this report. This study extends findings (2–5) of inverse associations between aspirin use and risk of colon cancer in earlier analyses in the same cohorts by providing additional follow-up and conducting interaction analyses to examine new hypotheses.

Although the COX-2 pathway is the major proposed underlying pathway to explain the observed inverse association between aspirin use and colon cancer risk, aspirin has also been hypothesized to alter colon cancer risk by other pathways including the insulin-related pathway (23). Obesity and physical inactivity are 2 determinants of hyperinsulinemia (24), and aspirin reverses hyperinsulinemia in obese rodents (25). We thus tested whether the aspirin-colon cancer association differed by plasma concentrations of C-peptide, a validated marker for insulin secretion (26).

MATERIALS AND METHODS

Study population

The NHS is a prospective cohort of 121,700 registered female nurses who were aged 30–55 years at baseline in 1976 in the United States. The HPFS is a prospective cohort study of 51,529 US male professionals who were aged 40–75 years at baseline in 1986. Participants in both studies have been mailed questionnaires every 2 years since baseline to collect data on demographics, lifestyle factors, medical history, and disease outcomes. The follow-up rate has been greater than 90% for both cohorts. These studies have been approved by the institutional review board at the Brigham and Women's Hospital, Boston, Massachusetts.

Identification of incident colon cancer cases

Participants in both cohorts reported cancer and other disease outcomes on the biennial questionnaires. Researchers were given permission by the study participants to obtain medical records and pathology reports on colon cancer. Researchers, blinded to exposure information, reviewed the medical records to abstract information on anatomic location, stage, and histologic type of the cancer. The *International Classification of Diseases*, Ninth Revision (27), was used to define colon cancer by codes 153.0–153.4 and 153.6–153.9. The National Death Index (28) was used to identify deaths among nonresponders.

Ascertainment of colon cancer controls in the nested case-control study

A nested case-control data set was created among participants who provided a blood sample. Detailed information on blood draw, transportation, and storage is reported elsewhere (29, 30). In brief, blood samples were collected from 32,826 NHS participants between 1989 and 1990 and from 18,225 HPFS participants between 1993 and 1995. The data set included incident colon cancer cases from 1990 to June 2004 in the NHS and from 1994 to January 2002 in the HPFS. We excluded participants with a previous cancer diagnosis (except nonmelanoma skin cancer). We further excluded participants with diabetes before blood draw because plasma C-peptide concentrations may not represent long-term insulin secretion among diabetic patients. Controls were matched 2:1 to colon cancer cases on age and year and month of blood donation, and, in the NHS only, on fasting status. Controls were alive and cancer free at the time of the diagnosis of the cases.

Assessment of aspirin use

Information on aspirin assessment has been reported in detail elsewhere (2–5). Briefly, in the NHS, information on aspirin use was first obtained in 1980 and every 2 years thereafter except in 1986. In 1980, participants were asked whether they currently took aspirin in most weeks and, if yes, answered questions on the number of aspirin taken per week and years of aspirin usage. In 1982, 1984, and 1988, the average number of aspirin tablets usually taken per day was asked. In 1990 and 1992, the average number of days per month of aspirin use was asked; information on the number of tablets taken per day was not obtained. For these 2 years, we assumed that 1 standard aspirin tablet (325 mg) was taken per day on the basis of a supplementary questionnaire sent to 4,238 participants (31). Beginning in 1994, the average number of tablets taken per week and the frequency of use were assessed. We calculated the duration in 1986 in the NHS by the information collected in 1984. In the HPFS, in 1986 and every 2 years thereafter, participants were asked whether they used aspirin 2 or more times per week. Beginning in 1992, the amount of aspirin taken and the frequency of use were assessed. For both cohorts, information on low dose ("baby") aspirin was not available until year 2000. However, participants were specifically asked in their biennial surveys to convert intake of 4 baby aspirin to 1 standard tablet aspirin before entering their responses. Thus, aspirin dose in our analysis accurately reflected standard tablet (325 mg) equivalents.

Assessment of anthropometric variables

Height was obtained by self-report in the NHS in 1976 and in the HPFS in 1986. Weight was obtained by self-report at baseline and in subsequent biennial questionnaires in both studies. The age-adjusted correlation coefficients between self-reported weight and measured weight were 0.96 for the NHS (32) and 0.97 for the HPFS (32).

