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Original Contribution

Circulating C-Reactive Protein Concentrations and Risks of Colon and Rectal Cancer: A Nested Case-Control Study Within the European Prospective Investigation into Cancer and Nutrition

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The authors investigated associations between serum C-reactive protein (CRP) concentrations and colon and rectal cancer risk in a nested case-control study within the European Prospective Investigation into Cancer and Nutrition (1992–2003) among 1,096 incident cases and 1,096 controls selected using risk-set sampling and matched on study center, age, sex, time of blood collection, fasting status, menopausal status, menstrual cycle phase, and hormone replacement therapy. In conditional logistic regression with adjustment for education, smoking, nutritional factors, body mass index, and waist circumference, CRP showed a significant nonlinear association with colon cancer risk but not rectal cancer risk. Multivariable-adjusted relative risks for CRP concentrations of $\geq$3.0 mg/L versus $<$1.0 mg/L were 1.36 (95% confidence interval (CI): 1.00, 1.85; *P*-trend = 0.01) for colon cancer and 1.02 (95% CI: 0.67, 1.57; *P*-trend = 0.65) for rectal cancer. Colon cancer risk was significantly increased in men (relative risk = 1.74, 95% CI: 1.11, 2.73; *P*-trend = 0.01) but not in women (relative risk = 1.06, 95% CI: 0.67, 1.68; *P*-trend = 0.13). Additional adjustment for C-peptide, glycated hemoglobin, and high density lipoprotein cholesterol did not attenuate these results. These data provide evidence that elevated CRP concentrations are related to a higher risk of colon cancer but not rectal cancer, predominantly among men and independently of obesity, insulin resistance, and dyslipidemia.

colorectal neoplasms; C-reactive protein; hyperglycemia; hyperinsulinism; hyperlipidemias; inflammation; obesity, abdominal

Abbreviations: CI, confidence interval; CRP, C-reactive protein; EPIC, European Prospective Investigation into Cancer and Nutrition; HDL, high density lipoprotein; ICD-10, *International Classification of Diseases*, Tenth Revision; IQR, interquartile range; NSAIDs, nonsteroidal antiinflammatory drugs; RR, relative risk.

Inflammation has been hypothesized to play an important role in carcinogenesis, particularly for colorectal cancer (1). This is supported by studies which have shown that persons with chronic inflammatory bowel disease have a higher risk of colorectal cancer than the general population (2–4) and that use of aspirin or

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other antiinflammatory drugs is associated with a lower risk (5).

C-reactive protein (CRP) is a sensitive, nonspecific marker of systemic low-grade inflammation that is produced mainly in the liver in response to stimulation by proinflammatory cytokines (6). The association of circulating CRP concentrations with risk of colorectal cancer has been examined in a number of prospective studies, but results to date have been inconsistent (7–15). A recent meta-analysis suggested that CRP concentrations are positively weakly associated with risk of colon cancer and that this association is stronger in men than in women, whereas no association was found for rectal cancer (16). The interpretation of these findings is limited, however, because only a few previous studies accounted for other potential predictors of colorectal cancer that may be related to CRP, including dietary and lifestyle factors, such as consumption of red and processed meat, fiber, and fruits and vegetables or physical activity (7–15). More importantly, while investigators in most studies adjusted for body mass index (weight (kg)/height $(m)^2$) as a marker for general obesity, they did not adjust for waist circumference as a marker for abdominal adiposity. Adipose tissue, particularly that from visceral fat depots, produces proinflammatory cytokines that induce hepatic CRP secretion, and circulating CRP concentrations are associated with abdominal obesity, insulin resistance, and dyslipidemia (17, 18). In addition, waist circumference is more closely related to colorectal cancer risk than is body mass index (19), and markers of hyperinsulinemia (high concentrations of C-peptide), hyperglycemia (high concentrations of glycated hemoglobin), or dyslipidemia (low concentrations of high density lipoprotein (HDL) cholesterol) have been suggested to be associated with colorectal cancer risk (20–23).

We conducted a nested case-control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) with the aim of examining the association between serum CRP concentrations and risk of colon and rectal cancer in men and women. Particularly, we were interested in assessing the effects of body mass index, waist circumference, and the biomarkers C-peptide, glycated hemoglobin, and HDL cholesterol on that association.

MATERIALS AND METHODS

Study population

The present study included subjects from 9 countries (Denmark, France, Germany, Greece, Italy, Spain, Sweden, the Netherlands, and the United Kingdom) who participated in EPIC, a large prospective study with over 520,000 participants aged 25–70 years recruited during the period 1992–2000 (24). Participants gave written informed consent, underwent anthropometric measurements, and completed questionnaires on sociodemographic and lifestyle characteristics (24–26). Approval was obtained from the ethics review board of the International Agency for Research on Cancer (Lyon, France) and the local review boards pertaining to the participating institutions.

Follow-up for cancer incidence and vital status

Incident cancer cases were identified through record linkage with regional cancer registries at all study centers except those in Germany, France, Greece, and Naples (Italy), where follow-up was based on a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next of kin. Closure dates for the present study were defined as the latest date of complete follow-up for both cancer incidence and vital status. Closure dates ranged from December 1999 to June 2003 for study centers using registry data and from June 2000 to December 2002 for study centers using active follow-up procedures.

