

## C-Reactive Protein and Colorectal Cancer Mortality in U.S. Adults

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### Abstract

**Background:** Chronic inflammation has been associated with colorectal cancer. Prediagnostic levels of C-reactive protein (CRP), a highly sensitive marker of inflammation, have been weakly associated with increased colorectal cancer incidence, but few data are available examining its relationship with colorectal cancer mortality.

**Methods:** In the Third National Health and Nutrition Examination Survey (NHANES III), 65% of the 15,924 adult participants had CRP levels  $\leq 0.21$  mg/dL. Using this as the reference group, we calculated hazard ratios (HR) for higher CRP categories and colorectal cancer mortality, and compared them with HRs for other mortality causes.

**Results:** Over a median follow-up period of 14.2 years, there were 92 deaths from colorectal cancer. Compared with the reference group, multivariable adjusted HRs for colorectal cancer mortality were 2.66 [95% confidence interval (CI), 1.36–5.20] for CRP levels 0.22–0.50 mg/dL; 3.40 (95% CI, 1.48–7.77) for levels 0.51–1.00 mg/dL; and 3.96 (95% CI, 1.64–9.52) for levels  $>1.00$  mg/dL. Estimates for colorectal cancer mortality did not change appreciably after excluding deaths within the first 3 years or by limiting follow-up to 5 or 10 years.

**Conclusions:** In a large representative study of U.S. adults, we observed strong dose–response associations between CRP levels and colorectal cancer mortality.

**Impact:** Further evaluation of CRP may help identify high-risk groups for colorectal cancer screening and those who might benefit most from prophylactic anti-inflammatory therapy. *Cancer Epidemiol Biomarkers Prev*; 23(8); 1609–18. ©2014 AACR.

### Introduction

Colorectal cancer is responsible for approximately 50,000 deaths annually in the United States (1). Chronic inflammation has been hypothesized to play an important role in colorectal carcinogenesis (2–6). Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) has also been associated with reduced risk of colorectal cancer (7–13). This has led to broad interest in identifying markers of chronic inflammation that might help detect high-risk groups for more intensive colorectal cancer screening, and those who might potentially benefit from prophylactic anti-inflammatory therapy.

C-reactive protein (CRP) is a highly sensitive marker of inflammation that has the potential to be used to predict colorectal cancer (14, 15). Recently, in 2 large prospective studies, prediagnostic CRP levels were weakly positively associated with increased colorectal cancer incidence (16, 17). Higher CRP levels at diagnosis have also been associated with tumor recurrence and worse survival in patients with colorectal cancer (18–21). However, to our knowledge, no previous study has evaluated the association between prediagnostic levels of CRP and colorectal cancer mortality.

We examined a cohort of 15,924 adults from the Third National Health and Nutrition Examination Survey, 1988 to 1994 (NHANES III), with mortality follow-up through December 2006. We hypothesized that elevated baseline CRP levels in the general population would predict increased colorectal cancer mortality.

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### Materials and Methods

#### Study population

NHANES III was conducted by the Centers for Disease Control and Prevention (CDC) from October 1988 to October 1994 to provide national health estimates of the United States' civilian population (22). Of the 16,573 participants ages  $\geq 20$  years who underwent medical examination, our study included 15,924 (96%) adults for

whom data on serum CRP levels and vital status were available. In age and multivariable adjusted models, missing data on covariates ranged from less than 1% to 9% of the study participants. We included only those individuals for whom complete information was available for these covariates as eligible for this study. NHANES III was approved by CDC's Institutional Review Board and all study participants provided written informed consent (23).

### Measures

During the survey, each participant underwent anthropometric measurements, provided a blood sample, and completed a detailed questionnaire on sociodemographic, lifestyle, and health-related factors. The laboratory assessment of CRP levels, our main exposure of interest, was done using latex-enhanced nephelometry (Behring Nephelometer Analyzer System, Behring Diagnostics Inc.; ref. 24). In this particle-enhanced assay, serum CRP particles bind with the corresponding anti-CRP antibodies. Light scattering is then used for quantitative determination of CRP levels. To ensure precision and reliability, the CRP results were standardized against the WHO International Reference Preparation standards of purified human CRP. Further details about the NHANES III laboratory procedures, including collection of specimens, processing, shipment, and quality control systems, have been described elsewhere (24, 25).

