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The dietary inflammatory index is associated with colorectal cancer in the National Institutes of Health–American Association of Retired Persons Diet and Health Study

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Abstract

Diet is a strong moderator of systemic inflammation, an established risk factor for colorectal cancer (CRC). The dietary inflammatory index (DII) measures the inflammatory potential of individuals' diets. The association between the DII and incident CRC was examined, using the National Institutes of Health–American Associations of Retired Persons Diet and Health Study individuals (*n* 489 422) aged 50–74 years at recruitment, starting between 1995–6, and followed for a mean of 9·1 (SD 2·9) years. Baseline data from a FFQ were used to calculate the DII; higher scores are more pro-inflammatory, and lower scores are more anti-inflammatory. First, primary CRC diagnoses were identified through linkage to state cancer registries. Anatomic location and disease severity also were examined. Cox proportional hazards models estimated CRC hazard ratios (HR) and 95 % CI using quartile 1 as the referent. DII quartile 4 compared to quartile 1 was associated with CRC risk among all subjects (HR 1·40, 95 % CI 1·28, 1·53; *P* for trend < 0·01). Statistically significant associations also were observed for each anatomic site examined, for moderate and poorly differentiated tumours, and at each cancer stage among all subjects. Effects were similar when stratified by sex; however, results were statistically significant only in males. The only result reaching statistical significance in females was risk of moderately differentiated CRC tumours (DII quartile 4 *v.* quartile 1 HR 1·26, 95 % CI 1·03, 1·56). Overall, the DII was associated with CRC risk among all subjects. The DII may serve as a novel way to evaluate dietary risk for chronic disorders associated with inflammation, such as CRC.

Key words: **Dietary inflammatory index: Inflammation: Colorectal cancer: American Association of Retired Persons**

Inflammation is a normal part of the biological immune response, which is necessary for proper wound healing and combating infections[1]. However, repeated insults and injuries (e.g. tobacco use, chronic infection, obesity and sleep disruption) can result in chronic systemic inflammation[1–5]. Chronic inflammation is an underlying pathophysiological process that has been associated with numerous chronic disorders including CVD, cancer, diabetes, stroke and the metabolic syndrome, as well as mortality[1,6,7]. Of all cancers, colorectal cancer (CRC) is the best described in terms of its association with inflammation. This is exemplified by epidemiologic evidence indicating increased rates of CRC among those with chronic inflammatory bowel disease[8], and reduced risk of CRC with regular non-steroidal anti-inflammatory drug use[9]. Currently, CRC is the third most commonly diagnosed cancer among both men and women, and the second most common cause of cancer death in the USA[10]. Worldwide, CRC is the third and second most commonly diagnosed, and the fourth and third most deadly cancers among men and women, respectively[11].

Diet is a strong moderator of chronic inflammation. Several dietary patterns have consistently been associated with systemic-inflammation[12]. For example, Mediterranean diets (i.e. high in fruit and vegetables, fish and olive oil) have been associated with lower levels of systemic inflammation[12,13], whereas Western-style diets (i.e. high in fats, protein, simple carbohydrates and sweets) have typically been associated with increased systemic inflammation[12,13]. Many previous studies have found associations between dietary patterns and CRC risk. For example, several recent reviews or meta-analyses have indicated generally that 'unhealthier' diets (e.g. Western, meat-oriented) have been associated with increased CRC risk, whereas 'healthier' diets

Abbreviations: CRC, colorectal cancer; DII, dietary inflammatory index; HR, hazard ratio; NIH–AARP, National Institutes of Health–American Association of Retired Persons; USDA, United States Department of Agriculture.

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(e.g. Mediterranean, prudent vegetarian) have been associated with decreased CRC risk[14–19].

Typically, dietary patterns or diet quality indices are derived by using two methodological techniques: *a priori* definitions based on dietary guidelines (e.g. Healthy Eating Index based on the Dietary Guidelines for Americans), or *a posteriori* analytic approaches (e.g. principal components analysis)[20,21]. A novel tool known as the dietary inflammatory index (DII) has been developed to characterise diet on a continuum from maximally anti- to pro-inflammatory[22]. Advantages of the DII over other dietary indices is that it is grounded in peer-reviewed literature focusing specifically on inflammation, and it is standardised to dietary intake from numerous populations around the world. In addition, the DII can be estimated from a variety of diet assessment instruments (e.g. 24 h recalls, 7 d dietary recalls and FFQ). The DII has been found to be associated with inflammatory cytokines including C-reactive protein and IL-6[23–25]; the glucose intolerance component of metabolic syndrome, increased odds of asthma and reduced FEV_1 (forced expiratory volume in 1s), shift-work, and CRC among women from the Iowa Women's Health Study, Women's Health Initiative, a case–control study from Spain, and prostate and pancreatic cancer studies in Italy[24–30].

