

Research Article

Dietary Inflammatory Index and Risk of Colorectal Cancer in the Iowa Women's Health Study

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Abstract

Background: Colorectal cancer, the third most common cancer in the United States, has a natural history that usually encompasses several decades. Dietary components have been implicated in the etiology of colorectal cancer, perhaps through their effect on inflammation.

Methods: We examined the ability of the dietary inflammatory index (DII) to predict colorectal cancer in the Iowa Women's Health Study. The DII was computed based on dietary intake assessed by a 121-item food frequency questionnaire in this cohort of 34,703 women, ages 55 to 69 years, free of any self-reported prior malignancy at enrollment in 1986. Incident colorectal cancer cases were identified through linkage with the State Health Registry of Iowa (a Surveillance, Epidemiology, and End Results program member). Cox proportional hazards regression was used to estimate HRs. Through the end of 2010, 1,636 incident colorectal cancers were identified, including 1,329 colon and 325 rectal cancers.

Results: Multivariable analysis, adjusting for body mass index, smoking status, pack-years of smoking, hormone replacement therapy, education, diabetes, and total energy intake, revealed positive associations between higher DII and colorectal cancer risk [HR for DII_{continuous}: 1.07 per unit increase in DII (corresponding to 0.5 SD unit increase); 95% confidence interval (CI), 1.01–1.13; HR for DII_{quintiles}: Q5 vs. Q1 = 1.20; 95% CI, 1.01–1.43]. HRs for DII were similar for colon cancer and rectal cancer, though not statistically significant for rectal cancer.

Conclusions: These results indicate that a proinflammatory diet, as indicated by higher DII scores, was associated with higher risk of developing colorectal cancer.

Impact: Proinflammatory diets are associated with increased risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*; 23(11); 2383–92. ©2014 AACR.

Introduction

Inflammation is a result of the body's response to tissue insult or injury, or the presence of inflammatory stimulants (1, 2). The acute inflammatory response represents an important step in the process of wound healing and tissue regeneration that, under normal circumstances, will lead to recovery within a few days (3, 4). Chronic inflammation is known to be associated with common epithelial cancers, with colorectal (5–7) being the most intensively

studied. There is growing evidence that specific dietary components influence both inflammation (8–10) and colorectal cancer (11–13).

Colorectal cancer is the third most common cancer among men and women in the United States. Primarily because of improvements in screening that have resulted in primary prevention of many cancers and detection at an earlier stage in others, the colorectal cancer death rate has decreased in the past 20 years (14, 15). Research into the role of diet in inflammation and colorectal cancer suggests that diet represents a complicated set of exposures which often interact, and whose cumulative effect modifies both inflammatory responses and health outcomes.

Several dietary indices exist to assess diet quality, but none had focused on diet's effects on inflammation until researchers at the University of South Carolina's Cancer Prevention and Control Program developed the Dietary Inflammatory Index (DII). The DII can be used in diverse populations to assess the inflammatory potential of diet assessed by various dietary assessment tools [e.g., 24-hour dietary recalls, food frequency questionnaires (FFQs), and food records; refs. 16–18]. Thus far, the DII has been successful in predicting inflammatory markers [e.g.,

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doi: 10.1158/1055-9965.EPI-14-0537

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C-reactive protein (CRP) and IL6] in several studies, including the Seasonal Variation of Blood Cholesterol Levels Study (SEASONS) and the Buffalo Cardio-Metabolic Police Stress Study (BCOPS) in the United States (17, 19), and in a study of asthmatics in Australia (18). However, the DII has not yet been applied to a population with cancer outcomes. The purpose of this study is to examine the association between the DII and colorectal cancer in a large prospective cohort of postmenopausal women, the Iowa Women's Health Study (IWHS). Our working hypothesis is that a higher DII score (indicating a proinflammatory diet) increases risk of incident colorectal cancer, including anatomic subtypes (i.e., colon cancer and rectal cancer).

Materials and Methods

Full details about the IWHS design have been published elsewhere (20). In brief, 41,836 older women, ages 55 to 69 years, were enrolled in 1986. Incident cancer cases and deaths were identified through annual linkage with the State Health Registry of Iowa (a Surveillance, Epidemiology and End Results program member) and the National Death Index. Emigration from Iowa was less than 1% annually, resulting in nearly complete follow-up of cancer incidence (21). Women with self-reported history of cancer before baseline, except non-melanoma skin cancer ($n = 3,830$), or extreme energy intake (< 600 kcal or $\geq 5,000$ kcal per day) or incomplete dietary data (≥ 30 items blank) on the FFQ ($n = 3,096$) were excluded from the present study, yielding a sample consisting of 35,216 study participants (exclusions were not mutually exclusive). After further exclusion for missing covariates, data from 34,703 women were included in the analysis.