Selection of case and control subjects

A total of 1,096 incident cases of colorectal cancer (696 colon, 400 rectum) were included in the present analyses as follows, according to tumor site (colon/rectum): 165/137 from Denmark, 22/5 from France, 12/13 from Greece, 78/47 from Germany, 92/35 from Italy, 83/44 from the Netherlands, 73/38 from Spain, 32/21 from Sweden, and 139/60 from the United Kingdom. According to the *International Classification of Diseases*, Tenth Revision (ICD-10), proximal colon tumors include those in the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (ICD-10 codes C18.0–18.5); distal colon tumors include those in the descending colon (ICD-10 code C18.6) and sigmoid colon (ICD-10 code C18.7); and rectal tumors are those occurring at the rectosigmoid junction (ICD-10 code C19) or in the rectum (ICD-10 code C20).

We used an incidence density sampling protocol for control selection, such that controls could include subjects who later became cases, while each control subject could also be sampled more than once. Matching characteristics were study center at the time of enrollment, sex, age at blood collection (6-month to 2-year intervals), time of blood collection (2- to 4-hour intervals), and fasting status (<3, 3–6, or >6 hours, to account for differences in analyte values by fasting status). Women were also matched on menopausal status (premenopausal, perimenopausal, postmenopausal, or surgically postmenopausal). Premenopausal women were matched on phase of the menstrual cycle at blood collection (early follicular, late follicular, ovulatory, early luteal, midluteal, or late luteal), and postmenopausal women were matched on current use of hormone replacement therapy (yes/no). These latter matching criteria among women were included because a separate study on the association between endogenous hormones and colorectal cancer risk was planned using the same matched case-control sets (20).

Laboratory analyses

CRP and HDL cholesterol concentrations were measured using a high-sensitivity assay (Beckman-Coulter, Woerden, the Netherlands) and a colorimetric method, respectively, on a Synchron LX-20 Pro autoanalyzer (Beckman-Coulter). The interassay coefficients of variation were 6.0% and 6.5% at

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CRP concentrations of 1.16 mg/L and 1.89 mg/L, respectively, and 4.1%, 3.4%, and 3.6% at HDL cholesterol concentrations of 0.62 mmol/L, 1.20 mmol/L, and 1.65 mmol/L, respectively. C-peptide was measured using a radioimmunoassay from Diagnostic System Laboratories (Webster, Texas) (20). Measurements of glycated hemoglobin in erythrocyte hemolysate were carried out using high-performance liquid chromatography with a Bio-Rad Variant II instrument (Bio-Rad Laboratories, Hercules, California) (21).

Statistical analysis

Case-control differences were assessed using Student's paired *t* test and Wilcoxon's signed rank test for continuous variables and by McNemar's test and Bowker's test of symmetry for categorical variables.

The association between CRP concentrations and risk of colon and rectal cancer was analyzed using multivariable conditional logistic regression, adjusted for possible confounders other than those controlled for by matching, including smoking status (never, former, current, or missing data), education (no school degree/primary school, technical/professional school, secondary school, university degree, or missing data), physical activity (inactive, moderately inactive, moderately active, active, or missing data), alcohol consumption (g/day), fiber intake (g/day), red and processed meat consumption (g/day), fruit and vegetable consumption (g/day), fish and shellfish consumption (g/day), body mass index, and waist circumference (cm). For waist circumference, there were 106 missing values which for the present analysis were substituted with the sex-specific median values in the controls. In additional analyses, we adjusted the association for C-peptide, glycated hemoglobin, and HDL cholesterol (all continuously) and for self-reported history of diabetes and cardiovascular disease.

With risk-set sampling, the odds ratio derived from conditional logistic regression directly estimates the hazard ratio and thus, the relative risk (27). Participants were divided into quintiles based on the distribution of CRP concentrations among the control population (28), and relative risks were calculated. In addition, we divided subjects into groups based on cutoffs for CRP proposed by the Centers for Disease Control and Prevention and the American Heart Association for classification of cardiovascular disease risk ($<$1.0 mg/L, 1.0–2.9 mg/L, and $\geq$3.0 mg/L) (29). To test for linear trend, we used the median CRP concentrations in the categories as a continuous variable.

To test for nonlinearity, we fitted restricted cubic splines, at the 5th, 50th, and 95th percentiles of the CRP distribution, to our conditional logistic regression model and used the likelihood ratio test to check whether a nonlinear term of CRP added significant information to the model (30). In addition, we repeated these analyses with log-transformed CRP to check whether log CRP sufficiently captured the association with colon cancer. Further, we estimated the multivariable-adjusted relative risk associated with an increase of log-transformed CRP concentrations by log 2, which corresponds to a doubling of CRP concentrations on the original scale.

We estimated the association in different strata and tested for effect modification with factors that may be relevant for colorectal cancer risk (including age, sex, body mass index, waist circumference, smoking status, alcohol consumption, red/processed meat consumption, menopausal status, and hormone replacement therapy) using interaction terms (log-transformed CRP concentrations multiplied by stratum variable). Similarly, we examined whether the associations differed by cancer site (proximal/distal colon or rectum) or length of follow-up (continuously). Further, we repeated the main multivariable analyses after excluding subjects with CRP concentrations $\geq$10 mg/L ($n = 174$), subjects with diabetes ($n = 168$), and cases that occurred during the first 3 years of follow-up ($n = 454$).

