

C-Reactive Protein Levels Are Not Associated with Increased Risk for Colorectal Cancer in Women

Shumin M. Zhang, MD, ScD; Julie E. Buring, ScD; I-Min Lee, MBBS, ScD; Nancy R. Cook, ScD; and Paul M. Ridker, MD, MPH

Background: Observations that risk for colorectal cancer is elevated in patients with inflammatory bowel disease and that long-term use of anti-inflammatory drugs may reduce colorectal cancer risk have raised the possibility that inflammation may play a role in the development of colorectal cancer. While a recent prospective study observed a positive association between C-reactive protein (CRP), a marker of inflammation, and risk for colon cancer, data testing this hypothesis are sparse.

Objective: To evaluate whether plasma CRP levels predict colorectal cancer risk in women.

Design: Prospective cohort study, with 97% morbidity follow-up and 100% mortality follow-up within the past 2 years.

Setting: Women's Health Study.

Participants: 27 913 apparently healthy women age 45 years or older who had CRP measured at entry into a trial of low-dose aspirin and vitamin E. Maximum length of intervention and follow-up was 10.8 years.

Measurements: Self-reported incident colorectal adenocarcinoma confirmed by medical record review.

Results: 169 women developed colorectal adenocarcinomas dur-

ing follow-up. Baseline CRP levels were not significantly associated with colorectal cancer risk. The multivariate hazard ratios according to cutoff points for CRP proposed in clinical guidelines were 0.79 (95% CI, 0.53 to 1.17) for the category of 1 to 3 mg/L and 0.66 (CI, 0.43 to 1.03) for the category of greater than 3 mg/L (*P* for trend = 0.09), as compared with the category of less than 1 mg/L. High CRP levels were also not associated with increased risk in analyses done according to tumor location and stage at diagnosis, according to alternative cutoff points for CRP, or in any of the subgroups evaluated.

Limitations: Despite multivariate analysis, residual confounding might still be present. Although this study was prospective, we cannot completely exclude undetected cancer at baseline. Measurements for CRP were available for only 71% of women in the cohort; however, the women who did and those who did not provide blood were mostly similar.

Conclusions: Plasma CRP levels do not appear to predict an increased risk for developing colorectal cancer in apparently healthy women. Low-grade inflammation may not play an important role in increasing the risk for colorectal cancer.

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For author affiliations, see end of text.

C-reactive protein (CRP), a marker of inflammation, is consistently associated with increased risk for cardiovascular disease (1). A recent epidemiologic study has raised the hypothesis that CRP levels might also be associated with incident colon cancer (2). This latter hypothesis is supported by clinical observations of an increased risk for colorectal cancer in patients with chronic, relapsing and remitting inflammatory disorders—ulcerative colitis and Crohn disease—collectively known as inflammatory bowel diseases (3, 4). Reduced risk for colorectal adenomas and cancer associated with long-term use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) in observational studies and some clinical trials also supports this hypothesis (5). Moreover, CRP levels in patients with colorectal cancer are correlated with tumor stage (6–10).

However, colorectal cancer associated with inflammatory bowel diseases accounts for only 1% to 2% of all cases of colorectal cancer in the general population (3). In addition, the mechanisms by which NSAIDs may reduce the risk for colorectal neoplasia are still under debate and may not necessarily reflect disease inflammatory pathways (11). Furthermore, abundant evidence suggests that inflammation is part of the host response to cancer (12, 13); thus, the elevations in CRP levels observed in patients with colorectal cancer may be a result rather than a cause of disease.

Because of the public health importance of this issue, we evaluated whether CRP levels predict colorectal cancer

risk among 27 913 participants in the Women's Health Study for whom CRP was measured at baseline; the maximum duration of follow-up was 10.8 years.

METHODS

Study Cohort

Beginning in 1993, 39 876 female U.S. health professionals age 45 years or older who were free of cancer and cardiovascular disease were enrolled into the Women's Health Study, a randomized, double-blind, placebo-controlled, 2 × 2 factorial trial evaluating the balance of benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cancer and cardiovascular disease (14). Upon study enrollment, all participants completed a baseline questionnaire about their medical history and life-

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Context

Some data suggest that low-grade inflammation may play a role in the development of colorectal cancer.

Contribution

In this 10-year prospective study involving 27 913 healthy women age 45 years or older, elevated C-reactive protein (CRP) levels at baseline were not associated with a higher likelihood of colorectal cancer.

Cautions

A single baseline CRP measurement may be an imperfect marker of inflammation. The investigators relied on a woman's report of cancer rather than an ongoing surveillance protocol for colorectal lesions.

Implications

Low-grade inflammation may not be associated with increased colorectal cancer risk.

—The Editors

style characteristics, including potential risk factors for colorectal cancer.