Our primary outcomes of interest were deaths from colorectal cancer, other cancers, and noncancer-related causes of death. The 2010 public release version of the NHANES III Linked Mortality File was used to obtain mortality data (26, 27). The causes of death were classified using the following ICD-10 codes: colorectal cancer, C18-21; other cancers, C00-C16 and C22-C97; and cardiovascular disease, I00-I78. The final mortality status was determined for more than 99% of the study participants (28).

### Statistical analysis

Of the 15,924 eligible adult participants for whom CRP levels and mortality data were available, NHANES III classified 65% of them as having CRP levels below detection ( $\leq 0.21$  mg/dL). To examine dose-response associations, we classified these participants as the reference group and categorized the remaining eligible subjects in 3 approximately equally sized groups with CRP levels of 0.22 to 0.50, 0.51 to 1.00, and  $>1.00$  mg/dL, respectively. To investigate dose-response associations using CRP levels as a continuous variable, we then created restricted cubic splines for the hazard function (29).

To accommodate for differential weighting and clustering, we used appropriate statistical weights to calculate all point estimates and confidence intervals (CI; ref. 30). The time metric used for the analyses was time on study. We used Cox proportional hazards models to estimate the hazard ratios (HR) and 95% CIs. To examine proportional hazards assumption, we created an interaction term

between the natural log of follow-up time and CRP levels, and tested its significance in various models. No violations of the proportional hazards assumption were observed with respect to CRP levels.

For trend analysis, we first calculated a weighted median score for each CRP category. Then, to test the significance of the parameter estimate for these scores, for continuous variables, we used *proc surveyreg*, for categorical variables, we used *proc surveylogistic*, and for the Cox proportional hazards models, we used *proc surveyphreg*. In all of these analyses for trend, we used appropriate *strata*, *cluster*, and *weight* statements to accommodate for differential clustering and weighting.

In our analysis, we selected covariates *a priori* based on their suspected roles as confounders. We first fit a model (model 1) adjusted for age (20–40, 41–60, and  $>60$  years) only. For multivariable analyses (model 2), we additionally included sociodemographic factors, including gender, race-ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other), level of education (less than high school, high school or more), annual family income ( $< \$20,000$ ,  $\geq \$20,000$ ), and lifestyle-related variables, including body mass index (BMI;  $< 25$ , 25–29.9, and  $\geq 30$  kg/m<sup>2</sup>), pack-years of smoking, serum cotinine levels, alcohol consumption (g/day), and physical activity (more active, less active or about the same compared with others of same age). In model 3, we further adjusted for hypertension status (systolic or diastolic blood pressure  $\geq 140$  or  $\geq 90$  mm Hg respectively, use of antihypertensive drugs or hypertension medical history), diabetes mellitus status (glycosylated hemoglobin  $\geq 6.5\%$ , use of antidiabetic drugs, or diabetes medical history), hypercholesterolemia (total cholesterol  $\geq 240$  mg/dL, use of cholesterol-lowering drugs or medical history of high blood cholesterol), use of vitamin or mineral supplements (in the past 1 month), hormone use in women (any estrogen or progesterone use, including oral contraceptive pills in the past 1 month), and regular NSAID use (use of NSAIDs  $\geq 15$  times in the past 1 month). The categories of variables used in the analysis were consistent with the NHANES III survey design (30).

For stratified analysis, we used the CRP cut-off proposed by the CDC and the American Heart Association for predicting cardiovascular disease risk (comparing those with CRP levels  $\geq 0.3$  mg/dL to those with levels  $< 0.3$  mg/dL; ref. 31). We assessed confounding (by using  $\geq 10\%$  change in  $\beta$  coefficients as the criteria) because of other covariates that have been previously associated with colorectal cancer, such as serum folate and C-peptide levels, dietary intake of fiber, total saturated fatty acids, calcium, and vitamin D, and other markers of inflammation, including white blood cell count, neutrophil-lymphocyte ratio, plasma fibrinogen levels, and serum albumin levels (all measured continuously; refs. 32–37).

