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The Dietary Inflammatory Index Is Associated with Colorectal Cancer Risk in the Multiethnic Cohort[1–3]

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Abstract

Background: Diet is known to influence systemic inflammation, a recognized risk factor for colorectal cancer (CRC). Studies in ethnically diverse populations that examine the association between dietary inflammatory potential and CRC incidence are limited.

Objectives: We used the Dietary Inflammatory Index to clarify the relation between the inflammatory potential of diet and CRC incidence across racial/ethnic groups. We hypothesized that proinflammatory diets would be associated with an increased risk of CRC, and that these associations may differ across racial/ethnic groups.

Methods: The Multiethnic Cohort (MEC) follows a prospective study design. It includes 190,963 white, African-American, native Hawaiian, Japanese-American, and Latino men and women aged 45–75 y at recruitment and followed over 20 y. Participants completed a food frequency questionnaire from which energy-adjusted Dietary Inflammatory Index (E-DII) scores were computed and categorized into quartiles. CRC incidence was documented through linkage to cancer registry programs. Cox proportional hazards regression was used to estimate HRs and 95% CIs, adjusting for known or expected CRC risk factors.

Results: Among all participants, more-proinflammatory diets (highest quartile compared with lowest quartile) were associated with an increased risk of CRC (HR: 1.21; 95% CI: 1.11, 1.32). However, the effect size was larger for men (HR: 1.28; 95% CI: 1.13, 1.45) than for women (HR: 1.16; 95% CI: 1.02, 1.33), although the interaction term for sex was not statistically significant (*P*-interaction = 0.17). When stratified by race/ethnicity, the association was significantly different between groups for men (*P*-interaction = 0.01), although not for women (*P*-interaction = 0.20). Significant associations with HRs ranging from 2.33 to 1.04 were observed in white, Japanese-American, and Latino men, and native Hawaiian women.

Conclusions: Overall, more-proinflammatory diets, as identified by the E-DII, were associated with increased CRC risk in MEC participants across racial/ethnic groups. This study adds to the evidence suggesting that diets with high proinflammatory potential may increase CRC risk. *J Nutr* 2017;147:430–8.

Keywords: chronic inflammation, racial/ethnic groups, colon cancer, rectal cancer, cancer stage

Introduction

Colorectal cancer (CRC)[9] is the third most commonly diagnosed cancer in the United States (1–3). A number of risk factors have been described for CRC, including family history, obesity, excessive alcohol consumption, tobacco use, low intake of dietary fiber or calcium, high red or processed meat intake, physical inactivity, and chronic inflammation (3). In recent decades, research on the biological link between chronic inflammation, diet, and CRC incidence has grown (4–6).

Inflammation represents a naturally occurring acute immune response that aids the body in healing wounds and fighting infection (7, 8). Although acute inflammation is consistent with good health, chronic inflammation is implicated in the onset and progression of cancer (9–11), with evidence of this effect being strongest for CRC (5). Epidemiologic evidence shows that the incidence of CRC is higher in individuals with inflammatory bowel disease (5, 12), whereas prolonged use of nonsteroidal anti-inflammatory drugs is shown to reduce risk (13).

Diet is an acknowledged set of CRC risk factors (14) in part because of its role in regulating inflammation (15). Diets rich in fruits and vegetables are associated with a reduction in CRC risk (16); whereas diets high in fat, added sugar, and protein are associated with increased inflammation (17, 18) and increased risk of CRC (16). Although research shows links between diet

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and inflammation (17, 18), and between chronic inflammation and the development of cancer (4, 19), the complexity of these relations is not yet fully understood. Dietary pattern analyses based on the recently developed Dietary Inflammatory Index (DII) may help clarify the relation between the overall inflammatory potential of individual diets and CRC incidence (20, 21).

The DII distinguishes dietary patterns on a continuum from anti-inflammatory to proinflammatory, where a higher, more positive DII score indicates a more proinflammatory diet and a lower, more negative score indicates a more anti-inflammatory diet (21). Higher DII scores have been linked to both inflammatory biomarkers (22–24) and a greater risk of CRC (25–29). To date, most DII research has been applied in examinations of primarily European and European-American populations (23, 25, 26, 28).

Associations between diet and disease incidence are known to vary across diverse populations (30, 31). Also, major dietary exposures are known to differ between racial and ethnic groups (32). However, with respect to the incidence of CRC, little work has been done to understand the role of proinflammatory diets in nonwhite populations. Therefore, this study used the DII to examine the relation between the inflammatory potential of dietary intake and CRC incidence within the Multiethnic Cohort (MEC), which consists of a large (>215,000 participants), racially and ethnically diverse population that has been followed for >20 y. We hypothesized that participants with more-proinflammatory diets (i.e., higher DII scores) would have a greater risk of CRC and that these associations may differ across the racial/ethnic groups represented in the MEC (African-American, Japanese-American, Latino, native Hawaiian, and white participants).

Methods

Study population. The MEC is a prospective cohort study investigating the association of lifestyle and genetic factors with the incidence of cancer and other diseases. The study's design and implementation have been described previously (33). Briefly, 215,000 men and women living in Hawaii or the Los Angeles area and 45–75 y old at recruitment were enrolled from 1993 to 1996. To obtain a multiethnic sample of African-American, Japanese-American, Latino, native Hawaiian, and white participants, driver's license files, voter registration lists, and Medicare files were used to identify potential participants. The institutional review boards at the University of Hawaii and the University of Southern California approved the study protocol.

