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Inflammatory potential of the diet and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition study

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Additional Supporting Information may be found in the online version of this article.

Key words: inflammatory potential of the diet, colorectal cancer, prospective cohort, Europe, epidemiology, association

Abbreviations: 24hDR: 24-hour dietary recall; BMI: body mass index; CI: confidence intervals; CRC: colorectal cancer; CRP: C-reactive protein; DII: dietary inflammatory index; EPIC: European Prospective Investigation into Cancer and Nutrition; FFQ: Food Frequency Questionnaire; HR: hazard ratio; HRT: hormone replacement therapy; IARC: International Agency for Research on Cancer; ICD-10: International Classification of Diseases; ICDO-2: International Classification of Disease for Oncology; IPS: inflammatory profile score; ISD: inflammatory score of the diet; LR: likelihood ratio; NIH-AARP: National Institute of Health-American Association of Retired Persons study; NOS: not otherwise specified; RR: relative risk; SD: standard deviation; TNF: tumor necrosis factor

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Proinflammatory diets are associated with risk of developing colorectal cancer (CRC), however, inconsistencies exist in subsite- and sex-specific associations. The relationship between CRC and combined lifestyle-related factors that contribute toward a low-grade inflammatory profile has not yet been explored. We examined the association between the dietary inflammatory potential and an inflammatory profile and CRC risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. This cohort included 476,160 participants followed-up of 14 years and 5,991 incident CRC cases (3,897 colon and 2,094 rectal tumors). Dietary inflammatory potential was estimated using an Inflammatory Score of the Diet (ISD). An Inflammatory Profile Score (IPS) was constructed, incorporating the ISD, physical activity level and abdominal obesity. The associations between the ISD and CRC and IPS and CRC were assessed using multivariable regression models. More proinflammatory diets were related to a higher CRC risk, particularly for colon cancer; hazard ratio (HR) for highest *versus* lowest ISD quartile was 1.15 (95% confidence interval [CI] 1.04–1.27) for CRC, 1.24 (95% CI 1.09–1.41) for colon cancer and 0.99 (95% CI 0.83–1.17) for rectal cancer. Associations were more pronounced in men and not significant in women. The IPS was associated with CRC risk, particularly colon cancer among men; HRs for the highest *versus* lowest IPS was 1.62 (95% CI 1.31–2.01) for colon cancer overall and 2.11 (95% CI 1.50–2.97) for colon cancer in men. Our study shows that more proinflammatory diets and a more inflammatory profile are associated with higher risk of CRC, principally colon cancer and in men.

What's new?

Chronic inflammation has been implicated in colorectal cancer (CRC), and diet plays an important role in modulating systemic inflammation. Two additional factors that contribute to chronic inflammation and also increase CRC risk are adiposity and lack of physical activity. In this large prospective study, the authors gained further insight into these relationships. They found that pro-inflammatory diets and a higher Inflammatory Profile Score (IPS, based on diet, physical activity, and abdominal obesity) are strong predictors of CRC, but principally of colon cancer and especially in men.

Introduction

Colorectal cancer (CRC) is the third most commonly occurring cancer globally, with an estimated 1.8 million new cases in 2018.[1] The incidence of CRC is much higher in men than women, with 324/100,000 compared to 253/100,000 new cases in 2018 in Europe, respectively.[1] The main lifestyle-related CRC risk factors are smoking, alcohol consumption, obesity, physical inactivity and certain dietary factors.[2] It has been estimated that approximately 70% of CRC cases could be avoided by following a healthy lifestyle[3] and diet is one of the key modifiable lifestyle factors.[4]

Chronic inflammation has been implicated in the onset and progression of CRC,[5] and diet plays an important role in modulating systemic inflammation. Therefore, the increased risk of CRC associated with certain dietary factors may be partly due to their effect on inflammatory biomarkers (cytokines/chemokines, acute-phase proteins, soluble adhesion molecules, etc.).[6] A high consumption of red and processed meat (foods shown to have proinflammatory properties) is strongly associated with a greater risk of CRC,[7] whereas a high consumption of fiber and whole grains (foods shown to have anti-inflammatory properties) is strongly associated with risk.[2] Evidence also suggests that consumption of fruit and vegetables may decrease risk of CRC.[2]

A widely applied tool designed to summarize the inflammatory potential of multiple dietary components is the Dietary Inflammatory Index (DII), which assigns inflammatory weights to different foods components according to their proinflammatory or anti-inflammatory properties.[8,9] The DII scores subjects along an inflammatory continuum; higher/more positive DII scores reflect more proinflammation diets and lower/ more negative scores reflect more anti-inflammatory diets. Higher DII scores have been associated with higher levels of inflammatory biomarkers[8,10–12] and a higher risk of CRC,[13–15] and several meta-analyses have reported around a 40% increased CRC risk for the highest *versus* lowest DII category. However, the risk estimates were substantially lower when

analyses were restricted to prospective cohort studies and inconsistencies between studies on gender- and site-specific associations warrant further investigation.[13,15]

Adiposity and lack of physical activity are two other major factors that can contribute to chronic inflammation and they are highly interrelated with diet, and also recognized as causes of CRC.[2] The inflammatory effects of diet, physical activity and abdominal obesity may individually increase risk of CRC or act in combination. In terms of obesity, enlarged adipocytes in obese individuals lead to overexpression of a host of inflammatory mediators which then produces chronic systemic inflammation.[16,17] This is particularly relevant when the enlarged mass of adipose tissue accumulates in the abdomen as visceral fat.[18] Although the relationship between physical activity and inflammation is complex, evidence shows that in the long-term habitual exercise reduces inflammatory markers.[19]

Therefore, the aim of our study was to assess the prospective association between the inflammatory potential of the diet and CRC, by anatomical subsite and gender, in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. In addition, the relationship between CRC and a low-grade inflammatory profile that considers the combined effect of the inflammatory potential of the diet along with abdominal obesity and physical activity was investigated.

Materials and Methods

Study setting and population

EPIC is a large on-going multicentric cohort study and the full methodological details for the recruitment procedure and data collection have been described previously.[20] In brief, between 1992 and 2000 a total of 521,324 subjects, mostly 30–70 years old, were recruited from 23 centers in 10 European countries. Participants were mainly recruited from the general population, with the exceptions detailed elsewhere.[20] All participants gave written informed consent. Ethical committees from the International Agency for Research on Cancer (IARC) and local centers approved the study. Participants were excluded if have had a prevalent cancer at baseline other than non-melanoma skin cancer (n = 25,184), missing end of follow-up data (n = 4,148), missing diet or lifestyle information (n = 6,259) or extreme energy intake/expenditure (n = 9,573), calculated as the top or bottom 1% of the distribution of the ratio of energy intake to energy requirement. Therefore, 476,160 participants (142,241 men and 333,919 women) were included in the final study population.