Dietary intake data were collected using a FFQ at baseline. This 121-item FFQ was adapted from the 126-item instrument developed by Willett and colleagues (22). Questions related to supplements were part of this FFQ. FFQ-derived dietary data were used to calculate DII scores for all participants.

The DII is based on literature published through 2010 linking diet to inflammation. Developing the DII involved screening approximately 6,000 scientific articles published from 1950 to 2010 on diet and six inflammatory markers [i.e., CRP, IL1 β , IL4, IL6, IL10, and TNF α]. Of these, nearly 2,000 articles from cell culture and laboratory animal experiments, and cross-sectional, longitudinal, and intervention trials in humans were reviewed and scored. Finally, 11 datasets were obtained from around the world to which individual dietary intakes could be compared to determine the final DII score. Individual intakes of food parameters on which the DII is based are then compared with a world-standard database. A complete description of the detailing development of the DII is available elsewhere (16, 23). Briefly, to calculate DII for the participants of this study, the dietary data were first linked to the world database that provided a robust estimate of a mean and SD for each parameter (16). This

was achieved by subtracting the "standard global mean" from the intake reported via the FFQ and dividing this value by the SD (both calculated from the world database) to get "z" scores. To minimize the effect of "right skewing," these "z" scores were then converted to a centered percentile score. The centered percentile score for each food parameter for each individual was then multiplied by the respective food parameter effect score (inflammatory potential for each food parameter), which was derived from the literature review, to obtain a food parameter-specific DII score for an individual. All of the food parameter-specific DII scores were then summed to create the overall DII score for each participant in the study (16). A description of validation work, including both dietary recalls and a structured questionnaire similar to an FFQ, is also available (17).

The DII was calculated from foods and supplements and from foods only. The foods-only DII was based on 37 parameters available in the IWHS FFQ. DII attributable to supplements only was calculated by creating a new variable that presents the difference between the food + supplements DII and the food-only DII. If the difference is zero, then either the woman did not take a vitamin supplement or the associated nutrient (e.g., calcium) was either not part of the DII or it had a negligible effect on DII. If the nutrient is considered antiinflammatory, then the difference variable should be negative (as virtually all supplements in the calculated DII are antiinflammatory) and represent a supplement user. Supplements commonly used in this study were calcium (46%), multivitamin (33%), vitamin C (12% seasonally, 17% monthly), and vitamin E (15%).

Associations with DII of demographics, lifestyle factors, self-reported diabetes mellitus, and anthropometric characteristics were examined using general linear models or χ^2 tests (see Table 1 for specific variables). The distribution of 30 different food groups was examined across quintiles of DII to characterize low (antiinflammatory) versus high (proinflammatory) DII in terms of food intake.

Both food + supplements DII and the food-only DII were analyzed both as continuous variables and by quintiles of exposure in relation to colorectal cancer outcome variables. For analyses examining the effect of supplement use alone, the reference category represents nonsupplement users; categories 1 to 3 represent tertiles of the supplement-associated DII among supplement users. Category 1 represents women with the greatest contribution from supplements to the DII score. Outcome variables included colorectal cancer overall and both colon (ICD-O codes, 18.0–18.9) and rectum (ICD-O codes 19.9 and 20.9) subsites. Proximal and distal colon cancers defined by codes 18.0 to 18.5 and 18.6 to 18.7, respectively, also were examined.

Person-years of exposure time were accumulated from baseline until first colorectal cancer diagnosis, move from Iowa, death, or administrative censoring on December 31, 2010. HRs and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression models,

Table 1. Prevalence of characteristics at baseline across quintiles of DII (with supplements), IWHS, 1986–2010

