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C-reactive Protein and Future Risk of Clinical and Molecular Subtypes of Colorectal Cancer

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ABSTRACT

Background: Inflammation has been implicated in colorectal cancer etiology, but the relationship between C-reactive protein (CRP) and colorectal cancer risk is unclear. We aimed to investigate the association between prediagnostic plasma CRP concentrations and the risk of clinical and molecular colorectal cancer subtypes.

Methods: We used prospectively collected samples from 1,010 matched colorectal cancer case–control pairs from two population-based cohorts in Northern Sweden, including 259 with repeated samples. Conditional logistic regression and linear mixed models were used to estimate relative risks of colorectal cancer, including subtypes based on *BRAF* and *KRAS* mutations, microsatellite instability status, tumor location, stage, lag time, and (using unconditional logistic regression) body mass index.

Results: CRP was not associated with colorectal cancer risk, regardless of clinical or molecular colorectal cancer subtype. For participants with advanced tumors and blood samples <5 years before diagnosis, CRP was associated with higher risk [OR per 1 unit increase in natural logarithm (ln) transformed CRP, 1.32; 95% confidence interval (CI), 1.01–1.73]. CRP levels increased over time, but average time trajectories were similar for cases and controls ($P_{interaction} = 0.19$).

Conclusions: Our results do not support intertumoral heterogeneity as an explanation for previous inconsistent findings regarding the role of CRP in colorectal cancer etiology. The possible association in the subgroup with advanced tumors and shorter follow-up likely reflects undiagnosed cancer at baseline.

Impact: Future efforts to establish the putative role of chronic, low-grade inflammation in colorectal cancer development will need to address the complex relationship between systemic inflammatory factors and tumor microenvironment, and might consider larger biomarker panels than CRP alone.

Introduction

Inflammation is a recognized hallmark of cancer, occurring not only in existing cancer but also promoting cancer development (1). Inflammation-induced tumorigenesis may be driven by local inflammatory conditions, such as inflammatory bowel disease (2). Whether a similar carcinogenic effect can be achieved by inflammatory factors reaching a tissue through the bloodstream, that is, a systemic effect, is less certain, although systemic inflammation is postulated to be one of the driving mechanisms behind the obesity–cancer link (3).

In inflammatory bowel disease, the degree of histologic inflammation influences the risk of developing colorectal cancer (4, 5). Elevated levels of C-reactive protein (CRP), an acute phase protein synthesized by the liver in response to acute and chronic inflammation, have been reported to associate with higher future risk of colorectal cancer in patients with inflammatory bowel disease (6). In contrast, a similar relationship when the cause of higher CRP is not local inflammation specifically has not been convincingly demonstrated. Results from previous studies of CRP in relation to colorectal cancer and colorectal adenoma risk, including meta-analyses, have been mixed (7–20). Some have been suggestive of a relation between higher CRP levels and increased risk of colorectal cancer (7–11) and colorectal adenoma (12, 13), whereas others have been inconclusive (14–16) or null (17–19). A large Mendelian randomization study of more than 30,000 colorectal cancer cases from three international consortia found no evidence of a causal relation between genetically determined inflammation reflected by CRP and colorectal cancer risk (20), while three other studies of CRP-related genetic variants suggested a relation (7–9).

Colorectal cancer is a heterogeneous disease with differences in etiology and prognosis depending on factors such as anatomic location of the tumor (21), disease stage (22), and well-defined molecular features (23, 24). Important molecular tumor characteristics in colorectal cancer, clinically used for both treatment strategies and prognosis, are mutations in the *KRAS* and *BRAF* genes and microsatellite instability (MSI) status (25). Some findings support different etiologic mechanisms or risk factors for different clinical and molecular colorectal cancer subtypes (26–29). Whether such intertumoral heterogeneity could explain some of the inconsistency in earlier findings for CRP and risk of colorectal cancer has not been explored.

The aim of this investigation was to study plasma concentrations of CRP in relation to future risk of developing colorectal cancer, including molecular and clinical colorectal cancer subtypes.

Materials and Methods

Study population

This was a nested case–control study using prospectively collected blood samples and data from 1,010 colorectal cancer cases and 1,010 matched control participants in the population-based Northern Sweden Health and Disease Study (NSHDS) cohorts (**Fig. 1**). The final

