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Biomarkers of inflammation are associated with colorectal cancer risk in women but are not suitable as early detection markers

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Initial studies have investigated the association between inflammation and colorectal cancer (CRC) using C-reactive protein (CRP) as a proinflammatory biomarker and have noted inconsistent results among women. We here report the findings from a large prospective study with repeat measurements of CRP, as well as serum amyloid A (SAA), an additional biomarker of inflammation, and risk of CRC. In the Women's Health Initiative Observational Study, we examined associations of CRP and SAA with CRC using repeat assessments (baseline and 3-year follow-up) among 953 matched case–control pairs for CRP and 966 pairs for SAA. Multivariate-adjusted conditional-logistic regression models were used with two-sided tests of significance. Receiver operating characteristic (ROC) curve analysis assessed their utility as early detection markers. Colon cancer risk (odds ratio [OR] and 95% confidence intervals) among women in the highest quintiles of CRP or SAA compared to those in the lowest quintiles was $OR_{colon/CRP}$ = 1.37 (0.95–1.97, *p*-trend = 0.04) and $OR_{colon/SAA}$ = 1.26 (0.88–1.80, *p*-trend = 0.10), respectively. Women with elevated concentrations of both CRP and SAA had an increased risk of OR_{colon} = 1.50 (1.12–2.00, *p*-value = 0.006) compared to those with low concentrations. No positive associations were observed with rectal cancer and weaker associations for CRC overall. Temporal changes in biomarkers more than 3 years did not predict risk. The area under the 6-month ROC curve for CRP+SAA was 0.62 (95% confidence interval = 0.55–0.68). Elevated inflammatory biomarkers are associated with an increased risk of CRC, mainly colon cancer. Nevertheless, changes in the biomarkers over time do not suggest that they merit consideration as early detection markers for CRC.

Key words: C-reactive protein (CRP), serum amyloid A (SAA), colorectal cancer, women, early detection
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What's new?

The pro-inflammatory markers C-reactive protein (CRP) and serum amyloid A (SAA) are of special interest in colorectal carcinogenesis but their associations with colorectal cancer (CRC) risk, especially among women, are uncertain. In this report where CRP and SAA were measured at baseline and year-3 follow-up, there was a positive association between the markers and CRC when the markers were combined, but changes in marker concentrations over a three-year period were not associated with CRC. This study supports a role for inflammation in CRC, but also demonstrates that these markers are not useful for early detection of CRC.

Inflammation plays a role in colorectal carcinogenesis based on experimental, clinical and epidemiological data.[1–4] Nonsteroidal anti-inflammatory drug (NSAID) use is associated with reduced risk of colorectal adenomas and cancer in both observational and randomized controlled studies.[1,5–8]

C-reactive protein (CRP) and serum amyloid A (SAA) are nonspecific hepatic inflammatory markers produced in response to infection, trauma and other inflammatory states.[9,10] Acutely, their serum concentrations increase and slowly return to normal over some days. However, a persistent elevation occurs with chronic inflammation.[9,10]

Although there is a positive correlation ($r = 0.52$) between CRP and SAA concentrations,[11,12] studies have shown that SAA may be a more sensitive marker of inflammation in certain disease states.[12] Also, SAA has been more strongly associated with breast cancer survival than CRP.[13] Prospective epidemiological studies that have investigated the association of serum CRP with colorectal cancer (CRC) risk have reported disparate results, particularly among women.[14–27] There have been no prospective studies on the association between SAA and CRC risk.

Apart from the limited sample size of some previous studies, CRP measurements were performed only once. Thus, these studies could not ascertain how long-term CRP, and changes in CRP, concentrations before cancer diagnosis may be related to CRC risk. Furthermore, no previous studies have investigated the clinical utility of CRP and SAA as early detection markers for CRC. Current screening modalities such as fecal occult blood testing (FOBT) have limited sensitivity and specificity,[28] whereas others (colonoscopy and sigmoidoscopy) are costly, associated with not insignificant complications and are underused.[28,29] Hence, there is a need for blood-based biomarkers of early detection for use in conjunction with other screening modalities.

To extend knowledge on the role of inflammation in CRC development, and to assess the utility of CRP and SAA as putative biomarkers of early detection, we investigated the associations of CRP and SAA with CRC risk using serum samples collected at baseline and year-3 follow-up in a large case–control study nested within the Women's Health Initiative Observational Study (WHI-OS).

Methods

Study population

The WHI-OS is a prospective cohort study that enrolled 93,676 women between 1993 and 1998 at 40 U.S. institutions, with detailed protocols and extensive quality control mechanisms.[30,31] Women were eligible for the WHI-OS if they were postmenopausal, 50–79 years old and unlikely to relocate or die within 3 years. Details on characteristics of the WHI-OS cohort and study design are described elsewhere.[30,31] CRC cases were annually identified and adjudicated through reviews of the medical records and pathology reports as of April 24, 2008.[32] Cancer cases were centrally reviewed, identified and classified using SEER program guidelines.[32] Clinical outcomes were reported annually by self-administered medical history update questionnaires and in a clinic follow-up visit at year-3. Here, we further excluded women with history of CRC ($n = 959$), CRC *in situ* ($n = 46$), CRC from death report only ($n = 52$) and body mass index (BMI) $\leq$15 or $\geq$50 kg/m^2 ($n = 502$). Controls, who were randomly selected using risk-set sampling, were women in the WHI-OS who were alive and cancer-free at the time of case diagnosis. Controls were matched based on age ($\pm$3 years), race/ethnicity, clinical center, date of blood-draw ($\pm$6 months for baseline and year-3 blood draws) and baseline hysterectomy status. Our study included 988 incident cases of CRC and 988 matched controls. Matched pairs for women where the CRP ($n = 35$) or SAA ($n = 22$) values were individually missing were excluded from the analysis. Thus, 953 matched pairs were available for the CRP analysis and 966 matched pairs for the SAA analysis.

Written informed consent was obtained and the study was IRB approved at the WHI Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center as well as at 40 clinical centers and the German Cancer Research Center.

