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Differences in Risk Factor-Colorectal Adenoma Associations According to Non-Steroidal Anti-Inflammatory Drug Use

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Abstract

Objective: Because multiple observational studies and large, randomized controlled trials indicate that non-steroidal anti-inflammatory drugs (NSAIDs) strongly reduce risk for colorectal neoplasms, we investigated whether NSAID use masks associations of various other risk factors with colorectal neoplasms.

Methods: Using pooled data from three case-control studies of incident, sporadic colorectal adenoma (pooled n = 789 cases, 2,035 polyp-free controls), using multivariable logistic regression, we investigated various risk factor-colorectal adenoma associations stratified by NSAID use.

Results: Example multivariable-adjusted odds ratios (OR) (95% confidence intervals [CI]) for those in the highest relative to the lowest quartiles of exposure, by regular non-aspirin NSAID non-use/use, respectively, were 1.57 (CI 0.96, 2.55) vs. 1.14 (0.37, 3.49) for total fat, 1.37 (CI 0.86, 2.18) vs. 0.70 (CI 0.23, 2.25) for saturated fat, 0.93 (CI 0.68, 1.28) vs. 1.30 (CI 0.61, 2.75) for calcium, 0.89 (CI 0.64, 1.23) vs. 1.38 (CI 0.65, 2.94) for total fruits and vegetables, and 0.85 (CI 0.65, 1.11) vs. 0.94 (CI 0.52, 1.71) for physical activity. For current versus never smokers, the ORs (95% CIs) among regular non-NSAID users/non-users were 2.91 (CI 2.22, 3.82) vs. 1.75 (CI 0.90, 3.41), and for those who were obese versus those who were normal weight, they were 1.67 (CI 1.28, 2.17) vs. 1.19 (CI 0.69, 2.04).

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Disclosure of Potential Conflicts of Interest

None of the authors has a conflict of interest to disclose.

Disclaimer

The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the National Cancer Institute, the Fullerton Foundation, or the Franklin Foundation. The National Cancer Institute, the Fullerton Foundation, and the Franklin Foundation had no influence on the analysis and interpretation of the data, the decision to submit the manuscript for publication, or the writing of the manuscript.

Conclusions: Our findings suggest that regular non-aspirin NSAID use may mask, beyond simple confounding, associations of major risk factors with colorectal adenoma, and support routinely assessing such associations stratified by regular non-aspirin NSAID use.

Keywords

colorectal adenoma; anti-inflammatory agents; non-steroidal; colorectal neoplasms; case-control studies; risk factors

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States (1). Colorectal adenomatous polyps, or adenomas, are the precursor lesions of most CRCs (2, 3). An approximately 20-fold variation (4, 5) in incidence rates globally (with industrialized nations having the highest incidence) (6), coupled with studies of immigrant populations (4, 7, 8), indicate that environmental factors strongly influence risk of sporadic CRC.

Some of the major risk factors considered to be causally directly associated with risk of colorectal neoplasms include age and a family history of CRC or adenoma in a first degree relative, and other major risk factors frequently directly associated with risk of colorectal neoplasms include obesity, height, smoking, alcohol consumption, and dietary intakes of total fat, saturated fat, and red and processed meats (9). Risk factors considered to be causally inversely associated with risk include regular use of non-steroidal anti-inflammatory drugs (NSAIDs), and other major risk factors frequently inversely associated with risk include physical activity, hormone replacement therapy (HRT) among postmenopausal women, and calcium, folate, fiber, and fruit and vegetable intakes (9). Although there is extensive epidemiologic literature regarding these various risk factors, with few exceptions, there are inconsistencies in the strengths of the associations of various risk factors with risk of CRC or adenoma. For example, the relative risk (RR)/odds ratio (OR) estimates for the association of calcium intake with colorectal neoplasms range from 0.5 to 1.8 (10, 11), from 0.4 to 1.53 for physical activity, from 0.58 to 0.95 for fiber intake, from 0.40 to 1.0 for HRT use, etc. On the other hand, the evidence for NSAID use (especially for non-aspirin NSAID use) is remarkably consistent, with virtually all of over 100 observational studies addressing non-aspirin NSAID use finding 30 – 39% lower risk (12), three major randomized clinical trials (RCTs) of non-aspirin NSAIDs finding 33 – 36% reduced adenoma recurrence (13–15), and smaller RCTs finding diminishment and even disappearance of adenomas among familial adenomatous polyposis (FAP) patients given non-aspirin NSAIDs (16–19). The strengths of these associations and treatment effects suggest that NSAID use may substantially impair our ability to detect associations of other risk factors (especially those whose mechanisms may also involve effects on inflammation) with colorectal neoplasms.

Therefore, one possible explanation for the inconsistencies of the associations of many risk factors with colorectal neoplasia across studies may be that the strengths of the associations may differ between those who do and do not regularly take NSAID, and that the prevalence

of NSAID use has increased over the past 30 years and may differ across different study populations. Indeed, the results from several recent studies, including observational studies (20–23) and RCTs (24, 25), suggest that the associations or effects of modifiable risk factors for colorectal neoplasms, particularly diet, may differ by non-aspirin NSAID and aspirin use. Thus, we hypothesize that regular NSAID use (particularly non-aspirin NSAID use, given that non-aspirin NSAIDs have stronger anti-inflammatory effects and longer duration of action) may mask, beyond simple confounding, associations of major risk factors with colorectal neoplasms, and that some of the past inconsistencies in risk factor-colorectal neoplasm associations may be explained by differential proportions of NSAID use across different study populations.

