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Genetic variation in C-reactive protein (CRP) in relation to colon and rectal cancer risk and survival

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Abstract

Background—C-reactive protein (CRP), a biomarker of inflammation has been shown to be influenced by genetic variation in the *CRP* gene.

Methods—In this study, we test the hypothesis that genetic variation in *CRP* influences both the risk of developing colon and rectal cancer and survival. Two population-based studies of colon cancer (n=1574 cases, 1970 controls) and rectal (n=791 cases, 999 controls) were conducted. We evaluated four *CRP* tagSNPs: rs1205 (G>A, 3' UTR); rs1417938 (T>A, intron); rs1800947 (G>C, L184L); and rs3093075 (C>A, 3' flanking).

Results—The *CRP* rs1205 AA genotype was associated with an increased risk of colon cancer (OR 1.3, 95%CI 1.1-1.7), whereas the rs3093075 A allele was associated with a reduced risk of rectal cancer (OR 0.7, 95%CI 0.5-0.9). The strongest association for the rs1205 polymorphism and colon cancer was observed among those with *KRAS2* mutations (OR 1.5, 95%CI 1.1-2.0). The *CRP* rs1205 AA genotype also was associated with an increased risk of CIMP+ rectal tumors (OR 2.5, 95% CI 1.2-5.3); conversely, the rs1417938 A allele was associated with a reduced risk of CIMP+ rectal tumors (OR 0.5, 95%CI 0.3-0.9). We observed interactions between *CRP* rs1800947 and BMI and family history of CRC in modifying risk of both colon and rectal cancer.

Conclusions—These data suggest that genetic variation in the *CRP* gene influences risk of both colon and rectal cancer development.

Keywords

inflammation; colon cancer; rectal cancer; C-reactive protein; BMI; family history; survival; genetic variation; polymorphism; *CRP*; CIMP+; *KRAS2*

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Introduction

Inflammation, a pathophysiologic process that can operate throughout the large intestinal tract, influences carcinogenesis through multiple pathways. Inflammation increases proliferation, causes oxidative stress, and facilitates angiogenesis[1]. Para-inflammation, the result of tissue stress and its adaptive response is most probably responsible for the chronic inflammatory state of the large intestine that leads to cancer[2]. C-reactive protein (CRP) is a systemic blood biomarker of inflammation, its production partially triggered by increases in plasma concentrations of IL6, a pro-inflammatory cytokine; serum levels of CRP have been associated with increased risk of colorectal cancer (CRC)[3, 4] in some, but not all studies. Several polymorphisms of the *CRP* gene have been shown to be associated with CRP levels in the blood in some, but not all studies [5-9]. It is less clear if intrinsic variation in CRP levels driven by genetic variation is associated with colorectal cancer and subsequent survival. A small study of 205 CRC cases reported borderline associations with four *CRP* polymorphisms[10]. A study of colorectal polyps observed a borderline finding with the 838 G>C polymorphism (rs1800947) of *CRP*[11].

The purpose of this study was to investigate the association between tagSNPs of the *CRP* gene and risk of colon and rectal cancer. We examined how these associations may be modified by other factors thought to be related to inflammation and possibly CRP levels, such as high body mass index (BMI, kg/m^2)[12, 13], and recent use of aspirin or nonsteroidal-anti-inflammatory drugs (NSAIDs) and by family history of CRC in first-degree relatives. We examined associations with CRP genotypes and specific tumor markers as it has been hypothesized that CIMP+ tumors and those with *TP53* mutations are linked to inflammation[14, 15] We evaluated differences in survival with *CRP* polymorphisms, as inflammation-related factors may influence angiogenesis and tumor promotion. We hypothesized that genetic variation in the *CRP* gene variants that increase CRP levels will increase risk of developing colorectal cancer and shorten survival[16]

Materials and Methods

Two study populations are included in these analyses. The first study, a population-based case-control study of colon cancer, included cases (n=1,574) and controls(n=1,970) identified between October 1, 1991 and September 30, 1994[17] living in the Twin Cities Metropolitan Area, Kaiser Permanente Medical Care Program of Northern California (KPMCP) and a seven county area of Utah. The second study, with identical data collection methods, included cases with cancer of the rectosigmoid junction or rectum (n=791) and controls (n=999) who were identified between May 1997 and May 2001 in Utah and KPMCP[18]. Eligible cases were between 30 and 79 years old at time of diagnosis, English speaking, mentally competent to complete the interview, had no previous history of CRC, and no known (as indicated on the pathology report)familial adenomatous polyposis, ulcerative colitis, or Crohn's disease.

