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The association between Dietary Inflammatory Index scores and the prevalence of colorectal adenoma

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Abstract

Objective: The Dietary Inflammatory Index (DII)™, which was developed to characterize the inflammatory potential of a person's diet, has been shown to be associated with inflammatory conditions such as cancer. The present study aimed to investigate the association between DII scores and colorectal adenoma (CRA), a pre-cancerous condition.

Design: Responses to baseline dietary questionnaires were used calculate DII scores. In a cross-sectional study design, the association between DII scores and CRA prevalence was determined in men and women separately using logistic regression models.

Setting: Ten cancer screening centres across the USA.

Subjects: Participants were those included in the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Results: Among the 44 278 individuals included in these analyses, men with diets in the most inflammatory quartile of DII scores had higher odds of all types of CRA (advanced, non-advanced and multiple (>1)) compared with those with diets in the least inflammatory quartile of DII scores. In fully adjusted models, compared with those with DII scores in quartile 1 (least inflammatory), males with DII scores in quartile 3 (adjusted odds ratio (aOR) = 1·28; 95 % CI 1·12, 1·47) and quartile 4 (aOR = 1·41; 95 % CI 1·23, 1·62) were more likely to have prevalent distal CRA. Higher DII scores, representing a more inflammatory diet, also were weakly associated with a higher prevalence of CRA in women.

Conclusions: Implementing an anti-inflammatory diet may be an effective means of primary prevention of CRA, especially in men.

Keywords
Colorectal adenoma
Dietary Inflammatory Index
Racial disparities

The biological effects of diet on inflammation are complex. Very simply, oxidative stress, which can occur after the ingestion of an energetically dense (i.e. high in fat or high in simple carbohydrates) meal, results in the production and release of free radicals and reactive oxygen and nitrogen species into the tissues. This in turn can lead to damaged tissues and inflammation[1,2]. Conversely, foods high in antioxidants and flavonoids, such as fruits and vegetables, reduce inflammation by scavenging free radicals, inhibiting pro-oxidant enzymes, binding free radicals and possibly modulating the expression of pro-inflammatory molecules[3,4]. Prolonged and unchecked inflammatory conditions create a micro-environment favourable for tumour growth and progression[5]. Identifying dietary factors that promote a less favourable environment for inflammatory conditions, in light of the association between diet and inflammation, may be one way to minimize the incidence of adenomas and cancer.

The Dietary Inflammatory Index (DII)™ was developed to characterize the inflammatory nature of a person's diet, with scores on a continuum from maximally inflammatory to maximally anti-inflammatory. This index has been shown to be associated with concentrations of several circulating inflammatory proteins, including C-reactive protein[6] and IL-6[7], in prospective and case–control studies. Previously published work has shown that a more inflammatory diet, as reflected by a higher DII score, is associated with a higher prevalence of asthma (an inflammatory condition)[7], pancreatic cancer[8] and

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prostate cancer[9] in hospital-based case–control studies. Most recently, higher scores on this index have been found to be associated with a higher incidence of colorectal cancer in the Women's Health Initiative and the Iowa Women's Health Study[10,11]. Another recent study showed an association between DII scores and polymorphisms in the gene for the anti-inflammatory cytokine IL-4 (rs2243250)[12]. In that study, individuals with a more inflammatory diet and the IL-4 polymorphism had a higher risk of colorectal cancer than those with the polymorphism who consumed a less inflammatory diet. Less favourable DII scores are reflective of diets lower in antioxidants and higher in pro-oxidants. This imbalance could lead to oxidative stress and genotoxic damage, which may then lead to abnormal growths and cancers in the colon[13]. Anti-inflammatory dietary factors exert their effects through the modulation and inhibition of inflammatory proteins and cytokines, such as transforming growth factor-β, cyclooxygenase-2, IFN-γ and NF-κB[14].

While these studies have shown an association between the incidence of colorectal cancer and a more inflammatory diet, it is unknown whether colorectal adenomas (CRA), which are precursors for colorectal cancer, are associated with a more inflammatory diet. The purpose of the current study was to examine whether or not a more inflammatory diet, as indicated by a higher DII score, was associated with the prevalence of CRA in a large cohort of older adults.

