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Original Research Article

Postdiagnostic intake of a more proinflammatory diet is associated with a higher risk of recurrence and all-cause mortality in colorectal cancer survivors

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A B S T R A C T

Background: The inflammatory potential of the diet has been associated with colorectal cancer (CRC) risk, but its association with CRC prognosis is unclear.
Objective: To investigate the inflammatory potential of the diet in relation to recurrence and all-cause mortality among persons diagnosed with stage I to III CRC.
Methods: Data of the COLON study, a prospective cohort among CRC survivors were used. Dietary intake, 6 mo after diagnosis, was assessed by using a food frequency questionnaire and was available for 1631 individuals. The empirical dietary inflammatory pattern (EDIP) score was used as a proxy for the inflammatory potential of the diet. The EDIP score was created by using reduced rank regression and stepwise linear regression to identify food groups that explained most of the variations in plasma inflammatory markers (IL6, IL8, C-reactive protein, and tumor necrosis factor-α) measured in a subgroup of survivors ($n = 421$). Multivariable Cox proportional hazard models with restricted cubic splines were used to investigate the relation between the EDIP score and CRC recurrence and all-cause mortality. Models were adjusted for age, sex, BMI, PAL, smoking status, stage of disease, and tumor location.
Results: The median follow-up time was 2.6 y (IQR: 2.1) for recurrence and 5.6 y (IQR: 3.0) for all-cause mortality, during which 154 and 239 events occurred, respectively. A nonlinear positive association between the EDIP score and recurrence and all-cause mortality was observed. For example, a more proinflammatory diet (EDIP score +0.75) compared with the median (EDIP score 0) was associated with a higher risk of CRC recurrence (HR: 1.15; 95% CI: 1.03, 1.29) and all-cause mortality (HR: 1.23; 95% CI: 1.12, 1.35).
Conclusions: A more proinflammatory diet was associated with a higher risk of recurrence and all-cause mortality in CRC survivors. Further intervention studies should investigate whether a switch to a more anti-inflammatory diet improves CRC prognosis.

Keywords: the inflammatory potential of the diet, cytokines, colorectal cancer, recurrence, mortality

Introduction

Inflammation is one of the enabling characteristics of cancer [1, 2]. Higher circulating levels of proinflammatory cytokines, including TNFα, IL6, and IL8, have also been associated with worse colorectal cancer (CRC) prognosis [3–7]. Human observational and intervention studies have shown that diet could affect systemic and gastrointestinal inflammation [8–13]. Therefore, diet potentially influences CRC prognosis by modifying inflammation [14].

Because diet could modify the inflammatory status of the body, researchers have investigated the inflammatory potential of the diet in relation to health outcomes [15]. Previous research has primarily focused on nutrient-based scores as a proxy for the inflammatory potential of the diet. The nutrient-based scores indicated that a more

Abbreviations: CRC, colorectal cancer; hsCRP, high-sensitivity C-reactive protein; DCRA, Dutch colorectal audit; EDIP, empirical dietary inflammatory pattern; RCS, restricted cubic splines; RRR, reduced rank regression.

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proinflammatory diet compared with a more anti-inflammatory diet was associated with an increased risk of all-cause mortality in CRC survivors [16, 17]. Contrastingly, we did not observe an association between a nutrient-based score and all-cause mortality in our previous work among CRC survivors [18]. Nowadays, nutritional epidemiologic research has moved from investigating single nutrients and nutrients patterns to analyzing food groups and dietary patterns. Analyzing patterns based on food groups may provide a more realistic picture as the intake of food groups, as opposed to the intake of nutrients, is closer to people's perception of the diet and easier to translate into dietary guidelines for public health [19].

The "Empirical dietary inflammatory pattern" (EDIP) score [20] is a food group-based index to assess the inflammatory potential of the diet and is derived from investigating associations between consumption of food groups and circulating inflammatory markers [20]. Previous studies have used the EDIP score to investigate the inflammatory potential of the diet in relation to CRC risk. Higher EDIP scores, representing a more proinflammatory diet, compared with lower EDIP scores, representing a more anti-inflammatory diet, were associated with an increased risk of developing CRC [21]. However, the inflammatory potential of the diet using a food group-based score in relation to CRC recurrence and mortality has not been investigated before. Therefore, the aim of this study was to investigate the association between the inflammatory potential of the diet and recurrence and all-cause mortality using a food group-based score.

Methods

Study design and population

Data from the "COlorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that influence colorectal tumor recurrence, survival, and quality of life" (COLON) study were used (ClinicalTrials.gov identifier:NCT03191110). The COLON study is a prospective cohort study of people with CRC enrolled from 11 hospitals in the Netherlands between 2010 and 2020 [22]. Participants were Dutch-speaking men and women aged ≥18 y, who were recently diagnosed with CRC in any stage of the disease. Participants were excluded from the study when they had a history of CRC, chronic inflammatory bowel disease, bowel resection, or hereditary CRC syndromes. The study was approved by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen. All participants provided written informed consent.

