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Association of Dietary Inflammatory Potential With Colorectal Cancer Risk in Men and Women

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IMPORTANCE Inflammation is important in colorectal cancer development. Diet modulates inflammation and may thus be a crucial modifiable factor in colorectal cancer prevention.

OBJECTIVE To examine whether proinflammatory diets are associated with increased colorectal cancer risk by using an empirical dietary inflammatory pattern (EDIP) score based on a weighted sum of 18 food groups that characterizes dietary inflammatory potential based on circulating levels of inflammation biomarkers.

DESIGN, SETTINGS, AND PARTICIPANTS Cohort study of 46 804 men (Health Professionals Follow-up Study: 1986-2012) and 74 246 women (Nurses' Health Study: 1984-2012) followed for 26 years to examine associations between EDIP scores and colorectal cancer risk using Cox regression. We also examined associations in categories of alcohol intake and body weight. Data analysis began January 17, 2017, and was completed August 9, 2017.

EXPOSURES EDIP scores calculated from food frequency questionnaires administered every 4 years.

MAIN OUTCOMES AND MEASURES Incident colorectal cancer.

RESULTS We documented 2699 incident colorectal cancer cases over 2 571 831 person-years of follow-up. Compared with participants in the lowest EDIP quintile (Q) who had a colorectal cancer incidence rate (per 100 000 person-years) of 113 (men) and 80 (women), those in the highest Q had an incidence rate of 151 (men) and 92 (women), leading to an unadjusted rate difference of 38 and 12 more colorectal cancer cases, respectively, among those consuming highly proinflammatory diets. Comparing participants in the highest vs lowest EDIP Qs in multivariable-adjusted analyses, higher EDIP scores were associated with 44% (men: hazard ratio [HR], 1.44; 95% CI, 1.19-1.74; $P < .001$ for trend), 22% (women: HR, 1.22; 95% CI, 1.02-1.45; $P = .007$ for trend), and 32% (men and women: pooled HR, 1.32; 95% CI, 1.12-1.55; $P < .001$ for trend) higher risk of developing colorectal cancer. In both men and women, associations were observed in all anatomic subsites except for the rectum in women. In subgroups ($P \leq .02$ for all interactions), associations differed by alcohol intake level, with stronger associations among men (Q5 vs Q1 HR, 1.62; 95% CI, 1.05-2.49; $P = .002$ for trend) and women (Q5 vs Q1 HR, 1.33; 95% CI, 0.97-1.81; $P = .03$ for trend) not consuming alcohol; and by body weight, with stronger associations among overweight/obese men (Q5 vs Q1 HR, 1.48; 95% CI, 1.12-1.94; $P = .008$ for trend) and lean women (Q5 vs Q1 HR, 1.31; 95% CI, 0.99-1.74; $P = .01$ for trend).

CONCLUSIONS AND RELEVANCE Findings suggest that inflammation is a potential mechanism linking dietary patterns and colorectal cancer development. Interventions to reduce the adverse role of proinflammatory diets may be more effective among overweight/obese men and lean women or men and women who do not consume alcohol.

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Author Audio Interview

Supplemental content

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Colorectal cancer is the third most commonly diagnosed cancer in both men and women in the United States.[1] Inflammation plays an important role in cancer development, including colorectal cancer.[2,3] Though epidemiological studies have not consistently reported significant associations between prediagnosis levels of widely used inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF), and colorectal cancer risk,[4] there is plausible evidence that inflammation plays an important role in colorectal cancer development. For example, obesity, a state of low-grade chronic inflammation,[5] has been associated with colorectal cancer risk.[6] Chronic inflammation may also contribute to insulin resistance and hyperinsulinemia, which are associated with colon cancer risk. Also, chronic inflammation has been implicated as a key predisposing factor to colorectal cancer in inflammatory bowel disease.[7] Furthermore, several studies have shown that the use of anti-inflammatory medications, such as aspirin, can reduce colorectal cancer development.[8] Intervention studies have shown that diet modulates inflammation[9,10]; therefore, dietary patterns with higher inflammatory potential may influence colorectal cancer risk.