Data collection

Self-reported data on demographic and health-related characteristics were collected at baseline.[30] Baseline height and weight were measured and BMI was computed (weight [kg]/height [m^2]). Blood was drawn at baseline and year-3 follow-up using standardized protocols.

Assays

CRP and SAA were quantified at baseline and year-3 follow-up at the Clinical Immunology Laboratory (University of Washington) by latex-enhanced nephelometry, (BNII, Siemens) including both internal laboratory controls and blinded WHI duplicates. Coefficients of variation for WHI blind duplicate samples were 4.9% for SAA and 4.1% for CRP.

Table 1. Baseline characteristics of CRC cases and controls in the WHI-OS

	Cases		Controls		
Characteristics	***n***	**Mean (SD) or %**	***n***	**Mean (SD) or %**	***p*-Value**
Age (years)	988	67 (7)	988	67 (7)	0.50
50–54	58	5.9	55	5.6	0.96
55–59	105	10.6	104	10.5	
60–64	190	19.2	192	19.4	
65–69	260	26.3	245	24.8	
70–74	230	23.3	246	24.9	
75–79	145	14.7	146	14.8	
BMI (kg/m^2)[1]	976	28.1 (6.0)	978	27.1 (5.9)	0.0001
<25.0	342	35.1	394	40.3	0.002
25.0–29.9	331	33.9	355	36.3	
30–34.9	187	19.2	143	14.6	
≥35.0	116	11.8	86	8.8	
Ethnicity (several categories)	988	100	988	100	1.0
White	842	85.2	842	85.2	
Black or African-American	88	8.9	88	8.9	
Others[2]	58	5.9	58	5.9	
Family Income ($)	950	100	940	100	0.08
<34,999	457	48.1	421	44.8	
35,000–74,999	343	36.1	329	35.0	
75,000 or more	125	13.1	162	17.2	
Do not know	25	2.6	28	3.0	
Education (high school or less)	195	19.9	223	22.8	0.12
Residence Location (U.S. region)	988	100	988	100	0.42
Northeast	255	25.8	227	22.3	
South	223	22.6	240	24.3	
Midwest	228	23.1	222	22.5	
West	282	28.5	299	30.3	
Pack-years smoking	951	13.0 (21.7)	951	8.9 (17.0)	<0.0001
NSAID use (ever)	180	18.2	176	17.8	0.81
Minutes of moderate or strenuous activity per week	975	95.9 (135.9)	979	109.1 (143.4)	0.04
Family history of CRC (yes)	192	21	163	18	0.10
History of colonoscopy or sigmoidoscopy (yes)	508	52	589	60	0.0003
History of colon polyp removal (yes)	123	25	105	18	0.008
Tumor location (proximal, distal and rectal)[3]	990	100			
Proximal	577	58.3	–	–	–
Distal	211	21.3	–	–	–
Rectal	184	18.6	–	–	–
Overlapping/unknown	18	1.8	–	–	–
Tumor grade[3]	990	100	–	–	–
Well differentiated	75	7.6	–	–	–
Moderately differentiated	616	62.2	–	–	–
Poorly differentiated	202	20.4	–	–	–
Anaplastic	12	1.2	–	–	–
Unknown/not done	85	8.6	–	–	–

Table 1. Baseline characteristics of CRC cases and controls in the WHI-OS (Continued)

	Cases		Controls		
Characteristics	*n*	Mean (SD) or %	*n*	Mean (SD) or %	*p*-Value
Tumor stage (SEER staging)[3]	989	100	–	–	–
Localized	431	43.6	–	–	–
Regional	409	41.3	–	–	–
Distant	127	12.8	–	–	–
Unknown/not done	22	2.2	–	–	–
CRP, median (IQR)					
Baseline (mg/L)	968	3.0 (4.7)	971	2.5 (4.2)	0.007
Year 3 (mg/L)	782	3.0 (4.8)	885	2.5 (4.2)	0.047
Difference (mg/L)	766	0.1 (2.3)	875	0.0 (2.1)	0.11
SAA, median (IQR)					
Baseline (IQR)	972	5.6 (6.2)	979	5.3 (5.9)	0.08
Year 3 (mg/L)	787	5.6 (6.2)	891	5.6 (6.2)	0.57
Difference (mg/L)	773	0.1 (3.1)	885	0.2 (2.8)	0.50

[1]Measured at baseline. [2]Others—Hispanic, Asian or Pacific Islander, American Indian or Alaskan Native, missing. [3]Two individuals are listed as having both colon cancer and CRC, and hence information on both tumors is reported here.

Statistical analysis

We compared the baseline characteristics of cases and controls using *t*-tests (for continuous variables) and Chi-square tests (for categorical variables). Odds ratios (OR) and 95% confidence intervals (CIs) (OR, 95% CI) were estimated using conditional logistic regression models. Baseline CRP and SAA were used in the primary analyses. All models were adjusted for age (50–54, 55–59, 60–64, 65–69, 70–74 and 75–79 years). Multivariate models included age and a set of baseline variables chosen *a priori* for adjustment of potential confounding, including baseline BMI, race/ethnicity (White, Black other race/ethnicity), past medical history of colonoscopy (yes/no), physical activity (0–3, 3≤11.75, >11.75 MET-hr/week), postmenopausal hormone use (HT) (never, past and current), pack-years of smoking (continuous variable; estimated as the product of the number of smoking years and the number of cigarettes smoked daily until the time of baseline examination) and NSAID use. Only age, BMI, HT use, previous history of colonoscopy and pack-years of smoking were included in the final model because they were the only covariates that affected the ORs by >10%.

Quintile cut-off points for both biomarkers were determined based on the distribution among controls. Tests of linear trend across increasing categories were conducted by modeling the median values of each category as a single continuous variable and assessing significance using Wald test. Furthermore, we investigated the impact of long-term biomarker concentrations on CRC risk by categorizing the study participants into four groups using a median split at baseline and year-3 follow-up as cut-off.