Controls were frequency matched to cases by sex, race, and by 5-year age groups. At KPMCP, controls were randomly selected from membership lists; in Utah, controls 65 years and older were randomly selected from the Health Care Financing Administration lists and controls younger than 65 years were randomly selected from driver's license lists. In Minnesota, controls were selected from driver's license and state-identification lists. Study details have been previously reported [19, 20].

Interview Data Collection

Data were collected by trained and certified interviewers using laptop computers. All interviews were audio-taped as previously described and reviewed for quality control

purposes[21]. The referent period for the study was two years prior to diagnosis for cases or selection for controls. Detailed information was collected on diet, physical activity, medical history, reproductive history, family history of cancer in first-degree relatives, regular use of aspirin and non-steroidal anti-inflammatory drugs, and body size.

Tumor Registry Data

Tumor registry data were obtained to determine disease stage at diagnosis and months of survival after diagnosis. Disease stage was categorized by Surveillance, Epidemiology, and End Results (SEER) staging of local, regional, and distant disease as well as by the American Joint Committee on Cancer (AJCC) staging criteria. Local tumor registries provided information on patient follow-up including vital status, cause of death, and contributing cause of death. Survival-months were calculated based on month and year of diagnosis and month and year of death, or of last contact for those individuals who were still alive.

Tumor Marker Data

We have previously evaluated tumors for CpG island methylator phenotype (CIMP), microsatellite instability (MSI), *TP53* mutations, and *KRAS2* mutations[22-25] and were therefore able to evaluate *CRP* genotypes in relation to tumors with specific characteristics or markers. Details for methods used to evaluate these epigenetic and genetic changes have been described in previous publications[22-25].

TagSNP selection

An identical tagSNP selection and genotyping procedure was used in both colon and rectal studies. The coding regions and 2 kB beyond the 5' and 3' ends of *CRP* had been resequenced in 23 individuals of European descent by Seattle SNPs (http://pga.mbt.washington.edu). TagSNPs were selected using the LD Select algorithm developed by Carlson and colleagues [26], with a cutoff minor allele frequency (MAF) of 4% (i.e., any variant that occurred twice) and an r^2 value of 0.90. This resulted in the selection of 7 tagSNPs in *CRP* that were estimated, by the Genome Variation Server (http://gvs.gs.washington.edu/GVS/index.jsp), to cover at least 85% of the common (≥4% MAF) variation in these loci. A total of 4 *CRP* SNPs were successfully converted to the Illumina™ GoldenGate genotyping platform: rs1205 (G>A, 3' UTR); rs1417938 (T>A, intron); rs1800947 (G>C, L184L); and rs3093075 (C>A, 3' flanking).

Genotyping and QC

All SNPs included in this analysis were genotyped using the Illumina™ GoldenGate bead-based genotyping technology at the Translational Genomics Institute (TGen, Phoenix, Arizona). Intraplate and interplate replicates at a rate of ~5% were included on all plates and in all batches. Blinded duplicates were also included on all plates as another QC measure. Genotype data from 30 CEPH trios (Coriell Cell Repository, Camden, NJ) that were genotyped by the HapMap project were used to confirm reliability and reproducibility of the genotyping. Genotypes were excluded from analyses by TGen if any of the following were true: GenTrain score<0.4, 10%GC score<0.25, AB T Dev.>0.1239, call frequency<0.85, replicate errors>2, P-P-C errors>2. Additional exclusions were made for SNPs that had <85% concordance with blinded or non-blinded duplicates and for Hardy-Weinberg Equilibrium (HWE) p values <0.0001. All SNPs shown were in HWE.