Colon and rectal cancer cases were identified through regular linkages with the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the statewide Hawaii Tumor Registry, all part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program. Migration to other states has been low in the MEC (7% at 10 y); therefore, Hawaii and California tumor registries cover the vast majority of incident cases, and this has been verified through Medicare linkage. Dates of death were identified by routine linkages with California and Hawaii vital records and the National Death Index databases. Complete case and/or death ascertainment was available up to 31 December 2010. Participants who identified as not being a member of 1 of the 5 major racial/ethnic groups (n = 13,988), who had a prevalent diagnosis of CRC at cohort entry either by self-report or registry information (n = 2564), or who had implausible dietary data (n = 8137) were excluded from this analysis. This left a remaining population of 190,963, with 4388 invasive colorectal adenocarcinoma cases (3372 colon, 981 rectum, and 35 with both colon and rectum) being identified. The 297 incident CRC cases with other histologies were censored at their date of diagnosis.

Data collection. Upon entry into the cohort, participants completed a 26-page baseline questionnaire. The questionnaire included questions on demographics, height and weight, personal and family medical history, family history of CRC, and physical activity, and a quantitative FFQ with >180 items, which has been described previously (33–35). The FFQ assessed usual intake over the previous year with the use of 8 response categories ("never or hardly ever" to "2 or more times a day"), and, for some beverage items, 9 response categories ("never or hardly ever" to "4 or more times a day"). Three portion sizes specific to each food item, shown as representative images, were used to assess quantity of food eaten. The FFQ was validated and calibrated in each race/ethnicity–sex group with the use of data from 1606 participants and 3 randomly scheduled 24-h dietary recalls (34). The MEC FFQ had several unique attributes, including the presence of ethnic-specific foods, reliance on a food composition table specific to the MEC, and use of a large recipe database (36).

DII. The development and construct validation of the DII have been described previously (21, 22). Briefly, nearly 2000 peer-reviewed articles published through 2010 on the association between diet and 6 inflammatory markers (i.e., C-reactive protein, IL-1β, IL-4, IL-6, IL-10, and TNF-α) were reviewed and scored to determine an inflammatory effect score. In this process, 45 food components were identified as having a sufficiently robust literature linking to ≥1 of the 6 markers. Not all of the 45 food components were available in the MEC data. Food components included in the DII calculation in the MEC were carbohydrate; protein; total fat; saturated, monounsaturated, and polyunsaturated fats; ω-3 and ω-6 FAs; alcohol; fiber; cholesterol; vitamins A, B-6, B-12, C, D, and E; thiamin; riboflavin; niacin; iron; magnesium; zinc; selenium; folate; β-carotene; isoflavones; and caffeine. Food components not included were eugenol, garlic, ginger, onion, *trans* fat, turmeric, green tea, black tea, falan-3-ol, flavones, flavonols, flavonones, anthocyanins, pepper, thyme, oregano, and rosemary. Unavailable food components were dropped from the DII calculation for the MEC. Only intake from foods, and not from supplements, was used in the DII calculations.

The DII was standardized to its current range with the use of dietary intake from surveys or studies in 11 countries, which were compiled to provide a reference mean ± SD intake value for each food component (21). A z score was created for each food component for each participant by subtracting the reference mean from the actual food component intake value and then dividing the difference by the reference SD. To minimize the effect of right skewing and to center the distribution on 0 (null), with a lower bound of −1 (maximally anti-inflammatory) and upper bound of +1 (maximally proinflammatory), these z scores were then converted to a centered proportion score. This was achieved by doubling the z score expressed on a scale of 0 to 1 and then subtracting 1. The product of each food component–specific centered proportion score and inflammatory effect score was calculated and summed for all food components, which created the overall DII score. DII calculations are based on the intake of each food component as expressed per 1000 kcal consumed, also known as the energy-adjusted Dietary Inflammatory

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[2] Author disclosures: JR Hébert owns controlling interest in Connecting Health Innovations, a company planning to license the right to his invention of the dietary inflammatory index from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. MD Wirth and N Shivappa are employees of Connecting Health Innovations. BE Harmon, CJ Boushey, LR Wilkens, E Draluck, SE Steck, L Hofseth, CA Haiman, and L Le Marchand, no conflicts of interest.

[3] Supplemental Table 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

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[9] Abbreviations used: CRC, colorectal cancer; DII, Dietary Inflammatory Index; E-DII, energy-adjusted Dietary Inflammatory Index; MEC, Multiethnic Cohort; NIH-AARP, NIH–American Association of Retired Persons.

Index (E-DII) (37–40). A higher DII score indicates a more proinflammatory diet and a lower score indicates a more anti-inflammatory diet. The E-DII scores within the MEC were converted to quartiles with the following ranges: quartile 1 = −6.64 to −3.66; quartile 2 = −3.65 to −2.32; quartile 3 = −2.31 to −0.53; and quartile 4 = −0.52 to 4.95. Although the range of scores for the E-DII may be similar to the DII scores in the literature (39), they cannot be compared directly, because the E-DII scores take into account nutrient density of the diet.