Because visceral obesity has been more closely related to colorectal cancer risk than BMI, we conducted a separate analysis using waist-to-hip ratio instead of BMI in the multivariable model (38–40). Furthermore, to exclude

the effects of anti-inflammatory drug and hormone use, we repeated the analysis after leaving out those with regular NSAID use, and women with any estrogen or progesterone use in the last month before the interview.

Finally, to assess whether colorectal cancer deaths that occurred early had appreciably higher levels of CRP because of occult disease, we repeated the analysis after excluding colorectal deaths within the first 3 years of the survey. We also calculated separate HRs for 5 and 10 years of follow-up from the time of survey. Because participants with a self-reported history of comorbidities may have changed their health-related behaviors, we conducted additional analyses after excluding those with known history of heart attack, congestive heart failure, stroke, or prior cancer.

All tests of statistical significance were 2 sided. All analyses were done using SAS (Version 9.3; SAS Institute Inc.).

## Results

Of the 15,924 study participants, 4,136 died over 209,860 person-years of follow-up (median follow-up period, 14.2 years). There were 92 deaths from colorectal cancer, 792 from other cancers, 1,871 from cardiovascular disease, and 1,381 from other remaining causes.

Table 1 summarizes the baseline characteristics of the cohort by categories of serum CRP levels. Higher CRP levels were associated with older age, being female or non-Hispanic black, having a higher BMI, being less physically active, having hypertension or diabetes, regular NSAID use, and hormone use in women. In addition, higher CRP levels were also associated with higher levels of serum C-peptide, white blood count, neutrophil-lymphocyte ratio, and plasma fibrinogen. Higher CRP levels were inversely associated with being non-Hispanic White, alcohol consumption, higher total daily intake of fiber, saturated fatty acids, calcium, and vitamin D, and higher serum albumin levels.

Table 2 provides the HRs between CRP levels and mortality from colorectal cancer and other causes of death. After adjusting for sociodemographic, lifestyle, and health-related variables (model 3), as compared with the reference group (CRP levels  $\leq 0.21$  mg/dL), HRs for colorectal cancer were 2.66 (95% CI, 1.36–5.20) for those with CRP levels from 0.22 to 0.50 mg/dL; 3.40 (95% CI, 1.48–7.77) for levels from 0.51 to 1.00 mg/dL; and 3.96 (95% CI, 1.64–9.52) for levels  $>1.00$  mg/dL, respectively ( $P_{\text{Trend}} < 0.01$ ). In participants with CRP levels  $\geq 0.22$  mg/dL, HR for one unit change in natural logarithm-transformed CRP levels was 1.50 (95% CI, 1.25–1.78). A restricted cubic spline investigating dose-response associations using CRP levels as a continuous variable is presented in Supplementary Fig. S1.

Using the same CRP level cut-offs, HRs for other cancers were 0.96 (95% CI, 0.66–1.39), 1.19 (95% CI, 0.83–1.72), and 1.89 (95% CI, 1.42–2.52); for cardiovascular disease, they were 1.27 (95% CI, 1.04–1.56), 1.30 (95% CI, 1.03–1.64), and

1.87 (95% CI, 1.39–2.51); and for other remaining mortality causes they were 1.19 (95% CI, 0.86–1.65), 1.18 (95% CI, 0.95–1.47), and 1.95 (95% CI, 1.51–2.51), respectively.

Table 3 shows the stratified results for the association between CRP levels and colorectal mortality in selected subgroups. The association was stronger in non-Hispanic whites, those with BMI  $<25$  kg/m<sup>2</sup>, current smokers, those who consume alcohol, use dietary supplements, or were physically less active.

The addition of potential confounders, including dietary factors, serum folate, and C-peptide levels or other markers of inflammation did not significantly change the results (Table 4). Repeating the analysis using waist-to-hip ratio instead of BMI, excluding those with regular NSAID use, women with a history of estrogen or progesterone use, or participants with a baseline history of heart attack, congestive heart failure, stroke, or cancer also did not lead to any appreciable change in the risk estimates. Exclusion of colorectal cancer deaths within the first 3 years of survey or limiting follow-up to only 5 or 10 years did not materially affect the findings.

