Research Article

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Association of Inflammatory Markers with Colorectal Cancer Incidence in the Atherosclerosis Risk in Communities Study

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Abstract

Background: Chronic inflammation has been implicated in the etiology of colorectal cancer (CRC), but epidemiologic findings on the association between circulating inflammatory markers and CRC risk are inconsistent. We hypothesized that increased concentrations of systemic inflammatory markers–white blood cell count (WBC), fibrinogen, von Willebrand factor (VWF), factor VIII (FVIII), and C-reactive protein (CRP)–and decreased albumin concentration would be associated with increased CRC risk in the Atherosclerosis Risk in Communities prospective cohort.

Methods: WBC, fibrinogen, VWF, FVIII, and albumin, measured in 1987–1989 in 13,414 men and women, were transformed to *z*-scores and summed up to construct a blood "inflammation *z*-score." Albumin was included with a negative sign, because its concentration decreases with greater inflammation. A total of 308 incident CRC cases were identified through 2006 in initially cancer-free participants. CRP was measured in 1996–1998 in 9,836 cancer-free people who developed 166 CRCs through 2006. Proportional hazard models were used to estimate the HR and 95% CI of CRC in relation to each individual marker and the inflammation *z*-score.

Results: After multivariate adjustment, for the highest versus lowest quartile, there was a statistically significant positive association of CRC risk with fibrinogen: HR = 1.50 (95% CI, 1.05–2.15), $P = 0.03$; inflammation *z*-score: HR = 1.65 (95% CI, 1.15–2.35), $P = 0.01$; and CRP: HR = 1.97 (95% CI, 1.13–3.43, $P = 0.02$.

Conclusions: These findings indicate that greater levels of fibrinogen, CRP, and blood inflammation *z*-score are associated with increased CRC risk.

Impact: The study provides further evidence that precancer inflammation may contribute to CRC etiology.
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Introduction

Chronic inflammation has been previously linked to the etiology of cancer (1, 2). The evidence is strongest for colorectal cancer (CRC). It has been shown that colonic inflammatory bowel disease, especially ulcerative colitis, increases CRC risk (3, 4), whereas nonsteroidal anti-inflammatory drugs (NSAIDs) reduce CRC risk (3, 5). Moreover, several epidemiologic studies observed positive associations between circulating C-reactive protein (CRP)—a nonspecific marker of systemic inflammation—and CRC risk (6–9). The OR of CRC was increased by 60% to 190% for the highest versus lowest CRP quartile in 3 studies (6, 7, 9), and by 40% per 1 unit of log-transformed CRP in the fourth study (8). However, data from other studies on CRP and CRC risk are inconsistent, and few studies have examined inflammatory biomarkers other than CRP in relation to incident CRC (10–12). More observational data on a wide range of inflammatory biomarkers, particularly from large prospective cohorts, are needed to further examine the role of inflammation in the etiology of CRC.

Our objective was to investigate associations of 6 circulating markers of systemic inflammatory response, including C-reactive protein (CRP), white blood cell (WBC) count, fibrinogen, von Willebrand factor (VWF), Factor VIII (FVIII), and albumin with CRC risk in the Atherosclerosis Risk in Communities (ARIC) prospective cohort. These acute phase reactants change their concen-

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trations in response to acute inflammation by at least 25%: the level of positive acute phase reactants such as WBC, fibrinogen, VWF, FVIII, and CRP increase, whereas the level of albumin–a negative reactant–decreases (13). The acute phase reactants are components of the innate immune system, mainly produced by hepatocytes under stimulation with inflammatory cytokines, such as interleukins (IL-6, IL1-β, IL-8), tumor necrosis factor-α, interferon-γ, and transforming growth factor-β (13). When excessive inflammation persists for a long time, it leads to chronic inflammation, which is associated with a modest increase in the levels of acute-phase reactants. It is characterized by infiltration with macrophages, lymphocytes, and plasma cells; the secretion of cyclo-oxygenase-2 (COX-2) and prostaglandins in macrophages and epithelial cells; and tissue destruction due to continuous production of reactive oxygen and nitrogen species (2). Taken together, these processes may lead to cell changes and development of cancer, particularly of CRC (14, 15). Colon may be especially prone to carcinogenesis via inflammation, because of rapidly dividing cells and the presence of microbial flora causing permanent low-grade inflammation of colon mucosa (4, 15).

Our hypothesis was that increased concentrations of positive acute phase reactants, CRP, WBC, fibrinogen, VWF, and FVIII, and decreased concentration of a negative-phase reactant, albumin, measured before CRC diagnosis, are associated with increased future incidence of CRC. We examined the associations of CRC risk in relation to each individual marker and to a combined inflammation *z*-score created from biomarkers at baseline. To the best of our knowledge, our study is the first to examine an inflammation score in relation to CRC incidence.

