# Genetic Variability in *IκBKβ* and *NFκB1*, Interactions with NSAID Use and Risk of Colorectal Cancer in the Colon Cancer Family Registry

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## Abstract

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The NFκB-signaling pathway is involved in promoting inflammation, colorectal carcinogenesis and the reduction of colorectal cancer risk induced by non-steroidal anti-inflammatory drugs (NSAIDs). We hypothesize that genetic variation in two key genes in this pathway, *NFκB1* and *IκBKβ,* may be associated with the risk of colorectal cancer and interact with NSAID use. In a population-based case-unaffected sibling control study of 1,584 incident colorectal cancer cases and 2,516 sibling controls, we investigated the role of 42 *NFκB1* and 10 *IκBKβ* single nucleotide polymorphisms (SNPs). A combined tagSNP and candidate SNP approach was used to maximize screening of genetic variability. In *IκBKβ*, carriers of the variant alleles in rs5029748 (C>A intron 2) and rs10958713 (G>A intron 19) had a 27-38% decreased risk of colon cancer (*p-trend* = 0.013 and 0.005, respectively) and individuals homozygous for the variant allele of rs9694958 (A>G intron 5) had a 74% decreased risk of colorectal cancer (*p* = 0.048). No SNP in *NFκB1* was significantly associated with the risk of colorectal cancer. Significant associations between SNPs of both *NFκB1* and *IκBKβ* and CRC risk reported in a previous study were replicated here with similar trends. Two SNPs in *IκBKβ* and three SNPs in *NFκB1* showed statistically significant interactions (*p*<0.05) with NSAID use. Ultimately, the findings of this study suggest genetic variability in these genes are likely associated with risk of colorectal cancer, with variation in *IκBKβ* particularly associated with a decreased risk of colon cancer. These findings increase evidence that the NFκB-signaling pathway plays a role in colorectal carcinogenesis. Additionally, the significant interactions between NSAID use and polymorphisms in *NFκB1* and *IκBKβ* strengthen the evidence that NSAIDs function, at least partially, through an NFκB-dependent pathway.

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# INTRODUCTION

Colorectal cancer (CRC) is the third most common incident cancer and cause of cancer death in the United States, with an estimated 141,210 new cases and 49,380 deaths in 2011 [1]. Chronic inflammation is thought to be the leading cause of CRC [2,3]. Evidence that inflammation leads to CRC originates from individuals with chronic forms of inflammatory bowel disease, such as  ulcerative colitis (UC) and Crohn's disease, who are at a 2.75-fold increased risk of CRC compared to the general population [4]. The extent to which colon and rectal cancers are impacted by inflammation may vary. Studies have shown that UC in the colon leads to an increased risk of colon cancer, but UC in the rectum does not lead to an increased risk of rectal cancer [5]. The mechanisms by which inflammation contribute to CRC are still being identified; however, growing evidence suggests that one mechanism that connects inflammation and colorectal tumor development is the nuclear factor-kappa B (NFκB)-signaling pathway [6].

The NFκB signaling pathway regulates the expression of a myriad of target genes that promote cell proliferation and apoptosis, and regulate immune and inflammatory responses, all through activation of an ubiquitous transcription factor, NFκB [6]. The activation of NFκB is a key survival mechanism of premalignant cells because it can block apoptosis by regulating anti-apoptosis proteins [7] and inhibiting accumulation of reactive oxygen species [8]. Furthermore, the NFκB transcription factor induces expression of cytokines and chemokines, which help sustain an inflammatory state [6]. Constitutive activation of NFκB has been observed in 40% of CRC tissues and 67% of CRC cell lines [9].

NFκB, the main protein in the NFκB-signaling pathway, is a homo- or heterodimeric complex composed from a family of five homologous subunits: RelA, RelB, c-Rel, NFκB1 (or p50) and NFκB2 (or p52) [10]. The most commonly studied activation pathway of NFκB involves the RelA:p50 heterodimer [11]. RelA:p50 is normally bound to an inhibitory protein, IκBα, in the cytoplasm which blocks its DNA binding regions, rendering it inactive. In response to a wide array of stimuli, including pro-inflammatory cytokines and chemokines, the IκB kinase (IKK) complex phosphorylates IκBα, which results in IκBα's degradation and activation of NFκB. Once activated, NFκB translocates to the nucleus where it binds to the promoter region of its target genes (**Figure 1)** [6,10]. The IKK inhibitory protein is composed of two catalytic subunits, IKKα and IKKβ. IKKβ is required for activation of the common RelA:p50 dimer. The gene that encodes p50 is *NFκB1,* and the gene that encodes IKKβ is *IκBKβ.*

Previous studies have shown that genetic variability in *NFκB1* and *IκBKβ* is associated with CRC risk. In a case-control study of CRC by Curtin *et al.* (2010), several single nucleotide polymorphisms (SNPs) in *NFκB1* and *IκBKβ* and composite genotypes of *NFκB1* and *IκBKβ* were associated with risk [12]. More specifically, variant genotypes of both *NFκB1* and *IκBKβ* were associated with decreased risk of colon cancer and variant genotypes of *NFκB1* were associated with increased and decreased risk of rectal cancer. Additionally, in a nested case-control study among a Danish cohort, carriers of a -94 base pair deletion in the promoter region of *NFKB1* were at a significantly increased risk of CRC [13]. These studies further support the role of the NFκB-signaling pathway in colorectal carcinogenesis and warrant further exploration of their findings.

Several studies, including randomized trials, have shown that the regular use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with both decreased incidence and mortality of CRC [14–16]. Reduction in inflammation from NSAIDs has typically been attributed to inhibition of the prostaglandin synthesis pathway, but evidence also suggests that several NSAIDs, including aspirin, inhibit NFκB activation [17]. Aspirin has also been shown to be a competitive inhibitor of the IKKβ ATP-binding site, thereby impairing phosphorylation of IκBα and preventing NFκB activation [18]. Experimental studies have shown that NSAIDs induce CRC cell apoptosis both *in vitro* and *in vivo* through an NFκB-dependent mechanism [19–21]. While it is has not been previously studied, it is biologically plausible that variation in NFκB signaling pathway genes, including *NFκB1 and IκBKβ,* may modify the inverse association of

NSAID use and CRC risk if these drugs function, at least partially, through an NFκB-dependent mechanism.

The purpose of this study is to further explore the association between genetic variability in *NFκB1 and IκBKβ* and the risk of CRC and to investigate the interaction between genetic variability in *NFκB1 and IκBKβ* and NSAID use using a case-unaffected sibling control study population from the Cooperative Family Registry for Colon Cancer Studies (Colon CFR). We examined associations with CRC risk combined, but also examined these associations stratified by cancer site.

# METHODS

## *Study Population and Questionnaire Data*

Colorectal cancer (CRC) cases and their unaffected siblings were recruited through the Colon Cancer Family Registry (Colon CFR) from six registry centers: University of Hawaii, Hawaii, USA, Fred Hutchinson Cancer Research Center, Seattle, USA, Mayo Clinic, MN, USA, University of Southern California Consortium (Dartmouth Medical School, University of Southern California, University of Colorado, University of Arizona, Cleveland Clinic Foundation, University of North Carolina and University of Minnesota), Cancer Care Ontario, Ontario, Canada and the University of Melbourne, Victoria, Australia. The Colon CFR defined cases as probands and affected relatives diagnosed with primary invasive CRC from 1998-2002 that were interviewed within 5 years of diagnosis (73% of cases were interviewed within 2 years of diagnosis). Controls were siblings without a CRC diagnosis at the time of ascertainment. The study was described previously [22]. Although eligibility requirements varied slightly between registry centers, inclusion criteria were typically ages 20-74, no known genetic susceptibility to CRC and no personal history of ulcerative colitis, Crohn’s disease, diverticulitis or irritable bowel syndrome.

Standard questionnaires were used to collect epidemiologic data from CFR study participants on demographic characteristics, medical history, NSAID use, family history of cancer, smoking history, selected diet, physical activity, height and weight. Cigarette smoking exposure was calculated in pack-years and regular NSAID use was defined as two pills per week for at least one month. Current NSAID use was defined as regular use in the two years prior to study enrollment, while former NSAID use was defined as regular use at any time prior to the two years before study enrollment. In this study population, current NSAID use was more strongly inversely associated with CRC risk than other aspects of NSAID use. Physical activity was defined as the average weekly total MET (metabolic equivalent of task) hours divided into four categories: inactive (0-6), less active (6.1-20), active (20.1-44) and very active (>44). Blood samples and tissue biopsies were collected according to standardized procedures. Individuals were excluded from this study if they did not have samples available for genotyping, did not have epidemiologic data or had missing genotypes at all SNPs. Additionally, each kinship had to have at least one case and one unaffected sibling control and each individual's sex determined by genotyping had to match reported sex.

Only Caucasian study participants ascertained through population-based recruiting were included in this case-unaffected sibling control study (sample sizes among other racial/ethnic groups and clinic-based populations were too small to assess associations). All sibling kinships had at least one case and one control; therefore some cases had multiple unaffected sibling controls and some cases share unaffected sibling controls. There are 1,584 cases and 2,516 controls amongst 1,534 sibling kinships after exclusion criteria were applied.

In those analyses stratified by cancer site, colon cancer was defined as tumors located in the cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon or sigmoid colon. Rectal cancer was defined as tumors located in the rectosigmoid junction or rectum. For colon cancer analyses, there are 959 cases and 1,535 controls among 943 sibling kinships. For rectal cancer analyses, there are 505 cases and 839 controls among 504 sibling kinships.

Informed consent was obtained from all participants. The Institutional Review Board at each Colon CFR site approved the methods for study population collection. In addition, the Fred Hutchinson Cancer Research Center Institutional Review Board approved this study.

### ***SNP Selection***

Selection of tagSNPs and SNP genotyping methods for the parent study have been published previously [23]. Briefly, TagSNPs for *NFκB1* (n=40) and *IκBKβ* (n=8) were selected using Haploview Tagger [24] and the following criteria: minor allele frequency (MAF) >5%, pairwise $r^2$ of >0.95, and distance from closest SNP of >60 base pairs (bp). The 5' and 3' untranslated regions (UTR) for each gene were extended to include the most up- or downstream SNP within the linkage disequilibrium (LD) block (~10 kb upstream and 5kb downstream). In regions of no or low LD, SNPs with a MAF >5% at a density of ~ 1 per kb were selected from either HapMap [24] or dbSNP [25]. Two non-synonymous candidate SNPs from *NFκB1* and two non-synonymous candidate SNPs from *IκBKβ* were included in the study (**Table 1**).

### *Genotyping and Quality Control*

DNA was extracted from peripheral blood leukocytes and genotyping was performed at Translational Genomics Institute (TGen, Phoenix, AZ). SNPs were genotyped on the Illumina 1536 GoldenGate platform [26]. Quality control checks based on Illumina metrics, as described previously [27], were implemented. Additional genotyping on 3 SNPs (rs4648099, rs6813322, rs6474387) that were not successfully genotyped on the Illumina platform was done using Sequenom's iPLEX Gold (Sequenom, Inc). For quality control, 5% of the total number of samples was re-genotyped to assess the reliability of the genotype identification protocols. Concordance among duplicates was greater than 99.8% for all genotypes. For additional quality control, genotypes were excluded if Hardy-Weinberg equilibrium amongst controls $p<0.0001$ or call rates <85%. Ultimately, the 2 non-synonymous candidate SNPs from *IκBKβ*, rs2272763 and rs17875749, were excluded from analysis because they were monomorphic. According to the newest update of the Genome Variation Server [28], rs2272763 was expected to be monomorphic, while rs17875749 was expected to have a minor allele frequency (MAF) of 2%. From *NFκB1* 8 SNPs were excluded: 2 SNPs failed due to Hardy-Weinberg equilibrium (one being a candidate SNP, rs4648099) (**Table 1**), and 6 SNPs were in linkage disequilibrium $r^2 > 0.90$ with another SNP in the gene (**Figure 2**).

