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Research Article

Cancer Prevention Research

C-reactive Protein and Risk of Colorectal Adenomas or Serrated Polyps: A Prospective Study

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Abstract

Serum C-reactive protein (CRP) is a sensitive marker of systemic inflammation. Because there is a well-recognized relationship between local inflammation and colorectal cancer, we aimed to evaluate whether serum CRP levels were associated with the occurrence of colorectal adenomas and serrated polyps using data from a large adenoma prevention trial. A total of 930 participants with a history of colorectal adenomas were enrolled in a randomized trial of calcium supplementation (1,200 mg/day) for the prevention of colorectal adenomas. Outcomes in this analysis are metachronous adenomas (and advanced neoplasms specifically), and serrated polyps at follow-up colonoscopy. High-sensitivity CRP levels were measured 1 year following baseline colonoscopy. Multivariate analysis was performed to estimate risk ratios (RR) using Poisson regression, controlling for potential confounders. We measured serum CRP levels in 689 participants (mean CRP, 3.62 ± 5.72 mg/L). There was no difference in CRP levels with respect to calcium versus placebo treatment assignment ($P = 0.99$). After adjustment for potential confounders, we found no association between CRP level and risk of recurrent adenoma or advanced lesion [quartile 4 vs. quartile 1: RR, 95% confidence interval (CI) = 0.99 (0.73–1.34) and 0.92 (0.49–1.75), respectively]. Similarly, no association was seen between CRP levels and risk of serrated polyps or proximal serrated polyps [quartile 4 vs. quartile 1: RR (95% CI) = 1.32 (0.85–2.03) and 1.19 (0.54–2.58), respectively]. In conclusion, this large prospective colorectal adenoma chemoprevention study found no significant relationship between CRP levels and occurrence of adenomas, advanced neoplasms, or serrated polyps. *Cancer Prev Res; 7(11); 1122–7. ©2014 AACR.*

Introduction

Inflammation is associated with colorectal carcinogenesis (1). Serum C-reactive protein (CRP) is a sensitive yet nonspecific marker of systemic inflammation that is elevated in association with chronic inflammatory conditions (2), coronary heart disease (3), obesity (4), and various cancers (5). Several case–control studies have reported elevated circulating CRP concentrations in patients with colorectal cancer compared with healthy controls (6, 7). In addition, a recent systematic review of prospective studies reported an increased risk of colorectal cancer associated with CRP elevation (8).

However, published data are less conclusive about the association between serum CRP and colorectal adenomas. Although some studies have reported that CRP is associated with higher risk of colorectal adenomas (9, 10), others have found null (11–13) or even inverse associations (14). To our knowledge, no study has previously examined the association between inflammatory markers and serrated polyps (SP), yet some of these lesions are now understood to be important colorectal cancer precursors as well.

A correlation of serum CRP levels with colonoscopic findings would suggest an important role of inflammation in the early phases of colorectal carcinogenesis. CRP could be a useful clinical biomarker for risk stratification and/or screening test selection. In this context, we aimed to investigate whether CRP elevation is associated with an increased risk of adenoma or SP occurrence using data from a large polyp chemoprevention trial.

Materials and Methods

Study design and participants

The details of the study design have been published elsewhere (15). Briefly, the Calcium Polyp Prevention Study was conducted at six centers across the United States

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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between November 1988 and December 1996. Subjects were recruited for participation if they had an index colonoscopy with at least 1 large-bowel adenoma within 3 months (and no remaining polyps in the large bowel), were >21 to <80 years old, in good health, and without a history of familial polyposis or invasive large-bowel cancer. Baseline data collection included demographics (age, gender, and race), smoking status, and measurement of height and weight. Body mass index (BMI) was calculated as [weight (kg)]/[height (m)]^2, and obesity was defined as a BMI $\geq$30 kg/m^2. A total of 930 subjects underwent randomization to calcium carbonate (3 g daily; 1.2 g elemental calcium) or placebo in blinded fashion. Participants underwent follow-up colonoscopies at approximately 1 and 4 years after the baseline examination to determine occurrence of colorectal polyps (Fig. 1). All participants provided written informed consent, and this study was approved by the Institutional Review Boards at all study sites.