With respect to CRC, no study has examined the DII in a large follow-up cohort of both men and women. The National Institutes of Health–American Association of Retired Persons (NIH–AARP) Diet and Health Study provides an excellent opportunity to examine the relationship between the DII and CRC incidence in a large population (approximately 500 000) of ageing (50–74 years of age at baseline) US adults followed-up for approximately 10 years. Specifically, the present study tested the hypothesis that those with more pro-inflammatory DII scores would have greater risk of developing CRC, compared to those with lower scores. Additionally, the study explored the relationship between the DII and CRC severity (i.e. tumour stage, grade and lymph node involvement) and location, as well as effect modification by sex.

Materials and methods

Study population

This analysis utilised the data from the NIH–AARP Diet and Health Study, which was described previously[31]. Briefly, about 3·5 million AARP members living in California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan) aged 50–74 years were mailed a self-administered questionnaire. The questionnaires were completed between 1995 and 1997, and they included information on demographic characteristics, medical history and diet. Exposure data only from this initial baseline questionnaire were utilised for the present analysis. Exclusions were applied to the baseline cohort and included those who used a proxy for questionnaire completion (*n* 15 760); those with self-reported prostate (*n* 10 640), breast (*n* 10 875), colon (*n* 4584), or other (*n* 23 219) cancer; those with self-reported end-stage renal disease (*n* 997); those with prevalent CRC (*n* 202) or any other cancer (*n* 1697) not self-reported; death certificate-only confirmation of CRC (*n* 272) or any other cancer (*n* 2187); and those with an FFQ-derived daily energy intake <500 kcal/d (<2090 kJ/d) (*n* 3563) or >6000 kcal/d (>25 100 kJ/d) (*n* 2718). The present study was approved by the National Cancer Institute Special Studies Institutional Review Board and the University of South Carolina Institutional Review Board.

Dietary inflammatory index

The baseline questionnaire (administered between 1995 and 1996) included an FFQ, which obtained self-reported frequency and portion size information on 124 food items[31]. Data from the FFQ were linked to the Continuing Survey of Food Intakes by Individuals of the United States Department of Agriculture (USDA) 1994–6, in order to estimate nutrients, foods and food group intakes. Various micro- and macronutrients as well as several individual food items (collectively termed 'food parameters') were used to calculate the DII. These food parameters included energy; carbohydrates; protein; total fat; unsaturated, monounsaturated and polyunsaturated fat; *trans*-fat; alcohol; fibre; cholesterol; vitamins B_1, B_2, B_6, B_{12}, A, C, D and E; Fe; Mg; Zn; Se; folate; β-carotene; anthocyanidins; flavan-3-ols; flavones; flavonols; flavanones; caffeine; green peppers; and tea. To calculate the content of flavonoid classes, FFQ-derived daily gram intakes of fruits and vegetables were linked to the Database for Flavonoid Content from Selected Foods of the USDA (Release 3.1, December 2013) by matching foods with the USDA's five-digit nutrient database numbers. Once linked, the content levels for each flavonoid class were applied to each fruit and vegetable and were summed to provide a total value for each flavonoid class.

The development and validation of the DII have been described previously[22,23]. In short, the food parameters were assigned scores based on research, summarising findings from 1943 articles published to 2010, describing the relationship between the forty-five possible food parameters and inflammation. DII calculation is linked to a regionally representative world database constructed by the authors that provided a mean and standard deviation for each food parameter. This world database included food consumption from eleven populations around the world (i.e. USA, UK, Bahrain, Mexico, Australia, South Korea, Taiwan, India, New Zealand, Japan and Denmark). More detail on the world database can be found elsewhere[23]. The 'standard mean' was subtracted from the actual food parameter value and divided by its standard deviation. This *z*-score was then converted to a percentile (in order to minimise the effect of outliers or right-skewing), and centred by doubling the value and subtracting 1. The product of each food parameter *z*-score and adjusted article score was calculated and summed across all food parameters to create the overall DII score, which was then converted to equally distributed quartiles (quartile ranges: quartile 1 = from −7·33 to −0·59; quartile 2 = −0·58 to 1·36; quartile 3 = 1·37 to 3·24; quartile 4 = 3·25 to 6·97). The greater the DII score, the more pro-inflammatory the diet, while lower values are more anti-inflammatory. These values lie within the theoretical limits of −9 to +8[23].

