Associations of Novel Dietary and Lifestyle Inflammation Scores with Incident, Sporadic Colorectal Adenoma

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ABSTRACT

Background: Colorectal carcinogenesis is mechanistically linked to inflammation and is highly associated with diet and lifestyle factors that may affect chronic inflammation. We previously developed dietary (DIS) and lifestyle (LIS) inflammation scores, comprising inflammation biomarker–weighted components, to characterize the collective contributions of 19 food groups and four lifestyle exposures to systemic inflammation. Both scores were more strongly directly associated with circulating inflammation biomarkers in three validation populations, including a subset of the study population described below, than were the previously reported dietary inflammatory index and empirical dietary inflammatory pattern.

Methods: We calculated the DIS and LIS in three pooled case–control studies of incident, sporadic colorectal adenoma ($N = 765$ cases and 1,986 controls) with extensive dietary and lifestyle data, and investigated their associations with adenoma using multivariable unconditional logistic regression.

Results: For those in the highest (more proinflammatory) relative to the lowest (more anti-inflammatory) quintiles of the DIS and LIS, the multivariable-adjusted ORs were 1.31 [95% confidence interval (CI), 0.98–1.75; $P_{trend} = 0.09$] and 1.98 (95% CI, 1.48–2.66; $P_{trend} < 0.001$), respectively. These associations were strongest for adenomas with high-risk characteristics and among men. Those in the highest relative to the lowest joint DIS/LIS quintile had a 2.65-fold higher odds (95% CI, 1.77–3.95) of colorectal adenoma.

Conclusions: These results support that diets and lifestyles with higher balances of pro- to anti-inflammatory exposures may be associated with higher risk for incident, sporadic colorectal adenoma.

Impact: Our findings support further investigation of the DIS and LIS in relation to colorectal neoplasms.

Introduction

Colorectal cancer is the second leading cause of cancer-related death in the United States among men and women combined (1). Chronically elevated inflammation may play a role in colorectal carcinogenesis (2–4). Diet and lifestyle exposures are also strongly associated with colorectal cancer risk, possibly, in part, through their effects on chronic inflammation (5–7).

The contributions of individual dietary and lifestyle exposures to systemic inflammation may be small, but collectively may be substantial. To address this, dietary inflammation scores (DIS) to characterize the collective contributions of dietary factors to systemic inflammation were developed, such as the dietary inflammatory index (DII; ref. 8) and the empirical dietary inflammatory pattern (EDIP; ref. 9). Both scores have limitations: the DII mostly includes specific nutrients, and may not account for the myriad other dietary constituents in whole foods that may contribute to inflammation, and the EDIP was derived using a primarily data-driven approach in an occupationally, relatively homogeneous population, limiting its generalizability. Neither score addressed lifestyle. Only the DII was investigated in relation to colorectal adenoma, and the results across three studies were somewhat mixed (10–12). Therefore, further investigation of associations of dietary- and lifestyle-associated inflammation with risk for colorectal neoplasms, using tools that address the scores' limitations, is needed.

We previously developed novel, biomarker panel–weighted DIS and lifestyle inflammation scores (LIS) to characterize the collective contributions of dietary and lifestyle exposures to systemic inflammation (13). The DIS predominantly comprises whole foods and beverages, which encompass thousands of bioactive substances. The LIS includes lifestyle-related exposures. We validated the scores in three populations, including a subset of the case–control study described herein, and found that both scores were more strongly, directly associated with biomarkers of inflammation than was the DII or the EDIP (13). As reported herein, we investigated associations of the DIS and LIS with first-ever diagnosed (hereafter termed "incident") sporadic adenoma in a pooled case–control study.

Materials and Methods

Study population

We pooled data from three case–control studies of incident, sporadic colorectal adenomas that were methodologically similar, led by principal investigator R.M. Bostick. The pooled studies comprised the Cancer Prevention Research Unit Study (CPRU, Minnesota, 1991–1994; ref. 14), the Markers of Adenomatous Polyps (MAP) Studies I (MAP I, North Carolina, 1994–1997; ref. 15), and II (MAP II, South Carolina, 2002; ref. 16), which were described previously. Previous studies were published using the pooled data (17–20). Institutional

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review boards approved each study at the institution where they were conducted. All participants gave written informed consent.

Patients scheduled to undergo outpatient, elective colonoscopy for gastrointestinal symptoms or screening in large, community-based gastroenterology practices were recruited to the three studies using identical recruitment, eligibility criteria, and data collection procedures. Eligible individuals were ages 30–74 years, could speak English, had no contraindications for colonoscopy, had no known genetic conditions associated with colonic neoplasia, and had no history of a colorectal adenoma, inflammatory bowel disease, or cancer (other than nonmelanoma skin cancer). The participation rates across the three studies were 68%–76%.