There are likely complex added effects and interactions of multiple foods and nutrients in diet. Furthermore, a change in the intakes of specific foods or nutrients is associated with changes in the intake of other foods and nutrients. Studies of single nutrients and foods do not account for complex interactions inherent in whole diets.[11] Therefore, the examination of whole diets or dietary patterns in relation to disease outcomes is an appealing approach that has been adopted in many studies in nutritional epidemiology. To elucidate the role of dietary inflammatory potential in colorectal cancer development, we investigated the association between a previously developed empirical food-based dietary inflammatory pattern score[12] with colorectal cancer risk in 2 prospective cohort studies, 1 of men and 1 of women. We further examined potential differences of this association in subgroups of factors that have been linked with colorectal cancer risk, including alcohol intake and body weight.

Key Points

Questions Do proinflammatory dietary patterns increase the risk of developing colorectal cancer?

Findings In this cohort study that followed 121 050 adults for 26 years, intake of proinflammatory diets as evidenced by higher scores on an empirical dietary inflammatory pattern score was associated with a significantly higher risk of developing colorectal cancer in both men and women.

Meaning Inflammation is a potential mechanism linking dietary patterns and colorectal cancer development, and strategies to reduce the adverse role of a proinflammatory diet may reduce colorectal cancer risk.

Methods

Study Population

We used data from 2 ongoing prospective cohorts: The Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The NHS recruited 121 701 registered female nurses ages 30 to 55 years at baseline in 1976, and the HPFS enrolled 51 529 male health professionals ages 40 to 75 years at baseline in 1986 in the United States. In both cohorts, questionnaires were sent at baseline and every 2 years thereafter to collect and update demographic, lifestyle, medical, and other health-related information.[13,14] Every 4 years, participants received validated semiquantitative food frequency questionnaires (FFQ) for dietary assessments.[15]

For the current study, we excluded participants who reported any cancer except nonmelanoma skin cancer, who did not complete an FFQ during follow-up or who had implausible values for total energy intake (<600 or >3500 kcal/d for women and <800 or >4200 kcal/d for men) at study entry. This resulted in the inclusion of 74 246 women from the NHS and 46 804 men from the HPFS for a total of 121 050 participants. The institutional review boards at Brigham and Women's Hospital and at Harvard T. H. Chan School of Public Health approved this study.

Assessment of the Empirical Dietary Inflammatory Pattern Score and Other Covariates

The development of the empirical dietary inflammatory pattern (EDIP) score in a sample of 5230 women in the Nurses' Health Study has been previously described.[12] The goal was to empirically create a score for overall inflammatory potential of whole diets defined using food groups. Briefly, 39 predefined food groups[16] were entered into reduced-rank regression models followed by stepwise linear regression analyses to identify a dietary pattern most predictive of 3 plasma markers of inflammation: IL-6, CRP, and TNFRSF1B (TNF receptor superfamily 1B, so-called TNF-α receptor 2, or TNF-R2).[12] The EDIP score is the weighted sum of 18 food groups and assesses the inflammatory potential of diet on a continuum from maximally anti-inflammatory to maximally proinflammatory. That is, lower (more negative) scores indicate anti-inflammatory diets and higher (more positive) scores indicate proinflammatory diets. The EDIP score was evaluated for validity in independent samples of men and women using dietary and inflammatory biomarker data from the HPFS (n = 2632) and Nurses' Health Study-II (NHS-II [n = 1002]).[12] A subsequent study that used data from a much larger sample of men in HPFS (n = 5227) and women in NHS-II (n = 5826) to compare the inflammation predictive ability of the EDIP score and a previously developed literature-derived nutrient-based dietary inflammatory index,[17] showed that the EDIP had a higher ability to predict concentrations of CRP, TNFRSF1B, and ADIPOQ (adiponectin).[18]

The component food groups comprising the EDIP score are the following: intakes of processed meat, red meat, organ meat, fish (other than dark-meat fish), other vegetables (ie, vegetables other than green leafy vegetables and dark yellow vegetables), refined grains, high-energy beverages (cola and other carbonated beverages with sugar, fruit drinks), low-energy beverages (low-energy cola and other low-energy carbonated

beverages), and tomatoes were positively related to concentrations of the inflammatory markers. Intakes of beer, wine, tea, coffee, dark yellow vegetables (comprising carrots, yellow squash, and sweet potatoes), green leafy vegetables, snacks, fruit juice, and pizza were inversely related to concentrations of the inflammatory markers.[12] We calculated EDIP scores for each participant based on self-administered FFQ data in eight 4-year data cycles from 1984 to 2010 in the NHS and in seven 4-year data cycles from 1986 to 2010 in the HPFS.

