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IL6 genotypes and colon and rectal cancer

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Abstract

Inflammation appears to play a key role in the development of colorectal cancer (CRC). In this study we examine factors involved in the regulation of inflammation and risk of CRC. Data from a multi-center case–control study of colon (*N* = 1579 cases and *N* = 1977 controls) and rectal (*N* = 794 cases and *N* = 1005 controls) cancer were used to evaluate the association between the rs1800795 and rs1800796 *IL6* polymorphisms and CRC. We evaluated the joint effects of *IL6* single nucleotide polymorphisms and regular use of aspirin/NSAIDs and vitamin D receptor (*VDR*) genotype. Having a C allele of the rs1800796 *IL6* polymorphisms and the GG genotype of the rs1800795 *IL6* polymorphisms was associated with a statistically significantly reduced the risk of colon (OR 0.76 95% CI 0.57, 1.00), but not rectal (OR 1.49 95% CI 1.02,2.16) cancer. Both *IL6* polymorphisms were associated with significant interaction with current use of aspirin/NSAIDs to alter risk of colon cancer: individuals with a C allele in either polymorphism who were current users of aspirin/NSAIDs had the lowest colon cancer risk. CRC risk also was associated with an interaction between *VDR* and *IL6* genotypes that was modified by current use of aspirin/NSAIDs. This study provides further support for inflammation-related factors in the etiology of CRC. Other studies are needed to explore other genes in this and other inflammation-related pathways.

Keywords

Aspirin; Colon cancer; *IL6*; Non-steroidal anti-inflammatory drugs; Rectal cancer; *VDR*

Introduction

Support for inflammation involvement in the etiology of colorectal cancer (CRC) has stemmed from many sources. People with chronic inflammation of the large bowel as seen in ulcerative colitis have a greater likelihood of developing colon cancer [1,2]. People who use aspirin/NSAIDs, a possible indicator of lower levels of inflammation, have consistently been shown to have reduced risk of CRC [3–5].

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The inflammatory process is initiated by the synthesis and secretion of pro-inflammatory cytokines such as IL–6 in response to an inflammatory insult. Elevated serum IL-6 has been shown to be associated with incidence or clinical outcome in several cancers, including prostate, bladder, colon, and breast cancer [6–8]. IL-6 has been shown to stimulate secretion of C-reactive protein (CRP), an important biomarker for pro-inflammatory status in several diseases; CRP has been associated with a two- to three-fold increased risk of CRC with associations stronger for colon than for rectal cancer in several prospective studies [9–11], although these findings are not universal [12,13].

Associations between CRC and genetic variation in genes involved in inflammation-related pathways also may lend support to the growing body of data that suggest inflammation-related factors are important in the etiology of CRC. Of potential etiologic importance are genes such as *IL6*, which may be a critical regulator of inflammation signaling. Polymorphisms in the *IL6* gene promoter have been reported to be related to levels of circulating C-reactive protein [14], to be associated with different profiles of plasma *IL6* response to immunization [15], and to modify the association between high BMI and incident type 2 diabetes [16]. The −174 polymorphism (rs1800795) of the *IL6* gene has been one of the most commonly studied polymorphisms and has been shown to be in linkage disequilibrium with other commonly studied markers (rs1800797 and rs2069832) [17]. It has been reported that the −174 polymorphism influences transcription, with the GG genotype having higher levels of IL-6 [18]. From a breast cancer study, it appears that the C allele of −174 is associated with lower risk of obesity and breast cancer [17]. A study by Theodoropoulos and colleagues observed that the C allele of the −174 variant reduced risk of colorectal cancer [19], while a study by Landi and colleagues showed an increased colorectal cancer risk among individuals with the C allele [20]. Another *IL6* variant, −572 (G > C) rs1800796, also has been examined previously and has been associated with body size, with individuals with the G allele having smaller waist-to-hip ratios [17].