Herein, we report the results of an analysis of data from three pooled case-control studies to investigate differences in associations of the major risk factors for colorectal neoplasms with incident, sporadic colorectal adenoma according to NSAID use.

Materials and Methods

Study Design and Population

We pooled and analyzed data from three methodologically similar case-control studies of incident, sporadic colorectal adenomas conducted by the same principal investigator (RMB). The detailed study protocols for all three studies were previously published. Briefly, the first study (the Cancer Prevention Research Unit [CPRU] study) was conducted as a collaboration between the University of Minnesota and Digestive Healthcare, PA (Minneapolis, Minnesota), a large, multi-clinic, private gastroenterology practice, from 1991 to 1994 (26); the second (the first Markers of Adenomatous Polyps study [MAP I]) was conducted in community gastroenterology practices in Winston-Salem and Charlotte, North Carolina from 1994 to 1997 (21); and the third (the second MAP study [MAP II]) was conducted at Consultants in Gastroenterology, PA, a large, private practice gastroenterology group in Columbia, South Carolina, in 2002 (27). The initial eligibility for study participation was age 30–74 years, English speaking, and scheduled to undergo outpatient, elective colonoscopy. Patients with a history of a colorectal adenoma, known hereditary syndromes associated with a predisposition to colonic neoplasia, or a personal history of inflammatory bowel disease (IBD), bowel resection, or past or prevalent cancer other than non-melanoma skin cancer were excluded. In the CPRU study, using the same eligibility and exclusion criteria other than being scheduled for colonoscopy, two additional sets of participants were recruited as controls: 1) screening flexible sigmoidoscopy patients who were polyp-free upon screening flexible sigmoidoscopy, and 2) community controls, who did not undergo sigmoidoscopy or colonoscopy at the time of the study. The community controls were randomly selected from the 1991 Minnesota State Driver's License Registry and frequency-matched to the colonoscopy cases on zip code, age (5-year intervals), and sex. Cumulatively, 3,317 patients were identified as potentially eligible for the three studies. All three studies had similar participation rates (68% to 76%).

The protocols of each study were approved by the institutional review boards at the institutions where they were conducted: the University of Minnesota and each Digestive Healthcare colonoscopy site for the CPRU study, Wake Forest University School of

Medicine for the MAP I study, and the University of South Carolina for the MAP II study. Each study participant provided written informed consent.

Data Collection

All study participants completed mailed questionnaires regarding demographic characteristics, personal medical history, family history of CRC, hormonal and reproductive history (women only), self-reported anthropometrics, alcohol and tobacco use, and usual physical activity. Self-administered semi-quantitative Willett food frequency questionnaires were used to assess intakes of food and nutritional supplements over the preceding twelve months. Aspirin and other NSAID use were assessed as the number of pills taken per week.

Endoscopy participants completed their questionnaires at home within the week prior to their endoscopy visit, and the completed questionnaires were collected and reviewed at the endoscopy visit. For colonoscopy participants, polyp locations and *in vivo* shapes and sizes were documented on standardized forms. All polyps found during the colonoscopy were removed and examined histologically by one index study pathologist using the diagnostic criteria established for the National Polyp Study (28). Based on the colonoscopy and pathology findings, participants were assigned final eligibility and classified into one of three groups if they underwent a complete, clean colonoscopy reaching the cecum: 1) cases (those found to have at least one adenoma, none of which contained invasive CRC); 2) a hyperplastic polyp group, which was excluded from further analysis; and 3) colonoscopy-negative controls (those found to have no adenomatous or hyperplastic polyps). As noted above, in the CPRU study there were two additional sets of controls: screening flexible sigmoidoscopy patients who were polyp-free upon screening flexible sigmoidoscopy and community controls; these controls were pooled with the colonoscopy-negative controls.

Of the 3,317 participants who agreed to participate and met the initial eligibility criteria, those found to have invasive CRC or incident IBD, non-cases with hyperplastic polyps, and those who left >10% of their food frequency questionnaire items blank and/or had implausible total energy intakes (<600 kcal/day or >6,000 kcal/day) (n= 493) were excluded from the final analyses, leaving 2,824 participants (n= 789 cases and 2,035 controls) for analysis.

Statistical Analysis:

Selected characteristics of the cases and controls were compared using Fisher's exact test and the two-sample *t*-test for categorical and continuous variables, respectively.

We used multivariable, unconditional logistic regression to estimate the associations of each risk factor with adenoma, overall and stratified by regular (once/week) non-aspirin NSAID use. Covariates/stratification variables were selected *a priori* based on their being established risk factors for colorectal neoplasms. Total intakes of micronutrients were calculated as dietary plus supplemental intakes. A questionnaire-derived, equal-weight oxidative balance score (OBS) was calculated as previously described (29, 30), and included pro-oxidant variables (smoking status, body mass index [BMI], and alcohol, saturated fat, and total iron intakes) and antioxidant variables (physical activity and total vitamin E, vitamin C, carotenoids, lutein, lycopene, vitamin E, omega-3 fatty acids, flavonoids, and glucosinolates).

intakes), such that a higher OBS represented higher antioxidant relative to pro-oxidant exposures.

All variables were analyzed as categorical variables, developed as follows. Sex, a family history of CRC in a first degree relative, and regular (once/week) aspirin and non-aspirin NSAID use were dichotomous. Age was categorized into quartiles based on the distribution among the controls. Smoking was categorized as current, former, or never. Alcohol consumption was categorized as none and low/high based on the sex-specific distribution among the controls. Physical activity was categorized according to the study-specific quartiles among the controls. Height was categorized according to quartiles based on the sex-specific distributions among the controls. BMI was categorized according to the World Health Organization (WHO) criteria as underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5 - 24.9 \text{ kg/m}^2$), overweight ($25.0 - 29.9 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$). HRT use among women was categorized as never, former, and current. Total intakes of energy, total fat, saturated fat, dietary fiber, total calcium, total folate, total fruits and vegetables, and total red and processed meats were categorized according to quartiles based on the study- and sex-specific distributions among the controls. The OBS was categorized into quartiles based on the study-specific distribution among the controls.