In total, 2134 participants were recruited (Figure 1). Participants were asked to fill out self-administered questionnaires and to donate blood samples at 6 mo after diagnosis. We specifically chose this post-diagnostic time point because future patients diagnosed with CRC could still change their intake after the diagnosis and thereby hopefully improve their prognosis, whereas prediagnostic intake cannot be changed anymore. In addition, previous research from our group also showed that CRC patients only marginally changed their diet in the first 2 y after diagnosis [23]. Participants with missing data on postdiagnostic dietary intake ($n = 347$) or with missing data on medical characteristics ($n = 45$) or stage 0 ($n = 9$) were excluded. In total, 1631 participants were included in the analyses with all-cause mortality as outcome. Participants who had no data available about recurrences ($n = 382$) or had a recurrent event in the first 6 mo after diagnosis ($n = 15$) were excluded, leaving 1234 survivors for the analyses with recurrence as outcome. Inflammatory markers, which were needed to construct the EDIP score (see below), were available in a subgroup ($n = 421$) of the population.

Data collection

Dietary intake and demographic characteristics

Habitual dietary intake over the previous month was assessed by using a semi-quantitative food frequency questionnaire (FFQ). The FFQ consisted of 204 items, in which the frequency of intake, portion size, number of portions, and type of product were assessed for each food item. Dietary supplement use in the past year was assessed with a self-administered dietary supplement questionnaire from Wageningen University, the Netherlands [22]. Participants filled out a self-administered lifestyle questionnaire containing questions on demographic and health characteristics. The Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) was used to assess physical activity [24]. Data on clinical factors were derived from the Dutch colorectal audit (DCRA), which included tumor location, disease stage, type of treatment, and presence of comorbidities [25].

Blood samples

Blood samples were centrifuged and aliquoted into plasma and stored in a freezer at −80°C. A custom-made multiplex assay using electrochemiluminescence detection was used to determine the plasma levels of IL6, IL8, and TNFα (Meso Scale Diagnostics) as has been described previously [26]. A Quick Plex SQ 120 plate reader was used

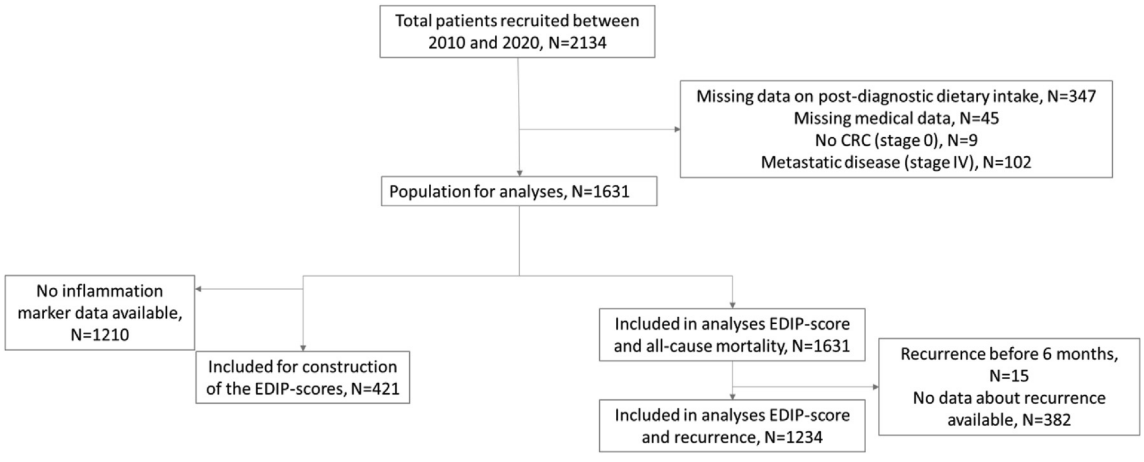


FIGURE 1. Flowchart representing patient selection for the current analysis. CRC, colorectal cancer; EDIP, empirical dietary inflammatory pattern.

to analyze the assay plates (Meso Scale Diagnostics). The inter- and intra-batch coefficients of variation for all inflammatory markers had a maximum of <8% [26]. Plasma high-sensitivity C-reactive protein (hsCRP) was measured by using an immune-MALDI mass spectrometry method (BEVITAL) [27]. The range of the inter-assay was between 3% and 6%.

EDIP score

The EDIP score was developed with the aim to evaluate the inflammatory potential of whole diets based on food groups [20]. A higher EDIP score implies a more proinflammatory diet, and a lower EDIP score indicates a more anti-inflammatory diet. The EDIP score was developed in the Nurses' Health Study (NHS) and has been validated in the NHS-II and the Health Professionals Follow-Up Study (HPFS) [20]. In the present study, the same methodology to construct the EDIP score was applied to the data of the COLON study. We chose to create the EDIP score based on our own data because dietary intakes are likely different in Dutch CRC survivors compared with US-based healthcare professionals.