Statistical Methods

All statistical analyses were performed using SAS® version 9.2 (SAS Institute, Cary, NC). We assessed odds ratios (ORs) and 95% confidence intervals (95%CIs) in multiple logistic

regression models for colon and rectal cancer separately. All tagSNPs were evaluated individually in a case-control comparison by first comparing the heterozygote and homozygote variant to the homozygote wildtype genotype carriers (codominant, or unrestricted additive model) and subsequently assessing the dominant and recessive models of inheritance; the best fitting model is presented. Individuals with missing values were dropped from the analyses; no missing values were imputed. Adjustments were made for age, sex, race, study center, BMI (kg/m^2), use of aspirin or NSAIDs within two years of the referent period, cigarette smoking status (ever or never regularly smoked), and family history of CRC in first-degree relatives. These variables were selected for adjustment because of their previous association with colon and rectal cancer and their possible association with CRP, given their hypothesized involvement in an inflammation-related pathway. Additionally, interaction models were constructed to jointly assess effects of and to test for interactions between *CRP* SNP genotypes and exposures: sex, age (30-64 or 65-79), recent aspirin or NSAID use, BMI (<25, 25-30, >30), and family history. *P* values for linear trend were assessed using three ordered categories of genotype variables and comparing the likelihood ratio of a model with the variable (as continuous) to the likelihood ratio of a model without the variable using a chi-square test with 1 degree of freedom. For dominant or recessive models, *P* values for association were calculated based on a likelihood ratio test of a model with a 2-category genotype variable (referent and combined dominant or recessive genotype) compared to a reduced model. *P* values for interaction between genotype and exposure were determined by comparing a full model including main effects and an ordinal multiplicative interaction term to a reduced model without an interaction term, using a likelihood ratio test (1 degree of freedom).

Tumors were defined by specific alterations detected; any *TP53* mutation, any *KRAS2* mutation, MSI+, or CIMP+ defined as at least two of five markers methylated. As the proportion of MSI+ tumors in the rectal cases was <3% [27], there was insufficient power to examine these tumor markers with genotype data. Population-based controls were used to assess associations for the population overall when examining multiple outcomes defined by tumor status. In order to compare specific types of mutations to population-based controls while adjusting for the tumor mutations simultaneously in cases, a generalized estimating equation (GEE) with a multinomial outcome was used [28], because case subjects could contribute from one to multiple outcome observations depending on the number of tumor alterations or mutations (*TP53, KRAS2*, CIMP+, and additionally for colon cases, MSI+ and *BRAF* V600E) an individual had [29]. The GEE accounts for correlation introduced by including subjects multiple times and was implemented in SAS using the GENMOD procedure as described by Kuss and McLerran [30].

Survival and tumor-stage data were available for 1,364 individuals with colon tumors and 697 individuals with rectal tumors who were also genotyped for *CRP*. Months of survival were determined for cases only based on date of diagnosis and date of last contact or death. We assessed five-year survival. Associations between *CRP* tagSNPs and risk of dying of colorectal cancer and all-cause mortality were evaluated using Cox proportional hazards models to provide multivariate hazard rate ratios (HRRs) and 95% confidence intervals adjusted for age at diagnosis, sex, and AJCC stage.

Results

The AA genotype of the *CRP* rs1205 polymorphism was associated with a 1.3-fold increased risk of colon cancer (*p* 0.02) (Table 1). The CA or AA genotypes of rs3093075 were associated with a 30% reduced risk of rectal cancer (*p*=0.01). No other associations of *CRP* tagSNP genotypes were observed in colon or rectal cancer overall and assessment of

haplotypes did not provide additional information on the associations between *CRP* and colon and rectal cancer.

Further evaluation of *CRP* polymorphisms and specific tumor markers (Table 2) showed that the AA genotype of *CRP* rs1205 was most strongly associated with a 50% increased risk of having a *KRAS2* colon mutation (recessive model; p=0.008), whereas having the AA genotype was associated with increasing risk of CIMP+ rectal tumors (p-trend=0.01). Conversely in rectal cancer, we observed that having a one or two copies of the A allele for rs1417938 was associated with half the risk of a CIMP+ rectal tumor; for *CRP* rs3093075, one or two copies of the A allele was associated with a 30-40% reduced risk of either a *TP53* and *KRAS2* mutation. It should be noted that few cases of rectal cancer had CIMP+ tumors, making the associations imprecise, although still statistically significant.