The vitamin D receptor (*VDR*) gene is involved in multiple pathways that include both inflammation and insulin [21]. Data have shown that *VDR* signaling is essential for regulation of inflammation in the gastrointestinal tract [22]. Polymorphisms of the *VDR* gene have been studied in conjunction with colorectal cancer and adenomas [23–28]. It has been reported that the “less active” *VDR* f, t, B, and S alleles are capable of facilitating a stronger cell-mediated immune response, as demonstrated by T lymphocyte response and human fibroblast cell lines [21,29,30]. Higher vitamin D hormone activity with the F allele than with the f allele of the Fok1 polymorphism also has been shown [29].

In this study we examine two commonly studied SNPs of the *IL6* gene (rs1800795 and rs1800796) with risk of colon and rectal cancer because of their representing different regions of the IL6 gene and because of previously reported associations with these SNPs. We used data collected as part of a large case–control study of colorectal cancer conducted in Northern California, Minnesota (colon cancer study only), and Utah. Beginning to take into account multiple variables along an inflammation-related pathway, we evaluated how polymorphisms in *VDR* interact with *IL6* polymorphisms and determined whether use of aspirin/NSAIDs importantly modify associations with *IL6*.

Methods

Data for the study come from two case–control studies that used identical methods to recruit and interview study participants. Cases of first primary colon cancer (ICD-O 2nd edition codes 18.0, 18.2–18.9) diagnosed between 1 October, 1991 and 30 September, 1994 conducted in the Northern California Kaiser Permanent Medical Care Program (KPMCP), the Wasatch Front area of Utah, and the Twin Cities Metropolitan area of Minnesota were included in the first

study. A subsequent study included cases that were diagnosed with a first primary tumor in the rectosigmoid junction or rectum and were identified between May 1997 and May 2001; this study was restricted to cases and controls from Utah and KPMCP. Case eligibility was determined by the Surveillance Epidemiology and End Results [31] Cancer Registries in Northern California and in Utah and the Minnesota Cancer Surveillance System (colon cancer cases only). Eligibility included being between 30 and 79 years of age at the time of diagnosis, English speaking, mentally competent to complete the interview, no previous history of colorectal cancer [32], and no known (as indicated on the pathology report for reason for colonoscopy or previous medical history) familial adenomatous polyposis, ulcerative colitis, or Crohn's disease. Of cases contacted, 83% participated at KPMCP, 76% in Utah, and 67% in Minnesota. For the rectal cancer study, the participation rates were 75.4% of cases from KPCMP and 69.7% of cases from Utah. The study was approved by the University of Utah Institutional Review Board as well as Institutional Review Boards at the Kaiser Permanente Medical Care Program of Northern California (KPMCP) and the University of Minnesota.

Controls were frequency matched to cases by sex and by 5-year age groups. At the KPMCP, controls were randomly selected from membership lists. In Utah, controls 65 years and older were randomly selected from lists provided by the Centers for Medicare and Medicaid Services (formerly HCFA) and controls younger than 65 were randomly selected from driver's license lists. In Minnesota, controls were randomly selected from driver's license lists. Of controls contacted for the colon cancer study, 73% participated at KPMCP, 53% participated from Minnesota and 69% participated from Utah. For the rectal cancer study, participation rates were 69.9% for KPMCP and 67.2% for Utah.

Data Collection

Trained and certified interviewers collected diet and lifestyle data [33,34]. The referent year for the study was the calendar year approximately 2 years prior to date of diagnosis (cases) or selection (controls). Information was collected on demographic factors such as age, sex, and study center; diet, physical activity, aspirin and non-steroidal drug use, body size, and other lifestyle factors including medical, family, and reproductive history.

Genotyping

DNA was extracted from blood drawn from study participants. Of the 1993 cases and 2410 controls interviewed as part of the colon cancer study, 1579 cases and 1977 controls had DNA for analyses. For the rectal cancer study, 952 cases and 1205 controls were interviewed, of which 794 cases and 1005 controls had DNA extracted and genotype analysis complete. Sample sizes varied slightly because of available DNA for testing and dropouts.