### *Statistical Analysis*

#### Single SNP Main Effects

Conditional logistic regression using sibling kinship as the matching variable was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between genotypes in *NFκB1* or *IκBKβ* and the risk of CRC, colon cancer or rectal cancer. All models were adjusted for age and sex. For each SNP, the risk of cancer among individuals with the homozygous wild-type genotype was compared separately to the risk of cancer among individuals with the heterozygous or homozygous variant genotypes (co-dominant model). If the number of cases with the homozygous variant genotype was less than 5, the dominant model was analyzed (combined heterozygous and homozygous variant genotypes). A global p-value (two degrees of freedom in the co-dominant model), which was determined using the likelihood ratio statistic, tested for significantly different risks among carriers of the variant allele compared to homozygous carriers of the wild-type allele. Additionally, a trend test was performed using the log-additive model (homozygous wild-type, heterozygous and homozygous variant genotypes coded as 0, 1 and 2, respectively) to determine if there is a dose-dependent effect from the variant allele. All tests of statistical significance used a two-sided p-value and $\alpha=0.05$. Analyses were carried out using SAS v.9.3 (SAS Institute Inc., Cary, NC).

NSAIDs Interaction

Conditional logistic regression was used to both estimates the OR and 95% CI for the association between current NSAID use and the risk of CRC, colon cancer or rectal cancer and to investigate the interaction between SNPs and NSAID use in the CRC, colon cancer or rectal cancer analyses. In the interaction analyses, OR estimates and 95% CIs were obtained for each combination of genotype (homozygous wild-type, heterozygous or homozygous variant) and NSAID use status (current or former/never) for each SNP. The reference group was comprised of individuals with the homozygous wild-type genotype who were never/former users of NSAIDs. If the number of cases with the homozygous variant genotype in either NSAID use stratum was less than 5, the dominant model was analyzed. The likelihood ratio test compared models with and without the NSAID multiplicative interaction term(s) to determine if the interaction between genotypes and NSAID use was statistically significant (p-interaction). Because use of NSAIDs may be associated with other known risk factors for CRC, NSAID-interaction analyses were adjusted for smoking, BMI and physical activity in addition to age and sex.

### SNP-SNP Interaction

Conditional logistic regression models investigating the association between SNPs of *NFκB1 and IκBKβ* and risk of CRC were examined. Each SNP identified as significantly associated with CRC, colon cancer or rectal cancer (global-$p<0.05$) was combined with the other SNPs in this study to create composite genotypes. The log-likelihood ratio test comparing models with and without the multiplicative term between SNPs was used to identify statistically significant interactions between SNPs. In order to avoid rare cell counts, only the dominant model and composite genotypes that represented at least 5% of the population were examined.

### Principal Component Analyses

The association between each gene and CRC, colon cancer or rectal cancer was examined through principal component analysis (PCA) [29]. PCA reduces highly correlated SNP data by creating non-correlated principal components. Principal components that accounted for at least 80% of the variance in each gene were used in conditional logistic regression matched on sibling kinship and adjusted for age and sex to investigate the association between the principal components and CRC risk. Gene-level significance was determined using a likelihood-ratio test, comparing a model that contained the principal components to one that did not.

### Multiple Testing Corrections

As shown by the linkage disequilibrium $r^2$ values between SNPs (**Figures 2 and 3**), the statistical tests for association studies between SNPs of a particular gene and the risk of disease are correlated. Multiple testing corrections such as the Bonferroni procedure are valid in the case of independent tests, but often too conservative for correlated tests. Therefore, the method developed by Conneely and Boehnke [30], which results in less conservative adjusted p-values for correlated tests, is more appropriate in these types of association studies. P-values adjusted for correlated tests are referred to as $P_{act}$. A $P_{act}$ less than 0.05 was considered significant. All p-value adjustments were conducted in R (version 2.14.1). The Conneely and Boehnke method is only valid for main effects analyses and therefore was not applied to interaction analyses.

Given the exploratory nature of candidate/tag SNP association studies and the high number of tests performed, the more conservative family-wise error rate (FWER) methods of multiple testing corrections often prevent the detection of true associations. The false discovery rate (FDR) control method developed by Benjamini and Hochberg [31–33] attempts to alleviate this issue by identifying noteworthy SNPs and indicating a percentage of these noteworthy SNPs that are in fact false and as follows, a percentage that are in fact true. For example, all SNPs that are identified as noteworthy by FDR at the 25% level have a 3 in 4 chance of actually being a true positive. In this study, the 25% and 50% FDR levels were tested on the global-p values from the main effect analyses and on the p-interaction from the NSAID interaction analyses.

### *Replication of Previous Findings*

Results from this study were compared to *NFκB1* and *IκBKβ* genotypes previously identified as associated with colon or rectal cancer by Curtin *et al.* [12]. This study used two case-control studies, one for colon cancer and another for rectal cancer, which used identical methods to recruit and interview study participants [34–36]. Cases in the two studies were individuals with either primary colon cancer or a primary tumor in the rectosigmoid junction or rectum. Population-based controls were frequency-matched on sex and 5-year age cohort. Ultimately, the colon cancer study population had 1556 cases and 1956 controls and the rectal cancer population had 754 cases and 959 controls. Curtin *et al.* examined associations for both individual SNPs and combined genotypes adjusted for age, sex, center and race. They ran analyses using the additive, dominant and recessive models. Only models identified as significant in this previous study were analyzed in the present study for comparison. Only ORs and 95% CIs are presented, as these were the only values presented in this previous study.

### ***Identifying Potential Functional Importance of Significant tagSNPs***

For those SNPs identified as significant in either the main effect or NSAIDs interaction analyses and those SNPs that replicated previous findings from the Curtin *et al.* study, any possible functionality of the polymorphisms was investigated. Ultimately, the goal of this procedure was to identify whether the SNP of interest or a SNP that is in high LD with the SNP of interest potentially impacts the gene's ability to function. Examples include non-synonymous SNPs, frame shift mutations, promoter or enhancer region polymorphisms, variable number repeat regions associated with disease or polymorphisms in highly conserved regions. Two databases, dbSNP [25] and Genetic Variation Server [28], were used to identify SNPs that were in high LD with the SNP of interest.

# RESULTS

## *Population Characteristics*

Characteristics of the study population are presented in **Table 2**. Cases and their unaffected sibling controls had similar age distributions, but the cases were more likely to be male. There were no obvious differences by regular NSAID use, cigarette smoking as measured by pack-years, physical activity and BMI. The distribution of proximal (cecum, ascending colon, hepatic flexure, transverse colon and splenic flexure), distal (descending and sigmoid colon), and rectal (recto-sigmoid junction and the rectum) tumors was similar among the cases.

## *Single SNP Main Effects*

Among the tagSNPs in *IκBKβ,* one SNP was significantly associated with CRC and two SNPs were significantly associated with colon cancer independently (global-p<0.05) (**Table 3**). The homozygous variant genotype of rs9694958 (A>G intron 5) was associated with a >70% decrease in CRC risk compared to the homozygous wild-type genotype (OR 0.26, 95% CI 0.07-0.99, global-p=0.048). There was no dose-dependent effect from the variant allele (p-trend=0.48). After correcting for multiple correlated tests, the association did not remain statistically significant ($P_{act}$=0.25). Given the low MAF of rs9694958 (7.8%), the number of homozygous variant cases was less than 5 when the analysis was stratified by colon and rectal cancer, and therefore these associations were analyzed using the dominant model. The tumor-site stratified associations were not statistically significant under the dominant model. At the 50% FDR level, rs9694958 and three other SNPs (rs2272733, rs5029748 and rs10217111) were identified as noteworthy in their association with CRC. Therefore, it is likely that two of these SNPs are true positives.

After stratifying by colon and rectal cancer, two SNPs in *IκBKβ* were significantly associated with colon cancer prior to correction for multiple correlated tests (global-p<0.05) (**Table 3**). Both individuals with the homozygous variant and heterozygous genotypes of rs5029748 (C>A intron 2) were associated with an approximate 28% decrease risk in colon cancer compared to individuals with the homozygous wild-type genotype, but the association was only significant for those with heterozygous genotype (het: OR 0.72, 95% CI 0.56-0.91; hom variant: OR 0.72, 95% CI 0.44-1.18, global-p=0.02). The variant allele showed a statistically significant dose-dependent effect (p-trend=0.01). However, after multiple correlated test correction, neither the global-p nor the p-trend remained significant ($P_{act}$=0.11 and 0.08, respectively). Another SNP, rs10958713 (A>C intron 19), was also significantly associated with colon cancer. Carriers of the variant allele had a significantly decreased risk compared to the individuals homozygous for the wild-type allele (hom variant: OR 0.73, 95% CI 0.57-0.92; het: OR 0.62, 95% CI 0.42-0.92, global-p=0.02) and the variant allele showed a statistically significant dose dependent effect (p-trend=0.01). After corrections for multiple correlated tests, the p-trend remained significant ($P_{act}$=0.03), but the global-p did not ($P_{act}$=0.09). These SNPs, rs5029748 and rs10958713, showed no association with rectal cancer (global-p=0.86 and 0.47, respectively). Both rs5029748 and rs10958713 were noteworthy at the 25% FDR level; thereby the chance that these SNPs are false positives is approximately 25%. At the 50% FDR level, the two SNPs described above, rs5029748 and rs10958713, and two other SNPs, rs3747811 and rs10217111, were identified as noteworthy.

No tagSNP in *IκBKβ* was significant when the analysis was restricted to rectal cancer. Only significant findings are presented in **Table 3**; the complete analysis of the associations between SNPs in *IκBKβ* and colorectal, colon and rectal cancer are presented in **Appendix A Tables A.1, A.2 and A.3.**

No SNP in *NFκB1* was significantly associated with CRC, colon cancer or rectal cancer (global-p<0.05) and no SNP was noteworthy at the 25% or 50% FDR level (**Appendix A Tables A.4, A.5 and A.6**). However, rs10489113 (A>G 3' outside UTR) did have a significant p-trend in association with colon cancer before correction for multiple correlated tests (p-trend=0.04, $P_{act}$=0.48) (**Table 4**). The homozygous variant genotype was significantly associated with a 50% decreased risk of colon cancer compared to the homozygous wild-type genotype (OR 0.53, 95%

CI 0.29-0.97). In contrast, the homozygous variant genotype in the same SNP was significantly associated with a two-fold increased risk of rectal cancer compared to the homozygous wild-type genotype (OR 2.13, 95% CI 1.02-4.46). The single candidate SNP in *NFκB1,* M507V (rs4648072), showed a slightly decreased, but non-significant, risk of CRC among individuals with the heterozygous genotype (there were no individuals with the homozygous variant genotype, MAF=1%).

### ***SNP-SNP Interactions***

Three SNPs were identified as having a significant association with CRC or colon cancer, rs9694958, rs5029748 and rs10958713, and therefore were examined for interactions among SNPs. The association between CRC and rs9694958 was only seen in the homozygous variant genotype. Given the small number of individuals with the homozygous variant genotype (<5% of the population), it was not possible to perform the SNP-SNP interaction analysis on this SNP. When rs5029748 and rs10958713 were combined with the other SNPs in *IκBKβ* and *NFκB1*, no 2-loci composite genotype resulted in a significant interaction between SNPs (p-interaction<0.05) (**Appendix A Tables A.7 and A.8**).

### ***NSAIDs Interactions***

Current NSAID use was associated with a non-significant decrease risk of colorectal cancer in the study population (OR 0.87, *p*=0.13) (**Table 5**). There was no substantial difference in the risk estimate when the analysis was stratified by tumor site (colon cancer: OR 0.85, *p*=0.17; rectal cancer: OR 0.80, *p*=0.22).