## Discussion

In this large, nationally representative study of U.S. adults, we observed a strong, dose-response association between prediagnostic CRP levels and colorectal cancer mortality. This association was particularly strong in non-Hispanic whites, current smokers, and those who were physically less active. The results were similar in men and women, and did not attenuate after adjusting for a number of potential confounders.

Current literature suggests that chronic inflammation may play a causal role in the development of colorectal cancer (2–6). Chronic inflammatory bowel conditions such as ulcerative colitis and Crohn's disease have been shown to substantially increase colorectal cancer risk (41–45). Possible mechanisms by which inflammation may contribute to colorectal carcinogenesis include generation of reactive oxygen and nitrogen species leading to oxidative DNA damage and instability, dysregulation of tumor suppressing genes like p53 as well as elevation of cytokines such as interleukin 6 that promote tumor growth (2, 5). We observed that prediagnosis CRP may also be associated with colorectal cancer mortality.

CRP is a nonspecific marker of systemic low-grade inflammation that is produced primarily in the liver in response to stimulation by proinflammatory cytokines, including interleukin 6 (14, 46). Unlike other markers of acute-phase inflammation such as coagulation and complement proteins, CRP is stable, and is usually unaffected by physiological and pathological processes other than the underlying inflammatory stimulus (14). It has, therefore, been used to predict several diseases associated with chronic inflammation, including ischemic heart disease, stroke, and peripheral vascular disease (14, 47).

Several population-based prospective studies have examined the association between CRP levels and

**Table 1.** Association between baseline characteristics and serum C-reactive protein levels in NHANES III participants<sup>a</sup>

	Serum C-reactive protein levels (mg/dL)				P <sub>Trend</sub>
	≤0.21	0.22–0.50	0.51–1.00	>1.00	
Age (mean), y	46.7	50.6	52.7	53.3	<0.01
Women	48.9	56.5	60.9	65.8	<0.01
Race-ethnicity					
Non-Hispanic white	43.5	43.2	39.0	38.4	<0.01
Non-Hispanic black	25.0	26.2	29.5	34.1	<0.01
Mexican-American	27.1	27.2	28.6	24.2	0.31
Other	4.4	3.4	2.9	3.2	0.22
Education: high school or more	61.8	58.5	52.0	49.4	<0.01
Annual family income: ≥\$20,000	53.8	51.3	45.5	40.4	<0.01
BMI					
<25 kg/m <sup>2</sup>	47.4	28.7	22.1	24.3	<0.01
25–29.9 kg/m <sup>2</sup>	35.5	37.8	35.8	29.1	0.03
≥30 kg/m <sup>2</sup>	17.1	33.6	42.1	46.6	<0.01
Waist:hip ratio (mean)	0.91	0.93	0.94	0.94	<0.01
Smoking status					
Current smoker	25.0	26.7	25.3	28.2	0.01
Former smoker	24.6	25.3	26.2	26.5	0.07
Never smoker	50.4	48.0	48.5	45.3	<0.01
Alcohol consumption	51.4	46.5	39.5	34.9	<0.01
Physical activity <sup>b</sup>					
More active	34.5	30.7	27.1	20.0	<0.01
Less active	19.6	22.8	26.2	34.2	<0.01
About the same	45.8	46.4	46.6	45.7	0.65
Hypertension	29.4	38.4	45.8	47.1	<0.01
Diabetes mellitus	7.5	13.6	17.6	22.2	<0.01
Hypercholesterolemia	27.9	35.8	36.3	32.6	<0.01
Supplement use	38.0	38.0	36.3	38.5	0.99
Regular NSAID use <sup>c</sup>	17.1	20.2	23.1	25.4	<0.01
Hormone use in women <sup>d</sup>	7.5	11.9	12.6	13.6	<0.01
Serum folate levels (mean), ng/mL	6.5	6.6	6.7	6.5	0.84
Fiber intake (mean), g/day	17.5	16.4	15.4	14.4	<0.01
Total saturated fatty acid intake (mean), g/day	27.3	25.3	23.6	22.9	<0.01
Total calcium intake (mean), mg/day	793.2	735.9	717.8	672.7	<0.01
Total vitamin D intake (mean), mcg/day	4.6	4.4	4.3	4.1	<0.01
Serum C-peptide (mean), pmol/mL	0.7	0.8	1.0	1.0	<0.01
White blood cell count (mean), 10 <sup>3</sup> /μL	6.8	7.4	7.7	8.5	<0.01
Neutrophil-lymphocyte ratio	2.0	2.1	2.2	2.6	<0.01
Plasma fibrinogen (mean), mg/dL	290.7	324.2	344.7	410.5	<0.01
Serum albumin (mean), g/dL	4.2	4.1	4.0	3.8	<0.01