Using standardized forms, the colonoscopists documented colon sites and *in vivo* sizes of polyps they found during complete, clean colonoscopies. An index study pathologist used diagnostic criteria established by the National Polyp Study to histologically classify the removed polyps (21). Cases included participants with a pathology-confirmed adenoma removed during colonoscopy, whereas controls included those with no adenomatous or hyperplastic polyps found during colonoscopy. The CPRU study included two additional sets of controls: (i) patients from the same community practices as the colonoscopy-based controls with no adenomatous or hyperplastic polyps upon flexible sigmoidoscopy colorectal cancer screening and (ii) individuals with no history of colorectal neoplasms selected randomly from the general population (using electronic drivers' license lists) and frequency matched to the colonoscopy patients by zip code, 5-year age group, and sex in the Minneapolis–St. Paul metropolitan region. For our analyses, all cases and controls were combined into a single case and a single control group, respectively (17–20).

Of the eligible cases and controls, we additionally excluded those with >15% missing food frequency questionnaire (FFQ) responses ($n = 2$), implausible estimated energy intakes (<500 or >4,500 kcal/day among women or <800 or >5,000 kcal/day among men; $n = 30$), and missing data on lifestyle characteristics ($n = 55$). The final analytic sample size was 765 cases and 1,986 controls.

Data collection

Prior to undergoing endoscopy and determination of case/control status, participants reported detailed information on their personal medical history, demographic characteristics, diet, lifestyle, and anthropometrics. Self-reported dietary and nutritional supplement intakes over the past 12 months were assessed using validated self-administered Willett FFQs (22). Each line item, referencing a standard portion size, allowed nine possible frequency-of-consumption responses, ranging from "never, or less than once per month" to "six or more times per day." Total daily energy and nutrient intakes were estimated by summing energy and nutrients, respectively, across all food and supplement sources using the Willett dietary database (22, 23). Physical activity was ascertained using modified Paffenbarger questionnaires (24). Height and weight were self-reported.

Description of the DIS and LIS

The DIS and LIS were developed to characterize the combined contributions of foods and beverages and lifestyle to systemic inflammation (13). They were developed in a heterogenous subset of the previously described Reasons for Geographic and Racial Differences in Stroke Study (REGARDS) cohort (25) with concentrations of circulating inflammation biomarkers measured at baseline ($N = 639$). REGARDS is a national, ongoing prospective cohort study comprising 30,239 men and women who were black or white, ≥45 years old, and resided in the United States' contiguous 48 states. To develop the DIS and LIS, we used a case–cohort sample nested in REGARDS (26) with a panel of plasma IL6, IL8, IL10, and high sensitivity C-reactive protein (hsCRP) measured at baseline. To be included in the analytic subsample, participants must have had <10% of their FFQ items missing, plausible total energy intakes (500–4,500 kcal/day among women, and 800–5,000 kcal/day among men), and <2 comorbidities. In addition, we excluded participants ≥75 years old, those with hsCRP concentrations ≥10 mg/dL (27) and other measured inflammation biomarkers with extreme outlying values, and end-stage renal disease.

The DIS included 19 *a priori*–selected score components comprising whole foods, beverages, and nutritional supplement use based on Block 98 FFQ (28, 29) responses in the REGARDS subset (Supplementary Table S1). The components were chosen based on biological plausibility and applicability across different commonly used FFQs. *A priori*–selected LIS components included: alcohol intake, physical activity, smoking status, and body mass index (BMI). We standardized each continuous food group, by sex, to a mean of 0 and SD of 1.0. For the categorical variables in the LIS, we created dummy variables. In REGARDS, as reported previously (13), to create weights for the score components, we used multivariable linear regression to estimate the association of each component with a biomarker inflammation score. The biomarker score was the sum of normalized circulating concentrations of IL6, IL8, IL10 (with a negative sign), and hsCRP. The sum of the weighted components yielded the score. A higher score represented a higher balance of proinflammatory to anti-inflammatory exposures. We applied the DIS scoring procedures and weights in three different external populations (one of which was the pooled MAP studies) with circulating inflammation biomarker measurements (13). The DIS and LIS were more strongly, positively associated with circulating inflammation biomarkers than were the DII or EDIP (13).

Constructing the DIS and LIS in the pooled case–control studies

The DIS and LIS were constructed in the pooled case–control studies as summarized in **Table 1**. Mixed dishes were disaggregated into their constituent foods using the "My Pyramid Equivalents Database," as described previously (30). Then, we assigned the disaggregated components into the appropriate DIS food groups. We accounted for vitamin/mineral intakes from supplements by calculating a supplement score. To do this, we ranked supplemental micronutrient intakes, based on the sex- and study-specific distributions among the controls, into tertiles. We then assigned each tertile a value of 0–2 and multiplied the value by +1 or −1 for hypothesized anti- or proinflammatory micronutrients, respectively, and then, we summed the values. After composing the DIS components based on Willett FFQ responses, we normalized them via natural-logarithm transformation, and then standardized each food group to a mean of 0 and SD of 1.0 based on the study- and sex-specific distribution among the controls.