CRP measurement

At enrollment and around the time of each of the two follow-up colonoscopies, we obtained specimens of venous blood. Serum was initially stored at −20°C or below, pending shipment to the central laboratory (Dartmouth) for storage at −70°C until analysis. High-sensitivity CRP measurements were performed on blood samples obtained at the year 1 follow-up visit. At the time of blood collection, participants had been taking the study drug for approximately 9 months. Serum CRP was measured using CRPHS Tina-quant testing kits on a Roche/Hitachi modular P analyzer with a limit of detection: 0.03 mg/L (0.00003 g/L).

Outcome measurement

For this study, only participants who had colonoscopies at year 4 were included, and the risk period was the time between years 1 and 4 following baseline colonoscopy. At each colonoscopy, the endoscopist recorded the size and location of all mucosal lesions. All polyps seen after randomization were removed and examined histologically by the study pathologist. Advanced neoplasms were defined as lesions with >25% villous histology, size $\geq$1 cm, or high-grade dysplasia/cancer. Although current understanding is that SPs can be categorized as hyperplastic polyps (HP), sessile serrated adenomas (SSA), and traditional serrated adenomas (TSA; ref. 16), at the time this study was done, essentially all serrated lesions were interpreted as HPs. Proximal (or right-sided) SPs were defined as polyps occurring in the cecum, ascending and transverse colon. We also performed a secondary cross-sectional analysis of year 1 colonoscopy results.

Statistical analysis

CRP was analyzed as a categorical variable (dichotomous, split at the median, and into quartiles). Bivariate comparisons were performed using the Student *t* tests or χ^2 tests. Generalized linear models (GLM) were performed using a Poisson distribution to estimate risk ratios (RR) and 95% confidence intervals (CI) adjusted for age, sex, center, baseline adenoma history, treatment arm, and surveillance colonoscopy interval. Quartile 1 (Q1) and median or below CRP levels were the referent groups used in modeling. Statistical analyses were performed using STATA and SAS.

Results

Participant characteristics

Baseline characteristics of participants are presented in Table 1. A total of 832 participants underwent a year 4 follow-up colonoscopy; 689 (83%) of these had CRP data and could be included in this analysis. There was no difference between the study treatment groups and those

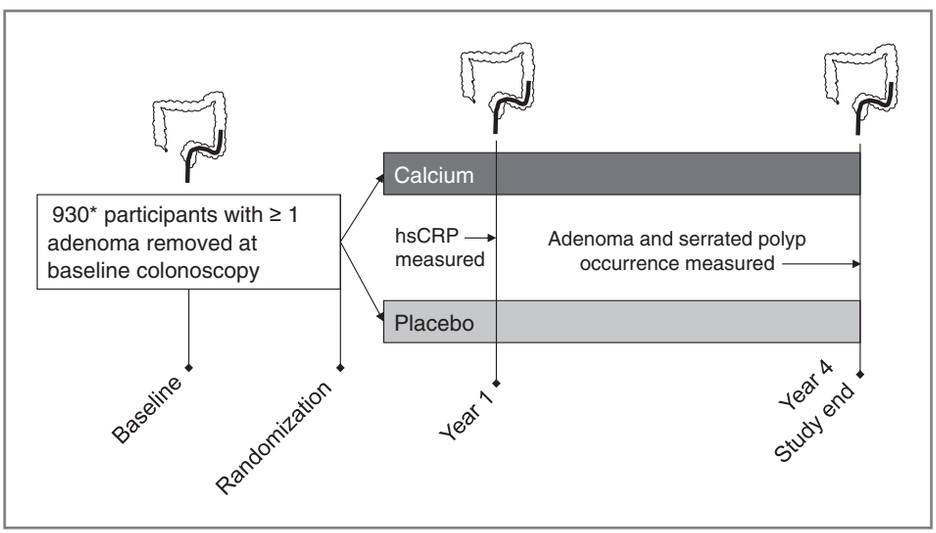

Figure 1. Study schematic showing timing of CRP measurement and study colonoscopies. *689 of 930 subjects had both a year 4 colonoscopy and a CRP measurement and were included in the study. Reasons for missing CRP data included refusal of blood draw or blood sample not obtained ($n = 17$), unevaluable specimen or lab error ($n = 11$), and unavailable or missing samples ($n = 115$). hsCRP, high-sensitivity CRP.