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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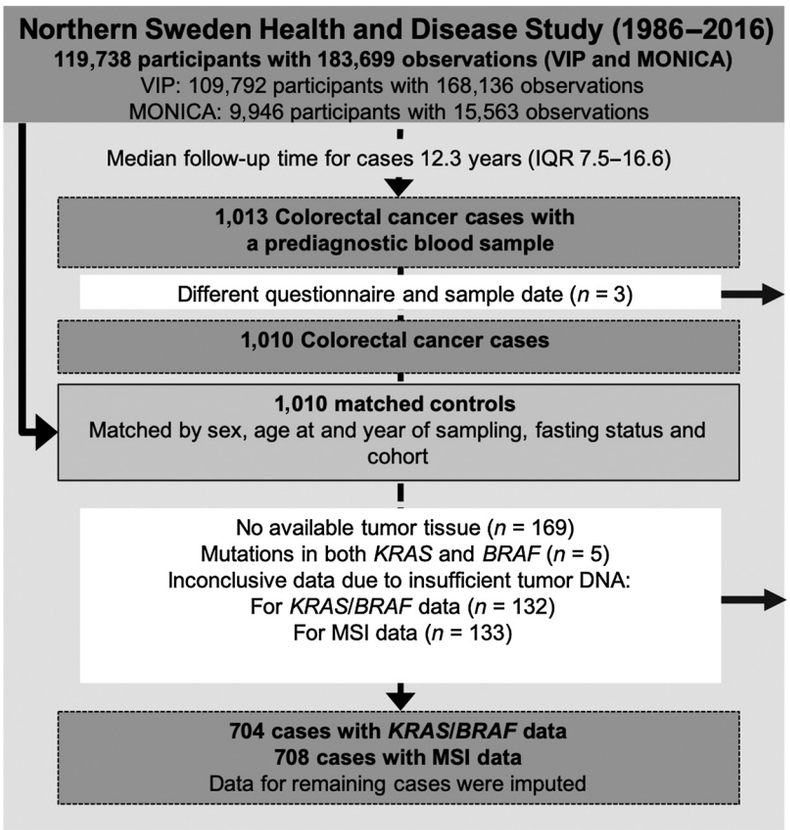

Figure 1.
Summary of the study design, including inclusions and exclusions of study participants.

population consisted of 1,854 participants (91.8%) from the larger cohort, the Västerbotten Intervention Programme (VIP), and 166 participants (8.2%) were from the Northern Sweden MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) study. The cohorts, described in detail elsewhere (30, 31), have very similar protocols and include health examinations and extensive health and lifestyle questionnaires.

Study participants

All study participants were recruited between October 1986 and May 2016 and followed until a first incident cancer diagnosis other than nonmelanoma skin cancer (identified through linkage to the Cancer Registry of Northern Sweden), death (linked to the Swedish Cause of Death Registry), migration (linked to the Swedish Registry of Total and Population Changes), or to the follow-up date for this study, May 31, 2016, whichever came first. International Classification of Diseases (ICD)-10 codes were used to identify colorectal adenocarcinoma cases: C18.0 and C18.2–18.9 for colon cancers and C19.9 and C20.9 for rectal cancers. Verification of colorectal cancer diagnosis and collection of data on anatomic site and tumor stage was done using the national Swedish Colorectal Cancer Register, and a gastrointestinal pathologist (R. Palmqvist) reviewed medical records when necessary to fill gaps or clarify uncertainty. Three cases with nonmatching blood sampling and questionnaire dates were excluded, leaving 1,010 cases for analysis. Each case was matched to one control based on cohort, sex, age, number of sample freeze thaw cycles, year of blood sampling and data collection, and fasting status at sample collection. The controls were required to be alive and have no cancer diagnosis other than nonmelanoma skin cancer at the time of diagnosis for their corresponding case.

For 265 of the colorectal cancer cases and their matched controls, data and blood samples were available from both the baseline health examination and a second measurement generally approximately 10 years later (87.6% had 9–11 years between measurements), due to the recruitment protocol of the VIP cohort. Six matched case-sets in which either the case, control, or both, had less than 5 years between the two sampling occasions were excluded, resulting in 259 complete case-sets ($n = 518$ participants) for repeated measurement analysis.

In total, 2,550 samples collected from 2,020 participants were analyzed in this study.

The study was approved by the Research Ethics Committee of Umeå University (Umeå, Sweden). All study subjects provided written informed consent at recruitment, and the study was conducted in accordance with the Declaration of Helsinki.

Blood sampling

Participants in the VIP cohort were asked to fast overnight (>8 hours) before the health examination at which venous blood samples were taken. In the MONICA cohort, venous blood samples were taken after 4 hours fasting until 1992, and after 8 hours fasting after 1992. In this study, 82% of the measurements (baseline and repeat) were taken after a fasting period >8 hours, 15% after 4–8 hours, and 3% after <4 hours. All blood samples in this study were collected in EDTA tubes and separated into plasma, buffy coat, and erythrocyte fractions. Samples were cryopreserved at −80°C within 1 hour or at −20°C for at most 1 week before storage at −80°C.

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CRP analysis

The methodology used for analysis of CRP is described elsewhere (32). Briefly, we used the V-PLEX Human CRP Kit (Meso Scale Discovery, catalog no.: K151STD), with readings performed on a MESO QuickPlex SQ 120 (MSD, catalog no.: AI0AA-0). Case–control status was kept blinded until the data preprocessing and analysis stages. All CRP levels were normalized to the last plate (plate 30) to account for any laboratory drift. Inter- and intra-assay coefficients of variation were 1.02% and 0.41%, respectively.

Tumor tissue analysis

DNA extractions and analyses of mutational status have been described in detail elsewhere (33). In this study, tumor tissue samples were available for 841 colorectal cancer cases (83%). Five cases had mutations in both *KRAS* and *BRAF* and were therefore excluded in the subtype analysis. A total of 132 cases had inconclusive *KRAS* or *BRAF* mutation status, and 133 cases had inconclusive MSI status, in both cases mostly due to lack of tumor DNA. In total, 387 cases had unavailable *KRAS, BRAF*, and/or MSI status ($n = 301$ lacked *KRAS/BRAF* status), of which 216 cases lacked data on all three molecular characteristics.