To construct the LIS, we categorized smoking as "current" or "former and never," and BMI as underweight/normal (≤24.99 kg/m^2), overweight (25–29.99 kg/m^2), or obese (≥30 kg/m^2). Heavy alcohol consumption for men and women was defined as >2 or >1 drinks/day, respectively, and moderate consumption as consuming some but fewer than these amounts. For physical activity, we ranked participants according to tertiles, based on the distribution among the controls, of weekly metabolic equivalents of task (MET)-hours of moderate plus vigorous physical activity.

Statistical analyses

We categorized participants into sex- and study-specific DIS and study-specific LIS quintiles of each inflammation score based on its

Table 1. Components of the DIS and LIS and their descriptions and weights in three pooled case–control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2003).

Components	Descriptions	β coefficient weights[a]
DIS components		
Leafy greens and cruciferous vegetables	Kale, spinach, broccoli, Brussels sprout, cabbage or coleslaw, cauliflower, and iceberg, head lettuce, romaine, or leaf lettuce	−0.14
Tomatoes	Tomatoes, tomato juice, tomato sauce, salsa, and ketchup	−0.78
Apples and berries	Fresh apples or pears, applesauce, apple juice or cider, strawberries, and blueberries	−0.65
Deep yellow or orange vegetables and fruit	Cantaloupe, peaches, and carrots	−0.57
Other fruits and real fruit juices	Pineapples, honeydew, watermelon, grapes, prunes, oranges, orange juice, grapefruit, grapefruit juice, and other real fruit juices	−0.16
Other vegetables	Beets, celery, eggplant, garlic, green peppers, mushrooms, and onions	−0.16
Legumes	String beans, peas, lima beans, lentils, and other beans	−0.04
Fish	Canned tuna fish or salmon, dark meat fish, other fish, and breaded fish cakes or fish sticks	−0.08
Poultry	Chicken and turkey with and without skin	−0.45
Red and organ meats	Beef, pork, lamb, liver, and other organ meats	0.02
Processed meats	Bacon, salami, bologna, other processed meats, and beef, pork, chicken, or turkey hot dogs	0.68
Added sugars	Soda, punch, lemonade, fruit drinks, chocolate candy bars, other mixed candy bars, candy without chocolate, jams, jellies, preserves, and syrup or honey	0.56
High-fat dairy	Whole milk, ice cream, cream cheese, full-fat cheeses, and sour cream	−0.14
Low-fat dairy	Low-fat yogurt, low-fat cottage or ricotta cheese, other low-fat cheeses, and skim, 1%, 2%, or low-fat milk	−0.12
Coffee and tea	Coffee (decaf and regular) and tea (herbal and nonherbal)	−0.25
Nuts	Peanuts, peanut butter, and other nuts	−0.44
Fats	Mayonnaise, margarine, and butter	0.31
Refined grains and starchy vegetables	Cold or cooked breakfast cereal, white or dark bread, bagels, English muffins, rolls, cornbread, white rice, pasta, pancakes or waffles, sweet potatoes or yams, potato chips, crackers, tortillas, popcorn, pretzels, cookies, brownies, doughnuts, cake, pie, sweet rolls or coffee cakes, and French fried, scalloped, baked, boiled, or mashed potatoes	0.72
Supplement score[b]	Ranked score of supplements, including: vitamins A, B_1, B_{12}, B_6, C, D, and E; and β-carotene, folate, niacin, riboflavin, calcium, iron, magnesium, selenium, and zinc	−0.80
LIS components		
Heavy drinker	Heavy (>7 drinks/week for women, >14 drinks/week drinks for men) vs. nondrinker	0.30
Moderate drinker	Moderate (1–7 drinks/week for women, 1–14 drinks/week for men) vs. nondrinker	−0.66
Moderately physically active	Based on distribution among controls, individuals in the middle tertile of MET-hours per week	−0.18
Heavily physically active	Based on distribution among controls, individuals in the highest tertile of MET-hours per week	−0.41
Current smoker	Currently smokes tobacco vs. does not currently smoke tobacco	0.50
Overweight BMI	Overweight BMI (25–29.99 kg/m^2) vs. underweight/normal BMI (<24.99 kg/m^2)	0.89
Obese BMI	Obese BMI (≥30 kg/m^2) vs. underweight/normal BMI (<24.99 kg/m^2)	1.57

[a]Weights are β coefficients from multivariable linear regression models, conducted in a sample ($N = 639$) of participants in the REGARDS, representing the average change in a summary inflammation biomarker z-score [sum of z-scores for hsCRP, IL6, IL8, and IL10 (the latter with a negative sign)] per 1 SD increase in a dietary component or the presence of lifestyle component. Covariates in the final models to develop the weights included: age, sex, race (Black or White), education (high school graduate or less vs. some college or more), region (stroke belt, stroke buckle, or other region in the United States), a comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), hormone replacement therapy (among women), total energy intake (kcal/day), season of baseline interview (spring, summer, fall, or winter), and regular use of aspirin, other NSAIDs, or lipid-lowering medications (≥twice/week); and all the dietary/lifestyle components in the DIS and LIS. For the case–control studies, all dietary components were standardized on the basis of their distribution among the controls, by sex, to a mean of zero and SD of 1, and all lifestyle components were dummy variables.