BMI interacted significantly with *CRP* rs1800947 for both colon and rectal cancer as shown in Table 3 (p-interaction 0.02 and 0.01, respectively). However, of interest is the observation that, whereas having one or two copies of the C allele of rs1800947 and a BMI of <25 was associated with increased colon cancer risk, these genotypes and BMI level were associated with a reduced risk of rectal cancer. Having a GG genotype and being obese (BMI≥30) also was associated with an increased risk of colon cancer.

There was a statistically significant and consistent interaction between family history of CRC in first-degree relatives and the *CRP* rs1205 polymorphism for both colon and rectal cancer (p-interaction 0.04 and 0.015, respectively; see Table 4). Although a recessive model was indicated for risk of colon cancer overall and for associations with tumor markers (Tables 1 and 2), a dominant model seemed most important in relation to family history and the patterns were identical across the two tumor sites. In addition to the association with *CRP* rs1205, the rs1800947 tagSNP also consistently interacted with family history in risk of both colon and rectal cancer. Having a G allele of the rs1800947 polymorphism was associated with a reduced risk of developing colon or rectal cancer among those with a family history of the disease. Furthermore, the rs1417938 tagSNP interacted with family history in rectal cancer; those whose genotypes contained the variant A allele and a positive family history were at a two-fold increased risk (p-interaction 0.03). We observed no interactions in risk of colon or rectal cancer for aspirin or other NSAID use.

We examined *CRP* tagSNPs and their association with colon or rectal cancer in relation to 5-year survival (Table 5). The AA genotype of the rs1205 polymorphism was associated with a slight reduced risk of dying of all causes after a diagnosis of colon cancer; this association was borderline statistically significant (HRR 0.7, 95%CI 0.5-0.98). The magnitude of the association was equivalent for risk of dying from CRC, which comprised 2/3 of deaths from all causes, although the upper confidence interval included 1.0. A decreased risk for rs1205 and all-cause mortality was observed in rectal cancer for genotypes containing a variant A allele,

Discussion

Polymorphisms in the *CRP* gene were associated with colon and rectal cancer. These polymorphisms appeared to have the strongest association with specific tumor markers and were modified by BMI and a family history of colorectal cancer in first-degree relatives. Additionally, the *CRP* rs1205 polymorphism may have influenced survival after a colon cancer diagnosis.

Few studies have examined these *CRP* variants with cancer. The study by Tsilidis and colleagues[10] did not observe an association with either *CRP* rs1205 or rs1800947 and colorectal cancer, but did observe a statistically significant increased risk with the *CRP*

rs2794521 polymorphism for carriers of the C allele. That study included ~200 cases of CRC and these associations were not evaluated for colon and rectal cancer separately. The study by Siemes and colleagues showed no association between three SNPs of CRP including rs1205 colorectal cancer [31] A study by Poole and colleagues[11] showed an increased risk of concurrent adenomas and hyperplastic polyps with the C allele of the rs1800947 polymorphism; they did not observe an alteration of risk with any of the other tagSNPs examined in this study. Most other studies of *CRP* polymorphisms have been examined with heart disease and outcomes other than CRC.

We observed statistically significant associations with *CRP* polymorphisms for both colon and rectal cancer; however, the markers of importance varied by tumor site. The rs1205 AA genotype was associated with a statistically significant increased risk of colon cancer. Although we did not observe a statistically significant association with the *CRP* rs1205 polymorphism and rectal cancer overall, we did observe an increased risk of CIMP+ rectal tumors; this finding lends support to the hypothesis that CIMP+ tumors are associated with inflammation-related pathways[39]. We have observed differences in risk for colon and rectal cancer and inflammation-related factors for colon and rectal cancer in the past[14, 18, 27, 40]. The current findings are consistent with different factors being important for different bowel segments, as well as with other recent important findings of differences by colon subsite.[41] More large epidemiological studies such as this are needed to verify the results reported.