Methods

Study population

Data were collected as part of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and have been described previously in detail[15–18]. In short, over 148 000 men and women, aged 55–74 years, were recruited between 1993 and 2000 at one of ten screening centres across the USA (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St Louis, MO; and Washington, DC). Each participant who was randomly assigned to the screening arm was asked to complete a detailed questionnaire at baseline with questions regarding sociodemographic characteristics, diet, physical activity, personal and family cancer history, smoking history and use of selected medications. Those with an abnormal finding on flexible sigmoidoscopy examination were referred for endoscopic follow-up. Results from diagnostic screening and treatment, including surgical procedures, were gathered by trained medical abstractors from each participant's medical record. Institutional review board approval was obtained from the National Cancer Institute and the ten screening centres involved with the study. Informed consent was provided by all study participants.

Data from screening-arm participants who returned the baseline questionnaire, which had questions regarding sociodemographic information, health history, medications and physical activity, were used for the present secondary analyses (n 75 611). Participants were excluded in this order: if flexible sigmoidoscopy examination was not adequate (defined as insertion to at least 50 cm with >90 % of mucosa visible or suspect lesion found) or not done (n 18 148); had a positive flexible sigmoidoscopy examination but had either no follow-up or ambiguous follow-up (n 3717); had a personal history of any cancer (except melanoma) or did not know their personal history of cancer before the dietary questionnaire (n 2081); had ulcerative colitis, Crohn's disease, Gardner's syndrome or familial polyposis (n 652); did not complete the dietary questionnaire (n 4937); had eight or more missing responses on the dietary questionnaire (n 385); had extreme energy intake reported on the dietary questionnaire (top or bottom 1 % of sex-specific energy intake; n 796); or did not specify race (n 9). Participants were further excluded if they were missing data on key variables (BMI, education, physical activity or smoking status; n 23). The final sample size was 44 278.

Adenomas

Any prevalent adenoma, not including hyperplastic polyps, in the distal region (rectum to the splenic flexure) at baseline was the main outcome of interest. Advanced adenomas were those that were villous or tubulovillous in nature, large (≥1·0 cm), or displayed severe or high-grade dysplasia. Physician and non-physician examiners followed standardized procedures to determine visual size estimates at sigmoidoscopy.

Dietary data

Questionnaire

Dietary data were collected using the dietary questionnaire developed by the National Cancer Institute[19]. The sixteen-page questionnaire asked about the usual frequency and portion size of 137 food items and ten dietary supplements over the year prior to enrolment. The dietary questionnaire has been shown to have good reliability and has been validated against both the Block and Willett FFQ[19]. Values for daily nutrients and food groups were determined from the national dietary data and the Pyramid food group servings database from the 1994–1996 Continuing Survey of Food Intakes by Individuals with a method developed by Subar *et al.*[19].

Dietary Inflammatory Index

The DII is a tool used to score the inflammatory nature of an overall diet and was developed using data from individuals consuming diverse diets[20]. Forty-five food/nutrient parameters were identified in the original index as being associated with six cytokines important in determining inflammatory response. Design and development of the DII have been described in detail previously[20,21].

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To calculate the DII score, dietary intake data from each participant in the PLCO cohort were linked to a previously developed global database that was created by calculating the global mean and global standard deviation for each of the forty-five foods/nutrients for eleven countries around the world[21]. A *Z*-score for each dietary factor was created for each PLCO participant by subtracting the global standard mean from the individual's reported amount of consumed food/nutrient, and dividing this value by its respective global standard deviation. This value was then converted to a percentile score to minimize the effect of 'right skewing' (fewer observations with higher intakes of dietary factors), which often occurs with dietary data.