Follow-up and colorectal cancer diagnoses

Follow-up began at the return of the baseline questionnaire (between 1995 and 1996) and continued until diagnosis of

first cancer, movement out of cancer registry catchment areas, death, or 31 December 2006, whichever came first. Incident CRC cases were identified through linkage of the NIH–AARP cohort data with cancer registries of the eight states listed above, plus Arizona and Texas. The case ascertainment protocol was described previously; linkage validity was found to identify about 90% of all cancer cases[32]. The cancer of interest was the first primary CRC. Information on anatomic location of the disease and severity also was obtained. Anatomic location was defined as ascending colon or caecum, transverse colon or flexures (i.e. hepatic and splenic), descending or sigmoid colon, and rectum or rectosigmoid; grade was defined as well differentiated, moderately differentiated, or poorly or un-differentiated; lymph node involvement was defined as 0 or >0; stage was defined as *in situ* or local (combined due to small sample size among *in situ*), regional, or distant.

Statistical analyses

All analyses were performed using SAS version 9.3®. Descriptive analyses included frequencies or means and standard deviations for population characteristics at baseline among all subjects, and stratified by sex. Differences by sex were determined using χ^2 or *t* tests. Possible confounders included age at baseline; BMI = kg/m^2; family history of CRC or any cancer; self-reported gallbladder disease, diabetes, or any circulatory disorder; smoking status; physical activity (frequency of ≥20 min bouts of exercise per week in the past 12 months that caused increases in breathing or heart rate, or working up a sweat); race; education; marital status; census-based annual household income; and perceived health. Model variable selections began with a series of bi-variable Cox proportional hazards regressions (i.e. the DII + covariate). If a covariate had a *P* value of ≤0·20, it was added to the full model. Backward elimination procedures were then used to develop the final models, which included all covariates that, when removed, led to a 10% change in the hazard ratio (HR) of the DII; statistically significant ($P<0·05$) covariates also were included in the final models. Confounders for which adjustments were made in the various models are located in Table 1, which displays whether confounders were categorical or continuous in nature. Final model selections for each analysis can be found in the footnotes of Tables 2 and 3. Smoking status, age and BMI were included in every model. Cox proportional hazards regression was used to estimate CRC HR and 95% CI for DII quartiles 2, 3 and 4, as compared to quartile 1; the comparison of interest was between quartiles 1 and 4. The proportional hazards assumption was tested using methods derived from the cumulative sums of Martingale residuals. Proportional hazards assumptions were fulfilled for the DII; however, several covariates among the models (see footnotes of Tables 2 and 3) did not fulfill these assumptions. The STRATA statement in the PHREG procedure in SAS was used for these covariates. In addition to examining CRC, each of the CRC anatomic locations and disease severity categories were analysed as outcomes. For sensitivity analyses, CRC cases diagnosed within 3 years of enrolment date were excluded.

Results

The present analysis included a total of 489 442 participants at baseline with a mean follow-up of 9·1 (SD 2·9) years per participant, contributing to a total of 4 451 383 accumulated person-years of observation. There were 6944 incident first primary CRC diagnoses (67% were in males). Most (63%) of them were localised or regional tumours (as opposed to distant); and 25% were unknown. A total of 342 870 participants had a complete follow-up; 74 754 were diagnosed with a cancer other than colorectal; 33 795 died; and 31 079 moved out of the cancer registry areas. For a graphical representation of study follow-up and censorship, see online Supplementary Fig. S1. Overall, participants (mean baseline age: 62·0 (SD 5·4) years) included in this analysis were predominantly (92%) European-American, somewhat well-educated (63% with at least some college education), married or living with a partner (69%), and overweight (mean BMI: 27·0 (SD 4·8) kg/m^2) with an average household income of about $54 000. Nearly, 50% of participants reported a family history of a cancer, with 9% specifically reporting a family history of CRC. The mean DII was 1·27 (SD 2·47), which was higher for females than for males (1·58 *v.* 1·06, respectively, $P<0·01$). This was partially due to the fact that males had higher absolute intake amounts of many anti-inflammatory components of the DII (see online Supplementary Table S1). Additionally, each covariate presented in Table 1 differed statistically significantly ($P<0·01$) between males and females. Online Supplementary Table S2 further stratifies these covariates by DII quartiles among males and females.

Individuals in DII quartile 4 were 1·40 (95% CI 1·28, 1·53) times more likely to develop CRC compared to quartile 1 (Table 2). Similar results were observed for tumours located in ascending colon or caecum, transverse colon or flexures, descending colon or sigmoid, and rectum or rectosigmoid. The results among all subjects were primarily driven by results among males. HR were between 27 and 74% greater among males in DII quartile 4 as compared to quartile 1 for all CRC cases and CRC at different anatomical locations; all of them were statistically significant. Statistically insignificant HR for females in DII quartile 4 were 12, 26 and 33% greater as compared to quartile 1 for all cases of CRC, ascending or caecum tumours, and descending or sigmoid tumours, respectively (Table 2). When the DII was analysed continuously among all subjects, a one-unit increase was associated with an increase in all CRC cases (HR 1·06, 95% CI 1·05, 1·08), ascending or caecum (HR 1·05, 95% CI 1·02, 1·07), transverse or flexures (HR 1·06, 95% CI 1·02, 1·10), descending or sigmoid (HR 1·08, 95% CI 1·05, 1·11), and rectum or rectosigmoid tumours (HR 1·08, 95% CI 1·05, 1·10) (data not tabulated).

