Supplementary Online Content

Supplementary Methods.

Supplementary Table 1. The Food Components of the Empirical Dietary Inflammatory Pattern (EDIP)

Supplementary Table 2. Age-adjusted Baseline Characteristics of Participants across Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores in the Nurses' Health Study (Women, 1984) and the Health Professionals Follow-up Study (Men, 1986)

Supplementary Table 3. Postdiagnostic Empirical Dietary Inflammatory Pattern Scores and Colorectal Cancer Mortality in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men)

Supplementary Table 4. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Components of Lymphocytic Reaction in the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men) Separately

Supplementary Table 5. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Microsatellite Instability Status in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men)

Supplementary Table 6. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Components of Lymphocytic Reaction in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men) by Further Adjustment for Body Mass Index

Supplementary Table 7. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Peritumoral Lymphocytic Reaction in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professional Follow-up Study (Men) by Adjustment for Different Covariates

Supplementary Table 8. Quartiles of Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Components of Lymphocytic Reaction in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men)

Supplementary Table 9. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Components of Lymphocytic Reaction in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men) Estimated by Marginal Structural Cox Proportional Hazards Regression Models

Supplementary Figure 1. Patterns of lymphocytic reaction to colorectal cancer. A Crohn's-like lymphoid reaction, characterized by discrete, well-formed lymphoid aggregates (arrows) associated with the tumor but separated from the invasive front (A). Peritumoral lymphocytic reaction, characterized by a band-like lymphocytic infiltrate

(arrows) at the invasive tumor front (B). Intratumoral periglandular reaction, characterized by lymphocytes within the tumor stroma (arrows) surrounding neoplastic glands (C). Tumor-infiltrating lymphocytes (arrows), defined as lymphocytes present on top of neoplastic tumor epithelium (D).

Supplementary Methods

Construction of Empirical Dietary Inflammatory Pattern (EDIP) Scores

Based on food frequency questionnaires administered to all participants, we calculated the diet frequencies of 18 food groups in each day (serving/day), including processed meat, red meat, organ meat, other fish, other vegetable, refined grain, high energy beverage, low energy beverage, tomato, beer, wine, tea, coffee, dark yellow vegetable, green leafy vegetable, snack, fruit juice and pizza. The construction of the empirical dietary inflammatory index was based on the frequency of each food group as the following formula: EDIP score=(165.03443 × processed meat) + (140.19344 × red meat) + (144.60554 × organ meat) + (252.44533 × other fish) + (136.14430 × other vegetables) + (81.21217 × refined grain) + (156.84543 × high energy beverage) + (94.77015 × low energy beverage) + (167.91804 × tomato) - (136.99127 × beer) - (249.70411 × wine) - (42.25228 × tea) - (83.17692 × coffee) - (165.37317 × dark yellow vegetable) - (190.28539 × green leafy vegetable) - (45.08391 × snack) - (58.94952 × fruit juice) - (1175.21060 × pizza).[1] The detailed components in each food group are listed as **Supplementary Table 1**.

The Assessment of Lymphocytic Reaction to Tumor

Crohn's-like lymphoid reaction was defined as transmural lymphoid reaction. Peritumoral lymphocytic reaction was defined as discrete lymphoid reactions surrounding tumor. Intratumoral periglandular reaction was defined as lymphocytic reaction in tumor stroma within tumor mass. Tumor-infiltrating lymphocytes were defined as lymphocytes on top of cancer cells (**Supplementary Figure 1**). For any given tumor, each of the 4 lymphocytic reaction patterns was scored as 0 (absent/low), 1+ (intermediate), 2+ (moderate) or 3+ (marked).[2] Since the sample size of moderate and marked scores in each lymphocytic reaction pattern was relatively small, we combined them into one category in our analysis.

The Assessment of Tumor Microsatellite Instability (MSI), CpG Island Methylator Phenotype (CIMP), *BRAF* Mutation and PTGS2 Expression

MSI status was determined using 10 microsatellite markers, D2S123, D5S346, D17S250, BAT25, BAT26, BAT40, D18S55, D18S56, D18S67 and D18S487.[3] MSI-high was defined as the presence of instability in ≥ 30% of the markers, non-MSI-high as no or < 30% unstable markers. CpG island methylator phenotype was determined by promoter methylation in 8 CIMP-specific genes (*CACNA1G*, *CDKN2A*, *CRABP1*, *IGF2*, *MLH1*, *NEUROG1*, *RUNX3* and *SOCS1*).[4-6] CIMP-high was defined as ≥ 6/8 methylated promoters using the 8-marker CIMP panel, CIMP-low/negative as 0 to 5 methylated promoters, according to the previously established criteria.[5] DNA from paraffin-embedded tissues was extracted, and PCR and Pyrosequencing targeted for *BRAF* codon 600 were performed.[7] PTGS2 expression was detected by immunohistochemical technique and classified into absent, weak, moderate or strong degree according to the expression intensity. Cancers with no immunohistochemical PTGS2 staining or with staining of weak intensity were classified as PTGS2-negative cancers. Cancers with immunohistochemical PTGS2 staining of moderate to strong intensity were classified as PTGS2-positive cancers.[8]

References

1. Tabung FK, Smith-Warner SA, Chavarro JE, et al. Development and Validation of an Empirical Dietary Inflammatory Index. J Nutr 2016;146:1560-1570.

2. Ogino S, Nosho K, Irahara N, et al. Lymphocytic reaction to colorectal cancer is associated with longer survival, independent of lymph node count, microsatellite instability, and CpG island methylator phenotype. Clin Cancer Res 2009;15:6412-6420.

3. Ogino S, Brahmandam M, Cantor M, et al. Distinct molecular features of colorectal carcinoma with signet ring cell component and colorectal carcinoma with mucinous component. Mod Pathol 2006;19:59-68.

4. Ogino S, Cantor M, Kawasaki T, et al. CpG island methylator phenotype (CIMP) of colorectal cancer is best characterised by quantitative DNA methylation analysis and prospective cohort studies. Gut 2006;55:1000-1006.

5. Ogino S, Kawasaki T, Kirkner GJ, et al. Evaluation of markers for CpG island methylator phenotype (CIMP) in colorectal cancer by a large population-based sample. J Mol Diagn 2007;9:305-314.

6. **Weisenberger DJ**, **Siegmund KD**, Campan M, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. Nat Genet 2006;38:787-793.

7. Ogino S, Kawasaki T, Kirkner GJ, et al. CpG island methylator phenotype-low (CIMP-low) in colorectal cancer: possible associations with male sex and KRAS mutations. J Mol Diagn 2006;8:582-588.

8. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 2007;356:2131-2142.

Author names in bold designate shared co-first authorship.