Before randomization, 28 345 women (71% of those randomly assigned) also provided baseline blood specimens, sent via overnight courier, using a kit that contained a gel-filled freezer pack as a coolant. Upon arrival at our laboratory, the samples were subjected to centrifugation; separated into plasma, leukocytes, and erythrocytes; and stored in liquid nitrogen. Baseline characteristics among women who did and did not provide blood specimens were largely similar (mean age, 54.7 years vs. 54.4 years; body mass index ≥ 25 kg/m², 48.4% vs. 51.1%; family history of colorectal cancer, 10.6% vs. 10.5%; current use of postmenopausal hormones, 43.5% vs. 37.5%; ever use of oral contraceptives, 69.6% vs. 69.4%; aspirin use before the trial, 11.7% vs. 10.8%; current use of multivitamin supplements, 29.4% vs. 28.6%; history of benign colon polyps, 2.5% vs. 2.5%; and median alcohol intake, 1.1 g/d vs. 0.9 g/d). The following were the exceptions: Women who provided blood specimens were more physically active (median, 598.6 kcal/wk vs. 526.0 kcal/wk) but were less likely to be current smokers (11.7% vs. 16.8%).

Of the 28 345 samples received, 27 939 usable samples were measured for plasma CRP by a validated high-sensitivity assay (Denka Seiken Co., Tokyo, Japan) in a core laboratory facility for ongoing standardization programs on the CRP measurement (15). The current analysis was restricted to 27 913 women after the additional exclusion of 21 women with prandomization cancer reported after randomization and confirmed by medical record review and 5 women with newly diagnosed nonadenocarcinoma colorectal cancer during follow-up.

Ascertainment of Cases of Colorectal Cancer

Every 6 months during the first year of follow-up and then annually thereafter, participants were sent questionnaires asking about newly diagnosed end points, including colon or rectal cancer. Family members or postal authorities reported deaths of participants. Within the past 2 years, morbidity follow-up is 97%, and mortality follow-up is nearly 100%. For those who reported a diagnosis of colorectal cancer and for those who are deceased, we sought medical records and other relevant information, which were reviewed by an Endpoints Committee consisting of physicians to confirm medical diagnoses. Of the self-reports, medical record review confirmed 96%. The reviewers additionally extracted information on anatomic location and tumor stage at diagnosis (Duke's A, spread to submucosa or muscle only; Duke's B, spread to pericolic or perirectal tissues, but no lymphatic involvement; Duke's C, lymph node involvement or metastasis). The current analysis included only confirmed incident cases of colorectal adenocarcinoma.

Statistical Analysis

We first compared the distribution of baseline risk factors for colorectal cancer by category of plasma CRP level to assess their potential for confounding. Participants were categorized into CRP levels of less than 1, 1 to 3, and greater than 3 mg/L, the cutoff points proposed in clinical guidelines for cardiovascular disease (16) and previously used in this cohort to define cardiovascular disease risk (15). For the analysis of total cancer of the colon and rectum, we also categorized women into quartiles of CRP based on the CRP distribution among never users or among ever users of postmenopausal hormones at baseline (postmenopausal hormone use elevates CRP level [17–19]).

We calculated person-years for each participant from the date of randomization to the date of diagnosis of confirmed cancer, death, or 20 February 2004, whichever occurred first. A Cox proportional hazards regression model, which treats disease outcome as a random variable that would change over time, was used to calculate the hazard ratios and 95% CIs. We first estimated the crude hazard ratios according to category of CRP and then additionally adjusted for age (in years) or age and randomized treatment assignment (aspirin vs. placebo, vitamin E vs. placebo) to control for potential confounding by the effects of these treatments. We further performed a multivariate analysis that additionally adjusted for postmenopausal hormone use (never, past, current); body mass index (<23, ≥ 23 to <25, ≥ 25 to <27, ≥ 27 to <30, ≥ 30 kg/m²); family history of colorectal cancer in first-degree relatives (yes or no); physical activity (total kcal/wk in quartiles); smoking status (never, past, current); aspirin use before the trial (yes or no); alcohol consumption (0, >0 to <15, ≥ 15 g/d); oral contraceptive use (never or ever); menopausal status (premenopausal, postmenopausal, uncertain/unknown); and multivitamin supplement use (never, past,

current) at baseline. We also conducted an analysis that additionally adjusted for history of self-reported colon polyps at baseline (yes or no). Of the 27 913 women in the current analysis, 1817 participants who had missing values for 1 or more covariates were dropped from multivariate analyses. Furthermore, we performed an analysis according to tumor location (proximal colon, distal colon, and rectum) and tumor stage at diagnosis (Duke's A, B, and C). Tests for trend were performed by using the median value for each CRP category as a continuous variable. The assumption of proportional hazards over time was tested by using log likelihood ratio tests to compare models with or without interaction terms between CRP and the logarithm of follow-up time in regression models. There was no indication that the proportionality assumption was violated.