The association of each selected risk factor with adenoma was adjusted for (except as noted below) age, sex, family history of CRC in a first-degree relative, smoking status, alcohol consumption, BMI, height, physical activity, HRT use (in women), regular aspirin use, and dietary intakes of energy, total fat, saturated fat, dietary fiber, total calcium, total folate, total fruits and vegetables, and total red and processed meats. The model for total fat did not include saturated fat (and vice versa), and the model for dietary fiber did not include total fruits and vegetables (and vice versa). The OBS-adenoma association was adjusted for age, sex, education, family history of CRC in a first-degree relative, regular aspirin use, HRT use (in women), and total calcium, total vitamin D, total folate, dietary fiber, and total energy intakes.

The associations were calculated from the multivariable-adjusted logistic regression models as odds ratios (ORs) and their corresponding 95% confidence intervals (CI). For each variable with more than two categories, a P-value for trend was calculated by including in the models a continuous variable based on the category ranking for variables collected as categorical variables and the median of the quartiles of variables that were collected as continuous variables. Differences in risk factor-adenoma associations according to regular non-aspirin NSAID use were assessed by comparing stratum specific ORs.

All analyses were conducted using SAS statistical software, version 9.4 (Institute Inc., Cary, North Carolina). All statistical tests were 2-sided, and a p-value <0.05 or a 95% confidence interval that excluded 1.0 was considered statistically significant.

Results

Selected characteristics of the study participants in the pooled studies are shown in Table 1. On average, cases were approximately 4 years older, consumed more alcohol, had a higher

BMI, were taller, and consumed more total energy, total fat, saturated fat, and red and processed meats. They were also more likely to be male and to smoke. Controls were more likely to take HRT (if a woman) and to regularly (once/week) take a NSAID, aspirin, or both. On average, they had higher intakes of total calcium, total folic acid, and total fruits and vegetables, and a higher OBS.

As shown in Table 2, preliminary to assessing associations of major CRC risk factors with adenoma according to regular non-aspirin NSAID use, we assessed the overall associations of the major risk factors with adenoma, adjusted for aspirin and non-aspirin NSAID use. There were statistically significant direct associations of adenoma with age, smoking, alcohol consumption, BMI, height, and total fat intake, and statistically significant inverse associations with the OBS and regular use of aspirin and other NSAIDs. There were no strong or statistically significant estimated associations with the other risk factors, although the estimated associations were in the hypothesized directions for a family history of CRC in a first degree relative (direct), physical activity (inverse), HRT use (inverse), and intakes of saturated fat (direct), total folate (inverse), and total fruits and vegetables (inverse); whereas the direction of the estimated association for dietary fiber was opposite (direct) to that hypothesized, and the estimated associations for sex (men) and total calcium and total red and processed meat intakes were very close to the null.

The results of our primary analysis, associations of major CRC risk factors with adenoma according to regular non-aspirin NSAID use, are shown in Table 3 and can be compared with the findings in Table 2. None of the differences between strata were of sufficient magnitude to suggest statistically significant multiplicative interactions. However, the following patterns were noted: among those who did not regularly take a non-aspirin NSAID, the estimated associations of multiple risk factors with adenoma tended to be stronger than those among those who did take a non-aspirin NSAID and/or among all participants combined (adjusted for regular non-aspirin NSAID use). These included stronger estimated direct associations of adenomas with age, family history of CRC in first degree relative, smoking, BMI, and total fat, saturated fat, and total red and processed meat intakes; and stronger estimated inverse associations with physical activity, the OBS, and total calcium and total fruit and vegetable intakes. On the other hand, among those who regularly took a non-aspirin NSAID, the estimated direct associations of adenoma for men and alcohol intake, and the estimated inverse association for HRT use tended to be stronger. Taking into account the ORs across the quantiles, there were no clear differences related to height or dietary fiber (the ORs in both strata were > 1.0) or total folate intakes.

Additional analyses were done to assess whether the overall associations of major risk factors with adenoma differed according to aspirin use alone (controlling for non-aspirin NSAID use) or aspirin and/or NSAID use. Our results did not indicate any substantial differences for any of the risk factor–adenoma associations when stratified by aspirin use alone, and the differences when stratified by aspirin and/or NSAID use were less than those when stratified by non-aspirin NSAID use alone.

Discussion

A substantial concordance of data from observational studies (12), and large RCTs indicates that NSAID use reduces the risk of colorectal neoplasms. A hallmark of colorectal tumorigenesis is chronic inflammation characterized by increased activity in the COX pathway (31), in particular that of COX-2. COX-2 overexpression is found in more than 80% of colon cancers in humans (32) and although the exact anti-tumor mechanism of action of NSAIDs remains unclear, it is hypothesized to be related to COX-2. COX-2 inhibitors reduced adenoma recurrence and tumor burden in RCTs in non-FAP (13–15) and FAP patients (16–19).

The risk factors we assessed in this study are extensively reported on in the literature. Higher risk for colorectal neoplasms with older age (33, 34), having a first degree relative with CRC (4), and being a male (1) are well established. The biological plausibility for and associations of selected other risk factors are summarized in Table 4.