Covariates

Covariates were selected for multivariable modeling based on their theoretical relevance as potential confounders of an association between CRP and colorectal cancer risk (i.e., putative causal relationship with CRP levels and with colorectal cancer risk independently of CRP). Covariates included smoking status, recreational physical activity, alcohol intake, diabetes, and body mass index (BMI). Smoking status was included as nonsmoker, ex-smoker, or current smoker, and recreational physical activity as a scale from 1 to 4, from inactive to active, based on two questions and then harmonized, in the VIP questionnaire (level and frequency of recreational physical activity the last 3 months) and MONICA questionnaire (level and frequency of recreational physical activity the last 12 months). Alcohol intake was self-reported and obtained from a validated food frequency questionnaire (34): zero intake or above/below sex-specific median (in grams/day). Diabetes was defined as self-reported diabetes mellitus or diabetes mellitus diagnosed at the health examination [according to the World Health Organization (WHO) diagnostic criteria: fasting plasma glucose concentration ≥7.0 mmol/L or 2-hour post load plasma glucose concentration ≥11.1 mmol/L in MONICA project or ≥12.2 mmol/L in VIP, which used capillary blood]. BMI (kg/m^2) was calculated from height and weight measured at the health examination, in light clothing and without shoes.

Statistical analysis

Baseline variables were compared across CRP categories using χ^2 tests for categorical variables and nonparametric Kruskal–Wallis tests for continuous variables. Mean baseline CRP levels (mg/L) in cases and controls were compared within BMI groups (<25, 25–30, and >30 kg/m^2) using *t* test. ORs for colorectal cancer were estimated by conditional logistic regression. CRP measurements were natural logarithm (ln) transformed to achieve approximate normality, and ORs were calculated per 1 unit increase in ln CRP. Three conditional multivariable logistic regression models, including ln CRP, and conditioned on the matched variables, were run. Model 1 included the matching variables age, sex, cohort, sample year, and fasting status. Risk estimates in model 2 were additionally adjusted for smoking status, physical activity, alcohol intake, and diabetes. Because excess body fat could act as both a confounder for CRP and/or as a factor on the same causal pathway (i.e., CRP could mediate an association between body size and colorectal cancer risk), we included BMI as an additional covariate in a separate model (model 3).

To investigate whether associations between circulating levels of CRP and colorectal cancer risk differ according to clinical and molecular tumor characteristics, we estimated ORs for the subtypes using conditional logistic regression. $P_{\text{heterogeneity}}$ between subtypes was tested with a Wald test, comparing the observed overall log ORs and subtype-specific log ORs from the final multivariable model 3 (for subgroups of BMI, model 2).

For the subset of 518 participants with repeated measurements, we modeled average intraindividual changes in CRP concentrations over time for cases and controls using linear mixed models. ln CRP concentrations were modeled with the coded identification numbers for participants and for matched case–control pairs included as random factors. Case–control status, time between sampling and diagnosis (time = 0 at the time of case diagnosis for each case–control pair), smoking status, recreational physical activity, alcohol intake, diabetes, and BMI were included in the model as fixed factors, thus accounting for within-individual variation in time between measurements, in time from measurement to diagnosis, and in the other covariates. To test for differences in average intraindividual changes in CRP between cases and controls, case–control status and time was included as an interaction term. Associations were tested using regression coefficient *t* tests with degrees of freedom from Satterthwaite approximation.

Missing values on tumor variables and some potential confounders in baseline and repeat samples were assumed to be missing at random (MAR), meaning that the propensity for a data point to be missing was assumed to be dependent on some observable characteristics. Therefore, missing values were imputed using multiple imputation by chained equations, also called fully conditional specification (35). First, 15 datasets were imputed in 10 iterations, with a predictive mean matching model for continuous variables and logistic regression models for categorical models. The imputation model included the exposure CRP (mg/L) and the potential confounders age, sex, cohort, fasting status (all used as predictors), smoking status, physical activity, alcohol intake, and BMI (all used as predictors and imputed for missing values). Then a combined dataset with the imputed values from the 15 imputed datasets was created. Finally, missing data specific to the cases were imputed, including tumor site, tumor stage, *KRAS* and *BRAF* mutation status, and MSI status. These variables were imputed in 30 imputed datasets in 20 iterations, including the same predictors as in the first imputation step, as well as tumor variables and age at and year of diagnosis (1986–2006, 2007–2012, and 2013–2016). To evaluate the plausibility of imputed variables, we compared distributions between imputed and nonmissing values.

Analyses of baseline association models as well as baseline and repeat characteristics were performed with IBM SPSS statistics version 26. Mixed models were fitted using the lme4R-package in R v.3.5.0 (R Foundation for Statistical Computing). All *P* values were two-tailed, and $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics

Mean (SD) level of CRP at baseline was 2.75 mg/L (5.59) for controls and 3.01 (5.27) for cases. Baseline characteristics according

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Table 1. Baseline characteristics of participants, *N* (%)[a] or median (IQR).