<sup>a</sup>Data are shown as percentages unless otherwise specified.

<sup>b</sup>Compared with others of same age.

<sup>c</sup>NSAID use ≥15 times in the past 1 month.

<sup>d</sup>Use of any estrogen or progesterone including oral contraceptive pills by women in the past 1 month.

colorectal cancer incidence. The two largest studies to date, European Prospective Investigation into Cancer and Nutrition (EPIC, 1,096 cases; ref. 16) and Women's Health Initiative Observational Study (WHI-OS, 953 cases; ref. 17) recently reported multivariable adjusted relative risks of 1.36 (95% CI, 1.00–1.85) and 1.37 (95%

CI, 0.95–1.97) for colon cancer, and 1.02 (95% CI, 0.67–1.57) and 0.88 (95% CI, 0.36–2.15) for rectal cancer comparing CRP levels ≥0.3 mg/dL versus <0.1 mg/dL, and >0.59 mg/dL versus ≤0.09 mg/dL, respectively. Of the remaining studies, all with much smaller number of colorectal cancer cases, some (48–54) have reported

**Table 2.** HRs by serum C-reactive protein levels in NHANES III participants

Mortality cause	Serum C-reactive protein levels (mg/dL)				P <sub>Trend</sub>
	≤0.21	0.22–0.50	0.51–1.00	>1.00	
Colorectal cancer ( <i>n</i> )	48	12	17	15	
Model 1 <sup>a</sup>	1 (Ref.)	1.94 (1.08–3.50)	2.98 (1.33–6.67)	3.82 (1.66–8.81)	<0.01
Model 2 <sup>b</sup>	1 (Ref.)	2.60 (1.38–4.90)	3.48 (1.59–7.61)	4.24 (1.57–11.46)	<0.01
Model 3 <sup>c</sup>	1 (Ref.)	2.66 (1.36–5.20)	3.40 (1.48–7.77)	3.96 (1.64–9.52)	<0.01
Other cancers ( <i>n</i> )	444	73	145	130	
Model 1	1 (Ref.)	0.94 (0.67–1.33)	1.24 (0.89–1.73)	2.19 (1.61–2.99)	<0.01
Model 2	1 (Ref.)	0.98 (0.67–1.44)	1.21 (0.83–1.76)	1.85 (1.37–2.49)	<0.01
Model 3	1 (Ref.)	0.96 (0.66–1.39)	1.19 (0.83–1.72)	1.89 (1.42–2.52)	<0.01
CVD ( <i>n</i> )	1,038	226	317	290	
Model 1	1 (Ref.)	1.23 (1.04–1.45)	1.37 (1.11–1.68)	2.12 (1.73–2.60)	<0.01
Model 2	1 (Ref.)	1.31 (1.09–1.58)	1.39 (1.12–1.73)	2.02 (1.56–2.61)	<0.01
Model 3	1 (Ref.)	1.27 (1.04–1.56)	1.30 (1.03–1.64)	1.87 (1.39–2.51)	<0.01
Other causes ( <i>n</i> )	767	149	259	206	
Model 1	1 (Ref.)	1.10 (0.81–1.48)	1.39 (1.12–1.73)	2.15 (1.66–2.78)	<0.01
Model 2	1 (Ref.)	1.21 (0.88–1.68)	1.24 (1.00–1.53)	2.07 (1.59–2.69)	<0.01
Model 3	1 (Ref.)	1.19 (0.86–1.65)	1.18 (0.95–1.47)	1.95 (1.51–2.51)	<0.01

NOTE: Data are given as HR (95% CIs).