IL6 SNPs were genotyped using TaqMan-based assays

For SNP rs1800795 (−174G > C), assays were performed according to Watanabe et al. [35] using primers IL6-174F 5′-TAGCCTCAATGACGACCTAAGCT-3′ and IL6-174R 5′-GGGCTGATTGGAAACCTTATTAAG-3′, and probes IL6-174G 5′-VIC-TGTCTTGC(G)ATGCTA-MGB-3′ and IL6-174C 5′-6FAM-TGTCTTGC(C)ATGCTA-MGB-3′. For SNP rs1800796 (−572 G > C, also known as −634 C > G) complete assay kits were purchased from Applied Biosystems (Foster City, CA). Briefly, each 5 μl PCR reaction contained 20 ng genomic DNA, 900 nM of each primer, 125 nM of each TaqMan probe, and 2.5 μl Taq-Man Universal PCR Master Mix (contains AmpErase UNG and AmpliTaq Gold enzymes, dNTPs, and reaction buffer). PCR was carried out under the following conditions: 50°C for 2 min to activate UNG, 95°C for 10 min, followed by 40 cycles of 92°C for 15 s, and 60°C for 1 min using a 384 well dual block ABI 9700. Fluorescence endpoint of the TaqMan reaction was measured using an ABI 7900HT real time PCR instrument. Control samples representing all three possible genotypes were included at four positions each in every 384-well tray. In

addition, internal replicates representing > 1% of the sample set were blinded and included with 99% concordance in genotypes. Any discrepancies were checked and re-run if necessary. The call rate was 99.6% for rs1800795, 99.7% for rs1800796, 99.2% for rs1800797, and 99.3% for rs1800796.

The intron 8 *Bsm* I (rs154410) and Fok1 (rs10735810) *VDR* polymorphisms were amplified from genomic DNA and digested as described previously [26,36]. Presence of the restriction site was scored as allele "b," and absence of the restriction site was scored as allele "B." Presence of the restriction site was scored as allele "f," absence of the restriction site was scored as allele "F."

Statistical Methods

The SAS statistical package, version 9.1 was used to conduct the analyses. We evaluated the distribution of the *IL6* genotypes, the independent associations of genetic polymorphisms with colon and rectal cancer. When evaluated by race and study, the *IL6* SNPs were in Hardy–Weinberg equilibrium among controls for both the colon and rectal cancer studies with the exception of rs1800796 within the few non-Hispanic white rectal study controls. The r-squared correlation coefficients for the two SNPs in controls ranged between 0.005 and 0.12 by race and study. Since associations were similar for the heterozygote and homozygote variant *IL6* polymorphisms, the dominant model was used in assessment of interaction to maximize power. Odds ratios (OR) and 95% confidence intervals (CI) are used to report associations obtained from multiple logistic regression models. Associations were evaluated for men and women separately, for proximal and distal colon tumors, and by age; however, because associations were similar across these various groups, data are presented for the entire population for colon and rectal cancer separately. Associations were adjusted for age, sex, and race. Other factors such as body mass index [37], physical activity, and family history of colorectal cancer, cigarette smoking, and dietary composition did not alter associations and are not included as covariates in the final logistic regression models. We report the joint effect of *IL6* genotypes and aspirin/NSAIDs and Bsm1 and Fok1 *VDR* polymorphisms. For joint effects, multivariate logistic regression models were used to calculate odds ratios for each category of exposure and each genotype. Effect modification between genotypes and exposure variables was evaluated by the likelihood-ratio test for a multiplicative interaction term in the logistic regression model.

Results

A description of the population is shown in Table 1. The majority of study participants are non-Hispanic white and from the KPMCP in California. Controls were more likely to report using aspirin/NSAIDs. As in other populations, the C allele was the minor allele for both the rs1800796 and rs1800795 *IL6* markers in both the colon and rectal cancer studies.