Follow-up and ascertainment of colorectal cancer cases

Incident CRC cases were identified *via* population cancer registries for Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom. In France, Germany, Naples and Greece different methods were used, including health insurance records, cancer and pathology registries and active follow-up of participants and their next of kin, with a subsequent medical verification of the diagnosis. Vital status data were obtained from regional or national mortality registries. Censoring dates for the last complete follow-up varied by center and ranged from 2005 to 2013. CRC cases were defined as tumors coded as C18–C20 in the 10th revision of the international classification of diseases (ICD-10), and the second revision of the International Classification of Disease for Oncology (ICDO-2). The CRC cases were further classified according to their anatomic location: proximal colon (C18.0–18.5), distal colon (C18.6–18.7), not otherwise specified (NOS) colon (C18.8–18.9) and rectum (C19–C20).

Assessment of lifestyle variables

At recruitment, anthropometric data were collected using standardized procedures and a lifestyle questionnaire was used to obtain information on sociodemographic factors, level of education, physical activity, medical history and consumption of alcohol and tobacco consumption. Dietary data was also collected at baseline, using validated country/center-specific questionnaires to record the usual diet during the previous year. Most countries used extensive quantitative food frequency questionnaires (FFQ) or semiquantitative FFQ, although a combination of diet records and FFQ or diet-history questionnaires were also used in some countries/centers.[20,21] Furthermore, standardized 24-hr dietary recall (24hDR) measurements were taken from a representative subsample of the EPIC cohort (5–12%) to correct for systematic differences between the dietary questionnaires and to minimize measurement error.[22] Country-specific food composition databases, which were standardized across EPIC countries, were used to calculate total energy, macronutrients and micronutrients and intake of other dietary parameters from the food consumption data.[23]

The inflammatory score of the diet

The diet's inflammatory potential was assessed using an Inflammatory Score of the Diet (ISD), which has been described previously.[24,25] The construction of the ISD is initially based on the DII,[9] an index comprised of 45 food components which were identified after a comprehensive literature review and included because of their anti-inflammatory or proinflammatory properties. Each food component has been given an inflammatory weighting according to its association with six well-known inflammatory biomarkers (IL-1b, IL-4, IL-6, IL-10, tumor necrosis factor (TNF) and C-reactive protein (CRP)); the weighting uses an algorithm that takes into account the level of evidence from the studies and numbers of articles that were reviewed. The construct of the DII has been validated by studying its relation to circulating levels of inflammatory biomarkers in many different populations and DII scores have been associated with level of CRP, as well as a summary score for low-grade inflammation (derived from 6 key inflammatory biomarkers).[10–12]

In the current study, the ISD included 28 dietary components that were available in the EPIC datasets for all centers (listed in Supporting Information Table S1). To calculate each

participant's ISD their intake of each food item was first calibrated using data from the 24-hr recall (full methods are detailed in statistical analysis section) and then standardized using the mean and standard deviation (SD) of the study population. Each participant's *z*-score was then converted to a centered percentile value by transforming it to a percentile (of a standard normal distribution), doubling each percentile and then subtracting 1. To obtain the ISD for each item each percentile value was multiplied by the respective inflammatory effect score, using the item specific weights reported previously[9](Supporting Information Table S1). The separate ISD's obtained for the 28 dietary components for each participant were then summed to give their overall ISD. The overall ISD is a score without units and expresses an individual's diet, relative to the other participants, at a point along on a continuous scale ranging from below to above zero. The most negative value indicates the maximum anti-inflammatory diet in the cohort, while the highest positive value indicates the maximum proinflammatory diet.

The slightly different procedures used to construct the ISD, compared to the DII, have been described and justified previously.[24] In brief, total fat was not included as part of the ISD because the three separate components of dietary fat are already included, a different weight for alcohol was used due to its dose-dependent effect, so for subjects who consumed >40 g/day, the weight for alcohol was set as 0. Finally, each subject's intake for the 28 dietary components was standardized the mean and SD of our study population to improve internal validity, as the aim of our study was to assess the association between the ISD and risk of CRC in this cohort, not to compare the inflammatory potential of the diet between populations.

The inflammatory profile score

An overall inflammatory profile score (IPS)[25] was created to explore the potential relationship between CRC and low-grade inflammation linked to diet along with level of physical activity and abdominal obesity, two additional factors that modulate inflammation. Each subject's IPS is the sum of the three corresponding values obtained from (*i*) the ISD (sex-specific tertiles; 1st tertile = 0, 2nd tertile = 1, 3rd tertile = 2), (*ii*) waist circumference defined using International Diabetes Federation cut-offs (men <94 cm or women <80 cm = 0, and men ≥94 cm or women ≥80 cm = 1) and (*iii*) physical activity level (active or moderately active = 0 and inactive or moderately inactive = 1). Physical activity categories were derived by combining occupational and recreational activity levels and have been previously described and validated.[26] The IPS ranged from 0 to 4, with 0 reflecting less inflammation in terms of consuming an anti-inflammatory diet, not having abdominal obesity and being physically active. In contrast, an IPS of four reflects more inflammation in terms of eating a proinflammatory diet, having abdominal obesity and being physically inactive. Previous research in this population has shown that the ISD is associated with increased risk of gastric cancer and the ISD and IPS with higher mortality, in particular deaths by cardiovascular disease.[24,25]

Statistical analysis

All analyses were carried out using R 3.2.1 software (R Foundation for Statistical Computing, Vienna, Austria). The ISD was described according to sociodemographic, lifestyle and dietary variables using the median, percentiles and age-, sex- and energy-adjusted mean and SD using linear regression. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between ISD and risk of CRC, overall and for anatomical subsites (colon and rectal). Entry time was defined as age at recruitment and exit time was defined as age at diagnosis for cases, death or end of follow-up, whichever occurred first. Multivariable models were stratified by center, sex and age at recruitment (1-year intervals) and adjusted by residuals of total energy intake on the ISD (quartiles), education (none and primary school, technical/professional school, secondary school, university or higher and not specified), smoking status and intensity (never, former quit <11 years, former quit 11–20 years, former quit >20 years, current ≤15 cigarettes/day, current 16–25 cigarettes/day, current >25 cigarettes/day, other smokers including occasional smokers and exclusive smokers of cigar or pipe, and smokers with unknown status or unknown amount), Cambridge physical activity index (inactive, moderately inactive, moderately active, active and not specified), body mass index (BMI; <25.0, 25–29.9 and ≥30.0 kg/m^2) and the residuals of the intake of dietary variables including alcohol (quartiles, g/day), red meat (quartiles, g/day) processed meat (quartiles, g/day) and fiber (quartiles, g/day) intakes. The residuals of a linear regression of the dietary variables on the ISD were included in the multivariable models because these dietary factors are also a source of components included in the ISD.