Two SNPs in *IκBKβ,* rs6474387 (C>T intron 20) and rs11986055 (A>C intron 2), showed a significant interaction with NSAID use on the risk of CRC (p-interaction<0.05) (**Table 6**). Only current NSAID-users who carried the variant allele in rs6474387 (heterozygous or homozygous variant genotypes) had a significant decreased risk of CRC compared to never/former NSAIDs users homozygous for the wild-type allele (OR 0.57, 95% CI 0.32-1.00). This reduction was not observed in the remaining NSAID use and genotype groups (never/former use, variant: OR

1.09, 95% CI 0.79-1.50; current use, wild-type: OR 0.92, 95% CI 0.76-1.11, p-interaction=0.04). The interaction between rs11986055 and NSAID use was very similar to the interaction between rs6474387 and NSAID use (LD $r^2$ between rs6474387 and rs11986055 was 0.50). Only current NSAID users that carried the variant allele in rs11986055 had a significant association with CRC (OR 0.48, 95% CI 0.23-0.98, p-interaction=0.03). FDR analysis identified the interactions with both rs6474387 and rs11986055 as noteworthy at the 25% level; thereby the chance that these interactions are true positives is approximately 75%.

When colon and rectal cancer were investigated separately, the interaction between rs647387 and NSAID use only remained significant in the colon cancer analysis (p-interaction=0.02). The interaction between rs119860155 and NSAID use was not significant in the stratified analyses. Interactions with rs647387 and rs11986055 were identified as noteworthy at the 25% FDR level in the colon cancer analysis, but were not noteworthy in the rectal cancer analysis. Interactions with three additional SNPs were identified as noteworthy at the 50% FDR level in the colon cancer analysis, rs2272733, rs9694958 and rs10958713. The full analysis of *IκBKβ* SNPs and NSAIDs interactions are presented in **Appendix A Tables A.9, A.10 and A.11.**

Two SNPs in *NFκB1*, rs230506 (A>G intron 5) and rs230490 (G>A 5' outside UTR), showed a significant interaction with NSAID use on the risk of CRC (p-interaction<0.05) (**Table 7**). While current NSAID users homozygous for the wild-type allele of rs230506 showed a significantly decreased risk of CRC compared to never/former users of the same genotype (OR 0.81, 95% CI 0.67-0.98), carriers of a variant allele showed no association with CRC among current NSAID users and a slightly decreased risk among never/former NSAID users (current users: OR 1.04, 95% CI 0.66-1.65; never/former users: OR 0.78, 95% CI 0.58-1.04, p-interaction=0.05). For rs230490, current NSAID users homozygous for the wild-type allele were significantly associated with a decreased risk of CRC (OR 0.62, 95% CI 0.46-0.85, p-interaction=0.02). There was no evidence of an association with CRC for individuals with the heterozygous or homozygous variant genotype among current NSAID users or never/former NSAID users. Interactions with rs230506 and rs230490 were not noteworthy at the 25% or 50% FDR level.

There were no significant interactions between *NFκB1* SNPs and NSAID use when the analysis was restricted to colon cancer. When restricted to rectal cancer, the interaction between rs230490 and NSAID use remained significant (p-interaction=0.02). There was also a significant interaction between rs230488 (G>A 5' outside UTR) and NSAID use in the rectal cancer analysis (p-interaction=0.04). While no individual OR was significant, current users of NSAIDs that were carriers of the variant allele trended towards a decreased risk of rectal cancer (OR 0.79, 95% CI 0.45-1.37), and current NSAIDs users that were homozygous for the wild-type allele trended toward an increased risk of rectal cancer (OR 1.14, 95% 0.75-1.74). Conversely, never/former users who were carriers of the variant allele trended toward an increased risk compared to individuals homozygous for the wild-type allele (OR 1.35, 95% CI 0.95-1.92). No *NFκB1* SNP was identified as noteworthy by FDR in the NSAID interaction analyses stratified by colon and rectal cancer. The complete *NFκB1* SNP and NSAIDs interactions are presented in **Appendix A Tables A.12, A.13 and A.14.**

### ***Principal Component Analysis***

No statistically significant associations using principal component analysis were observed between CRC, colon cancer or rectal cancer and *IκBKβ* or *NFκB1* (**Table 8**). The most significant association (p =0.11) was between the principal components that accounted for at least 80% of the variance in *IκBKβ* and colon cancer. In comparison, there was no evidence of an association between the principal components of *IκBKβ* and rectal cancer (p=0.93).

### ***Replication of Previous Findings***

**Tables 9 and 10** compare the findings of this study to a previous study of the association between genetic variability in *IκBKβ* and *NFκB1* and the risk of colon and rectal cancer by Curtin *et al.* [12]. Curtin *et al.* identified genotypes of one SNP in *IκBKβ* and two SNPs in *NFκB1* that were significantly inversely associated with colon cancer (**Table 9**). The comparable ORs from this study for the *IκBKβ* SNP (rs2272733) and one of the *NFκB1* SNPs (rs13117745) trended towards a similar inverse association. Individuals with the homozygous variant genotype of the other SNP in *NFκB1* (rs4648110) were associated with nearly identical risk estimates as seen in Curtin *et al.* study under both the additive and recessive models of inheritance (Curtin *et al.*: additive OR 0.65, 95% CI 0.44-0.94 vs. present study: additive OR 0.68, 95% CI 0.45-1.04; Curtin *et al.*: recessive OR 0.66, 95% CI 0.45-0.96 vs. present study: recessive OR 0.65, 95% CI 0.37-1.13).

Curtin *et al.* identified four SNPs in *NFκB1* that were associated with rectal cancer (**Table 9**). The homozygous variant genotype of rs13117745 trended towards an increased risk of rectal cancer in both studies under the additive model (Curtin *et al.*: additive OR 1.69, 95% CI 0.93-3.07 vs. present study: additive OR 1.22, 95% CI 0.65-2.26). Two of the remaining three SNPs were not genotyped in this study, but SNPs in high linkage disequilibrium (LD $r^2$>0.96) with those SNPs were identified and used as proxies; neither association replicated. The last SNP identified by Curtin *et al.* as associated with rectal cancer, rs230510, was inversely association with risk in one study and positively associated with risk in the other. However, given that the MAF of rs230510 is around 50% and it is unknown if the studies genotyped the same or complementary DNA strands, it is possible the two studies are comparing opposite associations.

Individuals who carried variants in both *IκBKβ* and *NFκB1* were identified by Curtin *et al.* as having associations with either colon or rectal cancer risk (**Table 10**). Using the same models of inheritance, these composite genotypes resulted in similar risk estimates in the present study. More specifically, the variant composite genotype of rs3747811 of *IκBKβ* and rs4648110 of *NFκB1* under the dominant and recessive models, respectively, was associated with a nearly identical decreased risk of colon cancer in the two studies (Curtin *et al.*: OR 0.54, 95% CI 0.34-0.87 vs. present study: additive OR 0.56, 95% CI 0.28-1.12). In the second composite genotype, between rs3747811 of *IκBKβ* and rs11722146 or rs12509517 (LD $r^2$=1.00) of *NFκB1,* carriers of variant alleles in both SNPs trended towards an increased risk of rectal cancer in both studies (Curtin *et al.*: OR 1.11, 95% CI 0.83-1.50 vs. present study: additive OR 1.02, 95% CI 0.63-1.65).

# DISCUSSION

The proteins encoded by *IκBKβ* and *NFκB1* are key components in the NFκB-signaling pathway, which is known to promote and sustain an inflammatory state and therefore thought to contribute to colorectal carcinogenesis [2,37]. NSAIDs, which may function partially by inhibiting NFκB activation [18], are used to reduce inflammation and are associated with a decreased risk in CRC [16,38].This study aimed to examine common genetic variants in *IκBKβ* and *NFκB1* to identify polymorphisms associated with CRC risk and interactions with NSAID use using the Cooperative Family Registry for Colon Cancer Studies (Colon CFR). While previous studies have examined the association between variation in these genes and CRC risk, this is the first study to comprehensively examine interactions with NSAID use. Given the overlapping but different etiologies of inflammation in colon and rectal cancer carcinogenesis [5,39,40], this study examined associations for both CRC combined and colon and rectal cancer individually.

Evidence from this study and a previous study of genetic variability in *IκBKβ* suggest that variation in this gene is associated with a decreased risk of CRC, particularly the risk of colon cancer [12]. Our data suggest that before correction for multiple correlated tests three of eight *IκBKβ* tagSNPs were independently associated with a decreased risk: two with colon cancer independently and one with CRC combined. The previous study of *IκBKβ* and risk of colorectal cancer by Curtin *et al.* identified one SNP in *IκBKβ* as associated with decreased colon cancer risk, but no *IκBKβ* SNP associated with rectal cancer risk [12]. Principal component analysis in this study identified *IκBKβ* as marginally associated with colon cancer risk at the gene level (p=0.11), but not rectal cancer risk (p=0.93). Given that this gene encodes IKKβ, a protein that activates NFκB [6,10], it is possible that variation in this gene negatively affects the function of IKKβ, thereby preventing NFκB activation and the resulting inflammation. Reduced levels of inflammation are known to reduce risk of CRC [2,3] and reduction of inflammation through this mechanism may have a stronger impact on colon cancer than rectal cancer.

The two *IκBKβ* SNPs associated with colon cancer independently, rs5029748 (C>A intron 2) and rs10958713 (G>A intron 19), were noteworthy at the 25% FDR level and the variant alleles showed significant dose-dependent effects. There was no evidence of decreased rectal cancer risk for these SNPs. These inverse association with colon cancer risk have been identified previously [12,41]. In a case-control study of metachronous colorectal neoplasia risk, rs1095713 was independently associated with a decreased risk of any metachronous colorectal adenoma (recessive OR 0.64, 95% CI 0.46-0.87, p=0.005) [41]. While not significant on its own, carriers of the variant allele of rs5029748 that also carried polymorphisms in *NFκB1* (rs4648110) and *IL6* (rs1800797) had a significantly decreased risk of colon cancer (OR 0.20, 95% CI 0.06-0.67) [12]. Rs5029748 and rs10958713 are in moderately high LD ($r^2$=0.63) with one another. Given that these risk-associated SNPs are not part of coding regions, but have been identified in multiple studies as modifying the risk of colon cancer, they should be considered for future studies to determine if they are tagging one or more causal variants, part of an un-annotated transcript, or part of a regulatory element [42].

The *IκBKβ* variant, rs9694958 (A>G intron 5, MAF=7%), was significantly associated with an approximately 70% decreased risk of CRC and was noteworthy at the 50% FDR level. The decreased risk was nearly consistent when the analysis was stratified by cancer site, thereby implying the functional change that results from, or is tagged by, this variation is affecting the etiology of both cancer types to the same extent. While this non-coding SNP is not in high LD with a previously identified functional SNP of *IκBKβ*, it is in moderately high LD ($r^2$=0.64) with another intronic SNP, rs3136717, from a nearby DNA polymerase gene important to base excision repair (BER). BER corrects DNA damage that results from oxidative stress and low folate and has been linked to CRC risk [43,44]. In a study examining the association between genetic variation in BER genes and advanced colorectal adenoma, individuals homozygous for the variant allele of rs3136717 had a non-significant decreased risk of advanced colorectal adenoma (OR 0.52, 95% CI 0.23-1.14) [45]. While individuals with the homozygous variant genotype for either of these SNPs may have decreased risk of CRC, the lack of identified functionality of either SNP makes it difficult to determine if the risk modification is a result of the NFκB-signaling pathway or BER.

Unlike the study by Curtin *et al.* [12], there were no SNPs in *NFκB1* significantly associated with the risk of CRC in this study. In the previous study, individual SNPs of *NFκB1* were mainly associated with the risk of rectal cancer and the only SNP that modified both colon and rectal cancer risk, modified the risks in opposing directions [12]. The present study was likely unable to identify genetic variants of *NFκB1* that significantly altered CRC risk because we had a smaller rectal cancer population compared to colon cancer population and family-based study designs have decreased power to identify main effects [46]. Additionally, if variation in *NFκB1* modifies the risk of colon and rectal cancer in opposite direction, the larger CRC combined population would not increase the power to identify such associations.