We investigated CRC risk using a combination of the two inflammatory biomarkers by stratifying the women into four groups based on their combined CRP and SAA concentrations. For each biomarker, the women were dichotomized into high and low based on median levels among controls. The four groups were (*i*) women with low CRP/SAA, (*ii*) women with high CRP/low SAA, (*iii*) women with low CRP/high SAA and (*iv*) women with high CRP/SAA.

We explored the impact of changes in biomarker concentrations over the 3-year follow-up period on CRC risk by calculating the percentage changes in each biomarker and relating to risk. Quintile cut-off points were determined based on the percentage changes among controls. To assess the clinical utility of CRP and SAA as early detection markers, we considered the receiver operating characteristic (ROC) curve analysis and used area under the ROC curve (AUC) as a global summary of the discriminatory capacity of the markers. Time-dependent ROC curves evaluated whether the biomarkers can signal CRC cases 6 months or 1 year prior to diagnosis from normal controls. For the ROC curves, we took biomarker measures (baseline or year-3) obtained within 6 months or 1 year of diagnosis from cases, and contrasted them to those from controls. Seventy-eight cases were eligible for the 6-month ROC curve analysis and 161 for the 1-year analysis. The ROC curve was considered first for individual markers. Further, we calculated the ROC curve for CRP and SAA combined with combinatory algorithm determined by adding up scores based on the quintiles of CRP and SAA for each participant. For example, a participant who was in the lowest quintile for both markers would score as $1+1=2$, whereas an individual in the highest quintiles would score as $5+5=10$.

Secondary analyses were carried out according to tumor site, stage and excluding cases with high CRP concentrations of >10 mg/L (n = 119), because such high values may indicate acute infection. We stratified the analyses by postmenopausal

Table 2. ORs and 95% CIs of CRC by quintile of baseline CRP concentrations

	Cases/ controls	Quintiles of baseline CRP (mg/L)[1]					
		1 ≤0.9	2 >0.9–1.9	3 >1.9–3.2	4 >3.2–5.9	5 >5.9	*p*-Trend[2]
All participants		377	357	363	397	445	
Age-adjusted OR (95% CI)	953/953[3]	1.0 (Ref)	0.90 (0.67,1.21)	1.03 (0.76,1.38)	1.15 (0.86,1.53)	1.29 (0.97,1.70)	0.01
Multivariate OR (95% CI)[4]	845/845	1.0 (Ref)	0.89 (0.64,1.23)	1.01 (0.72,1.40)	1.11 (0.80,1.55)	1.30 (0.93,1.82)	0.02
By tumor site							
Colon							
Age-adjusted OR (95% CI)	759/759	1.0 (Ref)	0.94 (0.68,1.30)	1.11 (0.79,1.54)	1.19 (0.86,1.64)	1.34 (0.98,1.82)	0.02
Multivariate OR (95% CI)	679/679	1.0 (Ref)	0.96 (0.67,1.38)	1.11 (0.77,1.61)	1.14 (0.79,1.64)	1.37 (0.95,1.97)	0.04
Proximal							
Age-adjusted OR (95% CI)	554/554	1.0 (Ref)	1.00 (0.68,1.47)	1.17 (0.79,1.73)	1.36 (0.93,1.98)	1.32 (0.92,1.91)	0.07
Multivariate OR (95% CI)	495/495	1.0 (Ref)	0.99 (0.65,1.51)	1.20 (0.78,1.86)	1.33 (0.87,2.04)	1.32 (0.86,2.03)	0.13
Distal							
Age-adjusted OR (95% CI)	205/205	1.0 (Ref)	0.78 (0.41,1.49)	0.90 (0.48,1.70)	0.77 (0.40,1.46)	1.32 (0.73,2.39)	0.15
Multivariate OR (95% CI)	184/184	1.0 (Ref)	1.01 (0.48,2.14)	0.89 (0.44,1.83)	0.66 (0.31,1.41)	1.60 (0.78,3.29)	0.12
Rectal							
Age-adjusted OR (95% CI)	178/178	1.0 (Ref)	0.64 (0.29,1.40)	0.63 (0.30,1.31)	0.97 (0.48,1.93)	0.97 (0.48,1.94)	0.49
Multivariate OR (95% CI)	150/150	1.0 (Ref)	0.56 (0.23,1.39)	0.50 (0.20,1.21)	1.01 (0.43,2.41)	0.88 (0.36,2.15)	0.59
By stage							
Local/regional							
Age-adjusted OR (95% CI)	814/814	1.0 (Ref)	0.79 (0.57,1.10)	0.89 (0.65,1.22)	1.12 (0.82,1.53)	1.19 (0.88,1.61)	0.02
Multivariate OR (95% CI)	717/717	1.0 (Ref)	0.75 (0.52,1.07)	0.86 (0.60,1.24)	1.10 (0.76,1.59)	1.16 (0.81,1.66)	0.05
Metastatic							
Age-adjusted OR (95% CI)	120/120	1.0 (Ref)	1.62 (0.72,3.65)	2.32 (0.91,5.92)	1.30 (0.59,2.86)	2.45 (1.02,5.90)	0.17
Multivariate OR (95% CI)	111/111	1.0 (Ref)	2.14 (0.84,5.50)	3.67 (1.22,11.0)	1.87 (0.73,4.77)	4.24 (1.34,13.4)	0.10

[1]Quintiles based on controls. CRP Q1 median = 0.6 mg/L, Q2 median = 1.4 mg/L, Q3 median = 2.5 mg/L, Q4 median = 4.5 mg/L and Q5 median = 9.1 mg/L. [2]*p*-Value based on quintile median trend test. [3]The numbers do not add up to 988 because there were 35 participants with missing CRP; hence, the women and their matched pairs were dropped from the analyses. [4]Multivariate model adjusted for age (50–54, 55–59, 60–64, 65–69, 70–74 and 75–79 years), BMI at baseline, hormone replacement therapy (HT) use (never, past and current), previous colonoscopy (yes/no) and pack-years of smoking.

HT and BMI. Finally, we conducted the analyses excluding cases diagnosed within 3 years of blood draw and the results were identical (data not shown). Statistical significance was defined as $p < 0.05$. All statistical tests were two-sided. Analyses were conducted using SAS (V9.2, SAS Institute, Cary, NC).