To calculate the EDIP score for all participants, we first determined which food groups were most relevant in relation to inflammation in 421 CRC survivors, of whom the following proinflammatory markers were available: IL6, IL8, CRP, and TNFα. Thirty-nine predefined food groups [28] were formed by categorizing FFQ items. Fish intake was separated in fatty and lean fish, leading to 40 food groups in total (Table 1). The mean daily intake of the food groups was calculated by summing up the mean daily intake of the grouped FFQ items. The intake from the food groups was adjusted for the total energy intake by using the residual method [29], and the inflammatory markers were log2-transformed before entering the reduced rank regression (RRR). The food groups were added to the RRR as the predictor variables, and the inflammatory markers were added as the response variables. The RRR extracts food groups that explain as much variation in the levels of inflammatory markers as possible [30]. The first factor of RRR explains most of the variation in the response variables and was saved for further analyses (Table 1). Stepwise linear regression analysis was subsequently used to distinguish the food groups that contributed the most to the first factor of the RRR. The first factor of the RRR was entered as the dependent variable, and the food groups, as the independent variables. The significance level for withholding or entering a food group into the model was set at $P = 0.05$. Food groups that explained <1% of the variation in inflammatory markers were not included because the effect on the inflammatory status of the body would be negligible. Ultimately, 23 of the 40 food groups were included to calculate the EDIP score in the total population. The energy-adjusted intake of the 23 food groups was multiplied by the regression coefficients of the final step of the stepwise linear regression analysis and summed up to create the EDIP score (Table 2). A negative score (EDIP score <0) is referred to as a more anti-inflammatory diet, whereas a positive score (EDIP score >0) is referred to as a more proinflammatory diet.

Study outcomes

Data on recurrence defined as a loco-regional or distant metastasis were obtained from the Netherlands Cancer Registry. All-cause mortality data were collected from the Municipal Personal Records Database of the Netherlands. Disease-free survival was defined by considering a recurrence or death from any cause in the analysis. Follow-up time for recurrence started with the date of dietary assessment 6 mo after diagnosis until the date of recurrence or until the date of the latest update on recurrence (February 2018) or end of follow-up, whichever came first.

TABLE 1
Median intake per food group (g/d) and percent variation accounted for by the first factor of the reduced rank regression

Food group	Median intake[1]	Contribution (%)
Fruit	144.5 [73.4–220.6]	14
High-fat dairy	87.4 [39.8–172.9]	13
Fruit juice	33.5 [0–107.1]	11
Poultry	10.7 [4.9–18.4]	9
Eggs	14.3 [7.1–17.9]	8
Nuts and seeds	7.8 [2.5–17.2]	6
Coffee	348.2 [232.1–464.3]	5
Fatty fish	5.1 [1.0–9.5]	4
Refined grains	43.3 [22.0–70.7]	4
Cold breakfast cereals	0 [0–37.3]	3
Red meat	32.8 [18.6–45.3]	3
Cruciferous vegetables	10.1 [5.2–17.0]	3
Oil and vinegar	0.0 [0.0–0.6]	3
Butter (solid frying oils)	0.3 [0–3.6]	2
Low-fat dairy	139.3 [53.6–247.3]	2
Condiments	20.2 [11.5–33.5]	2
Processed meat	21.4 [9.3–36.3]	1
Tea	232.1 [44.6–348.2]	1
Soup	35.7 [22.3–89.3]	1
Snacks	4.3 [0–9.9]	1
Yellow vegetables	11.6 [4.5–20.8]	1
Sweets and desserts	32.9 [19.7–51.1]	1
Legumes	19.7 [9.7–32.9]	1
Pizza	0 [0–12.8]	<1
Organ meat	0.1 [0–3.8]	<1
French fries	7.9 [0–16.5]	<1
Liquor	0 [0–0]	<1
Other vegetables	16.5 [6.6–30.1]	<1
Green, leafy vegetables	15.0 [6.7–25.8]	<1
High-energy drinks	0[0–21.0]	<1
Potatoes	49.9 [44.8–89.7]	<1
Tomatoes	5.7 [1.7–13.2]	<1
Lean fish	7.4 [3.1–11.8]	<1
Whole grains	107.1 [71.2–147.3]	<1
Wine	0 [0–34.7]	<1
Creamy salad dressings	1.9 [0.5–4.4]	<1
Margarine (liquid frying oils)	12.7 [4.5–24.4]	<1
Low-energy drinks	0 [0–5.3]	<1
Beer	0 [0–89.3]	<1
Garlic and onion	8.9 [0–20.9]	<1

[1]Median (IQR) intake per day in grams; the energy-adjusted intake of food groups was entered in the reduced rank regression analyses.