As noted above, for many of the established risk factors for colorectal neoplasms, the hypothesized mechanisms involve inflammation and oxidative stress. We postulate that the contributions of the individual risk factors to inflammation are small relative to the anti-inflammatory effects of NSAIDs—especially non-aspirin NSAIDs—and, thus, that risk factor-colorectal neoplasm associations involving factors that may affect risk through pro-inflammatory mechanisms may be particularly hard to detect among those with pharmacologically suppressed inflammation. This in turn suggests that combining NSAID users and non-users may attenuate associations of various risk factors with colorectal neoplasms, but does not rule out that in some cases that there may be synergistic effects.

Few studies reported on associations of the above-reviewed risk factors according to NSAID use. In two case-control studies (21, 22), the inverse association of physical activity with adenoma was restricted to those who did not use NSAIDs. Slattery et al. (20) also observed a higher risk of colon cancer with high consumption of trans-fatty acids among those who did not take a NSAID. Wu et al.(23), observed inverse associations of calcium intakes with risk of distal colon cancer only among those who did not take aspirin; a similar effect of calcium supplementation was noted in a RCT (25). In the Polyp Prevention Trial (24), the high-fiber, high-fruit and vegetable, low-fat dietary intervention was estimated to reduce adenoma recurrence only among those who did not take a NSAID. Our findings on physical activity, total intakes of fat, saturated fats, calcium and fruits and vegetables although not statistically significant, are consistent with those in these earlier studies.

Our study had several limitations and strengths. The primary strengths of our study included the collection of data on multiple risk factors/potential confounding and effect modifying variables; exposure assessment prior to colonoscopy and adenoma diagnosis, reducing the likelihood of recall bias; *the use of different types of control groups each, with their own strengths and limitations*; and pooling of data collected in almost identical fashion from three study populations in three states.

Limitations include that, despite the overall substantial sample size, among those who regularly took a non-aspirin NSAID, the number of cases in the categories of several

variables was relatively small. However, although the estimated associations among those who regularly took a non-aspirin NSAID, were unstable, among those who did not regularly take a non-aspirin NSAID, the estimated strengths of associations of multiple established risk factors for CRC with adenoma tended to be somewhat stronger than those estimated from the combined population, even adjusted for non-aspirin NSAID use. *Another limitation is that although our data are older, the pattern of findings across the three case-control studies was similar and our combined results are comparable to those in the published literature.* Other limitations include those inherent to case-control studies, such as recall error and the inability to assess temporality; however, most adenomas are asymptomatic and unlikely to affect someone's responses on questionnaires. While there was minimal outcome misclassification among the cases and controls confirmed via colonoscopy, such study participants may have been at higher risk and thus more similar to each other than would be the case in the general population. *Also, while the community controls and the sigmoidoscopy controls in the CPRU study may have been more representative of the general population, some of them may have been undiagnosed cases. These limitations regarding the controls may have resulted in attenuated estimated associations.* Other limitations include the well-known limitations of assessing diet via a food frequency questionnaire (e.g., recall error, limited numbers of response items, etc.) and that most of the study participants were white.

In conclusion, if our findings were to be consistently replicated in other studies, it would suggest that differential proportions of regular NSAID users between study populations may explain some of the inconsistencies in reported risk factor-colorectal neoplasm associations over time and among current studies. Furthermore, taken together with previous literature, our findings suggest that regular non-aspirin NSAID use may mask, beyond simple confounding, associations of multiple major CRC risk factors with incident, sporadic colorectal neoplasms, and support routinely assessing such associations stratified by regular non-aspirin NSAID use.

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Table 1.

Selected characteristics of cases and controls in three pooled case-control studies: CPRU study, 1991–1994; MAP I Study, 1994–1997; and MAP II study, 2002

Characteristics ^a	Cases (n = 789)	Controls (n = 2,035)	P-value ^b
Age (y)	58.1 (9.2)	54.5 (10.9)	<0.01
Men (%)	61.1	42.8	<0.01
First-degree relative with CRC (%)	16.9	17.9	0.54
Smoking status (%)			
Current	24.1	14	<0.01
Former	44.9	40	
Alcohol consumption (drinks/wk)	4.8 (8.1)	3.4 (6.8)	<0.01
Body mass index (kg/m ²)	27.5 (5.1)	26.8 (4.9)	<0.01
Height (inches)	67.3 (3.7)	66.2 (3.9)	<0.01
Physical activity (METs/wk) ^c	60.4 (56.8)	58.1 (54.1)	0.33
Dietary intakes			
Total energy (kcal/d)	2,071 (780)	1,991 (724)	0.01
% calories from fat	65.8 (32.1)	60.6 (27.8)	<0.01
% calories from saturated fat	22.5 (12.0)	20.7 (10.2)	<0.01
Dietary fiber (g/d)	21.7 (9.4)	22.0 (10.1)	0.50
Total ^d calcium (mg/d)	931 (520)	978 (531)	0.03
Total ^d folic acid (mcg/d)	412 (239)	443 (256)	<0.01
Total fruits & vegetables (servings/d)	6.0 (3.4)	6.3 (3.7)	0.02
Total red & processed meats (servings/d)	1.1 (1.0)	0.9 (0.7)	<0.01
Currently take HRT (women)	13.8	21.7	<0.01
Regularly take ^e aspirin &/or other NSAID	35.5	41.6	<0.01
Regularly take ^e NSAID	14.6	22.6	<0.01
Regularly take ^e aspirin	24.1	25.5	0.47
Oxidative balance score ^f	– 1.03 (5.4)	0.48 (5.6)	<0.01

Abbreviations: CPRU, Cancer Prevention Research Unit; CRC, colorectal cancer; HRT, hormone replacement therapy; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalents of task; NSAID, nonsteroidal anti-inflammatory drug.