Characteristics ^a [mean (SD) or %]	DII (with supplements) ^b				
	Quintile 1 <−2.75 Median = −3.29 (N = 6,940)	Quintile 2 −2.75 to −1.76 Median = −2.26 (N = 6,941)	Quintile 3 −1.75 to −0.57 Median = −1.21 (N = 6,941)	Quintile 4 −0.56 to 1.10 Median = 0.23 (N = 6,941)	Quintile 5 >1.10 Median = 2.13 (N = 6,940)
	Age (years)	62.0 (4.2)	61.7 (4.2)	61.6 (4.2)	61.4 (4.1)
Total energy intake (kcal/day)	2,119.1 (664.5)	2,009.5 (631.4)	1,816.4 (532.2)	1,684.8 (446.7)	1,362.9 (406.7)
Total fat (% kcal/day)	31.4 (5.4)	33.5 (5.3)	34.2 (5.5)	34.7 (5.6)	36.0 (6.0)
Dietary fiber (g/1,000 kcal/day)	13.5 (3.2)	11.6 (2.9)	10.8 (2.9)	10.5 (2.9)	9.5 (2.8)
Vitamin supplement use (% taking)					
Any	85.0	73.9	65.5	47.3	34.1
Multivitamin	68.9	50.2	35.3	9.9	2.0
Calcium	63.2	53.0	46.6	37.4	29.2
Vitamin C	32.0	21.9	16.9	9.5	3.8
Vitamin E	28.6	19.8	14.9	7.4	2.0
BMI (%; kg/m ²)					
≤24.9	42.5	40.2	39.4	38.5	38.6
25–30	37.1	37.1	37.4	36.9	36.2
≥30	20.5	22.7	23.2	24.7	25.2
Education (%)					
Less than high school	15.2	16.6	17.6	19.3	21.6
High school	36.4	40.8	42.1	43.7	47.5
More than high school	48.4	42.6	40.3	37.0	30.9
Smoking (%)					
Never	70.3	68.5	65.7	64.6	59.0
Former	20.3	19.1	19.1	19.7	18.9
Current	9.5	12.5	15.3	15.7	22.1
Alcohol intake (%)					
0 g/day	58.6	54.2	52.7	54.3	55.0
<15 g/day	34.1	39.8	41.1	39.4	38.2
≥15 g/day	7.4	6.0	6.2	6.4	6.8
Level of physical activity ^c (%)					
Low	33.7	42.3	48.4	51.9	61.2
Middle	29.8	30.2	27.4	27.4	22.8
High	36.5	27.5	24.2	20.7	16.1
Hormone therapy use (yes, %)	43.8	39.9	39.2	36.9	34.0
Diabetes at baseline (yes, %)	6.6	6.4	6.2	5.9	5.3
History of aspirin use (1992 survey, ever %)	73.5	72.7	71.6	71.4	71.0
History of NSAIDs use (1992 survey, ever %)	84.2	83.8	82.6	82.4	81.6

^aAll variables are measured at baseline (1986) unless otherwise noted. Some column percentages are presented; they do not always add to 100 because of rounding.

^bQuintile 1 refers to scores indicating the most antiinflammatory diet, and quintile 5 refers to scores indicating the most proinflammatory diet.

^cPhysical activity level: High, more than 4 times per week for moderate physical activities (e.g., bowling, golf, light sports or physical exercise, gardening, taking long walks) or more than 2 times per week for vigorous physical activities (e.g., jogging, racquet sports, swimming, aerobics, strenuous sports); Middle, more than 2 times per week for moderate physical activities or a few times a month for both moderate and vigorous physical activities; Low, those not belonging to activity level 2 or 3.

adjusting only for age in the crude model and additionally adjusting for body mass index [BMI = weight (kg)/weight (m)²], smoking status, pack-years of smoking, education,

hormone replacement therapy (HRT) use, total energy intake, and history of diabetes in another. The covariates were chosen *a priori*, as they previously were shown to be

strong risk factors for colorectal cancer in this cohort. Further adjustment for alcohol intake and physical activity did not substantially change the results; therefore, these variables were not included in the final model. A linear test for trend was conducted by including the median value for each DII quintile as a continuous term into the regression model (and for tertiles in the supplements-only analyses). The assumption of proportional hazards was tested by adding to the model an interaction term between follow-up time and DII; there was no evidence that violated.

Finally, to examine whether adjustment for aspirin and other NSAIDs use affects a DII-colorectal cancer association, we conducted a sensitivity analysis for the colorectal cancer outcome by including only those women who replied to the 1992 follow-up questionnaire about the use of aspirin and other NSAIDs ($N = 26,152$ still at risk and 998 colorectal cancer cases; NSAIDs use was not queried at baseline) and adjusting for ever use of these medications. For this analysis, all cancer cases diagnosed before 1992 were excluded, and the analytical cohort was followed from the time of the 1992 survey until the end of follow-up. Statistical tests were performed using SAS 9.3 (SAS Institute Inc.); all statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

The food + supplements DII had a mean (SD) value of -0.87 ($SD = \pm 2.02$), whereas the food-only DII mean was -0.06 ($SD = \pm 1.94$). The food + supplements DII was positively correlated with the food-only DII ($r = 0.82$); however, it was inversely correlated with DII from supplements only ($r = -0.25$).