A slight statistically non-significant reduction in colon cancer risk was observed for both *IL6* polymorphisms, however, having a C allele of the rs1800796 *IL6* polymorphisms and the GG genotype of the rs1800795 polymorphism was associated with a reduction in colon cancer risk (Table 2). The same *IL6* genotype combination was associated with a statistical significant increased risk of rectal cancer (OR = 1.49; 95% CI 1.02, 2.16).

Notwithstanding the differences in direction in the main-effect associations between colon and rectal cancer, the pattern of interactions between the *IL6* polymorphisms and use of aspirin/NSAIDs within 2 years prior to diagnosis (Table 3) was similar for the two cancer sites: individuals with the variant C allele were at a much reduced risk if they currently used aspirin/NSAIDs compared with the GG genotype among those who did not use aspirin/NSAIDs. For rectal cancer, the interaction between current aspirin/NSAID use and *IL6* genotypes was statistically significant only for the rs1800795 (−174G > C) polymorphism. For colon cancer,

those with the greatest reduction in risk were individuals who currently used aspirin/NSAIDs and had a C allele of either *IL6* polymorphism.

The association between *VDR* and *IL6* polymorphisms and colon and rectal cancer showed significant reduced risk of colon cancer for those with an f allele of the Fok1 *VDR* polymorphisms if they also had a C allele of either *IL6* polymorphisms, however the interaction term for *VDR* and *IL6* did not reach statistical significance (Table 4). Assessment of the interaction between *IL6* and *VDR* by aspirin/NSAID use showed that among current aspirin users, the rs1800796 *IL6* polymorphism interacted with the Fok1 *VDR* polymorphism: those with an f *VDR* allele were at reduced risk of colon cancer if they also had a C *IL6* allele (OR = 0.47; 95% CI 0.27,0.80; p interaction 0.05) (Table 5). Among current aspirin/NSAID users, the Bsm1 *VDR* and *IL6* rs1800795 interacted to alter risk of rectal cancer (p interaction 0.01): those with a bb *VDR* genotype and CC genotype for the *IL6* polymorphism had a statistically significantly lower risk of rectal cancer (OR = 0.49; 95% CI 0.29,0.83). The rs1800795 *IL6* polymorphism interacted with Bsm1 *VDR* polymorphism to alter risk of colon cancer among non-aspirin/NSAID users (p interaction 0.01).

Discussion

Our data suggest that *IL6* genotype may influence risk of colorectal cancer. Individuals with the C allele of the rs1800796 −572G > C SNP and the GG genotype for the rs1800795 (−174G > C) *IL6* polymorphism were at a slightly reduced risk of colon cancer, but possibly at a slightly increased risk of rectal cancer. Associations were similar for men and women and for all age groups and appeared to be modified by use of aspirin/NSAIDs: particularly, for colon cancer, users had a greater reduction in risk if they also had a C allele in either *IL6* polymorphism. Interaction between *VDR* genotype and *IL6* also was influenced by use of aspirin/NSAIDs.

Inflammation is increasingly implicated in the etiology of colorectal cancer. Regular use of aspirin/NSAIDs, in addition to independently reducing risk of colon and rectal cancer, has been shown to modify CRC risk associated with other diet, lifestyle, and genetic factors [38–41]. Regular aspirin/NSAID use reduces inflammation. High doses of aspirin and salicylates have been shown to inhibit nuclear factor kappa B (NF-κB) and its upstream activator the Iκ kinase β (*IKBKB*) that regulate immune cell differentiation and survival [42]. Salicylates may work via multiple pathways as they also have been shown to have a hypoglycemic effect [43–47] and high doses of salicylates have been shown to reverse hyperglycemia, hyperinsulinemia, and dyslipidemia by sensitizing insulin signaling [42]. Furthermore, in patients with type 2 diabetes, aspirin treatment has been shown to reduce fasting plasma glucose, total cholesterol, CRP, triglycerides, and insulin clearance; aspirin reduced hepatic glucose production and improved insulin-stimulated peripheral glucose uptake by 20% [48]. In our previous analyses we have shown that aspirin/NSAIDs modify the association between the Bsm1 *VDR* polymorphism and CRC risk [39]; data presented here suggest associations between *IL6* genotypes and CRC risk are modified by aspirin/NSAIDs.