The 'inflammatory effect score' for each dietary factor was calculated previously, based on results from experimental, prospective cohort, case–control, cross-sectional, animal experimental and cell-culture studies[21]. The dietary factor percentile score for each participant in the PLCO cohort was multiplied by its respective 'inflammatory effect score' to derive a 'food-specific dietary inflammatory score'. Each of the 'food-specific dietary inflammatory scores' were summed to derive an overall dietary inflammatory score, where negative scores are less inflammatory and positive scores are more inflammatory. Scores are based on both food and nutrient intakes. For these analyses, thirty-seven of the forty-five foods or nutrients from the original DII were available for use. Pro-inflammatory dietary factors included: vitamin B_{12}, carbohydrate, cholesterol, energy, total fat, Fe, protein, SFA and *trans*-fat. Anti-inflammatory dietary factors included: vitamin B_6, β-carotene, caffeine, fibre, folic acid, vitamins A, D, C and E, niacin, riboflavin, thiamin, Mg, Se, Zn, MUFA, *n*-3 fatty acids, *n*-6 fatty acids, PUFA, flavan-3-ols, flavones, flavonols, flavonones, anthocyanidins, isoflavones, green/black tea, alcohol and onion. DII scores were calculated per 4184 kJ consumed to account for inter-individual differences in energy intake, which is also termed the Energy-Density DII (E-DII). E-DII scores for the PLCO screening-arm population ranged between −5·87 (maximally anti-inflammatory) and 5·58 (maximally pro-inflammatory). For analytical purposes, the E-DII scores were then categorized into quartiles.

Covariate data

Potential covariates included: smoking (never, current, or former); sex (male or female); self-report of race (black, white, Asian or other); and non-steroidal anti-inflammatory use (regular use of aspirin/aspirin-containing or ibuprofen/ibuprofen-containing products or not). BMI (= [weight (kg)]/[height (m)]^2) was categorized as underweight ($<18{\cdot}5\,kg/m^2$), normal ($18{\cdot}5–24{\cdot}9\,kg/m^2$), overweight ($25{\cdot}0–30{\cdot}0\,kg/m^2$) or obese ($>30{\cdot}0\,kg/m^2$), and was based on self-reported height and weight. Physical activity was categorized as vigorous activities for <2 h/week (low) *v.* ≥2 h/week (high) to stay consistent with current recommendations[22]. Hormone status was categorized as never, current (ever taken or currently taking female hormones), former or unknown. Education was categorized into less than high school, high-school diploma, some college or post high-school training, and college or graduate degree. Age at randomization, alcohol intake (g/d), fibre intake (g/d), Ca intake (food and supplements; mg/d) and energy intake (kJ/d; kcal/d) were left as continuous variables.

Statistical analysis

Means and frequencies, with their respective standard deviations and percentages, were calculated for continuous and categorical characteristics, stratified by E-DII score quartiles. The χ^2 test and ANOVA were used to determine differences, if any, in descriptive characteristics between quartiles of E-DII score. Normal distribution was assessed with histograms (QQ plot or Shapiro–Wilk test) for each variable.

Multivariable logistic regression was used to calculate the odds of prevalent CRA for different quartiles of E-DII score[9]. Separate models were created for adenoma type (all prevalent, advanced, non-advanced or multiple (>1) adenoma). Regression models were initially adjusted for sex, race, smoking, age, physical activity, education, hormone status, regular use of aspirin/aspirin-containing or ibuprofen/ibuprofen-containing products, and daily Ca, energy and alcohol intakes. Additionally, an interaction term for sex and E-DII score category was included. All potential covariates and interaction terms were included in the initial model and then were evaluated for variable selection; if they were not significant in the model ($P<0{\cdot}20$), they were removed if their exclusion did not result in a lower Akaike information criterion statistic[23]. The most parsimonious model, indicated by a lower Akaike information criterion value, was selected. Covariates used in calculating the overall adenoma odds were used for subgroup analyses. The models were stratified by sex if the interaction between sex and E-DII score was significant ($P<0{\cdot}20$). Wald χ^2 was used to test for trends across E-DII categories. Models were also stratified by BMI status (overweight/obese *v.* normal/underweight) or smoking status (never *v.* former/current). All analyses were performed using the statistical software package SAS version 9.4 using a P value <0·05 to indicate significance, unless otherwise indicated.