Two-sided P values less than 0.05 were considered to indicate statistical significance. All statistical analyses were carried out using SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The median time between date of study recruitment and diagnosis of cancer among cases was 3.7 years. Men and women with colon cancer had higher CRP concentrations than their matched controls, although in stratified analysis among women, the difference was not significant at the 5% level (in men, the median value was 2.8 (interquartile range (IQR), 1.3–5.1) vs. 1.9 (IQR, 0.9–4.1), $P = 0.0003$; in women, it was 3.4 (IQR, 1.3–5.9) vs. 2.8 (IQR, 1.3–5.3), $P = 0.07$). Colon cancer cases had lower fish and shellfish intake than controls but higher body mass index and waist circumference than controls. Median concentrations of C-peptide and glycated hemoglobin were somewhat higher in colon cancer cases compared with controls, whereas HDL cholesterol concentrations were slightly lower. Cases with rectal cancer had a significantly lower physical activity level and higher alcohol consumption (Table 1).

Among controls, after adjustment for age and sex, CRP concentrations were positively associated with body mass index, waist circumference, waist:hip ratio, red meat intake, alcohol consumption, smoking, C-peptide, and glycated hemoglobin, whereas inverse associations were observed with educational level, physical activity, fiber intake, and HDL cholesterol (Table 2).

In the conditional logistic regression analysis, after adjustment for smoking, education, alcohol, physical activity, fiber, fruits and vegetables, red and processed meat, fish and shellfish, body mass index, and waist circumference, CRP was statistically significantly associated with risk of colon cancer (for highest quintile vs. lowest, relative risk (RR) = 1.42, 95% confidence interval (CI): 0.98, 2.05; P-trend = 0.01) but not with rectal cancer (RR = 0.91, 95% CI: 0.53, 1.54; P-trend = 0.90) (Table 3). In this multivariable-adjusted model, body mass index and waist circumference were the covariates that most strongly attenuated the association between CRP and colon cancer.

When we included CRP and a CRP cubic spline term as continuous variables in the regression model, the nonlinear CRP term added significant information to the model ($P = 0.04$), thus rejecting the null hypothesis of a linear association. In an attempt to linearize the regression model, we next

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Table 1. Baseline Characteristics of Incident Colon and Rectal Cancer Cases and Matched Controls ($n = 2{,}192$), European Prospective Investigation into Cancer and Nutrition, 1992–2003

	Colon Cancer							Rectal Cancer						
	Cases (n = 696)			Controls (n = 696)			P Value[a]	Cases (n = 400)			Controls (n = 400)			P Value[a]
	%	Mean (SD)	Median (IQR[b])	%	Mean (SD)	Median (IQR)		%	Mean (SD)	Median (IQR)	%	Mean (SD)	Median (IQR)	
Female sex[c]	52.2			52.2				45.5			45.5			
Age[c], years		59.0 (7.1)			59.0 (7.1)		0.97		58.3 (6.9)			58.3 (6.9)		0.33
Smoking status[d]														
Never smoker	41.8			44.5			0.63	40.3			39.0			0.82
Former smoker	33.8			33.5				33.0			30.7			
Current smoker	23.7			21.7				26.0			29.0			
Education[d]														
None or primary school	41.7			44.0			0.84	37.0			43.3			0.31
Technical or professional school	23.6			23.1				25.8			27.8			
Secondary school	15.7			13.4				14.5			9.8			
University degree	15.5			16.7				19.8			17.3			
Physical activity[d]														
Inactive	15.5			11.2			0.14	14.5			13.3			0.04
Moderately inactive	28.0			29.0				27.3			24.0			
Moderately active	42.1			43.4				42.3			40.5			
Active	9.2			10.9				10.3			15.0			
Menopausal status among women[c,d]														
Premenopausal	9.6			9.9			0.63	8.2			8.2			0.64
Postmenopausal	74.1			73.0				72.0			74.2			
Perimenopausal/ unknown	11.0			10.7				15.9			15.4			
Surgically postmenopausal	5.2			6.3				3.9			2.2			
HRT in postmenopausal women[c,d]	11.7			12.0			0.78	9.3			9.5			0.32
Body mass index[e]		27.2 (4.4)			26.6 (3.9)		0.01		26.8 (4.1)			26.6 (3.9)		0.49
Waist circumference, cm		91.4 (12.7)			89.2 (12.0)		<0.0001		91.1 (12.5)			90.3 (12.8)		0.25
Waist:hip ratio		0.874 (0.093)			0.886 (0.098)		0.001		0.888 (0.102)			0.892 (0.098)		0.38
Alcohol consumption, g/day			8.4 (2.3–19.1)			7.7 (2.8–17.9)	0.31			11.7 (3.4–26.1)			10.1 (3.3–21.2)	0.01
Fiber intake, g/day			21.8 (16.9–27.2)			22.3 (18.1–27.2)	0.15			21.9 (17.5–27.4)			22.0 (17.6–26.9)	0.91
Fruit and vegetable intake, g/day			365.9 (237.8–536.5)			392.4 (246.0–555.5)	0.12			353.0 (229.8–509.4)			358.1 (240.4–514.8)	0.84
Fish and shellfish intake, g/day			26.0 (13.9–44.3)			28.5 (14.0–49.7)	0.03			26.9 (14.9–47.5)			28.9 (14.0–49.4)	0.72
Red meat intake, g/day			46.4 (24.2–74.9)			47.9 (25.6–75.3)	0.86			56.0 (32.2–83.0)			49.6 (29.9–76.7)	0.06