The ISD was analyzed as a categorical variable, using sex-specific quartiles and with the first quartile as the reference, and as a continuous variable for each increase in 1-SD of the ISD. Trend tests for the categorical variables were calculated by entering the categorical variable in the model as a continuous variable. All analyses were carried out on the whole study sample and by sex. Potential effect modification on the association between the ISD and CRC by the variables in the Cox models was evaluated by including interaction terms between the ISD and these variables, and the likelihood ratio (LR) test assessed the significance of the interaction. Schoenfeld residuals were used to assess that the assumptions of proportional hazards were met. The Wald statistic was applied to assess the homogeneity of the risk between the ISD and colon and rectal cancer. The association between the ISD as a continuous variable and risk of CRC and its subtypes was also examined in analyses stratified by EPIC European region (South, Middle and North), age, smoking status, physical activity, education

Table 1. Main baseline characteristics, number of CRC cases and mean and median of the ISD in the EPIC study

				Inflammatory score of the diet (ISD)		
Baseline characteristics	***n***	**%**	**CRC (RC/CC)**	**Median (P25, P75)**	**Mean (95% CI)[1]**	***p*-value**
Sex						
Men	142,241	29.9	2,589 (1,032/1,557)	−0.46 (−1.56, 0.61)	−0.30 (−0.31, −0.29)	<0.001
Women	333,919	70.1	3,402 (1,062/2,340)	0.94 (−0.24, 1.93)	0.67 (0.67, 0.68)	
European Region[2]						
Northern	137,663	28.9	2,454 (912/1,542)	1.43 (0.32, 2.31)	1.26 (1.25, 1.27)	
Middle	199,891	42.0	2,136 (754/1,382)	−0.15 (−1.38, 0.91)	−0.34 (−0.35, −0.33)	<0.001
Southern	138,606	29.1	1,401 (428/973)	0.64 (−0.59, 1.68)	0.56 (0.55, 0.56)	
Age at recruitment, years						
<55	306,429	64.4	2,328 (898/1,430)	0.47 (−0.88, 1.64)	0.29 (0.28, 0.30)	
55 to <65	137,863	29.0	2,848 (964/1884)	0.56 (−0.58, 1.63)	0.53 (0.52, 0.53)	<0.001
≥65	31,868	6.7	815 (232/583)	0.86 (−0.34, 1.84)	0.66 (0.64, 0.67)	
Smoking status						
Never	233,096	49.0	2,446 (805/1,641)	0.43 (−0.83, 1.48)	0.11 (0.10, 0.12)	
Former	126,822	26.6	2029 (721/1,308)	0.20 (−1.07, 1.43)	0.24 (0.23, 0.25)	<0.001
Current	106,564	22.4	1,425 (545/880)	1.06 (−0.20, 2.18)	1.08 (1.08, 1.09)	
Pipe/cigar/occasional/other	9,678	2.0	91 (23/68)	1.40 (0.28, 2.24)	1.07 (1.04, 1.10)	
Physical activity						
Inactive	99,861	21.0	1,487 (457/1,030)	1.04 (−0.21, 2.01)	0.74 (0.71, 0.75)	
Moderately inactive	156,796	32.9	1954 (662/1,292)	0.47 (−0.76, 1.57)	0.29 (0.29, 0.30)	
Moderately active	125,488	26.4	1,334 (490/844)	0.50 (−0.75, 1.59)	0.34 (0.33, 0.35)	<0.001
Active	85,191	17.9	1,110 (447/663)	−0.07 (−1.29, 1.16)	0.09 (0.08, 0.10)	
Unknown	8,824	1.9	106 (38/68)	1.49 (0.27, 2.48)	1.40 (1.37, 1.43)	
Educational level						
None/Primary	142,782	30.0	2,187 (739/1,448)	1.17 (−0.08, 2.17)	1.00 (0.99, 1.01)	
Technical/professional	105,864	22.2	1,483 (545/938)	0.60 (−0.68, 1.78)	0.48 (0.47, 0.49)	
Secondary	97,204	20.4	935 (325/610)	0.60 (−0.49, 1.53)	0.33 (0.32, 0.34)	<0.001
Higher education	113,379	23.8	1,108 (390/718)	−0.32 (−1.51, 0.82)	−0.33 (−0.34, −0.32)	
Unknown	16,931	3.6	278 (95/183)	0.01 (−1.30, 1.11)	−0.30 (−0.33, −0.28)	
BMI, kg/m^2						
<25.0	246,060	51.7	2,486 (877/1,609)	0.44 (−0.84, 1.53)	0.16 (0.15, 0.16)	
25.0 to <30.0	166,134	34.9	2,503 (898/1,605)	0.53 (−0.73, 1.72)	0.58 (0.57, 0.59)	<0.001
≥30.0	63,966	13.4	1,002 (319/683)	0.87 (−0.44, 1.93)	0.74 (0.73, 0.76)	
Waist circumference (cm)						
<80 women, <94 men	195,633	41.1	2,170 (776/1,394)	0.00 (−1.34, 1.28)	−0.03 (−0.04, −0.02)	
≥80 women, ≥94 men	174,659	36.7	2,944 (1,005/1939)	0.56 (−0.68, 1.70)	0.54 (0.54, 0.55)	<0.001
Unknown	105,868	22.2	877 (313/564)	1.15 (0.26, 2.01)	0.88 (0.87, 0.89)	
Alcohol consumption, g/day[3]						
Nonconsumers	60,724	12.8	718 (221/497)	1.35 (0.27, 2.22)	0.87 (0.86, 0.89)	
Low-moderate	322,940	67.8	3,821 (1,330/2,491)	0.48 (−0.82, 1.62)	0.31 (0.31, 0.32)	<0.001
Moderate-high	92,496	19.4	1,452 (543/909)	0.14 (−1.00, 1.22)	0.32 (0.31, 0.33)	
Fiber intake g/day (quartiles)						
<17.4	119,040	25.0	1,556 (505/1,051)	1.73 (0.76, 2.49)	1.59 (1.58, 1.60)	
17.4–21.8	119,040	25.0	1,492 (533/959)	0.96 (−0.03, 1.80)	0.81 (0.80, 0.82)	<0.001
21.8–27.0	119,040	25.0	1,493 (514/979)	0.25 (−0.76, 1.16)	0.13 (0.12, 0.14)	
≥27.0	119,040	25.0	1,450 (542/908)	−0.96 (−2.01, 0.08)	−0.99 (−1.00, −0.98)	
Red meat intake, g/day (quartiles)						
<16.1	119,108	25.0	1,166 (384/782)	0.22 (−1.48, 1.58)	−0.29 (−0.30, −0.28)	
16.1–34.9	118,974	25.0	1,413 (477/936)	0.79 (−0.45, 1.85)	0.48 (0.47, 0.49)	<0.001