Decreasing trends were observed for energy and dietary fiber intake across DII quintiles (Table 1). Increasing trends were observed across quintiles of DII for percent energy from fat and proportion of women with $BMI \geq 30$ kg/m^2 , current smokers, and those reporting low levels of physical activity. Table 2 describes the distribution of servings of 30 food groups across DII quintiles, with percentage difference between quintiles 5 and 1. The food groups that showed the greatest reduction ($\geq 60\%$) from quintile 1 to quintile 5 are vegetables other than green leafy vegetables or potatoes (65%), low-fat dairy (63%), green leafy vegetables (62%), fish/seafood (62%), nuts (61%), fruits (61%), and whole grains (60%); and the food groups that showed greatest increase ($\geq 20\%$) were butter (56%), beer (37%), coffee (36%), fried food (29%), and liquor (24%). Food groups that differed little ($\leq 5\%$) across DII quintiles include refined grains, nitrate-processed meat, high-fat dairy, and chocolate.

During the follow-up period (mean \pm SD = 19.6 ± 7.0 years), 1,636 incident colorectal cancers were identified, including 1,329 colon and 325 rectal cancer cases. Of the 1,329 colon cancer cases, 903 were proximal colon and 388

were distal colon. When analyses were carried out using continuous DII, a 1-unit increment in DII (corresponding to a 0.5 SD increase) showed significant positive associations with risk of overall colorectal cancer after adjusting for age (HR, 1.09; 95% CI, 1.03–1.14). After additional adjustment for BMI, smoking status, pack-years of smoking, education, HRT use, total energy intake, and history of diabetes, the HR was slightly attenuated (1.07; 95% CI, 1.01–1.13). In a sensitivity analysis restricted to responders to the 1992 follow-up questionnaire, additional adjustment for the use of aspirin or other NSAIDs did not materially alter the results (HR_{continuous} = 1.10; 95% CI, 1.03–1.19; HR_{quintile 5 vs. 1} = 1.31; 95% CI, 1.05–1.63). In addition, the DII-colorectal cancer association was stronger among women who did not use aspirin or any other NSAIDs (30% of all women). Compared with the first quintile, the HRs were 1.39 (95% CI, 1.03–1.14), 1.37 (95% CI, 1.03–1.14), 1.62 (95% CI, 0.98–2.67), and 2.02 (95% CI, 1.21–3.39; P trend = 0.008) for the second, third, fourth, and fifth quintile, respectively.

For analysis focusing on specific anatomic subsites, a significant positive association was observed with colon cancer after age adjustment (HR, 1.08; 95% CI, 1.02–1.13), with slight attenuation observed after additional adjustment for other variables (HR, 1.05; 95% CI, 0.99–1.12). For rectal cancer, HRs for DII were of similar magnitude as for colon cancer, but did not achieve statistical significance, consistent with the smaller number of cases (Table 3).

Analysis with DII expressed as quintiles revealed significantly higher risk for women in the fifth quintile compared with women in the first quintile for overall colorectal cancer (HR, 1.20; 95% CI, 1.01–1.43, P trend = 0.03). Effect sizes were similar for colon and rectal cancers analyzed separately, though did not reach statistical significance (Table 3). Additional analyses were carried out with subtypes of colon cancer. The DII as a continuous variable showed a statistically significant association with proximal colon cancer (HR, 1.08; 95% CI, 1.02–1.16) in the crude model adjusted for age, but this was attenuated and no longer statistically significant with additional adjustment for other covariates (HR, 1.06; 95% CI, 0.98–1.14). Similar to colon cancer, the risk of proximal colon cancer increased across the DII quintiles (P trend = 0.01). Similar associations between the continuous DII and distal colon cancer were observed (HR_{age-adjusted} = 1.06; 95% CI, 0.96–1.18; HR_{multivariable adjustment} = 1.05; 95% CI, 0.93–1.18), though there was no evidence for a linear trend across DII quintiles (P trend = 0.33).