Although the literature shows that genetic variation in CRP influences serum levels of CRP, as shown above, studies are not consistent as to the association. The data are mixed on the association between this polymorphism and CRP serum concentrations[32-34]. The AA genotype of rs1205 has been associated with lower CRP levels [33, 35, 36] although the AA genotype also has been associated with more cardiovascular events[37] despite the fact of lower CRP levels. A study by Martinez-Calatrava and colleagues showed CRP levels were influenced by the minor alleles of rs1130864 (increased), rs1205 (decreased), and rs1800947 (decreased) [38]. Other studies shown that the G allele of rs1800947 increases CRP expression[33] We observed a statistically significantly reduced risk of rectal cancer with the A allele of the *CRP* rs3093075 variant, although studies have shown that this allele to be associated with increased CRP expression [33] *CRP* rs3093075 was grouped in the same linkage disequilibrium block as rs3093068 in a recent study[33] The variant *CRP* rs3093068 allele has previously been associated with a ~40% decreased risk of lung cancer in a Caucasian cohort[31], although no statistically significant association was reported with CRC. Lee and colleagues have shown that the minor allele of rs3093069 increased CRP concentrations [33]

We observed a statistically significant interaction between the *CRP* rs1800947 polymorphism and BMI and risk of both colon and rectal cancer. Although there were interactions for both colon and rectal cancer, the genotype carrying the greatest risk differed. Other studies also have examined the interaction between *CRP* genotypes and BMI as they influence CRP levels and shown a correlation between increase in CRP levels that was influenced by joint effect of *CRP* genotype and adiposity[42]. We observed no interactions with either aspirin or non-steroidal anti-inflammatory drugs and *CRP* polymorphisms for either colon or rectal cancer. Perhaps this is attributable to the fact that aspirin or other NSAIDs are not as strong determinants of CRP as is BMI.

Our finding of a statistically significant interaction between *CRP* genotypes and family history of CRC in our studies of both colon and rectal cancer is novel and interesting because identical patterns of associations replicated between the independent colon and rectal studies (Table 5). The association between rectal cancer and family history of CRC cancer has been shown to be weaker than the association observed for colon cancer[43]. Our

findings suggest that inflammatory processes play a stronger role among individuals with a positive family history, or perhaps that SNPs in *CRP* contribute to the risk associated with family history.

The *CRP* rs1205 polymorphism has been associated with non-cardiovascular diseases mortality in other studies[44]. We observed that both carrying the *CRP* rs1205 AA genotype and having a diagnosis of colon cancer was associated with a 30% decreased risk of mortality from all causes and from CRC (5-year survival), although the latter finding was not statistically significant. We also found a consistent, but not statistically significant improved survival in rectal cancer for those carrying 1 or 2 variant A alleles.

This study has many strengths, including its comprehensive nature in that we examined both colon and rectal cancer, several key tumor markers, and survival after diagnosis. The abundant health and lifestyle data allowed us to examine how genotypes influence susceptibility to cancer associated with other factors. However, these findings need replication in other studies with adequate power to examine colon and rectal cancer separately as we made multiple comparisons based on five tagSNPs, but in a hypothesis-driven investigation. A conservative Bonferroni correction in the analyses of either colon or rectal cancer implies a p-value ≤0.01 occurs apart from chance; we observed nominal p-values at the 0.01 level.

In summary, our findings suggest that genetic variants in *CRP* are associated with both risk of colon and rectal cancer, although associations varied. Furthermore, there are suggestions that these variants may contribute to specific types of tumors and may be modified by other factors including BMI and family history of CRC. Because of the association with survival, further work is needed to clarify how genetic variation in *CRP* and CRP level influences prognosis of colon or rectal cancer.