Abbreviations: CVD, cardiovascular disease; *n*, number of events; ref., reference group.

<sup>a</sup>Model 1: Adjusted for age.

<sup>b</sup>Model 2: Adjusted for age, gender, race–ethnicity, level of education, annual family income, BMI, pack-years of smoking, serum cotinine levels, alcohol consumption, and physical activity.

<sup>c</sup>Model 3: Adjusted for variables in model 2 and hypertension status, diabetes status, hypercholesterolemia, supplement use, nonsteroidal anti-inflammatory drug use, and hormone use in women.

significant positive associations whereas others (55–62) have been inconclusive.

CRP levels after a colorectal cancer diagnosis have also been shown to predict tumor recurrence and survival (18–21). A Danish colorectal cancer study group found that in 594 patients scheduled for elective resection, pre-operative CRP levels were independently predictive of overall survival even after adjusting for tumor location, Dukes classification, and other prognostic factors (HR, 1.4; 95% CI, 1.3–1.5 for every one unit increase in natural logarithm-transformed CRP levels; ref. 19).

Our results are consistent with these findings, suggesting that CRP can be used to predict colorectal cancer survival. However, because mortality is a function of both incidence and survival, predicting mortality may provide a more valid estimate of the overall prognostic value of a biomarker like CRP as compared with incidence or survival alone.

Another major strength of this study is that, by using the same multivariable models, it compares the risks for colorectal cancer mortality with other causes of death for which the evidence in favor of using CRP levels to identify high-risk groups is much more conclusive. For example, CRP has been extensively used in the risk prediction models for cardiovascular disease, especially for screening those who are at "intermediate" or "high" risks (63–66). In our analysis, as compared with those with CRP levels

≤0.21 mg/dL, those with levels >1.00 mg/dL had 3.96 times the hazard of dying from colorectal cancer. The corresponding estimate for cardiovascular disease mortality was 1.87. Thus, it is less likely that the CRP–colorectal cancer mortality association can be entirely explained by residual confounding or other biases as the association with cardiovascular disease has been observed in a number of studies and is smaller in magnitude for the same cut-points as used in our study. In addition, we were able to adjust for most covariates that have been previously shown to confound this association (32–40).

Other strengths of our study include the use of appropriate statistical weights, which helped to obtain estimates representative of the U.S. civilian adult population. Moreover, NHANES III used standardized and validated survey and laboratory methods, thereby reducing the potential for information bias. Also, the final mortality status was available for more than 99% of the participants, which minimized the possibility of selection bias.

Our study is limited by the relatively modest number of colorectal cancer outcomes. Therefore, we were unable to obtain precise estimates in stratified analysis. We did not have data on incidence or tumor location, so we could not compare HRs for incidence and mortality or assess site-specific HRs. Despite the exclusion of participants with any history of cancer, we cannot rule out the possibility