^aData presented as means (SD) unless otherwise specified.

^bFrom Fisher's exact test for categorical variables, and two-sample test for continuous variables.

^cModerate + vigorous.

^dTotal = diet + supplements.

^eonce/week.

^fSee definition in text; a higher oxidative balance score represents higher antioxidant relative to pro-oxidant dietary and lifestyle exposures.

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Table 2.

Multivariable-adjusted associations of risk factors with incident, sporadic, colorectal adenoma in three pooled case-control studies: CPRU study, 1991–1994; MAP I study, 1994–1997; and MAP II study, 2002

Risk factors ^a	Pooled analysis (n = 2,824)			
	No. of Cases	No. of Controls	OR ^b	95% CI
Age quartiles (years)				
1 (47)	101	552	1.00	Referent
2 (48 – 55)	187	491	2.12	1.60, 2.82
3 (56 – 63)	246	508	2.70	2.04, 3.56
4 (64)	255	484	3.45	2.60, 4.57
<i>P_{trend}</i> ^c			< 0.01	
Sex				
Female	307	1,164	1.00	Referent
Male	482	871	0.98	0.62, 1.54
First-degree relative with CRC (%)				
No	656	1,671	1.00	Referent
Yes	133	364	1.05	0.83, 1.32
Smoking status				
Never	190	284	1.00	Referent
Former	245	938	1.35	1.10, 1.65
Current	354	813	2.68	2.09, 3.44
<i>P_{trend}</i> ^c			< 0.01	
Alcohol consumption				
Nondrinker	328	890	1.00	Referent
Low	190	597	0.84	0.67, 1.04
High	271	548	1.24	1.00, 1.53
<i>P_{trend}</i> ^c			< 0.01	
Body mass index (kg/m ²)				
Normal weight (18.5 – 24.9)	244	799	1.00	Referent
Underweight (< 18.5)	11	22	1.36	0.62, 3.00
Overweight (25.0 – 29.9)	324	775	1.16	0.95, 1.43
Obese (≥ 30)	210	439	1.59	1.26, 2.02
<i>P_{trend}</i> ^c			0.16	
Height, quartiles (inches)				
1 (63.5)	156	432	1.00	Referent
2 (63.6 – 65.4)	245	647	1.00	0.78, 1.29
3 (65.5 – 69.4)	171	406	1.16	0.88, 1.52
4 (69.5)	217	550	1.40	1.08, 1.81
<i>P_{trend}</i> ^c			< 0.01	

Risk factors ^a	Pooled analysis (n = 2,824)			
	No. of Cases	No. of Controls	OR ^b	95% CI
Physical activity, quartiles				
1	227	517	1.00	Referent
2	188	501	0.89	0.70, 1.14
3	181	509	0.88	0.69, 1.12
4	193	508	0.85	0.67, 1.08
P_{trend}^c			0.27	
Dietary intakes % calories from total fat, quartiles				
1	182	512	1.00	Referent
2	186	506	1.09	0.82, 1.43
3	204	510	1.34	0.95, 1.89
4	217	507	1.52	0.97, 2.37
P_{trend}^c			0.02	
% calories from saturated fat, quartiles				
1	184	513	1.00	Referent
2	210	506	1.17	0.89, 1.53
3	185	509	1.12	0.80, 1.58
4	210	507	1.28	0.83, 1.95
P_{trend}^c			0.23	
Dietary fiber, quartiles				
1	189	512	1.00	Referent
2	218	508	1.22	0.95, 1.57
3	195	508	1.23	0.92, 1.63
4	187	507	1.25	0.89, 1.75
P_{trend}^c			0.28	
Total^d calcium, quartiles				
1	212	512	1.00	Referent
2	208	506	1.01	0.78, 1.30
3	176	510	0.86	0.66, 1.13
4	193	507	0.98	0.74, 1.31
P_{trend}^c			0.60	
Total^d folic acid, quartiles				
1	211	512	1.00	Referent
2	232	507	1.10	0.85, 1.43
3	171	509	0.81	0.61, 1.10
4	175	507	0.90	0.66, 1.21

Risk factors ^a	Pooled analysis (n = 2,824)			
	No. of Cases	No. of Controls	OR ^b	95% CI
P_{trend}^c			0.22	
Total fruits & vegetables, quartiles				
1	206	504	1.00	Referent
2	212	511	1.03	0.81, 1.32
3	185	518	0.89	0.69, 1.16
4	186	502	0.95	0.71, 1.28
P_{trend}^c			0.63	
Total red & processed meats, quartiles				
1	158	461	1.00	Referent
2	216	593	1.01	0.78, 1.31
3	194	463	1.04	0.78, 1.38
4	221	518	0.97	0.70, 1.34
P_{trend}^c			0.86	
HRT use (women)				
No	680	1,593	1.00	Referent
Yes	109	442	0.85	0.65, 1.11
NSAID use once/wk.				
No	674	1,576	1.00	Referent
Yes	115	459	0.63	0.50, 0.80
Aspirin use once/wk.				
No	599	1,517	1.00	Referent
Yes	190	518	0.79	0.64, 0.96
Oxidative balance score, quartiles^e				
1	297	509	1.00	Referent
2	185	509	0.65	0.51, 0.82
3	164	509	0.59	0.46, 0.76
4	143	508	0.54	0.41, 0.72
P_{trend}^c			< 0.01	

Abbreviations: CPRU, Cancer Prevention Research Unit; CRC, colorectal cancer; CI, confidence interval; HRT, hormone replacement therapy; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalents of task; OR, odds ratio; NSAID, nonsteroidal anti-inflammatory drugs excluding aspirin.