Statistical analysis. Analyses were performed with the use of SAS version 9.4. Frequencies or means ± SDs were calculated for participant characteristics at baseline. Variables investigated as possible confounders included previous disease diagnoses (i.e., heart attack, diabetes, hypertension, and others), use of dietary supplements, smoking status, year of enrollment, family history of CRC, hormone use (i.e., estrogen or progesterone), aspirin use, average sleep duration, physical activity (in metabolic equivalents), location (i.e., Hawaii or Los Angeles), marital status, education, age at cohort entry, and BMI (kg/m^2). The categories used in modeling are the same as those given in **Table 1**.

Sex and race/ethnicity were investigated for their role as effect modifiers. Minimally adjusted models were computed with the use of age, sex, and race as STRATA variables. Model confounder selection was determined with a series of bivariable Cox proportional hazards regressions (i.e., the E-DII + potential covariate). All covariates with a P value ≤ 0.20, along with the E-DII score, were included in a saturated adjustment model. A final adjustment model was created by including only covariates that, when removed, led to a ≥10% change in the HR of the E-DII and those that were statistically significant ($P < 0.05$) in the saturated model. However, hormone use (for women) and aspirin use were retained in the model regardless of significance because of their direct impact on inflammation (13, 41). See footnotes of tables for final model specifications.

To examine the relation between the E-DII scores and CRC incidence, Cox proportional hazards regression was used to estimate HRs and 95% CIs. Time (in years) elapsed since study entry was used as the time metric. The referent category was the lowest quartile (quartile 1) for E-DII, with the primary comparison of interest being between quartile 4 and quartile 1. The assumption of proportional hazards was examined by reviewing cumulative sums of Martingale residuals (42). The proportional hazards assumption was met by the E-DII; however, several covariates did not meet the assumptions. The STRATA statement in the PHREG procedure in SAS was then used for these covariates, along with age, sex, and race/ethnicity, because of the different underlying risk curves for these groups (**Tables 2–4**, footnotes). Additionally, tests for trend across E-DII quartiles were performed with the use of the median E-DII value per quartile as a continuous measure. For all models, the E-DII also was analyzed as a continuous variable in order to express the HRs per unit increase (i.e., ∼7% of its maximum range) in the E-DII.

All analyses were performed separately by sex and then by sex and race/ethnicity. Additionally, for women, stratifications by hormone use (i.e., not using, previously used, or currently using) were investigated. CRC incidence by anatomical location (colon, rectum, or both) and disease stage at diagnosis category (local, regional, or distant) were analyzed as additional outcomes. Lastly, in a sensitivity analysis to investigate the effect of preclinical disease on our findings, cases diagnosed within 3 y of enrollment were removed (n = 770), and the main models were rerun.

Results

A total of 190,963 participants were included in the analyses. The distribution of participant characteristics across increasing quartiles of the E-DII is provided in Table 1. A lower percentage of women (18%) and a higher percentage of men (34%) were in E-DII quartile 4 (most proinflammatory) compared with the other quartiles. White and African-American participants were equally distributed across the quartiles; however, native Hawaiians had the largest percentage in quartile 4 (35%). Quartile 4 included lower percentages of participants who were graduate-school educated (19%), nonsmokers (19%), supplement users (19%), and women who reported currently or previously using hormones, particularly estrogen (16% and 15%, respectively). Participants in quartile 4 also were younger (57.4 ± 8.8 y) and had a higher BMI (27.0 ± 5.3) than did participants in quartile 1 (62.0 ± 8.5 y and 26.0 ± 4.9, respectively). Only 18% of participants who reported a past diagnosis of diabetes were in quartile 4 compared with 31% in quartile 1.

In our analysis of CRC incidence (Table 2), a more proinflammatory diet (quartile 4 compared with quartile 1) was associated with an increased risk of CRC (HR: 1.21; 95% CI: 1.11, 1.32; P-trend <0.01) for all participants. The P value for the interaction between sex and the E-DII was 0.17, and analyses that used sex-specific quartiles showed no differences from the results presented here. The association for quartile 4 compared with quartile 1 was statistically significant in men (HR: 1.28; 95% CI: 1.13, 1.45; P-trend <0.01) and in women (HR: 1.16; 95% CI: 1.02, 1.33; P-trend = 0.13); however, the association across quartiles was not significant for women, as indicated by the nonsignificant P-trend. When examining the E-DII as a continuous measure, a 1-unit increase in the E-DII score was associated with a 4% (95% CI for HR: 1.02, 1.06), 5% (95% CI for HR: 1.03, 1.07), and 2% (95% CI for HR: 1.00, 1.05) increase in CRC risk in all participants, men, and women, respectively. After removal of cases diagnosed <3 y after baseline, results were unchanged for men. The association for women also was similar, but no longer statistically significant (HR: 1.14; 95% CI: 0.99, 1.32).

When analyses were stratified by race/ethnicity for men (E-DII by race/ethnicity interaction, P = 0.01) and for women (P = 0.20), a more proinflammatory diet was associated with an increased risk of CRC across groups (Table 3), although the association for women was not statistically significant for most of the racial/ethnic groups. The HRs for quartile 4 compared with quartile 1 of the E-DII ranged from 0.86 to 1.72 in men and from 0.98 to 2.33 in women. The largest increase in risk was seen in native Hawaiian women (quartile 4 compared with quartile 1, HR: 2.33; 95% CI: 1.38, 3.93; P-trend <0.01) and Latino men (HR: 1.72; 95% CI: 1.26, 2.34; P-trend <0.01). Statistically significant increases in risk also were seen for white men (HR: 1.39; 95% CI: 1.04, 1.84; P-trend = 0.08) and Japanese-American men (HR: 1.25; 95% CI: 1.02, 1.53; P-trend = 0.01). A statistically significant increase in CRC risk per 1-unit increase in the E-DII was observed for white, Japanese-American, and Latino men, as well as for native Hawaiian women (Table 3). After removal of cases diagnosed <3 y after baseline, there were no differences, except that the association for Japanese-American men was no longer statistically significant (HR: 1.18; 95% CI: 0.94, 1.47).