Table 3 displays HR for disease severity markers. DII quartile 4, as compared to quartile 1, was found, among all participants, to be statistically significantly associated with: moderately and poorly differentiated tumours; tumours with and without lymph node involvement; and local, regional and distant tumours. The same was true among males. Females in DII quartile 4, as compared to quartile 1, were

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Table 1. Baseline population characteristics by sex*

(Mean values and standard deviations; number of participants and percentages)

	All subjects (*n* 489 442)		Males (*n* 292 118)		Females (*n* 197 324)	
Characteristic	*n*	%	*n*	%	*n*	%
Age (years)						
Mean	62·0		62·1		61·8	
SD	5·4		5·4		5·4	
Race						
European-American	446 705	92	270 371	94	176 334	91
Other	36 396	8	18 385	6	18 011	9
Education						
≤ High school	124 577	26	62 416	22	62 161	33
Vocational school	48 179	10	27 127	10	21 052	11
Some college	113 468	24	64 699	23	48 769	26
College graduate	92 258	19	63 129	22	29 129	15
Graduate school	96 831	20	67 081	24	29 750	16
Marital status						
Married or living with partner	336 000	69	248 385	86	87 615	45
Widowed	53 269	11	8989	3	44 280	23
Divorced, separated, never married	96 419	20	32 870	11	63 549	33
Household income (per $10 000)†						
Mean	5·38		5·54		51·5	
SD	2·36		2·42		2·25	
Smoking status						
Never	172 077	37	85 235	30	86 842	46
Former	240 716	51	165 127	59	75 589	40
Current	58 172	12	30 292	11	27 880	15
Physical activity level‡						
Never/rarely	87 432	18	43 461	15	43 971	23
1–3 Times per month	66 211	14	38 096	13	28 115	14
1–2 Times per week	105 295	22	63 907	22	41 388	21
3–4 Times per week	131 174	27	81 864	28	49 310	25
≥ 5 Times per week	94 174	19	62 175	22	31 999	16
Self-reported perceived health						
Excellent	84 305	17	51 004	18	33 301	17
Very good	172 629	36	104 053	36	68 576	35
Good	166 734	35	99 406	34	67 328	35
Fair or poor	58 611	12	33 877	12	24 734	13
Self-reported diabetes						
Yes	43 863	9	29 448	10	14 415	7
No	445 579	91	262 670	90	182 909	93
Self-reported polyps						
Yes	45 099	9	32 203	11	12 896	7
No	444 343	91	259 915	89	184 428	93
Self-reported CVD						
Yes	73 525	15	54 817	19	18 708	9
No	415 917	85	237 301	81	178 616	91
Family history of cancer						
Yes	226 110	49	139 593	50	86 517	46
No	238 032	51	137 134	50	100 898	54
Family history of colorectal cancer						
Yes	42 612	9	24 046	9	18 566	10
No	421 530	91	252 681	91	168 849	90
BMI (kg/m^2)						
Mean	27·0		27·3		26·8	
SD	4·8		4·2		5·6	
Dietary inflammatory index						
Mean	1·27		1·06		1·58	
SD	2·47		2·40		2·54	

* Frequencies not equalling column frequencies are due to missing data. Strata frequencies not equalling 100 % are due to rounding.
† Income is based on United States census-derived median household income in American dollars.
‡ Refers to frequency of at least 20 min bouts of physical activity per week.

more likely to develop moderately differentiated tumours (HR 1·26, 95 % CI 1·03, 1·56). Several other HR among females were elevated, but did not achieve statistical significance (e.g. distant tumours HR 1·60, 95 % CI 0·99, 2·58). Among all subjects, a one-unit increase in the DII was found associated with an increase in: well- (HR 1·05, 95 % CI 1·01, 1·09), moderate- (HR 1·07, 95 % CI 1·05, 1·09) and poorly- (HR 1·07, 95 % CI 1·03, 1·10) differentiated tumours; tumours with lymph

Table 2. Any colorectal cancer (CRC) and location-specific hazard ratios (HR) among quartiles of the dietary inflammatory index (DII) stratified by sex*†
(Hazard ratios and 95 % confidence intervals)