[b]All vitamin and mineral supplement intakes measured (from multivitamin/mineral and individual supplements) were ranked into tertiles of intake and assigned a value of 0 (low or no intake), 1, or 2 (highest intake) for hypothesized anti-inflammatory supplements (e.g., vitamin E), and 0 (low or no intake), −1, or −2 (highest intake) for hypothesized proinflammatory supplements (e.g., iron).

distribution among the controls. We summarized and compared characteristics of the study population by case/control status based on χ^2 tests (categorical variables), ANOVA (normally distributed continuous variables), or nonparametric Kruskal–Wallis tests (continuous variables with nonnormal distributions). We assessed the DIS and LIS correlation with a Spearman correlation coefficient.

Using multivariable unconditional logistic regression, we estimated the associations of the DIS and LIS with incident, sporadic adenoma. We also investigated whether the associations of the inflammation scores with adenoma differed by adenoma location (right colon, left colon, or rectum) or by adenoma characteristics, including multiplicity (1/≥2 adenoma), size <1/≥1 cm, having a villous component (yes/no),

or moderate or severe atypia (yes/no). To test for trend, we included in each regression model for each score a continuous variable derived from the medians of the sex-specific score quintiles, based on the score's distribution among the controls. To test for heterogeneity by adenoma characteristics, we conducted a case-only multivariable logistic regression analysis with adenoma characteristic as the dependent variable, and took the *P* value for the continuous DIS and LIS to be the $P_{heterogeneity}$. To assess possible interaction between the DIS and LIS, we conducted a joint/combined, or cross-classification, analysis using the participants in the joint first quintile of both scores as the referent group and calculated a $P_{interaction}$ using the likelihood ratio test.

We considered including covariates in the above-described multivariable logistic regression models based on previous literature, biological plausibility, and the magnitude of change in the OR for the primary exposure variable upon addition or removal of the potential covariate from the model. Covariates considered for all models included age, sex, hormone replacement therapy use (for women), education, regular aspirin or other NSAID use, family history of colorectal cancer in a first-degree relative, study (MAP I, MAP II, or CPRU), and total energy intake. Covariates considered for the LIS models also included former smoking status and an equally weighted DIS (to reduce model size and account for the components' inflammation-related and other colorectal carcinogenic–related effects), which was created by assigning negative or positive equal weighting to dietary components we hypothesized *a priori* to be anti- or proinflammatory, respectively. Covariates considered for the DIS models also included smoking status, alcohol intake, BMI, and physical activity.

To investigate potential DIS- and LIS–adenoma association differences across participant subgroups, we conducted separate analyses within categories of age [dichotomized at 57 years old (the median among the controls)], sex, regular (≥once/week) use of aspirin or other NSAIDs (yes/no), family history of colorectal cancer in a first-degree relative (yes/no), and study (MAP I, MAP II, and CPRU), and for the DIS, within categories of current smoking status (never or former/current), BMI (<30/≥30 kg/m^2), moderate plus vigorous physical activity (dichotomized at 41.54 METS/week, the median among the controls), and alcohol consumption (current nondrinker/drinker). We compared stratum-specific estimates and calculated likelihood ratio test *P* values for model interaction terms to assess effect modification.

As a sensitivity analysis, we repeated the analyses after removal and replacement of each individual DIS and LIS component one at time to assess whether any single component overly impacted the observed DIS- and LIS–adenoma associations.

Two-sided $P < 0.05$ or 95% confidence intervals (CI) that did not include 1.0 were considered statistically significant. All analyses were conducted using R (version 3.6.1) and SAS (version 9.3) statistical software.

Results

Selected characteristics of the study participants are presented in **Table 2**. Cases were more likely than controls to be male, current smokers, overweight or obese, nondrinkers, and not regularly take aspirin or other NSAIDs. On average, cases were older and consumed greater total energy, percentage of energy from fat, and processed meats, but less total calcium and fruit. Cases also, on average, had a higher (more proinflammatory) DIS and LIS. Among the cases, 32.4% had multiple (≥2) adenomas, 31.9% had a large (≥1 cm) adenoma, 58.2% had their largest adenoma in the left colon, 29.0% had a villous or tubulovillous adenoma, 55.9% had an adenoma with moderate or severe atypia, and 25.1% had at least three high-risk adenoma characteristics. The Spearman correlation between the DIS and LIS was 0.11.

The associations of the DIS and LIS with incident, sporadic adenoma, overall and by adenoma location and number of high-risk adenoma characteristics (≥3 or <3 high-risk characteristics) are presented in **Table 3**. For those in the highest relative to the lowest DIS quintile, there were nearly statistically significant 31% higher odds of any adenoma; the direct association tended to be stronger for adenomas of the left and right colon than for the rectum, and for adenomas with ≥3 advanced characteristics. The odds of having any adenoma statistically significantly increased with an increasing LIS, and among those in the highest relative to the lowest LIS quintile, the odds of an adenoma were statistically significantly 2-fold higher (**Table 3**). The LIS was more strongly, directly associated with adenomas in the left and right colon than in the rectum, and with adenomas with ≥3 high-risk characteristics. Consistent with these findings, the DIS and LIS were most strongly associated with multiple, large (≥1 cm), and villous/tubulovillous adenomas, and adenomas with moderate or severe atypia (Supplementary Table S2).