When analyses were carried out with DII from food groups only, there was minimal change in the effect size of the association for colorectal cancer (HR_{continuous} = 1.07; 95% CI, 1.01–1.15; HR_{quintile 5 vs. 1} = 1.16; 95% CI, 0.95–1.42) and for cancer subtypes (Table 4). When analyses were carried out with DII from supplements only (i.e., obtained subtracting the food-only DII from the food + supplements DII), women in category 2 appeared to have lower risk of colorectal cancer (HR_{category 2 vs. 4} = 0.84; 95% CI,

Table 2. Distribution of food groups across quintiles of DII (with supplements)^a, IWHS, 1986–2010

Food groups (servings/week)	Direction increase with DII ^b	Difference (Q5 – Q1)/Q1	Quintile1 Mean	Quintile2 Mean	Quintile3 Mean	Quintile4 Mean	Quintile5 Mean
Other vegetables (other than green leafy vegetables or potatoes)	–	–65%	27.3	19.8	16.0	13.8	9.7
Low-fat dairy	–	–63%	10.6	9.1	7.9	6.6	3.9
Green leafy vegetables	–	–62%	7.5	5.5	4.4	3.9	2.8
Fish/seafood	–	–62%	2.6	1.9	1.5	1.3	1.0
Fruit (no juice)	–	–61%	19.9	15.6	12.9	11.2	7.7
Nuts	–	–61%	3.5	2.8	2.2	1.9	1.4
Whole grains	–	–60%	16.8	12.9	10.8	9.3	6.7
Beans without soy	–	–56%	0.7	0.6	0.5	0.4	0.3
Fruit juice	–	–52%	6.6	5.8	5.0	4.5	3.1
Poultry	–	–52%	2.6	2.0	1.8	1.6	1.2
Wine	–	–39%	0.7	0.6	0.5	0.5	0.4
Potatoes	–	–31%	3.5	3.5	3.2	3.1	2.4
Salty snacks	–	–30%	4.5	4.4	3.9	3.7	3.1
Margarine	–	–27%	10.4	10.1	9.6	9.2	7.6
Tea	–	–26%	3.4	3.3	3.0	2.9	2.5
Eggs	–	–24%	2.4	2.4	2.3	2.1	1.8
Sweets without chocolate	–	–22%	8.1	9.1	8.2	7.7	6.3
Low-calorie beverages	–	–20%	2.0	1.8	1.7	1.6	1.6
Red meat	–	–13%	5.8	6.5	6.2	5.9	5.0
Chocolate	0	–3%	0.6	0.8	0.8	0.7	0.6
High-fat dairy	0	–3%	9.6	10.9	10.4	10.2	9.3
Refined grains	0	0%	8.3	8.9	9.0	9.2	8.2
Nitrate processed meat	0	1%	1.8	2.1	2.1	2.0	1.8
French fries	+	6%	0.3	0.4	0.4	0.4	0.4
High-sugar beverages	+	18%	1.2	1.4	1.4	1.4	1.4
Liquor	+	24%	0.8	0.8	0.8	0.9	1.0
Fried food	+	29%	1.8	2.2	2.3	2.3	2.3
Coffee	+	36%	9.9	11.4	11.8	12.1	13.5
Beer	+	37%	0.5	0.6	0.6	0.7	0.7
Butter	+	56%	1.4	1.9	2.0	2.0	2.2

^aThe foods listed are meant to give the reader a sense of how dietary intake varies across DII quintiles; though some listed foods are indeed among the 37 parameters that are used in computation of DII in the IWHS, these are not meant to be a list of contributors to the DII.

^b+ indicates increase across quintiles; – indicates decrease across quintiles; 0 indicates no or <5% change.

0.73–0.98) than women in category 3 ($HR_{\text{category 3 vs. 4}} = 0.89$; 95% CI, 0.77–1.03), suggesting a nonlinear relationship in which an increasing benefit from the supplement is observed at moderate doses. However, there was no apparent benefit for more heavily exposed women [i.e., for in category 1 ($HR_{\text{category 1 vs. 4}} = 0.94$; 95% CI, 0.82–1.09; Table 4)].

Discussion

In this large, population-based, prospective cohort study of older women, consuming a more proinflammatory diet, as reflected in higher DII scores, was associated with increased risk of colorectal cancer.

Results were suggestive of a positive association between the DII and colon (both proximal and distal) and rectal cancers separately, after adjustment for multiple covariates.