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Table 1

Associations between CRP tagSNPs and colon and rectal cancer risk

		Colon cancer					Rectal cancer				
***CRP* genotype**[1]	**MAF**[2]	**n Controls**	**n Cases**	**OR**[3]	**(95%CI)**	***p***[4]	**n Controls**	**n Cases**	**OR**[3]	**(95%CI)**	***p***[4]
rs1205 (3' UTR)	0.32										
GG		882	700	1	Referent		406	295	1	Referent	
GA		845	659	1.0	(0.9, 1.1)		403	325	1.1	(0.9, 1.4)	
AA		157	163	1.3	(1.04, 1.7)	0.12	92	79	1.2	(0.8, 1.7)	0.24
AA vs. GG/GA				1.3	(1.1, 1.7)	0.02			1.1	(0.8, 1.6)	0.47
rs1417938 (intron)	0.30										
TT		901	758	1	Referent		472	362	1	Referent	
TA		810	629	0.9	(0.8, 1.1)		365	289	1.0	(0.8, 1.3)	
AA		172	133	1.0	(0.7, 1.2)	0.49	66	53	1.0	(0.7, 1.5)	0.75
TA/AA vs. TT				0.9	(0.8, 1.1)	0.43			1.0	(0.8, 1.3)	0.74
rs1800947 (L184L)	0.06										
GG		1687	1356	1	Referent		786	626	1	Referent	
GC		198	161	1.0	(0.8, 1.3)		115	76	0.9	(0.6, 1.2)	
CC		2	6	3.2	(0.6, 16.7)	0.48	2	3	1.9	(0.3, 11.3)	0.45
CC/GC vs. GG				1.1	(0.8, 1.3)	0.62			0.9	(0.6, 1.2)	0.37
rs3093075 (3' flank.)	0.06										
CC		1621	1315	1	Referent		771	631	1	Referent	
CA		240	198	1.0	(0.8, 1.2)		122	69	0.7	(0.5, 0.9)	
AA		14	10	0.8	(0.3, 1.8)	0.68	8	5	0.7	(0.2, 2.1)	0.01
CA/AA vs. CC				1.0	(0.8, 1.2)	0.76			0.7	(0.5, 0.9)	0.01

Abbreviations: tagSNP, tagging single nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio; 95%CI, 95% confidence interval.

[1] Recessive model is shown where indicated; dominant is model shown where indicated and for MAFs<0.10; both in bolded font.

[2] Minor allele frequency in combined colon and rectal study controls, non-Hispanic whites.

[3] Adjusted for age, sex, race, study center, BMI, recent aspirin/NSAID use, cigarette smoking status, and first-degree family history of colorectal cancer.

[4] *P* for linear trend used in additive models; *p* for association used in dominant or recessive models.

Table 2

Associations between *CRP* tagSNPs and colon and rectal tumor markers

Colon tumors: *CRP* genotype[1,2]	***TP53* Mutation**				***KRAS2* Mutation**				**CIMP+**			
	n	**OR[3]**	**(95% CI)**	***p*[4]**	***n***	**OR[3]**	**(95% CI)**	***p*[4]**	***n***	**OR[3]**	**(95% CI)**	***p*[4]**
rs1205 (3' UTR)												
GG	229	1	Referent		162	1	Referent		117	1	Referent	
GA	221	1.0	(0.9, 1.2)		135	0.9	(0.7, 1.1)		118	1.1	(0.9, 1.4)	
AA	54	1.1	(0.8, 1.5)	0.28	46	1.4	(1.0, 1.9)	0.27	33	1.3	(0.9, 1.9)	0.17
AA vs. GG/GA		1.1	(0.8, 1.5)	0.12	297	1.5	(1.1, 2.0)	<0.01	235	1.3	(0.9, 1.8)	0.06
rs1417938 (intron)												
TT	256	1	Referent		168	1	Referent		135	1	Referent	
TA/AA	248	0.9	(0.8, 1.1)	0.36	176	1.0	(0.8, 1.2)	0.92	133	1.0	(0.8, 1.2)	0.78
rs3093075 (3' flank.)												
CC	436	1	Referent		303	1	Referent		240	1	Referent	
CA/AA	70	1.0	(0.8, 1.3)	0.98	40	0.8	(0.6, 1.1)	0.20	28	0.7	(0.5, 1.1)	0.12
Rectal tumors: *CRP* genotype[1,2]	*TP53* Mutation				*KRAS2* Mutation				CIMP+			
	n	OR[3]	(95% CI)	*p*[4]	*n*	OR[3]	(95% CI)	*p*[4]	*n*	OR[3]	(95% CI)	*p*[4]
rs1205 (3' UTR)												
GG	102	1	Referent		77	1	Referent		16	1	Referent	
GA	126	1.2	(0.9, 1.6)		65	0.8	(0.6, 1.1)		28	1.7	(0.9, 3.2)	
AA	30	1.2	(0.8, 1.9)	0.12	19	1.0	(0.6, 1.7)	0.85	10	2.5	(1.2, 5.3)	0.01
AA vs. GG/GA		1.1	(0.8, 1.5)	0.45		1.1	(0.7, 1.8)	0.53		1.8	(1.0, 3.5)	0.10
rs1417938 (intron)												
TT	132	1	Referent		75	1	Referent		37	1	Referent	
TA/AA	128	1.1	(0.8, 1.4)	0.72	87	1.3	(1.0, 1.8)	0.14	17	0.5	(0.3, 0.9)	0.02
rs3093075 (3' flank.)												
CC	236	1	Referent		149	1	Referent		50	1	Referent	
CA/AA	25	0.7	(0.4, 1.0)	0.02	14	0.6	(0.3, 0.97)	0.02	4	0.6	(0.2, 1.5)	0.14