	All subjects				Males				Females			
DII quartile‡	Person-years	Diagnoses	Adjusted HR	95 % CI	Person-years	Diagnoses	Adjusted HR	95 % CI	Person-years	Diagnoses	Adjusted HR	95 % CI
CRC *v.* CRC-free participants												
1	1 002 822	1497	1·0	Reference	648 012	1055	1·0	Reference	354 810	442	1·0	Reference
2	1 018 090	1549	1·13	1·05, 1·22	649 860	1156	1·18	1·08, 1·29	368 230	393	0·90	0·78, 1·04
3	1 012 643	1594	1·27	(1·17, 1·38)	585 457	1065	1·28	(1·16, 1·41)	427 186	529	1·12	(0·93, 1·25)
4	1 002 557	1585	1·40	(1·28, 1·53)	499 344	955	1·44	(1·29, 1·61)	503 212	630		(0·95, 1·31)
Location: ascending/caecum *v.* CRC-free participants												
1	1 037 510	500	1·0	Reference	665 525	333	1·0	Reference	371 986	167	1·0	Reference
2	1 047 094	505	1·07	(0·94, 1·21)	665 193	352	1·11	(0·95, 1·30)	381 900	153	0·96	(0·76, 1·20)
3	1 041 325	519	1·16	(1·01, 1·33)	599 147	308	1·15	(0·94, 1·33)	442 178	211	1·19	(0·94, 1·51)
4	1 036 250	536	1·27	(1·09, 1·49)	513 597	286	1·27	(1·04, 1·54)	522 653	250	1·26	(0·98, 1·63)
Location: transverse/hepatic and splenic flexure *v.* CRC-free participants												
1	1 035 754	177	1·0	Reference	664 329	112	1·0	Reference	371 426	65	1·0	Reference
2	1 045 464	210	1·32	(1·07, 1·63)	664 108	158	1·53	(1·19, 1·98)	381 355	52	0·88	(0·59, 1·29)
3	1 039 668	210	1·46	(1·16, 1·83)	598 287	149	1·70	(1·29, 2·24)	441 381	61	0·96	(0·64, 1·43)
4	1 034 389	205	1·58	(1·23, 2·03)	512 700	122	1·74	(1·27, 2·39)	521 690	83	1·19	(0·78, 1·83)
Location: descending/sigmoid *v.* CRC-free participants												
1	992 781	389	1·0	Reference	641 569	292	1·0	Reference	351 212	97	1·0	Reference
2	1 007 762	390	1·14	(0·99, 1·32)	643 298	299	1·14	(0·96, 1·35)	364 464	91	0·99	(0·73, 1·34)
3	1 002 438	409	1·35	(1·15, 1·58)	579 173	285	1·31	(1·09, 1·57)	423 265	124	1·23	(0·90, 1·67)
4	993 310	426	1·61	(1·35, 1·91)	494 476	276	1·62	(1·31, 1·99)	498 833	150	1·33	(0·95, 1·86)
Location: rectum/rectosigmoid *v.* CRC-free participants												
1	1 006 594	403	1·0	Reference	648 632	288	1·0	Reference	357 962	115	1·0	Reference
2	1 019 916	428	1·20	(1·04, 1·39)	649 361	333	1·30	(1·10, 1·53)	370 554	95	0·78	(0·59, 1·04)
3	1 014 919	433	1·35	(1·16, 1·58)	585 064	303	1·43	(1·19, 1·71)	429 855	130	0·91	(0·68, 1·22)
4	1 005 736	416	1·45	(1·22, 1·73)	499 474	260	1·57	(1·27, 1·93)	506 261	156	0·91	(0·67, 1·25)

* Adjustments: all models adjusted for age, smoking status, BMI, self-reported diabetes and energy intake.
† Additional adjustments included: CRC = physical activity (frequency of ≥20 min bouts in the past 12 months, marital status, education, and age (STRATA statement); ascending/caecum = age (STRATA statement); transverse/hepatic and splenic flexures = race, and age; descending/sigmoid = marital status, education, perceived health, census-based income and age (STRATA statement); rectum/rectosigmoid = self-reported polyps, education, age and census-based income.
‡ DII quartile ranges: quartile 1 = from −7·33 to −0·59; quartile 2 = −0·58 to 1·36; quartile 3 = 1·37 to 3·24; quartile 4 = 3·25 to 6·97.

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Table 3. Tumour grade, node involvement, and stage-specific hazard ratios (HR) among quartiles of the dietary inflammatory index (DII) stratified by sex*

(Hazard ratios and 95 % confidence intervals)