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Processed meat intake, g/day	25.3 (13.4–41.7)	24.3 (12.6–43.2)	0.43	27.7 (14.3–47.3)	26.7 (14.0–46.4)	0.36
CRP concentration, mg/L	3.1 (1.3–5.6)	2.3 (1.1–4.7)	0.001	2.5 (1.0–4.4)	2.3 (1.0–4.2)	0.57
C-peptide level, ng/mL	4.1 (2.9–6.1)	3.9 (2.8–5.9)	0.09	4.1 (2.9–6.2)	4.2 (2.6–5.9)	0.31
Glycated hemoglobin concentration, %	5.8 (5.5–6.1)	5.7 (5.5–6.0)	0.04	5.8 (5.5–6.0)	5.7 (5.5–6.0)	0.91
HDL cholesterol concentration, mmol/L	1.3 (1.1–1.6)	1.4 (1.2–1.7)	<0.0001	1.4 (1.2–1.7)	1.4 (1.1–1.7)	0.38

Abbreviations: CRP, C-reactive protein; HDL, high density lipoprotein; HRT, hormone replacement therapy; IQR, interquartile range; SD, standard deviation.

[a] *P* values for the difference between cases and controls were determined by Student's paired *t* test for variables expressed as means, by Wilcoxon's signed rank test for variables expressed as medians, and by McNemar's test and Bowker's test of symmetry for variables expressed as percentages.

[b] 25th–75th percentiles.

[c] Sex, age, menopausal status, and use of hormone replacement therapy were among the matching criteria.

[d] Percentages do not sum to 100% because of missing values.

[e] Weight (kg)/height $(m)^2$.

repeated these steps with log-transformed CRP concentrations. In this analysis, the addition of a log-transformed CRP cubic spline term was not significant ($P = 0.14$), indicating that the log CRP term alone sufficiently captured the nonlinear association between CRP and colon cancer.

Based on the log-transformed CRP concentrations, an increase by log 2, which corresponds to a doubling of CRP concentrations on the original scale, was associated with a significant 1.09-fold (95% CI: 1.01, 1.18) relative risk of colon cancer (in men, RR = 1.13, 95% CI: 1.01, 1.27; in women, RR = 1.06, 95% CI: 0.95, 1.18; *P* for sex difference = 0.22), whereas no significant association was observed for rectal cancer (Table 4). In analyses based on CRP categories originally established for cardiovascular disease prediction, persons with CRP concentrations ≥3.0 mg/L had a 1.36-fold higher risk (95% CI: 1.00, 1.85; *P*-trend = 0.01) of colon cancer than persons with CRP concentrations <1.0 mg/L, after multivariable adjustment (Table 4). When results were stratified by sex, significantly increased risk in the higher CRP category as compared with the lower CRP category was seen in men but not in women.

The strength of the association did not essentially change when C-peptide, glycated hemoglobin, and HDL cholesterol concentrations were added to the multivariable model individually or in combination. For example, among participants who had biomarker information available for all case-control sets ($n = 1{,}298$), the multivariable-adjusted relative risk of colon cancer in subjects with CRP concentrations ≥3.0 mg/L compared with those with CRP concentrations <1.0 mg/L was 1.44 (95% CI: 0.95, 2.18; *P*-trend = 0.01) before adjustment for the 3 biomarkers and 1.37 (95% CI: 0.90, 2.08; *P*-trend = 0.03) after adjustment. Further adjustment for history of cardiovascular disease or diabetes did not substantively change the results (data not shown).

The association was stronger for proximal colon cancer (280 cases and 280 controls; in the multivariable model for CRP concentrations ≥3.0 mg/L vs. <1.0 mg/L, RR = 1.63, 95% CI: 0.99, 2.71; *P*-trend = 0.02) than for distal colon cancer (322 cases and 322 controls; RR = 1.11, 95% CI: 0.68, 1.81; *P*-trend = 0.14). When results were analyzed by sex, the trend for proximal colon cancer was statistically significant only in men (in the multivariable model for CRP concentrations ≥3.0 mg/L vs. <1.0 mg/L, RR = 2.81, 95% CI: 1.27, 6.21; *P*-trend = 0.01). The differences between proximal and distal colon cancers and rectal cancer were statistically significant at the 5% level for men (*P*-heterogeneity = 0.02) but not for women (*P*-heterogeneity = 0.52).

The association of CRP with colon cancer risk was stronger among participants with a high intake of processed meat compared with those with a low intake (*P*-interaction = 0.04). No significant interactions with CRP were observed for age, body mass index, waist circumference, smoking status, alcohol, or red meat intake (Table 5).

When we restricted the main analysis to postmenopausal women not using hormone replacement therapy (228 cases and 227 controls), the relative risk in the multivariable model for CRP concentrations ≥3.0 mg/L versus <1 mg/L was 1.04 (95% CI: 0.57, 1.89; *P*-trend = 0.50).