Assessment of physical activity

Recreational or leisure-time physical activity was asked in the questionnaires in both the NHS and the HPFS. Starting from 1986 in the NHS, participants reported their average time engaged in the following activities: walking or hiking outdoors, jogging, running, bicycling, lap swimming, tennis, calisthenics/aerobics/aerobic dance/rowing machine, and squash/racquet ball. Additionally, participants reported the number of flights of stairs climbed daily and their usual walking pace. The same questions were asked in subsequent biennial questionnaires with minor modifications. Similar questions were used in the HPFS starting in 1986. We derived the metabolic equivalent task (MET)-hour score (MET-hours/week) for each activity by multiplying the time spent for that activity group each week (hours/week) and its typical energy expenditure requirements expressed in MET values. The total MET-hour score was calculated as the sum of the values of each activity. The validity of the questionnaire-based physical activity assessment has been tested in the NHS II, a similar cohort of younger nurses (33), and in the HPFS (34). The correlation between reported physical activity on the questionnaire and that recorded in 4-week diaries was 0.62 in the NHS II (33). The correlation between vigorous activity and resting pulse was -0.45 in the HPFS (34).

Measurement of plasma C-peptide

The detailed lab assays on plasma C-peptide have been reported elsewhere (29, 35). In brief, plasma C-peptide was assayed by using an enzyme-linked immunosorbent assay in the laboratory of Dr. Michael Pollak. Samples from matched case-control sets were handled together and assayed in the same batch along with randomly inserted masked quality control samples. All laboratory personnel were blinded to case, control, and quality control status. The mean intra-assay coefficient of variation from quality control samples was less than 13%.

Statistical analyses

We treated 1980 as the baseline for the NHS and 1992 as the baseline in the HPFS (unless otherwise noted), because the number of tablets of aspirin used per week was first measured at these times. We excluded participants with a history of cancer (except for nonmelanoma skin cancer), ulcerative colitis, Crohn's disease, and familial adenomatous polyposis at baseline.

Because the current analyses extended findings from previous analyses of the same cohorts (2–5), to be consistent, we defined regular aspirin users as those participants who reported taking 2 or more standard (325 mg) tablets of aspirin per week. We further evaluated the dose and the duration of aspirin used. Body mass index was classified into 2 categories: normal weight (body mass index (BMI), 18.5 – 24.9 kg/m²) and overweight/obese (BMI, ≥ 25 kg/m²). Physical activity was also classified into 2 levels (low and high) by using different cutpoints for men and women because of the difference in reported physical activity levels in

the 2 studies. Because the information on aspirin use, body mass index, and physical activity was updated on almost every follow-up cycle, we modeled these as time-varying variables to take into account changes over time.

The person-time for each participant was calculated from the date of baseline questionnaire return to the date of death, loss to follow-up, colon cancer diagnosis, or the end of follow-up (June 1, 2006, for women and January 31, 2006, for men), whichever came first. In each study, we used the Cox proportional hazards model (36) to calculate relative risks and 95% confidence intervals and adjusted simultaneously for age (in months) and year of questionnaire return using SAS PROC PHREG (37).

We then conducted multivariable analyses in men and women separately (refer to Table 2 for the list of confounding variables). We used the most updated information for all covariates prior to each follow-up cycle. The trend tests across categories of aspirin dose and duration were performed by assigning median values of these categories and entering these values as continuous terms in the model. We investigated whether the associations between aspirin use, dose, and duration and colon cancer risk differed between women and men by using the Q statistic (38, 39), which follows an approximate χ^2 distribution with 1 df. We pooled the results using a random effects model (39, 40), because there was no statistically significant between-studies heterogeneity.

We examined whether the association between aspirin use and colon cancer risk varied by plasma C-peptide using a nested case-control design. These analyses included 384 incident cases (217 in the NHS and 167 in the HPFS) and 749 controls (419 in the NHS and 330 in the HPFS). We categorized plasma C-peptide levels into a binary variable using the median values specific to the control group in each cohort. We merged the NHS and HPFS data sets into 1 data set because of the relatively small number of cases who used aspirin in each cohort within each plasma C-peptide group ($n \leq 50$ cases). We recategorized duration of aspirin use into 2 groups (0–5, ≥ 6 years of use) because no cases occurred in the ≥ 11 -year group in the HPFS.