	All	CRP <1 mg/L	CRP 1–3 mg/L	CRP >3 mg/L	*P*[b]	Missing[c]
All participants	2,020	793 (39.3)	716 (35.4)	511 (25.3)	—	0
CRC status					0.164	
Cases	1,010 (50)	385 (48.5)	351 (49.0)	274 (53.6)		0
Controls	1,010 (50)	408 (51.5)	365 (51.0)	237 (46.4)		0
Sex					0.249	
Male	1,050 (52.0)	427 (53.8)	372 (52.0)	251 (49.1)		0
Female	970 (48.0)	366 (46.2)	344 (48.0)	260 (50.9)		
Age at baseline	56.3 (49.9–60.0)	50.3 (49.8–60.0)	59.3 (50.0–60.0)	59.8 (50.0–60.1)	<0.001	0
Age at diagnosis of cases	66.4 (60.5–72.6)	65.3 (57.4–71.2)	67.6 (61.7–73.6)	66.8 (61.9–73.0)	<0.001	0
Follow-up time of cases[d]	12.3 (7.5–16.6)	12.3 (7.7–16.5)	12.7 (7.9–17.9)	11.7 (6.4–15.6)	0.035	0
BMI, kg/m^2	25.7 (23.5–28.4)	24.4 (22.6–26.4)	26.2 (24.0–28.5)	27.6 (24.9–30.5)	<0.001	20 (1.0)
Recreational physical activity					0.109	161 (8.0)
No physical activity	793 (42.7)	298 (41.2)	277 (41.8)	218 (46.1)		
Low	472 (25.4)	181 (25.0)	183 (27.6)	108 (22.8)		
Moderate	504 (27.1)	217 (30.0)	167 (25.2)	120 (25.4)		
High	90 (4.8)	28 (3.9)	35 (5.3)	27 (5.7)		
Alcohol intake groups, gram/day					0.589	298 (14.8)
Zero	142 (8.2)	49 (7.5)	48 (7.7)	45 (10.1)		
Below median[e]	725 (42.1)	279 (42.7)	263 (42.1)	183 (41.1)		
Above median[e]	855 (49.7)	325 (49.8)	313 (50.2)	217 (48.8)		
Smoking status					0.001	43 (2.1)
Nonsmoker	832 (42.1)	358 (46.0)	300 (43.2)	174 (34.5)		
Ex-smoker	680 (34.4)	255 (32.7)	237 (34.1)	188 (37.3)		
Current smoker	465 (23.5)	166 (21.3)	157 (22.6)	142 (28.2)		
Diabetes[f]	122 (6.0)	27 (3.4)	47 (6.6)	48 (9.4)	<0.001	0
Education level					<0.001	43 (2.1)
No secondary	1,327 (67.1)	478 (61.2)	498 (71.3)	351 (70.5)		
Secondary	314 (15.9)	144 (18.4)	99 (14.2)	71 (14.3)		
Post-secondary	336 (17.0)	159 (20.4)	101 (14.5)	76 (15.3)		

Abbreviation: CRC, colorectal cancer.
[a]Percent of participants calculated within CRP categories, except for "all participants."
[b]χ^2 tests for differences between CRP groups (% of participants with existing data) for categorical variables, Kruskal–Wallis tests for differences between CRP groups for continuous variables.
[c]*N* and % of participants in total (*N* = 2,020). Missing category not included in the statistical comparisons.
[d]Follow-up time from baseline sample collection to CRC diagnosis.
[e]Sex-specific median.
[f]Obtained from self-reported question (yes/no) or from fasting plasma glucose levels or from 2-hour oral glucose tolerance test levels, according to WHO diagnostic criteria for diabetes mellitus.

to CRP categories based on clinically relevant cutoffs for low-grade inflammation (<1 mg/L, 1–3 mg/L, and >3 mg/L) are presented in **Table 1**. Participants with higher CRP levels were older, had higher BMI, higher frequencies of current or former smoking and diabetes, and lower education levels than participants with lower CRP. The median time between blood sampling and diagnosis of the cases was 12.3 years [interquartile range (IQR), 7.5–16.6; **Fig. 1**], and the median age at colorectal cancer diagnosis was 66.4 years (IQR, 60.5–72.6 years; **Table 1**). Baseline CRP concentrations were higher at higher levels of BMI for both cases and controls (Supplementary Fig. S1).

CRP and overall colorectal cancer risk

Baseline concentrations of ln CRP were not statistically significantly associated with colorectal cancer risk [OR per 1 unit increase in ln CRP, 1.04; 95% confidence interval (CI), 0.98–1.10 in model 2, adjusted for potential confounders; Supplementary Table S1], with very limited modification of results after additional adjustment for BMI (OR, 1.03; 95% CI, 0.97–1.09 in model 3; **Table 3**). No differences were seen in analyses stratified by sex or baseline BMI ($P_{heterogeneity}$ = 0.824 and 0.129, respectively; **Table 3**).

CRP and the risk of molecular and clinical subtypes of colorectal cancer

In Supplementary Table S2, it is demonstrated that cases with missing *KRAS* and *BRAF* mutation status, compared with cases with available data, were slightly younger at baseline and at diagnosis, and were more likely to have distal tumors and advanced disease stage. Of 704 colorectal cancer cases with *BRAF*/*KRAS* mutation data, 156 (22.2%) were *BRAF* mutated, 167 (23.7%) were *KRAS* mutated, and 381 (54.1%) were wild-type *KRAS*/*BRAF*. Cases with *BRAF*-mutated tumors were more often women ($P < 0.001$), were generally older at diagnosis compared with cases with *KRAS*-mutated and wild-type tumors ($P < 0.001$), and had a higher proportion of right-sided colon cancer ($P < 0.001$) and MSI ($P < 0.001$) compared with cases with *KRAS*-mutated tumors.