One *NFκB1* SNP, rs10489113 (A>G 3' outside UTR), had borderline significant associations with both colon and rectal cancer independently (global p-values=0.07 and 0.06, respectively). The homozygous variant genotype was associated with an approximately 50% decreased risk of colon cancer and 50% increased risk of rectal cancer. The polymorphism has no previously identified functionality. It is in high or moderately high LD with two other intronic SNPs, rs4648110 ($r^2$=0.80) and rs13117745 ($r^2$=0.57). Both of these SNPs showed similar opposing trends for colon and rectal cancer risk among individuals homozygous for the variant allele. In agreement with our findings, Curtin *et al.* found that the individuals with the homozygous variant genotype of rs13117745 had significant and opposing associations with colon and rectal cancer risk and individuals with the homozygous variant genotype of rs4648110 had a significant decreased risk of colon cancer [12]. These are not the first SNPs to be identified as having opposing associations with colon and rectal cancer [47–49] and these findings support the increasing evidence that colon and rectal cancer have distinct etiologies [39,40]. In particular, it suggests that the extent to which NFκB and the inflammation that results from its activation impacts colon and rectal cancer carcinogenesis may differ.

Several SNPs of *IκBKβ* and *NFκB1* were identified as significantly associated with either colon or rectal cancer by Curtin *et al.* [12] and most of these trends were replicated by this study. Already mentioned above were the replicated trends for rs4648110 and rs13117745 of *NFκB1*. Curtin *et al.* found that carriers of the variant allele of rs2272733 (G>A intron 5) in *IκBKβ* were at a significantly decreased risk of colon cancer. In the present study this trend was only seen among individuals homozygous for the variant allele. Given the significant amount of heterogeneity between candidate gene studies, replication is essential for validation and to reduce the risk of spurious results. The findings from this study and previous studies, particularly replicated findings, are contributing to the body of evidence that suggests that variation in these genes is associated with CRC risk. The SNPs identified here should be considered in future candidate SNP and genome-wide association studies in order to further verify their association with disease risk.

Investigating the interaction between multi-locus or “composite” genotypes in association studies where several models of inheritance are tested for each SNP results in multiple parallel analyses and hence an increased opportunity for false positive findings. In order to reduce the number of parallel analyses in this study, composite genotypes of *IκBKβ* and *NFκB1* were examined using only the dominant model of inheritance (to maintain large cell counts and power) and only for composite genotypes that contain at least one SNP that was associated with CRC risk independently. An interaction test was employed to determine if the composite genotypes significantly modified risk compared to the risk that resulted from the SNPs individually. In contrast, Curtin *et al.* used hapConstructor software (Genie, University of Utah) to perform exhaustive construction and testing of multi-locus data [12]. This allowed them to test all combinations of inheritance models with a large number of composite genotypes efficiently. To test for significance, they use successively more stringent empirical *P*-value thresholds as the number of loci in the composite genotypes increased (0.05, 0.01 and 0.001 for single, two, and three-locus sets, respectively). While no significant SNP interactions of *IκBKβ* and *NFκB1* were identified in the present study, Curtin *et al.* identified two 2-loci genotypes of *IκBKβ* and *NFκB1* with *P*-values below 0.01. Both of these composite genotypes included a SNP that was examined under the recessive model of inheritance and therefore would not have been identified in the present study design. For these two composite genotypes, we ran an identical analysis to that of Curtin *et al.* and found replicated results for one of the composite genotypes, thereby supporting the evidence that interactions between these genes may impact colorectal carcinogenesis.

Most studies point to the inhibition of the cyclooxygenases (COX-1 and COX-2) in the prostaglandin synthesis pathway as the main mechanism by which NSAIDs reduce inflammation and therefore reduce the risk of CRC [50]. However, current research also points to inhibition of the NFκB-signaling pathway, which could reduce inflammation and promote CRC cell apoptosis by inhibiting expression of anti-apoptosis proteins [19–21], as a mechanism through which NSAIDs could reduce CRC risk. In this study population, current NSAID use was associated with a non-significant decreased risk of colorectal cancer. Given that family-based studies have weakened power to identify main associations, this lack of significance is not surprising [46]. However, family-based studies do have increased power to identify gene-environment interactions and therefore, this study design is appropriate for investigating whether NSAID use modifies the association between common genetic variants in *IκBKβ* and *NFκB1* and colorectal cancer risk [51].

The significant interactions between genetic variation in *IκBKβ* and *NFκB1* and NSAID use identified here are further evidence that there is a link between NSAIDs and the NFκB-signaling pathway in modification of CRC risk. Studies indicate that some NSAIDs, including aspirin, directly impact the function of IKK (the enzyme encoded by *IκBKβ*) by competitively inhibiting the enzyme's ATP-binding site [18]. Therefore, it is possible that variation in this gene could impact the binding potential of NSAIDs to IKKβ, explaining the interaction between variation in *IκBKβ* and NSAID use. Other studies have found that NSAIDs may work at multiple steps in the NFκB-signaling pathway [17], not just through IKK. The fact that variation in both *IκBKβ* and *NFκB1* significantly interacts with NSAID use to modify CRC risk further confirms these findings and serves as increased evidence for future inclusion of the NFκB-signaling pathway in studies of the chemopreventative effects of NSAIDs.

In addition to increasing the evidence that NSAIDs function through an NFκB-dependent pathway, the findings here are also a preliminary step forward in a pharmacogenomic approach to chemopreventative NSAID use. Prolonged NSAID use is associated with potentially serious gastrointestinal toxicity issues [16,52]. Therefore, it would be valuable to identify individuals that are at increased benefit from NSAID use to ensure that the potential harm is outweighed by the benefits. Polymorphisms like rs6474387 (C>T intron 20) and rs11986055 (A>C intron 2) of *IκBKβ* may be of particular importance because they interact with NSAIDs such that carriers of the minor allele have a nearly 50% decreased risk of CRC, whereas carriers of the wild-type allele appeared to not have a lower risk associated with NSAID use. These findings could be used to in targeted preventative treatment.

There are several strengths to this study. The tagging approach maximized screening of the genetic variability in each gene while reducing the number of individual SNPs that had to be genotyped. In addition, the use of tagSNPs facilitated comparison with previous studies of SNPs not genotyped in this study. The study population allowed for generalizable results for several reasons. First, only population-based recruits were used, which prevented biases that result from clinic-based studies. Second, this study used the most clinically relevant outcome, primary invasive CRC. Many studies use polyps or adenoma as their outcome and these may or may not progress into CRC. Lastly, the large population size made it possible to examine colon and rectal cancer separately. Given their potential differences in etiologies, it is important for studies to be able to make distinctions between the two cancer types. Many studies of CRC focus on individuals affected by Crohn's disease and ulcerative colitis; therefore, this study has the advantage of not focusing on this limited population. The case-unaffected sibling control study design also helped to prevent false associations that could result from population stratification, in which allele frequencies differ due to differences in ancestry, and increased the power of gene-environment interaction analyses [51].

There are several weaknesses to this study as well. Important genetic variation could have been missed because it was not included in the public databases used in the tagging process. In particular, rare variants that were below our MAF cut-off (5%) and variants that were not well represented in the limited populations included in the database may have been missed. The power of the main effect analyses may be weakened by the family based study design [46] and the power to detect associations in the analyses restricted to colon or rectal cancer may be weak due to the smaller population size, especially when the MAF of the SNP is low or the association is weak. NSAID use was based on self-report which may be subject to recall bias. Studies have shown that five years of NSAID use may be needed in order to reduce CRC risk [53]. Therefore, our definition of NSAID use (2 pills per week for at least a month in the last two years) may have attenuated associations because individuals were included that did not take NSAIDs long enough to benefit from their chemopreventative effect.

Identifying common genetic variants associated with CRC can help predict patient risk and contribute to our understanding of mechanisms linked to colorectal carcinogenesis. Additionally, examining the pharmacogenetic interactions between these common genetic variants and NSAID use may allow for more targeted recommendations of NSAIDs as a chemopreventive agent. Ultimately, our findings, although not significant after correction for multiple correlated tests, suggest that variants of these genes are likely associated with CRC risk, particularly because some of these findings were replicating those of a previous study. These variants may alter colon and rectal cancer risk differently. Specially, genetic variability in *IκBKβ* may mainly decrease the risk of colon cancer risk and genetic variability in *NFκB1* may result in opposing risk modification for colon and rectal cancer. This study also begins to shed light on the link between variation in these key NFκB-signaling pathway genes and NSAIDs; suggesting that the prostaglandin synthesis pathway is not the only pathway that should be considered when researching the mechanism by which NSAIDs reduce CRC risk as prior studies have recently indicated. The common variants identified here should be considered for future research, not only in epidemiologic studies of CRC, but also in basic functional studies of these genes.

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# FIGURES AND TABLES

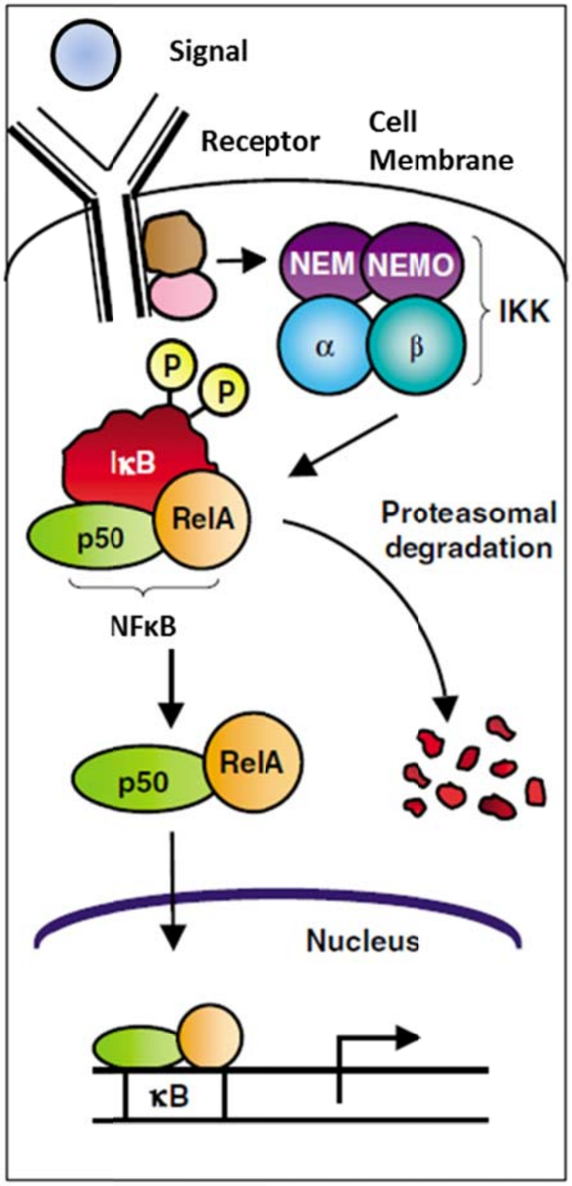

**Figure 1: The canonical NFkB-signaling pathway.** Under normal conditions, the NFkB heterodimer, RelA:p50 is rendered inactive by IκBα in the cytoplasm. In response to a variety of signals, including TNF-α, IL-1β, TLRs or viruses, the IκB kinase complex (IKK) phosphorylates IκBα which induces IκBα degradation. The now activated NFkB translocates to the nucleus where it binds to target genes and induces transcription. Adapted from **[54]**.