Additional analyses excluded incident cases diagnosed within 1, 2, and 5 years of follow-up, with further adjustment for symptomatic examination (yes or no) and regular screening (yes or no) by colonoscopy or sigmoidoscopy, which were asked on the 12-month follow-up questionnaire to address the potential effect of screening. We conducted analyses stratified by level of other risk factors for colorectal cancer to evaluate whether the association between baseline plasma CRP level and colon cancer risk may exist in subgroups. Tests for interaction between CRP and level of other risk factors in relation to colorectal cancer risk were carried out by using the median value for each CRP category as a continuous variable, an indicator variable for risk factor, and a product term of these 2 variables. The Wald test was used to assess the statistical significance of the interaction term. All *P* values were 2-sided. All analyses were performed by using SAS software, version 8 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The National Institutes of Health, the Doris Duke Foundation, and the Donald W. Reynolds Foundation sponsored the study. The sponsors did not participate in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. The authors had full access to the data files of the study.

RESULTS

Through 20 February 2004, 169 incident cases of invasive colorectal adenocarcinoma were confirmed: 70 cases of proximal colon cancer, 59 cases of distal colon cancer, 36 cases of rectal cancer, 3 cases with overlapping lesions in the colon, and 1 case of colon cancer in which the site was not specified. Median and maximum lengths of follow-up were 10.1 and 10.8 years, respectively. Age at diagnosis of colorectal cancer cases ranged from 47 to 86 years (mean, 65 years). The incidence rate of colorectal cancer among the 27 913 women for the current analysis was 63.1 cases/100 000 person-years, which was similar to the rate in the entire cohort of the Women's Health Study (62.7 cases/

100 000 person-years). Median values of baseline plasma CRP were 2.02 mg/L among all 27 913 women, 1.43 mg/L among the 12 910 women who had never used postmenopausal hormones at baseline, and 2.60 mg/L among the 14 949 women who had ever used postmenopausal hormones at baseline. The median value of baseline plasma CRP was 1.77 mg/L for the 169 colorectal cancer cases diagnosed during follow-up. Baseline CRP levels were higher for the 27 colorectal cancer cases diagnosed within the first 2 years of follow-up (median, 2.63 mg/L). Median values of baseline plasma CRP were 1.17 mg/L among the 81 patients with colorectal cancer who had never used postmenopausal hormones at baseline and 1.39 mg/L among the 11 patients with colorectal cancer who received the diagnosis within the first 2 years of follow-up and had never used postmenopausal hormones at baseline.

Table 1 shows the age-adjusted baseline characteristics of participants according to CRP category. Women who had higher baseline plasma CRP levels were more likely to be older, heavier, postmenopausal, aspirin users before the trial, current users of postmenopausal hormones, current smokers, physically inactive, and ever users of oral contraceptives, but they consumed less alcohol. However, a personal history of colon polyps, a family history of colorectal cancer in first-degree relatives, use of colonoscopy or sigmoidoscopy for screening or for symptoms, and current use of multivitamin supplements did not appear to vary appreciably by CRP category.

Baseline plasma CRP levels were not significantly associated with risk for colorectal cancer in univariate analysis and after adjustment for age and randomized treatment assignment or after additional adjustment for other potential risk factors for colorectal cancer (Table 2). In this population, 6 colorectal cancer cases were identified among 703 women who reported a diagnosis of benign colon polyps at baseline. The hazard ratios did not change after further adjustment for this self-reported history of colon polyps at baseline (Table 2). We also obtained similar hazard ratios after excluding all women who reported colon polyps at baseline; the multivariate hazard ratios were 1.00, 0.82 (95% CI, 0.55 to 1.23), and 0.64 (CI, 0.41 to 1.00) (*P* for trend = 0.06). The associations between baseline plasma CRP levels and colorectal cancer risk were not significantly modified by randomized aspirin treatment during follow-up (*P* for interaction = 0.47). When we analyzed data restricted to women age 55 years or older at baseline (mean, 62 years; 112 cases), the multivariate hazard ratios according to CRP category were 1.00, 0.92 (CI, 0.55 to 1.53), and 0.90 (CI, 0.52 to 1.55), respectively (*P* for trend = 0.74). Among women who were postmenopausal at baseline (128 cases), the multivariate hazard ratios were 1.00, 1.13 (CI, 0.69 to 1.84), and 1.02 (CI, 0.60 to 1.72) (*P* for trend = 0.84).

