Research Article

Cancer Epidemiology, Biomarkers & Prevention

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 ≤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.

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 ≥20 years who underwent medical examination, our study included 15,924 (96%) adults for

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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^2), 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 β 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^2, 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[a]

	Serum C-reactive protein levels (mg/dL)				
	≤0.21	0.22–0.50	0.51–1.00	>1.00	P_{Trend}
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^2	47.4	28.7	22.1	24.3	<0.01
25–29.9 kg/m^2	35.5	37.8	35.8	29.1	0.03
≥30 kg/m^2	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[b]					
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[c]	17.1	20.2	23.1	25.4	<0.01
Hormone use in women[d]	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), 10^3/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

[a]Data are shown as percentages unless otherwise specified.
[b]Compared with others of same age.
[c]NSAID use ≥15 times in the past 1 month.
[d]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

	Serum C-reactive protein levels (mg/dL)				
Mortality cause	**≤0.21**	**0.22–0.50**	**0.51–1.00**	**>1.00**	P_{Trend}
Colorectal cancer (*n*)	48	12	17	15	
Model 1[a]	1 (Ref.)	1.94 (1.08–3.50)	2.98 (1.33–6.67)	3.82 (1.66–8.81)	<0.01
Model 2[b]	1 (Ref.)	2.60 (1.38–4.90)	3.48 (1.59–7.61)	4.24 (1.57–11.46)	<0.01
Model 3[c]	1 (Ref.)	2.66 (1.36–5.20)	3.40 (1.48–7.77)	3.96 (1.64–9.52)	<0.01
Other cancers (*n*)	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 (*n*)	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 (*n*)	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.

[a]Model 1: Adjusted for age.

[b]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.

[c]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, preoperative 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[a]**
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^2	5.76 (2.32–14.31)	5.99 (2.20–16.27)
25–29.9 kg/m^2	1.37 (0.64–2.95)	1.28 (0.49–3.37)
≥30 kg/m^2	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[b]		
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)

[a]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.
[b]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

	HRs (95% CI) comparing those with CRP levels >0.3 mg/dL to levels ≤0.3 mg/dL
Model 3[a]	3.29 (1.87–5.79)
Additional analysis[b]	
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.

[a]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.

[b]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.

Authors' Contributions

Conception and design: A. Goyal, M.B. Terry, A.B. Siegel
Development of methodology: A. Goyal, A.B. Siegel
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Goyal
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Goyal, M.B. Terry, Z. Jin, A.B. Siegel
Writing, review, and/or revision of the manuscript: A. Goyal, M.B. Terry, A.B. Siegel
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.B. Siegel
Study supervision: A.B. Siegel

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
2. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.
3. Okada F, Kawaguchi T, Habelhah H, Kobayashi T, Tazawa H, Takeichi N, et al. Conversion of human colonic adenoma cells to adenocarcinoma cells through inflammation in nude mice. Lab Invest 2000;80:1617–28.
4. Itzkowitz SH, Yio X. Inflammation and cancer. IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 2004;287:G7–17.
5. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. Gastroenterology 2011;140:1807–16.
6. Terzic J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology 2010;138:2101–14.
7. Flossmann E, Rothwell PMBritish Doctors Aspirin T, the UKTIAAT. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007;369:1603–13.
8. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J Natl Cancer Inst 2009;101:256–66.
9. Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 2006;355:885–95.
10. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, et al. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 2006;355:873–84.
11. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;376:1741–50.
12. Ruder EH, Laiyemo AO, Graubard BI, Hollenbeck AR, Schatzkin A, Cross AJ. Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort. Am J Gastroenterol 2011;106:1340–50.
13. Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011;378:2081–7.
14. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111:1805–12.
15. Toriola AT, Ulrich CM. Is there a potential use for C-reactive protein as a diagnostic and prognostic marker for colorectal cancer? Future Oncol 2011;7:1125–8.
16. Aleksandrova K, Jenab M, Boeing H, Jansen E, Bueno-de-Mesquita HB, Rinaldi S, et al. Circulating C-reactive protein concentrations and risks of colon and rectal cancer: a nested case-control study within the European Prospective Investigation into Cancer and Nutrition. Am J Epidemiol 2010;172:407–18.
17. Toriola AT, Cheng TY, Neuhouser ML, Wener MH, Zheng Y, Brown E, et al. Biomarkers of inflammation are associated with colorectal cancer risk in women but are not suitable as early detection markers. Int J Cancer 2013;132:2648–58.
18. Nozoe T, Matsumata T, Kitamura M, Sugimachi K. Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. Am J Surg 1998;176:335–8.
19. Nielsen HJ, Christensen IJ, Sorensen S, Moesgaard F, Brunner N. Preoperative plasma plasminogen activator inhibitor type-1 and serum C-reactive protein levels in patients with colorectal cancer. The RANX05 Colorectal Cancer Study Group. Ann Surg Oncol 2000;7:617–23.
20. McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg 2003;90:215–9.
21. Canna K, McMillan DC, McKee RF, McNicol AM, Horgan PG, McArdle CS. Evaluation of a cumulative prognostic score based on the systemic inflammatory response in patients undergoing potentially curative surgery for colorectal cancer. Br J Cancer 2004;90:1707–9.
22. National Center for Health Statistics. The National Health and Nutrition Examination Survey (NHANES). [cited 2013 April 1]. Available from: http://www.cdc.gov/nchs/nhanes.htm
23. National Center for Health Statistics. Research Ethics Review Board (ERB) Approval. [cited 2013 April 1]. Available from: http://www.cdc.gov/nchs/nhanes/irba98.htm
24. National Center for Health Statistics. Laboratory Procedures Used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994 [cited 2013 April 1]. Available from: http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals/labman.pdf