Follow-up time for all-cause mortality started with the date of dietary assessment 6 mo after diagnosis until the date of death or until the date of the latest update on survival (September 2021) or the end of follow-up, whichever came first. Follow-up time for disease-free survival started with the date of dietary assessment 6 mo after diagnosis until the date of recurrence or death or until the last date vital status was updated, the last date recurrence status was updated, or the date of end of follow-up, whichever came first.

Statistical analysis

Descriptive information of variables is presented as medians with IQR and numbers with percentages for the total population and stratified by tertiles of the EDIP score.

Multivariable Cox proportional hazards models with restricted cubic splines (RCS) were used to explore and visualize the association between the EDIP score and recurrence, all-cause mortality, and disease-free survival. Three knots were placed on the 10th, 50th, and 90th percentiles, where the 50th percentile was used as the reference. Observed associations were nonlinear; therefore, Cox regression

TABLE 2
Weights of the energy-adjusted food groups retrieved from the stepwise linear regression

Food group	Weights[1]
Anti-inflammatory	
Oil and vinegar	−0.106
Fatty fish	−0.025
Cruciferous vegetables	−0.023
Nuts and seeds	−0.019
Poultry	−0.016
Red meat	−0.010
Snacks	−0.007
Refined grains	−0.005
Fruit	−0.003
Breakfast cereals	−0.004
Condiments	−0.004
Coffee	−0.001
Tea	−0.001
Proinflammatory	
Butter	0.022
Eggs	0.019
Yellow vegetables	0.010
Processed meat	0.006
Sweet and desserts	0.004
Legumes	0.004
High-fat dairy	0.003
Fruit juice	0.003
Low-fat dairy	0.001
Soup	0.001

[1] Weights are the betas of the energy-adjusted food groups derived from the stepwise linear regression.

analyses with RCS terms were used to further analyze the data [31]. In addition to the RCS plot, Hazard Ratios with 95% CI of several specific EDIP score values versus the median EDIP score (reference) were calculated by using the RCS analyses to provide better insight into the magnitude of the association. The SAS Macro %RCS_Regvs1.44 was used to perform the Cox proportional hazard regression with RCS analyses. First, a crude model was performed for both the EDIP scores in relation to CRC recurrence, all-cause mortality, and disease-free survival. Next, age (y), sex (male/female), stage of disease (I/II/III), and tumor location (colon/rectum) were added to the model [17,33]. Based on the directed acyclic graphs [32], BMI (kg/m^2., continuous), moderate-to-vigorous physical activity (h/wk., continuous), and smoking status (current/former/never) were added to the model. In the final adjusted model, age, sex, BMI, moderate-to-vigorous physical activity, smoking status, stage of disease, and tumor location were added. The results reported in the text in the results section are based on the adjusted models. To explore interaction by sex, tumor location, and stage, a product term was added to the models. No statistically significant P values for interaction were observed (data not shown).

Finally, to ease comparison of results with existing literature, analyses were repeated using the food groups and weights of the original EDIP score [20].

The data analysis was performed with the statistical software program, SAS version 9.4 (SAS Institute). P values <0.05 were considered statistically significant.

Results

Population characteristics

In total, 1631 participants were included in our data analyses. The median follow-up time for recurrence was 2.6 (IQR: 2.1) y, in which 154 recurrences were diagnosed. For all-cause mortality, the median follow-up time was 5.6 (IQR: 3.0) y, in which 239 deaths occurred. The population had a median age of 65.9 (IQR: 10.5) y, 37% were women and the median BMI was 26.0 (IQR: 4.6) kg/m^2 (Table 3). Furthermore, 69% of the tumors were located in the colon and 44% of the participants had a stage III tumor. Participants with a more proinflammatory diet, on average, were older, more often men, lower educated, less physically active, more often diagnosed with rectal cancer and more often had tumor stage III compared with participants with a more anti-inflammatory diet (Table 3).

EDIP score

Twenty-three of the 40 predefined food groups explained equal to or >1% of the variation in inflammation marker levels (Table 1). A higher intake of 10 of these food groups was associated with higher proinflammatory marker levels and was thus considered proinflammatory (butter, eggs, yellow vegetables, processed meat, sweet and desserts, legumes, high-fat dairy, fruit juices, low-fat dairy, and soup). A higher intake of 13 food groups were associated with lower proinflammatory marker levels and were thus considered anti-inflammatory (oil and vinegar, fatty fish, cruciferous vegetables, nuts and seeds, poultry, red meat, snacks, refined grains, fruit, breakfast cereals, condiments, coffee, and tea) (Table 2).