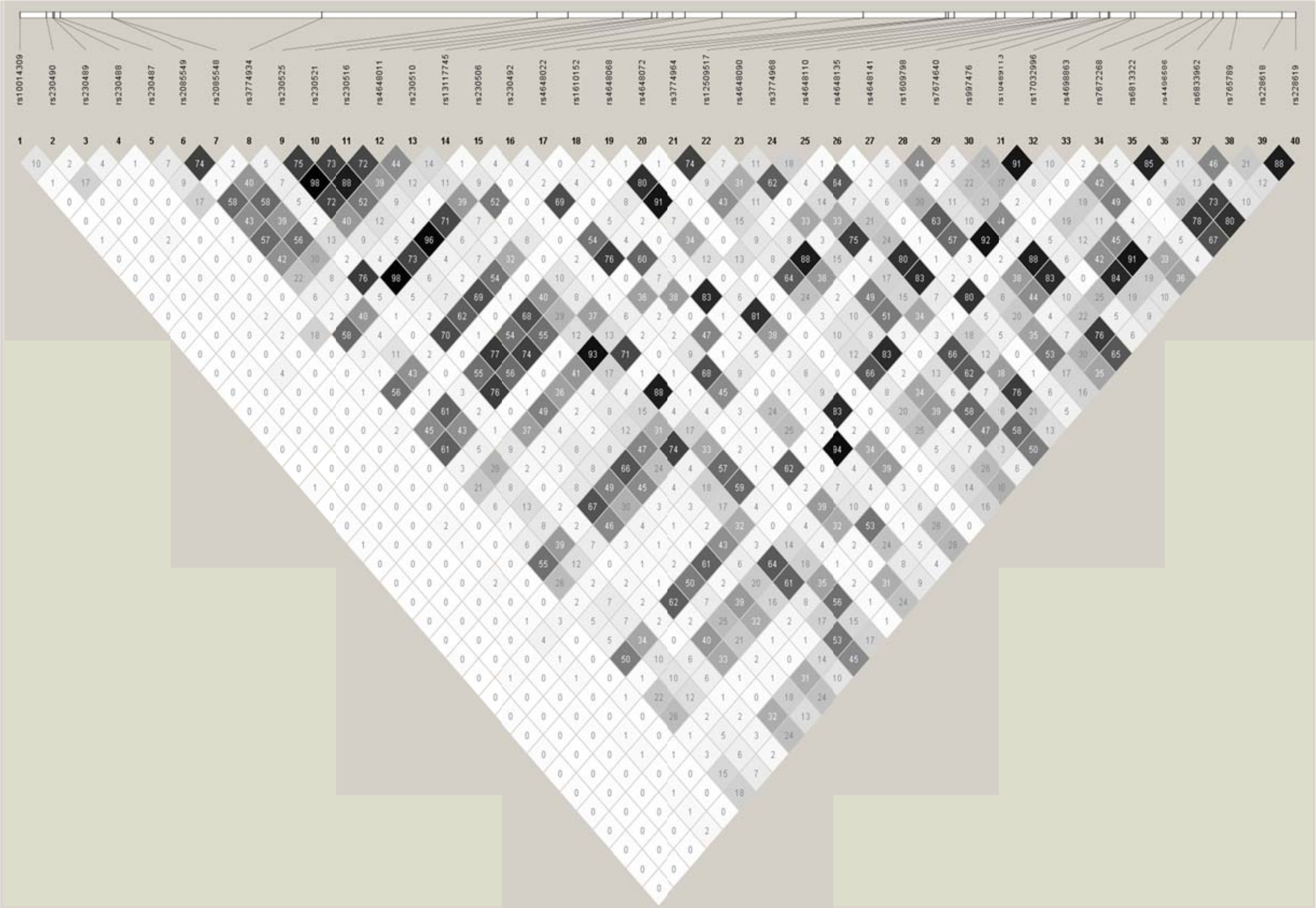

**Figure 2:** ***NFκB1*** **pairwise linkage disequilibrium ($r^2$) among Caucasian controls**

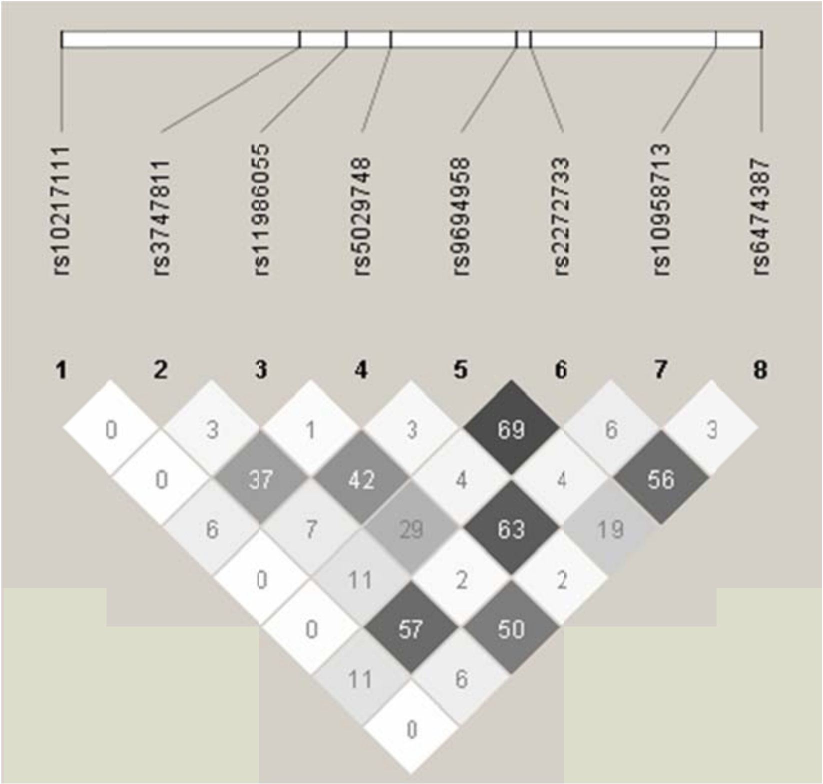

**Figure 3: *IκBKβ* pairwise linkage disequilibrium ($r^2$) among Caucasian controls**

**Table 1: List of candidate and tagSNPs in *IκBKβ* and *NFκB1***

| Gene | dbSNP ID | Chromosome Position | Nucleotide Change | Location | Minor Allele Frequency [a] |
|---|---|---|---|---|---|
| ***IκBKβ*, Chromosome 8, 8 tagSNPs, 2 candidate SNPs** | rs10217111 | 42100251 | G>C | 5' (outside UTR) | 0.19 |
| | rs3747811 | 42129505 | T>A | intron 1 | 0.47 |
| | rs11986055 | 42135178 | A>C | intron 2 | 0.04 |
| | rs5029748 | 42140549 | C>A | intron 2 | 0.25 |
| | rs9694958 | 42156046 | A>G | intron 5 | 0.08 |
| | rs2272733 | 42157902 | G>A | intron 5 | 0.11 |
| | *rs2272736* | *42177163* | *G>A* | *exon 15, R526Q* | *0.00* [b, d] |
| | *rs17875749* | *42178334* | *C>T* | *exon 16, R554W* | *0.00* [b, d] |
| | rs10958713 | 42180716 | G>A | intron 19 | 0.35 |
| | rs6474387 | 42186252 | C>T | intron 20 | 0.07 |
| ***NFκB1*, Chromosome 4, 40 tagSNPs, 2 candidate SNPs** | rs10014309 | 103383589 | G>A | 5' (outside UTR) | 0.12 |
| | rs230490 | 103387419 | G>A | 5' (outside UTR) | 0.42 |
| | rs230489 | 103388441 | A>G | 5' (outside UTR) | 0.11 |
| | rs230488 | 103388565 | G>A | 5' (outside UTR) | 0.27 |
| | rs230487 | 103389409 | A>C | 5' (outside UTR) | 0.29 |
| | rs2085549 | 103396923 | A>G | 5' (outside UTR) | 0.24 |
| | rs2085548 | 103397014 | G>A | 5' (outside UTR) | 0.30 |
| | rs3774934 | 103427476 | G>A | intron 1 | 0.10 |
| | rs230525 | 103458877 | A>G | intron 4 | 0.33 |
| | rs230521 | 103463328 | G>C | intron 5 | 0.39 |
| | *rs230516* | *103471251* | *A>G* | *intron 5* | *0.33* [e] |
| | rs4648011 | 103475444 | A>C | intron 5 | 0.40 |
| | rs230510 | 103476166 | T>A | intron 5 | 0.45 |
| | rs13117745 | 103478703 | G>A | intron 5 | 0.16 |
| | rs230506 | 103480450 | A>G | intron 5 | 0.08 |
| | *rs230492* | *103485780* | *G>A* | *intron 5* | *0.32* [e] |
| | rs4648022 | 103496437 | G>A | intron 6 | 0.09 |
| | rs1610152 | 103506374 | G>C | intron 11 | 0.05 |
| | *rs4648068* | *103518305* | *A>G* | *intron 14* | *0.32* [e] |
| | rs4648072 | 103518700 | A>G | exon 15, M507V | 0.01 [d] |
| | rs3774964 | 103519487 | A>G | intron 15 | 0.36 |
| | rs12509517 | 103525508 | C>G | intron 16 | 0.29 |
| | rs4648090 | 103527068 | G>A | intron 16 | 0.14 |
| | *rs4648099* | *103528817* | *T>G* | *exon 19, H712Q* | *n/a* [c,d] |
| | *rs3774968* | *103531112* | *G>A* | *intron 19* | *0.43* [e] |
| | rs4648110 | 103533821 | T>A | intron 22 | 0.20 |
| | *rs230547* | *103536261* | *G>A* | *intron 23* | *n/a* [c] |
| | rs4648135 | 103536670 | A>G | intron 23 | 0.05 |
| | rs4648141 | 103536901 | G>A | intron 23 | 0.17 |
| | rs1609798 | 103537442 | G>A | intron 23 | 0.31 |
| | rs7674640 | 103540780 | A>G | 3' (outside UTR) | 0.50 |
| | rs997476 | 103542005 | C>A | 3' (outside UTR) | 0.06 |
| | rs10489113 | 103542201 | A>G | 3' (outside UTR) | 0.19 |
| | *rs17032996* | *103545219* | *G>C* | *3' (outside UTR)* | *0.18* [e] |
| | rs4698863 | 103545848 | G>A | 3' (outside UTR) | 0.32 |
| | *rs7672268* | *103552858* | *G>A* | *exon 17 MANBA*[f] | *0.05* [e] |
| | rs6813322 | 103555619 | G>C | intron 16 MANBA | 0.50 |
| | rs4496586 | 103557311 | C>G | intron 14 MANBA | 0.48 |
| | rs6833962 | 103558731 | G>A | intron 14 MANBA | 0.10 |
| | rs765789 | 103560745 | A>T | intron 14 MANBA | 0.19 |
| | rs228618 | 103567348 | C>A | intron 13 MANBA | 0.48 |
| | rs228619 | 103569283 | G>A | intron 13 MANBA | 0.49 |

Note: *Italics indicates a SNP excluded from analysis*

[a] MAF based on Caucasian Controls, [b] Monomorphic, excluded from analysis,

[c] Failed QC due to Hardy-Weinberg equilibrium <0.001, excluded from analysis, [d] Candidate SNP,

[e] Not include in analysis because linkage disequilibrium $r^2 > 0.90$ with another SNP in the same gene,

[f] *MANBA* is a neighboring gene downstream of *NFκB1* that encodes a lysosomal mannosidase. The SNPs included here were part of linkage disequilibrium block used to tag *NFκB1.*

**Table 2: Selected Characteristics of Colorectal Cancer Cases and Unaffected Sibling Controls, the Cooperative Family Registry for Colon Cancer Studies, 1998-2002.**

| | Cases (N=1584)[a] | Unaffected Sibling Controls (N=2516)[a] |
|---|---|---|
| Characteristics | n (%) | n (%) |
| **Age (years) ± SD** | 53.5 ± 10.8 | 54.0 ± 11.7 |
| **Male** | 810 (51.1) | 1126 (44.8) |
| **Center Site** | | |
| Ontario | 296 (18.7) | 491 (19.5) |
| Los Angeles | 319 (20.1) | 444 (17.7) |
| Australia | 317 (20.0) | 554 (22.0) |
| Hawaii | 6 (0.4) | 7 (0.3) |
| Mayo | 266 (16.8) | 502 (20.0) |
| Seattle | 380 (24.0) | 518 (20.6) |
| **Tumor Site** | | |
| Proximal | 526 (33.2) | -- |
| Distal | 460 (29.0) | -- |
| Rectal | 523 (33.0) | -- |
| **Regular NSAID use**[b] | | |
| Never/Former | 1234 (78.3) | 1916 (76.9) |
| Current | 343 (21.8) | 577 (23.1) |
| **Physical Activity** | | |
| Inactive | 375 (23.7) | 585 (23.3) |
| Less Active | 424 (26.8) | 679 (27.0) |
| Active | 374 (23.6) | 564 (22.4) |
| Very Active | 338 (21.3) | 548 (21.8) |
| **BMI ± SD** | 27.4 ± 6.0 | 26.8 ± 5.5 |
| **Cigarette Smoking (Pack-Years) ± SD** | 12.9 ± 19.5 | 11.7 ± 19.3 |