In support of the asserted proinflammatory effect of higher DII, the DII–colorectal cancer association was accentuated among women who did not use aspirin or other NSAIDs (30% of all women). This was hypothesized *a priori* because NSAIDs exert a stronger antiinflammatory effect than what might be expected through a moderately antiinflammatory diet (characterized by low DII). Therefore, an unbiased estimate of the true impact of antiinflammatory diet may be seen by restricting to non-NSAIDs users. Antiinflammatory diet may confer protection

Table 3. DII from food and supplements and colorectal cancer risk; IWHS, 1986–2010

	Colorectal cancer		Colon cancer		Rectal cancer	
	Cases (n)	HR ^a (95% CI)	Cases (n)	HR ^a (95% CI)	Cases (n)	HR ^a (95% CI)
DII continuous	1,636	1.09 (1.03–1.14)	1,329	1.08 (1.02–1.13)	325	1.10 (0.99–1.23)
DII quintiles						
Quintile 1	290	1 (referent)	236	1 (referent)	58	1 (referent)
Quintile 2	318	1.11 (0.94–1.30)	267	1.14 (0.96–1.34)	54	0.93 (0.64–1.35)
Quintile 3	335	1.18 (1.01–1.38)	270	1.17 (0.98–1.40)	73	1.28 (0.91–1.81)
Quintile 4	341	1.20 (1.03–1.40)	270	1.17 (0.98–1.39)	71	1.24 (0.88–1.76)
Quintile 5	352	1.29 (1.10–1.51)	286	1.28 (1.08–1.53)	69	1.25 (0.87–1.80)
P trend		0.001		0.008		0.10

^aAge-adjusted.^bAdjusted for age, BMI, smoking status, pack-years of smoking, HRT use, education, diabetes, and total energy intake.

against colorectal cancer among nonusers of NSAIDs and therefore may be promising as a new approach for colorectal cancer prevention, especially in people who cannot tolerate NSAIDs.

The DII, which is based on evidence available in the biomedical literature, is different from other dietary indices, virtually all of which fall into three main categories: 1, those derived from specific dietary prescriptions based on some external standard [e.g., Healthy Eating Index (HEI), which was derived from the adherence to the United States Dietary guidelines (24)]; 2, those derived empirically from findings within particular study populations [e.g., computing a pattern using principal component analysis (PCA; ref. 13)]; or 3, those that link to particular cultural patterns of dietary intake [e.g., the Mediterranean diet score (25)]. Previously, studies have been conducted to examine various dietary patterns and indices in relation to colorectal cancer in women (13, 26). In a study conducted in the National Institutes of Health-American Association of Retired Persons (NIH–AARP) cohort, significant associations were observed between colorectal cancer incidence and the HEI-2005, but not the alternate HEI or Mediterranean diet scores after adjustment for multiple confounders (26). A case-control study conducted by Miller and colleagues (13) compared HEI-2005 and PCA-derived patterns of dietary intake and their association with colorectal cancer. The results showed significant associations between low HEI-2005 scores and a dietary pattern high in meat, potatoes, and refined grains and colorectal cancer risk among women (12). There are areas of substantial overlap in the diets that characterize these different dietary patterns; however, there also are differences among dietary pattern scores. Which food groups contribute to prediction of colorectal cancer in one score but not in another is a topic for further investigation.

Previous studies also have examined the effect of specific food items, such as red meat (12, 27), and nutrients, such as folate (28) and zinc (29), and their association with colorectal cancer. A limitation of this approach is that these whole foods or nutrients are usually consumed with other food items and nutrients; thus, dietary intercorrelations may attenuate or accentuate the actual effects of the whole food or nutrient under study. Very high correlations among nutrients and foods can result in instability in risk estimation due to multicollinearity and possible loss of statistical power. In formulating the DII (16, 23), an entirely different approach was taken by focusing on the functional effects of foods and nutrients. As such, it relies on careful review and scoring of the medical literature in specific relation to inflammation. Also, in contrast to more culture-bound indices, it standardizes individuals' dietary intakes of pro- and antiinflammatory food constituents to world referent values for easy comparison across populations.

One of the possible mechanisms for the positive association of the DII with colorectal cancer in IWHS might be through the effect of proinflammatory diet on insulin

Table 4. DII from foods only, DII from vitamin supplements, and colorectal cancer risk; IWHS, 1986–2010.