Materials and Methods

Study design and population

ARIC is a multicenter population-based prospective cohort study of atherosclerosis. Details of the ARIC cohort have been published elsewhere (16). In brief, in 1987–1989, 15,792 volunteers ages 45 to 69 years were recruited from 4 communities: suburban Minneapolis (MN), Forsyth County (NC), Jackson (MS), and Washington County (MD). The cohort underwent reexamination visits every 3 years, with 93% response for visit 2 (1990–1992), 86% response for visit 3 (1993–1995), and 81% response for visit 4 (1996–1998).

Local institutional review boards approved the ARIC protocol and all participants provided an informed consent, which included consent for follow-up for disease occurrence.

Data collection

Home interviews and medical examinations were conducted at each visit. At baseline (visit 1), participants were asked to report their demographic characteristics, education, and lifestyle behaviors including alcohol drinking status, smoking status, number of cigarettes per day, and duration of smoking (pack years were computed). Trained personnel collected blood (serum and plasma) samples and performed anthropometric measures, which were shown to be reliable (17). Data collection and quality-control methods have been described in detail (18). Usual food intake during the previous year was collected by using a modified version of the Willett 61-item semiquantitative food frequency questionnaire (19). Regular physical activity was assessed by the Baecke questionnaire and semicontinuous sport index was calculated (20). Prevalent diabetes mellitus was defined as a fasting glucose (≥126 mg/dL), nonfasting plasma glucose (>200 mg/dL), a self-reported physician diagnosis of diabetes, or current treatment for diabetes. Participants were queried about their history of cancer and about aspirin use during the last 2 weeks before the examination. Dosage and frequency of aspirin use was not ascertained. Participants were asked to bring to the clinic all medications taken during the 2 weeks prior to the examination; thus, data about oral contraceptives and hormone replacement therapy (HRT) were collected.

For the analysis of CRP, most of the variables were obtained from visit 4, as blood samples for CRP measurements were collected during that visit. Additional data about cancer risk factors were collected from the telephone interview in 1994–1996 (response 90%), which included history of non-aspirin NSAIDs use at visits 1 and 4, history of cancer in first-degree relatives, lifetime history of sigmoidoscopy/colonoscopy, testing for blood in the stool, history of polyps, and history of noncancerous tumors in the colon or rectum.

Biological markers

At each visit, ARIC technicians used standard protocols to draw fasting blood, centrifuge samples and freeze plasma and blood samples at −70°C until analysis (21). With the exception of WBC count, which was measured in local hospitals, all biomarkers at baseline-–fibrinogen (mg/dL), VWF (% of standard), FVIII activity (% of standard), and albumin (g/dL)-–were analyzed in ARIC research laboratories using standardized protocols (described in detail in ref. 22). The reliability coefficients, based on repeated testing of individuals over 1 to 2 weeks, were 0.72 for fibrinogen, 0.86 for FVIII activity, 0.68 for VWF, 0.69 for albumin, and 0.96 to 1.00 for WBC (23).

High-sensitivity CRP (mg/L) was measured in 2008 on plasma frozen at −70°C from visit 4 (1996–1998) by the immunoturbidimetric assay using the Siemens (Dade Behring) BNII analyzer (Dade Behring). Approximately 4% of the samples were split and measured as blinded replicates on different dates to assess repeatability. The reliability coefficient for blinded quality control replicates of CRP was 0.99 (421 blinded replicates; ref. 24).

Ascertainment of incident colorectal cancer cases

Incident cancers were ascertained in 1987–2006 by linkage to cancer registries and supplemented by hospital

records. Minneapolis, Forsyth County, and Washington County were covered by state or county cancer registries and reported high completeness of cancer data (25, 26). After 1995, a state registry also covered Jackson but it was not always complete. ARIC hospital surveillance was used to identify additional cancer cases. For participants who had hospital ICD (International Classification of Diseases) codes for cancer that were not in cancer registries, records of hospitalized events were obtained and reviewed. Primary site, date of cancer diagnosis, and source of diagnostic information (e.g., a pathology report) were recorded. Data on stage were not uniformly collected.

Statistical analysis

We created an inflammation *z*-score from 5 inflammatory biomarkers measured at baseline: fibrinogen, VWF, factor VIII, albumin, and WBC. Because WBC was not normally distributed, log-transformed WBC was used. Each biomarker was rescaled to have a mean of zero and a SD of 1, and normalized *z*-scores were obtained for each biomarker [$z = (x - \mu)/\sigma$, where x is the biomarker value, μ is the mean, and σ is the SD]. The *z*-scores from all biomarkers were summed up to create a combined *z*-score. Albumin was included with a negative sign because its concentration decreases in response to inflammation.

The only biomarker measured in samples from visit 4 was CRP. We examined covariates across quartiles of all the 5 biomarkers and the inflammation score at baseline and CRP at visit 4 using general linear models or χ^2 tests. In addition, we measured correlations between biomarkers at baseline using Pearson correlations.