Analyses conducted separately for colon and rectal cancers showed positive associations between a proinflammatory diet and disease risk regardless of location and stage at diagnosis (Table 4). The association was similar for colon cancer (HR: 1.20; 95% CI: 1.09, 1.33; P-trend < 0.01) and rectal cancer (HR: 1.22; 95% CI: 0.1.02, 1.47; P-trend = 0.01). Positive associations were found between quartile 4 and quartile 1 for advanced CRC (distant spread) (HR: 1.40; 95% CI: 1.11, 1.77; P-trend = 0.01), regional CRC (HR: 1.24; 95% CI: 1.08, 1.43; P-trend < 0.01) and, to a lesser extent, localized CRC (HR: 1.14; 95% CI: 1.00, 1.31; P-trend = 0.07). The association across quartiles was not significant for localized CRC, as indicated by the nonsignificant P-trend. The associations that used the continuous form of the E-DII were statistically significant for all locations and stages examined. A 1-unit increase in the E-DII was

TABLE 1 Baseline population characteristics by energy-adjusted Dietary Inflammatory Index quartile, Multiethnic Cohort, 1993–2010[1]

Characteristic	Quartile 1 (−6.64 to −3.66)[2] (*n* = 47,734)	Quartile 2 (−3.65 to −2.32) (*n* = 47,736)	Quartile 3 (−2.31 to −0.53) (*n* = 47,732)	Quartile 4 (−0.52 to 4.95)[2] (*n* = 47,761)
Categorical characteristics				
Sex				
M	14,955 (17)	18,595 (22)	23,570 (27)	28,790 (34)
F	32,779 (31)	29,141 (28)	24,162 (23)	18,971 (18)
Race/ethnicity				
White	12,068 (26)	12,568 (27)	11,211 (24)	11,147 (23)
African American	8139 (25)	8228 (25)	8134 (25)	8272 (25)
Japanese American	14,796 (27)	12,123 (22)	12,692 (24)	14,348 (27)
Latino	9844 (23)	12,033 (28)	12,453 (28)	9161 (21)
Native Hawaiian	2887 (21)	2784 (20)	3242 (24)	4833 (35)
Education				
Less than high school	8180 (24)	9078 (27)	9340 (27)	7471 (22)
High school or vocational	15,417 (24)	15,111 (23)	16,031 (25)	17,957 (28)
Some college	9941 (25)	9914 (24)	9912 (24)	10,761 (27)
College graduate	6640 (26)	6406 (25)	6244 (24)	6496 (25)
Graduate school	6989 (29)	6652 (28)	5650 (24)	4586 (19)
Missing	567 (26)	575 (26)	555 (25)	490 (22)
Marital status				
Married or living with partner	30,821 (24)	31,361 (25)	32,178 (26)	31,922 (25)
Separated, widowed, or divorced	13,441 (27)	13,021 (26)	12,015 (24)	11,998 (24)
Never married	3055 (24)	2948 (23)	3129 (25)	3493 (28)
Missing	417 (26)	406 (26)	410 (26)	348 (22)
Smoking status				
Current	3936 (13)	5498 (18)	7795 (26)	12,985 (43)
Former	18,177 (24)	18,680 (25)	19,504 (26)	18,617 (25)
Never	24,783 (30)	22,716 (27)	19,702 (24)	15,637 (19)
Missing	838 (29)	842 (29)	731 (25)	522 (18)
Location				
Hawaii	23,302 (26)	21,397 (23)	21,378 (23)	25,070 (28)
Los Angeles	24,432 (25)	26,339 (26)	26,354 (26)	22,691 (23)
Supplement use[3]				
Yes	28,071 (30)	24,958 (27)	21,660 (23)	17,717 (19)
No	19,663 (20)	22,778 (23)	26,072 (26)	30,044 (30)
Family history of colon cancer				
Yes	4155 (28)	3750 (25)	3589 (24)	3511 (23)
No or unknown	43,579 (25)	43,986 (25)	44,143 (25)	44,250 (25)
Past heart attack				
Yes	4419 (28)	4189 (26)	3894 (24)	3474 (22)
No	43,315 (25)	43,547 (25)	43,838 (25)	44,287 (25)
Past diabetes diagnosis				
Yes	6948 (31)	5882 (26)	5467 (24)	4136 (18)
No	40,786 (24)	41,854 (25)	42,265 (25)	43,625 (26)
Past asthma diagnosis				
Yes	13,081 (26)	12,766 (25)	12,333 (25)	12,005 (24)
No	34,653 (25)	34,970 (25)	35,399 (25)	35,756 (25)
Estrogen use				
Current	9785 (34)	8360 (29)	6503 (22)	4406 (15)
Former	6343 (34)	5257 (29)	3907 (21)	2875 (16)
Never	15,605 (29)	14,574 (27)	12,992 (24)	11,170 (21)
Missing	1046 (32)	950 (29)	760 (23)	520 (16)
Progesterone use				
Current	4216 (34)	3704 (29)	2830 (22)	1884 (15)
Former	3175 (33)	2690 (28)	2095 (22)	1551 (16)
Never	13,809 (32)	12,157 (28)	9775 (23)	7384 (17)
Missing	11,579 (29)	10,590 (27)	9462 (24)	8152 (20)
Aspirin use				
Current	9741 (25)	9723 (25)	9614 (25)	9433 (24)
Former	7944 (24)	8583 (26)	8637 (26)	8295 (25)