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Table 1. Circulating serum high-sensitivity CRP level by baseline subject characteristics

Baseline characteristic	*n*	Serum CRP mean (SD)	*P* value
Age, years			0.01
<50	96	1.20 (2.96)	
50–59	176	1.57 (3.32)	
60–69	316	1.85 (3.80)	
≥70	101	2.10 (3.37)	
Gender			0.01
Male	496	1.58 (3.52)	
Female	193	2.07 (3.46)	
Race/ethnicity			<0.0001
White	588	1.69 (3.40)	
Black	48	3.14 (3.63)	
Hispanic	23	1.80 (2.78)	
Other	30	0.66 (4.54)	
BMI			<0.0001
<25	212	1.21 (3.57)	
25–29	309	1.62 (3.31)	
30+	166	2.86 (3.33)	
Smoking status			0.03
Never	230	1.48 (3.47)	
Former	337	1.72 (3.56)	
Current	122	2.15 (3.43)	
Study treatment			0.99
Placebo	349	1.70 (3.62)	
Calcium	340	1.70 (3.43)	
Number of baseline adenomas			0.30
1	380	1.77 (3.54)	
2	155	1.48 (3.56)	
3 or more	154	1.77 (3.45)	
Advanced adenoma at baseline			0.95
No	442	1.70 (3.46)	
Yes	247	1.71 (3.64)	
Hyperplastic polyp at baseline			0.20
No	510	1.64 (3.48)	
Yes	179	1.89 (3.63)	

NOTE: *P* values reflect differences in log-transformed CRP between categories, and were obtained using the Student *t* tests. Two subjects had unknown BMI.

excluded for lack of CRP data with respect to age, gender, BMI, or smoking status (data not shown).

Serum CRP levels

The mean and median CRP serum levels among all participants were 3.62 and 1.79 mg/L, respectively (SD, 5.72; interquartile range, 0.75–3.94). For reference, CRP levels >10 mg/L suggest active infection or inflammation, so most participants in this study had low levels. Age, female sex, African American race, obesity, and smoking were associated with higher mean CRP levels (Table 1). CRP levels did not differ significantly based on baseline adenoma or SP status. There was no difference in CRP level (log-transformed) with respect to randomization to calcium versus placebo treatment ($P = 0.99$).

Serum CRP and adenoma recurrence

The RR for adenomas and advanced neoplasms did not vary with CRP levels in crude analyses. After adjustment for age, sex, treatment group, study center, colonoscopy interval, and adenoma history, there was also no statistically significant association between CRP level and risk of metachronous adenomas (Q4 vs. Q1: RR, 0.99; 95% CI, 0.73–1.34), or advanced neoplasms (Q4 vs. Q1: RR, 0.92; 95% CI, 0.49–1.75; Table 2). Analysis of dichotomized CRP levels revealed similar results. There was also no association between CRP levels and adenomas found on the year 1 colonoscopy (Supplementary Table S1). Risk for advanced neoplasms at the year 1 exam did appear to be increased among subjects whose CRP was in the highest quartile, though this estimate was imprecise with wide CIs. In all

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Table 2. Risk of conventional adenomas and SPs during follow-up (years 2–4) associated with categories of circulating serum high-sensitivity CRP levels