The joint/combined (cross-classification) associations of the DIS and LIS with incident, sporadic adenoma are presented in **Table 4**. Relative to those in the lowest, most anti-inflammatory joint DIS and LIS quintile, the highest estimated odds were among those in the most proinflammatory joint DIS and LIS quintile (OR, 2.65; 95% CI, 1.77–3.95). Among those in the lowest DIS quintile, there was a pattern of increasing odds of having an adenoma with an increasing LIS, culminating in statistically significant 2-fold higher odds of an adenoma among those in the highest LIS quintile. Among those in the lowest LIS quintile, the highest odds of an adenoma were among those in the highest DIS quintile (statistically significantly 34% higher).

The associations of the DIS and LIS with adenoma (Supplementary Table S3) were similar across the three case–control studies and most other stratification categories. However, the DIS–adenoma association tended to be stronger among men than women.

In sensitivity analyses, when comparing those in the highest relative to the lowest DIS quintile, removal of apples/berries, other fruits and real fruit juices, and the supplement score from the DIS attenuated the DIS–adenoma associations by approximately 15%. Removal of smoking from the LIS attenuated the odds of adenoma for those in the highest relative to the lowest LIS quintile by 36%. Removing any one of the other DIS or LIS components from the scores did not substantially change our findings (Supplementary Tables S4 and S5).

Discussion

Our findings suggest that a higher balance of more pro- to anti-inflammatory exposures, from either diet or lifestyle, perhaps especially jointly, may be associated with higher risk for incident, sporadic colorectal adenoma. Our findings also suggest that the direct associations of the DIS and LIS with adenoma may be strongest among men and for higher risk adenomas.

Strong evidence supports a role of systemic inflammation in all stages of sporadic colorectal carcinogenesis, including initiation, promotion, progression, and metastasis (2, 3, 31–33). For example, individuals with inflammatory bowel diseases have higher colorectal cancer risk (34). Also, multiple randomized clinical trials and observational studies found chemopreventive effects against/inverse associations of aspirin and other NSAIDs with risk for colorectal neoplasms (35–37), likely through inhibition of the proinflammatory

Table 2. Selected characteristics of participants in three pooled case–control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002; pooled $N = 2{,}751$) of incident, sporadic colorectal adenoma.

	Cases ($N = 765$)		Controls ($N = 1{,}986$)		
Characteristics	**Mean (SD)**	**%**	**Mean (SD)**	**%**	***P*[a]**
Demographics					
Age, years	58.2 (9.2)		54.5 (10.9)		<0.0001
Male		60.4		42.6	<0.0001
White		95.0		96.3	0.17
College graduate or higher		28.6		31.8	0.001
Medical history					
Takes aspirin/other NSAID ≥once/week		35.6		41.7	0.003
HRT user (among women)		34.7		37.7	0.02
Has family history of CRC[b]		17.0		17.8	0.67
Lifestyle					
Current smoker		24.2		13.9	<0.0001
Normal BMI[c]		32.8		40.9	0.0002
Nondrinker		35.7		32.9	<0.0001
Physical activity[d], MET-hours/week	60.5 (56.6)		57.9 (53.7)		0.32
LIS[e]	0.4 (0.8)		0.2 (0.8)		<0.0001
Dietary intakes					
DIS[e]	−0.5 (2.4)		−0.7 (2.4)		0.02
Total energy, kcal/day	2,054 (747)		1,985 (699)		0.02
Dietary fiber, g/1,000 kcal/day	10.9 (3.7)		11.3 (3.9)		0.01
Fat, % kcal	31.3 (6.7)		30.2 (6.8)		0.001
Carbohydrates, % kcal	51.2 (8.8)		53 (8.9)		<0.0001
Protein, % kcal	16.4 (3.2)		16.6 (3.1)		0.18
Total calcium[f], mg/1,000 kcal/day	474 (277)		511 (272)		<0.0001
Total fruit, servings/week	16.0 (12.4)		17.8 (12.8)		0.001
Total vegetables, servings/week	25.7 (16.3)		26.0 (16.3)		0.65
Red meat, servings/week	4.7 (3.7)		6.1 (11.1)		0.001
Processed meats, servings/week	2.7 (3.7)		2.1 (2.9)		<0.001

Abbreviations: CRC, colorectal cancer; HRT, hormone replacement therapy.

[a]*P* values were calculated using χ^2 test for categorical variables, ANOVA for continuous variables with normal distribution, and Kruskal–Wallis test for continuous variables with nonnormal distribution.

[b]In a first-degree relative.

[c]18.5–24.99 kg/m^2.

[d]Moderate + vigorous physical activity.

[e]For construction of DIS and LIS, see text and **Table 1**; higher scores indicate a higher balance of pro- versus anti-inflammatory exposures.