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Table 2. Age- and Sex-adjusted Characteristics of Controls at Baseline ($n = 1{,}093$[a]), by Quintile of C-Reactive Protein Concentration, European Prospective Investigation into Cancer and Nutrition, 1992–2003[b]

	Quintile of CRP Concentration					*P* for Trend[c]
	1 (<0.85 mg/L)	2 (0.85–<1.79 mg/L)	3 (1.79–<2.95 mg/L)	4 (2.95–<5.33 mg/L)	5 (≥5.33 mg/L)	
Age[d], years	57.6	58.7	58.3	59.7	59.3	0.01
Female sex[e], %	45.0	42.7	50.6	56.1	55.0	0.01
Smoking status[f], %						
Never smoker	49.4	47.2	42.3	37.1	36.2	0.001
Former smoker	33.8	29.8	31.5	31.4	34.2	0.59
Current smoker	16.8	21.6	25.7	30.3	27.3	0.01
Education[f], %						
None or primary school	32.6	39.8	44.6	48.6	52.7	<0.0001
Technical or professional school	30.4	20.5	24.7	24.4	23.8	0.48
Secondary school	12.4	14.2	15.3	12.2	6.3	0.01
University degree	22.6	22.7	13.6	11.8	14.0	0.01
Physical activity[f], %						
Inactive	10.6	14.7	12.8	10.8	10.5	0.42
Moderately inactive	25.9	25.9	23.8	26.8	33.6	0.03
Moderately active	40.7	43.1	48.4	39.4	40.2	0.46
Active	14.7	10.1	10.7	15.0	11.6	0.86
Menopausal status among women[f], %						
Premenopausal	1.6	14.8	14.8	10.2	5.6	0.35
Postmenopausal	76.6	71.0	71.8	77.8	69.6	0.36
Perimenopausal/unknown	18.6	11.1	9.8	8.8	13.9	0.71
Surgically postmenopausal	3.1	3.2	3.6	3.2	10.9	0.002
HRT in postmenopausal women[f], %	11.5	15.8	9.7	6.0	11.3	0.57
Body mass index[g]	24.9	25.9	26.8	27.2	28.1	<0.0001
Waist circumference, cm	85.3	87.3	90.0	91.1	94.0	<0.0001
Waist:hip ratio	0.856	0.866	0.879	0.889	0.904	<0.0001
Alcohol consumption, g/day	13.7	13.3	14.8	17.8	16.9	0.02
Fiber intake, g/day	23.9	23.8	22.9	22.5	22.2	0.01
Fish and shellfish intake, g/day	32.0	39.1	35.2	35.6	40.1	0.06
Fruit and vegetable intake, g/day	430.4	449.6	422.8	410.7	402.8	0.08
Red meat intake, g/day	49.8	49.6	53.2	56.5	64.7	<0.0001
Processed meat intake, g/day	33.6	28.7	34.4	30.0	32.6	0.88
C-peptide concentration, ng/mL	3.9	4.5	4.4	5.0	5.6	<0.0001
Glycated hemoglobin concentration, %	5.8	5.8	5.9	5.8	6.0	0.05
HDL cholesterol concentration, mmol/L	1.58	1.48	1.45	1.44	1.40	<0.0001

Abbreviations: CRP, C-reactive protein; HDL, high density lipoprotein; HRT, hormone replacement therapy.

[a] Duplicate controls were excluded from this analysis.

[b] Data are mean values unless otherwise indicated.

[c] *P* for trend from a linear model, calculated using the median CRP concentrations within quintiles as a continuous variable, adjusted for age and sex.

[d] Results for age were adjusted for sex only.

[e] Results for sex were adjusted for age only.

[f] Percentages do not sum to 100% because of missing values.

[g] Weight (kg)/height $(m)^2$.

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Table 3. Relative Risks of Colon and Rectal Cancer According to Quintile of Baseline C-Reactive Protein Concentration, European Prospective Investigation into Cancer and Nutrition, 1992–2003

	Quintile of CRP Concentration																		P for Trend[a]
	1[b] (<0.85 mg/L)		2 (0.85–<1.79 mg/L)				3 (1.79–<2.95 mg/L)				4 (2.95–<5.33 mg/L)				5 (≥5.33 mg/L)				
	No. of Cases	No. of Controls	No. of Cases	No. of Controls	RR	95% CI	No. of Cases	No. of Controls	RR	95% CI	No. of Cases	No. of Controls	RR	95% CI	No. of Cases	No. of Controls	RR	95% CI	
Colon Cancer																			
Overall	108	133	120	144			109	136			168	133			191	150			
Model 1[c]					1.03	0.72, 1.49			0.98	0.69, 1.41			1.59	1.12, 2.24			1.61	1.14, 2.26	0.001
Model 2[d]					1.03	0.71, 1.51			0.97	0.67, 1.42			1.50	1.04, 2.15			1.61	1.13, 2.29	0.001
Model 3[e]					1.04	0.71, 1.52			0.91	0.62, 1.33			1.40	0.97, 2.03			1.42	0.98, 2.05	0.01
Men	54	76	59	78			60	64			81	54			79	61			
Model 1					1.04	0.63, 1.72			1.30	0.80, 2.12			2.13	1.29, 3.54			1.77	1.09, 2.87	0.004
Model 2					1.06	0.62, 1.81			1.24	0.73, 2.09			1.84	1.07, 3.15			1.74	1.03, 2.94	0.01
Model 3					1.04	0.60, 1.79			1.14	0.67, 1.95			1.69	0.98, 2.93			1.52	0.88, 2.62	0.05
Women	54	57	61	66			49	72			87	79			112	89			
Model 1					0.97	0.57, 1.64			0.71	0.41, 1.22			1.19	0.73, 1.95			1.36	0.83, 2.22	0.04
Model 2					1.02	0.59, 1.76			0.75	0.43, 1.33			1.30	0.77, 2.18			1.55	0.92, 2.61	0.01
Model 3					1.04	0.60, 1.82			0.69	0.39, 1.23			1.20	0.70, 2.04			1.32	0.76, 2.28	0.09
Rectal Cancer																			
Overall	81	86	74	74			74	85			100	86			71	69			
Model 1					1.08	0.69, 1.69			0.92	0.60, 1.42			1.28	0.83, 1.98			1.12	0.71, 1.77	0.54
Model 2					1.00	0.63, 1.61			0.79	0.50, 1.25			1.20	0.76, 1.90			1.00	0.61, 1.62	0.79
Model 3					0.99	0.62, 1.59			0.77	0.48, 1.24			1.15	0.71, 1.85			0.91	0.53, 1.54	0.90
Men	40	44	49	47			43	45			51	43			35	39			
Model 1					1.17	0.65, 2.12			1.06	0.57, 1.95			1.39	0.72, 2.70			1.03	0.53, 1.97	0.94
Model 2					1.05	0.53, 2.07			1.02	0.51, 2.05			1.13	0.53, 2.42			0.75	0.35, 1.58	0.33
Model 3					1.06	0.54, 2.10			1.05	0.52, 2.13			1.14	0.53, 2.47			0.75	0.34, 1.63	0.34
Women	41	42	25	27			31	40			49	43			36	30			
Model 1					0.96	0.48, 1.95			0.79	0.43, 1.47			1.18	0.66, 2.12			1.26	0.65, 2.44	0.33
Model 2					0.89	0.40, 1.98			0.57	0.27, 1.19			1.31	0.68, 2.50			1.25	0.60, 2.61	0.27
Model 3					0.88	0.39, 1.96			0.55	0.25, 1.18			1.23	0.62, 2.44			1.05	0.45, 2.41	0.56