Previous studies have examined *IL6* and colorectal cancer and adenomas. A study using hospital-based controls [20] evaluated the association between *IL6* and CRC and observed a 70% increased risk of colon cancer associated with the C allele of *IL6* (−174), although a study of CRC adenomas by the same group did not observe an association with *IL6*. [49]. Another study of 222 colorectal cancer cases in Greece reported a reduced risk of CRC associated with the CC genotype [19]. We observed a reduced risk of colon cancer for the C allele although a possibly increased risk of rectal cancer associated with the same allele. However, in our data, the greatest reduced risk for *IL6* was among those with the C allele of the rs1800796 polymorphism and the G allele of the rs1800795 (−174G > C) polymorphism, an expected finding, based on the literature cited above. Associations of *IL6* polymorphisms with risk of

colon cancer differed according to NSAID use. Given our observation of differences in association for colon and rectal cancer and the modifying effect of aspirin/NSAIDs on these associations, it is possible that some of the discrepancies in the literature could stem from the proportion of cases who were colon versus rectal cancer in other study population as well as the underlying characteristics of the populations being studied. It is also of interest that associations differed for colon and rectal cancer in our data. It is possible that these findings are chance or that there is a biological basis for the observed associations. Since the inflammation pathway is very complex and interacts with insulin and hormone-related pathways, it is possible that the differences observed are the result of other modifying factors within the inflammation-related pathway. At this time we can only speculate why these differences are observed.

Polymorphisms of the *VDR* gene also have been studied in conjunction with colorectal cancer and adenomas because *VDR* may play a key role in vitamin D signaling, cell proliferation, and differentiation [23–28,50]. The *VDR* appears to be an important link in CRC etiology, possibly because it plays a role in both insulin and inflammation-related pathways and is at a point of convergence of these two important pathways [51–53]. The *VDR* has been shown to be an important immune system regulator that decreases the production of several cytokines and increases the production of other cytokines such as IL-2 and IL-4 [54–56]. Vitamin D deficiency has been shown to increase the severity of inflammatory bowel disease, which carries a markedly excess risk of CRC [22,57]. Studies have shown that VDR signaling plays an essential role in the regulation of inflammation in the gastrointestinal tract [22]. Our data provide some additional support for *VDR's* role in inflammation as it relates to CRC.

We were limited in the markers for both *VDR* and *IL6*, although we selected markers that were not in linkage disequilibrium and those that were evaluated for cancer risk in other studies. However, other markers may have been associated differently. Likewise, we present data for only two genes in a very complicated pathway. Although these genes were selected because we believed, based upon existing literature that they were at important points of pathway convergence, other genes involved in inflammation may be more critical to the etiology of CRC. Clearly, to obtain a better understanding of the pathway as it relates to CRC, assessment of other genes is necessary. Since we did not have funds to collect blood samples at the onset of the colon study we had to go back and collect blood in some instances over a year after people were interviewed, even though people usually were interviewed within 6 months of diagnosis. This could potential lead to selection bias, however we have not observed an association between *IL6* and survival with colon cancer. Given the lack of association with survival, for these analyses, survival bias may not be operating.

Our findings provide further support for the importance of inflammation in the etiology of CRC. However, although the data are supportive of genetic involvement in an inflammation-related pathway, additional work is needed and that will encompass more genes in this pathway to obtain a better understanding of associations between inflammation and CRC development.