Self-administered questionnaires were sent to participants biennially to assess medical and lifestyles factors, including smoking, physical activity, alcohol intake, multivitamin use, endoscopy status, regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), family history of colorectal cancer, weight, height, menopausal status, and postmenopausal hormone use (only for women), in both cohorts as previously described.[16,19,20]

Colorectal Cancer Ascertainment

Participants reported new colorectal cancer diagnoses on each biennial questionnaire. For self-reported cases, as well as colorectal cancer-related deaths identified through family members or the US National Death Index,[21] we obtained medical records related to the diagnoses. When we were unable to obtain medical records (approximately 10% of cases), we linked to the appropriate cancer registry to confirm the diagnosis. A pathologist reviewed medical records to confirm the diagnoses.

Statistical Analysis

We calculated person-years of follow-up from the return date of the first FFQ until the date of death, any cancer diagnosis (except nonmelanoma skin cancer), or end of follow-up (June 1, 2012, for NHS and January 31, 2012, for HPFS), whichever was earliest. EDIP scores were calculated as the cumulative average score from all prior reports up to the start of each 2-year follow-up interval to best represent habitual long-term dietary intake and reduce within-person variation. We adjusted EDIP scores for total energy intake using the residual method.[22] Owing to the high within-individual correlations in EDIP scores between adjacent data cycles, we carried forward non-missing dietary intake data from the previous data cycle to replace missing data in the next cycle. Covariate data were treated similarly.

We used Cox proportional hazards regression models with time-varying covariates to estimate hazard ratios (HR) and 95% CIs for EDIP scores in relation to colorectal cancer risk, with the lowest EDIP quintile as the reference group. We examined proportionality of hazards for each covariate included in the Cox models using time × covariate interaction terms and found no violations (all $P > .05$). Early symptoms of undiagnosed colorectal cancer may alter habitual dietary intake; therefore, to address this potential issue, we used a 2-year lag between dietary assessment and colorectal cancer incidence as the main analytic approach. For example, in NHS, we used cumulative average EDIP scores from 1986 to 1990 as the exposure for the follow-up period from 1992 to 1994 and cumulative average score from 1986 to 1994 for follow-up from 1996 to 1998, etc. All analyses were stratified by age in months and calendar year of the current questionnaire. Multivariable models were adjusted for risk factors for colorectal cancer, most of which were updated biennially. These included race, family history of cancer, history of endoscopy, multivitamin use, alcohol intake, physical activity, pack-years of smoking, regular aspirin use, regular NSAID use, and additionally for menopausal status and postmenopausal hormone use in women. Body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and diabetes are possible intermediates in the association of dietary inflammatory potential and colorectal cancer risk; therefore, we did not adjust for BMI and diabetes in the main analyses but additionally adjusted for these 2 covariates in sensitivity analyses. For analyses of linear trend across EDIP quintiles, we assigned the median EDIP score for each quintile to all participants in the quintile. We then pooled the sex-specific HR and corresponding standard errors using random effects meta-analyses methods to calculate the association between EDIP scores and risk of colorectal cancer combining men and women and tested for heterogeneity of risk estimates by sex using the likelihood ratio test. Also, we used duplication method cause-specific Cox models[23] to test for heterogeneity by anatomic location (proximal colon, distal colon, and rectum).

We used the likelihood ratio test to test for potential effect modification by comparing models with and without the interaction term of the EDIP score and potential effect modifier (ie, 1 degree of freedom). Potential effect modifiers included were total alcohol intake (no drink/d, 0.1 to 1 drink/d, and >1 drink day), and body weight (BMI, <25 vs ≥25). All analyses were performed using SAS software, version 9.4 for UNIX (SAS Institute), all P values were 2-sided, and significance was set at .05.