Results

Mean age was 67 ± 7 years for cases and controls (Table 1). Case women had significantly higher BMI, smoked more cigarettes, were less physically active compared to controls. Cases had higher CRP concentrations than controls at baseline (median; 3.0 *vs.* 2.5 mg/L, *p*-value = 0.007) and at year-3 follow-up (median; 3.0 *vs.* 2.5 mg/L, *p*-value = 0.047). For SAA, there were no significant differences in serum concentrations between cases and controls at baseline (median; 5.6 *vs.* 5.3 mg/L, *p*-value = 0.08) and year-3 follow-up (median; 5.6 *vs.* 5.6 mg/L, *p*-value = 0.57). There was a significant increase in mean CRP concentration from baseline to year-3 follow-up among cases (0.58 mg/L, *p*-value = 0.046) but not among controls (Supporting Information Table 1). CRP and SAA were moderately correlated at baseline and year-3 follow-up; $r = 0.53$ and 0.57 (*p*-values < 0.0001), respectively. Similarly, there were strong correlations between baseline and year-3 biomarker concentrations ($r = 0.69$, $p \leq 0.0001$ for CRP and $r = 0.71$, $p \leq 0.0001$ for SAA) (data not shown).

Baseline CRP concentrations were positively associated with CRC risk (Table 2). The ORs of CRC among women in the highest quintiles of CRP compared to those in the lowest quintiles were 1.29 (95% CI, 0.97–1.70; *p*-trend = 0.01) and 1.30 (0.93–1.82, *p*-trend = 0.02) in the age-and multivariate-adjusted analyses, respectively. Multivariate-adjusted ORs comparing highest to lowest quintiles of serum CRP for colon and rectal cancers were 1.37 (0.95–1.97, *p*-trend = 0.04) and 0.88 (0.36–2.15, *p*-trend = 0.59), respectively.

Though the ORs were in the same direction as for CRP, the associations between SAA and CRC risk were weaker

Table 3. ORs and 95% CIs of CRC by quintile of baseline SAA concentrations

	Cases/ controls	Quintiles of baseline SAA (mg/L)[1]					
		1 ≤3.0	2 >3.0–4.3	3 >4.3–6.2	4 >6.2 10.5	5 >10.5	*p*-Trend[2]
All participants		390	353	380	408	420	
Age-adjusted OR (95% CI)	966/966[3]	1.0 (Ref)	1.01 (0.76,1.35)	1.14 (0.85,1.53)	1.24 (0.94,1.65)	1.22 (0.92,1.62)	0.11
Multivariate OR (95% CI)[4]	857/857	1.0 (Ref)	0.98 (0.71,1.35)	1.18 (0.86,1.62)	1.16 (0.84,1.58)	1.19 (0.84,1.58)	0.23
By tumor site							
Colon							
Age-adjusted OR (95% CI)	772/772	1.0 (Ref)	0.92 (0.66,1.26)	1.22 (0.88,1.68)	1.36 (0.99,1.86)	1.30 (0.94,1.78)	0.04
Multivariate OR (95% CI)	691/691	1.0 (Ref)	0.87 (0.61,1.24)	1.30 (0.91,1.86)	1.29 (0.91,1.82)	1.26 (0.88,1.80)	0.10
Proximal							
Age-adjusted OR (95% CI)	565/565	1.0 (Ref)	1.07 (0.74,1.56)	1.24 (0.85,1.80)	1.60 (1.11,2.31)	1.33 (0.91,1.92)	0.09
Multivariate OR (95% CI)	506/506	1.0 (Ref)	1.07 (0.71,1.60)	1.31 (0.87,1.97)	1.56 (1.04,2.33)	1.26 (0.82,1.93)	0.27
Distal							
Age-adjusted OR (95% CI)	207/207	1.0 (Ref)	0.53 (0.27,1.03)	1.14 (0.58,2.21)	0.79 (0.42,1.50)	1.15 (0.61,2.19)	0.22
Multivariate OR (95% CI)	185/185	1.0 (Ref)	0.39 (0.18,0.88)	1.16 (0.55,2.44)	0.66 (0.32,1.37)	1.15 (0.56,2.37)	0.15
Rectal							
Age-adjusted OR (95% CI)	179/179	1.0 (Ref)	1.42 (0.69,2.96)	0.77 (0.36,1.68)	0.78 (0.38,1.60)	0.78 (0.40,1.52)	0.23
Multivariate OR (95% CI)	151/151	1.0 (Ref)	1.45 (0.62,3.43)	0.68 (0.28,1.65)	0.60 (0.25,1.42)	0.72 (0.33,1.57)	0.19
By stage							
Local/regional							
Age-adjusted OR (95% CI)	823/823	1.0 (Ref)	0.86 (0.62,1.17)	1.02 (0.74,1.40)	1.15 (0.85,1.55)	1.08 (0.80,1.47)	0.26
Multivariate OR (95% CI)	725/725	1.0 (Ref)	0.83 (0.58,1.17)	1.04 (0.74,1.47)	1.04 (0.75,1.47)	1.01 (0.71,1.44)	0.59
Metastatic							
Age-adjusted OR (95% CI)	124/124	1.0 (Ref)	2.89 (1.24,6.77)	2.72 (1.13,6.54)	2.24 (0.90,5.58)	2.98 (1.23,7.23)	0.17
Multivariate OR (95% CI)	115/115	1.0 (Ref)	2.89 (1.15,7.22)	2.90 (1.11,7.59)	1.91 (0.71,5.14)	3.49 (1.24,9.84)	0.16

[1]Quintiles based on controls. SAA Q1 median = 2.3 mg/L, Q2 median = 3.7 mg/L, Q3 median = 5.2 mg/L, Q4 median = 7.9 mg/L and Q5 median=15.15 mg/L. [2]*p*-Value based on quintile median trend test. [3]The numbers do not add up to 988 because there were 22 participants with missing SAA; hence, the women and their matched pairs were dropped from the analyses. [4]Multivariate model adjusted for age (50–54, 55–59, 60–64, 65–69, 70–74 and 75–79 years), BMI at baseline, hormone replacement therapy (HT) use (never, past and current), previous colonoscopy (yes/no) and pack-years of smoking.