Abbreviations: tagSNP, tagging single nucleotide polymorphism; OR, odds ratio; 95%CI, 95% confidence interval.

[1]Recessive model is shown where indicated; dominant is model shown where indicated and for MAFs<0.10; both in bolded font.

[2] Minor allele frequency in combined colon and rectal study controls, non-Hispanic whites.

[3] Adjusted for age, sex, race, study center, BMI, recent aspirin/NSAID use, cigarette smoking status, and first-degree family history of colorectal cancer.

[4] *P* for linear trend used in additive models; *p* for association used in dominant or recessive models.

Table 3

Interaction between *CRP* rs1800947 and body mass index in modifying colon or rectal cancer risk.

Colon cancer: Genotype[1]	**BMI <25**				**BMI 25-30**				**BMI ≥30**				
	***n* ctrl.**	***n* case**	**OR**[2]	**(95% CI)**	***n* ctrl.**	***n* case**	**OR**[2]	**(95% CI)**	***n* ctrl.**	***n* case**	**OR**[2]	**(95% CI)**	***p***[3]
rs1800947 (L184L)													
GG	654	429	1	Referent	696	559	1.3	(1.1, 1.5)	337	368	1.8	(1.4, 2.1)	
GC/CC	79	70	1.4	(1.01, 2.0)	80	62	1.2	(0.8, 1.7)	41	35	1.3	(0.8, 2.1)	0.02
Rectal cancer: Genotype[1]	BMI <25				BMI 25-30				BMI ≥30				
	n ctrl.	*n* case	OR[2]	(95% CI)	*n* ctrl.	*n* case	OR[2]	(95% CI)	*n* ctrl.	*n* case	OR[2]	(95% CI)	*p*[3]
rs1800947 (L184L)													
GG	254	212	1	Referent	337	254	0.9	(0.7, 1.2)	196	161	1.0	(0.8, 1.3)	
GC/CC	42	19	0.5	(0.3, 0.9)	51	33	0.8	(0.5, 1.3)	24	27	1.5	(0.8, 2.7)	0.01

Abbreviations: tagSNP, tagging single nucleotide polymorphism; OR, odds ratio; 95%CI, 95% confidence interval; ctrl., controls.

[1] Dominant is shown due to small numbers of subjects with homozygous CC genotypes.

[2] Adjusted for age, sex, race, study center, recent aspirin/NSAID use, cigarette smoking status, and first-degree family history of colorectal cancer.

[3] *P* for multiplicative interaction based on likelihood ratio test (see Methods).

Table 4

Interactions between *CRP* tagSNPs and first-degree family history of CRC in modifying colon or rectal cancer risk