Supplementary Table 1. The Food Components of the Empirical Dietary Inflammatory Pattern (EDIP)

EDIP Component	Food Item
Positive association	
Processed meat	hot dogs, processed meats (including processed meat sandwich), bacon
Red meat	hamburger, beef /pork /lamb sandwich, beef /pork/ lamb main dish
Organ meat	livers
Other fish	canned tuna, shrimp, breaded fish, lobster, scallops or other seafood
Other vegetables	corn, mixed vegetables, eggplant, celery, alfalfa sprouts, mushrooms, green/yellow/red peppers, zucchini, cucumbers
Refined grain	white bread, white rice, bagels/English muffins/rolls, muffins or biscuits, pasta, pancakes or waffles, refined cold breakfast cereals
High energy beverage	cola, Hawaiian punch, caffeine-free coke, pepsi, carbonated beverage with caffeine and sugar, other carbonated beverage with sugar
Low energy beverage	low calorie cola, low calorie caffeine -free cola, low calorie beverage with caffeine, other low calorie carbonated beverage, other low calorie beverage without caffeine
Tomato	fresh tomatoes, tomato juice, tomato sauce
Inverse association	
Beer	beer, light beer
Wine	white wine, red wine
Tea	tea, tea (not herbal)
Coffee	coffee, decaffeinated coffee
Dark yellow vegetable	carrots, sweet potatoes, winter squash
Green leafy vegetable	spinach, iceberg lettuce, romaine lettuce
Snack	potato/corn chips, popcorn, crackers
Fruit juice	apple juice, orange juice, grape juice, prune juice, other juice
Pizza	pizza

Supplementary Table 2. Age-adjusted Baseline Characteristics of Participants across Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores in the Nurses' Health Study (Women, 1984) and the Health Professionals Follow-up Study (Men, 1986)[a]

Characteristic	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores									
	Women (NHS)					Men (HPFS)				
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)
Participants, No.	15,422	15,367	15,370	15,399	15,459	9,642	9,515	9,394	9,484	9,381
Age, years[b]	51.1 (6.9)	51.3 (7.1)	51.1 (7.3)	50.8 (7.2)	50.0 (7.3)	53.2 (9.1)	54.6 (9.7)	54.8 (9.8)	55.2 (10.0)	54.2 (10.0)
Race (white), %	99	98	98	97	96	93	92	91	90	89
Body mass index, kg/m^2	23.8 (3.7)	24.3 (4.0)	24.9 (4.4)	25.6 (5.0)	26.7 (5.7)	25.3 (3.0)	25.3 (3.1)	25.4 (3.1)	25.5 (3.3)	26.1 (3.7)
Family history of colorectal cancer, %	8	8	8	8	8	9	9	8	8	8
Smoking, pack-years	15.5 (18.7)	12.9 (17.4)	11.4 (17.0)	10.6 (16.7)	11.5 (17.6)	16.7 (20.4)	13.6 (18.5)	12.1 (17.9)	12.1 (18.6)	12.6 (19.1)
Waist hip ratio	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.6 (0.4)	0.6 (0.4)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)
Energy intake, kcal/day	1622 (438)	1581 (427)	1601 (436)	1656 (445)	1836 (483)	1990 (598)	1882 (575)	1857 (573)	1948 (607)	2255 (659)
Total activity, METS - hours/week[c]	16.2 (24.6)	14.6 (20.3)	14.0 (21.2)	13.3 (19.6)	12.4 (18.4)	20.3 (26.3)	19.7 (26.9)	18.3 (24.5)	17.9 (25.7)	17.4 (26.0)
Current multivitamin use, %	39	39	37	36	34	44	43	43	41	38
History of endoscopy, %	54	55	56	55	55	27	27	25	26	24
Total alcohol intake, g/day	12.3 (13.8)	6.8 (9.2)	5.4 (8.5)	4.4 (7.8)	4.1 (8.3)	21.2 (20.7)	11.9 (13.9)	9.0 (12.3)	7.5 (11.5)	6.8 (12.1)
Regular aspirin use, %[d]	39	39	39	39	42	31	30	29	28	29
Postmenopausal hormone use, %[e]	46	45	46	46	45	-	-	-	-	-
Food group components of the empirical dietary inflammatory pattern										
Processed meat, serving/day	0.23 (0.24)	0.25 (0.24)	0.28 (0.27)	0.33 (0.31)	0.47 (0.49)	0.28 (0.31)	0.29 (0.31)	0.31 (0.34)	0.37 (0.37)	0.56 (0.65)
Red meat, serving/day	0.54 (0.34)	0.57 (0.35)	0.60 (0.37)	0.67 (0.39)	0.81 (0.48)	0.51 (0.38)	0.52 (0.39)	0.55 (0.41)	0.63 (0.43)	0.83 (0.59)
Organ meat, serving/day	0.02 (0.04)	0.02 (0.04)	0.02 (0.04)	0.03 (0.04)	0.03 (0.05)	0.01 (0.03)	0.02 (0.04)	0.02 (0.04)	0.02 (0.04)	0.02 (0.04)
Other fish, serving/day	0.26 (0.21)	0.26 (0.21)	0.27 (0.22)	0.29 (0.24)	0.34 (0.31)	0.29 (0.23)	0.30 (0.23)	0.30 (0.24)	0.34 (0.27)	0.39 (0.39)

Continued

Characteristic	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores									
	Women (NHS)					Men (HPFS)				
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)
Other vegetable, serving/day	0.79 (0.64)	0.76 (0.56)	0.79 (0.59)	0.82 (0.63)	0.98 (0.95)	0.78 (0.64)	0.77 (0.61)	0.77 (0.61)	0.83 (0.65)	0.99 (0.89)
Refined grain, serving/day	0.92 (0.72)	1.02 (0.78)	1.16 (0.91)	1.36 (1.03)	1.87 (1.36)	0.91 (0.76)	0.97 (0.81)	1.06 (0.89)	1.27 (1.05)	1.89 (1.55)
High energy beverage, serving/day	0.13 (0.26)	0.17 (0.30)	0.22 (0.37)	0.30 (0.46)	0.66 (1.02)	0.17 (0.30)	0.21 (0.35)	0.26 (0.41)	0.35 (0.50)	0.73 (1.01)
Low energy beverage, serving/day	0.38 (0.67)	0.42 (0.67)	0.48 (0.75)	0.63 (0.93)	1.18 (1.68)	0.32 (0.62)	0.37 (0.69)	0.41 (0.71)	0.50 (0.84)	0.90 (1.57)
Tomato, serving/day	0.50 (0.38)	0.50 (0.37)	0.52 (0.37)	0.57 (0.41)	0.71 (0.64)	0.53 (0.43)	0.53 (0.42)	0.54 (0.40)	0.60 (0.45)	0.78 (0.74)
Beer, serving/day	0.21 (0.69)	0.09 (0.32)	0.06 (0.24)	0.04 (0.19)	0.03 (0.18)	0.65 (1.14)	0.29 (0.54)	0.19 (0.39)	0.15 (0.35)	0.12 (0.29)
Wine, serving/day	0.68 (0.96)	0.25 (0.37)	0.17 (0.28)	0.12 (0.21)	0.09 (0.19)	0.64 (0.96)	0.26 (0.36)	0.17 (0.26)	0.12 (0.21)	0.09 (0.19)
Tea, serving/day	0.72 (1.23)	0.72 (1.19)	0.70 (1.13)	0.68 (1.09)	0.65 (1.06)	0.48 (1.01)	0.45 (0.89)	0.42 (0.82)	0.41 (0.80)	0.40 (0.80)
Coffee, serving/day	4.03 (2.01)	3.03 (1.79)	2.27 (1.64)	1.76 (1.53)	1.36 (1.44)	3.45 (2.13)	2.34 (1.75)	1.67 (1.55)	1.29 (1.42)	1.07 (1.32)
Dark yellow vegetable, serving/day	0.37 (0.45)	0.31 (0.29)	0.29 (0.27)	0.28 (0.26)	0.27 (0.25)	0.38 (0.52)	0.33 (0.35)	0.31 (0.31)	0.30 (0.29)	0.30 (0.30)
Green leafy vegetable, serving/day	1.12 (0.94)	0.86 (0.59)	0.78 (0.54)	0.72 (0.51)	0.70 (0.53)	0.93 (0.86)	0.77 (0.60)	0.68 (0.51)	0.65 (0.49)	0.63 (0.53)
Snack, serving/day	0.88 (1.38)	0.64 (0.96)	0.56 (0.82)	0.53 (0.75)	0.56 (0.76)	0.67 (0.97)	0.55 (0.74)	0.51 (0.65)	0.50 (0.59)	0.55 (0.66)
Fruit juice, serving/day	0.81 (0.92)	0.76 (0.79)	0.73 (0.72)	0.70 (0.67)	0.68 (0.69)	0.90 (1.17)	0.83 (0.86)	0.77 (0.74)	0.73 (0.71)	0.72 (0.77)
Pizza, serving/day	0.08 (0.10)	0.07 (0.07)	0.06 (0.06)	0.06 (0.06)	0.06 (0.06)	0.12 (0.15)	0.08 (0.09)	0.07 (0.08)	0.07 (0.07)	0.06 (0.07)

Abbreviation: HPFS, Health Professionals Follow-up Study; METS, metabolic equivalent task score; NHS, Nurses' Health Study.