Results

Descriptive characteristics for the quartiles of the E-DII are presented in Table 1. Compared with quartile 4, quartile 1 (least inflammatory) had a higher percentage of females (65·0 *v.* 26·0 %), Asians (7·4 *v.* 1·6 %), individuals with a college education (45·5 *v.* 27·7 %), individuals with a high amount of physical activity (68·2 *v.* 42·4 %), never smokers (52·4 *v.* 40·8 %) and individuals with a normal BMI (41·5 *v.* 22·4 %). Women in quartile 1 (least inflammatory) were

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Table 1 Baseline characteristics of the screening-arm participants (*n* 44 278) by quartile of Energy-Density Dietary Inflammatory Index (E-DII) score; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, USA, 1993–2000

	Quartile 1 (least inflammatory) (E-DII < −2·93)		Quartile 2 (E-DII = −2·93 to −1·80)		Quartile 3 (E-DII = −1·81 to −0·45)		Quartile 4 (most inflammatory) (E-DII > −0·45)	
Characteristic	*n*	%	*n*	%	*n*	%	*n*	%
Categorical variables								
Sex								
Male	3879	35·0	5273	47·6	6444	58·2	8192	74·0
Female	7190	65·0	5797	52·4	4625	41·8	2878***	26·0
Race								
White	9625	87·0	10 107	91·3	10 141	91·6	10 195	92·1
Black	400	3·6	364	3·3	402	3·6	442	4·0
Asian	815	7·4	381	3·4	284	2·6	183	1·6
Other	229	2·1	218	2·0	242	2·2	250***	2·3
Education								
College	5034	45·5	4389	39·6	4012	36·2	3067	27·7
Some college	3616	32·7	3815	34·5	3732	33·7	3820	34·5
High school	2034	18·4	2290	20·7	2644	23·9	3042	27·5
Less than high school	385	3·5	576	5·2	681	6·2	1141***	10·3
Physical activity†								
High	7545	68·2	6678	60·3	5957	53·8	46 949	42·4
Low	3524	31·8	4392	39·7	5112	46·2	6367***	57·6
Smoking								
Never	5801	52·4	5703	51·5	5214	47·1	4512	40·8
Current	569	5·1	759	6·9	1068	9·6	1746	15·8
Former	4694	42·4	4608	41·6	4787	43·2	4812***	43·5
Anti-inflammatory use‡								
Yes	2272	20·5	2187	19·8	2254	20·4	2216	20·0
No	8797	79·5	8883	80·2	8815	79·6	8854	80·0
Hormone therapy (females)								
Current	4069	56·6	3083	53·2	2377	51·4	1331	46·3
Former	1115	15·5	908	15·7	715	15·5	468	16·3
Never	1976	27·5	1779	30·7	1513	32·7	1064	37·0
Unknown	23	0·3	20	0·4	17	0·4	9***	0·3
BMI (kg/m^2)								
0–18·5	100	0·9	70	0·6	59	0·5	40	0·4
18·5–25·0	4592	41·5	3725	33·6	3223	29·1	2478	22·4
25·0–30·0	4318	39·0	4819	43·6	4973	44·9	5194	46·9
>30·0	2059	18·6	2453	22·2	2814	25·4	3358***	30·3
Missing (*n* 430)								
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Continuous variables								
Age (years)	62·9	5·4	62·8	5·3	62·4	5·2	61·7***	5·1
Ca intake (supplements and food; mg/d)	1349·7	578·6	1256·2	587·9	1212·1	601·5	1168·4***	641·6
Energy intake (kJ/d)	7684·3	2717·9	8203·2	3026·7	8758·8	3273·1	9939·9***	3811·6
Alcohol intake (g/d)	8·4	14·1	9·0	17·0	10·9	21·0	15·9***	34·9
Fibre intake (g/d)	26·8	10·8	24·7	10·1	22·6	9·3	19·9***	8·1

***$P < 0·0001$; χ^2 test for categorical and ANOVA for continuous variables.
†Vigorous activities for <2 h/week (low) *v.* ≥2 h/week (high).
‡Regular use of aspirin/aspirin-containing or ibuprofen/ibuprofen-containing products or not.

more likely to be current hormone users than women in quartile 4 (most inflammatory; 56·6 *v.* 46·3 %). Additionally, compared with those in quartile 4, those in quartile 1 were older (62·9 *v.* 61·7 years), had a higher intake of Ca (1349·7 *v.* 1168·4 mg/d) and a lower energy intake (7684·3 *v.* 9939·9 kJ/d).