	All subjects				Males				Females			
DII quartile†	Person-years	Diagnoses	Adjusted HR	95 % CI	Person-years	Diagnoses	Adjusted HR	95 % CI	Person-years	Diagnoses	Adjusted HR	95 % CI
Grade: well- differentiated *v.* CRC-free participants												
1	1 006 471	174	1·0	Reference	648 425	120	1·0	Reference	358 046	54	1·0	Reference
2	1 019 975	176	1·09	(0·87, 1·35)	649 135	128	1·14	(0·88, 1·48)	370 840	48	0·85	(0·56, 1·28)
3	1 014 996	185	1·22	(0·97, 1·55)	584 965	130	1·34	(1·01, 1·78)	430 031	55	0·84	(0·55, 1·30)
4	1 005 875	178	1·27	(0·98, 1·66)	499 454	109	1·39	(1·00, 1·92)	506 421	69	0·90	(0·56, 1·43)
Grade: moderately differentiated *v.* CRC-free participants												
1	1 016 766	897	1·0	Reference	655 309	630	1·0	Reference	361 457	267	1·0	Reference
2	1 029 339	944	1·17	(1·06, 1·29)	656 628	710	1·23	(1·10, 1·37)	372 711	234	0·93	(0·77, 1·12)
3	1 022 274	951	1·30	(1·18, 1·45)	590 695	647	1·32	(1·17, 1·50)	431 579	304	1·10	(0·91, 1·34)
4	1 015 748	990	1·52	(1·35, 1·70)	505 507	602	1·54	(1·34, 1·78)	510 240	388	1·26	(1·03, 1·56)
Grade: poorly or undifferentiated *v.* CRC-free participants												
1	997 100	233	1·0	Reference	643 476	153	1·0	Reference	353 624	80	1·0	Reference
2	1 012 453	248	1·16	(0·96, 1·40)	645 130	174	1·25	(0·99, 1·57)	367 323	74	0·95	(0·68, 1·33)
3	1 007 065	264	1·34	(1·10, 1·64)	580 925	173	1·49	(1·17, 1·91)	426 140	91	1·06	(0·75, 1·49)
4	997 383	259	1·45	(1·16, 1·82)	495 276	141	1·56	(1·17, 2·07)	502 108	118	1·21	(0·83, 1·75)
Nodes: 0 *v.* CRC-free participants												
1	1 018 250	521	1·00	Reference	655 707	365	1·00	Reference	362 543	156	1·00	Reference
2	1 031 856	575	1·22	(1·08, 1·38)	657 084	428	1·26	(1·09, 1·46)	374 771	147	1·01	(0·79, 1·28)
3	1 024 593	568	1·33	(1·16, 1·52)	591 077	394	1·37	(1·17, 1·61)	433 516	174	1·10	(0·85, 1·41)
4	1 017 286	565	1·48	(1·27, 1·72)	505 250	335	1·47	(1·22, 1·77)	512 036	230	1·31	(1·00, 1·72)
Nodes: 1 + *v.* CRC-free participants												
1	1 007 548	345	1·00	Reference	649 057	226	1·00	Reference	358 491	119	1·00	Reference
2	1 021 030	341	1·07	(0·92, 1·25)	649 913	246	1·19	(0·99, 1·44)	371 118	95	0·80	(0·60, 1·06)
3	1 016 174	384	1·31	(1·11, 1·54)	585 704	252	1·45	(1·18, 1·77)	430 470	132	0·99	(0·74, 1·32)
4	1 007 138	376	1·41	(1·17, 1·70)	500 085	212	1·55	(1·22, 1·96)	507 053	164	1·08	(0·79, 1·48)
Stage: *in situ* or local *v.* CRC-free participants												
1	987 376	460	1·00	Reference	638 922	338	1·00	Reference	348 455	122	1·00	Reference
2	1 003 693	453	1·09	(0·95, 1·25)	640 792	338	1·09	(0·93, 1·28)	362 901	115	0·98	(0·75, 1·28)
3	997 948	454	1·21	(1·05, 1·41)	577 070	310	1·19	(1·99, 1·42)	420 878	144	1·12	(0·84, 1·48)
4	987 406	412	1·25	(1·06, 1·48)	491 487	255	1·25	(1·02, 1·54)	495 919	157	1·08	(0·79, 1·47)
Stage: regional *v.* CRC-free participants												
1	1 006 666	439	1·00	Reference	648 644	310	1·00	Reference	358 022	129	1·00	Reference
2	1 019 921	437	1·10	(0·96, 1·27)	649 219	317	1·11	(0·94, 1·31)	370 702	120	0·97	(0·75, 1·26)
3	1 014 949	440	1·21	(1·04, 1·41)	585 081	310	1·28	(1·07, 1·52)	429 868	130	0·95	(0·72, 1·28)
4	1 006 027	471	1·43	(1·21, 1·68)	499 588	270	1·39	(1·13, 1·70)	506 439	201	1·30	(0·97, 1·74)
Stage: distant *v.* CRC-free participants												
1	1 026 672	153	1·00	Reference	659 737	106	1·00	Reference	366 935	47	1·00	Reference
2	1 037 903	168	1·21	(0·96, 1·52)	659 893	126	1·24	(0·95, 1·63)	378 010	42	1·01	(0·65, 1·57)
3	1 030 994	182	1·42	(1·11, 1·81)	593 880	111	1·25	(0·93, 1·70)	437 114	71	1·61	(1·05, 2·48)
4	1 024 598	189	1·60	(1·22, 2·10)	508 534	113	1·54	(1·10, 2·15)	516 064	76	1·60	(0·99, 2·58)

CRC, colorectal cancer.