[a] The mean ± standard deviation (SD) for continuous variables and percentage for categorical variables.

[b] All variables are age standardized except age.

[c] Physical activity is represented by the product sum of the METS of each specific recreational activity and hours spent on that activity per week.

[d] A standard tablet contains 325 mg aspirin, and regular users were defined as those who used at least two tablets per week.

[e] Proportion of postmenopausal hormone use was calculated among postmenopausal women only.

Supplementary Table 3. Postdiagnostic Empirical Dietary Inflammatory Pattern Scores and Colorectal Cancer Mortality in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men)

		Colorectal cancer-specific mortality			Overall mortality		
EDIP scores	N of cases[a]	N of events	Univariable HR[b] (95% CI)	Multivariable HR[bc] (95% CI)	N of events	Univariable HR[b] (95% CI)	Multivariable HR[bc] (95% CI)
Tertile 1	412	53	1 (referent)	1 (referent)	182	1 (referent)	1 (referent)
Tertile 2	326	63	1.54 (1.06-2.24)	1.52 (1.04-2.23)	168	1.31 (1.05-1.62)	1.29 (1.03-1.61)
Tertile 3	382	62	1.27 (0.87-1.84)	1.21 (0.82-1.78)	198	1.42 (1.16-1.75)	1.43 (1.15-1.77)
Per tertile increase			1.12 (0.93-1.33)	1.09 (0.91-1.31)		1.19 (1.08-1.32)	1.19 (1.07-1.33)
P_{trend}[d]			.23	.36		<.001	.002

Abbreviations: CI, confidence interval; EDIP, empirical dietary inflammatory pattern; HR, hazard ratio.

[a] Survival analyses were restricted in colorectal cancer cases with lymphocytic reaction status.

[b] All analyses were stratified by age group at diagnosis, tumor stage and sex.

[c] The multivariable HRs were further adjusted for age at diagnosis, year of diagnosis, tumor stage, tumor location, tumor differentiation, family history of colorectal cancer, prediagnostic empirical dietary index pattern scores (tertiles), postdiagnostic aspirin use, postdiagnostic pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), postdiagnostic alcohol use (0 vs. 1-5 vs. 6-15 vs. >15 g/day), postdiagnostic body mass index (<25 vs. 25-29.9 vs. ≥30kg/m^2) and postdiagnostic physical activity [0-3 vs. >3-9 vs. >9-18 vs. >18 mean metabolic equivalent task score (METS) - hours per week].

[d] Trend test for each tertile increase of EDIP score.

Supplementary Table 4. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Components of Lymphocytic Reaction in the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men) Separately

Analysis	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores					P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)		
Women (NHS)							
Person-years	405,701	406,676	378,177	394,498	375,243		
Overall colorectal cancer							
N of cases (n=676)	152	127	142	132	123		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.76 (0.64-0.90)	0.91 (0.77-1.07)	0.88 (0.75-1.04)	0.97 (0.82-1.15)	.81	
Multivariable HR (95% CI)[d]	1 (referent)	0.77 (0.65-0.92)	0.92 (0.77-1.09)	0.89 (0.75-1.05)	0.96 (0.80-1.14)	.93	
Crohn's-like lymphoid reaction							.85
Absent/low							
N of cases (n=431)	94	81	96	83	77		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.83 (0.61-1.12)	0.96 (0.72-1.29)	0.87 (0.64-1.18)	0.97 (0.71-1.31)	.90	
Multivariable HR (95% CI)[d]	1 (referent)	0.84 (0.62-1.14)	0.97 (0.72-1.30)	0.88 (0.64-1.19)	0.96 (0.70-1.31)	.90	
Intermediate							
N of cases (n=88)	20	20	10	19	19		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.83 (0.44-1.55)	0.56 (0.27-1.19)	0.97 (0.52-1.81)	1.17 (0.63-2.20)	.54	
Multivariable HR (95% CI)[d]	1 (referent)	0.83 (0.44-1.55)	0.56 (0.26-1.20)	0.97 (0.51-1.83)	1.15 (0.61-2.18)	.58	
High							
N of cases (n=47)	11	7	10	10	9		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.52 (0.20-1.36)	0.79 (0.32-1.91)	0.88 (0.36-2.12)	0.98 (0.39-2.44)	.89	
Multivariable HR (95% CI)[d]	1 (referent)	0.53 (0.21-1.39)	0.80 (0.33-1.92)	0.88 (0.36-2.14)	0.97 (0.39-2.39)	.91	
Peritumoral lymphocytic reaction							.16
Absent/low							
N of cases (n=91)	17	17	18	19	20		
Age-adjusted HR (95% CI)[c]	1 (referent)	1.15 (0.58-2.27)	1.24 (0.63-2.44)	1.28 (0.66-2.47)	1.71 (0.89-3.29)	.13	
Multivariable HR (95% CI)[d]	1 (referent)	1.17 (0.59-2.31)	1.25 (0.63-2.46)	1.30 (0.67-2.55)	1.69 (0.88-3.27)	.13	
Intermediate							
N of cases (n=465)	115	85	94	86	85		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.65 (0.48-0.87)	0.76 (0.57-1.01)	0.73 (0.54-0.98)	0.84 (0.63-1.12)	.36	
Multivariable HR (95% CI)[d]	1 (referent)	0.66 (0.49-0.89)	0.77 (0.58-1.03)	0.74 (0.55-0.99)	0.82 (0.61-1.11)	.34	
High							
N of cases (n=116)	20	23	29	27	17		
Age-adjusted HR (95% CI)[c]	1 (referent)	1.03 (0.56-1.89)	1.44 (0.81-2.56)	1.42 (0.79-2.54)	1.03 (0.53-2.00)	.45	
Multivariable HR (95% CI)[d]	1 (referent)	1.03 (0.56-1.89)	1.44 (0.81-2.55)	1.39 (0.77-2.50)	0.99 (0.51-1.92)	.52	