Baseline plasma CRP levels were also not significantly associated with risk for colorectal cancer in analyses based on the quartile distribution among never users of post-

Table 1. Comparison of Age-Adjusted Baseline Characteristics of 27 913 Women according to Category of Plasma C-Reactive Protein*

Baseline Characteristics	Category of C-Reactive Protein		
	<1 mg/L (n = 8320)	1–3 mg/L (n = 9242)	>3 mg/L (n = 10 351)
Median C-reactive protein level (25th–75th percentiles), mg/L	0.5 (0.3–0.7)	1.8 (1.4–2.3)	5.5 (4.0–8.0)
Mean age, y	51.1	53.3	54.2
Mean body mass index, kg/m ²	23.2	25.6	28.4
Postmenopausal women, %	51.3	55.1	58.3
Aspirin users before trial, %	10.6	12.0	12.2
Current users of postmenopausal hormones, %	31.1	43.4	53.9
Current smokers, %	10.1	11.5	13.1
Median physical activity, kcal/wk	1083.3	1003.1	895.3
Ever users of oral contraceptives, %	67.8	69.6	70.7
Mean alcohol intake, g/d	4.7	4.3	3.5
Women with colon polyps, %	2.2	2.6	2.7
Women with family history of colorectal cancer, %	10.4	10.7	10.9
Women having colonoscopy or sigmoidoscopy during the past year for screening†, %	5.3	5.4	5.9
Women having colonoscopy or sigmoidoscopy during the past year for symptom‡, %	2.3	2.2	2.6
Current users of multivitamins, %	28.7	30.0	29.0

* All factors except age and C-reactive protein are directly standardized.

† From the 12-month questionnaire.

menopausal hormones at baseline (<0.58, 0.58 to 1.43, 1.44 to 3.36, and >3.36 mg/L); the multivariate hazard ratios comparing the 3 higher categories of CRP to the lowest category were 1.41 (CI, 0.85 to 2.34), 0.89 (CI, 0.52 to 1.53), and 0.85 (CI, 0.48 to 1.48), respectively (*P* for trend = 0.13). Moreover, CRP levels were not significantly associated with risk for colorectal cancer in analyses based on the quartile distribution among ever users of postmenopausal hormones at baseline (<1.17, 1.17 to 2.60, 2.61 to 5.16, and >5.16 mg/L); the multivariate hazard ratios comparing the 3 higher categories of CRP to the lowest category were 0.71 (CI, 0.46 to 1.09), 0.83 (CI, 0.53 to 1.29), and 0.61 (CI, 0.36 to 1.02), respectively (*P* for trend = 0.11). We again found no significant association in an analysis that used CRP as a continuous variable after log transformation. For a 2.72-mg/L (equivalent to 1 natural logarithm) increment of CRP, the multivariate hazard ratio was 0.89 (CI, 0.76 to 1.04).

We further conducted an analysis by tumor location and found no significant positive association of baseline plasma CRP with risk for cancer of the proximal colon, distal colon, or rectum (Table 3); in fact, we noted an inverse association with risk for proximal colon cancer in multivariate analysis. We also found no significant associations between CRP level and colorectal cancer risk according to tumor stage at diagnosis (Table 3). Moreover, we observed no significant positive associations between baseline plasma CRP and colon cancer risk among never users of postmenopausal hormones at baseline and other subgroups evaluated (Appendix Table, available at www.annals.org). An inverse association was found among women who had ever used oral contraceptives at baseline.

To address the potential bias that colorectal cancer itself, before it was diagnosed, may have affected plasma CRP levels, we excluded incident cases of colorectal cancer that were diagnosed within 1, 2, and 5 years of follow-up. The remaining

Table 2. Hazard Ratios of Colorectal Cancer by Category of Plasma C-Reactive Protein*

Variable	Category of C-Reactive Protein			P Value for Trend
	<1 mg/L	1–3 mg/L	>3 mg/L	
All cases of colorectal cancer, n	57	56	56	
Crude hazard ratio	1.00	0.89 (0.62–1.29)	0.80 (0.55–1.15)	0.24
Age-adjusted hazard ratio†	1.00	0.77 (0.53–1.11)	0.67 (0.46–0.97)	0.05
Age- and treatment-adjusted hazard ratio‡	1.00	0.77 (0.53–1.11)	0.67 (0.46–0.97)	0.05
Multivariate-adjusted hazard ratio§	1.00	0.79 (0.53–1.17)	0.66 (0.43–1.03)	0.09
Multivariate-adjusted hazard ratio	1.00	0.79 (0.53–1.17)	0.66 (0.43–1.03)	0.09

* Numbers in parentheses are 95% CIs.

† Adjusted for age in years.

‡ Adjusted for age in years and randomized treatment assignment (aspirin vs. placebo; vitamin E vs. placebo).

§ Adjusted for age, randomized treatment assignment, body mass index, family history of colorectal cancer, physical activity, smoking status, aspirin use before the trial, menopausal status, postmenopausal hormone use, oral contraceptive use, alcohol intake, and multivitamin supplement use.

|| Additionally adjusted for self-reported colon polyps.