^aQuartiles of age were based on the distribution among the controls. Quartiles of physical activity were based on the study-specific distributions among the controls. Cutpoints for alcohol intake were based on the sex-specific distributions among the controls, and were defined as follows: low intake / high intake: 2.5 / > 7 drinks/week among males, and 1 / > 4 drinks /week among females. Cut-points for height quartiles were based on the sex-specific distribution among the controls, and were defined as follows: 67.4, 69.4, and 71.4 inches among men, and 62.5, 63.5, and 65.4 inches among women. Quartiles for all dietary intake variables were based on the sex- and study-specific distributions among controls. Quartiles for the oxidative balance score were based on the study-specific distributions among the controls.

^b Odds ratios and 95% confidence intervals from unconditional logistic regression models. Covariates for all models, except as noted below, included age, sex, family history of colorectal cancer in a first-degree relative, smoking, alcohol intake, body mass index, height, physical activity, hormone therapy (among women), regular aspirin use once/wk., regular NSAID use once/wk., and total calcium, folate, dietary fiber, total energy, total fat, saturated fat, total fruit and vegetable, and total red and processed meats intakes. The model for fat did not include total saturated fat, the model for saturated fat did not include total fat, the model for dietary fiber did not include total fruits and vegetables, and the model for total fruits and vegetables did not include dietary fiber. Covariates for the model for the oxidative balance score included age, sex, education, family history of colorectal cancer in a first-degree relative, regular aspirin use, regular NSAID use, hormone replacement therapy (among women), and total calcium, total vitamin D, total energy, total folate, and dietary fiber intakes.

^c P_{trend} values (2-sided) were calculated by including the median of each quartile of each variable as a continuous variable in the multivariable models, except the model for body mass index, where the median of the underweight category was excluded.

^d Total = dietary + supplemental.

^e Oxidative balance score (OBS) calculated as described in the text; a higher OBS reflects higher antioxidant relative to pro-oxidant dietary and lifestyle exposures.

Table 3.

Multivariable-adjusted associations of risk factors with incident, sporadic colorectal adenoma in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II, 2002), stratified by regular non-aspirin NSAID use

Risk factors ^a	Regular use of non-aspirin NSAID (n = 574)				No regular use of non-aspirin NSAID (n = 2,250)			
	No. of Cases	No. of Controls	OR*	95% CI	No. of Cases	No. of Controls	OR ^b	95% CI
Age quartiles (years)								
1 (47)	14	132	1.00	Referent	87	420	1.00	Referent
2 (48 – 55)	31	114	2.97	1.44, 6.10	156	377	2.00	1.47, 2.73
3 (56 – 63)	41	109	4.05	1.98, 8.26	205	399	2.52	1.86, 3.41
4 (64)	29	104	3.16	1.51, 6.61	226	380	3.51	2.58, 4.77
<i>P_{trend}</i> ^c			<0.01				<0.01	
Sex								
Female	52	314	1.00	Referent	255	850	1.00	Referent
Male	63	145	1.19	0.41, 3.47	419	726	0.94	0.56, 1.55
First-degree relative with CRC (%)								
No	96	370	1.00	Referent	560	1,301	1.00	Referent
Yes	19	89	0.87	0.49, 1.54	114	275	1.09	0.84, 1.40
Smoking status								
Never	41	183	1.00	Referent	204	755	1.00	Referent
Former	54	213	0.86	0.53, 1.41	300	600	1.47	1.18, 1.80
Current	20	63	1.75	0.90, 3.41	170	221	2.91	2.22, 3.82
<i>P_{trend}</i> ^c			0.27				<0.01	
Alcohol consumption								
Non-drinker	49	200	1.00	Referent	279	690	1.00	Referent
Low	24	144	0.66	0.38, 1.17	166	453	0.87	0.69, 1.11
High	42	115	1.41	0.85, 2.36	229	433	1.20	0.95, 1.52
<i>P_{trend}</i> ^c			0.08				0.01	
Body mass index, (kg/m ²)								
Normal weight (18.5 – 24.9)	37	163	1.00	Referent	207	636	1.00	Referent
Underweight (<18.5)	0	2	n/a	n/a n/a	11	20	1.49	0.66, 3.33
Overweight (25.0 – 29.9)	32	148	0.73	0.41, 1.28	292	627	1.25	1.00, 1.56
Obese (30)	46	146	1.19	0.69, 2.04	164	293	1.67	1.28, 2.17
<i>P_{trend}</i> ^c			0.44				0.06	