CRP levels	Events/*N* (%)	Crude RR (95% CI)	Adjusted[a] RR (95% CI)
All adenomas			
Dichotomous			
≤Median	121/337 (35.9%)	1.00 (REF.)	1.00 (REF.)
>Median	126/335 (37.6%)	1.05 (0.86–1.28)	0.99 (0.80–1.21)
Quartiles			
Q1: ≤0.74 mg/L	55/164 (33.5%)	1.00 (REF.)	1.00 (REF.)
Q2: 0.74–1.785 mg/L	66/173 (38.2%)	1.14 (0.86–1.51)	1.11 (0.83–1.49)
Q3: 1.785–3.90 mg/L	66/169 (39.1%)	1.16 (0.88–1.55)	1.09 (0.82–1.46)
Q4: >3.90 mg/L	60/166 (36.1%)	1.08 (0.80–1.44)	0.99 (0.73–1.34)
Advanced neoplasms[b]			
Dichotomous			
≤Median	30/330 (9.1%)	1.00 (REF.)	1.00 (REF.)
>Median	36/325 (11.1%)	1.22 (0.77–1.93)	0.98 (0.62–1.55)
Quartiles			
Q1: ≤0.74 mg/L	16/162 (9.9%)	1.00 (REF.)	1.00 (REF.)
Q2: 0.74–1.785 mg/L	14/168 (8.3%)	0.84 (0.43–1.67)	0.85 (0.43–1.67)
Q3: 1.785–3.90 mg/L	17/164 (10.4%)	1.05 (0.55–2.01)	0.89 (0.47–1.70)
Q4: >3.90 mg/L	19/161 (11.8%)	1.19 (0.63–2.25)	0.92 (0.49–1.75)
SPs			
Dichotomous			
≤Median	69/343 (20.1%)	1.00 (REF.)	1.00 (REF.)
>Median	75/346 (21.7%)	1.08 (0.81–1.44)	1.10 (0.81–1.48)
Quartiles			
Q1: ≤0.74 mg/L	32/167 (19.2%)	1.00 (REF.)	1.00 (REF.)
Q2: 0.74–1.785 mg/L	37/176 (21.0%)	1.10 (0.72–1.67)	1.19 (0.77–1.84)
Q3: 1.785–3.90 mg/L	35/173 (20.2%)	1.06 (0.69–1.62)	1.10 (0.71–1.71)
Q4: >3.90 mg/L	40/173 (23.1%)	1.21 (0.80–1.83)	1.32 (0.85–2.03)
Proximal SPs			
Dichotomous			
≤Median	24/343 (7.0%)	1.00 (REF.)	1.00 (REF.)
>Median	23/346 (6.7%)	0.95 (0.55–1.65)	1.00 (0.59–1.71)
Quartiles			
Q1: ≤0.74 mg/L	11/167 (6.6%)	1.00 (REF.)	1.00 (REF.)
Q2: 0.74–1.785 mg/L	13/176 (7.4%)	1.12 (0.52–2.44)	1.17 (0.55–2.48)
Q3: 1.785–3.90 mg/L	11/173 (6.4%)	0.97 (0.43–2.17)	1.01 (0.46–2.22)
Q4: >3.90 mg/L	12/173 (6.9%)	1.05 (0.48–2.33)	1.19 (0.54–2.58)

Abbreviation: Q, quartile.

[a]Adjusted for treatment arm, age, sex, center, baseline adenoma history, and surveillance colonoscopy interval; RRs obtained by GLM with Poisson distribution.

[b]Advanced neoplasm defined as an adenoma ≥10 mm, and/or with villous histology, or high-grade dysplasia/cancer.

analyses, additional adjustment for BMI did not materially affect RRs found (data not shown).

Serum CRP and occurrence of SPs

Higher CRP levels were also not associated with increased risk of SPs in crude analyses. Multivariable analysis also did not demonstrate an association between CRP level and risk of any SP (Q4 vs. Q1: RR, 1.32; 95% CI, 0.85–2.03) or right-sided SP (Q4 vs. Q1: RR, 1.19; 95% CI, 0.54–2.58) occurrence during follow-up (Table 2). CRP levels greater than the median were also not associated with occurrence of any SP or proximal SPs specifically. There was also no association between CRP levels and SPs found on the year 1 colonoscopy (Supplementary Table S1).

Discussion

In this large multicenter prospective study, we found that CRP levels were not associated with an increased risk of

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recurrence of conventional adenomas. We also did not find any association between CRP levels and occurrence of SPs during follow-up. In addition, we found no effect of calcium supplementation on CRP levels, similar to other studies (17, 18).

CRP is an acute-phase protein that is synthesized in the liver in response to proinflammatory cytokine signaling, primarily via IL6 and TNFα (19). An important role of CRP is to bind phosphocholine on pathogens as well as apoptotic or necrotic host cells, which in turn activates the complement system and recruits phagocytes (19). Serum CRP rises rapidly in response to tissue injury or infection, but CRP elevation (generally at low levels) is also seen in chronic inflammatory or neoplastic states, a process that is likely mediated by different signaling mechanisms (20).