(Table 3). The age-and multivariate-adjusted ORs were 1.22 (0.92–1.62, *p*-trend = 0.11) and 1.19 (0.84–1.58, *p*-trend = 0.23), respectively. For colon and rectal tumors, the multivariate-adjusted ORs were 1.26 (0.88–1.80, *p*-trend = 0.10) and 0.72 (0.33–1.57, *p*-trend = 0.19), respectively.

In stratified analyses among women with data on both biomarkers (Table 4), women with high CRP/SAA had an OR of 1.38 (1.07–1.79, *p*-value = 0.01) compared to women with low CRP/SAA. As previously observed, the increased risk was apparent for colon cancer (OR = 1.50, 1.11–2.00, *p*-value = 0.006), but not rectal cancer. The association between CRP/SAA and CRC risk was slightly stronger in analyses not including BMI in the multivariate model (Table 5).

We also investigated the impact of long-term high CRP concentrations on CRC risk and observed marginally significant increased risk ($OR_{high/high}$ *vs.* $OR_{low/low}$ for CRC = 1.25, 1.00–1.56, *p*-value = 0.05) in the age-adjusted, but not in the multivariate-adjusted ($OR_{high/high}$ *vs.* $OR_{low/low}$ for CRC = 1.23, 0.95–1.58, *p*-value = 0.11) model. (Supporting Information Table 2). Compared to analyses using baseline CRP concentrations, somewhat stronger and statistically significant associations were observed for proximal colon cancer; $OR_{high/high}$ *versus* $OR_{low/low}$ = 1.43 (1.03–1.97, *p*-value = 0.03). Similar to CRP, long-term high SAA concentrations were associated with significantly increased risk of proximal colon cancer, $OR_{high/high}$ *versus* $OR_{low/low}$ = 1.50 (1.10–2.04, *p*-value = 0.01) (Supporting Information Table 3).

In analyses stratified by BMI categories, there was no indication of an increased risk among women with BMI < 25 kg/m^2 (Supporting Information Table 4). However, among overweight women (BMI, 25–30 kg/m^2), the ORs of colorectal, colon and proximal colon cancers associated with elevated CRP concentrations were 1.46 (0.83–2.56, *p*-trend = 0.04), 1.36 (0.74–2.48, *p*-trend = 0.11) and 1.85 (0.91–3.76, *p*-trend = 0.03), respectively. Similarly elevated risks, although not statistically significant, were observed among

Table 4. ORs and 95% CIs of CRC associated with combined CRP and SAA concentrations

	Cases/ controls	Combined CRP and SAA[1]						
		Low CRP Low SAA	Low CRP High SAA		High CRP Low SAA		High CRP High SAA	
			OR	*p*-Value	OR	*p*-Value	OR	*p*-Value
All participants		701	325		318		586	
Age-adjusted OR (95% CI)	945/945	1.0 (Ref)	1.16 (0.88,1.52)	0.31	1.20 (0.90,1.58)	0.21	1.35 (1.08,1.69)	0.008
Multivariate OR (95% CI)[2]	837/837	1.0 (Ref)	1.17 (0.86,1.58)	0.31	1.19 (0.87,1.62)	0.28	1.38 (1.07,1.79)	0.01
By tumor site								
Colon								
Age-adjusted OR (95% CI)	754/754	1.0 (Ref)	1.29 (0.95,1.76)	0.11	1.08 (0.79,1.47)	0.63	1.48 (1.15,1.90)	0.002
Multivariate OR (95% CI)	674/674	1.0 (Ref)	1.36 (0.97,1.91)	0.07	1.10 (0.78,1.54)	0.60	1.50 (1.12,2.00)	0.006
Proximal								
Age-adjusted OR (95% CI)	550/550	1.0 (Ref)	1.42 (1.00,2.03)	0.053	1.10 (0.76,1.57)	0.62	1.48 (1.11,1.97)	0.008
Multivariate OR (95% CI)	491/491	1.0 (Ref)	1.49 (1.01,2.18)	0.04	1.13 (0.76,1.67)	0.55	1.50 (1.07,2.09)	0.02
Distal								
Age-adjusted OR (95% CI)	204/204	1.0 (Ref)	0.86 (0.46,1.66)	0.66	0.94 (0.50,1.76)	0.84	1.42 (0.85,2.36)	0.18
Multivariate OR (95% CI)	183/183	1.0 (Ref)	0.89 (0.42,1.91)	0.77	0.88 (0.43,1.82)	0.73	1.52 (0.83,2.77)	0.18
Rectal								
Age-adjusted OR (95% CI)	176/176	1.0 (Ref)	0.56 (0.28,1.10)	0.09	1.89 (0.92,3.90)	0.08	0.91 (0.53,1.56)	0.74
Multivariate OR (95% CI)	148/148	1.0 (Ref)	0.39 (0.17,0.92)	0.03	1.73 (0.72,4.14)	0.22	0.90 (0.46,1.78)	0.77
By stage								
Local/regional								
Age-adjusted OR (95% CI)	807/807	1.0 (Ref)	1.12 (0.83,1.52)	0.47	1.24 (0.91,1.68)	0.17	1.34 (1.05,1.70)	0.02
Multivariate OR (95% CI)	710/710	1.0 (Ref)	1.11 (0.79,1.55)	0.55	1.27 (0.90,1.79)	0.17	1.35 (1.02,1.79)	0.03
Metastatic								
Age-adjusted OR (95% CI)	120/120	1.0 (Ref)	1.04 (0.51,2.15)	0.91	0.92 (0.44,1.92)	0.82	1.77 (0.89,3.51)	0.10
Multivariate OR (95% CI)	111/111	1.0 (Ref)	1.11 (0.50,2.49)	0.79	0.98 (0.42,2.26)	0.95	2.35 (1.00,5.54)	0.05

[1]Categories based on CRP and SAA baseline medians among controls. CRP median = 2.5 mg/L; SAA median = 5.3mg/L. [2]Multivariate model adjusted for age (50–54, 55–59, 60–64, 65–69, 70–74 and 75–79 years), BMI at baseline, hormone replacement therapy (HT) use (never, past and current), previous colonoscopy (yes/no) and pack-years of smoking.

obese women (p-interaction =0.59, 0.23 and 0.17 for CRC, colon and proximal colon, respectively). There was no evidence of effect modification by any HT use (p-interaction = 0.75 for CRC). The associations did not differ by type of HT (estrogen alone and estrogen + progesterone combination) (data not shown).