(Continued)

TABLE 1 *Continued*

Characteristic	Quartile 1 (−6.64 to −3.66)[2] (*n* = 47,734)	Quartile 2 (−3.65 to −2.32) (*n* = 47,736)	Quartile 3 (−2.31 to −0.53) (*n* = 47,732)	Quartile 4 (−0.52 to 4.95)[2] (*n* = 47,761)
Never	27,903 (25)	27,368 (25)	27,557 (25)	28,418 (26)
Missing	2146 (28)	2062 (27)	1924 (25)	1615 (21)
Continuous characteristics				
Age at entry, y	62.0 ± 8.5	60.8 ± 8.7	59.5 ± 8.8	57.4 ± 8.8
BMI, kg/m^2	26.0 ± 4.9	26.5 ± 5.0	26.8 ± 5.1	27.0 ± 5.3

[1] Categorical characteristic values are *n* (%) and continuous characteristic values are mean ± SD, *n* = 190,963. Column percentages may not equal 100% due to rounding. *P* values for categorical variables were based on chi-square tests, and those for continuous measures were based on a trend test with the use of general linear models. $P < 0.01$ for all comparisons across quartiles.
[2] Quartile 1 = most anti-inflammatory; quartile 4 = most proinflammatory.
[3] Defined as long-term supplement use for ≥1 y.

associated with a 5% (95% CI for HR: 1.01, 1.08) and 4% (95% CI for HR: 1.02, 1.06) increase in risk of rectal and colon cancers, respectively. The increase in CRC risk associated with a 1-unit increase in the E-DII ranged from 7% (95% CI for HR: 1.03, 1.11) for distant disease to 3% (95% CI for HR: 1.01, 1.06) for local disease. After removal of cases diagnosed <3 y after follow-up, the association for localized disease remained the same, but was nonsignificant (HR: 1.14; 95% CI: 0.99, 1.33).

Discussion

Unlike other dietary patterns and diet-quality indexes, the DII was designed to assess dietary quality based on a biological mechanism (i.e., inflammation), which makes it particularly important in examining the role of diet and risk of CRC. This analysis is the first to examine associations between the E-DII and CRC risk across racial/ethnic groups. In this examination of data from the MEC, a more proinflammatory diet was associated with an increased risk of CRC in men and, to a lesser degree, in women. The analysis of the E-DII stratified by sex and race/ethnicity was statistically significant for white, Japanese-American, and Latino men, as well as native Hawaiian women. The strongest associations were seen in native Hawaiian women and Latino men, in whom a more proinflammatory diet was associated with an increased risk of CRC. Increased risks of both colon and rectal cancers also were observed with a more proinflammatory diet, as was a greater risk of more advanced cancers.

The DII and its association with CRC have been examined in several cohort and case-control studies (25–29). To our knowledge, this is one of the first DII-CRC studies to use the method of adjusting the DII for energy intake; so although E-DII scores in this study had a range similar to previous studies, absolute scores

TABLE 2 HRs (95% CIs) for colorectal cancer incidence by quartile of E-DII score for all participants and by sex, Multiethnic Cohort, 1993–2010[1]

E-DII	Person-years (cases)	Minimally adjusted HR (95%CI)[2]	Fully adjusted HR (95%CI)[3]
All participants			
Quartile 1 (−6.64 to −3.66)	705,288 (1090)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	702,448 (1055)	1.03 (0.94, 1.18)	1.02 (0.93, 1.11)
Quartile 3 (−2.31 to −0.53)	700,933 (1028)	1.03 (0.95, 1.13)	0.99 (0.91, 1.08)
Quartile 4 (−0.52 to 4.95)	697,966 (1215)	1.31 (1.20, 1.43)	1.21 (1.11, 1.32)
Continuous	—	—	1.04 (1.02, 1.06)
P-trend	—	—	<0.01
Men			
Quartile 1 (−6.64 to −3.66)	211,424 (381)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	264,408 (476)	1.08 (0.94, 1.23)	1.06 (0.92, 1.21)
Quartile 3 (−2.31 to −0.53)	335,686 (613)	1.15 (1.01, 1.31)	1.09 (0.95, 1.24)
Quartile 4 (−0.52 to 4.95)	412,418 (827)	1.39 (1.23, 1.58)	1.28 (1.13, 1.45)
Continuous	—	—	1.05 (1.03, 1.07)
P-trend	—	—	<0.01
Women			
Quartile 1 (−6.64 to −3.66)	493,864 (709)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	438,040 (579)	1.00 (0.90, 1.12)	1.00 (0.90, 1.12)
Quartile 3 (−2.31 to −0.53)	365,247 (415)	0.94 (0.83, 1.06)	0.91 (0.81, 1.03)
Quartile 4 (−0.52 to 4.95)	285,548 (388)	1.26 (1.11, 1.43)	1.16 (1.02, 1.33)
Continuous	—	—	1.02 (1.00, 1.05)
P-trend	—	—	0.13

[1] *n* = 190,963. E-DII, energy-adjusted Dietary Inflammatory Index; Ref, reference.
[2] Age, sex, and race included in STRATA statement.
[3] Self-reported previous diagnosis of diabetes, asthma, and heart attack; use of supplements; smoking status; family history of colon cancer; education; hormone (i.e., estrogen or progesterone) use; aspirin use; and BMI with age, sex, and race/ethnicity in the STRATA statement. Sex-stratified models did not include sex in the STRATA statement.