Results

Over the entire follow-up period in both cohorts (26 years in NHS and 24 years in HPFS), participants consuming the most proinflammatory diets (EDIP quintile 5) reported lower physical activity, higher BMI, and were more likely to have diabetes. They were also less likely to be using multivitamins and reported lower intakes of dietary fiber, dietary calcium, and whole grains, than those consuming the most anti-inflammatory diets (EDIP quintile 1) (**Table 1**).

We documented 2699 cases of incident colorectal cancer (1441 in women and 1258 in men) over 2 571 831 person-years of follow-up. Compared with men in the lowest fifth of the EDIP score, who had a colorectal cancer incidence rate of 113 per 100 000 person years, men in the highest fifth had an incidence rate of 151 per 100 000 person years, leading to an unadjusted rate difference of 38 more cases of colorectal cancer in men consuming the most proinflammatory diets. Also, compared with women in the lowest EDIP quintile, who had a colorectal cancer incidence rate of 80 per 100 000 person years, women in the highest quintile had an incidence rate of 92 per 100 000 person years, leading to an unadjusted rate difference of 12 more cases of colorectal cancer in women consuming the most proinflammatory diets. Hazard ratios from

Table 1. Distribution of Participant Characteristics Weighted by Person-years Across the Entire Follow-up Period in Quintiles of the EDIP Scores in the NHS (1984-2012) and the HPFS (1986-2012)[a]

	NHS (74 246 Women)			HPFS (46 804 Men)		
Characteristic	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Median EDIP score	−1.20	0.03	1.16	−1.20	0.04	1.14
Age, mean (SD), y	62.0 (9.5)	64.0 (9.9)	61.9 (9.9)	61.9 (10.3)	64.0 (10.9)	61.9 (11.0)
Alcohol drinkers, %	77.6	57.3	41.3	86.2	71.9	55.0
Total alcohol among drinkers, drinks/wk	7.6 (8.0)	3.9 (4.9)	3.6 (5.5)	12.3 (10.8)	6.4 (6.7)	5.3 (6.9)
Current smoker, %	16.8	10.8	11.9	6.2	4.0	4.8
Aspirin use, yes, %	62.8	60.7	58.9	47.2	45.1	40.3
Other NSAIDs use, yes, %	32.6	32.9	34.6	20.3	18.1	16.1
Family history of colorectal cancer, yes, %	25.8	25.6	24.6	17.4	17.5	14.8
History of endoscopy, yes, %	20.4	21.9	19.4	24.8	25.1	20.0
Diabetes, yes, %	2.0	4.7	10.2	3.8	6.2	9.5
Multivitamin use, yes, %	55.2	55.9	49.5	52.3	50.2	43.4
Total energy intake, Kcal/d	1809 (451)	1698 (438)	1810 (488)	2073 (541)	1892 (527)	2080 (597)
Dietary fiber, g/d	19.2 (5.9)	19.5 (5.8)	18.1 (5.7)	23.0 (7.5)	23.8 (7.6)	21.6 (7.3)
Dietary calcium, mg/d	781 (289)	792 (303)	733 (290)	840 (308)	865 (328)	806 (324)
Vitamin D, IU/d	202 (113)	212 (117)	198 (116)	244 (148)	267 (150)	260 (155)
Whole grains, g/d	24.2 (17.7)	25.8 (18.8)	20.2 (17.3)	31.3 (21.7)	32.5 (22.7)	24.8 (20.2)
Physical activity, Metabolic Equivalent of Task h/wk	20.1 (23.7)	17.6 (21.2)	15.3 (19.0)	34.0 (28.8)	31.6 (26.8)	29.8 (25.9)
BMI	24.9 (4.1)	26.1 (4.7)	28.0 (5.8)	25.0 (5.8)	24.6 (6.5)	25.6 (6.9)
Overweight or obese, BMI ≥25, %	46.0	57.5	70.1	48.0	46.8	55.9)
Postmenopausal, %	82.8	86.2	81.8	NA	NA	NA
Hormone therapy use ever among postmenopausal women, %	67.7	67.9	64.0	NA	NA	NA

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; EDIP, empirical dietary inflammatory pattern; HPFS, Health Professionals Follow-up Study; NA, not applicable; NHS, Nurses' Health Study; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Weighted by follow-up time (person-years) accrued by each participant. EDIP scores were adjusted for energy intake using the residual method. Lower scores indicate anti-inflammatory diets whereas higher scores indicate proinflammatory diets.