(Continues)

Table 1. Main baseline characteristics, number of CRC cases and mean and median of the ISD in the EPIC study (Continued)

Baseline characteristics	*n*	%	CRC (RC/CC)	Inflammatory score of the diet (ISD)		
				Median (P25, P75)	Mean (95% CI)[1]	*p*-value
34.9–63.1	119,038	25.0	1,634 (553/1,081)	0.73 (−0.43, 1.78)	0.65 (0.64, 0.66)	
≥63.1	119,040	25.0	1,778 (680/1,098)	0.32 (−0.77, 1.34)	0.70 (0.69, 0.70)	
Processed meat intake, g/day (quartiles)						
<10.5	119,040	25.0	1,168 (379/789)	0.15 (−1.47, 1.48)	−0.32 (−0.32, −0.31)	
10.5–24.3	119,040	25.0	1,620 (548/1,072)	0.72 (−0.47, 1.80)	0.42 (0.41, 0.43)	<0.001
24.3–43.9	119,063	25.0	1,623 (588/1,035)	0.73 (−0.40, 1.77)	0.65 (0.64, 0.66)	
≥43.9	119,017	25.0	1,580 (579/1,001)	0.39 (−0.75, 1.52)	0.78 (0.77, 0.79)	

[1]Age, sex, and energy-adjusted means (95 Confidence Levels) obtained from linear regression models.
[2]European regions defined as Northern (Norway, Denmark and Sweden), Middle (United Kingdom, Germany, Holland and EPIC centers in northern France) and Southern (Spain, Italy, Greece and EPIC centers in southern France).
[3]Alcohol consumption: Nonconsumers (<0.1 g/day), low-moderate (<15 g/day women, <30 g/day men), moderate-high (≥15 g/day women, ≥30 g/day men).
Abbreviation: CRC (RC/CC), Colorectal cancer (rectal cancer / colon cancer).

level, BMI, weight circumference, alcohol consumption and intake of processed meat. The heterogeneity of HRs for the ISD across countries was explored with the use of a meta-analytic random-effects model.

The dietary data used to construct the ISD was calibrated to improve the comparability of the dietary data across EPIC centers and to minimize measurement error. Country- and sex-specific linear regression calibration models were applied using the data from the subsample of subjects with 24 hr dietary recalls (24hrDR).[22] To obtain predicted (calibrated) values of dietary intake for all subjects, the 24hrDR measurements were regressed onto the dietary intakes from the questionnaires, while including in the following covariates: total energy intake, age at recruitment, center, education, smoking, BMI and physical activity. The models were weighted by day of the week and season of the year in which the 24hrDR recall was administered. When zero consumption was reported on the main questionnaire, a zero was directly assigned as the calibrated intake. The calibrated values of each food item were used to calculate the ISD. A bootstrap sampling method (with 400 repetitions to ensure stability) was used to compute the mean and SD of the predicted intake of each food item in the ISD.

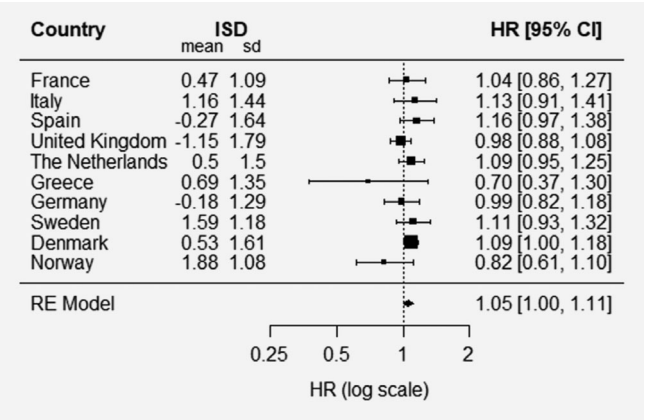

Figure 1. Association between inflammatory score of the diet (ISD) and colorectal cancer and mean ISD (SD) by EPIC country. Hazards ratio (HR; 95% confidence interval) for each 1-SD of the ISD, estimated from Cox model stratified by age, center and sex and adjusted for energy intake (residual), tobacco smoking, physical activity, educational level, BMI, alcohol consumption and intake of red meat, processed meat and fiber. RE model: overall effect from a random effects meta-analysis. Heterogeneity test: Q (9 df) = 9.705, *p*-value = 0.37.

Adjusted HR and 95% CI for CRC were calculated for each of the five levels of the inflammatory profile. Subjects with unknown or missing information on physical activity level and waist circumference (112,654 subjects including 961 CRC cases) were put together in an IPS category labeled "nonspecified" to avoid excluding them from the inflammatory profile analysis. Sensitivity analyses were carried out to assess possible reverse causality caused by modifying habitual diet or lifestyle habits due to pre-existing subclinical conditions, by excluding cases with less than 2 years of follow-up (462 subjects). In addition, the Cox models were repeated using an ISD constructed without the alcohol component, due to its nonlinear relationship with key inflammatory markers.[27,28] Finally, Cox models in women were repeated while additionally adjusting for hormonal factors: menopausal status (premenopausal, postmenopausal, perimenopausal/unknown menopausal status or surgical postmenopausal), hormone replacement therapy (HRT) use (yes, no and unknown) and oral contraceptive use (yes, no and unknown), to evaluate their potential confounding effect in the association of interest.

Data availability

The data that support the findings of our study are available from the corresponding author upon reasonable request.

Results

After following up 476,160 participants (70% women) for a mean of 13.9 years (SD 4.0 years), 5,991 incident primary

Table 2. Adjusted HRs and 95% CI for colorectal cancer, by tumor subsite, according to the Inflammatory Score of the Diet (ISD) in the EPIC study