We evaluated whether the associations with aspirin use differed by body mass index, physical activity, and plasma C-peptide levels using multiplicative and additive interaction analyses. We focused on regular aspirin use in the interaction analyses because we had limited power to look at details of dose and duration. To evaluate the multiplicative interaction, we constructed a cross-product term between aspirin use and body mass index, physical activity, or C-peptide level and used a Wald test to examine whether the coefficient was statistically significant. For the analyses evaluating whether plasma C-peptide modified the aspirin association, we used unconditional logistic regression analyses.

For the additive interaction analyses, we calculated the Synergy Index (S) (41), relative excess risk due to interaction (renamed as “interaction contrast ratio” later on), and attributable proportion due to interaction (41, 42). We used the programs developed by Lundberg et al. (43) and Andersson et al. (44) to conduct the analyses by creating cross-classified variables between aspirin use and the potential effect

Table 1. Baseline Characteristics of the Nurses' Health Study (1980) and the Health Professionals Follow-up Study (1992)

Characteristics	Nurses' Health Study (<i>n</i> = 104,607)				Health Professionals Follow-up Study (<i>n</i> = 34,703)			
	Not Regular Users ^a		Regular Users ^a		Not Regular Users ^a		Regular Users ^a	
	Mean	%	Mean	%	Mean	%	Mean	%
Age, years	46.6		46.5		58.0		60.1	
Body mass index, kg/m ^{2b}	24.4		24.8		25.6		26.0	
Physical activity, MET-hours/week ^c	14.4		13.4		36.8		36.5	
History of colorectal cancer in a parent or sibling		6		8		13		12
Former or current smokers		50		58		48		54
Alcohol consumption, g/day	6		7		10		11	
Multivitamin use		23		38		38		48
Total calcium intake, mg/day ^d	737		727		900		923	
Total folate intake, µg/day ^d	361		371		486		526	
Beef, pork, or lamb as a main dish, servings/week	2.5		2.6		1.9		1.9	
Processed meat intake, servings/week	1.1		1.2		1.2		1.1	

Abbreviation: MET, metabolic equivalent task.

^a Regular aspirin use was defined as consumption of 2 or more 325-mg tablets per week.

^b Body mass index was calculated as follows: weight (kg)/height (m)².

^c For the Nurses' Health Study, 1986 data were used. MET-hours = sum of the average time/week spent in each activity × MET value of each activity; 1 MET, the energy spent sitting quietly, is equal to 3.5 mL of oxygen uptake per kilogram of body weight per minute for a 70-kg adult.

^d Nutrient values for calcium and folate were the energy-adjusted intake from foods and supplements.

modifier modeled as a binary variable. The delta method (45) was used to derive the 95% confidence intervals for each measure. Given that the study-specific results were similar for these 3 measures, we present only *S* in our tables.

All statistical analyses were 2 sided, and *P* < 0.05 was considered statistically significant. We conducted all analyses using SAS, version 9, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

In the NHS, 1,253 incident colon cancer cases were documented among 104,607 women during 2,537,286 person-years from 1980 to 2006. In the HPFS, 448 incident cases of colon cancer were documented among 34,703 men during 441,295 person-years from 1992 to 2006. Regular aspirin users were comparable to nonregular aspirin users in terms

of age, body mass index, family history of colorectal cancer, alcohol consumption, physical activity level, and intake of folate, calcium, beef, pork, or lamb as a main dish and processed meat; in contrast, regular aspirin users were slightly more likely to use multivitamins and to smoke (Table 1). In addition, approximately 30%–40% of the participants were regular aspirin users in each 2-year follow-up period with a slightly increasing consumption trend observed in more recent follow-up (data not shown).

Because the age- and multivariable-adjusted results for aspirin use, dose, and duration were similar for the total study population, we present only the multivariable results (Table 2). As reported previously in these cohorts for a shorter follow-up period (2–5), aspirin use was associated with a statistically significant lower risk of colon cancer with significant inverse dose-response relations being observed for both increasing aspirin dose and duration (Table 2). The results of aspirin use on colorectal cancer were similar

Table 2. Pooled^a Multivariable Relative Risks of Colon Cancer According to Aspirin Use by Body Mass Index (kg/m²) in the Nurses' Health Study (1980–2006) and the Health Professionals Follow-up Study (1992–2006)