the minimally adjusted model that included only age, alcohol intake, and calendar year of current questionnaire were similar to the multivariable-adjusted results (eTable 1 in the Supplement). Comparing participants in the highest vs the lowest EDIP quintile in multivariable-adjusted analyses, colorectal cancer risk was 44% higher in men (HR, 1.44; 95% CI, 1.19-1.74; $P < .001$ for trend), 22% higher in women (HR, 1.22; 95% CI, 1.02-1.45; $P = .007$ for trend), and 32% higher in men and women combined (pooled HR, 1.32; 95% CI, 1.12-1.55; $P < .001$ for trend) (**Table 2**). In both men and women, associations were observed in all anatomic locations, except for the rectum in women. Pooled HRs comparing men and women in the highest EDIP quintile to those in the lowest quintile were 1.35 (95% CI, 1.16-1.56; $P < .001$ for trend) for overall colon cancer, 1.38 (95% CI, 1.13-1.68; $P < .001$ for trend) for proximal colon cancer, 1.46 (95% CI, 1.14-1.86; $P = .002$ for trend) for distal colon cancer and 1.19 (95% CI, 0.60-2.38; $P = .53$ for trend) for rectal cancer. There was significant heterogeneity ($P = .03$) in rectal cancer risk between men (HR, 1.70; 95% CI, 1.14-2.54; $P < .001$ for trend) and women (HR, 0.84; 95% CI, 0.57-1.24; $P = .57$ for trend) (Table 2). Further adjusting for BMI and diabetes did not materially change the results (eTable 2 in the Supplement). We have provided the full multivariable-adjusted model separately for women and men in eTable 3 in the Supplement.

In subgroups defined by BMI categories and alcohol intake levels, there were significant differences ($P \leq .02$ for all interactions) in the association between dietary inflammatory potential and colorectal cancer risk for both men and women (**Table 3**). There was a 48% higher risk (HR,1.48; 95% CI, 1.12-1.94; $P = .004$ for trend) among overweight or obese men consuming the most proinflammatory diets (quintile 5) and an indication for higher risk in other quintiles compared with the lowest quintile (though this did not attain statistical significance). Though risk was also elevated among lean men, the difference between lean and overweight/obese men was significant ($P = .01$ for interaction). In contrast, risk was elevated among lean women (HR,1.31; 95% CI, 0.99-1.74; $P = .01$ for trend) but not among overweight or obese women. Differences were more pronounced by alcohol intake levels. Comparing extreme EDIP quintiles, there was a 62% higher risk of colorectal cancer among men (HR, 1.62; 95% CI, 1.05-2.49; $P = .002$ for trend) and a 33% higher risk among women (HR, 1.33; 95% CI, 0.97-1.81; $P = .03$ for trend) not consuming alcohol. This association was weaker among men and women consuming any amount of alcohol (Table 3).

Discussion

We conducted a large prospective study in men and women, using a food-based dietary index—the EDIP score—to characterize the inflammatory potential of diet and elucidate its role

Table 2. Colorectal Cancer Risk in Quintiles of the Empirical Dietary Inflammatory Pattern Scores Among 121 050 Men and Women[a]