	Inflammatory Score of the Diet (ISD), HR (95% CI)[1]				ISD continuous[2]	
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-trend	HR (95% CI)
Colorectal cancer, *n*	1,167	1,439	1,517	1,868		
All	Referent	1.09 (1.00, 1.18)	1.12 (1.03, 1.23)	1.15 (1.04, 1.27)	0.009	1.06 (1.01, 1.10)
Men	Referent	1.13 (0.99, 1.29)	1.23 (1.07, 1.41)	1.23 (1.05, 1.44)	0.006	1.08 (1.01, 1.15)
Women	Referent	1.05 (0.95, 1.18)	1.05 (0.93, 1.19)	1.09 (0.95, 1.25)	0.279	1.03 (0.98, 1.10)
Colon cancer, *n*	756	925	952	1,264		
All	Referent	1.09 (0.98, 1.21)	1.11 (0.99, 1.24)	1.24 (1.09, 1.41)	0.001	1.10 (1.04, 1.16)
Men	Referent	1.17 (0.99, 1.40)	1.29 (1.07, 1.54)	1.44 (1.18, 1.76)	<0.001	1.16 (1.07, 1.26)
Women	Referent	1.05 (0.92, 1.20)	1.02 (0.88, 1.18)	1.14 (0.96, 1.35)	0.188	1.06 (0.99, 1.14)
Proximal colon cancer, *n*	350	452	451	624		
All	Referent	1.14 (0.98, 1.32)	1.14 (0.96, 1.34)	1.29 (1.07, 1.55)	0.012	1.13 (1.04, 1.22)
Distal colon cancer, *n*	353	395	438	557		
All	Referent	0.99 (0.84, 1.15)	1.07 (0.91, 1.27)	1.14 (0.94, 1.37)	0.113	1.08 (1.00, 1.17)
Rectal cancer, *n*	411	514	565	604		
All	Referent	1.08 (0.94, 1.24)	1.14 (0.99, 1.33)	0.99 (0.83, 1.17)	0.997	0.98 (0.91, 1.05)
Men	Referent	1.08 (0.88, 1.32)	1.16 (0.94, 1.43)	0.98 (0.77, 1.25)	0.970	0.98 (0.88, 1.08)
Women	Referent	1.07 (0.88, 1.30)	1.13 (0.91, 1.39)	0.98 (0.76, 1.26)	0.983	0.98 (0.88, 1.08)

[1]Multivariate model: stratified by age, sex and center, and adjusted for energy intake (residual), tobacco smoking, physical activity, educational level, BMI, alcohol consumption, and intake of red meat, processed meat and fiber.
[2]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD.

CRC cases were diagnosed (1.02% of women and 1.82% of men developed CRC). Out of these cases, 3,897 were identified as having colon tumors (including 1,877 proximal, 1,743 distal and 277 not specified) and 2,094 as having rectal tumors.

The distribution of the baseline characteristics of the participants according to CRC cases and the ISD (mean and median) is shown in Table 1. At recruitment, approximately half the participants were inactive or moderately inactive and overweight or obese. Almost a quarter of the participants were current smokers and a third had an education level only up to primary school. The ISD, reflecting the inflammatory potential of the diet, had a mean of 0.38 (SD 1.7) and ranged from −6.44 to 5.67, with a median of 0.53 (25th percentile −0.75 and 75th percentile 1.65; data not tabulated). Figure 1 shows the mean ISD scores by EPIC country; the highest mean ISD (most proinflammatory) was in Norway and Sweden, while the United Kingdom and Spain had the lowest mean ISD (most anti-inflammatory). On average, women had a more proinflammatory diet than men and the inflammatory potential of the diet increased across age groups. Overall, the northern EPIC countries had more proinflammatory scores compared to other EPIC regions. The ISD values were higher among smokers and participants with a higher BMI and abdominal obesity and lower in more physically active participants. The score tended to decrease across categories of alcohol consumption and fiber intake.

The multivariable HR for the association between the ISD and CRC overall and by subsites are shown in Table 2. For the whole population, there was a higher risk of CRC associated with higher values of the ISD (reflecting a more proinflammatory diet). The positive association was clear for both categorical and continuous ISD variables. In sex-specific models the higher risk of CRC across quartiles of ISD was evident in men but not in women; HR = 1.23 (95% CI 1.05–1.44) and HR = 1.09 (95% CI 0.95–1.25), respectively. In analyses by anatomical subsite, we observed a strong association between the ISD and colon cancer, and this was more pronounced and only significant in men; HR = 1.24 (95% CI 1.09–1.41) for colon cancer overall HR = 1.44, 95% CI 1.18–1.76) for colon cancer in men, for the highest *versus* lowest ISD quartile. Every 1-SD increase in ISD related to a 10% (HR = 1.10, 95% CI 1.04–1.16) higher risk of colon cancer overall. In the analysis of colon cancer subsites the magnitude of risk appeared higher for proximal compared to distal colon cancer; HR = 1.29 (95% CI 1.07–1.55) and HR = 1.14 (95% CI 0.94–1.37), respectively, for the highest *versus* the lowest ISD quartile (Table 2). No statistically significant associations were observed between the ISD and rectal cancer, overall or by sex. The Wald test indicated there was significant heterogeneity of the association by subsite overall and in men (p-value = 0.01 in both), but not in women (p-value = 0.18). There was no departure from linearity in any of the models, assessed using the likelihood ratio test.

Although the risk estimates varied in analyses stratified by potential effect modifiers (Table 3 shows p values for interaction and Fig. 1 shows the associations between the ISD and CRC by EPIC country), there was little evidence that the association between the ISD and risk of CRC was modified by

Table 3. Adjusted HR and 95% CI for CRC according to cohort subgroups in relation to the Inflammatory Score of the Diet (ISD) in the EPIC study