**Table 3.** HRs for colorectal cancer mortality stratified by baseline variables

	HRs (95% CI) comparing those with CRP levels >0.3 mg/dL to those with levels ≤0.3 mg/dL	
	Age adjusted	Multivariable adjusted <sup>a</sup>
All participants	2.85 (1.67–4.88)	3.29 (1.87–5.79)
Gender		
Male	3.09 (1.54–6.18)	3.28 (1.56–6.89)
Female	2.79 (1.05–7.44)	3.38 (1.00–11.42)
Race-ethnicity		
Non-Hispanic white	4.06 (2.11–7.83)	5.01 (2.40–10.44)
Non-Hispanic black	0.72 (0.32–1.61)	1.09 (0.51–2.37)
Mexican-American	2.67 (0.74–9.67)	3.26 (0.71–14.83)
BMI		
<25 kg/m <sup>2</sup>	5.76 (2.32–14.31)	5.99 (2.20–16.27)
25–29.9 kg/m <sup>2</sup>	1.37 (0.64–2.95)	1.28 (0.49–3.37)
≥30 kg/m <sup>2</sup>	2.24 (0.75–6.68)	3.13 (1.11–8.80)
Smoking status		
Current smoker	5.86 (1.73–19.52)	5.28 (1.21–22.93)
Former smoker	3.11 (1.29–7.51)	4.35 (2.01–9.40)
Never smoker	1.92 (1.06–3.46)	2.16 (0.77–6.06)
Alcohol consumption		
Yes	3.24 (1.40–7.48)	5.31 (1.75–16.15)
No	2.57 (1.25–5.30)	2.54 (1.16–5.53)
Physical activity <sup>b</sup>		
More active	1.71 (0.70–4.16)	1.26 (0.47–3.40)
Less active	8.34 (1.37–50.70)	6.89 (2.12–22.36)
About the same	4.04 (1.89–8.61)	5.10 (2.20–11.85)
Hypertension status		
Yes	2.17 (1.21–3.90)	2.91 (1.49–5.68)
No	3.69 (1.56–8.71)	3.51 (1.20–10.23)
Diabetes mellitus status		
Yes	1.23 (0.32–4.72)	1.36 (0.25–7.37)
No	3.25 (1.66–6.33)	3.29 (1.89–5.70)
Hypercholesterolemia		
Yes	2.95 (1.01–8.61)	2.45 (0.88–6.80)
No	2.85 (1.54–5.25)	3.78 (1.93–7.38)
Supplement use		
Yes	3.02 (1.16–7.80)	5.15 (1.62–16.34)
No	2.69 (1.27–5.69)	2.49 (1.13–5.47)

<sup>a</sup>Adjusted for age, gender, race-ethnicity, level of education, annual family income, BMI, pack-years of smoking, serum cotinine levels, alcohol consumption, physical activity, hypertension status, diabetes status, hypercholesterolemia, supplement use, nonsteroidal anti-inflammatory drug use, and hormone use in women.

<sup>b</sup>Compared with others of same age.

that some subjects had undiagnosed colorectal cancer at baseline. However, our results did not change appreciably after we excluded subjects with a follow-up time of less than 3 years.

Finally, in this study, CRP levels were measured at only one point in time and it is possible that use of NSAIDs and statins and occurrence of conditions not evident at baseline may affect inflammation, and therefore, levels of CRP. However, any change in CRP levels because of these factors would most likely be nondifferential and would

therefore, only bias the results toward the null. Furthermore, our findings did not change significantly with limiting the follow-up to 5 or 10 years, indicating that a single CRP measurement may be used to predict colorectal cancer. Previous studies have also demonstrated that CRP levels remain relatively stable over time (17, 67, 68). To assess whether a single CRP measurement adequately reflects long-term levels in prospective studies, a recent study examined CRP levels at years 2, 4, and 6 for 50 men in the Prostate Cancer Prevention Trial (PCPT). The

**Table 4.** Additional analysis for colorectal cancer mortality in NHANES III participants

	<b>HRs (95% CI) comparing those with CRP levels &gt;0.3 mg/dL to levels ≤0.3 mg/dL</b>
Model 3 <sup>a</sup>	3.29 (1.87–5.79)
Additional analysis <sup>b</sup>	
Using waist-to-hip ratio instead of BMI in the model	3.10 (1.77–5.41)
Excluding those with regular NSAID use	3.99 (2.01–7.90)
Excluding women with any hormone use	3.02 (1.65–5.52)
Excluding those with h/o heart attack, CHF, stroke, or cancer	3.79 (1.86–7.71)
Excluding those who died of colorectal cancer within 3 years of survey	3.34 (1.77–6.28)
Duration of follow-up: 5 years	2.55 (0.64–10.14)
Duration of follow-up: 10 years	3.72 (1.44–9.59)
Adjusting for additional covariates	
Model 3 + fiber intake, g/day	2.99 (1.63–5.46)
Model 3 + total saturated fatty acid intake, g/day	2.98 (1.63–5.42)
Model 3 + total calcium intake, mg/day	2.98 (1.64–5.44)
Model 3 + total vitamin D intake, mcg/day	2.99 (1.64–5.43)
Model 3 + serum C-peptide concentration, pmol/mL	3.36 (1.89–5.97)
Model 3 + serum folate levels, ng/mL	3.29 (1.84–5.89)
Model 3 + white blood cell count	3.37 (1.83–6.21)
Model 3 + neutrophil-lymphocyte ratio	3.05 (1.60–5.81)
Model 3 + plasma fibrinogen, mg/dL	3.43 (1.56–7.51)
Model 3 + serum albumin, g/dL	2.97 (1.69–5.20)