Disease	Quintile 1[b]	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* Value for Trend[c]
Colorectal Cancer						
Incidence per 100 000 person-years, men	113	121	140	130	151	
HR (95% CI)	1 [Reference]	0.99 (0.82-1.20)	1.15 (0.96-1.39)	1.10 (0.91-1.33)	1.44 (1.19-1.74)	<.001
Incidence per 100 000 person-years, women	80	85	91	99	92	
HR (95% CI)	1 [Reference]	1.05 (0.88-1.25)	1.11 (0.93-1.32)	1.22 (1.03-1.45)	1.22 (1.02-1.45)	.007
Pooled, HR (95% CI)[d]	1 [Reference]	1.02 (0.90-1.16)	1.13 (1.00-1.28)	1.17 (1.03-1.32)	1.32 (1.12-1.55)	<.001
Colon Cancer						
Incidence per 100 000 person-years, men	91	94	116	103	114	
HR (95% CI)	1 [Reference]	0.97 (0.78-1.20)	1.19 (0.97-1.46)	1.09 (0.88-1.36)	1.37 (1.10-1.69)	<.001
Incidence per 100 000 person-years, women	60	64	74	77	77	
HR (95% CI)	1 [Reference]	1.03 (0.85-1.26)	1.17 (0.96-1.42)	1.23 (1.01-1.50)	1.33 (1.09-1.62)	.001
Pooled, HR (95% CI)[d]	1 [Reference]	1.00 (0.87-1.16)	1.18 (1.02-1.36)	1.17 (1.01-1.35)	1.35 (1.16-1.56)	<.001
Proximal Colon Cancer						
Incidence per 100 000 person-years, men	39	36	51	43	53	
HR (95% CI)	1 [Reference]	0.85 (0.60-1.18)	1.16 (0.85-1.59)	1.02 (0.74-1.42)	1.44 (1.04-1.98)	.01
Incidence per 100 000 person-years, women	38	39	45	51	49	
HR (95% CI)	1 [Reference]	0.98 (0.76-1.27)	1.10 (0.86-1.41)	1.28 (1.01-1.64)	1.35 (1.05-1.72)	.002
Pooled, HR (95% CI)[d]	1 [Reference]	0.93 (0.76-1.14)	1.13 (0.93-1.37)	1.18 (0.95-1.46)	1.38 (1.13-1.68)	<.001
Distal Colon Cancer						
Incidence per 100 000 person-years, men	34	35	38	37	42	
HR (95% CI)	1 [Reference]	1.03 (0.73-1.47)	1.16 (0.81-1.64)	1.22 (0.85-1.73)	1.44 (1.01-2.05)	.02
Incidence per 100 000 person-years, women	18	24	28	24	26	
HR (95% CI)	1 [Reference]	1.29 (0.92-1.83)	1.47 (1.05-2.07)	1.28 (0.90-1.83)	1.47 (1.04-2.08)	.05
Pooled, HR (95% CI)[d]	1 [Reference]	1.16 (0.91-1.48)	1.31 (1.03-1.67)	1.25 (0.97-1.60)	1.46 (1.14-1.86)	.002
Rectal Cancer						
Incidence per 100 000 person-years, men	22	27	23	27	37	
HR (95% CI)	1 [Reference]	1.08 (0.71-1.63)	1.00 (0.65-1.53)	1.09 (0.72-1.68)	1.70 (1.14-2.54)	.01
Incidence per 100 000 person-years, women	20	21	17	22	15	
HR (95% CI)	1 [Reference]	1.10 (0.78-1.55)	0.92 (0.63-1.33)	1.19 (0.84-1.69)	0.84 (0.57-1.24)	.57
Pooled, HR (95% CI)[d]	1 [Reference]	1.09 (0.83-1.42)	0.95 (0.72-1.26)	1.15 (0.88-1.51)	1.19 (0.60-2.38)[f]	.53

Abbreviations: EDIP, empirical dietary inflammatory pattern; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] EDIP scores were adjusted for total energy intake using the residual method. Lower scores indicate anti-inflammatory diets, whereas higher scores indicate proinflammatory diets. Heterogeneity for risk by anatomic subsite (*P* heterogeneity = .84 in men and .10 in women) was tested using duplication method cause-specific Cox regression analyses. All analyses were adjusted for the following potential confounding variables: age (months) calendar year of current questionnaire, race (white, nonwhite); family history of cancer (yes, no); history of endoscopy (yes, no); multivitamin use (yes, no); alcohol intake (continuous, g/d); physical activity (continuous, Metabolic Equivalent of Task h/wk); pack-years of smoking (continuous); regular aspirin use (yes, no); and regular NSAIDs use (yes, no); and additionally for menopausal status (premenopausal, postmenopausal) and postmenopausal hormone use (yes, no) in women.

[b] Quintile 1 is the reference for comparisons.

[c] The *P* value for linear trend was obtained using EDIP quintile medians as an ordinal variable adjusted for age (months) calendar year of current questionnaire, race, family history of cancer, history of endoscopy, multivitamin use, alcohol intake, physical activity, pack-years of smoking, regular aspirin use, regular NSAIDs use, and for menopausal status and postmenopausal hormone use in women.