	Colorectal cancer			Colon cancer			Rectal cancer		
Cohort subgroup	***n*, cases**	**ISD continuous[1] HR (95% CI)**	***p*-value[2]**	***n*, cases**	**ISD continuous[1] HR (95% CI)**	***p*-value[2]**	***n*, cases**	**ISD continuous[1] HR (95% CI)**	***p*-value[2]**
Sex									
Male	2,589	1.08 (1.01, 1.15)	0.159	1,557	1.16 (1.07, 1.26)	0.082	1,032	0.98 (0.88, 1.08)	0.758
Female	3,402	1.03 (0.98, 1.10)		2,340	1.06 (0.99, 1.14)		1,062	0.98 (0.88, 1.08)	
Age, years									
<55	2,328	1.02 (0.95, 1.09)		1,430	1.08 (0.98, 1.18)		898	0.94 (0.84, 1.05)	
55–65	2,848	1.09 (1.03, 1.16)	0.465	1884	1.14 (1.06, 1.23)	0.444	964	1.01 (0.91, 1.12)	0.453
65+	815	1.02 (0.90, 1.14)		583	1.01 (0.88, 1.16)		232	1.04 (0.83, 1.30)	
European region									
North	2,454	1.09 (1.02, 1.17)		1,542	1.17 (1.07, 1.28)		912	0.98 (0.88, 1.09)	
Middle	2,136	1.02 (0.95, 1.09)	0.067	1,382	1.05 (0.97, 1.15)	0.073	754	0.97 (0.87, 1.09)	0.199
South	1,401	1.11 (0.99, 1.24)		973	1.10 (0.96, 1.26)		428	1.14 (0.93, 1.40)	
Smoking status									
Never	2,446	1.00 (0.93, 1.08)		1,641	1.03 (0.94, 1.13)		805	0.96 (0.85, 1.08)	
Former	2029	1.12 (1.04, 1.20)	0.482	1,308	1.14 (1.05, 1.25)	0.918	721	1.07 (0.95, 1.20)	0.309
Smoker	1,425	1.03 (0.95, 1.12)		880	1.15 (1.03, 1.29)		545	0.86 (0.75, 0.99)	
Physical activity									
Inactive	1,487	1.02 (0.93, 1.12)		1,030	1.04 (0.93, 1.16)		457	1.00 (0.85, 1.18)	
Moderately inactive	1954	1.05 (0.97, 1.14)	0.761	1,292	1.14 (1.03, 1.25)	0.847	662	0.92 (0.80, 1.05)	0.285
Moderately active	1,334	1.08 (0.98, 1.19)		844	1.16 (1.03, 1.30)		490	0.98 (0.84, 1.14)	
Active	1,110	1.07 (0.97, 1.17)		663	1.09 (0.96, 1.22)		447	1.04 (0.90, 1.21)	
Educational level									
None/primary	2,187	1.02 (0.94, 1.10)		1,448	1.06 (0.96, 1.17)		739	0.95 (0.83, 1.08)	
Technical/ professional	1,483	1.04 (0.95, 1.13)	0.287	938	1.13 (1.01, 1.26)	0.184	545	0.92 (0.80, 1.05)	0.520
Secondary	935	1.00 (0.89, 1.13)		610	1.03 (0.89, 1.19)		325	0.95 (0.79, 1.16)	
Higher education	1,108	1.19 (1.08, 1.32)		718	1.20 (1.06, 1.36)		390	1.18 (1.00, 1.40)	
BMI, kg/m^2									
<25.0	2,486	1.01 (0.94, 1.08)	0.187	1,609	1.06 (0.97, 1.15)	0.250	877	0.92 (0.82, 1.03)	0.535
≥25.0	3,505	1.11 (1.05, 1.17)		2,288	1.15 (1.08, 1.24)		1,217	1.03 (0.93, 1.13)	
Waist circumference (cm)									
<80 women, <94 men	2,170	1.03 (0.96, 1.10)	0.520	1,394	1.06 (0.97, 1.16)	0.847	776	0.97 (0.86, 1.09)	0.55
≥80 women, ≥94 men	2,944	1.09 (1.03, 1.16)		1939	1.14 (1.05, 1.22)		1,005	1.01 (0.91, 1.12)	
Alcohol consumption, g/day[3]									
Nonconsumers	718	0.98 (0.86, 1.12)		497	0.99 (0.85, 1.16)		221	0.96 (0.76, 1.21)	
Low-moderate	3,821	1.04 (0.98, 1.09)	0.232	2,491	1.09 (1.02, 1.16)	0.317	1,330	0.95 (0.87, 1.04)	0.648
Moderate-high	1,452	1.12 (1.03, 1.21)		909	1.15 (1.03, 1.28)		543	1.06 (0.93, 1.22)	
Processed meat intake, g/day									
Low, <25	2,856	1.03 (0.97, 1.10)		1905	1.08 (1.00, 1.16)		951	0.95 (0.86, 1.05)	
Moderate, 25–50	1860	1.08 (1.00, 1.17)	0.368	1,185	1.09 (0.99, 1.21)	0.082	675	1.07 (0.94, 1.22)	0.568
High, ≥50	1,275	1.07 (0.97, 1.18)		807	1.19 (1.05, 1.36)		468	0.90 (0.76, 1.06)	

[1]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD.
[2]Significance level for the interaction between participant's characteristics and the ISD.
[3]Alcohol consumption: nonconsumers (<0.1 g/day), low-moderate (<15 g/day women, <30 g/day men), moderate-high (≥15 g/day women, ≥30 g/day men).

Table 4. Adjusted HR and 95% CI for CRC according to the inflammatory profile score (IPS)

	Inflammatory profile score (IPS)[1]					
Colorectal cancer	**Level 0 HR (95% CI)**	**Level 1 HR (95% CI)**	**Level 2 HR (95% CI)**	**Level 3 HR (95% CI)**	**Level 4 HR (95% CI)**	***p*-value trend**
Colorectal cancer	352	1,020	1,445	1,423	790	
All	Referent	1.13 (1.00, 1.28)	1.20 (1.05, 1.37)	1.28 (1.11, 1.48)	1.37 (1.16, 1.62)	‹0.001
Men	Referent	1.20 (0.99, 1.45)	1.30 (1.07, 1.58)	1.47 (1.18, 1.82)	1.62 (1.25, 2.09)	‹0.001
Women	Referent	1.06 (0.90, 1.26)	1.11 (0.93, 1.33)	1.11 (0.92, 1.36)	1.17 (0.93, 1.48)	0.195
Colon cancer	200	664	918	945	553	
All	Referent	1.27 (1.08, 1.49)	1.30 (1.09, 1.54)	1.45 (1.20, 1.74)	1.62 (1.31, 2.01)	‹0.001
Men	Referent	1.41 (1.09, 1.83)	1.50 (1.14, 1.97)	1.80 (1.34, 2.41)	2.11 (1.50, 2.97)	‹0.001
Women	Referent	1.16 (0.94, 1.43)	1.15 (0.92, 1.44)	1.21 (0.95, 1.55)	1.32 (0.99, 1.74)	0.102
Rectal cancer	152	356	527	478	237	
All	Referent	0.95 (0.78, 1.15)	1.07 (0.87, 1.32)	1.04 (0.83, 1.31)	1.02 (0.78, 1.35)	0.612
Men	Referent	0.99 (0.75, 1.30)	1.10 (0.82, 1.46)	1.13 (0.82, 1.55)	1.12 (0.76, 1.65)	0.543
Women	Referent	0.91 (0.68, 1.21)	1.05 (0.78, 1.41)	0.94 (0.68, 1.32)	0.91 (0.61, 1.37)	0.903

[1]Inflammatory profile score calculated as Inflammatory Score of the Diet (sex-specific Tertile 1 = 0; Tertile 2 = 1; Tertile 3 = 2) + waist circumference (men ‹ 94 cm and women ‹ 80 cm = 0; men ≥ 94 cm and women ≥ 80 cm = 1) + physical activity (active or moderately active = 0; inactive or moderately inactive = 1).