Continued

Analysis	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores					P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)		
Intratumoral periglandular reaction							.13
Absent/low							
N of cases (n=85)	16	14	18	21	16		
Age-adjusted HR (95% CI)[c]	1 (referent)	1.04 (0.50-2.16)	1.38 (0.69-2.73)	1.60 (0.82-3.10)	1.56 (0.77-3.16)	.11	
Multivariable HR (95% CI)[d]	1 (referent)	1.06 (0.51-2.21)	1.38 (0.70-2.75)	1.63 (0.83-3.20)	1.54 (0.76-3.13)	.11	
Intermediate							
N of cases (n=496)	120	95	101	87	93		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.72 (0.54-0.95)	0.79 (0.60-1.04)	0.71 (0.53-0.95)	0.88 (0.67-1.17)	.39	
Multivariable HR (95% CI)[d]	1 (referent)	0.73 (0.55-0.97)	0.80 (0.60-1.05)	0.72 (0.54-0.97)	0.87 (0.65-1.16)	.37	
High							
N of cases (n=92)	16	17	22	24	13		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.80 (0.40-1.62)	1.32 (0.68-2.57)	1.46 (0.76-2.82)	0.97 (0.45-2.10)	.41	
Multivariable HR (95% CI)[d]	1 (referent)	0.80 (0.40-1.62)	1.31 (0.68-2.56)	1.45 (0.75-2.79)	0.94 (0.44-2.02)	.46	
Tumor-infiltrating lymphocytes							.18
Absent/low							
N of cases (n=481)	115	88	104	91	83		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.71 (0.53-0.94)	0.86 (0.65-1.13)	0.79 (0.60-1.05)	0.86 (0.64-1.15)	.48	
Multivariable HR (95% CI)[d]	1 (referent)	0.72 (0.54-0.96)	0.87 (0.66-1.14)	0.80 (0.60-1.07)	0.85 (0.63-1.14)	.46	
Intermediate							
N of cases (n=118)	21	24	24	20	29		
Age-adjusted HR (95% CI)[c]	1 (referent)	1.12 (0.61-2.04)	1.23 (0.67-2.26)	1.07 (0.57-2.02)	1.74 (0.97-3.12)	.08	
Multivariable HR (95% CI)[d]	1 (referent)	1.13 (0.61-2.07)	1.23 (0.67-2.29)	1.07 (0.56-2.02)	1.68 (0.94-3.02)	.09	
High							
N of cases (n=77)	16	15	14	21	11		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.72 (0.35-1.46)	0.88 (0.42-1.85)	1.32 (0.68-2.55)	0.85 (0.39-1.87)	.80	
Multivariable HR (95% CI)[d]	1 (referent)	0.74 (0.37-1.51)	0.89 (0.43-1.87)	1.33 (0.68-2.59)	0.84 (0.38-1.86)	.82	
Men (HPFS)							
Person-years	219,667	213,902	206,810	203,426	194,159		
Overall colorectal cancer							
N of cases (n=635)	125	121	117	125	147		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.95 (0.78-1.16)	0.87 (0.71-1.07)	1.06 (0.87-1.28)	1.27 (1.05-1.54)	.01	
Multivariable HR (95% CI)[d]	1 (referent)	1.02 (0.84-1.25)	0.98 (0.80-1.21)	1.20 (0.98-1.47)	1.48 (1.21-1.82)	<.001	

Continued

Analysis	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores					P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)		
Crohn's-like lymphoid reaction							.39
Absent/low							
N of cases (n=382)	74	76	68	80	84		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.94 (0.68-1.31)	0.83 (0.59-1.16)	1.11 (0.81-1.52)	1.10 (0.80-1.52)	.43	
Multivariable HR (95% CI)[d]	1 (referent)	1.04 (0.75-1.45)	0.95 (0.68-1.34)	1.28 (0.94-1.76)	1.30 (0.94-1.79)	.08	
Intermediate							
N of cases (n=95)	17	19	18	14	27		
Age-adjusted HR (95% CI)[c]	1 (referent)	1.07 (0.56-2.07)	0.93 (0.47-1.85)	0.86 (0.41-1.80)	1.66 (0.88-3.13)	.24	
Multivariable HR (95% CI)[d]	1 (referent)	1.17 (0.60-2.27)	1.08 (0.54-2.15)	1.00 (0.47-2.11)	1.92 (1.00-3.69)	.11	
High							
N of cases (n=33)	9	6	8	3	7		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.50 (0.18-1.40)	0.81 (0.33-2.00)	0.21 (0.06-0.76)	0.78 (0.30-1.98)	.40	
Multivariable HR (95% CI)[d]	1 (referent)	0.53 (0.20-1.43)	0.89 (0.37-2.14)	0.24 (0.06-0.90)	0.88 (0.34-2.24)	.54	
Peritumoral lymphocytic reaction							<.001
Absent/low							
N of cases (n=91)	10	14	14	22	31		
Age-adjusted HR (95% CI)[c]	1 (referent)	1.82 (0.77-4.33)	1.40 (0.60-3.26)	2.68 (1.22-5.93)	4.50 (2.11-9.59)	<.001	
Multivariable HR (95% CI)[d]	1 (referent)	2.00 (0.84-4.75)	1.59 (0.68-3.72)	3.05 (1.39-6.71)	5.35 (2.52-11.39)	<.001	
Intermediate							
N of cases (n=442)	90	86	82	85	99		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.90 (0.66-1.21)	0.84 (0.62-1.13)	0.99 (0.73-1.34)	1.10 (0.82-1.47)	.47	
Multivariable HR (95% CI)[d]	1 (referent)	0.96 (0.71-1.30)	0.94 (0.69-1.28)	1.14 (0.84-1.54)	1.28 (0.95-1.73)	.09	
High							
N of cases (n=100)	24	20	21	18	17		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.81 (0.45-1.45)	0.79 (0.43-1.45)	0.72 (0.39-1.35)	0.73 (0.39-1.35)	.28	
Multivariable HR (95% CI)[d]	1 (referent)	0.87 (0.49-1.55)	0.89 (0.49-1.63)	0.81 (0.43-1.51)	0.84 (0.45-1.56)	.53	
Intratumoral periglandular reaction							.02
Absent/low							
N of cases (n=79)	15	11	13	17	23		
Age-adjusted HR (95% CI)[c]	1 (referent)	1.05 (0.46-2.38)	0.94 (0.43-2.05)	1.59 (0.76-3.31)	2.60 (1.33-5.09)	.005	
Multivariable HR (95% CI)[d]	1 (referent)	1.14 (0.50-2.58)	1.05 (0.48-2.29)	1.81 (0.88-3.73)	3.06 (1.57-5.94)	.001	
Intermediate							
N of cases (n=480)	96	90	87	95	112		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.88 (0.66-1.19)	0.83 (0.62-1.11)	1.00 (0.75-1.34)	1.17 (0.89-1.55)	.23	
Multivariable HR (95% CI)[d]	1 (referent)	0.95 (0.70-1.27)	0.93 (0.69-1.26)	1.15 (0.87-1.54)	1.38 (1.04-1.83)	.02	

Continued

Analysis	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores					P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)		
High							
N of cases (n=78)	14	20	18	13	13		
Age-adjusted HR (95% CI)[c]	1 (referent)	1.35 (0.69-2.64)	1.16 (0.57-2.36)	0.91 (0.42-1.97)	0.88 (0.42-1.86)	.46	
Multivariable HR (95% CI)[d]	1 (referent)	1.46 (0.75-2.82)	1.33 (0.66-2.68)	1.03 (0.48-2.22)	1.02 (0.48-2.16)	.77	
Tumor- infiltrating lymphocytes							.83
Absent/low							
N of cases (n=503)	92	99	96	98	118		
Age-adjusted HR (95% CI)[c]	1 (referent)	1.06 (0.79-1.41)	0.97 (0.73-1.30)	1.11 (0.83-1.49)	1.37 (1.04-1.81)	.05	
Multivariable HR (95% CI)[d]	1 (referent)	1.13 (0.85-1.52)	1.09 (0.81-1.46)	1.27 (0.95-1.69)	1.60 (1.20-2.12)	.003	
Intermediate							
N of cases (n=81)	20	14	10	20	17		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.71 (0.36-1.42)	0.45 (0.20-0.99)	1.18 (0.63-2.21)	0.93 (0.48-1.80)	.69	
Multivariable HR (95% CI)[d]	1 (referent)	0.77 (0.38-1.54)	0.51 (0.23-1.13)	1.35 (0.72-2.56)	1.08 (0.55-2.12)	.41	
High							
N of cases (n=51)	13	8	11	7	12		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.53 (0.22-1.24)	0.78 (0.34-1.78)	0.44 (0.17-1.11)	1.00 (0.44-2.26)	.92	
Multivariable HR (95% CI)[d]	1 (referent)	0.57 (0.25-1.31)	0.87 (0.38-1.98)	0.52 (0.20-1.32)	1.21 (0.52-2.78)	.80	

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; NHS, Nurses' Health Study.