EDIP score in relation to recurrence, all-cause mortality, and disease-free survival

Consumption of a more proinflammatory diet (EDIP score >0) was associated with a higher risk of recurrence compared with the median score (EDIP score 0; reference) (Figure 2A). A more anti-inflammatory diet (EDIP score <0) compared with the median score was not associated with a risk of recurrence. For example, when EDIP scores of 0.50 points and 0.75 points were compared with the reference EDIP score of 0 points, HRs of 1.08 (95% CI: 1.01, 1.17) and 1.15 (95% CI: 1.03, 1.29) were observed, respectively. For EDIP scores of −0.50 points and −0.75 points in comparison with the reference, HRs of 1.01 (95% CI: 0.94, 1.10) and 1.05 (95% CI: 0.92, 1.20) were shown, respectively.

A more proinflammatory diet compared with the median score was also associated with a higher risk of all-cause mortality, whereas no association was observed for a more anti-inflammatory diet (Figure 2B). For example, when EDIP scores of 0.50 points and 0.75 points were compared with the reference, HRs of 1.13 (95% CI: 1.07, 1.20) and 1.23 (95% CI: 1.12, 1.35) were observed, respectively. For EDIP scores of −0.50 points and −0.75 points in comparison with the reference, HRs of 0.95 (95% CI: 0.88, 1.03) and 0.95 (95% CI: 0.83, 1.08) were shown, respectively.

A more proinflammatory diet compared with the median score was also associated with a higher risk of recurrence or death from any cause (disease-free survival) (Figure 2C). For example, when EDIP scores of 0.50 points and 0.75 points were compared with the reference, HRs of 1.10 (95% CI: 1.04, 1.15) and 1.19 (95% CI: 1.08, 1.30) were observed, respectively. For EDIP scores of −0.50 points and −0.75 points in comparison with the reference, HRs of 0.98 (95% CI: 0.90, 1.05) and 0.99 (95% CI: 0.87, 1.11) were shown, respectively.

Similar associations were observed when using the food groups and weights of the original EDIP score. In addition, here, a more proinflammatory diet compared with the median score was associated with a higher risk of recurrence, all-cause mortality, and recurrence or death from any cause (disease-free survival) (Supplemental Figure 1).

TABLE 3
Characteristics of colorectal cancer survivors across tertiles of the EDIP score

Characteristics	Total population (n = 1631)	EDIP score in tertiles		
		T1 (n = 543)	T2 (n = 544)	T3 (n = 544)
EDIP score	−0.03 [−0.64 to 0.61]	−0.93 [−1.36 to −0.64]	−0.03 [−0.22 to 0.16]	0.93 [0.61–1.38]
Age (y)	65.9 [61.0–71.5]	64.6 [59.1–69.6]	65.8 [61.2–71.6]	67.3 [62.8–73.7]
Female (%)	605 (37)	225 (41)	189 (35)	191 (35)
BMI (kg/m^2)	26.0 [23.9–28.5]	25.7 [23.5–28.3]	26.5 [24.2–28.7]	25.8 [24.0–28.5]
Normal weight (<25)	625 (39)	227 (42)	194 (36)	204 (38)
Overweight (25–29)	735 (45)	242 (45)	250 (46)	243 (45)
Obese (≥30)	259 (16)	69 (13)	96 (18)	94 (17)
Unknown	12	5	4	3
Education[1]				
Low	667 (41)	175 (32)	238 (44)	254 (47)
Medium	420 (26)	137 (25)	131 (24)	152 (28)
High	531 (33)	228 (42)	170 (32)	133 (25)
Unknown (n)	13	3	5	5
Family history cancer (%)				
Yes	1100 (73)	369 (73)	373 (74)	358 (73)
Unknown	133	40	39	54
Smoking habits				
Current	107 (7)	23 (4)	46 (8)	38 (7)
Former	990 (61)	327 (61)	345 (64)	318 (59)
Never	527 (32)	190 (35)	152 (28)	185 (34)
Unknown (n)	7	3	1	3
Physical activity (h/wk.)[2]	8.5 [4.1–15.0] 0	9.3 [5.0–16.0] 0	7.8 [4.0–14.0] 0	8.3 [3.5–14.8] 0
Total energy intake (kcal)	1775 [1462–2118]	1814 [1503–2147]	1723 [1411–2055]	1779 [1475–2138]
Dietary supplement use (%)	674 (41)	259 (48)	198 (36)	217 (40)
Regular NSAID use (%)	139 (9)	46 (9)	50 (9)	43 (8)
Unknown	9	2	3	4
Type of cancer				
Colon	1118 (69)	408 (75)	376 (69)	334 (61)
Rectum	513 (31)	135 (25)	168 (31)	210 (39)
Tumor stage				
I	440 (27)	170 (32)	141 (26)	129 (24)
II	465 (29)	154 (29)	162 (30)	149 (28)
III	708 (44)	215 (39)	230 (43)	263 (49)
Unknown	18	4	11	3
Type of treatment				
Only surgery	901 (56)	329 (61)	307 (57)	265 (50)
Neoadjuvant treatment	345 (21)	79 (15)	107 (20)	159 (29)
Adjuvant treatment	404 (25)	139 (26)	133 (24)	132 (24)
Adjuvant chemotherapy	389 (24)	133 (25)	132 (24)	124 (23)
Unknown	20	5	4	11
Comorbidities				
Total yes	977 (66)	312 (64)	315 (65)	350 (68)
Unknown	151	58	60	33
Cardiovascular yes	687 (47)	203 (42)	226 (47)	258 (51)
Unknown	160	61	65	34
Diabetes	167 (11)	54 (11)	48 (10)	70 (13)
unknown	171	62	69	40
Inflammatory markers[3]				
IL6 (pg/mL)	0.96 [0.69–1.67]	0.87 [0.63–1.57]	0.95 [0.67–1.51]	1.12 [0.81–1.96]
IL8 (pg/mL)	4.93 [3.86–6.50]	4.61 [3.57–5.65]	5.10 [3.91–6.61]	5.54 [4.20–7.42]
TNFα (pg/mL)	2.32 [1.88–2.75]	2.09 [1.77–2.48]	2.35 [1.88–2.77]	2.52 [2.14–3.18]
$_{hs}$CRP (μg/mL)	1.69 [0.91–3.82]	1.27 [0.72–2.94]	1.82 [1.01–3.76]	2.00 [1.04–4.68]