[f]Total = diet + supplements.

cyclooxygenase 2 (COX-2) enzyme, which is upregulated in 85% of colorectal adenocarcinomas (3, 31, 32, 38–41).

Risk for colorectal neoplasms is also highly associated with dietary and other lifestyle exposures (5). In general, dietary patterns characterized by high intakes of fruits, vegetables, whole grains, low-fat dairy products, fish, poultry, olive oil, and legumes have been inversely associated with colorectal neoplasms; whereas, dietary patterns characterized by high intakes of red and processed meats, white potatoes, and refined grains have been positively associated with colorectal neoplasms (42). There is even stronger evidence for positive associations of obesity, heavy alcohol intake, and smoking with colorectal cancer, and for an inverse physical activity–colorectal cancer association (43–48). As summarized in Supplementary Table S1, there is also considerable biological plausibility for associations of individual food groups and lifestyle characteristics with systemic inflammation. Collectively, the above-summarized literature strongly supports inflammation as a major pathway underlying the associations of dietary/lifestyle exposures with colorectal carcinogenesis.

We found that the associations of the inflammation scores with adenoma tended to be strongest for adenomas with high-risk characteristics. The normal mucosa to small/low-risk adenoma to large/advanced adenomas to carcinoma progression is accompanied by progressively higher COX-2 expression (49). Also, larger adenomas may be more exposed to proinflammatory, mutagenic, and mitogenic exposures in the fecal stream, and larger/advanced adenomas may have impaired defenses against these exposures. Furthermore, inflammation has been more strongly, consistently associated with higher risk for advanced adenoma and colorectal cancer (49–59). So, it is plausible that a higher balance of pro- relative to anti-inflammatory dietary and lifestyle exposures may have a stronger role in the progression of adenomas to carcinomas than in their initial appearance.

Our inflammation scores tended to be more strongly associated with colon adenomas, particularly of the right colon. The left colon and right colon/rectum differ with respect to their embryologic origin and physiologic functions (60, 61). During the fecal stream's proximal to distal progression, its composition of metabolically active molecules and gut microbiota change and immune cell activity may decrease, suggesting that inflammation may be especially relevant to the etiology and/or progression of right colon neoplasms (33, 61).

In our study, the DIS was strongly, directly associated with adenomas, particularly among men. The previously developed DII (8) was used to investigate associations of diet-associated inflammation with colorectal adenoma in three studies. In a cross-sectional analysis of the

Table 3. Multivariable-adjusted associations of the DIS and LIS with incident, sporadic colorectal adenomas in three pooled case–control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002; pooled $N = 2{,}751$), overall and according to selected adenoma characteristics.

	Inflammation scores[a]			
	DIS[b]		LIS[c]	
Adenoma characteristics/inflammation score quintiles	***N***	**Adjusted OR (95% CI)**	***N***	**Adjusted OR (95% CI)**
Any adenoma				
1	129	1.00 (ref)	102	1.00 (ref)
2	158	1.16 (0.87–1.56)	118	1.13 (0.83–1.55)
3	144	1.05 (0.78–1.41)	170	1.48 (1.11–1.99)
4	157	1.16 (0.87–1.56)	181	1.61 (1.20–2.16)
5	177	1.31 (0.98–1.75)	194	1.98 (1.48–2.66)
P_{trend}		0.09		<0.0001
Adenoma location				
Left colon[d]				
1	73	1.00 (ref)	61	1.00 (ref)
2	81	1.01 (0.70–1.46)	71	1.17 (0.80–1.72)
3	86	1.06 (0.74–1.53)	100	1.49 (1.04–2.14)
4	95	1.19 (0.83–1.71)	105	1.53 (1.07–2.20)
5	110	1.39 (0.98–1.98)	108	1.79 (1.25–2.57)
P_{trend}		0.04		0.0004
$P_{heterogeneity}$		0.06		0.32
Right colon[e]				
1	25	1.00 (ref)	19	1.00 (ref)
2	48	1.96 (1.16–3.40)	29	1.36 (0.74–2.55)
3	29	1.12 (0.63–2.01)	30	1.29 (0.70–2.40)
4	35	1.45 (0.83–2.58)	45	2.10 (1.20–3.81)
5	45	1.72 (1.00–3.00)	59	3.30 (1.92–5.90)
P_{trend}		0.22		<0.0001
$P_{heterogeneity}$		0.56		0.001
Rectum				
1	27	1.00 (ref)	21	1.00 (ref)
2	23	0.79 (0.44–1.43)	16	0.81 (0.41–1.59)
3	26	0.94 (0.53–1.67)	30	1.32 (0.74–2.40)
4	24	0.89 (0.49–1.62)	29	1.34 (0.75–2.45)
5	20	0.79 (0.42–1.46)	24	1.29 (0.70–2.41)
P_{trend}		0.63		0.17
$P_{heterogeneity}$		ref		ref
Adenoma characteristics				
<3 high-risk characteristics[f]				
1	74	1.00 (ref)	59	1.00 (ref)
2	93	1.17 (0.82–1.67)	58	0.93 (0.62–1.40)
3	81	1.04 (0.72–1.50)	101	1.56 (1.09–2.25)
4	79	1.03 (0.71–1.49)	104	1.64 (1.14–2.36)
5	84	1.11 (0.77–1.60)	89	1.59 (1.10–2.32)
P_{trend}		0.73		0.001
$P_{heterogeneity}$		ref		ref
≥3 high-risk characteristics[f]				
1	31	1.00 (ref)	19	1.00 (ref)
2	31	0.92 (0.53–1.59)	26	1.37 (0.74–2.60)
3	37	1.11 (0.65–1.88)	35	1.58 (0.88–2.90)
4	40	1.09 (0.64–1.85)	53	2.43 (1.41–4.34)
5	53	1.51 (0.92–2.52)	59	3.13 (1.83–5.57)
P_{trend}		0.09		<0.0001
$P_{heterogeneity}$		0.18		0.05