Table 3. Hazard Ratios of Colorectal Cancer according to Tumor Location and Stage at Diagnosis by Category of Plasma C-Reactive Protein*

Tumor Location and Stage at Diagnosis	Category of C-Reactive Protein			P Value for Trend
	<1 mg/L	1–3 mg/L	>3 mg/L	
Tumor location				
Proximal colon				
Cases, <i>n</i>	23	25	22	
Crude hazard ratio	1.00	0.99 (0.56–1.74)	0.77 (0.43–1.39)	0.34
Age-adjusted hazard ratio†	1.00	0.83 (0.47–1.47)	0.64 (0.35–1.14)	0.13
Age- and treatment-adjusted hazard ratio‡	1.00	0.83 (0.47–1.46)	0.64 (0.35–1.14)	0.13
Multivariate-adjusted hazard ratio§	1.00	0.70 (0.38–1.29)	0.44 (0.22–0.89)	0.03
Distal colon				
Cases, <i>n</i>	18	20	21	
Crude hazard ratio	1.00	1.01 (0.53–1.90)	0.95 (0.50–1.77)	0.82
Age-adjusted hazard ratio†	1.00	0.87 (0.46–1.64)	0.79 (0.42–1.49)	0.49
Age- and treatment-adjusted hazard ratio‡	1.00	0.87 (0.46–1.64)	0.79 (0.42–1.49)	0.50
Multivariate-adjusted hazard ratio§	1.00	1.28 (0.63–2.59)	1.27 (0.59–2.73)	0.68
Rectum				
Cases, <i>n</i>	15	10	11	
Crude hazard ratio	1.00	0.60 (0.27–1.35)	0.59 (0.27–1.29)	0.27
Age-adjusted hazard ratio†	1.00	0.57 (0.25–1.27)	0.55 (0.25–1.20)	0.21
Age- and treatment-adjusted hazard ratio‡	1.00	0.57 (0.25–1.27)	0.55 (0.25–1.21)	0.22
Multivariate-adjusted hazard ratio§	1.00	0.44 (0.18–1.04)	0.44 (0.18–1.08)	0.18
Tumor stage				
Duke's A				
Cases, <i>n</i>	20	13	18	
Crude hazard ratio	1.00	0.59 (0.29–1.18)	0.73 (0.39–1.38)	0.53
Age-adjusted hazard ratio†	1.00	0.50 (0.25–1.01)	0.60 (0.32–1.14)	0.29
Age- and treatment-adjusted hazard ratio‡	1.00	0.50 (0.25–1.01)	0.61 (0.32–1.15)	0.30
Multivariate-adjusted hazard ratio§	1.00	0.58 (0.28–1.23)	0.71 (0.33–1.52)	0.65
Duke's B				
Cases, <i>n</i>	11	15	14	
Crude hazard ratio	1.00	1.24 (0.57–2.69)	1.03 (0.47–2.27)	0.89
Age-adjusted hazard ratio†	1.00	1.08 (0.50–2.36)	0.88 (0.40–1.94)	0.64
Age- and treatment-adjusted hazard ratio‡	1.00	1.08 (0.50–2.36)	0.88 (0.40–1.94)	0.64
Multivariate-adjusted hazard ratio§	1.00	0.87 (0.38–1.99)	0.63 (0.25–1.59)	0.30
Duke's C				
Cases, <i>n</i>	23	28	24	
Crude hazard ratio	1.00	1.10 (0.64–1.91)	0.85 (0.48–1.50)	0.43
Age-adjusted hazard ratio†	1.00	0.94 (0.54–1.64)	0.70 (0.40–1.25)	0.18
Age- and treatment-adjusted hazard ratio‡	1.00	0.94 (0.54–1.64)	0.70 (0.40–1.25)	0.18
Multivariate-adjusted hazard ratio§	1.00	1.01 (0.56–1.84)	0.72 (0.36–1.43)	0.25

* Numbers in parentheses are 95% CIs.

† Adjusted for age in years.

‡ Adjusted for age in years and randomized treatment assignment (aspirin vs. placebo; vitamin E vs. placebo).

§ Adjusted for age, randomized treatment assignment, body mass index, family history of colorectal cancer, physical activity, smoking status, aspirin use before the trial, menopausal status, postmenopausal hormone use, oral contraceptive use, alcohol intake, multivitamin supplement use, and self-reported colon polyps.

numbers of cases were 156, 142, and 84, respectively. The multivariate hazard ratios of colorectal cancer according to CRP category were 1.00 for CRP level less than 1 mg/L, 0.76 (CI, 0.50 to 1.15) for CRP level of 1 to 3 mg/L, and 0.70 (CI, 0.44 to 1.10) for CRP level greater than 3 mg/L (*P* for trend = 0.19) after excluding cases within 1 year of follow-up. The corresponding hazard ratios for the analysis excluding cases within 2 and 5 years of follow-up were 1.00, 0.67 (CI, 0.44 to 1.04), and 0.59 (CI, 0.36 to 0.95) (*P* for trend = 0.06) and 1.00, 0.69 (CI, 0.40 to 1.20), and 0.54 (CI, 0.29 to 1.00) (*P* for trend = 0.07), respectively.