[a] Linear trend test using the median value of each EDIP score quintile.

[b] The Wald test was used to test for the heterogeneity of the associations between EDIP scores and colorectal cancer risk according to the components of lymphocytic reaction. The heterogeneity test was adjusted for time-varying pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level [quintiles of mean metabolic equivalent task score (METS) - hours per week], total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use, regular aspirin use and postmenopausal hormone use (only for women).

[c] Duplication-method Cox proportional cause-specific hazards regression weighted by inverse probabilities based on immune marker availability for competing risks data was used to compute HRs and 95% CIs. All analyses were stratified by age (in month) and year of questionnaire return.

[d] Multivariable HR was further adjusted for time-varying pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level (quintiles of METS - hours per week), total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use and regular aspirin use. Models were adjusted for postmenopausal hormone use in the analyses of women.

Supplementary Table 5. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Microsatellite Instability Status in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men)

Analysis	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores					P_{trend} [a]	$P_{heterogeneity}$ [b]
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)		
Microsatellite Instability							0.72
Non-MSI-high							
N of cases (n=999)	208	196	192	197	206		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.86 (0.71-1.05)	0.88 (0.72-1.07)	0.92 (0.76-1.13)	1.05 (0.86-1.27)	0.53	
Multivariable HR (95% CI)[d]	1 (referent)	0.91 (0.75-1.12)	0.95 (0.78-1.17)	1.01 (0.83-1.24)	1.13 (0.93-1.39)	0.14	
MSI-high							
N of cases (n=187)	39	32	46	34	36		
Age-adjusted HR (95% CI)[c]	1 (referent)	0.73 (0.45-1.17)	1.05 (0.68-1.62)	0.79 (0.50-1.25)	0.94 (0.59-1.48)	0.90	
Multivariable HR (95% CI)[d]	1 (referent)	0.78 (0.49-1.26)	1.14 (0.74-1.75)	0.85 (0.54-1.36)	1.02 (0.64-1.62)	0.83	

Abbreviations: CI, confidence interval; HR, hazard ratio; MSI, microsatellite instability.

[a] Linear trend test using the median value of each EDIP score quintile.

[b] The Wald test was used to test for the heterogeneity of the associations between EDIP scores and colorectal cancer risk according to microsatellite instability status. The heterogeneity test was adjusted for time-varying pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level [quintiles of mean metabolic equivalent task score (METS) - hours per week], total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use and regular aspirin use.

[c] Duplication-method Cox proportional cause-specific hazards regression weighted by inverse probabilities based on microsatellite instability status availability for competing risks data was used to compute HRs and 95% CIs. All analyses were stratified by age (in month), year of questionnaire return and sex.

[d] Multivariable HR was further adjusted for time-varying pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level (quintiles of METS - hours per week), total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use and regular aspirin use.

Supplementary Table 6. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Components of Lymphocytic Reaction in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men) by Further Adjustment for Body Mass Index

Analysis	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores					P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)		
Overall							
Multivariable HR (95% CI)[c]	1 (referent)	0.85 (0.74-0.97)	0.92 (0.80-1.04)	0.96 (0.85-1.10)	1.09 (0.95-1.25)	.08	
Crohn's-like lymphoid reaction							.54
Absent/low							
Multivariable HR (95% CI)[c]	1 (referent)	0.89 (0.71-1.11)	0.93 (0.75-1.17)	1.00 (0.80-1.25)	1.06 (0.84-1.32)	.47	
Intermediate							
Multivariable HR (95% CI)[c]	1 (referent)	0.92 (0.59-1.46)	0.70 (0.43-1.16)	0.90 (0.55-1.46)	1.41 (0.90-2.21)	.19	
High							
Multivariable HR (95% CI)[c]	1 (referent)	0.56 (0.28-1.12)	0.86 (0.46-1.59)	0.62 (0.30-1.29)	0.94 (0.48-1.82)	.77	
Peritumoral lymphocytic reaction							<.001
Absent/low							
Multivariable HR (95% CI)[c]	1 (referent)	1.29 (0.75-2.21)	1.25 (0.73-2.15)	1.66 (1.00-2.76)	2.50 (1.54-4.06)	<.001	
Intermediate							
Multivariable HR (95% CI)[c]	1 (referent)	0.76 (0.62-0.94)	0.82 (0.67-1.01)	0.86 (0.69-1.06)	0.95 (0.77-1.17)	.90	
High							
Multivariable HR (95% CI)[c]	1 (referent)	0.94 (0.62-1.43)	1.14 (0.76-1.72)	1.08 (0.71-1.65)	0.87 (0.55-1.39)	.84	
Intratumoral periglandular reaction							.04
Absent/low							
Multivariable HR (95% CI)[c]	1 (referent)	0.93 (0.54-1.62)	1.10 (0.65-1.86)	1.45 (0.88-2.39)	1.79 (1.10-2.92)	.005	
Intermediate							
Multivariable HR (95% CI)[c]	1 (referent)	0.81 (0.66-0.99)	0.84 (0.68-1.02)	0.86 (0.70-1.06)	1.02 (0.83-1.25)	.76	
High							
Multivariable HR (95% CI)[c]	1 (referent)	1.03 (0.64-1.67)	1.32 (0.81-2.14)	1.26 (0.77-2.07)	0.92 (0.53-1.59)	.86	
Tumor-infiltrating lymphocytes							.54
Absent/low							
Multivariable HR (95% CI)[c]	1 (referent)	0.85 (0.70-1.05)	0.93 (0.76-1.14)	0.94 (0.76-1.15)	1.06 (0.86-1.30)	.45	
Intermediate							
Multivariable HR (95% CI)[c]	1 (referent)	0.92 (0.59-1.45)	0.86 (0.53-1.38)	1.10 (0.70-1.72)	1.35 (0.87-2.09)	.13	
High							
Multivariable HR (95% CI)[c]	1 (referent)	0.68 (0.40-1.16)	0.87 (0.50-1.50)	0.99 (0.58-1.70)	0.99 (0.56-1.75)	.74	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Linear trend test using the median value of each EDIP score quintile.

[b] The Wald test was used to test for the heterogeneity of the associations between the EDIP scores and colorectal cancer risk according to the components of lymphocytic reaction. The heterogeneity test was adjusted for time-varying body mass index (<25 vs. 25-29.9 vs. ≥30 kg/m^2), pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level [quintiles of mean metabolic equivalent task score (METS) - hours per week], total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use and regular aspirin use.

[c] Duplication-method Cox proportional cause-specific hazards regression weighted by inverse probabilities based on immune marker availability for competing risks data was used to compute HRs and 95% CIs. All analyses were stratified by age (in month), year of questionnaire return and

sex. Multivariable HR was further adjusted for time-varying body mass index (<25 vs. 25-29.9 vs. ≥30 kg/m^2), pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level (quintiles of METS - hours per week), total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use and regular aspirin use.