For analyses of CRC in relation to the inflammatory *z*-score and biomarkers measured at baseline, person-years at risk were calculated from the baseline examination date to the date of CRC diagnosis, death, loss to follow-up, or December 31, 2006, whichever occurred first. For the analysis of CRP, person-years were calculated from visit 4.

Poisson regression was used to calculate incidence rates of CRC, adjusted for age, sex, race, and center, and 95% CI. The proportional hazards model was used to estimate the HRs of incident CRC and 95% CI for quartiles of each biomarker and the inflammation score. Tests for trend across the quartiles of each biomarker were computed by treating the quartiles as continuous ordinal variables. Proportional hazards assumptions were tested by including an interaction term between each inflammatory marker and follow-up time in a Cox regression model. There was no evidence that these assumptions were violated for any marker. For each inflammatory marker, there were 2 models: (i) adjusted for age, sex, race, and center and (ii) multivariate adjusted, which included covariates associated with any inflammatory marker under study and with CRC. The multivariate model for biomarkers at baseline included age (continuous), race (Caucasian, African American), center, education level (less than high school, high school, more than high school), body mass index (BMI <25, 25–29.9, and $\geq$30 kg/m^2), aspirin use (yes/no), smoking status (never, former, current), pack-years of smoking (continuous), gender–HRT (men, women never taking HRT, and women who were former or current HRT users), and diabetes (yes/no) measured at baseline. Additional variables that were tested for confounding but were not included in the final models were alcohol intake, sport index, consumption of red meat, dietary fiber, calcium, history of non-aspirin NSAIDs use, and family history of CRC. The multivariate model for the analysis of CRP included baseline variables, race, center, and education level, and variables collected at visit 4, age, gender–HRT, BMI, smoking status, aspirin, and diabetes. For this analysis, variables measured in 1994–1996 history of non-aspirin NSAIDs use, history of sigmoidoscopy/colonoscopy, test for blood in the stool, history of polyps, and history of noncancerous tumors in the colon or rectum–– were also tested as potential confounders. Because none of these variables, nor dietary factors, materially changed the association between CRP and CRC risk, they were not included in the final multivariate model. Because information on acute inflammatory diseases was not collected, to exclude acute inflammatory response, we repeated the main analysis after excluding people with CRP values more than 10 mg/L ($n = 767$). Additionally, participants were categorized into 3 CRP groups according to the cutoff points proposed in clinical guidelines for cardiovascular disease: less than 1, 1 to 3, and greater than 3 mg/L (27).

We also ran exploratory analyses separately for colon and rectal cancers for each biomarker associated with CRC risk. We tested statistically whether observed associations varied across race, sex, smoking status, BMI, or aspirin use by introduction of cross-product interaction terms into a multivariate model for each biomarker associated with CRC. Because the *P* values for all interaction terms were greater than 0.2, we assumed that there were no interactions. Of note, power was limited, especially for the analysis of CRP. Finally, we repeated analyses by excluding CRC cases that occurred within 1, 2, and 5 years of follow-up, to exclude the potential influence of subclinical CRC on the levels of biomarkers.

All analyses were conducted using SAS (SAS Institute, Inc.; version 9.2). Participants, who had prevalent cancer at the start of follow-up or did not give consent to participate in cancer studies, or had missing information about the biomarkers under study, were excluded from the analyses.

Results

At baseline, the mean age of the cohort was 53.9 years, 26% were African American (74% Caucasian) and 54% were women. During 230,509 person-years of follow-up (mean follow-up was 17.2 years) from 1987 through 2006, there were 308 incident CRC cases (232 colon and 78 rectal) in 13,414 people at risk.

Table 1. Incidence rates of CRC (1987–2006) adjusted for age, gender, race, and center in relation to selected characteristics at visit 1, ARIC study[a]

Characteristic at visit 1 (1987–1989)	CRC cases ($n = 308$)	PY	Incidence rate per 1,000 PYs (95% CI)
Age[b]			
45–49	47	66,489	0.69 (0.52–0.92)
50–54	85	62,102	1.34 (1.08–1.66)
55–59	89	54,886	1.60 (1.29–1.97)
60–64	87	47,033	1.83 (1.48–2.26)
Gender[c]			
Male	160	128,428	1.48 (1.26–1.74)
Female	148	102,080	1.09 (0.92–1.29)
Race[d]			
African American	92	58,611	1.58 (1.29–1.94)
Caucasian	216	171,897	1.17 (1.01–1.34)
BMI, kg/m^2			
≤24.99	84	75,943	1.11 (0.89–1.37)
25–29.99	119	91,949	1.17 (0.97–1.41)
≥30	105	62,337	1.57 (1.29–1.92)
Diabetes			
No	262	23,549	1.21 (1.15–1.28)
Yes	46	20,905	1.64 (1.44–1.88)
Aspirin			
No	173	122,899	1.29 (1.20–1.39)
Yes	131	105,668	1.21 (1.12–1.31)
Education			
<High school	85	50,801	1.36 (1.07–1.72)
High school	97	75,423	1.30 (1.06–1.59)
>High school	126	103,944	1.18 (0.99–1.41)
Smoking			
Never	133	99,817	1.18 (0.99–1.41)
Former	98	75,136	1.30 (1.06–1.59)
Current	77	55,422	1.36 (1.07–1.72)
Alcohol			
Never	77	58,336	1.18 (0.92–1.52)
Former	56	41,320	1.18 (0.90–1.55)
Current	173	129,861	1.31 (0.11–1.53)
HRT (in women)			
Never	99	81,948	1.15 (1.06–1.26)
Ever	48	41,947	1.10 (0.99–1.23)