Table 5. Sensitivity analyses for the association between colorectal cancer, by tumor subsite, according to the Score of the Diet (ISD) in the EPIC study

	Inflammatory Score of the Diet (ISD), HR (95% CI)[1]				ISD continuous[2]	
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***p*-trend**	**HR (95% CI)**
Excluding first 2 year follow-up[3]						
Colorectal cancer	Referent	1.08 (0.99, 1.18)	1.12 (1.02, 1.23)	1.16 (1.04, 1.29)	0.007	1.06 (1.02, 1.11)
Colon cancer	Referent	1.11 (0.99, 1.23)	1.12 (0.99, 1.26)	1.26 (1.11, 1.44)	0.001	1.11 (1.05, 1.17)
Rectal cancer	Referent	1.03 (0.89, 1.20)	1.12 (0.96, 1.31)	0.98 (0.82, 1.18)	0.925	0.98 (0.91, 1.06)
ISD excluding alcohol[4]						
Colorectal cancer	Referent	1.08 (1.00, 1.18)	1.10 (1.01, 1.21)	1.15 (1.04, 1.27)	0.012	1.05 (1.01, 1.10)
Colon cancer	Referent	1.09 (0.98, 1.21)	1.10 (0.98, 1.23)	1.25 (1.11, 1.42)	0.001	1.10 (1.04, 1.16)
Rectal cancer	Referent	1.08 (0.94, 1.24)	1.12 (0.96, 1.29)	0.97 (0.81, 1.15)	0.756	0.98 (0.91, 1.05)
Additional adjustment in women[5]						
Colorectal cancer	Referent	1.05 (0.94, 1.17)	1.05 (0.93, 1.18)	1.08 (0.94, 1.24)	0.328	1.03 (0.97, 1.09)
Colon cancer	Referent	1.04 (0.92, 1.19)	1.02 (0.88, 1.17)	1.13 (0.95, 1.33)	0.224	1.06 (0.99, 1.14)
Rectal cancer	Referent	1.07 (0.88, 1.30)	1.12 (0.91, 1.39)	0.98 (0.76, 1.26)	0.955	0.97 (0.88, 1.08)

[1]Multivariate model: stratified by age, sex and center and adjusted for energy intake (residual), tobacco smoking, physical activity, educational level, BMI, alcohol consumption and intake of red meat, processed meat and fiber.
[2]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD.
[3]Multivariate model excluding incident cases occurring during the first 2 years of follow-up.
[4]Multivariate model with the ISD calculated without including the alcohol component.
[5]Multivariate model in women with additional adjustment for hormone replacement therapy, menopausal status and contraceptive pill use.

these factors, except for a possible suggestion of interaction by sex (*p*-interaction 0.082), region (*p*-interaction 0.073) and processed meat (*p*-interaction 0.082). Within these respective subgroups, the association was only observed in men, Northern EPIC regions and individuals with a high intake of processed meat.

Table 4 shows the association between CRC and the IPS. Participants classified as having level 4 on the IPS had significantly higher risk of developing CRC compared to subjects classified in level 0 (HR = 1.37, 95% 1.16–1.62). This association was more pronounced in men (HR 1.62 (95% CI 1.25–2.09 for highest *versus* lowest IPS) and was not significant in women. A similar pattern was observed in analyses of colon cancer, although the positive association was even stronger, especially in men.

In sensitivity analyses excluding participants with less than 2 years of follow-up, excluding the alcohol component from the ISD or additionally adjusting for hormone-related factors

in women, the risk estimates did not change substantially (Table 5).

Discussion

The results of our study show that a proinflammatory diet, assessed using the ISD, was related to a higher risk of developing CRC in an adult European population. In this cohort, the diet's inflammatory potential was related to colon cancer but not rectal cancer and the association was more pronounced in men. When the inflammatory potential of the diet was combined with two other potential contributors to low-grade chronic inflammation to create an inflammatory profile, then the impact on risk of CRC, in particular, colon cancer, was even greater. Individuals with a high inflammatory profile, defined as a more proinflammatory diet, a sedentary or moderately inactive lifestyle and also abdominal obesity, had a 37% higher risk of colon cancer compared to subjects with a low inflammatory profile (more anti-inflammatory diet, moderate or high physical activity levels and without abdominal obesity).

Overall, our results are in agreement with four recent meta-analyses of the association between CRC and the inflammatory potential of the diet, measured using the DII.[13–15,29] The meta-analyses including all study designs (up to five case–control and four prospective cohort studies) reported an approximately 40% increased risk of CRC associated with being in the highest compared to the lowest DII score category, which is much larger than the 15% increased risk of CRC observed in our study. However, when the meta-analyses were stratified by study design the summary risk estimate obtained from cohort studies was much lower than that from case–control studies.[12,13] Results from case–control studies may be less reliable due to their susceptibility to recall and selection bias, and so our results are more comparable to other prospective studies. The summary relative risks for CRC derived from cohort studies for a 1-unit increment in the DII ranged from 3% (95% CI 2–4%)[14] to 4% (95% CI 3–5%),[29] that was fairly similar in magnitude to the 6% found in our study.

In analyses stratified by anatomical subsite, it was clear that the association between the ISD and risk of CRC was driven by the results for colon cancer; the highest category of the ISD significantly increased the risk of colon cancer by 24% while there was no association with rectal cancer. In addition, the Wald test results confirmed that the differential effect of the ISD by subsite was statistically significant. The magnitude of the association we observed is comparable to that reported in the multiethnic cohort, where participants in the highest DII quartile were 20% more likely to develop colon cancer than participants in the lowest quartile.

The differing results by anatomical sites in our study are consistent with findings from two other prospective studies, the Iowa Women's Study[18] and Women's Health Initiative,[30] which found evidence of an association between the DII and colon cancer, but not rectal cancer. In contrast, two other prospective studies, the NIH-AARP study and multiethnic cohort, did observe that the DII was significantly related to risk of rectal cancer. The explanation for these disparities is unclear, but could partly relate to differences in cohort characteristics or methodological issues between studies, such as adjustment for confounding factors or which dietary components were used to calculate the diet's inflammatory potential. In addition, although CRC is often considered a single tumor entity in research and clinical practice, the two anatomical subsites differ in numerous epidemiological features, their molecular carcinogenesis[31] and their risk factors.[5,32,33] In terms of dietary risk factors, a meta-analysis of the evidence on red and processed meat, whole-grains and dairy products found that the summary relative risks were significant for colon cancer but not rectal cancer.[2] Such etiological differences between subsites may also extend to the differential impact of the inflammatory potential of the diet on developing colon and rectal cancer.