Supplementary Table 7. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Peritumoral Lymphocytic Reaction in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professional Follow-up Study (Men) by Adjustment for Different Covariates

Analysis	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores					P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)		
Peritumoral lymphocytic reaction							
Absent/low							
Multivariable HR (95% CI)[c]	1 (referent)	1.27 (0.74-2.18)	1.22 (0.72-2.09)	1.63 (0.99-2.70)	2.47 (1.52-4.00)	<.001	.001
Multivariable HR (95% CI)[d]	1 (referent)	1.25 (0.73-2.14)	1.20 (0.70-2.05)	1.59 (0.96-2.64)	2.41 (1.49-3.90)	<.001	.001
Multivariable HR (95% CI)[e]	1 (referent)	1.26 (0.74-2.16)	1.21 (0.71-2.06)	1.58 (0.96-2.62)	2.41 (1.49-3.89)	<.001	.001
Multivariable HR (95% CI)[f]	1 (referent)	1.24 (0.72-2.12)	1.18 (0.69-2.02)	1.56 (0.94-2.58)	2.35 (1.46-3.81)	<.001	.001
Multivariable HR (95% CI)[g]	1 (referent)	1.25 (0.73-2.14)	1.20 (0.70-2.05)	1.59 (0.96-2.63)	2.38 (1.47-3.86)	<.001	.001
Multivariable HR (95% CI)[h]	1 (referent)	1.31 (0.77-2.25)	1.29 (0.75-2.20)	1.74 (1.05-2.89)	2.68 (1.64-4.36)	<.001	.001
Multivariable HR (95% CI)[i]	1 (referent)	1.25 (0.73-2.14)	1.20 (0.70-2.04)	1.59 (0.96-2.62)	2.39 (1.48-3.87)	<.001	.001
Multivariable HR (95% CI)[j]	1 (referent)	1.25 (0.73-2.14)	1.19 (0.70-2.04)	1.59 (0.96-2.63)	2.41 (1.49-3.89)	<.001	.001
Multivariable HR (95% CI)[k]	1 (referent)	1.23 (0.72-2.10)	1.17 (0.69-2.00)	1.54 (0.93-2.55)	2.29 (1.41-3.70)	<.001	.001
Multivariable HR (95% CI)[l]	1 (referent)	1.14 (0.47-2.74)	2.05 (0.89-4.74)	2.37(1.07-5.26)	3.54 (1.65-7.60)	<.001	<.001
Multivariable HR (95% CI)[m]	1 (referent)	1.11 (0.64-1.93)	1.30 (0.73-2.32)	1.65 (0.97-2.79)	2.25 (1.33-3.80)	.002	<.001
Intermediate							
Multivariable HR (95% CI)[c]	1 (referent)	0.75 (0.60-0.92)	0.80 (0.65-0.98)	0.83 (0.67-1.02)	0.94 (0.77-1.15)	.79	
Multivariable HR (95% CI)[d]	1 (referent)	0.74 (0.60-0.91)	0.78 (0.63-0.96)	0.81 (0.66-1.00)	0.92 (0.75-1.13)	.65	
Multivariable HR (95% CI)[e]	1 (referent)	0.74 (0.60-0.91)	0.78 (0.64-0.96)	0.81 (0.65-1.00)	0.91 (0.74-1.11)	.54	
Multivariable HR (95% CI)[f]	1 (referent)	0.73 (0.59-0.90)	0.77 (0.63-0.95)	0.80 (0.65-0.99)	0.90 (0.74-1.11)	.52	
Multivariable HR (95% CI)[g]	1 (referent)	0.74 (0.60-0.91)	0.78 (0.64-0.96)	0.81 (0.66-1.00)	0.91 (0.74-1.11)	.54	
Multivariable HR (95% CI)[h]	1 (referent)	0.77 (0.63-0.96)	0.84 (0.68-1.04)	0.89 (0.72-1.10)	1.02 (0.83-1.26)	.57	
Multivariable HR (95% CI)[i]	1 (referent)	0.74 (0.60-0.91)	0.78 (0.63-0.96)	0.81 (0.66-1.00)	0.91 (0.74-1.12)	.59	
Multivariable HR (95% CI)[j]	1 (referent)	0.74 (0.60-0.91)	0.78 (0.63-0.96)	0.81 (0.66-1.00)	0.92 (0.75-1.13)	.65	
Multivariable HR (95% CI)[k]	1 (referent)	0.73 (0.59-0.90)	0.77 (0.62-0.94)	0.79 (0.64-0.97)	0.88 (0.71-1.08)	.36	
Multivariable HR (95% CI)[l]	1 (referent)	0.70 (0.35-1.37)	1.17 (0.63-2.15)	1.26 (0.69-2.30)	1.37 (0.76-2.45)	.04	
Multivariable HR (95% CI)[m]	1 (referent)	0.68 (0.53-0.89)	0.74 (0.57-0.97)	0.88 (0.67-1.15)	0.87 (0.66-1.16)	.39	
High							
Multivariable HR (95% CI)[c]	1 (referent)	0.93 (0.61-1.41)	1.12 (0.74-1.70)	1.08 (0.71-1.65)	0.88 (0.56-1.40)	.87	
Multivariable HR (95% CI)[d]	1 (referent)	0.92 (0.60-1.40)	1.10 (0.73-1.67)	1.07 (0.70-1.62)	0.87 (0.55-1.38)	.81	
Multivariable HR (95% CI)[e]	1 (referent)	0.91 (0.60-1.38)	1.09 (0.72-1.64)	1.04 (0.68-1.58)	0.84 (0.53-1.33)	.69	
Multivariable HR (95% CI)[f]	1 (referent)	0.91 (0.60-1.39)	1.09 (0.72-1.64)	1.04 (0.68-1.58)	0.84 (0.53-1.34)	.70	
Multivariable HR (95% CI)[g]	1 (referent)	0.92 (0.60-1.40)	1.11 (0.73-1.67)	1.06 (0.70-1.62)	0.85 (0.54-1.36)	.74	
Multivariable HR (95% CI)[h]	1 (referent)	0.96 (0.63-1.46)	1.18 (0.78-1.79)	1.16 (0.76-1.77)	0.96 (0.60-1.53)	.77	
Multivariable HR (95% CI)[i]	1 (referent)	0.91 (0.60-1.39)	1.10 (0.73-1.66)	1.06 (0.69-1.61)	0.86 (0.54-1.36)	.76	
Multivariable HR (95% CI)[j]	1 (referent)	0.91 (0.60-1.38)	1.09 (0.72-1.65)	1.05 (0.69-1.60)	0.86 (0.54-1.36)	.77	

Continuous

Analysis	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores					P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)		
Multivariable HR (95% CI)[k]	1 (referent)	0.90 (0.59-1.38)	1.07 (0.71-1.62)	1.02 (0.67-1.56)	0.82 (0.52-1.30)	.60	
Multivariable HR (95% CI)[l]	1 (referent)	0.83 (0.38-1.83)	1.82 (0.88-3.77)	1.46 (0.71-2.99)	1.16 (0.55-2.44)	.19	
Multivariable HR (95% CI)[m]	1 (referent)	0.82 (0.53-1.29)	1.16 (0.74-1.79)	1.01 (0.64-1.59)	0.73 (0.44-1.23)	.26	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Linear trend test using the median value of each EDIP score quintile.

[b] The Wald test was used to test for the heterogeneity of the associations between the EDIP scores and risk of colorectal cancer subtypes according to the degrees of peritumoral lymphocytic reaction.