TABLE 3 HRs (95% CIs) for colorectal cancer incidence by E-DII quartile for all participants and stratified by sex and race/ethnicity, Multiethnic Cohort, 1993–2010[1]

	Men			Women		
E-DII	Person-years (cases)[2]	Minimally adjusted HR (95%CI)[3]	Fully adjusted HR (95%CI)[4]	Person-years (cases)[2]	Minimally adjusted HR (95%CI)[3]	Fully adjusted HR (95%CI)[4]
White						
Quartile 1 (−6.64 to −3.66)	61,182 (77)	1.00 (Ref)	1.00 (Ref)	120,341 (139)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	75,467 (119)	1.32 (0.99, 1.75)	1.29 (0.96, 1.71)	112,518 (114)	0.95 (0.74, 1.21)	0.93 (0.72, 1.19)
Quartile 3 (−2.31 to −0.53)	81,717 (100)	1.08 (0.80, 1.45)	0.99 (0.74, 1.34)	84,222 (87)	1.04 (0.79, 1.36)	0.93 (0.71, 1.23)
Quartile 4 (−0.52 to 4.95)	96,141 (155)	1.62 (1.23, 2.13)	1.39 (1.04, 1.84)	65,835 (71)	1.22 (0.92, 1.63)	1.06 (0.78, 1.43)
Continuous	—	—	1.05 (1.00, 1.10)	—	—	1.02 (0.96, 1.07)
P-trend	—	—	0.08	—	—	0.78
African American						
Quartile 1 (−6.64 to −3.66)	26,000 (78)	1.00 (Ref)	1.00 (Ref)	89,579 (188)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	34,197 (71)	0.73 (0.53, 1.01)	0.71 (0.52, 0.99)	80,428 (142)	0.90 (0.72, 1.12)	0.93 (0.75, 1.17)
Quartile 3 (−2.31 to −0.53)	43,109 (82)	0.71 (0.52, 0.97)	0.67 (0.49, 0.92)	71,129 (97)	0.77 (0.60, 0.98)	0.82 (0.63, 1.05)
Quartile 4 (−0.52 to 4.95)	54,607 (122)	0.91 (0.68, 1.12)	0.86 (0.63, 1.16)	60,784 (115)	1.21 (0.95, 1.53)	1.24 (0.97, 1.60)
Continuous	—	—	1.00 (0.95, 1.06)	—	—	1.03 (0.98, 1.08)
P-trend	—	—	0.70	—	—	0.20
Japanese American						
Quartile 1 (−6.64 to −3.66)	65,180 (151)	1.00 (Ref)	1.00 (Ref)	154,584 (267)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	66,789 (156)	1.06 (0.85, 1.33)	1.03 (0.82, 1.29)	113,174 (184)	1.01 (0.84, 1.22)	0.98 (0.81, 1.82)
Quartile 3 (−2.31 to −0.53)	93,320 (217)	1.15 (0.94, 1.42)	1.07 (0.87, 1.32)	95,799 (116)	0.85 (0.68, 1.05)	0.81 (0.65, 1.01)
Quartile 4 (−0.52 to 4.95)	139,893 (340)	1.43 (1.17, 1.74)	1.25 (1.02, 1.53)	75,113 (102)	1.12 (0.89, 1.42)	0.94 (0.74, 1.21)
Continuous	—	—	1.04 (1.01, 1.08)	—	—	0.98 (0.94, 1.02)
P-trend	—	—	0.01	—	—	0.28
Latino						
Quartile 1 (−6.64 to −3.66)	47,793 (61)	1.00 (Ref)	1.00 (Ref)	99,370 (89)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	74,656 (106)	1.15 (0.84, 1.58)	1.17 (0.85, 1.60)	105,499 (106)	1.16 (0.87, 1.53)	1.16 (0.87, 1.54)
Quartile 3 (−2.31 to −0.53)	97,796 (167)	1.47 (1.10, 1.97)	1.49 (1.10, 2.00)	87,751 (87)	1.20 (0.89, 1.61)	1.14 (0.84, 1.54)
Quartile 4 (−0.52 to 4.95)	82,994 (148)	1.69 (1.25, 2.28)	1.72 (1.26, 2.34)	53,147 (54)	1.32 (0.94, 1.85)	1.21 (0.85, 1.71)
Continuous	—	—	1.13 (1.07, 1.18)	—	—	1.05 (0.98, 1.11)
P-trend	—	—	<0.01	—	—	0.32
Native Hawaiian						
Quartile 1 (−6.64 to −3.66)	11,268 (14)	1.00 (Ref)	1.00 (Ref)	29,989 (26)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	13,300 (24)	1.51 (0.78, 2.93)	1.43 (0.74, 2.78)	26,421 (33)	1.54 (0.92, 2.58)	1.68 (0.99, 2.83)
Quartile 3 (−2.31 to −0.53)	19,743 (47)	2.11 (1.16, 2.93)	1.95 (1.07, 3.56)	26,345 (28)	1.41 (0.82, 2.42)	1.43 (0.82, 2.48)
Quartile 4 (−0.52 to 4.95)	38,784 (62)	1.58 (0.88, 2.85)	1.29 (0.71, 2.35)	30,669 (46)	2.32 (1.42, 3.81)	2.33 (1.38, 3.93)
Continuous	—	—	1.00 (0.93, 1.08)	—	—	1.14 (1.05, 1.24)
P-trend	—	—	0.90	—	—	<0.01