Prevalent distal adenoma

There was significant interaction between E-DII score and sex ($P = 0·02$), so models for prevalent distal adenoma were stratified by sex. In fully adjusted models (adjusted for race, education, smoking status, BMI, age and Ca intake), compared with those with E-DII scores in quartile 1 (least inflammatory), males with E-DII scores in quartile 3 (adjusted odds ratio (aOR) = 1·28; 95 % CI 1·12, 1·47) and quartile 4 (aOR = 1·41; 95 % CI 1·23, 1·62; Table 2) were more likely to have prevalent distal CRA. Males with E-DII scores in quartile 3 (aOR = 1·34; 95 % CI 1·12, 1·60) and quartile 4 (aOR = 1·42; 95 % CI 1·19, 1·68) also were more likely to have a non-advanced adenoma, compared with those in the lowest quartile of E-DII scores. Males with E-DII scores in quartile 4 (aOR = 1·39; 95 % CI 1·13, 1·71;

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Table 2 Associations between prevalent colorectal adenoma and quartile of Energy-Density Dietary Inflammatory Index (E-DII) score† in the screening-arm participants (*n* 44 255) by sex‡; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, USA, 1993–2000

	Quartile 1 (least inflammatory; reference)	Quartile 2		Quartile 3		Quartile 4 (most inflammatory)		Wald χ^2 *P* trend
		OR	95 % CI	OR	95 % CI	OR	95 % CI	
Men (*n* 23 788)§								
All distal adenoma								**<0·0001**
No. of cases	327		496		741		1091	
Multivariable-adjusted OR (95 % CI)	1·00	1·06	0·92, 1·23	**1·28**	**1·12, 1·47**	**1·41**	**1·23, 1·62**	
Non-advanced adenoma								**0·0002**
No. of cases	193		310		449		630	
Multivariable-adjusted OR (95 % CI)	1·00	1·14	0·95, 1·38	**1·34**	**1·12, 1·60**	**1·42**	**1·19, 1·68**	
Advanced adenoma								**0·0003**
No. of cases	129		184		284		441	
Multivariable-adjusted OR (95 % CI)	1·00	0·97	0·77, 1·22	1·21	0·98, 1·50	**1·39**	**1·13, 1·71**	
Multiple adenomas (>1)								**0·0004**
No. of cases	80		136		193		327	
Multivariable-adjusted OR (95 % CI)	1·00	1·18	0·89, 1·56	**1·32**	**1·01, 1·72**	**1·63**	**1·26, 2·11**	
Women (*n* 20 467)‖								
All distal adenoma								**0·03**
No. of cases	469		358		356		225	
Multivariable-adjusted OR (95 % CI)	1·00	0·90	0·78, 1·04	1·13	0·98, 1·31	1·08	0·91, 1·29	
Non-advanced adenoma								0·07
No. of cases	291		222		217		142	
Multivariable-adjusted OR (95 % CI)	1·00	0·92	0·77, 1·10	1·14	0·95, 1·38	1·17	0·94, 1·45	
Advanced adenoma								0·29
No. of cases	177		132		135		83	
Multivariable-adjusted OR (95 % CI)	1·00	0·86	0·68, 1·08	1·09	0·86, 1·38	0·96	0·72, 1·27	
Multiple adenomas (>1)								0·06
No. of cases	91		60		69		57	
Multivariable-adjusted OR (95 % CI)	1·00	0·77	0·55, 1·07	1·08	0·79, 1·49	1·28	0·90, 1·82	

Significant ($P < 0·05$) results are indicated in bold font.
†Quartile 1, E-DII < −2·93; quartile 2, E-DII = −2·93 to −1·80; quartile 3, E-DII = −1·81 to −0·45; quartile 4, E-DII > −0·45.
‡Interaction *P* values for sex × E-DII score for adenoma (overall), non-advanced adenoma, advanced adenoma and multiple (>1) adenoma are, respectively, 0·03, 0·16, 0·20 and 0·29.
§Adjusted for BMI, education, smoking status, race, Ca intake, alcohol intake and age.
‖Adjusted for BMI, smoking, race, hormone status, total daily energy intake, Ca intake, alcohol intake and age.