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Table 1

Description of study population

	Colon Cancer				Rectal cancer			
	Cases		Controls		Cases		Controls	
	n	%	n	%	n	%	n	%
Total	1583		1979		797		1011	
Age								
30–39	24	1.5	41	2.1	20	2.5	22	2.2
40–49	102	6.4	128	6.5	101	12.7	110	10.9
50–59	296	18.7	335	16.9	206	25.8	253	25.0
60–69	547	34.6	683	34.5	272	34.1	348	34.4
70–79	614	38.8	792	40.0	198	24.8	278	27.5
Race								
White, non-Hispanic	1446	91.3	1846	93.3	658	82.6	862	85.3
White, Hispanic	61	3.9	76	3.8	64	8.0	71	7.0
Black	73	4.6	55	2.8	33	4.1	44	4.4
Asian or Pacific Islander	0	0.0	0	0.0	40	5.0	31	3.1
Other or unknown	3	0.2	2	0.1	2	0.3	3	0.3
Study site								
KPMCP	760	48.0	804	40.6	512	64.2	624	61.7
Minnesota	572	36.1	796	40.2	0	0.0	0	0.0
Utah	251	15.9	379	19.2	285	35.8	387	38.3
Aspirin/NSAID use								
No Recent Aspirin/NSAID Use	1090	68.9	1161	58.7	511	64.1	560	55.4
Recent Aspirin/NSAID Use	493	31.1	818	41.3	286	35.9	451	44.6
rs1800796 (IL6 5′ promoter −634 (−572))								
GG	1387	87.8	1719	86.9	648	81.6	863	85.9
GC	187	11.8	247	12.5	124	15.6	119	11.8
CC	5	0.3	11	0.6	22	2.8	23	2.3
rs1800795 (IL6 5′ promoter −237 (−174))								
GG	631	40.1	728	36.9	321	41.3	411	41.3
GC	696	44.2	897	45.5	347	44.7	438	44.0
CC	246	15.6	347	17.6	109	14.0	146	14.7
VDR Bsm1								
bb	564	36.4	691	35.7	307	40.3	365	37.7
bB	748	48.2	910	47.1	343	45.0	462	47.7
BB	239	15.4	332	17.2	112	14.7	142	14.7
VDR Fok1								
FF	621	41.8	687	37.2	281	37.8	381	40.0
Ff	679	45.7	884	47.8	362	48.7	445	46.7
ff	186	12.5	277	15.0	101	13.6	126	13.2

Table 2

Association between rs1800795 and rs1800796 *IL6* polymorphisms and colon and rectal cancer

	Controls	Cases				Controls	Cases				Controls	Cases			
	n	n	OR[a]	95%	CI	n	n	OR	95%	CI	n	n	OR	95%	CI
Colon cancer						GG					GC/CC				
			rs1800796			1719	1387	1.00	Reference		258	192	0.90	0.74	1.11
rs1800795											Combined rs1800795 and rs1800796				
GG	728	631	1.00	Reference		577	525	1.00	Reference		151	105	0.76	0.57	1.00
GC	897	696	0.93	0.80	1.07	793	610	0.87	0.74	1.03	103	84	0.92	0.67	1.25
CC	347	246	0.85	0.70	1.03	345	244	0.81	0.66	0.99	1	1	1.12	0.07	18.02
Rectal cancer						GG					GC/CC				
			rs1800796			863	648	1.00	Reference		142	146	1.27	0.96	1.68
rs1800795											Combined rs1800795 and rs1800796				
GG	411	321	1.00	Reference		320	217	1.00	Reference		91	102	1.49	1.02	2.16
GC	438	347	1.08	0.87	1.33	386	306	1.18	0.93	1.49	48	40	1.21	0.77	1.92
CC	146	109	1.03	0.76	1.38	144	108	1.12	0.82	1.52	0	1			

[a] Adjusted for 5 year age category, sex, and race

Table 3

Association between aspirin/NSAID use and *IL6* and risk of colon and rectal cancer