Abbreviation: PY, person-year.
[a]Total number of participants = 13,414.
[b]Adjusted for race, gender, and center.
[c]Adjusted for age (continuous), race, and center.
[d]Adjusted for age (continuous) and gender.

CRP was measured at visit 4 in 1996–1998. The mean age of the cohort at visit 4 was 62.6 years, 23% were African American and 54% were women. There were 166 incident cases of CRC (133 colon and 35 rectal) in 9,836 people at risk followed from visit 4 through 2006 (more than 87,585 person-years of follow-up with mean of 8.9 years).

Incidence rates of CRC adjusted for age, sex, race, and study center in 1987–2006 are presented in Table 1. Rates of CRC increased with age, BMI, and lower education level. They were higher in men than in women and in African Americans than in Caucasians. CRC rates were also higher among current smokers, alcohol users, and slightly lower among users of aspirin or HRT compared with never users.

Baseline inflammatory markers were correlated: FVIII with VWF (Pearson's $r = 0.71$); fibrinogen with FVIII

Table 2. Mean value or prevalence (%) of characteristics across inflammation *z*-score quartiles in 13,414 participants free of cancer, at visit 1 (1987–1989), ARIC study

ARIC characteristics	*z*-score quartiles			
	<−2.12	−2.12 to −0.32	−0.31 to 1.72	≥1.73
Age, y	52.6	53.6	54.5	55.0
Race, % Caucasian	80.8	78.1	75.2	61.9
Sex, % Female	48.4	54.1	56.4	61.4
BMI, kg/m^2	26.1	27.0	28.0	29.8
Sport index	2.6	2.5	2.4	2.3
>High school education, %	51.9	47.4	42.7	36.5
Current smoker, %	13.9	21.5	29.3	35.2
Current alcohol intake, %	64.5	59.2	54.8	47.0
Aspirin, recent use %	45.2	46.8	46.3	47.0
Current HRT, % in women	22.8	27.3	26.3	23.6
Diabetes, %	5.0	7.2	10.7	20.5
Fibrinogen, mg/dL	256	282	308	357
WBC count[a], $\times 10^9$ cells/L	5.7	5.8	5.8	6.0
VWF, %	81	102	122	162
FVIII, %	101	119	135	167
Albumin, g/dL	4.05	3.92	3.84	3.70

[a]Geometric means are presented for WBC because WBC count was log transformed.

($r = 0.25$) or VWF ($r = 0.28$); albumin with FVIII ($r = -0.19$), VWF ($r = -0.16$), or fibrinogen ($r = -0.21$); and WBC with fibrinogen ($r = 0.27$). Although CRP was not measured for all participants at baseline, it was measured in a cohort random sample and was shown to be positively associated with fibrinogen ($r = 0.53$), WBC count ($r = 0.23$), VWF ($r = 0.29$), and FVIII ($r = 0.31$; unpublished data).

Table 2 shows that inflammation *z*-score increased with a greater age, BMI, and percentages of women, African Americans, current smokers, aspirin users, and diabetics. The *z*-score was inversely associated with sport index, current alcohol and HRT use, and education beyond high school. Age, education, BMI, diabetes, and sport index were distributed in a similar way across all biomarkers at baseline (inverse directions for albumin). However, several covariates were distributed differently across the biomarkers: as WBC count increased, the percentage of alcohol users and Caucasians increased and percentage of women decreased (Supplementary Table S1). FVIII and VWF were inversely associated with smoking, and albumin was inversely associated with HRT use (Supplementary Tables S2 and S3). The findings for individual markers are in agreement with findings from other studies (10, 11, 28).

Similar to the patterns for *z*-score, the percentage of African Americans and females was higher among those with higher CRP (Table 3). CRP was positively associated with BMI, smoking, and diabetes, and inversely associated with sport index and alcohol intake. The percentage of HRT users increased with increasing CRP. These relations were similar to those observed in other studies on CRP (7, 9, 29, 30).