Risk factors ^a	Regular use of non-aspirin NSAID (n = 574)				No regular use of non-aspirin NSAID (n = 2,250)			
	No. of Cases	No. of Controls	OR*	95% CI	No. of Cases	No. of Controls	OR ^b	95% CI
Height, quartiles (inches)								
1 (63.5)	25	102	1.00	Referent	131	330	1.00	Referent
2 (63.6 – 65.4)	29	141	0.76	0.40, 1.43	216	506	1.08	0.82, 1.41
3 (65.5 – 69.4)	24	92	0.99	0.50, 1.93	147	314	1.20	0.89, 1.62
4 (69.5)	37	124	1.51	0.82, 2.80	180	426	1.39	1.05, 1.85
P_{trend}^c			0.10				0.01	
Physical activity, quartiles								
1	35	121	1.00	Referent	192	396	1.00	Referent
2	26	107	0.91	0.50, 1.68	162	394	0.89	0.69, 1.17
3	25	110	0.88	0.48, 1.62	156	399	0.89	0.68, 1.16
4	29	121	0.94	0.52, 1.71	164	387	0.85	0.65, 1.11
P_{trend}^c			0.86				0.31	
Dietary Intakes Percent calories from total fat, quartiles								
1	30	110	1.00	Referent	152	402	1.00	Referent
2	21	100	0.81	0.39, 1.67	165	406	1.14	0.85, 1.54
3	28	119	0.92	0.38, 2.21	176	391	1.42	0.97, 2.06
4	36	130	1.14	0.37, 3.49	181	377	1.57	0.96, 2.55
P_{trend}^c			0.72				0.02	
Percent calories from saturated fat, quartiles								
1	28	99	1.00	Referent	156	414	1.00	Referent
2	27	118	0.76	0.38, 1.53	183	388	1.24	0.92, 1.67
3	29	113	0.80	0.33, 1.97	156	396	1.15	0.79, 1.67
4	31	129	0.70	0.23, 2.15	179	378	1.37	0.86, 2.18
P_{trend}^c			0.66				0.17	
Dietary fiber, quartiles								
1	25	113	1.00	Referent	164	399	1.00	Referent
2	25	110	1.15	0.59, 2.27	193	398	1.26	0.95, 1.66
3	37	114	1.52	0.74, 3.09	158	394	1.17	0.86, 1.59
4	28	122	1.34	0.57, 3.17	159	385	1.26	0.87, 1.82
P_{trend}^c			0.50				0.34	
Total^d calcium, quartiles								
1	23	118	1.00	Referent	189	394	1.00	Referent

Risk factors ^a	Regular use of non-aspirin NSAID (n = 574)				No regular use of non-aspirin NSAID (n = 2,250)			
	No. of Cases	No. of Controls	OR*	95% CI	No. of Cases	No. of Controls	OR ^b	95% CI
2	29	112	1.36	0.70, 2.63	179	394	0.95	0.72, 1.25
3	35	106	2.07	1.03, 4.17	141	404	0.72	0.53, 0.97
4	28	123	1.30	0.61, 2.75	165	384	0.93	0.68, 1.28
P_{trend}^c			0.72				0.42	
Total^d folic acid, quartiles								
1	25	117	1.00	Referent	186	395	1.00	Referent
2	36	103	1.54	0.79, 3.01	196	404	1.04	0.78, 1.38
3	33	118	1.16	0.56, 2.40	138	391	0.74	0.54, 1.03
4	21	121	0.73	0.34, 1.56	154	386	0.92	0.66, 1.28
P_{trend}^c			0.10				0.49	
Total fruits & vegetables, quartiles								
1	23	113	1.00	Referent	183	391	1.00	Referent
2	32	112	1.62	0.86, 3.08	180	399	0.95	0.73, 1.23
3	32	124	1.39	0.71, 2.71	153	394	0.83	0.62, 1.11
4	28	110	1.38	0.65, 2.94	158	392	0.89	0.64, 1.23
P_{trend}^c			0.58				0.44	
Total red & processed meats, quartiles								
1	27	98	1.00	Referent	131	363	1.00	Referent
2	29	131	0.82	0.43, 1.56	187	462	1.07	0.80, 1.42
3	29	108	0.89	0.44, 1.81	165	355	1.08	0.79, 1.49
4	30	122	0.70	0.31, 1.56	191	396	1.04	0.73, 1.49
P_{trend}^c			0.42				0.86	
HRT use (women)								
No	94	909	1.00	Referent	586	1,270	1.00	Referent
Yes	21	136	0.77	0.41, 1.42	88	306	0.87	0.64, 1.18
Oxidative balance score, quartiles^e								
1	37	116	1.00	Referent	260	393	1.00	Referent
2	34	113	1.02	0.58, 1.79	151	396	0.59	0.45, 0.76
3	21	121	0.67	0.35, 1.28	143	388	0.58	0.44, 0.77
4	23	109	0.77	0.39, 1.54	120	399	0.50	0.37, 0.69
P_{trend}^c			0.33				<0.01	

Abbreviations: CPRU, Cancer Prevention Research Unit; CRC, colorectal cancer; CI, confidence interval; HRT, hormone replacement therapy; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalents of task; NSAID, nonsteroidal anti-inflammatory drugs excluding aspirin; OR, odds ratio.

^a Quartiles of age were based on the distribution among the controls. Quartiles of physical activity were based on the study-specific distribution among the controls. Cutpoints for alcohol intake were based on the sex-specific distribution among the controls and were defined as follows for low / high intake: 2.5 / > 7 drinks/week among males, and 1 / > 4 drinks/week among females. Cut-points for height quartiles were based on the sex-specific distribution among the controls and were defined as follows: 67.4, 69.4, and 71.4 inches among men, and 62.5, 63.5, and 65.4 inches among women. Quartiles for all dietary intake variables were based on the sex- and study-specific distribution among controls. Quartiles for the oxidative balance score were based on the study-specific distribution among controls.

^b Odds ratios and 95% confidence intervals from unconditional logistic regression models. Covariates for all models, except as noted below included age, sex, family history of colorectal cancer in a first-degree relative, smoking, alcohol intake, body mass index, height, physical activity, hormone therapy (among women), regular aspirin use, and total calcium, folate, dietary fiber, total energy, total fat, saturated fat, total fruit and vegetable, and total red and processed meats intakes. The model for fat does not include total saturated fat, the model for saturated fat does not include total fat, the model for dietary fiber does not include total fruits and vegetables, and model for total fruits and vegetables intakes does not include dietary fiber. Covariates for the model for the oxidative balance score include age, sex, education, family history of colorectal cancer in a first-degree relative, regular aspirin use, hormone replacement therapy (among women), and total calcium, total vitamin D, total energy, total folate, and dietary fiber intakes.