The largest quintile increase in CRP concentration from baseline to year-3 follow-up (>73%) was associated with a nonsignificant increased risk of CRC (OR = 1.34, 0.91–1.95, p-trend = 0.13) (Table 6). No tumor-site-specific differences were observed. For SAA, the associations were weaker and the ORs were closer to unity (Table 7).

We tested the value of CRP as a biomarker for early detection by evaluating the AUC for cancers diagnosed within 6 months of blood-draw. The AUCs for CRP and SAA were 0.62 (95% CI, 0.55–0.68) and 0.60 (0.53–0.67), respectively, indicating that the markers, when used alone, are not adequate early detection markers. We also explored whether combining SAA and CRP will lead to clinically meaningful incremental value compared to using CRP alone. However, SAA did not provide improvement on the ROC curve (AUC = 0.62, 95% CI, 0.56–0.68) (Supporting Information Fig. 1). Identical AUCs were obtained for cancers diagnosed within 1-year of blood-draw (data not shown).

The results were not altered in secondary analyses excluding cases with high CRP values (>10 mg/L) or cases diagnosed within 2 years of enrolment (data not shown).

Discussion

In the largest prospective study to date, among women, we observed a modest positive association between baseline CRP concentrations and CRC risk which was limited to colon cancers; no corresponding significant associations were observed for SAA. Women with high levels of both CRP and SAA combined had an increased risk of CRC, particularly colon cancer, compared to those with low levels of both biomarkers. Women with consistently high levels of either CRP or SAA

Table 5. ORs and 95% CIs of CRC associated with combined CRP and SAA concentrations (excluding BMI in the multivariate adjustment)

	Cases/ controls	Combined CRP and SAA[1]							
		Low CRP Low SAA	Low CRP High SAA		High CRP Low SAA		High CRP High SAA	
			OR	*p*-Value	OR	*p*-Value	OR	*p*-Value
All participants		701	325		318		586	
Multivariate OR (95% CI)[2]	857/857	1.0 (Ref)	1.16 (0.86,1.57)	0.32	1.28 (0.95,1.74)	0.11	1.49 (1.17,1.90)	0.001
By tumor site								
Colon								
Multivariate OR (95% CI)	690/690	1.0 (Ref)	1.38 (0.99,1.93)	0.06	1.17 (0.84,1.64)	0.35	1.64 (1.25,2.16)	0.0004
Proximal								
Multivariate OR (95% CI)	503/503	1.0 (Ref)	1.50 (1.03,2.19)	0.04	1.18 (0.80,1.73)	0.42	1.62 (1.19,2.22)	0.003
Distal								
Multivariate OR (95% CI)	187/187	1.0 (Ref)	0.91 (0.43,1.91)	0.80	1.03 (0.51,2.07)	0.94	1.64 (0.91,2.95)	0.10
Rectal								
Multivariate OR (95% CI)	152/152	1.0 (Ref)	0.37 (0.16,0.85)	0.02	1.77 (0.77,4.08)	0.18	0.86 (0.46,1.62)	0.65
By stage								
Local/regional								
Multivariate OR (95% CI)	729/729	1.0 (Ref)	1.09 (0.78,1.52)	0.61	1.36 (0.97,1.90)	0.07	1.43 (1.10,1.86)	0.008
Metastatic								
Multivariate OR (95% CI)	112/112	1.0 (Ref)	1.18 (0.53,2.63)	0.69	0.98 (0.43,2.25)	0.96	2.75 (1.20,6.27)	0.02

[1]Categories based on CRP and SAA baseline medians among controls. CRP median = 2.5 mg/L; SAA median = 5.3mg/L. [2]Multivariate model adjusted for age (50–54, 55–59, 60–64, 65–69, 70–74 and 75–79 years), hormone replacement therapy (HT) use (never, past and current), previous colonoscopy (yes/no) and pack-years of smoking.

concentrations had a significantly increased risk of proximal colon cancer. No positive associations were observed between the inflammatory factors and rectal cancer. CRP does not, however, appear suitable as an early detection marker for CRC, either used alone or in combination with SAA.

In spite of the compelling data linking chronic inflammation with colorectal carcinogenesis,[2–4,7] epidemiological studies investigating the association of CRP and CRC risk have been equivocal. The three studies conducted among women[19,22,24] have mainly reported inverse associations, contrary to what is expected.[16,18] In the Women's Health Study[19] with 169 CRC cases more than a 10-year period, women with CRP of >3.0 mg/L had a borderline statistically significantly reduced risk of CRC (OR = 0.66, 0.43–1.03) and a 56% significantly reduced risk of colon cancer. Similarly, within the Nurses' Health Study (280 CRC cases),[24] elevated CRP concentrations were associated with a 35% lower risk of CRC.

Our study with 953 cases (for CRP), the largest to date among women, supports the role of inflammation in colorectal carcinogenesis, mainly within the colon. Prior to our study, the EPIC study with 1,096 cases of which 545 were women, reported a significant 74% increased risk of colon cancer among men with high CRP concentrations; however, the excess risk among women was nonsignificant (+6%).[26]

We specifically investigated BMI, as it is closely linked to CRP, as well as other mechanisms related to CRC risk (*e.g.*, insulin levels and sex hormone levels). Although there were somewhat stronger associations between CRP and CRC risk in analyses excluding BMI, and our stratified analyses suggest stronger associations between CRP and CRC risk in heavier women, we observed no significant interactions between BMI and CRC risk.