HRs of CRC were slightly increased for the highest versus lowest quartile of fibrinogen, VWF, FVIII, and WBC (Table 4). However, only the association between fibrinogen and CRC incidence was statistically significant: multivariate-adjusted HR = 1.50 (95% CI, 1.05–2.15) for the highest versus lowest quartile ($P = 0.03$). There was also a positive association of the inflammation *z*-score with CRC risk: HR = 1.65 (95% CI, 1.15–2.35) for the highest versus lowest quartile ($P = 0.01$; Table 4). The associations with fibrinogen and *z*-score were stronger for colon cancer, and no associations with rectal cancer were observed (Table 5). To examine whether the association between inflammation *z*-score and CRC risk was driven by fibrinogen, a new inflammation score was created, which summed up *z*-scores for logarithm of WBC count, VWF, and FVIII, and subtracted the *z*-score for albumin (fibrinogen was not included). The multivariate HR of CRC was also increased for the new *z*-score: 1.52 (95% CI, 1.08–2.15) for the highest versus lowest quartile ($P = 0.04$).

After excluding CRC cases within 1, 2, or 5 years of follow-up, positive associations of fibrinogen and the inflammation *z*-score with CRC incidence remained statistically significant. For instance, after excluding CRCs within 5 years of follow-up, multivariate-adjusted HRs for the highest versus lowest quartile were 1.67 (95% CI, 1.13–2.45; $P = 0.01$) for the *z*-score and 1.65 (95% CI, 1.11–2.46; $P = 0.01$) for fibrinogen.

CRP was positively associated with CRC risk: in the multivariate-adjusted model, HR = 1.97 (95% CI,

Table 3. Mean value or prevalence (%) of characteristics across quartiles of CRP in 9,836 participants free of cancer at visit 4 (1996–1998), ARIC study

Characteristics	CRP (mg/L) quartiles			
	<1.1 (n = 2,454)	1.1–2.4 (n = 2,460)	2.5–5.6 (n = 2,461)	>5.6 (n = 2,461)
Age, y	62.5	62.8	62.7	62.4
Race, % Caucasian	82.7	86.0	80.7	75.4
Sex, % Female	42.5	48.5	60.7	70.0
BMI, kg/m^2	26.1	28.3	29.7	31.5
Sport index[a]	2.7	2.6	2.5	2.4
>High school education, %	53.7	48.8	44.7	41.7
Current smokers, %	11.2	13.6	15.2	18.7
Current alcohol intake, %	54.1	53.7	48.4	41.4
Aspirin, recent use %	52.9	54.7	57.9	61.7
Diabetes, %	10.4	14.0	19.3	24.6
Current HRT, % of women	29.3	34.6	42.5	51.0

[a]Data were collected at visit 3 (1993–1995).

1.13–3.43) for the highest versus lowest quartile ($P = 0.02$; Table 6). The multivariate-adjusted HR of colon cancer incidence was slightly higher: 2.06 (95% CI, 1.12–3.79) for the highest versus lowest CRP quartile ($P = 0.02$). No association of CRP with rectal cancer was observed, but the number of rectal cancers was low ($n = 35$; Table 6).

When CRP was presented as standard categories, the statistically significant association remained: compared with CRP < 1 mg/L, multivariate-adjusted HRs were 1.43 (95% CI, 0.86–2.38) for CRP = 1–3 mg/L and 1.76 (95% CI, 1.05–2.93) for CRP > 3 mg/L ($P = 0.03$).

Exclusion of people with CRP values > 10 mg/L ($n = 767$), that is, those with potential acute inflammatory responses, yielded similar results: multivariate-adjusted HR = 1.99 (95% CI, 1.10–3.60) for the highest versus lowest CRP quartile ($P = 0.02$). After excluding cancer cases within 1, 2, or 5 years after the visit 4 examination, the HRs for the highest versus lowest CRP quartile were 2.04 (95% CI, 1.13–3.70; $P = 0.02$), 1.77 (95% CI, 1.01–3.09; $P = 0.05$), and 2.12 (95% CI, 0.88–5.11; $P = 0.33$), respectively.

Discussion

This prospective study found a 97% increased HR of incident CRC for the highest versus lowest CRP quartile ($P = 0.02$). There were also statistically significant positive associations of CRC in relation to fibrinogen level (50% greater for the highest than for the lowest quartile, $P = 0.03$), and the inflammation z-score (65% greater for the highest than for the lowest quartile, $P = 0.01$). These associations were limited to colon cancer, with no associations observed for rectal cancer. The inflammation z-score without fibrinogen was also positively associated with CRC risk (51% greater for the highest than for the lowest quartile, $P = 0.04$), although no association was detected for any individual marker. Thus, a combination of several inflammatory markers may be a better indicator of inflammatory processes associated with CRC risk than any of these markers individually.