[a] Numbers may not add to total because of missing data

[b] Regular use defined as at least two pills per week for at least one month

## Table 3: Association between selected SNPs[f] in *IκBKβ* and colorectal cancer, colon cancer or rectal cancer risk adjusted for age and sex

| | Colorectal Cancer | | | | | Colon Cancer | | | | | Rectal Cancer | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Genotype** | **Cases/ Controls[a]** | **OR** | **95% CI** | **Global-p ($P_{act}$)** | **p-trend ($P_{act}$)** | **Cases/ Controls[a]** | **OR** | **95% CI** | **Global-p ($P_{act}$)** | **p-trend ($P_{act}$)** | **Cases/ Controls[a]** | **OR** | **95% CI** | **Global-p ($P_{act}$)** | **p-trend ($P_{act}$)** |
| **rs2272733 (G>A intron 5)** | | | | | | | | | | | | | | | |
| **G/G** | 1255/1981 | **1.00** | ref. | | | 757/1200 | **1.00** | ref. | | | 401/674 | **1.00** | ref. | | |
| **G/A** | 311/487 | **0.98** | (0.79-1.21) | | | 190/306 | **1.00** | (0.76-1.32) | | | 99/148 | **0.99** | (0.67-1.46) | | |
| **A/A** | 18/46 | **0.46** | (0.21-1.02) | *0.12*[c] | 0.33 | 12/28 | **0.61** | (0.22-1.65) | 0.54 | 0.70 | 5/16 | **0.31** | (0.08-1.24) | 0.22 | 0.48 |
| **rs3747811 (T>A intron 1)** | | | | | | | | | | | | | | | |
| **T/T** | 453/727 | **1.00** | ref. | | | 292/442 | **1.00** | ref. | | | 136/241 | **1.00** | ref. | | |
| **T/A** | 784/1243 | **0.91** | (0.75-1.11) | | | 472/767 | **0.82** | (0.64-1.05) | | | 249/406 | **0.95** | (0.68-1.33) | | |
| **A/A** | 346/545 | **0.93** | (0.72-1.21) | 0.68 | 0.58 | 195/325 | **0.77** | (0.55-1.06) | *0.22*[c] | 0.10 | 120/192 | **1.05** | (0.66-1.67) | 0.86 | 0.84 |
| **rs5029748 (C>A intron 2)** | | | | | | | | | | | | | | | |
| **C/C** | 908/1411 | **1.00** | ref. | | | 580/873 | **1.00** | ref. | | | 267/457 | **1.00** | ref. | | |
| **C/A** | 587/961 | **0.86** | (0.71-1.03) | | | 325/573 | **0.72** | (0.56-0.91) | | | 208/334 | **1.08** | (0.78-1.49) | | |
| **A/A** | 89/144 | **0.83** | (0.56-1.22) | *0.25*[c] | 0.11 | 54/89 | **0.72** | (0.44-1.18) | ***0.02***[b]<br>(0.11) | **0.01**<br>(0.08) | 30/48 | **1.17** | (0.60-2.28) | 0.86 | 0.59 |
| **rs9694958 (A>G intron 5)** | | | | | | | | | | | | | | | |
| **A/A** | 1344/2122 | **1.00** | ref. | | | 809/1286 | **1.00** | ref. | | | 431/721 | **1.00** | ref. | | |
| **A/G** | 232/366 | **1.01** | (0.79-1.29) | | | 146/234 | **1.06** | (0.78-1.45) | | | 71/107 | **1.06** | (0.68-1.64) | | |
| **G/G** | 8/27 | **0.26** | (0.07-0.99) | ***0.048***[c]<br>(0.25)[e] | 0.48 | 4/14 | **0.32** | (0.04-2.42) | 0.98[d] | -- | 3/11 | **0.26** | (0.04-1.54) | 0.99[d] | -- |
| **rs10217111 (G>C 5' outside UTR)** | | | | | | | | | | | | | | | |
| **G/G** | 1031/1656 | **1.00** | ref. | | | 618/1011 | **1.00** | ref. | | | 339/557 | **1.00** | ref. | | |
| **G/C** | 475/766 | **1.04** | (0.85-1.26) | | | 290/467 | **1.11** | (0.86-1.44) | | | 145/249 | **0.87** | (0.62-1.22) | | |
| **C/C** | 77/93 | **1.51** | (0.98-2.33) | *0.17*[c] | 0.20 | 51/56 | **1.79** | (1.03-2.92) | *0.15*[c] | 0.10 | 20/33 | **0.91** | (0.38-2.19) | 0.73 | 0.52 |
| **rs10958713 (A>C intron 19)** | | | | | | | | | | | | | | | |
| **G/G** | 693/1097 | **1.00** | ref. | | | 451/671 | **1.00** | ref. | | | 197/362 | **1.00** | ref. | | |
| **G/A** | 712/1122 | **0.91** | (0.75-1.09) | | | 410/698 | **0.73** | (0.57-0.92) | | | 246/365 | **1.23** | (0.89-1.69) | | |
| **A/A** | 178/295 | **0.81** | (0.59-1.09) | 0.36 | 0.15 | 97/166 | **0.62** | (0.42-0.92) | ***0.015***[b]<br>(0.09) | **0.005**<br>(**0.03**) | 62/110 | **1.13** | (0.66-1.93) | 0.47 | 0.40 |

[a] Unaffected Sibling Controls

[b] *Noteworthy at 25%*

[c] *Noteworthy at 50%*

[d] Dominant Analysis results, cases <5

[e] The adjusted p-value is only presented for p-values <0.05

[f] SNPs with a significant global-p or p-trend or noteworthy by FDR

### Table 4: Association between selected SNPs[d] in *NFκB1* and colorectal cancer, colon cancer or rectal cancer risk adjusted for age and sex

| | **Colorectal Cancer** | | | | | **Colon Cancer** | | | | | **Rectal Cancer** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Genotype** | **Cases/ Controls[a]** | **OR** | **95% CI** | **Global -p $(P_{act})$[b]** | **p-trend $(P_{act})$** | **Cases/ Controls[a]** | **OR** | **95% CI** | **Global -p $(P_{act})$[b]** | **p-trend $(P_{act})$** | **Cases/ Controls[a]** | **OR** | **95% CI** | **Global -p $(P_{act})$[b]** | **p-trend $(P_{act})$** |
| **rs10489113 (A>G 3' outside UTR)** | | | | | | | | | | | | | | | |
| A/A | 1054/1639 | **1.00** | ref. | | | 643/996 | **1.00** | ref. | | | 332/549 | **1.00** | ref. | | |
| A/G | 465/782 | **0.87** | (0.72-1.05) | | | 289/480 | **0.85** | (0.66-1.08) | | | 145/260 | **0.89** | (0.63-1.26) | | |
| G/G | 64/94 | **0.95** | (0.62-1.47) | 0.36 | 0.28 | 27/59 | **0.53** | (0.29-0.97) | 0.07 | **0.04** (0.48)[c] | 28/29 | **2.13** | (1.02-4.46) | 0.06 | 0.49 |
| **rs4648072 (M507V)** | | | | | | | | | | | | | | | |
| A/A | 1565/2475 | **1.00** | ref. | | | 949/1512 | **1.00** | ref. | | | 499/826 | **1.00** | | | |
| A/G[e] | 19/41 | **0.62** | (0.24-1.60) | 0.50 | -- | 10/23 | **0.63** | (0.20-1.97) | 0.689 | **--** | 6/13 | **0.64** | (0.10-4.12) | 0.84 | -- |

[a] Unaffected Sibling Controls

[b] No SNP noteworthy at the 50% or 25% FDR level

[c] The adjusted p-value is only presented for p-values <0.05

[d] SNPs with a significant global-p or p-trend or a candidate SNP

[e] No individuals with the G/G genotype

## Table 5: Association between current NSAID use and the risk of colorectal cancer, colon cancer or rectal cancer risk

| | Colorectal Cancer | | | | | Colon Cancer | | | | | Rectal Cancer | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **NSAID Use** | **Cases** | **Controls[b]** | **OR[c]** | **95% CI** | **p-value** | **Cases** | **Controls[b]** | **OR[c]** | **95% CI** | **p-value** | **Cases** | **Controls[b]** | **OR[c]** | **95% CI** | **p-value** |
| Never/Former | 1234 | 1916 | **1.00** | -- | | 736 | 1148 | **1.00** | -- | | 412 | 659 | **1.00** | -- | |
| Current[a] | 343 | 577 | **0.87** | 0.72-1.04 | 0.13 | 218 | 373 | **0.85** | 0.67-1.07 | 0.17 | 92 | 173 | **0.80** | 0.55-1.15 | 0.22 |

[a] 2 or more pills per week for at least a month in the two years prior to study enrollment

[b] Unaffected Sibling Controls

[c] Adjusted for age, sex, BMI, smoking and physical activity

## Table 6: Association between NSAID use and colorectal cancer, colon cancer or rectal cancer risk stratified by selected *IκBKβ* SNP genotypes[d,e]