One reason why the results from our study differ from those of other studies may be because of the sample size. We had almost twice the number of CRC cases as the previous largest study among women, the EPIC study. This large number allowed us to obtain fairly robust risk estimates for the different tumor sites. Thus, the results from our large study offer important new evidence that inflammation, determined by serum CRP and SAA concentrations, is positively associated with CRC risk among women. However, there may also be other possible reasons for divergent results: for example, compared to the EPIC study, our population was more homogenous, all postmenopausal (*vs.* 74% of the women in the EPIC study), more likely to use HT and on the average older (68 *vs.* 59 years).[26] We had a comparable number of rectal cancer cases (184 cases) as in the EPIC study (182 cases) and similar to the results from the EPIC study, we observed no association between elevated CRP concentrations and rectal cancer risk. This lack of association, noted in the previous studies and confirmed in our study most likely reflects the difference in the biology of the colon and rectum.

To the best of our knowledge, no previous study has evaluated the association of SAA with CRC risk. Although CRP and SAA are major acute-phase reactants, they differ in

Table 6. ORs and 95% CIs of CRC associated with percentage changes in CRP concentrations from baseline examination to 3-year follow-up

		Quintiles of percentage change in CRP[1]					
	Cases/ controls	1 ≤−45.3%	2 >−45.3to−15.7%	3 >−15.7–12.1%	4 >12.1–73.4%	5 >73.4%	*p*-Trend[2]
All participants		310	316	326	349	340	
Age-adjusted OR (95% CI)	748/748	1.0 (Ref)	1.05 (0.75,1.47)	1.05 (0.75,1.48)	1.28 (0.92,1.78)	1.19 (0.84,1.69)	0.29
Multivariate OR (95% CI)[3]	662/622	1.0 (Ref)	1.17 (0.81,1.69)	1.06 (0.73,1.54)	1.40 (0.98,2.01)	1.34 (0.91,1.95)	0.13
By tumor site							
Colon							
Age-adjusted OR (95% CI)	610/610	1.0 (Ref)	0.97 (0.67,1.41)	1.07 (0.73,1.57)	1.18 (0.82,1.69)	1.11 (0.75,1.65)	0.47
Multivariate OR (95% CI)	544/544	1.0 (Ref)	1.05 (0.70,1.59)	1.07 (0.71,1.62)	1.23 (0.83,1.82)	1.23 (0.80,1.90)	0.28
Proximal							
Age-adjusted OR (95% CI)	450/450	1.0 (Ref)	1.07 (0.69,1.66)	1.00 (0.65,1.55)	1.17 (0.78,1.77)	1.25 (0.78,1.99)	0.29
Multivariate OR (95% CI)	401/401	1.0 (Ref)	1.12 (0.70,1.81)	1.02 (0.64,1.62)	1.21 (0.78,1.89)	1.33 (0.80,2.21)	0.24
Distal							
Age-adjusted OR (95% CI)	160/160	1.0 (Ref)	0.85 (0.40,1.82)	1.35 (0.61,2.97)	1.36 (0.64,2.91)	0.95 (0.44,2.06)	0.83
Multivariate OR (95% CI)	143/143	1.0 (Ref)	1.11 (0.48,2.58)	1.32 (0.55,3.21)	1.51 (0.65,3.51)	1.24 (0.52,3.00)	0.68
Rectal							
Age-adjusted OR (95% CI)	131/131	1.0 (Ref)	1.23 (0.57,2.65)	0.87 (0.38,2.00)	1.87 (0.81,4.31)	1.46 (0.65,3.27)	0.33
Multivariate OR (95% CI)	111/111	1.0 (Ref)	1.62 (0.63,4.16)	1.01 (0.38,2.67)	2.94 (1.04,8.29)	1.65 (0.68,4.03)	0.33
By stage							
Local/regional							
Age-adjusted OR (95% CI)	660/660	1.0 (Ref)	1.00 (0.70,1.43)	1.06 (0.74,1.52)	1.31 (0.92,1.87)	1.12 (0.76,1.61)	0.50
Multivariate OR (95% CI)	581/581	1.0 (Ref)	1.10 (0.74,1.62)	1.05 (0.71,1.57)	1.41 (0.95,2.01)	1.22 (0.80,1.84)	0.30
Metastatic							
Age-adjusted OR (95% CI)	79/79	1.0 (Ref)	1.34 (0.45,4.04)	0.90 (0.27,3.00)	1.21 (0.45,3.25)	1.89 (0.67,5.39)	0.17
Multivariate OR (95% CI)	73/73	1.0 (Ref)	1.44 (0.41,5.05)	0.99 (0.25,3.87)	1.73 (0.58,5.16)	2.03 (0.63,6.54)	0.20

[1]Quintiles based on controls. CRP Q1 median = −62.5 mg/L, Q2 median = −31.3 mg/L, Q3 median = 0.0 mg/L, Q4 median = 35.5 mg/L and Q5 median = 178.8 mg/L. [2]*p*-Value based on quintile median trend test. [3]Multivariate model adjusted for age (50–54, 55–59, 60–64, 65–69, 70–74 and 75–79 years), BMI at baseline, hormone replacement therapy (HT) use (never, past and current), previous colonoscopy (yes/no), pack-years of smoking.

many respects. The cytokine regulation of SAA production is different from that of CRP and it is suggested that SAA and CRP may respond differently to various stimuli.[33] CRP has many immune-related functions, such as opsonization and activation of the classical complement binding, whereas SAA participates in cholesterol transport, extracellular matrix degradation and recruitment of inflammatory cells.[13,34,35] In our study, the risk estimates of CRC in relation to SAA were in the same direction as those for CRP but of slightly differing magnitudes, suggesting that though these biomarkers may be able to predict CRC, their abilities vary. The reasons why SAA was less predictive of an inflammatory etiology for CRC are not clear as it is a more sensitive inflammatory biomarker in certain conditions.[36] When CRP and SAA were categorized dichotomously, there was significant improvement in the fit of the colon cancer model if both biomarkers were considered in combination *versus* individually. Here, a 1.5-fold increased risk of colon cancer was observed among women with elevated concentrations of both biomarkers. This suggests a somewhat greater robustness for a combination of both biomarkers in relation to colon cancer risk, similar to what was recently observed for lung cancer where the combination of CRP and IL-8 was more robustly related to lung cancer risk than either marker alone.[37]