	Aspirin/NSAID Use							
	No Current Aspirin/NSAID Use				Current Aspirin/NSAID Use			
	Controls	Cases			Controls	Cases		
	n	n	OR	(95% CI)	n	n	OR	(95% CI)
Colon Cancer								
rs1800796								
GG	1006	940	1.00		713	447	0.67	(0.58, 0.78)
GC/CC	154	147	1.00	(0.78, 1.28)	104	45	0.46	(0.32, 0.66)
p interaction	0.08							
rs1800795								
GG	442	417	1.00		286	214	0.80	(0.64, 1.00)
GC/CC	715	664	1.02	(0.86, 1.22)	529	278	0.58	(0.47, 0.71)
p interaction	0.02							
Rectal Cancer								
rs1800796								
GG	470	409	1.00		393	239	0.70	(0.57, 0.87)
GC/CC	84	99	1.26	(0.90, 1.78)	58	47	0.86	(0.56, 1.32)
p interaction	0.91							
rs1800795								
GG	230	195	1.00		181	126	0.84	(0.62, 1.14)
GC/CC	320	304	1.20	(0.93, 1.55)	264	152	0.73	(0.55, 0.97)
p interaction	0.04							

Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, sex, and race.

Table 4

Associations between *VDR* and *IL6* genotypes and colon and rectal cancer

	Bsm[a]								**Fok1**							
	bb				**bB/BB**				**FF**				**Ff/ff**			
	Controls	**Cases**			**Controls**	**Cases**			**Controls**	**Cases**			**Controls**	**Cases**		
	n	**n**	**OR**	**(95% CI)**	**n**	**n**	**OR**	**(95% CI)**	**n**	**n**	**OR**	**(95% CI)**	**n**	**n**	**OR**	**(95% CI)**
Colon cancer																
rs1800796 (IL6 5′ promoter −634(−572))																
GG	600	489	1.00		1077	869	1.00	(0.86, 1.16)	603	534	1.00		1005	766	0.88	(0.76, 1.02)
GC/CC	90	73	0.98	(0.70, 1.37)	164	116	0.86	(0.66, 1.12)	84	83	1.08	(0.78, 1.50)	154	99	0.73	(0.55, 0.96)
p interaction	0.55								0.22							
rs1800795 (IL6 5′ promoter −237(−174))																
GG	279	228	1.00		435	390	1.12	(0.90, 1.40)	259	258	1.00		424	338	0.83	(0.66, 1.04)
GC/CC	409	333	1.05	(0.83, 1.32)	804	591	0.94	(0.77, 1.16)	425	359	0.88	(0.71, 1.11)	734	523	0.75	(0.61, 0.93)
p interaction	0.14								0.86							
Rectal Cancer																
rs1800796 (IL6 5′ promoter −634(−572))																
GG	308	241	1.00		524	380	0.94	(0.75, 1.16)	327	225	1.00		488	378	1.13	(0.91, 1.40)
GC/CC	54	65	1.32	(0.83, 2.09)	78	74	1.18	(0.82, 1.69)	54	55	1.37	(0.89, 2.12)	78	84	1.41	(0.96, 2.06)
p interaction	0.87								0.73							
rs1800795 (IL6 5′ promoter −237(−174))																
GG	151	143	1.00		244	165	0.78	(0.57, 1.08)	162	116	1.00		232	187	1.13	(0.83, 1.54)
GC/CC	213	162	0.88	(0.63, 1.22)	358	283	0.93	(0.68, 1.25)	218	159	1.09	(0.79, 1.51)	338	275	1.21	(0.89, 1.62)
p interaction	0.15								0.92							

[a] Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, sex, and race.

Table 5

Association between *IL6 (rs1800796 and rs1800795)* and *VDR* and risk of colon and rectal cancer by current use of aspirin/NSAIDs