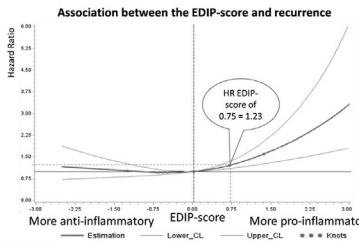
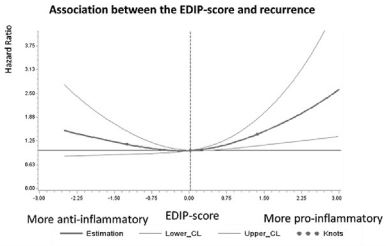
EDIP, empirical dietary inflammatory pattern; hsCRP, high-sensitivity C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug.
[1] Education: Low education is defined as primary school and general lower secondary school; Medium as lower vocational training and higher general secondary education; and High as high vocational training and university. Values presented are median (Q1–Q3) or number (percentage).
[2] Physical activity: metabolic equivalent score ≥3 is considered moderate-to-vigorous physical activity.
[3] Only available for the subgroup of survivors with inflammation markers n = 421.

Discussion

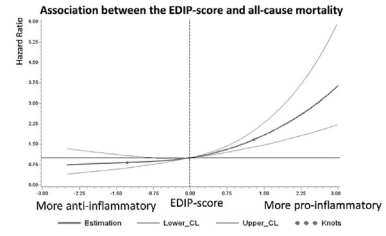
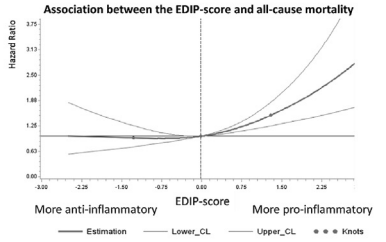
In this study, we investigated the association between the inflammatory potential of the diet and CRC outcomes by using a food group-based approach. Our main and novel finding is the increased risk of recurrences with a more proinflammatory diet compared with the median score. In addition, a more proinflammatory diet was associated with a higher risk of all-cause mortality and recurrence or death from any cause (disease-free survival).

To the best of our knowledge, this is the first study investigating and observing an association between the inflammatory potential of the diet and CRC recurrence with a food group-based score. In our

A: Recurrence

Crude model Number / events: 1234/154		Adjusted model Number / events: 1213/152	
			
Test for overall association p<0.001 Test for non-linearity p=0.01		Test for overall association p=0.01 Test for non-linearity p=0.01	
EDIP-score[1]	HR 95%CI	EDIP-score[1]	HR 95%CI
-2.25	1.13 (0.74, 1.72)	-2.25	1.45 (0.86, 2.36)
-1.25	1.02 (0.82, 1.27)	-1.25	1.16 (0.90, 1.52)
-0.75	0.97 (0.87, 1.10)	-0.75	1.05 (0.92, 1.20)
-0.50	0.96 (0.90, 1.03)	-0.50	1.01 (0.94, 1.10)
-0.25	0.97 (0.93, 1.00)	-0.25	1.00 (0.96, 1.04)
0	Ref	0	Ref
+0.25	1.05 (1.02, 1.09)	+0.25	1.03 (1.00, 1.06)
+0.50	1.13 (1.06, 1.20)	+0.50	1.08 (1.01, 1.17)
+0.75	1.23 (1.11, 1.37)	+0.75	1.15 (1.03, 1.29)
+1.25	1.52 (1.23, 1.87)	+1.25	1.37 (1.10, 1.71)
+2.25	2.38 (1.53, 3.77)	+2.25	1.99 (1.25, 3.20)