Our study showed that, although CRP is associated with an increased risk of CRC, it is too nonspecific to be suitable as an early-detection marker. Also, based on the ROC analysis, the incremental value of adding SAA to CRP in predicting CRC or colon cancer risk was not strong. Today's screening modalities for CRC are effective, but costly or invasive (colonoscopy) or have limited sensitivity and specificity (FOBT). Thus, the development of new blood-based markers is a high priority. Elevations in CRP concentrations could potentially aid in risk prediction and targeted screening; however, the rise in CRP levels among cases was too small and inconsistent to be an independent marker for early detection. Nevertheless, we do not want to exclude that CRP may have utility as part of a multivariate panel of blood-based biomarkers or used in conjunction with other screening modalities.

Strengths of our study include its prospective design, large size and the fact that we measured the inflammatory biomarkers at two time points which allowed us to investigate

Table 7. ORs and 95% CIs of CRC associated with percentage changes in SAA concentrations from baseline examination to 3-year follow-up

	Quintiles of percentage change in SAA[1]						
	Cases/ controls	1 ≤ −27.9%	2 >−27.9–−5.56%	3 >−5.56–13.3%	4 >13.3–49.1%	5 >49.1%	*p*-Trend[2]
All participants		326	351	306	337	338	
Age-adjusted OR (95% CI)	765/765	1.0 (Ref)	1.06 (0.76,1.47)	0.80 (0.56,1.13)	1.00 (0.72,1.40)	0.97 (0.69,1.36)	0.82
Multivariate OR (95% CI)[3]	678/678	1.0 (Ref)	1.08 (0.76,1.55)	0.81 (0.55,1.18)	0.96 (0.67,1.38)	1.05 (0.72,1.51)	0.94
By tumor site							
Colon							
Age-adjusted OR (95% CI)	626/626	1.0 (Ref)	1.05 (0.73,1.52)	1.83 (0.56,1.22)	1.05 (0.72,1.53)	0.99 (0.67,1.45)	0.96
Multivariate OR (95% CI)	559/559	1.0 (Ref)	1.07 (0.72,1.59)	0.81 (0.54,1.24)	1.04 (0.69,1.56)	1.04 (0.69,1.56)	0.99
Proximal							
Age-adjusted OR (95% CI)	462/462	1.0 (Ref)	1.03 (0.67,1.57)	0.71 (0.45,1.12)	1.15 (0.75,1.77)	0.95 (0.61,1.49)	0.98
Multivariate OR (95% CI)	413/413	1.0 (Ref)	1.01 (0.64,1.60)	0.69 (0.42,1.12)	1.16 (0.73,1.86)	0.99 (0.61,1.61)	0.87
Distal							
Age-adjusted OR (95% CI)	164/164	1.0 (Ref)	1.17 (0.56,2.46)	1.13 (0.52,2.44)	0.77 (0.34,1.74)	1.02 (0.48,2.20)	0.87
Multivariate OR (95% CI)	146/146	1.0 (Ref)	1.38 (0.58,3.27)	1.21 (0.49,2.95)	0.68 (0.26,1.75)	0.99 (0.41,2.39)	0.70
Rectal							
Age-adjusted OR (95% CI)	132/132	1.0 (Ref)	0.94 (0.40,2.21)	0.82 (0.35,1.86)	0.85 (0.39,1.86)	0.92 (0.41,2.04)	0.80
Multivariate OR (95% CI)	112/112	1.0 (Ref)	0.87 (0.35,2.18)	0.95 (0.34,2.62)	0.73 (0.31,1.74)	1.06 (0.44,2.52)	0.94
By stage							
Local/regional							
Age-adjusted OR (95% CI)	672/672	1.0 (Ref)	0.98 (0.69,1.40)	0.74 (0.51,1.07)	0.93 (0.65,1.32)	0.89 (0.62,1.28)	0.55
Multivariate OR (95% CI)	592/592	1.0 (Ref)	0.97 (0.66,1.43)	0.68 (0.46,1.03)	0.88 (0.60,1.31)	0.90 (0.60,1.35)	0.61
Metastatic							
Age-adjusted OR (95% CI)	83/83	1.0 (Ref)	1.59 (0.56,4.56)	1.61 (0.52,5.04)	2.37 (0.72,7.81)	1.94 (0.70,5.40)	0.24
Multivariate OR (95% CI)	77/77	1.0 (Ref)	1.64 (0.51,5.23)	2.31 (0.63,8.41)	3.31 (0.85,12.89)	2.70 (0.83,8.18)	0.11

[1]Quintiles based on controls. SAA Q1 median = −44.6 mg/L, Q2 median = −16.1 mg/L, Q3 median = 4.08 mg/L, Q4 median = 26.7 mg/L and Q5 median = 83.8 mg/L. [2]*p*-Value based on quintile median trend test. [3]Multivariate model adjusted for age (50–54, 55–59, 60–64, 65–69, 70–74 and 75–79 years), BMI at baseline, hormone replacement therapy (HT) use (never, past and current), previous colonoscopy (yes/no), pack-years of smoking.

the impact of changes in, and long-term, biomarker concentrations on CRC risk. Compared to the previous studies among women, our study had the largest number of cases which enabled us to undertake stratified analyses by tumor site and stage. We also assessed CRC risk by combining the two inflammatory markers, thereby, providing more robust risk estimates for accurate classification of chronic inflammatory exposure. A limitation of our study is that it is limited to postmenopausal women. Also, as our study is an observational study, we cannot completely rule out residual confounding although we adjusted for known confounders.

We have demonstrated that elevated biomarkers of inflammation are associated with CRC risk, notably colon cancer, thereby supporting the role of inflammation in colorectal carcinogenesis. Nevertheless, the ROC curve and analyses involving multiple measurements preclude the use of CRP and SAA as independent early-detection markers for CRC.

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