	Total Study Population (n = 139,310)			Stratified by BMI ^b					
	No. of Cases	RR ^d	95% CI	No. of Cases	RR ^d	95% CI	No. of Cases	RR ^d	95% CI
Regular use ^e									
No	1,112	1	Referent	548	1	Referent	564	1	Referent
Yes	589	0.73	0.66, 0.81	247	0.74	0.63, 0.87	342	0.75	0.60, 0.93
Dosage, no. of tablets/week									
0–<2	1,112	1	Referent	548	1	Referent	564	1	Referent
2–5	310	0.75	0.66, 0.85	136	0.76	0.63, 0.93	174	0.76	0.64, 0.91
≥6	279	0.71	0.62, 0.82	111	0.72	0.58, 0.89	168	0.74	0.55, 0.99
<i>P</i> _{trend}			<0.001			0.001			0.01
Duration, years of regular use									
0–5	1,232	1	Referent	598	1	Referent	634	1	Referent
6–10	211	0.81	0.70, 0.94	76	0.70	0.51, 0.97	135	0.88	0.72, 1.07
≥11	258	0.69	0.60, 0.80	121	0.76	0.62, 0.94	137	0.66	0.52, 0.84
<i>P</i> _{trend}			<0.001			0.09			<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; NHS, Nurses' Health Study; RR, relative risk.

^a A random effects model was used to pool the results. No statistically significant heterogeneity was observed between men and women.

^b For multiplicative interaction analyses, a Wald test was used to test the beta-coefficients of the cross-product terms between regular aspirin use and BMI ($P = 0.75$). For additive interaction analyses, we calculated the Synergy Index as $S = 1$ under the null hypothesis of no additive interaction. For the test for additive interaction, $S = 1.12$ (95% CI: 0.69, 1.81) ($P = 0.66$).

^c Normal weight was defined as BMI = 18.5–<25 kg/m²; overweight/obese was defined as BMI ≥25 kg/m².

^d Multivariable relative risks were adjusted for age (in months), smoking before age 30 years (0, 1–4, 5–10, or >10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), current multivitamin use (yes or no), consumption of processed meat (quintiles), consumption of beef, pork, or lamb as a main dish (quintiles), alcohol consumption (0–<5, 5–<10, 10–<15, 15–<30, or ≥30 g/day), energy-adjusted total folate (quintiles) and total calcium (quintiles) intake, physical activity (<6, ≥6 MET-hours/week for NHS; <15, ≥15 MET-hours/week for HPFS), and postmenopausal hormone use (premenopausal, never, past, or current user) in the NHS only. BMI (<25, ≥25 kg/m²) was adjusted in the total study population.

^e Regular aspirin use was defined as consumption of 2 or more 325-mg tablets per week.

according to median age of diagnosis. Also consistent with previous analyses of the same cohorts (11, 12), the present analysis showed positive associations with higher body mass index, low physical activity, and increased levels of plasma C-peptide for both men and women (data not shown).

When we stratified the study population by their body mass index level, the pooled multivariable relative risks comparing regular aspirin use versus nonuse were 0.74 (95% confidence interval (CI): 0.63, 0.87) for the normal weight group and 0.75 (95% CI: 0.60, 0.93) for the overweight/obese group (Table 2; test for multiplicative interaction, $P = 0.75$). In addition, when we categorized body mass index into 3 groups, the risk estimates were similar for normal weight (BMI, 18.5–24.9 kg/m²), overweight (BMI, 25–<30 kg/m²), and obese (BMI, ≥30 kg/m²) strata (data not shown). There also was no evidence of an additive interaction; the synergy

index was close to 1.0 ($S = 1.12$, 95% CI: 0.69, 1.81; test for additive interaction, $P = 0.66$).

The association with regular aspirin use was not significantly modified by level of physical activity, although the strongest inverse association for regular aspirin use was observed in the more physically active group (test for multiplicative interaction, $P = 0.47$) (Table 3). Similarly, no significant additive interaction was observed between aspirin use and physical activity ($S = 0.67$, 95% CI: 0.41, 1.10; test for additive interaction, $P = 0.11$).

We present the results adjusted for the matching factors only for the analyses by plasma C-peptide, because the results adjusted for the matching factors (i.e., season of blood draw, fasting time) were similar to the multivariable results and were more precise. The risk of colon cancer comparing regular aspirin users versus nonusers was similar in the low (multivariable relative risk = 0.74, 95% CI: 0.50,

Table 3. Pooled^a Multivariable Relative Risks of Colon Cancer According to Aspirin Use by Physical Activity (MET-hours/week) in the Nurses' Health Study (1986–2006) and the Health Professionals Follow-up Study (1992–2006)