[d] Hazard ratios for men and women were pooled using random effects meta-analyses, and the likelihood ratio test was used to test for heterogeneity in risk between men and women for each anatomic subsite. The difference in risk by sex for the rectum was significant (*P* = .03 for heterogeneity). All other *P* values for heterogeneity by sex were greater than .36.

in colorectal cancer development. The study conveys 2 important findings. First, higher dietary inflammatory potential was associated with higher risk of developing colorectal cancer in men and women. In both men and women, associations were observed in all anatomic sites, except for the rectum in women. Second, risk of developing colorectal cancer was even higher among overweight or obese men and lean women and among men and women not consuming alcohol. The differences by body weight category may partly underlie the differences by sex observed for rectal cancer risk; whereas

Table 3. Multivariable-Adjusted Associations of the Empirical Dietary Inflammatory Pattern Score With Colorectal Cancer Risk Among Men and Women in Subgroups of Potential Effect Modifiers[a]

	EDIP Quintiles, HR (95% CI)					*P* Value	
Subgroups	Quintile 1[b]	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Trend[c]	Heterogeneity[d]
BMI							
Men							.01
<25 (n = 612)	1 [Reference]	0.80 (0.61-1.05)	1.04 (0.80-1.34)	1.00 (0.76-1.31)	1.39 (1.06-1.82)	.006	
≥25 (n = 646)	1 [Reference]	1.22 (0.93-1.61)	1.27 (0.96-1.67)	1.23 (0.93-1.63)	1.48 (1.12-1.94)	.008	
Women							.01
<25 (n = 580)	1 [Reference]	1.14 (0.88-1.47)	1.01 (0.77-1.33)	1.47 (1.14-1.90)	1.31 (0.99-1.74)	.01	
≥25 (n = 861)	1 [Reference]	0.95 (0.75-1.20)	1.10 (0.87-1.38)	1.02 (0.81-1.28)	1.11 (0.89-1.39)	.26	
Alcohol Consumption, drinks/d							
Men							.02
No drink/d (n = 368)	1 [Reference]	1.02 (0.63-1.66)	1.18 (0.74-1.87)	1.31 (0.84-2.04)	1.62 (1.05-2.49)	.002	
0.1 to 1 drink/d (n = 525)	1 [Reference]	0.95 (0.70-1.29)	0.96 (0.71-1.30)	0.92 (0.67-1.25)	1.35 (0.99-1.83)	.05	
>1 Drink/d (n = 365)	1 [Reference]	1.00 (0.74-1.36)	1.39 (1.02-1.88)	1.23 (0.87-1.75)	1.23 (0.83-1.81)	.08	
Women							.02
No drink/d (n = 605)	1 [Reference]	1.05 (0.75-1.47)	1.24 (0.90-1.71)	1.28 (0.93-1.75)	1.33 (0.97-1.81)	.03	
0.1 to 1 drink/d (n = 643)	1 [Reference]	1.11 (0.87-1.41)	0.99 (0.77-1.28)	1.21 (0.94-1.55)	1.27 (0.97-1.65)	.07	
>1 Drink/d (n = 193)	1 [Reference]	0.93 (0.61-1.41)	1.23 (0.80-1.88)	1.65 (1.07-2.57)	0.87 (0.48-1.56)	.34	

Abbreviations: BM, body mass index, calculated as weight in kilograms divided by height in meters squared; EDIP, empirical dietary inflammatory pattern; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] EDIP scores were adjusted for total energy intake using the residual method. Except when stratifying by the potential effect modifier, all analyses were adjusted for the following potential confounding variables: age, calendar year of current questionnaire, race (white, nonwhite); family history of cancer (yes, no); history of endoscopy (yes, no); multivitamin use (yes, no); alcohol intake (continuous, drinks/d); physical activity (continuous, Metabolic Equivalent of Task hrs/wk); pack-years of smoking status (continuous); regular aspirin use (yes, no); and regular NSAIDs use (yes, no).

[b] Quintile 1 is the reference for comparisons.

[c] The *P* value for linear trend was obtained using EDIP quintile medians as an ordinal variable adjusted for all covariates listed in footnote a.