Table 2) were more likely to have advanced CRA, compared with those with E-DII scores in quartile 1. Males with E-DII scores in quartile 3 (aOR = 1·32; 95 % CI 1·01, 1·72) and quartile 4 (aOR = 1·63; 95 % CI 1·26, 2·11) were more likely to have more than one distal CRA, compared with those with E-DII scores in quartile 1. In fully adjusted models, there were no differences in the odds of CRA (advanced, non-advanced or multiple (>1)) between E-DII quartile 1 and E-DII quartile 4 in females. However, there was a trend that higher E-DII scores were associated with higher odds of adenoma, overall.

When results were stratified by smoking status or BMI classification, the odds of adenoma among overweight/obese men with the most inflammatory diet *v.* those with the least inflammatory diet (aOR = 1·39; 95 % CI 1·18, 1·63) were similar to those of normal/underweight men (aOR = 1·50; 95 % CI 1·14, 1·96; data not shown). However, the odds of adenoma among male smokers with the most inflammatory diet *v.* the least inflammatory diet (aOR = 1·63; 95 % CI 1·38, 1·93) were higher than those of men who did not smoke (aOR = 1·22; 95 % CI 0·97, 1·53; data not shown). Females showed similar patterns (smokers aOR = 1·43; 95 % CI 1·12, 1·83; non-smokers aOR = 0·97; 95 % CI 0·76, 1·25; data not shown).

Discussion

In this large cohort of men and women, enrolled as part of the PLCO screening arm, we sought to investigate the association between CRA and E-DII score and found that a more inflammatory diet was associated with distal CRA prevalence in men, and to a limited extent in women. Specifically, males who consumed a more inflammatory diet were more likely to have non-advanced adenomas, advanced adenomas and multiple (>1) adenomas than men who consumed a less inflammatory diet.

It is believed that inflammation promotes an environment that increases genetic mutations and disables the mechanisms that repair these errors[24]. There also is evidence that inflammation may promote growth factors that enhance tumour growth, particularly through enhanced angiogenesis[22]. Further, a vicious cycle is created in that tumour cells produce cytokines that attract leucocytes, which further promote inflammation[5]. Higher systemic concentrations of inflammatory cytokines may then lead to the development of CRA[25]. Diet can affect systemic inflammation both positively and negatively. A high intake of energy and certain types of fat (e.g. *trans*-fats) may lead to pro-inflammatory states[26,27], while fruits and vegetables

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contain antioxidants that counteract inflammation[28]. The DII has recently been developed as a way for researchers to characterize the overall inflammatory nature of diet[6]. This index has been shown to be associated with inflammatory conditions, such as colon, prostate and pancreatic cancers, and asthma[8,9,11,12,29], as well as circulating inflammatory proteins[6,7].

Findings of the present study are generally consistent with those from other studies that have found lower odds of prevalent CRA among those who consume a 'healthy' diet[29,30]. For example, men with higher scores on several dietary indices (Healthy Eating Index, Mediterranean diet, Dietary Approach to Stop Hypertension) were less likely to have a prevalent CRA compared with men consuming a less healthy diet[29]. These results suggest that there may be a common element, such as an anti-inflammatory dimension, among the dietary indices which confers adenoma-protective effects, and that the specific type of diet may be less important than this common beneficial element (e.g. anti-inflammatory dimension). Indeed, for several of the dietary indices mentioned, better scores have been associated with lower concentrations of inflammatory markers[31,32].