B: All-cause mortality

Crude model Number / events: 1613/239		Adjusted model Number / events: 1596/236	
			
Test for overall association p<0.001 Test for non-linearity p=0.07		Test for overall association p<0.001 Test for non-linearity p=0.07	
EDIP-score[1]	HR 95%CI	EDIP-score[1]	HR 95%CI
-2.25	0.76 (0.45, 1.28)	-2.25	1.00 (0.59, 1.68)
-1.25	0.83 (0.64, 1.07)	-1.25	0.96 (0.75, 1.24)
-0.75	0.88 (0.77, 0.99)	-0.75	0.95 (0.83, 1.08)
-0.50	0.90 (0.83, 0.98)	-0.50	0.95 (0.88, 1.03)
-0.25	0.95 (0.92, 0.98)	-0.25	0.97 (0.94, 1.00)
0	Ref	0	Ref
+0.25	1.08 (1.05, 1.12)	+0.25	1.06 (1.03, 1.09)
+0.50	1.19 (1.12, 1.26)	+0.50	1.13 (1.07, 1.20)
+0.75	1.31 (1.20, 1.44)	+0.75	1.23 (1.12, 1.35)
+1.25	1.64 (1.38, 1.94)	+1.25	1.49 (1.24, 1.78)
+2.25	1.99 (1.25, 3.20)	+2.25	2.20 (1.51, 3.20)

C: Recurrence or death from any cause (disease-free survival)

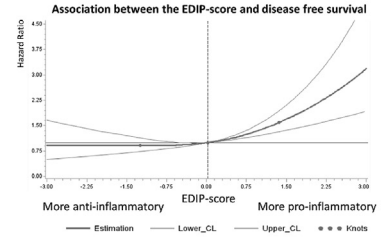
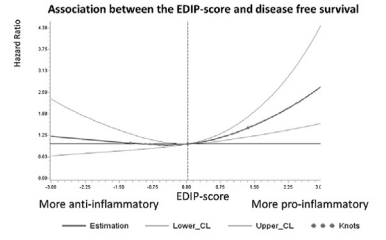
Crude model Number / events: 1237/260		Adjusted model Number / events:1213/257	
			
Test for overall association p<0.001 Test for non-linearity p=0.02		Test for overall association p<0.001 Test for non-linearity p=0.01	
EDIP-score[1]	HR 95%CI	EDIP-score[1]	HR 95%CI
-2.25	0.91 (0.60, 1.41)	-2.25	1.14 (0.72, 1.81)
-1.25	0.91 (0.73, 1.15)	-1.25	1.03 (0.81, 1.32)
-0.75	0.92 (0.82, 1.03)	-0.75	0.99 (0.87, 1.11)
-0.50	0.93 (0.87, 1.00)	-0.50	0.98 (0.90, 1.05)
-0.25	0.96 (0.93, 0.99)	-0.25	0.98 (0.94, 1.01)
0	Ref	0	Ref
+0.25	1.05 (1.03, 1.08)	+0.25	1.04 (1.01, 1.06)
+0.50	1.14 (1.08, 1.21)	+0.50	1.10 (1.04, 1.15)
+0.75	1.24 (1.14, 1.36)	+0.75	1.19 (1.08, 1.30)
+1.25	1.53 (1.28, 1.82)	+1.25	1.41 (1.18, 1.67)
+2.25	2.32 (1.62, 3.32)	+2.25	2.04 (1.41, 2.96)

FIGURE 2. Associations between the inflammatory potential of the diet, measured 6 mo after diagnosis by means of the EDIP score, and CRC recurrence, all-cause mortality, and recurrence or death from any cause (disease-free survival).[1]The EDIP score ranges between −11 and 5, median is 0.0, and IQRs between −0.6 and 0.6. HRs shown in this table represent the HR and 95% CI for that particular EDIP score in comparison with an EDIP score of 0. An EDIP score <0 is considered a more anti-inflammatory diet and an EDIP score of >0 is considered a more proinflammatory diet. For the RCS Cox regression analyses, knots were placed on the 10th, 50th, and 90th percentiles, where the 50th percentile was used as the reference. Adjusted models are adjusted for age, sex, BMI, hours of moderate-to-vigorous physical activity, smoking status, stage of disease, and tumor location. CL, confidence level; CRC, colorectal cancer; EDIP, empirical dietary inflammatory pattern; RCS, restricted cubic splines; Ref, reference.

previous work in the COLON study, we investigated the inflammatory potential of the diet in relation to CRC recurrence by using a nutrient-based score, that is, the adapted dietary inflammatory index (ADII) [18]. Then, we observed no association between the ADII and CRC recurrence ($HR_{continuous}$: 0.96; 95% CI: 0.91, 1.02). An explanation for the different findings could be the construction of the score. For the ADII, inflammatory weights of nutrients were based on previous literature, whereas for the EDIP score, the inflammatory weights of food groups were based on associations between energy-adjusted intake of the food groups and inflammatory marker levels in the study population itself. As a result, the EDIP score, compared with the ADII, may better reflect the inflammatory potential of the diet for our specific study population.