Abbreviations: CI, confidence interval; CRP, C-reactive protein; RR, relative risk.

[a] *P* value for trend, calculated using the median CRP concentrations within quintiles as a continuous variable.

[b] Reference category (RR = 1).

[c] Results were based on conditional logistic regression matching characteristics: age, sex, study center, follow-up time since blood collection, time of blood collection, and fasting status. Women were further matched by menopausal status and phase of the menstrual cycle at blood collection; postmenopausal women were matched by use of hormone replacement therapy.

[d] Results were based on conditional logistic regression (matching factors) with adjustment for smoking status, education, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, consumption of red and processed meat, consumption of fish and shellfish, body mass index, and waist circumference.

[e] Results were adjusted for all model 2 variables plus body mass index (weight (kg)/height $(m)^2$) and waist circumference.

Table 4. Relative Risks of Colon and Rectal Cancer According to Category of C-Reactive Protein Concentration in a Multivariable Model[a], European Prospective Investigation into Cancer and Nutrition, 1992–2003

	Category of CRP Concentration										*P* for Trend[b]	RR (Continuously per Doubling)[c]	95% CI	*P* Value[d]
	<1.0 mg/L[e]		1.0–<3.0 mg/L				≥3.0 mg/L							
	No. of Cases	No. of Controls	No. of Cases	No. of Controls	RR	95% CI	No. of Cases	No. of Controls	RR	95% CI				
Colon Cancer														
Overall	132	158	209	256	0.94	0.68, 1.29	355	282	1.36	1.00, 1.85	0.01	1.09	1.01, 1.18	0.02
Men	61	93	115	126	1.28	0.82, 2.00	157	114	1.74	1.11, 2.73	0.01	1.13	1.01, 1.27	0.03
Women	71	65	94	130	0.66[f]	0.41, 1.07	198	168	1.06[f]	0.67, 1.68	0.13	1.06	0.95, 1.18	0.29
Rectal Cancer														
Overall	98	104	134	142	0.87	0.59, 1.29	168	154	1.02	0.67, 1.57	0.65	0.99	0.88, 1.10	0.82
Men	53	58	81	78	0.99	0.57, 1.74	84	82	0.82	0.43, 1.57	0.47	0.99	0.84, 1.17	0.92
Women	45	46	53	64	0.68[f]	0.35, 1.32	84	72	1.18[f]	0.62, 2.23	0.26	0.98	0.82, 1.17	0.81

Abbreviations: CI, confidence interval; CRP, C-reactive protein; RR, relative risk.

[a] Results were based on conditional logistic regression (matching factors: age, sex, study center, follow-up time since blood collection, time of blood collection, and fasting status), with adjustment for smoking status, education, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, consumption of red and processed meat, consumption of fish and shellfish, body mass index, and waist circumference. Women were further matched by menopausal status and phase of the menstrual cycle at blood collection; postmenopausal women were matched by use of hormone replacement therapy.

[b] *P* value for trend, calculated using the median CRP concentrations within categories of CRP as a continuous variable.

[c] Estimated multivariable-adjusted RR associated with an increase in continuous log-transformed CRP concentrations by log 2.

[d] *P* value for continuous log-transformed CRP concentrations by log 2.

[e] Reference category (RR = 1).

[f] *P* for interaction with sex: colon cancer, $P = 0.22$; rectal cancer, $P = 0.39$.