It is interesting that lower E-DII scores, indicating a less-inflammatory diet, were not strongly associated with distal CRA prevalence in women, although there was a trend across quartiles of higher odds of CRA with higher E-DII scores. Some previous studies have shown that women with more inflammatory diets, as reflected by higher DII scores, were more likely to have developed colorectal cancer, compared with those with less inflammatory diets[10,11]. However, another larger study using individuals in the American Association of Retired Persons Diet and Health Study found that the association between a less inflammatory diet and lower risk of colorectal cancer was significant only in men[33]. Since adenomas are precursors to cancer, we expected to find a positive association between E-DII scores and CRA prevalence in women. However, dietary predictors for adenomas may not be the same as dietary predictors for colon cancer in women. It has been estimated that only half of studies on the association between diet indices (e.g. Mediterranean diet and Healthy Eating Index) and colorectal cancers report sex-specific risks[34], suggesting that the current literature may not fully capture the effects of diet on adenoma prevalence or cancer incidence in males and females, individually. Of those studies that have reported on dietary factors for CRA in men and women separately, several did not find a protective effect of diet in women[29,30,35]. Another explanation for the discrepancy in findings between the current study and previous studies may have to do with lower (less inflammatory) E-DII scores in the present study (−2·1 (SD 1·6) *v.* −0·9 (SD 2·0); $P < 0{\cdot}0001$[11]). The generally lower scores in the present study may have limited the ability to see beneficial dietary effects because the diets were generally 'adequate' for adenoma prevention.

To further explore the association between E-DII scores and adenoma status in women, sensitivity analyses were performed combining quartiles 1 and 2 and comparing the odds of adenoma with those of quartile 3 or 4. Alternatively, cut points used in another study using the E-DII also were used[9]. In both instances, results were similar to those presented in Table 2. The results appear to have a curvilinear response in women, which may suggest a differential effect of diet between sexes. A possible explanation is that these analyses were cross-sectional in nature and those who were consuming the most anti-inflammatory diet were doing so because they had concerns about a higher risk of adenoma. Another possible explanation is that women who have very anti-inflammatory diets also engage in other behaviours not fully accounted for in the analyses, which weaken the effect of a healthy diet, or because women misestimate their actual intake because of social desirability and underreport total fat and energy intakes[36]. Differences in actual *v.* reported intakes between men and women may also at least partly explain why the E-DII was associated with adenoma in men but not in women.

It is unknown to what extent the results of the current study can be applied to proximal adenomas. One study found that the risk adenoma and diet (fibre and fruit and vegetables) was lower for adenomas occurring in the proximal *v.* distal region[37]. However, results from other studies, including a literature review, are unclear as to whether or not there are anatomical site differences in the effects of diet on cancer or adenoma development or occurrence[33,38,39]. Future research would need to be done to more fully understand the association between diet and adenoma occurrence in site-specific areas.

One of the strengths of the present study is the large, diverse cohort of individuals with varied dietary habits, enabling the analysis of adenoma outcomes across a broad spectrum of food intakes. Another study strength is the novel way to characterize the inflammatory nature of diet. Inflammation is an important factor in disease occurrence and the E-DII is the first index to be developed specifically for measuring the inflammatory potential of an individual's diet. Finally, participants in the PLCO study were screened uniformly, allowing for equal opportunity of adenoma detection.

A limitation of the study is that the E-DII was not able to fully determine the inflammatory nature of the diets due to some of the E-DII components not being included in the dietary questionnaire (e.g. eugenol, garlic, ginger, saffron, turmeric, pepper, rosemary and thyme/oregano). However, most items for the E-DII were included in the calculations and these represented the most commonly consumed foods/nutrients. Another limitation to these analyses is recall bias, most notably for the dietary recall. This may have resulted in biased estimates, particularly

among women where the potential for misclassification was greater, thus resulting in estimates closer to the null.

Conclusion

A more inflammatory diet was associated with a higher risk of CRA, particularly in men. The results for women were less conclusive. Therefore, future research should use large prospective studies to replicate these findings with a focus on gender differences and the potential for recall bias in influencing these associations. Also, future work could be done to determine whether these results apply to incident or recurrent adenomas, as well as adenomas in the proximal region of the colon. Results from the present study support an inflammatory mechanism for the development of CRA. From a public health perspective, future work should focus on helping individuals understand and incorporate anti-inflammatory elements into their diet.

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