Our observation that a more proinflammatory diet is associated with a higher risk of all-cause mortality is in line with previous research investigating the association between the EDIP score and all-cause and cancer-specific mortality in the general population [34]. A previous study in 25,500 US adults observed an HR of 1.19; 95% CI: 1.08, 1.32 for all-cause mortality when comparing the highest quantile of the EDIP score with the lowest quantile [34]. As with recurrence, our previous work showed no association between the ADII and all-cause mortality ($HR_{continuous}$: 1.00; 95% CI: 0.95, 1.05) [18]. However, several other studies in CRC survivors, by using a nutrient-based approach to examine the inflammatory potential of the diet, did observe an increased risk of all-cause mortality with a more proinflammatory diet [16, 17, 35, 36]. Thus, the results of the current analyses and previous studies taken together indicate worse survival with a more proinflammatory potential of the diet.

The findings of the current study, especially regarding recurrence, need confirmation in other large prospective studies. In addition, future studies should consider molecular tumor subtypes. A previous study investigating the association between the proinflammatory potential of the diet and CRC risk observed an interaction between the inflammatory potential of the diet and the degree of immune-cell infiltration in tumors, where a proinflammatory diet was associated with an increased risk of tumors with absent or limited infiltration of immune cells but not with tumors with an intermediate or high infiltration of immune cells [37]. The inflammatory potential of the diet could potentially also influence CRC prognosis differently according to molecular tumor subtypes.

In addition, intervention studies could be set-up to investigate whether shifting to a more anti-inflammatory diet changes the levels of inflammatory markers in CRC survivors, which may ultimately result in a better CRC prognosis. These intervention studies should investigate the levels of inflammatory markers, response to treatment, recurrence rate, and CRC-specific mortality as outcomes. If confirmed in intervention studies, these results could be translated into dietary guidelines for CRC survivors.

There are several strengths to the current study. To the best of our knowledge, the current study is the first to investigate the association between the inflammatory potential of the diet and CRC recurrence and survival in CRC survivors by using a food group-based score. Furthermore, the EDIP score is based on inflammatory markers that are drivers of CRC development and progression [4] and are associated with worse prognosis [3, 5, 38–40]. This makes the score suitable for investigating the associations with CRC outcomes. Comprehensive information was available on diet, lifestyle, and other covariates, which allowed for the adjustment for most potential confounders. However, residual confounding can never be completely excluded. Finally, when repeating our analyses by using the food groups and weights of the original EDIP score developed by Tabung et al. [20], similar associations were observed regarding CRC outcomes. Thus, the EDIP score seems to be robust. The food groups that made up the EDIP score based on our own data in CRC survivors in the Netherlands and the original EDIP score developed in a population of healthcare professionals in the United States, however, were different. This could be because of the differences in the inflammatory markers that were used or because of the differences in the population studied. It is likely that dietary patterns and habits of a specific country influences the contributions of food groups to the EDIP score. This is supported by the results of the validation of the EDIP score in a Brazilian population [41]. This may indicate that if enough evidence is available to formulate guidelines, these recommendations should be context (for example, country) specific.

This study is not without limitations. When creating the EDIP score in the COLON study, some food groups attracted attention when observing their association with inflammatory markers. Condiments, refined grains, and red meat were inversely associated with inflammatory markers, whereas yellow vegetables and legumes were positively associated with inflammation. There is no biological explanation for the unexpected direction of the above-mentioned food groups with inflammatory markers. Given the role of the above-mentioned food groups in an overall healthy diet [42], it is not advised to increase the intake of condiments, refined grains, and red meat nor to decrease the intake of yellow vegetables and legumes. Furthermore, examining food groups most relevant in relation to inflammation was done in a subpopulation in which inflammatory markers were measured. The subpopulation was small ($n = 421$) compared with the total population ($n = 1631$). However, no differences were observed between the survivors of whom inflammatory data were available compared with survivors of whom no inflammatory data were available (Supplemental Table 1). This indicates that the subpopulation is representative of the total population.

In conclusion, a more proinflammatory diet was associated with an increased risk of recurrence and all-cause mortality. When our results are confirmed in other studies and tumor characteristics are taken into account, specific intervention studies could be set-up to investigate whether changing to a more anti-inflammatory diet results in a better CRC prognosis.

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Data availability

Since the data consist of identifying cohort information, some access restrictions apply, and therefore, the data cannot be made publicly available. Data will be shared with permission from the steering committee of the COLON Study. Requests for data and analytic code can be sent to Dr.Fränzel van Duijnhoven, Division of Human Nutrition and Health, Wageningen University & Research, The Netherlands. e-mail: franzel.vanduijnhoven@wur.nl.

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Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2022.11.018.

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