Abbreviations; CHF, congestive heart failure; h/o, history of.

<sup>a</sup>Adjusted for age, gender, race-ethnicity, level of education, annual family income, BMI, pack-years of smoking, serum cotinine levels, alcohol consumption, physical activity, hypertension status, diabetes status, hypercholesterolemia, supplement use, NSAID use, and hormone use in women.

<sup>b</sup>HRs adjusted for variables in model 3.

intraclass correlation coefficient in the study was 0.66 over 4 years. Interestingly, the authors also found that a single CRP measurement underestimated the true strength of the association. They estimated that if the true relative risks were 1.50, 2.00, and 3.00 when comparing high with low CRP concentrations, then the observed relative risks would be 1.31, 1.58, and 2.06, respectively (69).

Our findings may have implications for prevention and treatment strategies for colorectal cancer. Measuring CRP is easy and inexpensive and could be studied as a way to identify high-risk groups that may benefit from early or more intensive screening by colonoscopy or other methods. In patients with colorectal cancer, CRP levels might also be used to determine prognosis and select appropriate treatments.

Several studies, including clinical trials, have shown a 30% to 60% reduced risk of developing colorectal cancer with the use of aspirin or other NSAIDs (7–13). Aspirin use after colorectal cancer diagnosis has also been associated with lower colorectal and overall mortality (70–74). Furthermore, in patients with myocardial infarction, use of NSAIDs has been associated with lower CRP concentrations (75, 76). These results as well as findings from our study provide further evidence to suggest that CRP levels may help recognize candidates for possible prophylactic

and adjuvant therapy with anti-inflammatory drugs in the future.

CRP has the potential to be used as a marker for colorectal cancer. However, before it can be used clinically, large, prospective studies are needed where CRP levels are measured repeatedly to ascertain how long-term changes in concentrations predict colorectal risk and outcomes (17, 61). Moreover, similar to cardiovascular disease risk prediction models where CRP has been shown to improve risk stratification and reclassification (63–66), clinical significance of the predictive value of CRP over conventional risk factors in colorectal cancer needs to be assessed by including CRP levels in colorectal cancer risk prediction models. None of the current models use CRP to predict colorectal cancer risk (77).

Because CRP is a nonspecific marker of inflammation, we will also need to evaluate whether or not it is causally associated with colorectal cancer. Future studies should examine specific cytokines and other intermediate markers of inflammation to understand the mechanisms by which inflammation may play a role in colorectal carcinogenesis. Another approach could be examining associations between CRP gene polymorphisms and colorectal cancer risk by using Mendelian principals that help to rule out residual confounding (78). In a recent

population-based study with 2,365 colorectal cancer cases and 2,969 controls, genetic differences in the CRP gene variants influenced colon and rectal cancer risks as well as survival (79). Finally, clinical trials assessing use of NSAIDs in colorectal cancer could evaluate CRP as one of the markers to identify high-risk groups as well as to monitor treatment efficacy.

In conclusion, in a nationally representative cohort of U.S. adults, we demonstrated that prediagnosis elevated CRP levels are independent predictors of colorectal cancer mortality. These findings are consistent with the current evidence that supports the role of chronic inflammation in colorectal carcinogenesis. Further evaluation of CRP as a predictive marker may help recognize high-risk groups for colorectal cancer screening, and, given the recent evidence for NSAID use for colorectal cancer, potentially identify those who might benefit most from anti-inflammatory prophylaxis or therapy.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** A.B. Siegel

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