Multivariable ORs for colorectal cancer risk per 1 unit increase in ln CRP by molecular and clinical subtypes of colorectal cancer are presented in **Table 3**. Relative risk estimates for *BRAF*-mutated, *KRAS*-mutated, and wild-type tumors were similar and all nonsignificant (OR: 1.11, 95% CI, 0.96–1.27; OR: 1.05, 95% CI, 0.91–1.20; and OR: 0.99, 95% CI, 0.91–1.08, respectively), and there was no sign of heterogeneity ($P_{heterogeneity}$ = 0.354; **Table 3**). Furthermore, CRP

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increase was not associated with the risk of either MSI or microsatellite stability (MSS) tumors (OR: 1.05, 95% CI, 0.87–1.27; and OR: 1.03, 95% CI, 0.96–1.09, respectively; $P_{heterogeneity} = 0.833$) or tumor location (right colon: OR: 1.02, 95% CI, 0.91–1.13; left colon: OR: 1.09, 95% CI, 0.98–1.22; and rectum: OR: 0.99, 95% CI, 0.90–1.09; $P_{heterogeneity} = 0.426$; **Table 3**).

Associations between ln CRP and colorectal cancer stratified by stage at diagnosis were also null (stage I–II: OR: 1.01, 95% CI, 0.93–1.10; stage III–IV: OR: 1.04, 95% CI, 0.96–1.14 in model 3; $P_{heterogeneity} = 0.641$; **Table 3**). Stratification for lag time from sample collection to diagnosis yielded nonsignificant ORs. However, there was a possible difference between cases being diagnosed with stage III–IV

Table 2. Baseline and follow-up characteristics of participants with repeated measures.

	Baseline ($n = 518$)	Repeat ($n = 518$)	P[a]	Missing	
				Baseline	Repeat
CRC status			—		
Cases	259 (50)	259 (50)			
Controls	259 (50)	259 (50)			
Sex			—		
Male	292 (56.4)	292 (56.4)			
Female	226 (43.6)	226 (43.6)			
Follow-up time[b], years	15.6 (12.9–19.0)	5.83 (2.9–9.1)		0	0
Age at sampling, years	50.0 (40.5–50.2)	59.9 (51.0–60.1)	<0.001	0	0
CRP mg/L					
Cases	1.26 (0.52–2.69)	1.90 (0.95–4.06)	<0.001	0	0
Controls	1.14 (0.51–2.21)	1.48 (0.78–3.21)	<0.001	0	0
BMI, kg/m^2					
Cases	25.3 (23.4–27.6)	26.4 (24.3–29.1)	<0.001	5 (1.9)	0
Controls	24.6 (22.8–27.0)	26.0 (23.4–28.4)	<0.001	2 (0.8)	0
Recreational physical activity					
Cases			0.244	42 (16.2)	27 (10.4)
No physical activity	104 (40.2)	108 (41.7)			
Low	47 (18.1)	52 (20.1)			
Moderate	61 (23.6)	58 (22.4)			
High	5 (1.9)	14 (5.4)			
Controls			0.791	47 (18.1)	31 (12.0)
No physical activity	98 (37.8)	106 (40.9)			
Low	56 (21.6)	52 (20.1)			
Moderate	49 (18.9)	60 (23.2)			
High	9 (3.5)	10 (3.9)			
Alcohol intake groups, grams/day					
Cases			0.331	44 (17.0)	2 (0.3)
Zero	6 (2.8)	10 (3.9)			
Below median[c]	95 (44.2)	97 (37.7)			
Above median[c]	114 (53.0)	150 (58.4)			
Controls			0.740	41 (15.8)	0
Zero	13 (6.0)	17 (6.6)			
Below median[c]	87 (39.9)	111 (42.9)			
Above median[c]	118 (54.1)	131 (50.6)			
Smoking status					
Cases			0.001	6 (2.3)	5 (1.9)
Nonsmoker	97 (37.5)	112 (43.2)			
Ex-smoker	82 (31.7)	103 (39.8)			
Current smoker	74 (28.6)	39 (15.1)			
Controls			0.003	6 (2.3)	8 (3.1)
Nonsmoker	110 (42.5)	114 (44.0)			
Ex-smoker	80 (30.9)	103 (39.8)			
Current smoker	63 (24.3)	34 (13.1)			
Diabetes[d]					
Cases	7 (2.7)	16 (6.2)	0.055	0	0
Controls	2 (0.8)	8 (3.1)	0.055	0	0

Note: *N* (%) or median (IQR).
Abbreviation: CRC, colorectal cancer.
[a]Paired Wilcoxon signed rank test within the matched case sets for continuous variables, χ^2 tests for categorical variables. Cells showing missing data were not included in the statistical comparisons.
[b]Follow-up time from sample collection to CRC diagnosis.
[c]Sex-specific median.
[d]Obtained from self-reported question (yes/no) and/or from fasting plasma glucose levels and/or from 2-hour oral glucose tolerance test levels, according to WHO diagnostic criteria for diabetes mellitus.