Recently, several studies showed that an increased inflammation score including albumin and CRP (Glasgow prognostic score) predicts poorer survival of CRC patients (31, 32). To our knowledge, no other study has examined a combination of inflammatory markers in relation to CRC risk. The fact that we found positive associations of CRP, fibrinogen, and inflammation z-scores with CRC risk supports the hypothesis that chronic inflammation, reflected by acute-phase reactants measured before cancer diagnosis, may play a role in CRC development. Similar results were observed after excluding CRC cases within 1, 2, and 5 years of follow-up, that is, excluding the potential influence of preclinical CRC on the concentration of the inflammatory markers.

Overall, previous epidemiologic data on CRP and CRC risk are contradictory. Our results for CRP are in agreement with the findings of 4 nested case–control studies (6–9). Three among them reported OR = 1.6–2.9 of CRC for the highest versus lowest CRP quartile (6, 7, 9), and the remaining study reported OR = 1.44 (95% CI, 1.03–2.02) per 1 unit of log CRP (8). In our cohort, the HR of CRC per 1 unit of log-transformed CRP was 1.26 (95% CI, 1.06–1.49). Similar to our study, Erlinger and colleagues (6) observed a stronger association of CRP with colon cancer and no association with rectal cancer. A prospective study from the Netherlands reported no association of CRP with total CRC risk, but a positive association for nonsigmoid colon cancer: RR = 1.48 (95% CI, 1.14–1.94) per 1 SD of CRP (33). In contrast, 3 studies—the Japan Collaborative Cohort Study, the European Prospective Investigation into Cancer and Nutrition in Greece, and the Women's Health Study—did not find statistically

Table 4. HR of CRC in relation to inflammatory markers and inflammation *z*-score at visit 1 in the ARIC study, 1987–2006

Inflammatory marker (quartiles)	Number of CRC	Person-years	HR (95% CI)[a]	HR (95% CI)[b]
Fibrinogen, mg/dL				
≤259	58	60,556	Reference	Reference
260–294	75	59,613	1.27 (0.90–1.79)	1.30 (0.91–1.85)
295–336	90	56,962	1.55 (1.11–2.16)	1.50 (1.06–2.13)
≥337	85	53,378	1.55 (1.10–2.18)	1.50 (1.05–2.15)
P			0.001	0.03
VWF, %				
≤83	61	60,013	Reference	Reference
84–109	85	58,827	1.33 (0.95–1.84)	1.30 (0.93–1.84)
110–142	73	57,826	1.11 (0.79–1.56)	1.07 (0.76–1.52)
≥143	89	53,842	1.37 (0.98–1.92)	1.30 (0.93–1.84)
P			0.17	0.33
FVIII, %				
≤104	66	58,721	Reference	Reference
105–126	83	61,355	1.13 (0.82–1.57)	1.13 (0.82–1.58)
127–150	71	56,076	1.03 (0.73–1.44)	1.03 (0.73–1.46)
≥151	88	54,357	1.26 (0.90–1.75)	1.17 (0.83–1.65)
P			0.84	0.54
WBC, $\times 10^9$ cells/L				
≤4.8	79	62,251	Reference	Reference
4.9–5.8	65	59,428	0.89 (0.64–1.24)	0.86 (0.61–1.21)
5.9–7.0	86	53,894	1.32 (0.97–1.79)	1.26 (0.91–1.74)
≥7.1	78	54,935	1.21 (0.88–1.66)	1.13 (0.79–1.60)
P			0.07	0.20
Albumin, g/dL				
≤3.7	94	68,412	Reference	Reference
3.8	41	34,395	0.86 (0.60–1.24)	0.89 (0.61–1.29)
3.8–3.9	99	68,633	1.05 (0.79–1.39)	1.09 (0.81–1.46)
≥3.9	74	59,069	0.92 (0.79–1.26)	0.94 (0.68–1.30)
P			0.85	0.94
z-score				
<−2.12	58	59,810	Reference	Reference
−2.12 to −0.32	76	58,240	1.30 (0.92–1.83)	1.30 (0.91–1.84)
−0.31 to 1.72	74	57,608	1.23 (0.87–1.75)	1.19 (0.83–1.71)
≥1.73	100	54,851	1.73 (1.24–2.42)	1.65 (1.15–2.35)
P			0.002	0.01

[a]Adjusted for age, race, sex, and center.