In our population, the positive association between the ISD and colon cancer was more pronounced and only statistically significant in men. These findings are in line with the NIH-AARP study[34] which found that the association between the DII and CRC was also only statistically significant in men, and in the multiethnic cohort[35] where the effect size was larger for men than women. In addition, a meta-analysis of both case–control and cohort studies reported that the pooled relative risk (RR) of CRC in men was double that in women.[14] The explanation of why some studies, including ours, observe weaker and/or nonsignificant associations in women is unclear, but several theories can be considered. CRC is strongly influenced by gender, illustrated by substantial differences between sexes in incidence, survival and various clinical and pathological characteristics.[36] This has been partly attributed to sex differences in biological and environmental risk factors.[37] In terms of hormonal influences, estrogen plays an important protective role in the pathogenesis of CRC in women,[38] therefore menopause-related changes in estrogen levels and HRT might be potential confounders of the ISD-CRC association.[38,39] However, in sensitivity analyses, the lack of association in women remained identical after additionally adjusting for menopausal status, HRT and oral contraceptive pill use. Nevertheless, other hormonal-related factors might not have been accounted for. Alternatively, because the incidence of CRC is higher in men,[37] the inflammatory potential of the diet might have a greater impact in men due to a higher background risk. In line with our findings, the World Cancer Research Fund/ American Institute for Cancer Research 2017 CRC report presents meta-analyses of several foods that were significantly related to increased/ decreased risk of CRC in men (red and processed meat/fruit and nonstarch vegetables) but did not reach statistical significance in women.[2] Finally, we cannot rule out gender differences in unmeasured risk factors, or in dietary intake reporting[40] and social desirability[41] that could introduce measurement error in estimating the ISD and confounding variables.

A novel aspect of our work was the construction of an IPS, a combination of the inflammatory potential of the diet, physical activity and abdominal obesity. Low-grade chronic inflammation, a state of persistent and unresolved inflammation, is characterized by modestly elevated levels of proinflammatory markers. The DII has been associated with higher concentrations of inflammatory biomarkers such as CRP, Interleukin (IL)-6, and homocysteine,[10,11] as well as a low-grade inflammation summary score.[12] The abundance of inflammatory cells in visceral adipose tissue leads to systemic inflammation[18] and abdominal obesity is associated with elevated levels of tumor necrosis factor-α and high-sensitivity C-reactive protein (CRP).[42] On the other hand, regular physical exercise is associated with lower levels of inflammatory markers such as IL-6 and CRP.[43] In our study, a proinflammatory profile, characterized by a more proinflammatory diet, lower levels of physical activity and abdominal obesity was a strong predictor of CRC, particularly colon cancer and in men. The differences by anatomical site probably reflect the strong evidence that physical activity protects against colon but not rectal cancer and that obesity may have a stronger negative impact on colon cancer.[2] The differential association between the ISD and the IPS and risk of colon and rectal cancer supports the fact that CRC is a heterogeneous group of diseases that should be investigated separately.[44]

The biological plausibility behind these findings is supported by the fact that chronic inflammation is a well-documented pathological feature of colon cancer.[5,45] This is supported by the evidence that prolonged use of aspirin and other nonsteroidal anti-inflammatory drugs reduces risk of colon cancer,[2] whereas inflammatory bowel disease is a known cause of colon cancer.[46] In addition, a meta-analysis of 18 studies showed that a 1-unit increase in the natural logarithm (ln) of CRP related to a 13% increased risk of colon cancer, while no significant association was found with rectal cancer or in women.[47] The speculated inflammatory pathways could involve the effect of proinflammatory diets, abdominal obesity or low levels of physical activity on systemic inflammation, which can lead to insulin resistance.[48] Another hypothesis is related to the anti-inflammatory effects on local mircrobiota from omega-3 fatty acids and antioxidant components in certain foods (i.e., fruit, vegetables, tea and coffee).[49] In addition, dietary factors can affect local inflammation and oxidation in the colon which leads to focal proliferation, angiogenesis and mutagenesis.[48]

Strengths of the study are its large sample size, prospective and population-based design, extended follow-up and a large number of cases, allowing sufficient statistical power to explore gender- and site-specific associations and additional subgroup analyses. We also adjusted for multiple potential confounding factors, including the residuals of red meat, processed meat and fiber. These dietary factors are important sources of items included in the calculation of the ISD, and therefore including them directly in the model, along with the ISD, could result in over-adjustment or collinearity. However, excluding them could produce residual confounding because they are strongly related to CRC, operating through mechanisms other than inflammation.[2] To resolve these issues we calculated the residuals of a linear regression of the ISD on each dietary variable to use in the multivariable model. This ensured that the HR of the ISD was solely due to the inflammatory potential of the diet and that confounding by other dietary factors *via* noninflammatory mechanisms was still controlled for.

There are also several limitations that should be considered when interpreting the results, mainly due to methodological issues relating to the construction of the ISD score. First, only 28 of the original 45 items included in the DII were used to create the ISD. This was due to the availability of dietary data in the EPIC database and our exclusion of total fat. However, a previous cohort study found that seven components, all of which were included in the ISD, explained 91% of the inter-individual variance in the DII.[12] Therefore, the fewer number of dietary components included in the ISD is likely to have had minimal influence on the estimations of the diet's total inflammatory potential. Second, since the construction of the ISD is based on the DII, it has similar inherent methodological limitations,[8] one of which is that the ISD is constructed using inflammatory weights derived from data from other studies and so does not directly relate to inflammatory biomarkers measured in our specific population. Thus, further studies that assess the inflammatory potential of the diet based on alternative methods from DII would help corroborate our findings. Third, potential measurement error derived from self-reported country-specific dietary questionnaires could have led to systematic and random errors in the dietary data used to construct the ISD. However, subjects with implausible dietary intake were excluded from the analyses and we adjusted for total energy intake. We also used models stratified by country/center to account for potential systematic between-country differences in dietary assessment and used calibrated dietary intakes (from the 24hDR) to calculate the ISD. In addition, comparability of nutrient intakes across the EPIC countries has been improved through harmonizing nutrient databases.[23] A further limitation is that diet and lifestyle variables were only assessed at recruitment, so any potential changes during follow-up were not taken into account. Potential reverse causality due to modification of diet during the early prediagnostic period of the disease is also possible, however, in sensitivity analyses, the associations did not materially change when we excluded incident cases diagnosed in the first 2 years of follow-up. We also lacked information on the use of anti-inflammatory drugs[50] and supplements.

In summary, our results show that a diet with a higher inflammatory potential is associated with increased risk of CRC, particularly colon cancer among men. In addition, an inflammatory profile incorporating the inflammatory potential of the diet, physical activity and abdominal obesity, was a

strong predictor of colon cancer. Public health initiatives that jointly target these modifiable risk factors may be particularly effective for preventing colon cancer. Future research should identify specific dietary patterns that are related to plasma levels of inflammatory biomarkers in the same population (using reduced rank regression). Studying biomarker patterns and CRC risk[51] also takes into account complex interactions between biomarkers and would help clarify the pathways involved.

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Conflict of interest

None declared.

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