	Colorectal cancer			Colon cancer			Rectal cancer		
	Cases (n)	HR ^a (95% CI)	HR ^b (95% CI)	Cases (n)	HR ^a (95% CI)	HR ^b (95% CI)	Cases (n)	HR ^a (95% CI)	HR ^b (95% CI)
DII from foods only ^c									
Continuous	1,636	1.09 (1.03–1.14)	1.08 (1.01–1.15)	1,329	1.08 (1.02–1.14)	1.06 (0.99–1.14)	325	1.11 (0.99–1.24)	1.13 (0.98–1.31)
Quintiles ^d									
Quintile 1	294	1 (referent)	1 (referent)	237	1 (referent)	1 (referent)	58	1 (referent)	1 (referent)
Quintile 2	323	1.11 (0.95–1.30)	1.07 (0.90–1.26)	271	1.15 (0.96–1.37)	1.10 (0.91–1.32)	60	1.07 (0.74–1.54)	1.07 (0.73–1.56)
Quintile 3	338	1.16 (0.99–1.36)	1.12 (0.94–1.33)	268	1.12 (0.94–1.34)	1.07 (0.88–1.30)	73	1.35 (0.95–1.92)	1.37 (0.93–2.01)
Quintile 4	351	1.21 (1.03–1.43)	1.16 (0.97–1.40)	293	1.23 (1.03–1.47)	1.16 (0.95–1.43)	61	1.16 (0.80–1.68)	1.20 (0.79–1.84)
Quintile 5	330	1.17 (0.99–1.38)	1.12 (0.91–1.38)	260	1.12 (0.93–1.35)	1.06 (0.84–1.33)	73	1.43 (0.99–2.05)	1.48 (0.94–2.34)
P trend		0.004	0.08		0.02	0.27		0.10	0.13
DII from supplements ^e									
Continuous	1,636	1.04 (0.99–1.10)	1.02 (0.97–1.08)	1,329	1.04 (0.98–1.09)	1.02 (0.96–1.08)	325	1.05 (0.93–1.17)	1.02 (0.91–1.15)
Categories ^f									
1 (N = 5,824)	273	0.91 (0.79–1.04)	0.94 (0.82–1.09)	226	0.84 (0.69–1.02)	0.84 (0.69–1.03)	52	1.10 (0.74–1.64)	1.10 (0.73–1.64)
2 (N = 5,824)	236	0.81 (0.70–0.94)	0.84 (0.73–0.98)	186	0.91 (0.74–1.11)	0.89 (0.72–1.09)	53	1.30 (0.88–1.92)	1.21 (0.81–1.81)
3 (N = 5,826)	256	0.89 (0.77–1.02)	0.89 (0.77–1.03)	199	1.09 (0.94–1.27)	1.05 (0.90–1.23)	61	1.08 (0.79–1.49)	1.02 (0.74–1.42)
4 (N = 17,229)	871	1 (referent)	1 (referent)	718	1 (referent)	1 (referent)	159	1 (referent)	1 (referent)
P trend		0.09	0.29		0.15	0.36		0.56	0.88

^aAdjusted for age and the other DII variable.^bAdjusted for age, the other DII variable, BMI, smoking status, pack-years of smoking, HRT use, education, diabetes, and total energy intake.^cThese are for foods only, exclusive of supplement intake.^dReference category is the lowest (i.e., most antiinflammatory) quintile; increasing quintiles of DII from food groups represent increasing inflammatory scores.^eThis is obtained by subtracting the DII score for foods only from the DII derived by including both foods and supplements.^fReference category represents nonsupplement users; categories 1 to 3 represent tertiles of the DII from supplement users. Category 1 represents women with the greatest contribution from supplements to the DII score. DII score median (range): categories 1, –3.00 (<–2.0552); 2, –1.31 (–2.0552 to –0.7616); 3, –0.34 (–0.7615 to 0.0000); 4, 0.00 (0.0000 to 0.1765).

resistance through increasing systemic inflammation (30, 31). Consumption of food items such as meat and butter has been shown to increase systemic inflammation by increasing levels of high-sensitivity CRP, E-selectin, and soluble vascular cell adhesion molecule-1 (30), which then are responsible for increasing insulin resistance (31). Increasing insulin resistance is associated with colorectal cancer by increasing circulating levels of insulin, triglycerides, and nonesterified fatty acids (32, 33), which promote excessive proliferation of colonic epithelial cells and expose them to reactive oxygen species, thereby increasing risk of colorectal cancer. Another theory suggests the role of diet on local inflammation and oxidation in the colon; local inflammation and oxidative stress as a result of activation of the COX-2 enzyme in colonic epithelial cells result in focal proliferation and mutagenesis (33). As mentioned previously, there are various dietary factors which have different effects on inflammation; for example, red meat consumption increases inflammation and green leafy vegetables reduce inflammation (32, 33). Supporting our findings, previous work in the IWHS examining diet and colorectal cancer has shown significant inverse associations between antiinflammatory food parameters such as vitamin D (34), magnesium (35), and vitamin E (36) intake and colon cancer and between catechins and rectal cancer (37). A significant positive association was observed between sugar, meat, and fat intake and colon cancer (38).