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colorectal cancer within 5 years after the blood sample collection (OR, 1.32; 95% CI, 1.01–1.73) compared with those diagnosed at least 5 years after sampling (stage III–IV/lag time 5–10 years: OR: 0.96, 95% CI, 0.77–1.19; stage III–IV/lag time 10–15 years: OR: 1.01, 95% CI, 0.87–1.18; and stage III–IV/lag time >15 years: OR: 1.02, 95% CI, 0.88–1.18; $P_{heterogeneity} = 0.288$). Estimates from complete-case analyses were similar to those from the multiple imputation analyses (Supplementary Table S1).

CRP and colorectal cancer risk using repeated measurements

For baseline and repeated measurements of 518 participants, characteristics are presented in **Table 2**. Median age was 50 years at baseline and 59.9 years at the repeated sampling occasion. Median lag time from the repeated sampling occasion to the colorectal cancer diagnosis of cases was 5.8 years, and 43% of all participants with a second measurement were women. BMI increased in both cases and controls during the approximately 10-year time period between the two measurements. The number of current smokers significantly decreased in both cases and controls, while no significant changes in physical activity level or alcohol intake were seen. Plasma CRP concentrations increased during the time period between measurements in both cases and controls (**Table 2**). Estimated average intraindividual changes in ln CRP concentrations (using linear mixed models) are shown in **Fig. 2**. The crude model (**Fig. 2A**) showed an increase in ln CRP over time ($P_{time} < 0.0001$) in both cases and controls, with no difference in the rate of increase between them ($P_{interaction} = 0.21$). Results did not change in the adjusted model also including smoking, physical activity, alcohol, diabetes, and BMI ($P_{time} = 0.007$; $P_{interaction} = 0.19$; **Fig. 2B**).

Discussion

In this large population-based study using prospectively collected blood samples and data, we found no evidence of a relation between higher plasma levels of CRP and future risk of colorectal cancer. ORs were similar in men and women and no clear differences were observed

Table 3. ORs[a] and 95% CI of colorectal cancer and colorectal cancer subtypes per 1 unit increase in ln plasma CRP concentrations[b].

CRC subgroup	*n* complete cases/controls[c]	OR (95% CI)	$P_{heterogeneity}$[d]
All CRC	835/817	1.03 (0.97–1.09)	
Sex			
Male	437/428	1.03 (0.95–1.12)	0.824
Female	398/389	1.02 (0.94–1.11)	
BRAF/KRAS mutation status			
BRAF mutated	123/116	1.11 (0.96–1.27)	0.354
KRAS mutated	137/138	1.05 (0.91–1.20)	
BRAF/KRAS wild-type	320/314	0.99 (0.91–1.08)	
MSI status			
MSI	78/70	1.05 (0.87–1.27)	0.833
MSS	504/498	1.03 (0.96–1.09)	
Tumor location			
Right colon	258/245	1.02 (0.91–1.13)	0.426
Left colon	247/248	1.09 (0.98–1.22)	
Rectum	324/318	0.99 (0.90–1.09)	
Disease stage			
Stage I–II	395/385	1.01 (0.93–1.10)	0.641
Stage III–IV	390/383	1.04 (0.96–1.14)	
Lag time			
<5 years	134/134	1.13 (0.96–1.32)	0.583
5–10 years	202/198	0.98 (0.85–1.12)	
10–15 years	251/245	1.01 (0.90–1.13)	
>15 years	248/240	1.03 (0.93–1.14)	
Disease stage/lag time			
Stage III–IV/lag time <5 years	64/61	1.32 (1.01–1.73)	0.288
Stage III–IV/lag time 5–10 years	90/88	0.96 (0.77–1.19)	
Stage III–IV/lag time 10–15 years	124/122	1.01 (0.87–1.18)	
Stage III–IV/lag time >15 years	112/112	1.02 (0.88–1.18)	
BMI[e], kg/m^2			
<25	317/354	0.99 (0.97–1.02)	0.129
25–30	384/343	1.03 (1.00–1.06)	
>30	134/120	1.02 (0.98–1.06)	

Abbreviation: CRC, colorectal cancer.

[a]Multivariable ORs adjusted for age, sex, cohort, sample year and fasting status, smoking status, recreational physical activity, alcohol intake, diabetes mellitus, and BMI (model 3). For estimates from model 1 and 2, see Supplementary Table S1.

[b]From multiple imputation data.

[c]Numbers (*n*) per subgroup represent complete cases and controls with complete covariate data, molecular data for the remaining cases were imputed. Complete estimates for all adjusted models for imputed and complete case data are presented in Supplementary Table S1 for comparison.

[d]$P_{heterogeneity}$ between subtypes was tested with Wald test comparing the observed overall log OR and subtype-specific log ORs from the final multivariable model (model 3).

[e]ORs from unconditional logistic regression model (model 2) adjusted for all covariates listed above, except BMI.