	Bsm1								Fok1							
	bb				bB/BB				FF				Ff/ff			
	Controls	Cases			Controls	Cases			Controls	Cases			Controls	Cases		
	n	n	OR	(95% CI)	n	n	OR	(95% CI)	n	n	OR	(95% CI)	n	n	OR	(95% CI)
Colon Cancer																
No Current Aspirin/NSAID Use																
rs1800796																
GG	336	328	1.00		643	596	0.97	(0.80, 1.17)	360	372	1.00		579	514	0.87	(0.72, 1.05)
GC/CC	56	54	0.97	(0.65, 1.46)	95	91	0.97	(0.70, 1.35)	54	61	1.06	(0.71, 1.57)	86	78	0.87	(0.62, 1.23)
p interaction	0.89								0.82							
rs1800795																
GG	170	141	1.00		262	269	1.27	(0.96, 1.69)	163	172	1.00		249	223	0.87	(0.66, 1.16)
GC	141	184	1.67	(1.21, 2.29)	359	304	1.10	(0.83, 1.45)	185	186	1.00	(0.74, 1.36)	291	276	0.96	(0.72, 1.26)
CC	78	56	0.93	(0.62, 1.41)	117	110	1.22	(0.86, 1.73)	64	74	1.17	(0.78, 1.75)	124	90	0.73	(0.52, 1.04)
p interaction	0.01								0.35							
Current Aspirin/NSAID Use (< 2 years)																
rs1800796																
GG	264	161	1.00		434	273	1.04	(0.81, 1.33)	243	162	1.00		426	252	0.91	(0.71, 1.18)
GC/CC	34	19	0.90	(0.49, 1.65)	69	25	0.60	(0.36, 0.98)	30	22	1.10	(0.61, 1.99)	68	21	0.47	(0.27, 0.80)
p interaction	0.25								0.05							
rs1800795																
GG	109	87	1.00		173	121	0.88	(0.61, 1.27)	96	86	1.00		175	115	0.75	(0.51, 1.09)
GC	146	71	0.62	(0.41, 0.92)	232	125	0.68	(0.47, 0.98)	134	75	0.63	(0.41, 0.95)	230	111	0.55	(0.38, 0.80)
CC	44	22	0.62	(0.34, 1.12)	96	52	0.68	(0.43, 1.06)	42	24	0.64	(0.35, 1.15)	89	46	0.58	(0.36, 0.93)
p interaction	0.36								0.49							
Rectal Cancer																
No Current Aspirin/NSAID Use																
rs1800796																
GG	164	155	1.00		290	240	0.89	(0.67, 1.18)	178	142	1.00		261	245	1.17	(0.88, 1.56)
GC/CC	31	44	1.21	(0.68, 2.16)	46	52	1.15	(0.73, 1.83)	33	40	1.38	(0.81, 2.34)	46	55	1.24	(0.75, 2.05)
p interaction	0.85								0.44							
rs1800795																
GG	85	83	1.00		137	105	0.92	(0.61, 1.40)	89	73	1.00		131	112	1.02	(0.68, 1.52)
GC	87	82	1.12	(0.71, 1.77)	147	136	1.14	(0.75, 1.74)	84	73	1.16	(0.74, 1.82)	142	143	1.32	(0.88, 1.96)
CC	26	34	1.63	(0.87, 3.02)	53	46	1.08	(0.64, 1.83)	38	31	1.10	(0.62, 1.96)	39	45	1.56	(0.91, 2.67)
p interaction	0.56								0.54							
Current Aspirin/NSAID Use (< 2 years)																
rs1800796																
GG	144	86	1.00		234	140	1.01	(0.71, 1.42)	149	83	1.00		227	133	1.06	(0.75, 1.49)
GC/CC	23	21	1.49	(0.68, 3.28)	32	22	1.08	(0.58, 2.00)	21	15	1.23	(0.56, 2.69)	32	29	1.56	(0.86, 2.83)
p interaction	0.5								0.69							
rs1800795																
GG	66	60	1.00		107	60	0.61	(0.37, 1.00)	73	43	1.00		101	75	1.28	(0.78, 2.09)
GC	73	40	0.59	(0.34, 1.02)	122	80	0.69	(0.43, 1.12)	73	46	1.09	(0.63, 1.88)	118	72	1.04	(0.63, 1.72)
CC	27	6	0.23	(0.09, 0.60)	36	21	0.63	(0.32, 1.23)	23	9	0.67	(0.28, 1.60)	39	15	0.66	(0.32, 1.37)
p interaction	0.01								0.38							

Odds ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, sex, and race