After exclusion of cases that occurred during the first 3 years of follow-up in the main multivariable analysis ($n = 454$), the relative risks for CRP concentrations of 1.0–2.9 mg/L and ≥3.0 mg/L versus <1.0 mg/L were 1.07 (95% CI: 0.99, 1.16) and 1.37 (95% CI: 0.90, 2.09; *P*-trend = 0.09), respectively. There was no significant interaction with the time of follow-up (in a model adjusted for matching factors, *P*-interaction = 0.42). Exclusion of participants with CRP concentrations ≥10 mg/L or subjects with diabetes from our main analysis did not markedly change the pattern of the results (data not shown).

DISCUSSION

In this prospective nested case-control study, we found a positive association between circulating CRP concentrations and risk of colon cancer which was predominant among men. This association was independent of body mass index, waist circumference, and concentrations of C-peptide, glycated hemoglobin, and HDL cholesterol. No significant association was observed for rectal cancer. These data support the hypothesis that elevated CRP concentrations, as a marker of systemic low-grade inflammation, are related to a higher risk of colon cancer independently of general and abdominal adiposity, hyperinsulinemia, hyperglycemia, and dyslipidemia.

Our findings regarding CRP and colon and rectal cancer risk in general are in line with results from a recent meta-analysis of prospective studies (16). However, it was unclear to what extent the associations of CRP with colon cancer risk reported in the meta-analysis were accounted for by other potential predictors of colon cancer closely related to inflammation. CRP concentrations are associated with abdominal adiposity, hyperinsulinemia, dyslipidemia, and hyperglycemia (17, 18), and an increasing body of evidence indicates that these metabolic abnormalities may be related to a higher risk of colon cancer (19–23). To our knowledge, the present study is among the first to have controlled for these markers when examining the association of CRP with colorectal cancer risk. Results of our study show that CRP is related to a higher risk of colon cancer even when these factors are accounted for, suggesting that the association of low-grade inflammation with cancer risk cannot be fully explained by concomitant hyperinsulinemia, hyperglycemia, or dyslipidemia.

The observed differential associations with CRP by cancer subsite suggest that the proximal colon, distal colon, and rectum may differ in terms of cancer susceptibility to inflammation. This is supported by the observation that patients with ulcerative colitis who have inflammation primarily in the colon are at higher risk of colon cancer, whereas those who have inflammation limited to the rectum are not at increased cancer risk (31). Similar differences between colorectal cancer subsites have previously been shown to exist for associations with other factors, including excess body weight, waist circumference, and physical inactivity (19, 32, 33). These differences should be further investigated and taken into account in future epidemiologic studies.

It is unclear why the association between CRP and colon cancer risk in our study was significantly present in men but not in women; however, similar findings were reported

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Table 5. Relative Risk of Colon Cancer by Category of C-Reactive Protein Concentration in a Multivariable Model[a], According to Selected Baseline Risk Factors for Colorectal Cancer, European Prospective Investigation into Cancer and Nutrition, 1992–2003

	Category of CRP Concentration										*P* for Trend[b]	RR (Continuously per Doubling)[c]	95% CI	*P* Value[d]	*P* for Interaction[e]
	<1.0 mg/L[f]		1.0–<3.0 mg/L				≥3.0 mg/L								
	No. of Cases	No. of Controls	No. of Cases	No. of Controls	RR	95% CI	No. of Cases	No. of Controls	RR	95% CI					
Median age, years															0.30
<59.5	78	87	108	129	0.88	0.58, 1.34	157	125	1.30	0.85, 1.99	0.08	1.06	0.95, 1.19	0.30	
≥59.5	54	71	101	127	0.96	0.61, 1.52	198	157	1.40	0.91, 2.15	0.03	1.12	1.01, 1.24	0.03	
Median body mass index[g]															0.99
<26.4	89	115	100	131	0.97	0.65, 1.45	140	116	1.45	0.98, 2.15	0.03	1.09	0.99, 1.20	0.09	
≥26.4	43	43	109	125	0.86	0.50, 1.46	215	166	1.21	0.73, 2.01	0.10	1.09	0.97, 1.22	0.14	
Waist circumference, cm															0.36
<88 (women) or <102 (men)	113	145	145	193	0.99	0.70, 1.40	204	177	1.52	1.08, 2.15	0.004	1.12	1.03, 1.22	0.009	
≥88 (women) or ≥102 (men)	19	13	64	63	0.59	0.26, 1.38	151	105	0.87	0.40, 1.91	0.31	1.04	0.89, 1.20	0.65	
Smoking status															0.37
Never smoker	61	78	82	116	0.97	0.61, 1.55	153	121	1.50	0.97, 2.33	0.02	1.13	1.02, 1.25	0.03	
Ever smoker	71	80	127	140	0.91	0.60, 1.39	202	161	1.25	0.84, 1.88	0.09	1.06	0.96, 1.17	0.26	
Sex-specific median alcohol intake, g/day															0.46
Low (<14.8 for women, <3.2 for men)	66	79	110	136	0.94	0.60, 1.45	185	135	1.53	0.98, 2.37	0.01	1.12	1.01, 1.24	0.03	
High (≥14.8 for women, ≥3.2 for men)	66	79	99	120	0.94	0.60, 1.47	170	147	1.25	0.82, 1.91	0.15	1.06	0.96, 1.18	0.24	
Median red meat intake, g/day															0.32
<48.8	79	88	98	138	0.77	0.50, 1.19	191	134	1.44	0.96, 2.18	0.004	1.13	1.02, 1.25	0.02	
≥48.8	53	70	111	118	1.18	0.74, 1.89	164	148	1.31	0.83, 2.05	0.28	1.05	0.95, 1.17	0.33	
Median processed meat intake, g/day															0.04
<25.5	73	75	109	137	0.76	0.50, 1.18	168	152	1.02	0.67, 1.54	0.43	1.02	0.92, 1.13	0.68	
≥25.5	59	83	100	119	1.23	0.77, 1.95	187	130	1.92	1.23, 3.00	0.001	1.18	1.06, 1.31	0.003	

Abbreviations: CI, confidence interval; CRP, C-reactive protein; RR, relative risk.