Abbreviation: ref, referent.

[a]For construction of inflammation scores, see text and **Table 1**; higher scores indicate a higher balance of pro- versus anti-inflammatory exposures.

[b]Covariates in the DIS unconditional logistic regression models were age, sex, education (less than college graduate or college graduate or higher), regular aspirin or other NSAID use (≥once/week), hormone therapy use (among women), family history of colorectal cancer in a first-degree relative (yes/no), smoking status (never, former, or current smoker), BMI (kg/m^2), alcohol intake (nondrinker, moderate drinker, or heavy drinker), physical activity (categorized into tertiles of MET-hours/week), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU).

[c]Covariates in the LIS unconditional logistic regression models were age, sex, regular aspirin or other NSAID use (≥once/week), hormone therapy use (among women), family history of colorectal cancer in a first-degree relative (yes/no), former smoking status (former smoker or nonformer smoker), total energy intake (kcal/day), study (MAP I, MAP II, or CPRU), and the equally-weighted DIS.

[d]Right colon, the largest adenoma was located in the cecum, ascending, hepatic flexure, or transverse colon.

[e]Left colon, the largest adenoma was located in the splenic flexure, descending, or sigmoid colon.

[f]High-risk adenoma characteristics include multiplicity (≥2 adenomatous polyps), size ≥1 cm, moderate or severe degree of atypia, or having a villous component.

Table 4. Joint/combined associations of the DIS and LIS with incident, sporadic adenoma in three pooled case–control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002; pooled $N = 2{,}751$).

	LIS quintiles[a,b]										
	1		2		3		4		5		
	N^c	OR (95% CI)	N^c	OR (95% CI)	N^c	OR (95% CI)	N^c	OR (95% CI)	N^c	OR (95% CI)	$P_{interaction}{}^d$
DIS quintiles[a,b]											
1	24/86	1.00 (ref)	29/83	1.13 (0.82–1.55)	23/99	1.49 (1.11–2.00)	24/82	1.63 (1.21–2.19)	29/50	1.97 (1.47–2.65)	
2	25/95	1.20 (0.90–1.61)	28/82	1.36 (0.89–2.09)	42/71	1.80 (1.19–2.72)	31/71	1.96 (1.30–2.97)	32/79	2.38 (1.58–3.58)	
3	18/101	1.09 (0.82–1.47)	15/73	1.23 (0.80–1.91)	42/75	1.63 (1.08–2.47)	40/93	1.78 (1.18–2.69)	29/54	2.16 (1.42–3.28)	
4	20/90	1.20 (0.90–1.61)	17/66	1.36 (0.88–2.10)	33/81	1.79 (1.18–2.72)	43/78	1.96 (1.29–2.96)	44/83	2.37 (1.58–3.57)	
5	15/76	1.34 (1.01–1.79)	29/63	1.51 (0.99–2.32)	30/73	2.00 (1.33–3.02)	43/84	2.18 (1.45–3.29)	60/98	2.65 (1.77–3.95)	0.08

[a]For construction of inflammation scores, see text and **Table 1**; higher scores indicate a higher balance of pro- versus anti-inflammatory exposures.
[b]Covariates in the joint/combined unconditional logistic regression models were age, sex, education (less than college graduate or college graduate or higher), hormone therapy use (among women), family history of colorectal cancer in a first-degree relative (yes/no), regular aspirin or other NSAID use (≥once/week), former smoking status (yes/no), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU).
[c]Number of cases/controls.
[d]From lifestyle score*diet score interaction term in the full logistic regression model, calculated using the likelihood ratio test.

Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data, men in the highest (most proinflammatory) DII quartile relative to those in the lowest, had a statistically significant 40% higher adenoma prevalence, whereas women in the highest quartile had an estimated nonstatistically significant 8% higher prevalence (10). In an observational analysis of data from a clinical trial of wheat bran cereal fiber supplementation and adenoma recurrence, the DII–adenoma recurrence association was null (11). Finally, in a case–control study in Iran, those in the third relative to first DII tertile had a statistically significant 2.3-fold higher odds of adenoma (12).