[b]Multivariate adjusted for age, race, center, education, BMI, aspirin use, smoking status and pack-years of smoking, gender–HRT, and diabetes.

significant associations between CRP concentration and incident CRC (29, 34, 35). In the Women's Health Study, there was an indication of an inverse CRP–CRC association (29). The Women's Health Study could be different from other studies in a number of ways because it included only female health professionals who participated in a clinical trial of low aspirin and vitamin E and used HRT more frequently than populations in other studies. Two meta-analyses of prospective studies of CRP and risk of CRC were published in 2008 (36, 37). Both reported a slightly increased risk of CRC in relation to CRP: HR = 1.09 (95% CI, 0.98–1.21) and 1.12 (95% CI, 1.01–1.25) per 1 unit in log-transformed high-sensitivity CRP in Heikkila and colleagues (36) and Tsilidis and colleagues (37), respectively. The analysis by Tsilidis and colleagues (37) reported slightly increased risk of colon cancer and no risk of rectal cancer in relation to greater CRP, which is in line with our results. Heikkila and colleagues indicated that the "results of some studies were inconsistent," with relatively high heterogeneity among the effect estimates as reflected by $I^2 = 50.2$. They concluded that there was a need for large prospective

Table 5. Multivariate-adjusted HR of colon and rectal cancers in relation to fibrinogen and inflammation *z*-score, ARIC study, 1987–2006

Inflammatory marker (quartiles)	HR (95% CI)[a]	
	Colon cancer	Rectal cancer
Fibrinogen, mg/dL		
≤259	Reference	Reference
260—294	1.24 (0.82–1.88)	1.55 (0.79–3.03)
295—336	1.48 (0.98–2.22)	1.65 (0.84–3.24)
≥337	1.75 (1.16–2.63)	0.89 (0.40–1.95)
P	0.005	0.84
z-score		
<−2.12	Reference	Reference
−2.12 to −0.32	1.41 (0.92–2.16)	1.14 (0.62–2.11)
−0.31 to 1.72	1.49 (0.97–2.29)	0.70 (0.35–1.39)
≥1.73	2.18 (1.43–3.31)	0.76 (0.38–1.53)
P	0.0003	0.25

[a]Multivariate adjusted for age, race, center, education, BMI, aspirin use, smoking status and pack-years of smoking, diabetes, and gender–HRT at visit 1.

studies specifically designed to investigate the relation between CRP concentration and CRC risk (36). Recently, a Danish prospective cohort reported an increased multivariate-adjusted HR of incident CRC for the highest versus lowest quintile of CRP: 1.7 (95% CI, 0.8–3.2; $P = 0.33$), but the number of CRC cases was small ($n = 93$; ref. 30). There is no clear explanation for the different findings among studies but some reasons may include different study populations and insufficient adjustment for confounding factors such as obesity, smoking, use of NSAIDs, or diabetes.

The epidemiologic evidence for other acute-phase reactants and CRC risk is sparse and inconsistent. Two studies reported positive statistically significant associations between WBC and incident CRC: HRs were 1.15–1.24 for the upper versus lowest WBC quartile, which are slightly higher than HR = 1.13 observed in our cohort (10, 11). Two other studies had contradictory findings on serum albumin concentrations in relation to CRC incidence: Knekt and colleagues (38) observed positive associations between albumin concentrations and risk of distal colon cancer, whereas Ko and colleagues (12) reported an inverse relation between albumin and colon cancer risk ($P = 0.02$). To our knowledge, no epidemiologic studies examined associations of incident CRC in relation to fibrinogen, VWF, or FVIII. A large meta-analysis of prospective studies reported a positive association of fibrinogen with mortality from CRC: HR = 1.71 (95% CI, 1.30–2.25) per 1 g/L increment in fibrinogen (28).

Several lines of evidence support a role of colonic inflammation in colorectal carcinogenesis. Laboratory animal studies indicate that inflammation promotes the conversion of colonic adenoma cells to adenocarcinoma cells (39). In humans, reactive oxygen species and NF-κB, which activates the cytokine cascade and other proinflammatory mediators, have been shown to be expressed in colon tissues (2, 14). Genetic polymorphisms of COX-2 (2, 10) and several genetic polymorphisms in inflammatory cytokine genes (40–42) have been associated with an increased risk of colorectal adenomas or CRC. An increased CRC risk in patients with inflammatory bowel disease (the risk markedly increases with the extent and duration of disease; refs. 3, 4) and protective effects of long-term use of NSAIDs for incident CRC in observational studies and randomized trials (3, 5) strongly support a link between inflammation and CRC.

The mechanisms explaining the biological association between inflammatory markers and CRC development are unclear but acute phase reactants measured before CRC diagnosis may play several roles in the process. First, any association between acute-phase reactants and CRC incidence may be causal, that is, acute-phase reactants themselves may increase the CRC risk most likely by perpetuating inflammation. For instance, in mice, fibrinogen (its $\alpha_M\beta_2$ binding motif) has been shown to cause local inflammatory processes (secretion of IL-6) and epithelial alterations that result in epithelial hyperplasia and secondary transformation events leading to colitis-associated colon cancer (43). Further, WBCs produce oxygen metabolites causing DNA damage in mammalian cells (44), and CRP activates endothelial cells, monocytes, and smooth muscle cells and induces the NF-κβ inflammatory pathway, which may lead to CRC (45, 46).