[1] *n* = 190,963. E-DII, energy-adjusted Dietary Inflammatory Index; Ref, reference.
[2] Person-year totals may not equal sex stratified totals because of rounding.
[3] Age was included in the STRATA statement.
[4] Self-reported previous diagnosis of diabetes, asthma, and heart attack; use of supplements; smoking status; family history of colon cancer; education; hormone (i.e., estrogen or progesterone) use; aspirin use; and BMI with age in the STRATA statement.

are not directly comparable. Both the Women's Health Initiative and the Iowa Women's Health Study found that women who consumed the most proinflammatory diets had an ∼20% increased risk of CRC compared with women who consumed the most anti-inflammatory diets (25, 26). In the Iowa Women's Health Study, when the DII was based on food without the inclusion of supplements, the association was weaker and not statistically significant for the highest quintile compared with the lowest quintile (25). In this analysis within the MEC, the calculation of the E-DII also included foods only, and a 16% increase in risk of CRC was seen in women for the highest compared with the lowest quartile; however, the association was no longer statistically significant after cases diagnosed within the first 3 y of follow-up were excluded.

Examinations of the DII in the NIH–American Association of Retired Persons (NIH-AARP) Diet and Health Study, as well as a case-control study in Italy, included both men and women. In the NIH-AARP study, a statistically significant increased risk of CRC with consumption of a more proinflammatory diet was observed in men, but not in women (28). In the Italian case-control study, the increased risk of CRC with a more proinflammatory diet was statistically significant for men and women, with the association being stronger for men (29). The reasons some analyses of the DII and CRC risk show weaker or nonsignificant results for women are not clear. Given evidence that hormone use may play a strong role in CRC risk in women (41), we explored whether associations between the E-DII and CRC risk differed for women who were not using, previously used, or were currently using estrogen and progesterone therapy. No differences were seen between groups defined by hormone use. Analyses of other diet-quality indexes and CRC also found inconsistent results in women compared with those in

TABLE 4 HRs (95% CIs) for colorectal cancer incidence by E-DII quartile for all participants and stratified by tumor location or stage, Multiethnic Cohort, 1993–2010[1]

E-DII	Person-years (cases)[2]	Minimally adjusted HR (95%CI)[3]	Fully adjusted HR (95%CI)[4]
Colon			
Quartile 1 (−6.64 to −3.66)	703,565 (855)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	700,803 (846)	1.06 (0.96, 1.16)	1.05 (0.96, 1.16)
Quartile 3 (−2.31 to −0.53)	699,157 (790)	1.04 (0.94, 1.15)	1.00 (0.91, 1.11)
Quartile 4 (−0.52 to 4.95)	695,379 (881)	1.27 (1.15, 1.41)	1.20 (1.09, 1.33)
Continuous	—	—	1.04 (1.02, 1.06)
P-trend	—	—	<0.01
Rectum or both			
Quartile 1 (−6.64 to −3.66)	698,137 (235)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	695,685 (209)	0.91 (0.76, 1.10)	0.90 (0.74, 1.08)
Quartile 3 (−2.31 to −0.53)	694,310 (238)	1.02 (0.85, 1.22)	0.95 (0.79, 1.14)
Quartile 4 (−0.52 to 4.95)	690,734 (334)	1.43 (1.20, 1.70)	1.22 (1.02, 1.47)
Continuous	—	—	1.05 (1.01, 1.08)
P-trend	—	—	0.01
Local			
Quartile 1 (−6.64 to −3.66)	700,359 (485)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	697,901 (474)	1.03 (0.91, 1.18)	1.02 (0.90, 1.17)
Quartile 3 (−2.31 to −0.53)	696,331 (459)	1.03 (0.90, 1.17)	0.99 (0.87, 1.14)
Quartile 4 (−0.52 to 4.95)	692,386 (519)	1.23 (1.08, 1.40)	1.14 (1.00, 1.31)
Continuous	—	—	1.03 (1.01, 1.06)
P-trend	—	—	0.07
Regional			
Quartile 1 (−6.64 to −3.66)	699,778 (422)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	697,122 (395)	1.00 (0.87, 1.15)	0.99 (0.86, 1.14)
Quartile 3 (−2.31 to −0.53)	695,627 (388)	1.02 (0.89, 1.18)	0.97 (0.85, 1.12)
Quartile 4 (−0.52 to 4.95)	691,731 (466)	1.34 (1.17, 1.54)	1.24 (1.08, 1.43)
Continuous	—	—	1.04 (1.01, 1.06)
P-trend	—	—	<0.01
Distant			
Quartile 1 (−6.64 to −3.66)	697,673 (149)	1.00 (Ref)	1.00 (Ref)
Quartile 2 (−3.65 to −2.32)	695,386 (171)	1.19 (0.96, 1.49)	1.19 (0.95, 1.49)
Quartile 3 (−2.31 to −0.53)	693,841 (159)	1.14 (0.91, 1.43)	1.09 (0.87, 1.38)
Quartile 4 (−0.52 to 4.95)	689,836 (200)	1.53 (1.22, 1.91)	1.40 (1.11, 1.77)
Continuous	—	—	1.07 (1.03, 1.11)
P-trend	—	—	0.01