| | **Colorectal Cancer** | | | | **Colon Cancer** | | | | **Rectal Cancer** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Never or Former NSAID Use** | | **Current NSAID use** | | **Never or Former NSAID Use** | | **Current NSAID use** | | **Never or Former NSAID Use** | | **Current NSAID use** | |
| | **OR** | 95% CI | **OR** | 95% CI | **OR** | 95% CI | **OR** | 95% CI | **OR** | 95% CI | **OR** | 95% CI |
| **rs2272733 (G>A intron 5)** | | | | | | | | | | | | |
| G/G | **1.00** | ref. | **0.89** | (0.73-1.08) | **1.00** | ref. | **0.89** | (0.70-1.14) | **1.00** | ref. | **0.89** | (0.70-1.14) |
| G/A or A/A[c] | **1.03** | (0.80-1.32) | **0.77** | (0.51-1.15) | **1.16** | (0.85-1.60) | **0.69** | (0.40-1.20) | **1.00** | (0.65-1.54) | **0.69** | (0.34-1.40) |
| | | | | *p interaction* = 0.43 | | | | *p interaction = 0.16* [b] | | | | *p interaction* = 0.54 |
| **rs5029748 (C>A intron 2)** | | | | | | | | | | | | |
| C/C | **1.00** | ref. | **0.89** | (0.70-1.12) | **1.00** | ref. | **0.75** | (0.56-1.01) | **1.00** | ref. | **1.12** | (0.71-1.77) |
| C/A | **0.84** | (0.68-1.04) | **0.74** | (0.55-0.99) | **0.65** | (0.49-0.86) | **0.65** | (0.44-0.96) | **1.14** | (0.80-1.63) | **0.75** | (0.44-1.27) |
| A/A | **0.85** | (0.54-1.32) | **0.54** | (0.27-1.09) | **0.63** | (0.34-1.16) | **0.44** | (0.21-0.93) | **1.39** | (0.66-2.93) | **0.74** | (0.19-2.89) |
| | | | | *p interaction* = 0.71 | | | | *p interaction* = 0.45 | | | | *p interaction* = 0.24 |
| **rs6474387 (C>T intron 20)** | | | | | | | | | | | | |
| C/C | **1.00** | ref. | **0.92** | (0.76-1.11) | **1.00** | ref. | **0.91** | (0.72-1.15) | **1.00** | ref. | **0.90** | (0.63-1.29) |
| C/T or T/T[c] | **1.09** | (0.79-1.50) | **0.57** | (0.32-1.00) | **1.22** | (0.80-1.86) | **0.45** | (0.21-1.01) | **1.13** | (0.68-1.88) | **0.64** | (0.27-1.49) |
| | | | | *p interaction =* ***0.04*** [a] | | | | *p interaction =* ***0.02*** [a] | | | | *p interaction* = 0.32 |
| **rs9694958 (A>G intron 5)** | | | | | | | | | | | | |
| A/A | **1.00** | ref. | **0.90** | (0.74-1.09) | **1.00** | ref. | **0.88** | (0.69-1.12) | **1.00** | ref. | **0.90** | (0.63-1.27) |
| A/G or G/G[c] | **1.09** | (0.82-1.43) | **0.75** | (0.48-1.18) | **1.22** | (0.86-1.74) | **0.72** | (0.40-1.32) | **1.11** | (0.69-1.77) | **0.69** | (0.31-1.53) |
| | | | | *p interaction* = 0.28 | | | | *p interaction = 0.20* [b] | | | | *p interaction* = 0.41 |
| **rs10958713 (G>A intron 19)** | | | | | | | | | | | | |
| G/G | **1.00** | ref. | **0.87** | (0.67-1.14) | **1.00** | ref. | **0.71** | (0.51-0.98) | **1.00** | ref. | **1.12** | (0.68-1.86) |
| G/A | **0.89** | (0.72-1.10) | **0.83** | (0.63-1.11) | **0.64** | (0.49-0.84) | **0.66** | (0.46-0.96) | **1.28** | (0.90-1.81) | **0.92** | (0.55-1.55) |
| A/A | **0.82** | (0.58-1.17) | **0.52** | (0.32-0.85) | **0.56** | (0.35-0.90) | **0.36** | (0.19-0.68) | **1.17** | (0.63-2.17) | **0.81** | (0.36-1.81) |
| | | | | *p interaction* = 0.39 | | | | *p interaction = 0.20* [b] | | | | *p interaction* = 0.39 |
| **rs11986055 (A>C intron 2)** | | | | | | | | | | | | |
| A/A | **1.00** | ref. | **0.90** | (0.75-1.08) | **1.00** | ref. | **0.87** | (0.69-1.09) | **1.00** | ref. | **0.90** | (0.64-1.26) |
| A/C or C/C[c] | **1.16** | (0.77-1.75) | **0.48** | (0.23-0.98) | **1.28** | (0.76-2.17) | **0.47** | (0.19-1.20) | **1.35** | (0.72-2.53) | **0.54** | (0.17-1.73) |
| | | | | *p interaction =* ***0.03*** [a] | | | | *p interaction = 0.05* [b] | | | | *p interaction* = 0.20 |

[a] *Noteworthy at 25% FDR level*

[b] *Noteworthy at 50% FDR level*

[c] Dominant Analysis results, cases<5

[d] Adjusted for age, sex, BMI, pack-years and physical activity

[e] SNPs with a significant interaction-p or noteworthy by FDR

**Table 7: Association between NSAID use and colorectal cancer, colon cancer or rectal cancer risk stratified by selected *NFκB1* SNP genotypes[c,d]**

| | Colorectal Cancer | | | | Colon Cancer | | | | Rectal Cancer | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Never or Former NSAID Use | | Current NSAID use | | Never or Former NSAID Use | | Current NSAID use | | Never or Former NSAID Use | | Current NSAID use | |
| | **OR** | 95% CI | **OR** | 95% CI | **OR** | 95% CI | **OR** | 95% CI | **OR** | 95% CI | **OR** | 95% CI |
| **rs230506 (A>G intron 5)** | | | | | | | | | | | | |
| A/A | **1.00** | ref. | **0.81** | (0.67-0.98) | **1.00** | ref. | **0.77** | (0.61-0.98) | **1.00** | ref. | **0.78** | (0.55-1.11) |
| A/G or G/G[b] | **0.78** | (0.58-1.04) | **1.04** | (0.66-1.65) | **0.75** | (0.51-1.09) | **0.98** | (0.56-1.7) | **0.83** | (0.46-1.49) | **1.45** | (0.61-3.48) |
| | | | | *p interaction* = **0.05** | | | | *p interaction* = 0.08 | | | | *p interaction* = 0.11 |
| **rs230490 (G>A 5' outside UTR)** | | | | | | | | | | | | |
| G/G | **1.00** | ref. | **0.62** | (0.46-0.85) | **1.00** | ref. | **0.67** | (0.45-0.99) | **1.00** | ref. | **0.50** | (0.27-0.91) |
| G/A | **0.88** | (0.71-1.10) | **0.81** | (0.61-1.07) | **0.95** | (0.71-1.26) | **0.82** | (0.57-1.17) | **0.76** | (0.53-1.09) | **0.66** | (0.39-1.11) |
| A/A | **0.92** | (0.67-1.25) | **1.19** | (0.77-1.83) | **1.08** | (0.72-1.6) | **1.17** | (0.67-2.04) | **0.63** | (0.36-1.11) | **1.32** | (0.6-2.87) |
| | | | | *p interaction* = **0.02** | | | | *p interaction* = 0.31 | | | | *p interaction* = **0.02** |
| **rs230488 (G>A 5' outside UTR)** | | | | | | | | | | | | |
| G/G | **1.00** | ref. | **0.89** | (0.70-1.13) | **1.00** | ref. | **0.77** | (0.57-1.05) | **1.00** | ref. | **1.14** | (0.75-1.74) |
| G/A or A/A[b] | **1.04** | (0.85-1.28) | **0.86** | (0.65-1.13) | **0.92** | (0.71-1.20) | **0.82** | (0.59-1.16) | **1.35** | (0.95-1.92) | **0.79** | (0.45-1.37) |
| | | | | *p interaction* = 0.66 | | | | *p interaction* = 0.51 | | | | *p interaction* = **0.04** |
| **rs4648072 (M507V)** | | | | | | | | | | | | |
| A/A | **1.00** | ref. | **0.87** | (0.71-1.05) | **1.00** | ref. | **0.83** | (0.66-1.04) | **1.00** | ref. | **0.86** | (0.61-1.20) |
| A/G[e] | **0.71** | (0.26-1.90) | **0.26** | (0.02-2.80) | **0.57** | (0.16-2.01) | **0.57** | (0.05-6.13) | **0.62** | (0.11-3.64) | --[f] | -- |
| | | | | *p interaction* = 0.41 | | | | *p interaction* = 0.89 | | | | *p interaction* = 0.31 |

[a] No SNP noteworthy at the 50% or 25% FDR level

[b] Dominant Analysis results, cases<5

[c] SNPs with a significant interaction-p or a candidate SNP

[d] Adjusted for age, sex, BMI, pack-years and physical activity

[e] No individuals with the G/G genotype

[f] No cases and one control with A/G genotype

**Table 8: Principal component analysis of *IκBKβ* and *NFκB1* SNPs and risk of colorectal cancer**[a]

| | **Cancer Site** | **PCA p-value**[b] |
|---|---|---|
| ***IκBKβ*** | Colorectal | 0.22 |
| | Colon | 0.11 |
| | Rectal | 0.93 |
| ***NFκB1*** | Colorectal | 0.12 |
| | Colon | 0.99 |
| | Rectal | 0.99 |

[a] Exclude failed SNPs
[b] Adjusted for age and sex

**Table 9: Comparison between significant findings for single SNPs of *IκBKβ* and *NFκB1* in a study by Curtin *et al.* [12] and the findings in the CFR population. The comparison and model indicate the specific OR that is presented and what model was used to obtain that OR. When the additive model OR was presented, the co-dominant OR was presented for the CFR population in addition to the additive model.**

| | | | | | Curtin *et al.* [13] | | CFR | | CFR co-dominant model[d] | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Cancer Site** | **Gene** | **SNP** | **Comparison** | **Model** | **OR[e]** | **95%CI** | **OR[f]** | **95%CI** | **OR[f]** | **95%CI** |
| **Colon** | ***IκBKβ*** | rs2272733<br>(G>A intron 5) | TT vs CC | Additive | **0.56[g]** | (0.34-0.93) | **0.90[g]** | (0.54-1.52) | **0.61** | (0.22-1.65) |
| | ***NFκB1*** | rs4648110<br>(T>A intron 22) | AA vs TT | Additive | **0.65** | (0.44-0.94) | **0.68** | (0.45-1.04) | **0.59** | (0.33-1.06) |
| | | | AA vs TT/TA | Recessive | **0.66** | (0.45-0.96) | **0.65** | (0.37-1.13) | **n/a** | |
| | ***NFκB*** | rs13117745<br>(G>A intron 5) | TT vs CC | Additive | **0.61** | (0.37-1.00) | **0.80** | (0.50-1.28) | **0.82** | (0.40-1.67) |
| | | | TT vs CC/CT | Recessive | **0.64** | (0.39-1.04) | **0.89** | (0.45-1.76) | **n/a** | |
| **Rectal** | ***NFκB1*** | rs230510[a]<br>(T>A intron 5) | TT vs AA | Additive | **0.65** | (0.49-0.87) | **1.13** | (0.73-1.79) | **1.12** | (0.70-1.78) |
| | | | TT vs AA/AT | Dominant | **0.79** | (0.51-0.94) | **1.17** | (0.84-1.63) | **n/a** | |
| | ***NFκB1*** | rs3821958[b] or<br>rs230521<br>(G>C intron 5) | GG vs AA | Additive | **1.32** | (1.00-1.75) | **0.80** | (0.50-1.29) | **0.97** | (0.74-1.28) |
| | ***NFκB1*** | rs11722146[c] or<br>rs12509517<br>(C>G intron 16) | GA/AA vs GG | Dominant | **1.24** | (1.03-1.51) | **0.99** | (0.71-1.37) | **n/a** | |
| | ***NFκB1*** | rs13117745<br>(G>A intron 5) | TT vs CC | Additive | **1.69** | (0.93-3.07) | **1.22** | (0.65-2.26) | **1.78** | (0.74-4.30) |

[a] The MAF of rs230510 is 0.448 and the polymorphism results in a complementary base change (A to T), therefore it is not possible the studies are investigating opposing associations

[b] rs3821958 was not genotyped in CFR, rs3821958 and rs230521 have a LD $r^2$ of 0.966 according to the Genome Variation Server

[c] rs11722146 was not genotyped in CFR, rs11722146 and rs12509517 have a LD $r^2$ of 1.000 according to the Genome Variation Server

[d] The co-dominant model was not run in the Curtin et al. study, but is presented here when the results of the additive model were presented

[e] Adjusted for age, sex, center and race

[f] Restricted to Caucasian and adjusted for age and sex

[g] The OR is two times the β from the log additive model

**Table 10: Comparison between significant findings for composite genotypes of *IκBKβ* and *NFκB1* in a study by Curtin *et al.* [12]and the findings in the CFR population. The ORs presented represent the OR for the indicated comparison under the indicated model.**

| Cancer Site | Gene | | Comparison | Model | Curtin et al. | | CFR | |
|---|---|---|---|---|---|---|---|---|
| | ***IκBKβ*** | ***NFκB1*** | | | **OR[b]** | **95%CI** | **OR[c]** | **95%CI** |
| **Colon** | rs3747811<br>(T>A intron 1) | rs4648110<br>(T>A intron 22) | TT / TT vs<br>(TA or AA) / AA | Dom/Rec | **0.54** | (0.34-0.87) | **0.56** | (0.28-1.12) |
| **Rectal** | rs3747811<br>(T>A intron 1) | rs11722146[a] or<br>rs12509517<br>(C>G intron 16) | TT/CC vs<br>(TA or AA) /<br>(CG or GG) | Dom/Dom | **1.11** | (0.83-1.50) | **1.02** | (0.63-1.65) |