* Adjustments: all models adjusted for smoking status, BMI and energy intake. Grade: well-differentiated = education and age (STRATA statement); grade: moderately differentiated = self-reported diabetes and polyps, physical activity, marital status, perceived health, age and census-based income (STRATA statement); grade: poorly or undifferentiated = self-reported polyps, race, education and age. Nodes: 0 = self-reported diabetes and circulatory disorders, physical activity, race and age (STRATA statement); nodes: 1 = self-reported diabetes and polyps, education and age; stage: *in situ* or local: self-reported diabetes, marital status, race, with age, census-based income, education and physical activity in STRATA statement; stage: regional = self-reported diabetes and polyps, education, age and census-based income; stage: distant = self-reported diabetes and polyps, physical activity and age.

† DII quartile ranges: quartile 1 = from −7·33 to −0·59; quartile 2 = −0·58 to 1·36; quartile 3 = 1·37 to 3·24; quartile 4 = 3·25 to 6·97.

node involvement (HR 1·07, 95% CI 1·05, 1·10) and without lymph node involvement (HR 1·06, 95% CI 1·03, 1·09); and in localised (HR 1·05, 95% CI 1·01, 1·09), regional (HR 1·05, 95% CI 1·01, 1·09) and distant tumours (HR 1·05, 95% CI 1·01, 1·09). The *P* for trend was statistically significant for all outcomes presented in Tables 2 and 3 for all subjects, especially for males. However, for females, only CRC, located in ascending colon or caecum, descending colon or sigmoid, moderately differentiated tumours, tumours with no lymph node involvement, and distant tumours had significant trend *P* values (data not tabulated).

Results did not differ after additional adjustment for hormone use among women (data not shown). After excluding cases (*n* 1984) that were diagnosed within 3-years of enrolment, the HR for ascending or caecum (HR 1·21, 95% CI 0·96, 1·52) or local (HR 1·21, 95% CI 0·95, 1·54) tumours among males and tumours with no node involvement among females (HR 1·26, 95% CI 0·94, 1·70) for DII quartile 4 were attenuated and became non-significant. However, the HR for DII quartile 4, as compared to quartile 1 for distant tumours became significant for females (HR 1·85, 95% CI 1·04, 3·26). An additional *post hoc* sensitivity analysis, using sex-specific DII quartiles, produced a marginally significant HR for DII quartile 4, as compared to quartile 1 for all CRC cases combined (HR 1·18, 95% CI 1·00, 1·38).

Discussion

Higher (i.e. more pro-inflammatory) DII scores for all subjects, especially males, were found to be associated with increased risk of any case of CRC: i.e. CRC at each anatomic site examined; for moderately and poorly differentiated tumours; tumours with and without lymph node involvement; and local, regional, and distant tumours. The direction of effect among females was similar; however, HR were only statistically significant for moderately differentiated tumours and tumours with no lymph node involvement. Previously, individual food groups, micronutrients and macronutrients were hypothesised to be associated with increases or decreases in CRC risks including red and processed meat, fibre, vitamin D, animal fat and Se[33,34]. For example, excessive alcohol consumption was shown to increase CRC by 8–52%, which is generally stronger among males than among females[33]; no alcohol consumption also was shown to be associated with increased inflammation as compared to moderate consumption[35]. However, analysis of individual dietary factors does not allow one to take into account the complicated interactions or high inter-correlations between dietary factors. Additionally, the effect of any single nutrient may be too small to detect or may be confounded by dietary habits and patterns[20,36]. Compared to other dietary indices, the DII was designed on the basis of a specific biologic mechanism (i.e. inflammation), and was standardised to dietary intake from numerous populations around the world[23].

Previous studies of dietary indices and CRC are generally consistent with the findings of the present analysis. Studies using *a posteriori* or *a priori* methods for describing dietary patterns have typically found that 'healthier' diet patterns (e.g. high in fruits and vegetables, fish, poultry and whole grains) are associated with lower CRC risk; whereas 'less healthy' diets (e.g. high in red or processed meat, refined grains and sweets) are associated with increased CRC risk, including some specific to the NIH–AARP Diet and Health Study[14–16,19,37–40]. However, there are other studies that have found no association between various dietary patterns and CRC risk[41–43]. Not surprisingly, these 'healthier' dietary patterns also are typically associated with lower levels of inflammation[12].