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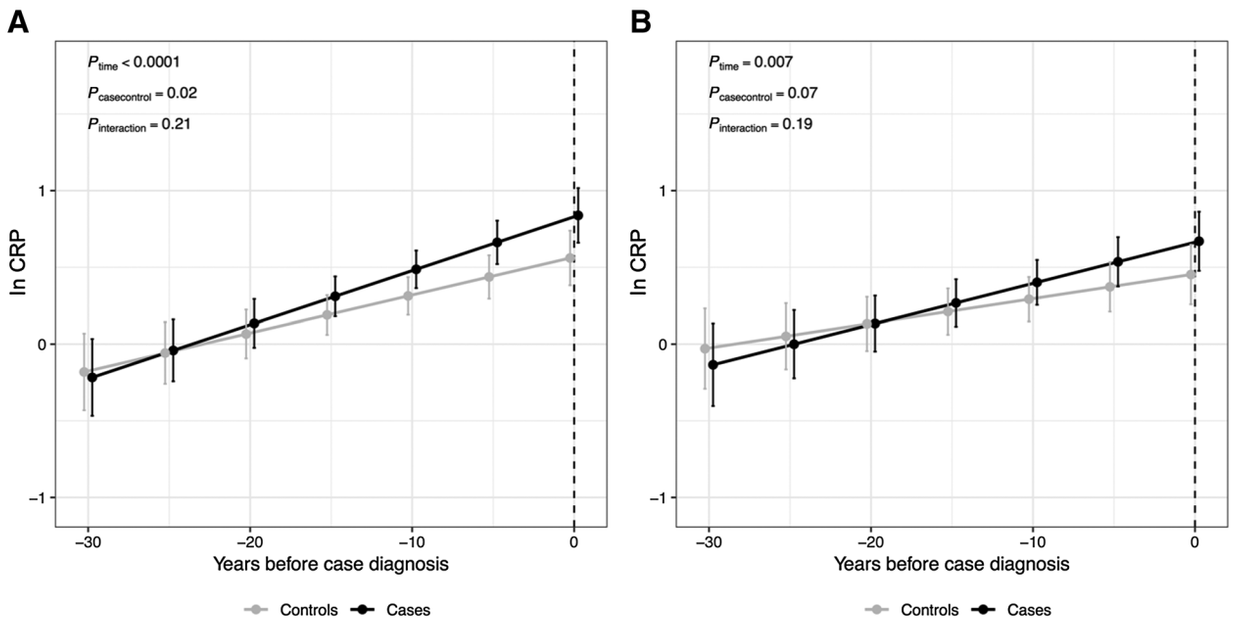

Figure 2.

Estimated average intraindividual changes in ln plasma CRP concentrations over time in colorectal cancer cases and matched controls. Linear mixed models were used to estimate marginal effects of time and 95% CIs in 259 cases and 259 matched controls with matched repeated measurements prior to case diagnosis. **A,** The crude model included participants and matched case–control pairs as random factors, and time between sample collection and case diagnosis, case–control status, and an interaction term between time and case–control status as fixed factors. **B,** The adjusted model was additionally adjusted for smoking status, recreational physical activity, alcohol intake, diabetes, and BMI, which were included as fixed factors.

across clinical or molecular subtypes, including *BRAF* and *KRAS* mutation, and MSI status. Higher CRP concentrations were possibly associated with an increased colorectal cancer risk in the subgroup of advanced colorectal cancer (stage III–IV) within 5 years of blood sample collection, likely reflecting undiagnosed cancer at the time of sampling.

In comparison with other similar studies of CRP in colorectal carcinogenesis, our study population appears to be representative regarding CRP levels (although analysis methods, cutoffs, and exclusion criteria have varied; refs. 7, 12, 19) and for distribution of potential confounders such as age, smoking, and BMI (14, 15, 36). The relationships between molecular subtypes and other patient characteristics were also as expected (25, 37, 38). Genetic disruption of the *KRAS* gene, generally mutated in as much as 30%–50% of colorectal cancer cases (25), was somewhat less frequent in our study population (24%). *BRAF* mutations are, for example, associated with aging, female gender, right-sided location in the colon, advanced disease stage, and MSI, characteristics that could be confirmed also in this study. While more cases in this study had *BRAF*-mutated tumors compared with other populations, we have no obvious explanation for this observation. For all but a few colorectal cancer cases diagnosed prior to March 2009, genotyping for the *BRAF* V600E mutation was done earlier and by a different method than cases diagnosed later, with a similar mutational frequency of 24% reported (41). Thus, genotyping methodology is not the explanation. Furthermore, a similar *BRAF* mutation frequency was observed in another Swedish population–based study on metastatic colorectal cancer (42).

The null finding for CRP in relation to colorectal cancer risk is inline with several studies presenting null (17–20) and conflicting results (14–16). A meta-analysis from 2014 presented summary risk ratios pointing toward a positive relationship, but only for colon and not rectum cancer, and only for men, not women (10). A meta-analysis on the association between CRP and risk of colorectal adenoma reported a positive association with the risk of advanced adenomas, but with substantial heterogeneity among included studies (12). Thus, if systemic inflammation is a causal factor in colorectal carcinogenesis, it does not appear to be captured by CRP. Although some preclinical findings support a role for systemic inflammation (43, 44), much of the evidence to date is based on the proinflammatory nature of major colorectal cancer risk factors, in particular excess body fat (3, 45). Future experimental efforts are needed to elucidate the effects of systemic inflammation on the healthy colorectal mucosa, the already inflamed mucosa, and the tumor microenvironment, in addition to effects on tumorigenesis. With respect to molecular epidemiologic studies, single inflammatory markers measured in plasma alone might not reflect specific inflammatory pathways relevant to colorectal cancer, and multifaceted approaches to investigating the relationship between inflammatory pathways and cancer development may be necessary (46).