[1] n = 190,963. E-DII, energy-adjusted Dietary Inflammatory Index; Ref, reference.
[2] A total of 101 cases were missing stage data and were excluded from this analysis.
[3] Age, sex, and race included in STRATA statement.
[4] Self-reported previous diagnosis of diabetes, asthma, and heart attack; use of supplements; smoking status; family history of colon cancer; education; hormone (i.e., estrogen or progesterone) use; aspirin use; and BMI with age, sex, and race/ethnicity in the STRATA statement.

men (43, 44). Both of the previous studies noted dairy as an index component that contributed toward protective effects for women and CRC risk (43, 44). Dietary calcium and vitamin D have been identified as potentially important in reducing CRC risk (45); however, although the DII accounts for vitamin D in its calculation, because of its methods of construction, it does not include calcium (21, 22).

When E-DII quartiles were examined for the various sex–racial/ethnic groups present in the MEC, the increased risk of CRC with a proinflammatory diet appeared greatest for native Hawaiian women and Latino men. Previous examinations of hypothetically derived dietary intake patterns in participants in the MEC found that native Hawaiian and Latino participants had higher odds of being in the "fat and meat" dietary pattern than did white participants (30). This pattern was characterized by a higher intake of discretionary fat and meat, including organ and processed meats, as well as a higher intake of white potatoes, nonwhole grains, eggs, and cheese (30). An examination of the correlation between the E-DII and red and processed meat found the association to be relatively weak (r = 0.14), but significant (P < 0.0001). An examination of the DII food components showed that Latino men had a higher mean intake of protein per 1000 kcal than did the other racial/ethnic groups for men (**Supplemental Table 1**). Native Hawaiian women did not show a higher intake of meat and fat per 1000 kcal than did other women when the DII food components were examined; however, their mean intake per 1000 kcal of a variety of other food components (e.g., fiber, magnesium, vitamin A, folic acid, and β-carotene) was lower than that of the other racial/ethnic groups for women (Supplemental Table 1).

In this study, a statistically significant increase in risk of both colon and rectal cancers was observed in quartile 4 compared with quartile 1 of the E-DII. Although findings related to colon cancer have been consistent, other studies have been mixed with

regard to an increased risk of rectal cancer with a more proinflammatory diet (25–29). Although cancers classified as both colon and rectal were included in the rectal cancer category for this study, they totaled only 35 cases, and their inclusion is in line with other analyses that have examined DII scores in relation to rectal cancer (26, 28). To our knowledge, few studies have examined the DII and stage of disease. A statistically significant increase in risk of cancers categorized as regional and distant was seen in our analyses. Participants with E-DII scores in quartile 4 had a 25% increased risk of regional disease and a 43% increased risk of distant disease compared with those in quartile 1. Although the magnitude of risk was higher in the NIH-AARP analysis than in this study, the same trend was seen, suggesting a connection between more advanced disease and a more proinflammatory diet (28).

Limitations of this study include the small number of CRC cases in certain subgroups (e.g., native Hawaiians). In addition, analyses were based on a single assessment of diet at baseline. However, changes in diet over time for adults may be minimal and have little effect on CRC risk (46–48). The MEC dietary data included only 28 of the 45 food components used to calculate the DII. The use of fewer variables can lead to skewing toward the right for DII values. However, E-DII scores are generally low (more anti-inflammatory) in the MEC. Furthermore, the DII has been calculated with the use of as few as 19 food components. Validation studies have shown that the statistical relation is unchanged when fewer food components are included compared with a larger or full set of DII food components, and the DII's predictive abilities with regard to inflammatory markers are not reduced (22–24). Differences in dietary intake reporting (49, 50), social desirability (51), or the etiology of CRC may exert sex-differential effects on the associations seen between the DII and CRC risk. Among commonly used socioeconomic status variables, only education was available in the MEC, which limited our ability to adjust analyses for such factors. In addition, factors such as screening behaviors may affect overall and early detection of CRC. CRC screening participation by sex and race/ethnicity has previously been examined in the MEC (52). Although women had lower E-DII scores than did men in this study, men were more likely to be screened for CRC than were women, and all racial/ethnic groups, especially native Hawaiians and Mexican-born Latinos, were less likely to be screened than were white subjects (52). These findings differ from the patterns seen in associations between the E-DII and CRC incidence, suggesting that participants in the MEC with more-proinflammatory diets are not necessarily also less likely to adopt other preventive behaviors. These study limitations and the multifactorial nature of cancer limits our ability to make statements of causality.

Despite its limitations, the study has several strengths. The MEC is a large population-based cohort with a well-established history of research demonstrating associations between diet and cancer across racial/ethnic groups. To our knowledge, this examination is the first to look at potential differences across racial/ethnic groups in associations between the E-DII and CRC. The study also adds to the literature on CRC risk in men, by anatomic location and by severity of disease. More research is needed to understand the inconsistent results across studies of diet and CRC risk for women and whether our findings across racial/ethnic groups can be replicated in other multiethnic populations.

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