We observed reduced levels of mean fiber and energy intake in quintile 5 compared with quintile 1. This could be because people with lower DII scores consume higher amounts of food in general; this overall higher intake would encompass many antiinflammatory dietary components that also would contribute to higher overall energy intake. We found that the addition of micronutrients from supplements to the DII scoring had an impact on the mean DII, though did not materially change effect estimates of the DII with colorectal cancer. We also observed inconsistent associations with colorectal cancer when the supplements-associated DII was considered (i.e., the difference between the food + supplements DII and the food-only DII shown in Table 4).

Previous published results with DII include the SEASONS study, where we tested DII with two dietary assessment tools, the 24HR recall and 7-Day Dietary Record (7DDR). For the 24HR recall, we had information on 44 of the 45 food parameters, and for 7DDR, we had information on 28 of the 45 food parameters. We observed a significant association between DII and CRP (>3 mg/L) for both tools; 1-point increase in score was associated with an increased odds of elevated hs-CRP using either dietary assessment method (OR, 1.08; 95% CI, 1.01–1.16 for 24HR and OR, 1.10; 95% CI, 1.02–1.19 for 7DDR; ref. 17). In an Australian study, we calculated DII from FFQ and we had information on 25 food parameters, where we observed for every unit increase in DII score the odds of being asthmatic increased by 70% (OR, 1.70; CI, 1.03–2.14,

$P = 0.020$). Also in that study, logIL6 was significantly positively associated with DII ($\beta = 0.13$, 95% CI, 0.05–0.21; $P = 0.002$; ref. 18).

Strengths of the present study include large sample size, prospective data collection with extended follow-up, near-complete case ascertainment, ability to adjust for multiple potential confounding factors, and consideration of colorectal cancer risks overall and by anatomic subsite. One recognized limitation is that dietary data were collected by a single FFQ at baseline. However, adult dietary patterns appear to remain relatively stable over time (39–44), and there was no specific dietary intervention applied to participants during the course of the study. Also, evidence from other studies suggests that modest changes in diet over adulthood may have a minimal effect on estimated colorectal cancer risk (11).

In conclusion, older women who consumed a more proinflammatory diet were at increased risk of colorectal cancer compared with women who consumed a more antiinflammatory diet. Our results provide further evidence for the benefits of a diet high in vegetables and fruits, nuts, low-fat dairy, fish, and whole grains and low in fried foods, processed meats, refined grains, and alcohol. The logical next steps would be to use DII to predict incidence of other inflammation-related cancers and cardiovascular diseases and to examine effects on mortality among women. The results from the current study are restricted to women, so using DII in studies with men would help to discern the generalizability of DII across the sexes. It also would be interesting to compare the results of DII with other indices with colorectal cancer and other cancers as outcomes.

Disclosure of Potential Conflicts of Interest

D.R. Jacobs Jr is a consultant/advisory board member for California Walnut Commission. J.R. Hébert has an ownership interest in Connecting Health Innovations LLC. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Shivappa, D.R. Jacobs Jr
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Shivappa, A.E. Prizment, C.K. Blair, D.R. Jacobs Jr, S.E. Steck, J.R. Hébert
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D.R. Jacobs Jr
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Acknowledgments

The authors thank the IWHS staff for assistance in data preparation.

Grant Support

The IWH was supported by the NCI grant R01 CA39742 (to D.R. Jacobs Jr and C.K. Blair). J.R. Hébert was supported by an Established Investigator Award in Cancer Prevention and Control from the Cancer Training Branch of the NCI (K05 CA136975). A.E. Prizmet was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR000114.

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Received May 16, 2014; revised August 4, 2014; accepted August 11, 2014; published OnlineFirst August 25, 2014.

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Cancer Epidemiol Biomarkers Prev 2014;23:2383-2392. Published OnlineFirst August 25, 2014.

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