Colon cancer: Genotype[1]	**No family history**				**Positive family history**				
	***n* ctrl.**	***n* case**	**OR**[2]	**(95% CI)**	***n* ctrl.**	***n* case**	**OR**[2]	**(95% CI)**	***p***[3]
rs1205 (3' UTR)									
GG	809	579	1	Referent	73	121	2.4	(1.7, 3.2)	
GA/AA	899	700	1.1	(1.0, 1.3)	104	123	1.7	(1.3, 2.2)	0.04
rs1417938 (intron)									
TT	809	631	1.0	Referent	93	128	1.8	(1.3, 2.4)	
TA/AA	897	646	0.9	(0.8, 1.1)	85	116	1.8	(1.3, 2.4)	0.69
rs1800947 (L184L)									
GG	1538	1137	1	Referent	150	220	2.0	(1.6, 2.5)	
GC/CC	172	143	1.2	(0.9, 1.5)	28	24	1.2	(0.7, 2.0)	0.03
Rectal cancer: Genotype[1]	No family history				Positive family history				
	n ctrl.	*n* case	OR[2]	(95% CI)	*n* ctrl.	*n* case	OR[2]	(95% CI)	*p*[3]
rs1205 (3' UTR)									
GG	382	257	1	Referent	26	39	2.3	(1.4, 3.9)	
GA/AA	445	365	1.2	(1.0, 1.5)	50	39	1.2	(0.8, 1.9)	0.015
rs1417938 (intron)									
TT	431	331	1	Referent	43	31	1.0	(0.6, 1.6)	
TA/AA	398	294	1.0	(0.8, 1.2)	33	49	2.0	(1.2, 3.2)	0.03
rs1800947 (L184L)									
GG	726	551	1	Referent	62	76	1.7	(1.2, 2.4)	
GC/CC	103	75	1.0	(0.7, 1.4)	14	4	0.4	(0.1, 1.2)	0.01

Abbreviations: tagSNP, tagging single nucleotide polymorphism; CRC, colorectal cancer; OR, odds ratio; 95%CI, 95% confidence interval; ctrl., controls.

[1] Dominant model is shown due to small number of subjects with homozygous variant genotypes and positive family history.

[2] Adjusted for age, sex, race, study center, recent aspirin/NSAID use, and cigarette smoking status.

[3] *P* for multiplicative interaction based on likelihood ratio test (see Methods).

Table 5

Survival following a diagnosis of colon or rectal cancer in relation to *CRP* tagSNPs.

	Colon cancer					Rectal cancer				
		CRC deaths		All causes			CRC deaths		All causes	
***CRP* genotype**[1]	***n***	**HRR**[2]	**(95%CI)**	**HRR**[2]	**(95%CI)**	***n***	**HRR**[2]	**(95%CI)**	**HRR**[2]	**(95%CI)**
rs1205 (3' UTR)										
GG	628	1	Referent	1	Referent	293	1	Referent	1	Referent
GA	579	1.1	(0.8, 1.4)	1.1	(0.9, 1.1)	323	1.0	(0.7, 1.5)	0.8	(0.6, 1.0)
AA	153	0.7	(0.4, 1.1)	0.9	(0.7, 1.0)	75	1.1	(0.6, 2.0)	0.8	(0.6, 1.1)
AA vs. GG/GA		0.7	(0.4, 1.0)	0.7	(0.5, 0.98)		1.1	(0.7, 1.8)	1.0	(0.6, 1.6)
rs1417938 (intron 1)										
TT	674	1	Referent	1	Referent	356	1	Referent	1	Referent
TA/AA	684	1.1	(0.9, 1.4)	1.1	(0.9, 1.4)	340	0.9	(0.6, 1.3)	0.9	(0.6, 1.2)
rs1800947 (L184L)										
GG	1210	1	Referent	1	Referent	620	1	Referent	1	Referent
GC/CC	152	0.9	(0.6, 1.4)	0.9	(0.6, 1.2)	77	1.0	(0.6, 1.6)	0.9	(0.6, 1.4)
rs3093075 (3' flank.)										
CC	1179	1	Referent	1	Referent	624	1	Referent	1	Referent
CA/AA	182	1.1	(0.7, 1.6)	1.1	(0.8, 1.5)	73	0.8	(0.5, 1.5)	0.9	(0.5, 1.5)

Abbreviations: tagSNP, tagging single nucleotide polymorphism; HRR, hazard rate ratio; 95%CI, 95% confidence interval; CRC, colorectal cancer.

[1] Recessive model for rs1205 is shown in bolded font.

[2] Based on 5-year survival, CRC and all-cause mortality; adjusted for age, sex, and American Joint Committee on Cancer disease stage at diagnosis.