In the prospective NIH-AARP Diet and Health Study ($N = 453{,}465$), we found that among participants in the highest relative to those in the lowest DIS and LIS quintiles, colorectal cancer risk was statistically significantly 27% and 38% higher, respectively (62); these associations were strongest among men and for colon cancers, and were stronger than the EDIP–colorectal cancer associations. In a meta-analysis of four prospective cohort studies and five case–control studies, colorectal cancer risk was estimated to be 9% and 5% higher per one-unit increase in the DII among men and women, respectively ($P_{heterogeneity} < 0.05$; ref. 63). In the Health Professionals Follow-up Study (all men) and the Nurses' Health Study (NHS; all women) cohorts, those in the highest relative to the lowest EDIP quintile had 44% and 22% higher colorectal cancer risk, respectively (64). Of note, our findings and the above-summarized literature suggests stronger associations among men than women; however, it is unclear whether this is due to artifacts of dietary measurement (e.g., in reporting; refs. 65–68) or to true biological differences (69–71).

One strength of our study is that our DIS and LIS address several limitations of the DII and EDIP. The DII is primarily based on commonly measured nutrients and does not account for the myriad unmeasured, natural anti- or proinflammatory compounds in whole foods. Also, the DII uses a somewhat arbitrary literature review–based weighting scheme to characterize the contributions of dietary factors to systemic inflammation, and some of the methods and data underlying the weights are proprietary. The EDIP is whole foods based, but was developed in the NHS cohort, a relatively homogenous population, using reduced rank regression, which is a population-dependent, *a posteriori*, data-driven (vs. driven by biological plausibility) approach (72); hence, it may be less replicable in populations with different characteristics. Neither the EDIP nor the DII addresses lifestyle. Our scores address these limitations in that: (i) they incorporate whole foods/beverages and lifestyle exposures, facilitating translation into clinical/public health recommendations, (ii) their weights are biologically plausible, and (iii) they were developed in a clear, reproducible fashion in a diverse population with heterogenous exposures. Furthermore, we validated the scores by assessing and comparing their associations with multiple circulating inflammation-related biomarkers in three populations, and both the DIS and LIS were more strongly associated with the circulating biomarkers than were the DII and EDIP (13).

Other strengths of our study include: (i) to our knowledge, this is the first study to investigate a validated LIS, alone and jointly with a DIS, with colorectal adenomas, (ii) standardized pathologic verification of adenomas, thus reducing outcome misclassification, (iii) participants completed their questionnaires prior to case/control status determination, minimizing recall bias, and (iv) the inflammation scores–adenoma associations were robust to removal/replacement of each DIS and LIS component one at a time.

Our study also had limitations. First, inherent to case–control studies, is that temporality of associations involving modifiable exposures cannot be assessed, although dietary and lifestyle exposures typically remain relatively consistent over time (73). The control group included sigmoidoscopy and community controls, possibly resulting in misclassification of some cases as controls; however, excluding these control groups did not change our findings meaningfully. The DIS and LIS also have limitations. The weights were based on cross-sectional associations of the dietary/lifestyle components with a limited inflammation biomarker panel; however, we previously found that the scores were more strongly, directly associated with inflammation markers in three validation populations (across which diet was assessed with different FFQs), including a population with a comprehensive inflammation biomarker panel, than were the DII and EDIP (13). Finally, FFQs have known limitations (e.g., recall error and limited food choices); however, findings from multiple studies that used various FFQs (including the Block and Willett FFQs) and other dietary assessment methods over the years have yielded remarkable consistency for multiple diet–colorectal neoplasm associations (63, 74, 75).

In conclusion, our findings, taken together with those from previous studies, suggest that a higher balance of pro- to anti-inflammatory dietary and lifestyle exposures, particularly in interaction, may be associated with higher risk for colorectal adenoma, especially adenomas that are advanced, and thus more likely to be clinically important in relation to colorectal cancer prevention (76, 77). Reducing inflammation, such as through dietary or lifestyle interventions, could

potentially reduce risk for adenoma, and thus colorectal cancer. Our findings support further study of dietary- and lifestyle-derived inflammation using our novel DIS and LIS in relation to colorectal neoplasms.

Disclosure of Potential Conflicts of Interest

S. Judd reports grants from NIH during the conduct of the study. W.D. Flanders reports ownership of Epidemiologic Research & Methods, LLC, which provides consulting services to clients. R.M. Bostick reports grants from NCI, NIH (grants P01 CA50305 and R01 CA66539), The Fullerton Foundation, and The Anne and Wilson P. Franklin Foundation during the conduct of the study. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

D.A. Byrd: Conceptualization, formal analysis, writing–original draft, writing–review and editing. **S. Judd:** Writing–original draft, writing–review and editing. **W.D. Flanders:** Writing–original draft, writing–review and editing. **T.J. Hartman:** Writing–original draft, writing–review and editing. **V. Fedirko:** Writing–original draft, writing–review and editing. **R.M. Bostick:** Conceptualization, supervision, funding acquisition, writing–original draft, writing–review and editing.

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