[d] The *P* value for heterogeneity was calculated using the likelihood ratio test comparing models with and without the interaction term (ie, 1 df).

the differences by alcohol intake category may indicate that the influence of alcohol on colorectal cancer risk through mechanisms other than inflammation, may be stronger than that of its effects on the EDIP.

Previous studies[24,25] have used a literature-derived nutrient-based dietary inflammatory index[17,26] to examine the association of dietary inflammatory potential and colorectal cancer risk. Given that the nutrient-based index scores are influenced by nutritional supplements,[27,28] findings from these previous studies that are directly comparable to the current study results are from studies that calculated the nutrient-based index scores from food sources only (ie, without including supplements). In a study conducted using data from the Iowa Women's Health Study,[28] there was a statistically significant 20% higher risk of colorectal cancer (HR, 1.20; 95% CI, 1.01-1.43; comparing extreme EDIP quintiles) that became nonsignificant when supplements were excluded (HR, 1.12; 95% CI, 0.90-1.38; comparing extreme EDIP quintiles). However, in a study conducted using data from the Multiethnic Cohort with the inclusion of 190 963 men and women and 4388 colorectal cancer cases diagnosed during up to approximately 20 years of follow-up, investigators calculated the nutrient-based index scores from foods sources only, and found significant associations with colorectal cancer risk as follows (comparing participants in quintile 5 vs 1): 21% higher risk in men and women combined, 28% higher risk in men, and 16% higher risk in women. These results align with findings in the current study, though we found stronger associations with the empirically derived food-based score.

It is not entirely clear why associations for rectal cancer were stronger in men than in women but are unlikely to be due to chance given the large significant heterogeneity by sex. Though most risk factors for colorectal cancer are common between men and women, the pattern of risk differs. For example, higher body weight strongly predisposes men to higher risk of proximal colon cancer, distal colon cancer, and rectal cancer, and predisposes women to mainly higher risk of distal colon cancer but not rectal cancer.[29,30] Also, early-life obesity seems to be the primary risk factor for colorectal cancer in women, whereas for men, adult weight gain rather than early life, predominates.[31] This pattern may be due to differences in sex hormones, given that in men and postmenopausal women, estrogen is produced mainly in fat tissue.[32] In women, a high estrogen:testosterone ratio is protective against colorectal cancer risk but in men it may have an adverse effect.[33,34] Regarding differences by alcohol intake, high intake of alcohol has been associated with higher risk of cancer, including colorectal cancer, in both men and women.[6] It is possible that the adverse effects of alcohol intake through other mechanisms may be more dominant than those of its effect on the EDIP and may partially explain the stronger associations among men and women not consuming alcohol than among alcohol consumers.

Strengths and Limitations

Major strengths of our study include the use of a food-based EDIP score that is correlated with levels of inflammatory markers associated with colorectal cancer risk. The large number of

colorectal cancer cases enabled us to conduct analyses stratified by levels of other colorectal cancer risk factors. We also had comprehensive information on diet and important covariates, which reduces the potential for residual confounding, and the data were prospectively collected, thus reducing the potential for recall bias. Also, dietary and covariate data were assessed at multiple times throughout follow-up, which allowed us to use long-term cumulative average exposures, thus reducing within-person variation. To reduce potential reverse causation by subclinical colorectal cancer symptoms that may influence dietary intake, we used a 2-year lagged approach as our main analytic approach. However, our study is not without limitations. There is potential measurement error in the self-reported dietary and lifestyle data, though prior studies in these cohorts that evaluated the relative validity of FFQ data have shown reasonably good correlations between FFQ and diet records, suggesting that dietary intake is generally well measured.[14,15,35] In addition, the multiple FFQ administrations during follow-up approximate habitual long-term diet and reduce measurement error. Also, a proinflammatory dietary pattern may be associated with other factors not included in the current study (eg, insulin secretion or insulin resistance). Though we adjusted for several potential confounding variables, we cannot completely rule out confounding by unmeasured variables.

Conclusions

Findings from this large prospective study support a role for the inflammatory potential of diet in colorectal cancer development, suggesting inflammation as a potential mechanism linking dietary patterns and colorectal cancer development. Strategies to reduce the adverse role of a proinflammatory dietary pattern in colorectal cancer development may have higher benefits among overweight or obese men and among lean women or among men and women not consuming alcohol.

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