Whether CRP levels are associated with the development of adenomas and SPs is an important question, because these are the chief known precursor lesions of sporadic colorectal cancer. If elevated serum CRP levels predict polyp risk, this could have important implications for colorectal cancer screening and prevention. However, the existing literature on this topic is inconsistent. A recent Japanese study reported that CRP levels >90th percentile were associated with a >2-fold increase in the odds of large colorectal adenomas (9). A cross-sectional Chinese study also reported that elevated CRP levels were associated with increased risk of advanced adenomas and multiple adenomas (10). However, several studies have reported no significant association between CRP and adenomas (11–13). Interestingly, one study suggested that CRP levels may be inversely associated with risk of colorectal neoplasia; using data from the Prostate, Lung, Colorectal, and Ovarian Cancer screening trial, Gunter and colleagues (14) reported that participants with the highest CRP levels had the lowest risk of incident colorectal adenoma (Q4 vs. Q1: OR, 0.65; 95% CI, 0.41–1.03; P for trend = 0.03).

A possible explanation for discordant risk of colorectal adenomas seen in different studies may be related to differences in CRP metabolism among different subjects. A number of studies have demonstrated that CRP levels vary based on genetic variations in the CRP gene (21, 22). A few studies have investigated CRP gene polymorphisms and risk of colorectal neoplasia. Ognjanovic and colleagues (13) reported that certain SNPs in the CRP gene (rs1205C and rs1130864A) were associated with both higher CRP levels and a decreased adenoma risk. In contrast, Poole and colleagues (23) also reported different CRP polymorphisms that were associated with increased risk of both adenomas and hyperplastic polyps. CRP gene polymorphisms have also been associated with the risk of colorectal cancer, and specifically CPG-island methylator phenotype cancers (24). Given these findings, it is possible that heterogeneity of CRP alleles within the study population and the associated differences in CRP elevations and corresponding risk of polyps could explain our and other reported null associations between CRP levels and colorectal cancer precursors.

We are not aware of any other studies that have examined the relationship between CRP serum levels and SPs. Because a key mechanism of SP development is thought to be inhibition of apoptosis (25) and CRP plays a role in apoptosis, this relationship could shed light on the molecular pathology of the serrated pathway. In this study, we found no substantial relationship between CRP levels and occurrence of SPs or right-sided SPs in particular. Nevertheless, it is possible that CRP might be associated with more advanced SPs, such as SSAs or TSAs. In addition, relatively small numbers of SPs limited our ability to detect a statistically significant association.

This was a large, prospective study of participants with a history of colorectal adenomas. CRP measurements were obtained in standardized fashion from serum collected at 1 year after their baseline colonoscopy, which we believed to be an optimal time to measure a potential biomarker of colonic neoplasia. All pathology from follow-up colonoscopies was centrally reviewed, to optimize the fidelity of outcome measurements (i.e., adenoma and SP occurrence). Furthermore, we used a high-sensitivity CRP assay because it measures very low levels of CRP, an important consideration in our cohort of relatively healthy colonoscopy screenees. However, CRP may only be associated with risk of adenoma recurrence at very high levels, and thus the distribution of our data (most subjects had very low CRP measurements) could obscure this relationship. We considered the possibility that obesity confounded the association between CRP and polyp occurrence. However, when we adjusted for BMI, our estimates did not change substantially. It is possible that change or rise in CRP levels may correlate with polyp occurrence, but we were unable to determine this based on our data. Finally, not all participants in the parent trial provided CRP samples, which could introduce selection bias, though the nonparticipation rate was relatively small, and those with missing CRP data were similar with respect to age, gender, race, BMI, and smoking status compared with those included in this analysis.

In summary, in this large prospective study, we found no significant relationship between CRP levels and occurrence of adenomas or SPs. It is possible, however, that CRP is a more useful marker of colorectal neoplasia during later stages of carcinogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.D. Crockett, R.S. Sandler, J.A. Baron

Development of methodology: J.A. Baron

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.A. Burke, G.J. Baxter, R.S. Sandler, J.A. Baron

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.D. Crockett, L.A. Mott, J.C. Figueiredo, R.S. Sandler, J.A. Baron

Writing, review, and/or revision of the manuscript: S.D. Crockett, E.L. Barry, J.C. Figueiredo, C.A. Burke, R.S. Sandler, J.A. Baron

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