	Stratified by Physical Activity ^b					
	Low ^c			High ^c		
	No. of Cases	RR ^d	95% CI	No. of Cases	RR ^d	95% CI
Regular use ^e						
No	230	1	Referent	562	1	Referent
Yes	174	0.86	0.66, 1.11	337	0.67	0.58, 0.77
Dosage, no. of tablets/week						
0–<2	230	1	Referent	562	1	Referent
2–5	84	0.88	0.62, 1.25	183	0.67	0.57, 0.79
≥6	90	0.84	0.65, 1.09	154	0.65	0.54, 0.78
<i>P</i> _{trend}			0.18			<0.001
Duration, years of regular use						
0–5	271	1	Referent	619	1	Referent
6–10	71	0.91	0.69, 1.20	123	0.68	0.56, 0.83
≥11	62	0.65	0.49, 0.87	157	0.68	0.56, 0.82
<i>P</i> _{trend}			0.01			<0.001

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; NHS, Nurses' Health Study; RR, relative risk.

^a A random effects model was used to pool the results. No statistically significant heterogeneity was observed between men and women.

^b For multiplicative interaction analyses, a Wald test was used to test the beta-coefficients of the cross-product terms between regular aspirin use and physical activity ($P = 0.47$). For additive interaction analyses, we calculated the Synergy Index as $S = 1$ under the null hypothesis of no additive interaction. For the test for additive interaction, $S = 0.67$ (95% CI: 0.41, 1.10) ($P = 0.11$).

^c Low physical activity was defined as <6 MET-hours/week in the NHS and <15 MET-hours/week in the HPFS; high physical activity was defined as ≥6 MET-hours/week in the NHS and ≥15 MET-hours/week in the HPFS.

^d Multivariable relative risks were adjusted for age (in months), smoking before age 30 years (0, 1–4, 5–10, or >10 pack-years), history of colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), current multivitamin use (yes or no), consumption of processed meat (quintiles), consumption of beef, pork, or lamb as a main dish (quintiles), alcohol consumption (0–<5, 5–<10, 10–<15, 15–<30, or ≥30 g/day), energy-adjusted total folate (quintiles) and total calcium (quintiles) intake, body mass index (<25, ≥25 kg/m²), and postmenopausal hormone use (premenopausal, never, past, or current user) in the NHS only.

^e Regular aspirin use was defined as consumption of 2 or more 325-mg tablets per week.

1.10) and high (multivariable relative risk = 0.65, 95% CI: 0.46, 0.92) plasma C-peptide groups with no significant multiplicative ($P = 0.55$) or additive ($S = 1.62$, 95% CI: 0.56, 4.72; $P = 0.38$) (Table 4) interaction.

DISCUSSION

Aspirin use was associated with a statistically significant 27% lower risk of colon cancer in our analyses of 2 large ongoing cohorts of US health professionals. Our analyses did not suggest that the associations between aspirin use and colon cancer risk differed significantly across levels of body mass index, physical activity, or plasma C-peptide.

The observed inverse association with aspirin use is consistent with results from earlier analyses of the same cohorts

(2–5) and most previous epidemiologic studies (8). Although the underlying mechanisms are unclear, current evidence from cell culture studies, animal models, and epidemiologic research attributes the potential protective effect of aspirin mainly to its inhibition of COX-2-mediated synthesis of PGE₂ (16, 46), a risk factor for colorectal cancer. Increased levels of PGE₂ (13) resulting from a higher body mass index and physical inactivity also have been proposed as a potential mechanism for the positive association observed here and in previous epidemiologic studies (11, 12, 22) for body mass index and physical inactivity. Given that aspirin use, higher body mass index, and physical inactivity may influence colon cancer risk through the same pathway, we conducted multiplicative and additive interaction analyses to address whether the aspirin-colon cancer association was

Table 4. Multivariable Relative Risks of Colon Cancer According to Aspirin Use by Plasma C-Peptide in the Case-Control Study Nested Within the Nurses' Health Study (1990–2004) and the Health Professionals Follow-up Study (1994–2002)

	Stratified by Plasma C-Peptide ^a							
	≤ Median				> Median			
	No. of Cases	No. of Controls	RR ^b	95% CI	No. of Cases	No. of Controls	RR ^b	95% CI
Regular use ^c								
No	104	218	1	Referent	140	195	1	Referent
Yes	58	160	0.74	0.50, 1.10	82	176	0.65	0.46, 0.92
Dosage, no. of tablets/week								
0–<2	104	218	1	Referent	140	195	1	Referent
2–5	30	89	0.69	0.43, 1.12	35	84	0.59	0.37, 0.92
≥6	28	71	0.82	0.49, 1.36	47	92	0.71	0.47, 1.08
<i>P</i> _{trend}				0.39				0.10
Duration, years of regular use								
0–5	124	259	1	Referent	162	252	1	Referent
≥6	38	119	0.64	0.42, 0.99	59	119	0.78	0.53, 1.14

Abbreviations: CI, confidence interval; RR, relative risk.