[a] Results were based on conditional logistic regression (matching factors: age, sex, study center, follow-up time since blood collection, time of blood collection, and fasting status), with adjustment for smoking status, education, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, consumption of red and processed meat, consumption of fish and shellfish, body mass index, and waist circumference. Women were further matched by menopausal status and phase of the menstrual cycle at blood collection; postmenopausal women were matched by use of hormone replacement therapy.

[b] *P* value for trend, calculated using the median CRP concentrations within categories of CRP as a continuous variable.

[c] Estimated multivariable-adjusted RR associated with an increase in continuous log-transformed CRP concentrations by log 2.

[d] *P* value for continuous log-transformed CRP concentrations by log 2.

[e] *P* value for interaction between log-transformed CRP concentrations and stratified variables in a conditional logistic regression model.

[f] Reference category (RR = 1).

[g] Weight (kg)/height $(m)^2$.

previously (16). Differences between the sexes have also been observed for the association of CRP with other outcomes, including cardiovascular disease (34) and type 2 diabetes (35, 36). Among postmenopausal women, use of exogenous hormones is associated with a reduced risk of colon cancer (37, 38), and our previous work suggested that hormone replacement therapy may attenuate the positive association between waist circumference and risk of colon cancer (19). In our analysis, the association between CRP and colon cancer risk did not become stronger when we restricted the results to postmenopausal women not using hormone replacement therapy, arguing against the possibility that hormone replacement therapy is one of the reasons for the weaker association of CRP with colon cancer among women as compared with men.

In subgroup analysis, the association between CRP and colon cancer risk was observed among participants with higher consumption of processed meat but not among those with lower consumption of processed meat. Previous research has shown that a higher intake of processed meat is positively associated with colorectal cancer risk (39, 40) and that dietary patterns characterized by a high intake of processed meat are associated with higher CRP concentrations (41). However, the mechanism by which processed meat may modify the association of CRP with colon cancer is unclear, and future studies are warranted to shed light on these potential interactions.

Among the strengths of our study are the prospective design and the largest number of cases to date, which allowed analysis by cancer subsite and sex. The study included participants with a broad range of characteristics from several European countries, and the biologic relations between CRP concentrations and risk of colon and rectal cancer observed in our study should be generalizable to men and women of this age range.

Among the limitations of the study is the lack of information on the existence of inflammatory diseases at baseline (e.g., inflammatory bowel disease, rheumatoid arthritis), which may be associated with higher CRP concentrations. However, our results did not markedly change when we excluded people with CRP concentrations $\geq$10 mg/L; therefore, it is unlikely that our study included a substantial number of persons with chronic inflammatory diseases.

The use of nonsteroidal antiinflammatory drugs (NSAIDs) may be inversely related to CRP concentrations and may reduce colorectal cancer risk. Unfortunately, information about NSAID use is not available in EPIC, and therefore we were not able to adjust for this variable. However, we speculate that any effect of NSAIDs on CRP concentrations is more likely to reflect intermediary mechanisms, rather than confounding, for the beneficial effects of NSAIDs on cancer risk. Similarly, information about family history of colorectal cancer, which is a predictor of colorectal cancer, is not available in EPIC; however, there is no evidence that family history is related to CRP concentrations, and prior studies do not suggest that family history is a strong confounder of the association with colorectal cancer risk (7, 9, 11).

The use of a single CRP measurement at baseline might have caused regression dilution bias. However, previous studies have shown that CRP concentrations are relatively stable, with an intraclass correlation coefficient of 0.67 over a 4-year period (42).

We used C-peptide and glycated hemoglobin as more long-term markers for insulin and glucose concentrations (43, 44). Although C-peptide concentrations also depend on fasting status, previous studies have shown that circulating concentrations measured in nonfasting subjects are a significant predictor of colon cancer risk (20). Nevertheless, the adjustment for a single measurement or the use of surrogate markers in our analysis may not have fully controlled for the effects of hyperinsulinemia and hyperglycemia.

Despite the exclusion of participants with cancer at baseline, we cannot exclude the possibility that some subjects had yet-undiagnosed cancer. However, results did not change appreciably after we excluded subjects with a follow-up time of less than 3 years. Although we adjusted for relevant variables in the analyses, because of the observational nature of the study, we cannot avoid the possibility of residual confounding. Finally, we performed several subgroup analyses, and multiple testing in association studies may increase the likelihood of false-positive results. In addition, it should be noted that we examined differences in the association of CRP with colon cancer between subgroups on a relative scale; the absolute risks may be different across subgroups.

In conclusion, elevated concentrations of CRP are associated with a higher risk of colon cancer, but not rectal cancer, predominantly among men. Further, our study suggests that the association of CRP with colon cancer risk is independent of general and abdominal obesity, hyperinsulinemia, hyperglycemia, and dyslipidemia. Our research gives further credence to the hypothesis that chronic low-grade inflammation may be involved in colon carcinogenesis.

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