DISCUSSION

In this large prospective cohort, baseline plasma CRP levels were not significantly associated with increased risk

for developing colorectal cancer. Furthermore, there were no significant positive associations between CRP levels and colorectal cancer risk in analyses done according to tumor location and stage at diagnosis, according to alternative cutoff points for CRP, or in any of the other subgroups evaluated. Because relatively few events occurred, the 95% CIs (the range within which the true magnitude of effect lies with 95% confidence) were moderately wide. Since the upper bounds of the 95% CIs for most hazard ratios were slightly above the null value (1.00), we cannot rule out the possibility of a small positive association.

Findings suggesting possible inverse relationships between CRP levels and colorectal cancer risk in some subgroups are intriguing. Such findings for which we have no easy explanations merit further investigations. Inflammation

tion is closely related to the immune responses (20). Increased CRP levels may reflect both inflammatory status and an attempt by the host to suppress tumor formation or growth. This is supported by observations that the pro-inflammatory cytokine tumor necrosis factor antagonists used to treat rheumatoid arthritis and Crohn disease are related to increased risk for lymphoma (21).

The prospective cohort study design and high follow-up rates in this study minimize the possibility that our null findings result from methodologic biases. Because medical record review confirmed incident colorectal cancer cases, it is also unlikely that our findings are due to misclassification of outcome measurement. Our results are also unlikely to be explained by the cutoff points chosen because we consistently found no associations by using the cutoff points for CRP proposed in clinical guidelines for cardiovascular disease (16), by using the quartile distribution based on CRP values among either never users or ever users of postmenopausal hormones at baseline, or by using CRP as a continuous variable after log transformation.

Acute-phase proteins such as CRP are components of the innate immune responses that increase after infections, trauma, burns, tissue infarction, inflammatory processes, and tumors (12). Preoperative CRP levels in patients with late-stage colorectal tumors were considerably higher than those in patients with early-stage malignant conditions in most studies (6–10) except one (22). Moreover, elevated levels of CRP or interleukin-6, a positive regulatory cytokine for CRP (12, 23), in patients with colorectal cancer were associated with tumor stage and recurrence and reduced survival (10, 24–32). In addition, interleukin-6 levels in colorectal tumor tissue were substantially higher than those in normal tissue (25, 33). Finally, 3 small case-control studies reported higher CRP or interleukin-6 levels in patients with colorectal cancer than in controls (22, 25, 31). All of these data are consistent with the hypothesis that CRP levels increase *after* onset of colorectal cancer. Apparently higher baseline plasma CRP values among colorectal cancer cases diagnosed within the first 2 years of follow-up in the present study are also consistent with this hypothesis.

By contrast, it is largely unknown whether CRP levels are elevated before biological onset of cancer or whether CRP is also a risk factor for the *de novo* development of colorectal cancer. Recently, a nested case-control analysis within the CLUE II cohort, a prospective study of 22 887 residents of Washington County, Maryland (named for its campaign slogan, “Give Us A Clue to Cancer and Heart Disease”), with 172 colorectal cancer cases and maximum of 11 years of follow-up, found that prediagnostic plasma CRP levels were significantly associated with increased risk for colon cancer but not rectal cancer (2). The positive association existed among subgroups defined by smoking status, body mass index, and use of aspirin and NSAIDs (2). These data in the CLUE II cohort thus conflict with those in the current analysis.

Similarities as well as differences in these 2 prospective studies merit consideration. Although the number of rectal cancer cases was small in both studies, neither found a positive association. The disagreement in the association between baseline plasma CRP and colon cancer risk between the 2 studies is probably not due to the number of colorectal cancer cases, CRP levels, or length of follow-up, since these were similar. Disparity in findings between the 2 studies is also unlikely to be the result of different age distribution because we observed no positive association in the analysis limited to women age 55 years or older; the average age in women 55 years of age or older, 62 years, was similar to the mean age of 63 years in the study within the CLUE II cohort (2). A potential limitation of the study in the CLUE II cohort is its lack of adjustment for physical activity, alcohol intake, and colorectal cancer screening. Inadequate control for use of aspirin and postmenopausal hormones is also possible in the CLUE II cohort because these variables were assessed only within the last 48 hours before blood collection (34). A further potential difference is that the Women’s Health Study did not include patients with inflammatory bowel disease because the elevated CRP levels (35) and increased risk for colorectal cancer (3) in these patients is well documented. Some of the observed risk in the CLUE II cohort may result from inclusion of such patients; however, the results were unchanged when persons with a baseline history of inflammatory bowel diseases were excluded (2). Although the incidence rate of colorectal cancer in the Women’s Health Study was lower than that in the CLUE II cohort (2), this difference is probably explained by the fact that the CLUE II cohort participants were on average 10 years older and that approximately 40% of them were male. The incidence rate of colorectal cancer increases with age and is approximately 30% lower in women than in men (36).