[c] Duplication-method Cox proportional cause-specific hazards regression weighted by inverse probabilities based on immune marker availability for competing risks data was used to compute HRs and 95% CIs. All analyses were stratified by age (in month), year of questionnaire return and sex. Multivariable HR was further adjusted for time-varying pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years).

[d] Multivariable HR was further adjusted for time-varying family history of colorectal cancer (no/yes).

[e] Multivariable HR was further adjusted for time-varying endoscopy status (no/yes).

[f] Multivariable HR was further adjusted for time-varying physical activity level [quintiles of mean metabolic equivalent task score (METS) - hours per week].

[g] Multivariable HR was further adjusted for time-varying total energy intake (quintiles of kcal/day).

[h] Multivariable HR was further adjusted for time-varying total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day).

[i] Multivariable HR was further adjusted for time-varying current multivitamin use (no/yes).

[j] Multivariable HR was further adjusted for time-varying regular aspirin use (no/yes).

[k] Multivariable HR was further adjusted for time-varying body mass index (<25 vs. 25-29.9 vs. ≥30 kg/m^2).

[l] Multivariable HR was further adjusted for time-varying body mass index (<25 vs. 25-29.9 vs. ≥30 kg/m^2), pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level (quintiles of METS - hours per week), total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use, regular aspirin use and interactions between EDIP scores and alcohol intake.

[m] Multivariable HR was further adjusted for time-varying body mass index (<25 vs. 25-29.9 vs. ≥30 kg/m^2), pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level (quintiles of METS - hours per week), total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use, regular aspirin use and interactions between EDIP scores and body mass index.

Supplementary Table 8. Quartiles of Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Components of Lymphocytic Reaction in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men)

Analysis	Quartiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores				P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4 (Highest)		
Overall colorectal cancer						
Age-adjusted HR (95% CI)[c]	1 (referent)	0.93 (0.83-1.04)	0.98 (0.88-1.10)	1.06 (0.95-1.19)	0.22	
Multivariable HR (95% CI)[d]	1 (referent)	0.98 (0.87-1.10)	1.05 (0.94-1.18)	1.14 (1.01-1.29)	0.02	
Crohn's-like lymphoid reaction						.56
Absent/low						
Age-adjusted HR (95% CI)[c]	1 (referent)	0.90 (0.74-1.10)	1.00 (0.82-1.21)	1.05 (0.86-1.27)	.56	
Multivariable HR (95% CI)[d]	1 (referent)	0.95 (0.78-1.16)	1.07 (0.87-1.30)	1.12 (0.92-1.37)	.21	
Intermediate						
Age-adjusted HR (95% CI)[c]	1 (referent)	0.97 (0.65-1.46)	0.81 (0.51-1.27)	1.34 (0.90-1.99)	.23	
Multivariable HR (95% CI)[d]	1 (referent)	1.01 (0.67-1.52)	0.86 (0.54-1.35)	1.41 (0.92-2.11)	.15	
High						
Age-adjusted HR (95% CI)[c]	1 (referent)	0.77 (0.42-1.40)	0.78 (0.42-1.45)	0.90 (0.49-1.67)	.65	
Multivariable HR (95% CI)[d]	1 (referent)	0.81 (0.45-1.47)	0.84 (0.46-1.54)	0.96 (0.52-1.77)	.80	
Peritumoral lymphocytic reaction						.006
Absent/low						
Age-adjusted HR (95% CI)[c]	1 (referent)	1.52 (0.95-2.42)	1.31 (0.81-2.10)	2.16 (1.39-3.37)	.001	
Multivariable HR (95% CI)[d]	1 (referent)	1.60 (1.01-2.55)	1.41 (0.87-2.26)	2.33 (1.50-3.63)	<.001	
Intermediate						
Age-adjusted HR (95% CI)[c]	1 (referent)	0.81 (0.67-0.98)	0.91 (0.75-1.09)	0.94 (0.78-1.13)	.74	
Multivariable HR (95% CI)[d]	1 (referent)	0.85 (0.70-1.03)	0.97 (0.80-1.18)	1.01 (0.83-1.22)	.68	
High						
Age-adjusted HR (95% CI)[c]	1 (referent)	1.11 (0.77-1.62)	1.18 (0.81-1.72)	0.94 (0.63-1.42)	.92	
Multivariable HR (95% CI)[d]	1 (referent)	1.16 (0.80-1.68)	1.25 (0.86-1.82)	0.99 (0.66-1.49)	.86	
Intratumoral periglandular reaction						.09
Absent/low						
Age-adjusted HR (95% CI)[c]	1 (referent)	1.10 (0.68-1.76)	1.22 (0.76-1.95)	1.65 (1.06-2.58)	.02	
Multivariable HR (95% CI)[d]	1 (referent)	1.15 (0.72-1.85)	1.31 (0.82-2.09)	1.78 (1.14-2.77)	.009	
Intermediate						
Age-adjusted HR (95% CI)[c]	1 (referent)	0.85 (0.71-1.02)	0.92 (0.77-1.10)	0.97 (0.82-1.16)	.94	
Multivariable HR (95% CI)[d]	1 (referent)	0.90 (0.75-1.08)	0.98 (0.82-1.18)	1.05 (0.87-1.25)	.48	
High						
Age-adjusted HR (95% CI)[c]	1 (referent)	1.30 (0.85-2.00)	1.21 (0.78-1.89)	1.10 (0.69-1.75)	.73	
Multivariable HR (95% CI)[d]	1 (referent)	1.35 (0.88-2.08)	1.29 (0.83-2.01)	1.16 (0.73-1.85)	.54	

Continued

Analysis	Quartiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores				P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4 (Highest)		
Tumor-infiltrating lymphocytes						.46
Absent/low						
Age-adjusted HR (95% CI)[c]	1 (referent)	0.95 (0.79-1.14)	0.97 (0.81-1.17)	1.04 (0.87-1.25)	.62	
Multivariable HR (95% CI)[d]	1 (referent)	1.00 (0.83-1.20)	1.04 (0.87-1.26)	1.12 (0.93-1.34)	.21	
Intermediate						
Age-adjusted HR (95% CI)[c]	1 (referent)	0.93 (0.62-1.40)	0.96 (0.64-1.46)	1.32 (0.90-1.94)	.15	
Multivariable HR (95% CI)[d]	1 (referent)	0.98 (0.65-1.47)	1.02 (0.67-1.55)	1.40 (0.95-2.06)	.09	
High						
Age-adjusted HR (95% CI)[c]	1 (referent)	0.78 (0.48-1.26)	1.09 (0.68-1.73)	0.84 (0.50-1.41)	.75	
Multivariable HR (95% CI)[d]	1 (referent)	0.81 (0.50-1.32)	1.16 (0.72-1.85)	0.90 (0.53-1.52)	.98	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Linear trend test using the median value of each EDIP score quartile.

[b] The Wald test was used to test for the heterogeneity of the associations between the EDIP scores and colorectal cancer risk according to the components of lymphocytic reaction. The heterogeneity test was adjusted for time-varying pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level [quintiles of mean metabolic equivalent task score (METS) - hours per week], total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use and regular aspirin use.

[c] Duplication-method Cox proportional cause-specific hazards regression weighted by inverse probabilities based on immune marker availability for competing risks data was used to compute HRs and 95% CIs. All analyses were stratified by age (in month), year of questionnaire return and sex.

[d] Multivariable HR was further adjusted for time-varying pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level (quintiles of METS - hours per week), total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), current multivitamin use and regular aspirin use.