^a For multiplicative interaction analyses, a Wald test was used to test the beta-coefficients of the cross-product terms between regular aspirin use and plasma C-peptide ($P = 0.55$). For additive interaction analyses, we calculated the Synergy Index as $S = 1$ under the null hypothesis of no additive interaction. For the test for additive interaction, $S = 1.62$ (95% CI: 0.56, 4.72) ($P = 0.38$).

^b Adjusted for age, gender, year and month of blood draw, and fasting time.

^c Regular aspirin use was defined as consumption of 2 or more 325-mg tablets per week.

stronger among overweight/obese or physically inactive individuals. The multiplicative interaction analyses examined whether the relative benefit of aspirin use on colon cancer risk was the same across low- and high-risk groups. From a public health point of view, the absolute reduction in colon cancer risk is also important. Relative risks may be identical in the low- and high-risk groups, but the high-risk group may benefit more from aspirin use because of the underlying higher risk of developing colon cancer in this group. We thus further conducted additive interaction analyses that evaluated whether the absolute reduction in colon cancer risk differed by low- and high-risk groups. Our study suggested that the aspirin-colon cancer association was not significantly modified by body mass index or physical activity level in either the multiplicative or additive interaction analyses, although the additive interaction estimates had relatively wide confidence intervals.

Among the few studies we identified, all have found that the association with aspirin use was not modified (on the multiplicative scale) by body mass index (47–49) or physical activity level (50, 51). In each of these studies, no detailed information on dose or duration of aspirin use was presented. Our results were consistent with these studies, indirectly suggesting that body mass index and physical activity may only weakly influence PGE₂ levels (52). In addition, these null results suggest that obesity or physical activity may be associated with colon cancer risk through mechanisms that are independent of those related to aspirin

use. For example, physical activity may also influence colon cancer risk by decreasing body mass index, increasing gut motility, enhancing the immune system, and enhancing free radical scavenger systems (51).

Additionally, the insulin-related pathway has been suggested to explain the inverse association between aspirin use and colon cancer risk (23). Aspirin has been shown to inhibit tumor formation and growth of the cyclooxygenase-deficient cell line (53) and to reverse hyperinsulinemia in obese rodents (25). Further, a statistically significant interaction has been observed between aspirin use and the insulin receptor substrate 1 (IRS1) genotype on colorectal cancer risk, which provides support for the possibility that aspirin may operate through the insulin-related pathway (23). Our study found no statistically significant interaction between aspirin use and plasma C-peptide level, a marker of insulin secretion (26). However, given the relatively smaller number of colon cancer cases in those analyses, we cannot exclude the possibility that we may have missed a potential interaction.

Several limitations need to be considered in our analyses. First, the possibility that our results are confounded by unmeasured factors cannot be ruled out. Second, we had data on leisure-time physical activity but not on household or occupational physical activity, although occupational activity is low for most male health professionals (54). Third, blood specimens were not available for all study participants, and we had only a single measurement of plasma

C-peptide, which may not represent long-term status. However, previous studies have suggested a reasonable within-person correlation for plasma C-peptide levels measured 4 years apart ($r = 0.57$) (55).

Strengths of this study include its prospective design with long follow-up time and a high follow-up rate, large size, measurement of many risk factors for colon cancer, and availability of updated information on aspirin use. Additionally, we conducted multiplicative and additive interaction analyses in which we could evaluate both biologic and public health interactions to some extent (44).

In summary, regular aspirin use was associated with a 27% lower risk of colon cancer. However, our current study suggests that the aspirin-colon cancer association was not significantly modified by body mass index, physical activity, or plasma C-peptide level. Given the relatively larger confidence intervals for the measures of additive interactions, we cannot exclude the possibility that aspirin use may have a greater absolute benefit among certain groups. More research on the mechanisms by which aspirin use and other determinants affect colon carcinogenesis is warranted and may help to identify potential subgroups among whom the benefits of aspirin use may outweigh its side effects.

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