Given the multiple mechanisms postulated to mediate the effect of excess body fat in carcinogenesis, including insulin resistance, altered adipokine production, and disruption of the microbiome in addition to chronic low-grade inflammation (47), we adjusted for BMI in a separate multivariable model, in addition to all other covariates. ORs for CRP did not change markedly, and we found no significant association between CRP and colorectal cancer risk in BMI subgroups (<25, 25–30, and >30 kg/m^2). Thus, although BMI was the baseline variable that most strongly related to CRP levels, BMI did not appear to confound the null relationship between CRP and colorectal cancer risk in this study.

For more advanced disease stage (20), and for measurements taken closer to diagnosis (19, 48), evidence supports a stronger relationship between higher CRP levels and increased risk of colorectal cancer. We observed a significant result for the subgroup of cases diagnosed at stage III–IV together with shorter follow-up time between blood sampling and diagnosis (<5 years). The clear difference in risk association compared with cases diagnosed more than 5 years after measurement probably reflects the systemic response to the developing tumor, so-called reverse causality, and can be interpreted as a sign of disease burden, rather than risk (19, 48). CRP is not an established early detection marker for colorectal cancer (49), but relevant as a prognostic marker in patients with colorectal cancer (50), and used clinically together with albumin levels, in the Glasgow Prognostic Score for cancer outcomes, including colorectal cancer (51).

In colorectal cancer, distinct etiologic pathways lead to different tumor characteristics, and some findings support pathway-specific risk factors (21, 28, 52). But for molecular subtype analysis in this study, there were no associations between CRP and colorectal cancer risk. To the best of our knowledge, no other study has investigated the association between prediagnostic levels of CRP and molecular subtypes of colorectal cancer, according to *BRAF* and *KRAS* mutation status and/or MSI status specifically. One study on regular intake of NSAIDs, highly relevant for the relationship between systemic inflammation and cancer risk, did find a risk reduction for MSI-high colorectal cancer without *KRAS* or *BRAF* mutation, but small subgroups of 6–12 cases were a limitation (39). Analyses stratified by anatomic tumor site yielded no statistically significant associations in our study, although some previous findings suggest a possible stronger link to colon compared with rectal cancer (10, 15, 49).

Our longitudinal analysis demonstrated an increase in estimated average intraindividual trajectories for CRP concentrations over time, which, in contrast to our findings for lag time and stage, was not stronger in cases compared with controls. Thus, changes in CRP over time in our study population do not support consideration of CRP as an early detection marker for colorectal cancer.

The main limitation of our study was the lack of molecular tumor data for approximately 30% of the colorectal cancer cases. This is on par with or better than other similar molecular pathologic epidemiology studies (26), but can introduce selection bias. We used multiple imputation to help account for missing tumor data, because missing was assumed to be MAR (35), meaning that tumor data availability depended on some of the observed characteristics such as tumor site and stage. Under this condition, multiple imputation can reduce bias and increase statistical power, compared with complete case analysis (53). We did, however, also run the risk analyses using complete case data, with very similar results (Supplementary Table S1). Another limitation of the study was the lack of information about some potentially relevant factors, such as more detailed measures of body composition than BMI, regular use of aspirin and other NSAIDs, inflammatory comorbidities and related immunosuppressive therapies, and family history of colorectal cancer. We also had no data on colonoscopy screening, but there was no population screening in northern Sweden during the study period. Finally, self-reported variables like smoking, physical activity, and alcohol intake can be under- or overestimated.

The study also has several strengths, in particular the population-based nature of the NSHDS cohorts with a high participation rate of approximately 70% and long follow-up times (median 12.3 years from baseline measurement to colorectal cancer diagnosis of cases) allowing for lag time stratification. We also had information on several potentially important confounders, including BMI measured by a health professional. Involving as many as 1,010 cases also allowed for the molecular and clinical subgroup analyses, essential for a molecular pathologic epidemiology study like this (23). Furthermore, reporting cancer cases to the Swedish cancer registry is mandatory, which means that linking the data to the registry gives nearly identical colorectal cancer incidence in the cohorts as in the underlying population. Another major strength in our study is the repeated measurements for a substantial part of the study population, allowing for longitudinal analysis taking intra- and interindividual variation into account.

In conclusion, the null results of this large, population-based, nested case–control study do not support intertumoral heterogeneity as an explanation for previous inconsistent findings for CRP in relation to the risk of developing colorectal cancer. If chronic, low-grade systemic inflammation is a causal factor in colorectal carcinogenesis, it does not appear to be adequately reflected by CRP. The possible association between higher CRP and higher colorectal cancer risk in the subgroup with advanced tumors and shorter follow-up likely reflects undiagnosed cancer at baseline.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Writing, review, and/or revision of the manuscript: S. Bodén, R. Myte, J. Harbs, A. Sundkvist, C. Zingmark, A. Löfgren Burström, R. Palmqvist, S. Harlid, B. Van Guelpen
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C-reactive Protein and Future Risk of Clinical and Molecular Subtypes of Colorectal Cancer

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