Supplementary Table 9. Empirical Dietary Inflammatory Pattern Scores and Risk of Colorectal Cancer by Components of Lymphocytic Reaction in the Pooled Cohorts of the Nurses' Health Study (Women) and the Health Professionals Follow-up Study (Men) Estimated by Marginal Structural Cox Proportional Hazards Regression Models

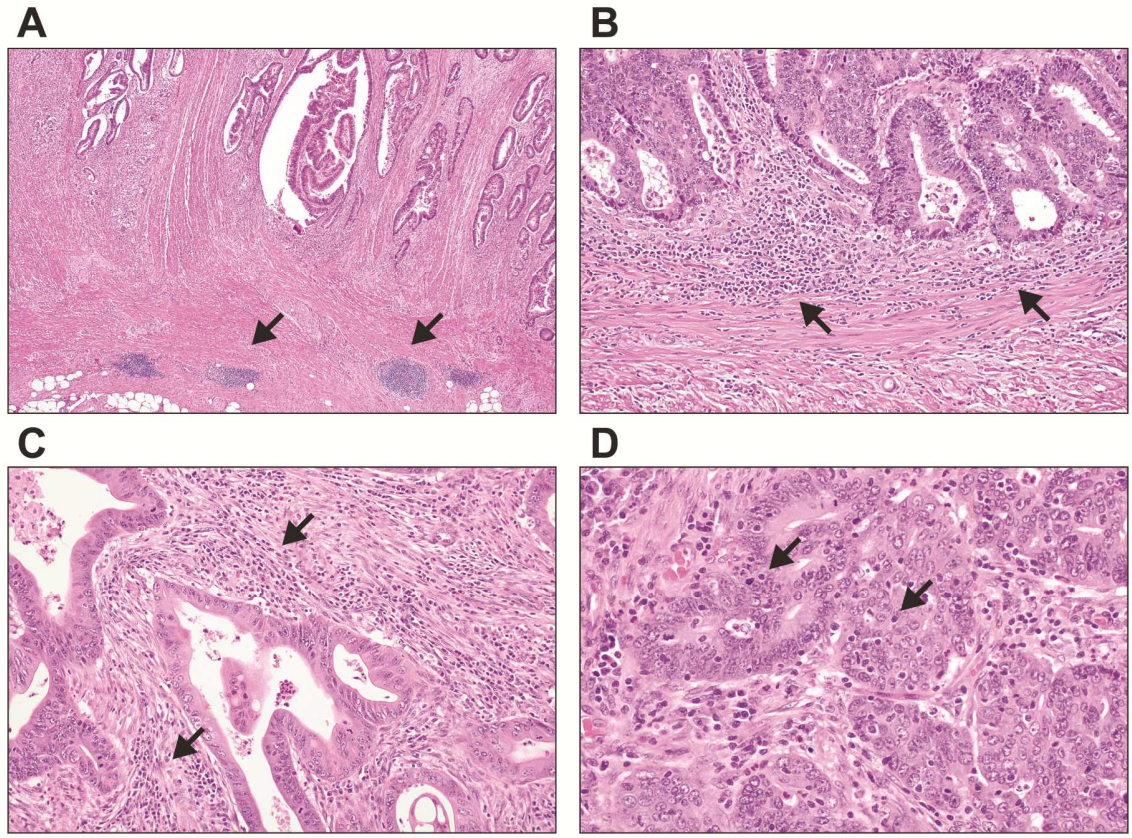
Analysis	Quintiles of the Empirical Dietary Inflammatory Pattern (EDIP) Scores					P_{trend}[a]	$P_{heterogeneity}$[b]
	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)		
Overall colorectal cancer							
Multivariable HR (95% CI)[c]	1 (referent)	0.85 (0.71-1.01)	0.97 (0.81-1.15)	0.93 (0.78-1.11)	1.10 (0.92-1.32)	0.18	
Crohn's-like lymphoid reaction							.56
Absent/low							
Multivariable HR (95% CI)[c]	1 (referent)	0.85 (0.68-1.07)	0.98 (0.78-1.23)	0.94 (0.75-1.18)	1.07 (0.85-1.34)	.41	
Intermediate							
Multivariable HR (95% CI)[c]	1 (referent)	1.08 (0.68-1.70)	0.82 (0.50-1.35)	0.91 (0.55-1.49)	1.48 (0.95-2.33)	.19	
High							
Multivariable HR (95% CI)[c]	1 (referent)	0.64 (0.31-1.30)	0.99 (0.51-1.90)	0.70 (0.33-1.50)	0.91 (0.47-1.79)	.77	
Peritumoral lymphocytic reaction							.004
Absent/low							
Multivariable HR (95% CI)[c]	1 (referent)	1.10 (0.65-1.88)	1.29 (0.76-2.20)	1.58 (0.95-2.61)	2.27 (1.40-3.67)	<.001	
Intermediate							
Multivariable HR (95% CI)[c]	1 (referent)	0.77 (0.62-0.95)	0.87 (0.70-1.08)	0.82 (0.66-1.01)	0.98 (0.80-1.21)	.99	
High							
Multivariable HR (95% CI)[c]	1 (referent)	0.98 (0.64-1.51)	1.25 (0.82-1.90)	1.13 (0.73-1.74)	0.96 (0.60-1.53)	.83	
Intratumoral periglandular reaction							.21
Absent/low							
Multivariable HR (95% CI)[c]	1 (referent)	0.78 (0.45-1.34)	1.06 (0.63-1.80)	1.30 (0.79-2.14)	1.49 (0.92-2.41)	.03	
Intermediate							
Multivariable HR (95% CI)[c]	1 (referent)	0.80 (0.65-0.98)	0.90 (0.73-1.10)	0.84 (0.68-1.03)	1.07 (0.87-1.31)	.51	
High							
Multivariable HR (95% CI)[c]	1 (referent)	1.19 (0.72-1.94)	1.43 (0.87-2.34)	1.29 (0.77-2.14)	0.99 (0.58-1.70)	.76	
Tumor-infiltrating lymphocytes							.62
Absent/low							
Multivariable HR (95% CI)[c]	1 (referent)	0.84 (0.68-1.03)	0.99 (0.80-1.21)	0.90 (0.73-1.11)	1.07 (0.87-1.31)	.42	
Intermediate							
Multivariable HR (95% CI)[c]	1 (referent)	0.91 (0.58-1.44)	0.93 (0.58-1.49)	1.02 (0.65-1.60)	1.35 (0.87-2.11)	.16	
High							
Multivariable HR (95% CI)[c]	1 (referent)	0.77 (0.44-1.34)	0.90 (0.52-1.56)	1.05 (0.61-1.80)	0.99 (0.57-1.75)	.74	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Linear trend test using the median value of each EDIP score quintile.

[b] The Wald test was used to test for the heterogeneity of the associations between the EDIP scores and colorectal cancer risk according to the components of lymphocytic reaction. The heterogeneity test was adjusted for baseline pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level [quintiles of mean metabolic equivalent task score (METS) - hours per week], total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), multivitamin use and regular aspirin use.

[c] The Cox proportional hazards regression model weighted by stabilized inverse probability weights (the products of stabilized inverse probability of treatment weights and stabilized inverse probability of censoring weights) was used to compute HRs and 95% CIs. All analyses were stratified by age (in month), year of questionnaire return and sex. Multivariable HR was adjusted for baseline pack-years of smoking (0 vs. 1-19 vs. 20-39 vs. ≥40 pack-years), family history of colorectal cancer, endoscopy status, physical activity level (quintiles of METS - hours per week), total energy intake (quintiles of kcal/day), total alcohol intake (0 vs. 1-5 vs. 6-15 vs. >15 g/day), multivitamin use and regular aspirin use.


A
B
C
D