^c P_{trend} values (2-sided) were calculated by including the median of each quartile of each variable as a continuous variable in the multivariable models, except the model for body mass index, where the median of the underweight category was excluded.

^d Total = dietary + supplemental.

^e Oxidative balance score calculated as described in the Statistical Analysis section of the text; a higher OBS reflects higher antioxidant relative to pro-oxidant dietary and lifestyle exposures.

Table 4.

Summary of biological plausibility of and epidemiologic evidence for established risk factors for colorectal neoplasia

Risk factors	Biological plausibility	Association with CRC risk
Smoking	Carcinogens and pro-oxidants in smoke may initiate colorectal carcinogenesis (35) and increase oxidative stress and consequent inflammation (36).	Direct association. EPIC CRC Working Group: Important risk factor (37).
Alcohol	High intakes may increase DNA hypomethylation, which may lead to decreased regulation of proto-oncogene expression (38).	Direct association. WCRF/AICR: Convincing evidence among men, probable risk factor among women (39). EPIC CRC Working Group: Important risk factor (37). Also endorses the 2007 WCRF/AICR guidelines on alcohol consumption for cancer prevention (40)
Obesity	Obesity linked to insulin resistance and alterations in the IGF-1/IGF-1R axis, impaired redox balance, increased lipid peroxidation, and increased inflammation (41) (36).	Direct association. WCRF/AICR: Convincing evidence (39). EPIC CRC Working Group: Strong risk factor (37).
Height	Taller stature may be associated with higher IGF-1 concentrations, which is linked to oxidative stress, cellular proliferation, and inhibition of apoptosis in genetically damaged cells (42).	Direct association. WCRF/AICR: Convincing evidence (39).
Physical activity	More frequent physical activity may reduce inflammation (43–45), and increase PGF ₂ , which reduces colonic cell proliferation (46).	Inverse association. WCRF/AICR: Convincing evidence (39). EPIC Working Group: Endorses 2007 WCRF/AICR guidelines on physical activity for cancer prevention (37, 40).
Total & saturated fats	Promote synthesis of bile acids, which are converted to metabolites that, via an oxidative mechanism, are mutagenic and mitogenic and promote inflammation (47).	Direct association. WCRF/AICR: Limited evidence for food containing animal fats (39). No definitive association of a low-fat diet with CRC risk.
Dietary fiber	Fermented by colonic microflora to short chain fatty acids (48, 49), which regulate homeostasis and maintain epithelial integrity in the gut (49).	Inverse association. WCRF/AICR: Convincing evidence (39). EPIC Working Group: Low intake of dietary fiber (particularly cereal fiber) associated with higher risk of CRC (37).
Calcium	Directly binds to free fatty acids and bile acids in bowel lumen, which reduces their oxidation-related mutagenic and mitogenic and resultant inflammatory effects (50). Via binding to the calcium sensing receptor reduces proliferation and increases differentiation of epithelial cells (51).	Inverse association. WCRF/AICR: Probable inverse association (at least 1,200 mg/day of calcium intake) (39). Meta-RR from 3 RCTs (52) of the efficacy of supplemental calcium in reducing colorectal adenoma recurrence = 0.80 (95% CI 0.68, 0.93).
Folate	Folate depletion disrupts DNA repair, alters DNA and RNA methylation, and alters gene expression and increases DNA damage (53).	Inverse association. Meta-RR from 9 cohort studies = 0.92 (95% CI: 0.81, 1.05). Summary OR from 18 case-control studies = 0.85 (95% CI: 0.74, 0.99)(54).
Fruits & vegetables	Contain fiber and multiple anti-	Inverse association.

Risk factors	Biological plausibility	Association with CRC risk
	oxidant, anti-inflammatory, and other anti-carcinogenic compounds (47).	WCRF/AICR: Limited evidence (39). EPIC Working Group: Fruit & vegetable intakes inversely associated with CRC. Endorses the 2007 WCRF/AICR guidelines on consumption of fruits and non-starchy vegetables (37, 40).
Red & processed meats	Prominent source of fats, especially saturated fats (see above). Heme in red meats, and nitrosyl heme in processed meats promote lipid peroxidation (and thus inflammation) (55), DNA damage, and adduct formation which lead to mutagenesis.	Direct association. WCRF/AICR: Convincing risk factors (39). EPIC Working Group: High intakes associated with higher CRC risk (37). Also endorses the 2007 WCRF/AICR recommendations for consumption of red and processed meats (40).
HRT use	May reduce estrogen receptor gene hypermethylation (56) and decrease bowel lumen bile acid concentrations (57).	Inverse association. Meta-estimates from 8 case-control, 8 cohort studies, and 4 RCTs (58): combined HRT RR 0.74 (95% CI: 0.68, 0.81); estrogen replacement alone: RR 0.79 (95% CI: 0.69, 0.91).
Oxidative stress	Higher reactive oxygen and nitrogen species levels, and disrupted redox signaling and control (59) induce lipid, protein, and DNA damage (and thus inflammation), and impair intracellular signaling.	Direct association. EPIC Working Group: Strong risk factor (37).

Abbreviations: CRC, colorectal cancer; EPIC, European Prospective Investigation into Cancer and Nutrition; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; PGF₂, prostaglandin F₂; RR, relative risk; OR, odds ratio; RCT, randomized, controlled trial; CI, confidence interval; HRT, hormone replacement therapy