CRC risks among men tended to be elevated with higher DII scores, whereas there was less consistent evidence of elevated risk observed among women in the present study. This is somewhat similar to previous studies that have found no association between various dietary patterns and CRC among women[37,39,44,45]. In the present study, use of sex-specific DII quartile cut-points did not change the overall interpretation of results. Social desirability has been shown to influence dietary reports and the bias is expressed much more strongly among women than men[46,47]; social desirability was unmeasured in the NIH–AARP Diet and Health Study. Previously, the DII was shown to be associated with CRC among women in the Iowa Women's Health Study (HR for DII quintiles: Q5 *v.* Q1 1·20, 95% CI 1·01, 1·43)[27] and in the Women's Health Initiative (HR for DII quintiles: Q5 *v.* Q1 1·22, 95% CI 1·05, 1·43)[30]. A similar magnitude of effect was observed in the present study; however, results did not achieve statistical significance. Differences in cohort characteristics and available data on food parameters comprising the DII may, at least partially, explain the differences in results among women in the NIH–AARP Diet and Health Study as compared to other studies.

Several investigations have examined the effect of dietary patterns on CRC risk for different anatomic locations (e.g. distal or proximal colon and rectum)[38,39,41,42,48,49]. Magalhaes *et al.*[15] recently published a meta-analysis and found elevated risks for the proximal (relative risk 1·11, 95% CI 0·93, 1·32) and distal (relative risk 1·32, 95% CI 0·99, 1·77) colon for Western-type diets. However, these risks did not achieve statistical significance. The authors concluded that, overall, there were no differences in CRC risk by anatomic location. This is somewhat consistent with the present findings.

This was one of the first studies to examine the association between a dietary index and severity of CRC. Elevated CRC risk by disease severity seemed to be restricted to males. Except for local tumours, DII quartile 4 conferred between 25 and 60% greater risk as compared to quartile 1 for all CRC cases regardless of disease severity among males. Interestingly, the HR for DII quartile 4 as compared to quartile 1 increased, as tumour stage increased. If confirmed by further studies, these results may indicate that more virulent cancers may be associated with greater dietary inflammatory potential.

Numerous pathways exist through which dietary patterns influence CRC risk. Pro-inflammatory diets can increase insulin resistance by increasing systemic inflammation[13,50] which, in turn, could increase levels of insulin, TAG, and NEFA[51,52]. These factors could then promote excessive proliferation of colonic epithelial cells and potentially expose them to reactive oxygen species[51,52]. Diets high in red and

processed meat can be high in *N*-nitroso compounds, which could damage DNA[33,53]. Diets high in fruits and vegetables (more anti-inflammatory) contain antioxidants and micronutrients with antitumour capabilities, as well as fibre which can decrease transit time for food in the digestive tract[33].

The present study had several weaknesses. A small number of CRC cases by some anatomic locations or by disease severity might have limited the ability to detect statistically significant associations in women. A measure of social desirability was not obtained, and there might have been other unmeasured factors that differed by sex which could have influenced self-report measures, or exposure to CRC risk factors, or both. The longitudinal nature of the NIH–AARP Diet and Health Study has a major strength in that diet is assessed prior to disease diagnosis; however, only baseline diet assessment was used in the present analysis. Therefore, changes in dietary patterns could not be examined. Also, the FFQ has been shown to be subject to both random and systematic errors[46,47]. Despite its weaknesses, the NIH–AARP Diet and Health Study is a large (*n* approximately 500 000) well-established follow-up cohort with a strong record of publication. This was one of the first studies to examine both CRC location and disease severity by levels of a dietary index. Additionally, this is the first report of the association between the DII and CRC among males. The use of the DII has several unique advantages over other dietary measures and was designed specifically in reference to inflammation[23], a strong risk factor for CRC[8].

In conclusion, the present study found that the novel DII predicted CRC incidence among NIH–AARP Diet and Health Study participants. As noted by Fung *et al.*[14], no dietary indices or patterns have been developed specifically for CRC prevention. The DII was designed on the basis of peer-reviewed literature on diet and inflammation, an established risk factor for CRC. Future research should test whether changing the inflammatory potential of diet can reduce chronic inflammation and the risk of CRC. The utility of the DII can be extended to clinical settings to address inflammatory potency of one's diet, and possibly reduce future risk of chronic inflammatory-related diseases.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S000711451500104X

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The contributions of the authors are as follows: M. D. W. performed all analyses and was the lead author; N. S. aided in the data analysis, interpretation of the study results, and drafting of the manuscript; S. E. S. aided in the interpretation of the study results and drafting of the manuscript; T. G. H. aided in the data analysis, interpretation of the study results, and drafting of the manuscript; and J. R. H. aided in the interpretation of the study results and drafting of the manuscript.

J. R. H. owns a controlling interest in Connecting Health Innovations LLC (CHI), 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 counselling and dietary intervention in clinical settings. M. D. W. and N. S. are employees of CHI. However, none of these professional interests and commitments declared had any influence on the present project.

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