Given that participants in the Women’s Health Study are health professionals who were enrolled into a trial of low-dose aspirin and vitamin E, with 71% providing blood specimens at baseline, the generalizability of the present findings merits discussion. Several observations suggest that our choice of participants is unlikely to pose a major problem to the interpretation of the findings. First, randomized low-dose aspirin treatment did not significantly modify the association between baseline plasma CRP levels and colorectal cancer risk in the present study. Second, the incidence rate of colorectal cancer among participants in the present study was similar to that in the entire cohort. Third, the baseline characteristics of participants in the Women’s Health Study who did and did not provide blood specimens were generally similar. Fourth, the rate of colorectal cancer screening with colonoscopy or sigmoidoscopy in the present study was similar to that in the general population (37). Fifth, although the incidence rate of colorectal cancer in the present study was lower than that in the general population (36), the stage distribution of tumors was largely similar (38). It seems unlikely that the biolog-

ical relation between CRP level and colorectal cancer risk among women in this cohort will differ significantly from the relation among women in the general population. In previous analyses from the Women's Health Study, we have observed associations for CRP and cardiovascular disease that are generally similar to those in the populations at large (1). Finally, although the proportion of women in the present study who used postmenopausal hormones at baseline was higher than that in the general population (39), we found no positive associations between CRP and colon cancer risk among never users of postmenopausal hormones at baseline, suggesting that our findings are also unlikely to be due to confounding by postmenopausal hormone use.

Potential limitations of our study include the following. First, while we considered several potential risk factors for colorectal cancer in multivariate analyses, we cannot exclude the possibility of residual confounding. Second, there was the possibility that some women might have had cancerous lesions that were not yet detected because women were not enrolled in a protocol with ongoing prospective surveillance for colorectal lesions. This concern was minimized by analyses that excluded cases diagnosed within 1, 2, and 5 years after blood collection. Third, although this study used only a single measurement at baseline, CRP levels are stable over long periods (40), with little or no diurnal variation (41). Furthermore, this single measurement of baseline CRP has strongly predicted the risk for coronary heart disease (15), diabetes mellitus (42), and hypertension (43) in this cohort. Finally, although the baseline characteristics of women who did and did not provide blood specimens were generally similar, women with the CRP measurements were more physically active but less frequently smoked. However, this is unlikely to influence the generalizability of the present findings because the observed associations between CRP and colon cancer risk did not significantly differ according to level of physical activity and smoking status.

In summary, our findings do not appear to support a positive association between prediagnostic plasma CRP and colorectal cancer risk among apparently healthy women. The present data suggest that low-grade inflammation may not play an important role in increasing the risk for colorectal cancer.

From Brigham and Women's Hospital, Harvard Medical School, and Harvard School of Public Health, Boston, Massachusetts.

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Requests for Single Reprints: Shumin M. Zhang, MD, ScD, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, MA 02215; e-mail, shumin.zhang@channing.harvard.edu.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Zhang, Buring, Cook, Lee, and Ridker: Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, MA 02215.

Author Contributions: Conception and design: S.M. Zhang, P.M. Ridker.

Analysis and interpretation of the data: S.M. Zhang, N.R. Cook, P.M. Ridker.

Drafting of the article: S.M. Zhang, P.M. Ridker.

Critical revision of the article for important intellectual content: S.M. Zhang, J.E. Buring, I.-M. Lee, N.R. Cook, P.M. Ridker.

Final approval of the article: S.M. Zhang, J.E. Buring, I.-M. Lee, N.R. Cook, P.M. Ridker.

Statistical expertise: S.M. Zhang, N.R. Cook, P.M. Ridker.

Obtaining of funding: J.E. Buring, P.M. Ridker.

Administrative, technical, or logistic support: S.M. Zhang, I.-M. Lee, P.M. Ridker.

Collection and assembly of data: S.M. Zhang, J.E. Buring, I.-M. Lee, P.M. Ridker.