Alternatively, an association between acute-phase reactants and CRC incidence may be noncausal with acute-phase reactants simply being indicators of chronic inflammation. The inflammation may start directly in the colon or may be a consequence of systemic inflammation:

Table 6. HR of CRC in relation to CRP, ARIC study, 1996–2006

CRP quartiles (mg/L)	Number of cancers	Person-years	HR (95% CI)[a]	HR (95% CI)[b]
CRC				
<1.09	28	22,232	Reference	Reference
1.09–2.44	45	22,078	1.62 (1.01–2.60)	1.53 (0.90–2.60)
2.44–5.64	49	21,836	1.83 (1.15–2.93)	1.84 (1.08–3.13)
>5.64	29	14,799	1.70 (1.04–2.76)	1.97 (1.13–3.43)
P			0.03	0.02
Colon cancer				
<1.09	22	22,128	Reference	Reference
1.09–2.44	36	22,001	1.67 (0.98–2.84)	1.48 (0.83–2.65)
2.44–5.64	38	21,717	1.85 (1.09–3.15)	1.78 (0.99–3.20)
>5.64	37	21,328	1.90 (1.11–3.26)	2.06 (1.12–3.78)
P			0.02	0.02
Rectal cancer				
<1.09	7	22,297	Reference	Reference
1.09–2.44	10	22,208	1.39(0.53–3.65)	1.67 (0.54–5.20)
2.44–5.64	11	21,960	1.52 (0.58–3.95)	1.78 (0.56–5.71)
>5.64	7	21,560	0.95 (0.33–2.77)	1.37 (0.38–4.92)
P			0.98	0.63

[a]Adjusted for age, race, sex, and center.

[b]Multivariate adjusted for age, race, center, education, BMI, aspirin use, smoking status, gender–HRT, and diabetes.

circulating proinflammatory mediators increase gut permeability and exposure to luminal antigens, which induces a local immune response and mucosal inflammation in the colon (47). Although this study cannot determine whether acute phase reactants are actively involved in the carcinogenesis or are merely bystanders, the positive associations of these biomarkers with subsequent CRC risk may help predict cancer risk in the future.

Our study has several important strengths: prospective design, large sample size, long follow-up with a high participation rate, detailed information about potential confounding variables, and accurate measurement of several acute-phase reactants. The ARIC study used standardized validated protocols in 4 centers. Availability of data on 5 acute-phase reactants-–nonspecific markers of systemic inflammation at baseline-–allowed us not only to study the association for each individual marker but also to examine their combined association with CRC incidence.

However, there are important limitations. ARIC was not designed for cancer research. Information about some cancer risk factors and cancer screening became available only 7 to 8 years after baseline. Although we adjusted for many confounders, as in any observational study, we cannot exclude residual confounding, for instance by dietary factors, which are difficult to measure and adjust for (36). Further, there was likely incomplete ascertainment of cancer cases in the Mississippi cohort. However, we do not have a reason to presume that these missing cases were associated with inflammatory markers. In addition, data on cancer stage or CRC subsites were not uniformly available from the registries.

Another concern is that our markers reflect not only chronic but also acute phase response. To address this issue, we excluded participants with CRP > 10 mg/L (mild and acute inflammation; ref. 48) and obtained similar associations of CRP with CRC risk. Further, misclassification could arise from using single measurements of inflammatory markers, which most likely results in underestimation of HRs, although the reliability coefficients based on repeated testing of individuals over 1 to 2 weeks were greater than or equal to 0.69 for baseline markers in ARIC (23). Most studies reported reliability coefficients for CRP of at least 0.6 (8, 49). Another limitation is that we do not know whether the measured circulatory markers correlate with relevant inflammatory markers in normal colon tissue. Moreover, it was impossible to distinguish whether elevated levels of those biomarkers are associated with CRC risk only through inflammation or because of some other functions such as procoagulant properties of fibrinogen or endothelial dysfunction of VWF (50). However, because 2 individual inflammatory markers and 2 combinations of markers (2 *z*-scores) were associated with CRC risk, this argues for a more general role of inflammation. Finally, there were only 166 CRC for the CRP analysis, so there was limited power to examine associations between CRP and CRC risk across different subgroups.

In conclusion, CRP, fibrinogen, and inflammation *z*-score were associated with CRC risk in this prospective cohort after adjustment for other CRC risk factors. These

biomarkers either reflect inflammation, localized in the colorectum or generalized inflammation, or they may also contribute to stimulating inflammation. This offers further evidence that inflammation plays a role in colorectal carcinogenesis. Inflammation is a potentially modifiable risk factor, so interventions decreasing inflammation (such as aspirin and other NSAIDs) may reduce the CRC risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Association of Inflammatory Markers with Colorectal Cancer Incidence in the Atherosclerosis Risk in Communities Study

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