25. Gunter EW, McQuillan G. Quality control in planning and operating the laboratory component for the Third National Health and Nutrition Examination Survey. J Nutr 1990;120 Suppl 11:1451–4.
26. National Center for Health Statistics. The Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality File. [cited 2013 April 1]. Available from: http://www.cdc.gov/nchs/data/datalinkage/nh3_file_layout_public_2010.pdf
27. World Health Organization. International statistical classification of diseases and related health problems, 10th revision. Geneva, Switzerland: World Health Organization; 1992.
28. National Center for Health Statistics. The Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality File, Mortality follow-up through 2006: Matching Methodology May 2009. [cited 2013 April 1]. Available from: http://www.cdc.gov/nchs/data/datalinkage/matching_methodology_nhanes3_final.pdf
29. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 2010;29: 1037–57.
30. National Center for Health Statistics. The Third National Health and Nutrition Examination Survey (NHANES III), 1988–94. Analytic and Reporting Guidelines. [cited 2013 April 1]. Available from: http://www.cdc.gov/nchs/data/nhanes/nhanes3/nh3gui.pdf
31. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.
32. Jenab M, Riboli E, Cleveland RJ, Norat T, Rinaldi S, Nieters A, et al. Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2007;121:368–76.
33. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr 2007;86:s836–42.
34. Ko WF, Helzlsouer KJ, Comstock GW. Serum albumin, bilirubin, and uric acid and the anatomic site-specific incidence of colon cancer. J Natl Cancer Inst 1994;86:1874–5.
35. Lee YJ, Lee HR, Nam CM, Hwang UK, Jee SH. White blood cell count and the risk of colon cancer. Yonsei Med J 2006;47:646–56.
36. Stocks T, Lukanova A, Johansson M, Rinaldi S, Palmqvist R, Hallmans G, et al. Components of the metabolic syndrome and colorectal cancer risk; a prospective study. Int J Obes 2008;32:304–14.
37. Huxley RR, Lean M, Crozier A, John JH, Neil HA, Oxford F, et al. Effect of dietary advice to increase fruit and vegetable consumption on plasma flavonol concentrations: results from a randomised controlled intervention trial. J Epidemiol Community Health 2004; 58:288–9.
38. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999;19:972–8.
39. Festa A, D'Agostino R Jr., Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42–7.
40. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjonneland A, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006;98:920–31.
41. Levin B. Inflammatory bowel disease and colon cancer. Cancer 1992;70:1313–6.
42. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526–35.
43. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. Clin Gastroenterol Hepatol 2012;10:639–45.
44. Jess T, Gamborg M, Matzen P, Munkholm P, Sorensen TI. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. Am J Gastroenterol 2005;100:2724–9.
45. Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. Aliment Pharmacol Ther 2006;23:1097–104.
46. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448–54.
47. Emerging Risk Factors C Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132–40.
48. Il'yasova D, Colbert LH, Harris TB, Newman AB, Bauer DC, Satterfield S, et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev 2005;14:2413–8.
49. Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane SJapan Public Health Center-Based Prospective Study G. Plasma C-reactive protein and risk of colorectal cancer in a nested case-control study: Japan Public Health Center-based prospective study. Cancer Epidemiol Biomarkers Prev 2006;15:690–5.
50. Gunter MJ, Stolzenberg-Solomon R, Cross AJ, Leitzmann MF, Weinstein S, Wood RJ, et al. A prospective study of serum C-reactive protein and colorectal cancer risk in men. Cancer Res 2006;66:2483–7.
51. Allin KH, Bojesen SE, Nordestgaard BG. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. J Clin Oncol 2009;27:2217–24.
52. Chiu HM, Lin JT, Chen TH, Lee YC, Chiu YH, Liang JT, et al. Elevation of C-reactive protein level is associated with synchronous and advanced colorectal neoplasm in men. Am J Gastroenterol 2008;103:2317–25.
53. Prizment AE, Anderson KE, Visvanathan K, Folsom AR. Association of inflammatory markers with colorectal cancer incidence in the atherosclerosis risk in communities study. Cancer Epidemiol Biomarkers Prev 2011;20:297–307.
54. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ. C-reactive protein and the risk of incident colorectal cancer. JAMA 2004;291:585–90.
55. Zhang SM, Buring JE, Lee IM, Cook NR, Ridker PM. C-reactive protein levels are not associated with increased risk for colorectal cancer in women. Ann Intern Med 2005;142:425–32.
56. Ito Y, Suzuki K, Tamakoshi K, Wakai K, Kojima M, Ozasa K, et al. Colorectal cancer and serum C-reactive protein levels: a case-control study nested in the JACC Study. J Epidemiol 2005;15 Suppl 2:S185–9.
57. Siemes C, Visser LE, Coebergh JW, Splinter TA, Witteman JC, Uitterlinden AG, et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. J Clin Oncol 2006;24:5216–22.
58. Trichopoulos D, Psaltopoulou T, Orfanos P, Trichopoulou A, Boffetta P. Plasma C-reactive protein and risk of cancer: a prospective study from Greece. Cancer Epidemiol Biomarkers Prev 2006;15:381–4.
59. Heikkila K, Harris R, Lowe G, Rumley A, Yarnell J, Gallacher J, et al. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. Cancer Causes Control 2009;20:15–26.
60. Chan AT, Ogino S, Giovannucci EL, Fuchs CS. Inflammatory markers are associated with risk of colorectal cancer and chemopreventive response to anti-inflammatory drugs. Gastroenterology 2011;140: 799–808.
61. Van Hemelrijck M, Holmberg L, Garmo H, Hammar N, Walldius G, Binda E, et al. Association between levels of C-reactive protein and leukocytes and cancer: three repeated measurements in the Swedish AMORIS study. Cancer Epidemiol Biomarkers Prev 2011;20:428–37.
62. Song M, Wu K, Ogino S, Fuchs CS, Giovannucci EL, Chan AT. A prospective study of plasma inflammatory markers and risk of colorectal cancer in men. Br J Cancer 2013:108:1891–8.
63. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. J Am Coll Cardiol 2007;49: 2129–38.
64. Koenig W, Lowel H, Baumert J, Meisinger C. C-reactive protein modulates risk prediction based on the Framingham Score: implications for future risk assessment: results from a large cohort study in southern Germany. Circulation 2004;109:1349–53.

65. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation 2008;118:2243–51.
66. Wilson PW, Pencina M, Jacques P, Selhub J, D'Agostino R Sr, O'Donnell CJ. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. Circ Cardiovasc Qual Outcomes 2008;1:92–7.
67. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. Circulation 2003;108:155–60.
68. Gunter MJ, Cross AJ, Huang WY, Stanczyk FZ, Purdue M, Xue X, et al. A prospective evaluation of C-reactive protein levels and colorectal adenoma development. Cancer Epidemiol Biomarkers Prev 2011;20: 537–44.
69. Platz EA, Sutcliffe S, De Marzo AM, Drake CG, Rifai N, Hsing AW, et al. Intra-individual variation in serum C-reactive protein over 4 years: an implication for epidemiologic studies. Cancer Causes Control 2010; 21:847–51.
70. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA 2009;302:649–58.
71. Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Yamauchi M, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. N Engl J Med 2012;367:1596–606.
72. McCowan C, Munro AJ, Donnan PT, Steele RJ. Use of aspirin post-diagnosis in a cohort of patients with colorectal cancer and its association with all-cause and colorectal cancer specific mortality. Eur J Cancer 2013;49:1049–57.
73. Walker AJ, Grainge MJ, Card TR. Aspirin and other non-steroidal anti-inflammatory drug use and colorectal cancer survival: a cohort study. Br J Cancer 2012;107:1602–7.
74. Bastiaannet E, Sampieri K, Dekkers OM, de Craen AJ, van Herk-Sukel MP, Lemmens V, et al. Use of aspirin postdiagnosis improves survival for colon cancer patients. Br J Cancer 2012;106:1564–70.
75. Kennon S, Price CP, Mills PG, Ranjadayalan K, Cooper J, Clarke H, et al. The effect of aspirin on C-reactive protein as a marker of risk in unstable angina. J Am Coll Cardiol 2001;37:1266–70.
76. Monakier D, Mates M, Klutstein MW, Balkin JA, Rudensky B, Meerkin D, et al. Rofecoxib, a COX-2 inhibitor, lowers C-reactive protein and interleukin-6 levels in patients with acute coronary syndromes. Chest 2004;125:1610–5.
77. Win AK, Macinnis RJ, Hopper JL, Jenkins MA. Risk prediction models for colorectal cancer: a review. Cancer Epidemiol Biomarkers Prev 2012;21:398–410.
78. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 2003;32:1–22.
79. Slattery ML, Curtin K, Poole EM, Duggan DJ, Samowitz WS, Peters U, et al. Genetic variation in C-reactive protein in relation to colon and rectal cancer risk and survival. Int J Cancer 2011; 128:2726–34.