Appendix Table. Hazard Ratios of Colon Cancer according to Category of Plasma C-Reactive Protein, by Other Baseline Risk Factors for Colorectal Cancer*

Variable	Category of C-Reactive Protein			P Value for Trend	P Value for Interaction†
	<1 mg/L	1–3 mg/L	>3 mg/L		
Postmenopausal hormones					
Never users					
Cases, <i>n</i>	27	23	16		
Age- and treatment-adjusted hazard ratio†	1.00	0.86 (0.49–1.51)	0.65 (0.35–1.22)	0.18	
Multivariate-adjusted hazard ratio‡	1.00	0.80 (0.44–1.46)	0.50 (0.23–1.05)	0.06	
Ever users					
Cases, <i>n</i>	15	23	29		
Age- and treatment-adjusted hazard ratio†	1.00	0.91 (0.48–1.75)	0.88 (0.47–1.64)	0.71	
Multivariate-adjusted hazard ratio‡	1.00	1.07 (0.52–2.19)	0.96 (0.46–1.98)	0.77	0.33
Body mass index					
< 25 kg/m ²					
Cases, <i>n</i>	29	20	15		
Age- and treatment-adjusted hazard ratio†	1.00	0.74 (0.42–1.31)	0.74 (0.39–1.38)	0.40	
Multivariate-adjusted hazard ratio§	1.00	0.88 (0.48–1.59)	1.10 (0.55–2.17)	0.74	
≥ 25 kg/m ²					
Cases, <i>n</i>	11	26	30		
Age- and treatment-adjusted hazard ratio†	1.00	0.95 (0.47–1.92)	0.68 (0.34–1.36)	0.15	
Multivariate-adjusted hazard ratio	1.00	0.95 (0.45–2.01)	0.60 (0.28–1.30)	0.08	0.30
Smoking status					
Never smokers					
Cases, <i>n</i>	21	22	21		
Age- and treatment-adjusted hazard ratio†	1.00	0.85 (0.47–1.54)	0.73 (0.40–1.34)	0.33	
Multivariate-adjusted hazard ratio‡	1.00	0.91 (0.48–1.73)	0.82 (0.40–1.68)	0.58	
Ever smokers					
Cases, <i>n</i>	21	24	24		
Age- and treatment-adjusted hazard ratio†	1.00	0.83 (0.46–1.49)	0.69 (0.38–1.24)	0.23	
Multivariate-adjusted hazard ratio‡	1.00	0.91 (0.47–1.74)	0.67 (0.32–1.37)	0.23	0.99
Alcohol intake					
Nondrinkers					
Cases, <i>n</i>	17	27	24		
Age- and treatment-adjusted hazard ratio†	1.00	1.18 (0.64–2.16)	0.82 (0.44–1.53)	0.31	
Multivariate-adjusted hazard ratio‡	1.00	1.29 (0.67–2.49)	0.92 (0.44–1.93)	0.49	
Drinkers					
Cases, <i>n</i>	25	19	21		
Age- and treatment-adjusted hazard ratio†	1.00	0.59 (0.32–1.07)	0.62 (0.34–1.11)	0.21	
Multivariate-adjusted hazard ratio‡	1.00	0.66 (0.34–1.26)	0.61 (0.30–1.25)	0.28	0.93
Oral contraceptives					
Never users					
Cases, <i>n</i>	16	27	24		
Age- and treatment-adjusted hazard ratio†	1.00	1.25 (0.68–2.33)	1.00 (0.53–1.88)	0.71	
Multivariate-adjusted hazard ratio‡	1.00	1.50 (0.75–2.99)	1.22 (0.58–2.57)	0.99	
Ever users					
Cases, <i>n</i>	26	19	19		
Age- and treatment-adjusted hazard ratio†	1.00	0.58 (0.32–1.05)	0.49 (0.27–0.89)	0.04	
Multivariate-adjusted hazard ratio‡	1.00	0.60 (0.32–1.14)	0.47 (0.23–0.97)	0.07	0.17
Physical activity					
≤ Median value of 599.2 kcal/week					
Cases, <i>n</i>	17	19	20		
Age- and treatment-adjusted hazard ratio†	1.00	0.85 (0.44–1.64)	0.70 (0.37–1.34)	0.29	
Multivariate-adjusted hazard ratio‡	1.00	0.70 (0.35–1.42)	0.50 (0.23–1.08)	0.10	
> Median value of 599.2 kcal/week					
Cases, <i>n</i>	24	27	25		
Age- and treatment-adjusted hazard ratio†	1.00	0.86 (0.49–1.49)	0.77 (0.44–1.35)	0.39	
Multivariate-adjusted hazard ratio‡	1.00	1.09 (0.60–1.99)	0.99 (0.51–1.94)	0.86	0.42

* Because of missing values, the number of cases in some risk factors is less than the total number of colon cancer cases. Numbers in parentheses are 95% CIs.

† Adjusted for age in years and randomized treatment assignment (aspirin vs. placebo; vitamin E vs. placebo).

‡ Adjusted for age, randomized treatment assignment, body mass index, family history of colorectal cancer, physical activity, smoking status, aspirin use before the trial, menopausal status, postmenopausal hormone use, oral contraceptive use, alcohol intake, multivitamin supplement use, and self-reported colon polyps. Stratified variable was excluded from each multivariate model.

§ Additionally adjusted for body mass index of <23 or 23–24.9 kg/m².

|| Additionally adjusted for body mass index of 25–26.9, 27–29.9, or ≥30 kg/m².