[a] rs11722146 was not genotyped in CFR, rs11722146 and rs12509517 have a LD $r^2$ of 1.000 according to the Genome Variation Server

[b] Adjusted for age, sex, center and race

[c] Restricted to Caucasian and adjusted for age and sex

# APPENDIX A: SUPPLEMENTARY TABLES

**Table A.1: Associations between tagSNPs in *IκBKβ* and risk of colorectal cancer adjusted for age and sex**

| Genotype | Cases/ Controls[a] | OR | 95% CI | Global-p ($P_{act}$) | p-trend ($P_{act}$) |
|---|---|---|---|---|---|
| **rs2272733 (G>A intron 5)** | | | | | |
| **G/G** | 1255/1981 | **1.00** | ref. | | |
| **G/A** | 311/487 | **0.98** | (0.79-1.21) | | |
| **A/A** | 18/46 | **0.46** | (0.21-1.02) | *0.12*[b] (0.49) | 0.33 (0.80) |
| **rs3747811 (T>A intron 1)** | | | | | |
| **T/T** | 453/727 | **1.00** | ref. | | |
| **T/A** | 784/1243 | **0.91** | (0.75-1.11) | | |
| **A/A** | 346/545 | **0.93** | (0.72-1.21) | 0.68 | 0.58 (1.00) |
| **rs5029748 (C>A intron 2)** | | | | | |
| **C/C** | 908/1411 | **1.00** | ref. | | |
| **C/A** | 587/961 | **0.86** | (0.71-1.03) | | |
| **A/A** | 89/144 | **0.83** | (0.56-1.22) | *0.25*[b] (0.72) | 0.11 (0.49) |
| **rs6474387 (C>T intron 19)** | | | | | |
| **C/C** | 1362/2160 | **1.00** | ref. | | |
| **C/T** | 192/308 | **0.95** | (0.73-1.25) | | |
| **T/T** | 9/18 | **0.83** | (0.31-2.22) | 0.91 | 0.68 |
| **rs9694958 (A>G intron 5)** | | | | | |
| **A/A** | 1344/2122 | **1.00** | ref. | | |
| **A/G** | 232/366 | **1.01** | (0.79-1.29) | | |
| **G/G** | 8/27 | **0.26** | (0.07-0.99) | ***0.048***[b] (0.25) | 0.48 (0.88) |
| **rs10217111 (G>C 5' outside UTR)** | | | | | |
| **G/G** | 1031/1656 | **1.00** | ref. | | |
| **G/C** | 475/766 | **1.04** | (0.85-1.26) | | |
| **C/C** | 77/93 | **1.51** | (0.98-2.33) | *0.17*[b] (0.64) | 0.20 (0.71) |
| **rs10958713 (G>A intron 19)** | | | | | |
| **G/G** | 693/1097 | **1.00** | ref. | | |
| **G/A** | 712/1122 | **0.91** | (0.75-1.09) | | |
| **A/A** | 178/295 | **0.81** | (0.59-1.09) | 0.36 (0.82) | 0.15 (0.58) |
| **rs11986055 (A>C intron 1)** | | | | | |
| **A/A** | 1472/2333 | **1.00** | ref. | | |
| **A/C or C/C**[c] | 112/182 | **0.98** | (0.69-1.39) | 0.99 | -- |

[a] Unaffected Sibling Controls

[b] SNP noteworthy at the 50% FDR level

[c] When cases<5, only the dominant model was analyzed

**Table A.2: Associations between tagSNPs in *IκBKβ* and risk of colon cancer adjusted for age and sex**

| Genotype | Cases/ Controls[a] | OR | 95% CI | Global-p ($P_{act}$) | p-trend ($P_{act}$) |
|---|---|---|---|---|---|
| **rs2272733 (G>A intron 5)** | | | | | |
| **G/G** | 757/1200 | **1.00** | ref. | | |
| **G/A** | 190/306 | **1.00** | (0.76-1.32) | | |
| **A/A** | 12/28 | **0.61** | (0.22-1.65) | 0.54 (1.00) | 0.70 |
| **rs3747811 (T>A intron 1)** | | | | | |
| **T/T** | 292/442 | **1.00** | ref. | | |
| **T/A** | 472/767 | **0.82** | (0.64-1.05) | | |
| **A/A** | 195/325 | **0.77** | (0.55-1.06) | *0.22*[c] (0.57) | 0.10 (0.38) |
| **rs5029748 (C>A intron 2)** | | | | | |
| **C/C** | 580/873 | **1.00** | ref. | | |
| **C/A** | 325/573 | **0.72** | (0.56-0.91) | | |
| **A/A** | 54/89 | **0.72** | (0.44-1.18) | ***0.02***[b] (0.11) | **0.01** (0.08) |
| **rs6474387 (C>T intron 19)** | | | | | |
| **C/C** | 825/1308 | **1.00** | ref. | | |
| **C/T** | 115/192 | **0.97** | (0.69-1.38) | | |
| **T/T** | 7/14 | **0.70** | (0.21-2.31) | 0.85 | 0.74 |
| **rs9694958 (A>G intron 5)** | | | | | |
| **A/A** | 809/1286 | **1.00** | ref. | | |
| **A/G or G/G[d]** | 150/248 | **1.04** | (0.76-1.42) | 0.98 | -- |
| **rs10217111 (G>C 5' outside UTR)** | | | | | |
| **G/G** | 618/1011 | **1.00** | ref. | | |
| **G/C** | 290/467 | **1.11** | (0.86-1.44) | | |
| **C/C** | 51/56 | **1.79** | (1.03-2.92) | *0.15*[c] (0.50) | 0.10 (0.38) |
| **rs10958713 (G>A intron 19)** | | | | | |
| **G/G** | 451/671 | **1.00** | ref. | | |
| **G/A** | 410/698 | **0.73** | (0.57-0.92) | | |
| **A/A** | 97/166 | **0.62** | (0.42-0.92) | ***0.015***[b](0.09) | **0.005** (**0.03**) |
| **rs11986055 (A>C intron 1)** | | | | | |
| **A/A** | 887/1415 | **1.00** | ref. | | |
| **A/C or C/C** | 72/119 | **1.03** | (0.65-1.63) | 0.99 | -- |

[a] Unaffected Sibling Controls

[b] *Noteworthy at the FDR 25% level*

[c] *Noteworthy at the FDR 50% level*

[d] When cases<5, only the dominant model was analyzed

**Table A.3: Associations between tagSNPs in *IκBKβ* and risk of rectal cancer adjusted for age and sex**

| Genotype | Cases/ Controls[a] | OR | 95% CI | Global-p[b] ($P_{act}$) | p-trend ($P_{act}$) |
|---|---|---|---|---|---|
| **rs2272733 (G>A intron 5)** | | | | | |
| **G/G** | 401/674 | **1.00** | ref. | | |
| **G/A** | 99/148 | **0.99** | (0.67-1.46) | | |
| **A/A** | 5/16 | **0.31** | (0.08-1.24) | 0.22 (0.75) | 0.48 (0.97) |
| **rs3747811 (T>A intron 1)** | | | | | |
| **T/T** | 136/241 | **1.00** | ref. | | |
| **T/A** | 249/406 | **0.95** | (0.68-1.33) | | |
| **A/A** | 120/192 | **1.05** | (0.66-1.67) | 0.86 | 0.84 |
| **rs5029748 (C>A intron 2)** | | | | | |
| **C/C** | 267/457 | **1.00** | ref. | | |
| **C/A** | 208/334 | **1.08** | (0.78-1.49) | | |
| **A/A** | 30/48 | **1.17** | (0.60-2.28) | 0.86 | 0.59 |
| **rs6474387 (C>T intron 19)** | | | | | |
| **C/C** | 430/730 | **1.00** | ref. | | |
| **C/T or T/T[c]** | 67/101 | **1.00** | (0.63-1.57) | 0.99 | -- |
| **rs9694958 (A>G intron 5)** | | | | | |
| **A/A** | 431/721 | **1.00** | ref. | | |
| **A/G or G/G** | 74/118 | **1.04** | (0.67-1.61) | 0.99 | -- |
| **rs10217111 (G>C 5' outside UTR)** | | | | | |
| **G/G** | 339/557 | **1.00** | ref. | | |
| **G/C** | 145/249 | **0.87** | (0.62-1.22) | | |
| **C/C** | 20/33 | **0.91** | (0.38-2.19) | 0.73 | 0.52 (1.00) |
| **rs10958713 (G>A intron 19)** | | | | | |
| **G/G** | 197/362 | **1.00** | ref. | | |
| **G/A** | 246/365 | **1.23** | (0.89-1.69) | | |
| **A/A** | 62/110 | **1.13** | (0.66-1.93) | 0.47 (0.97) | 0.40 (0.94) |
| **rs11986055 (A>C intron 1)** | | | | | |
| **A/A** | 470/787 | **1.00** | ref. | | |
| **A/C or C/C** | 35/52 | **1.10** | (0.62-1.95) | 0.96 | -- |

[a] Unaffected Sibling Controls

[b] No SNP was noteworthy at the 25% or 50% FDR level

[c] When cases<5, only the dominant model was analyzed

**Table A.4: Associations between candidate SNPs and tagSNPs in *NFκB1* and risk of colorectal cancer adjusted for age and sex**

| DB SNP ID | Genotype | Cases/ Controls[a] | OR | 95% CI | Global-p[b] ($P_{act}$) | p-trend ($P_{act}$) |
|---|---|---|---|---|---|---|
| Candidate SNP | | | | | | |
| **rs4648072** | A/A | 1565/2475 | **1.00** | ref. | | |
| **M507V** | A/G[d] | 19/41 | **0.62** | (0.24-1.6) | 0.50 | -- |
| TagSNPs | | | | | | |
| **rs7674640** | A/A | 414/668 | **1.00** | ref. | | |
| | A/G | 771/1239 | **0.98** | (0.8-1.19) | | |
| | G/G | 399/608 | **1.01** | (0.77-1.32) | 0.92 | 0.95 |
| **rs765789** | A/A | 1052/1643 | **1.00** | ref. | | |
| | A/T | 468/780 | **0.92** | (0.76-1.11) | | |
| | T/T | 64/92 | **1.07** | (0.69-1.64) | 0.57 | 0.66 |
| **rs6833962** | G/G | 1259/1947 | **1.00** | ref. | | |
| | G/A | 257/427 | **0.91** | (0.71-1.17) | | |
| | A/A | 16/25 | **0.78** | (0.35-1.76) | 0.68 | 0.41 (0.99) |
| **rs6813322** | G/G | 402/657 | **1.00** | ref. | | |
| | G/C | 769/1233 | **0.98** | (0.81-1.2) | | |
| | C/C | 391/596 | **1.04** | (0.8-1.36) | 0.85 | 0.76 |
| **rs4698863** | G/G | 754/1173 | **1.00** | ref. | | |
| | G/A | 654/1067 | **0.96** | (0.8-1.15) | | |
| | A/A | 175/276 | **1.06** | (0.77-1.45) | 0.74 | 0.96 |
| **rs4648141** | G/G | 1113/1735 | **1.00** | ref. | | |
| | G/A | 420/709 | **0.87** | (0.71-1.07) | | |
| | A/A | 51/71 | **1.14** | (0.7-1.86) | 0.27 (0.99) | 0.50 (1.00) |
| **rs4648135** | A/A | 1421/2248 | **1.00** | ref. | | |
| | A/G or G/G[d] | 162/265 | **1.00** | (0.72-1.38) | 1.00 | -- |
| **rs4648110** | T/T | 1025/1594 | **1.00** | ref. | | |
| | T/A | 492/819 | **0.90** | (0.75-1.09) | | |
| | A/A | 67/103 | **0.97** | (0.64-1.47) | 0.56 | 0.44 (0.99) |
| **rs4648090** | G/G | 1201/1861 | **1.00** | ref. | | |
| | G/A | 354/610 | **0.86** | (0.69-1.07) | | |
| | A/A | 28/44 | **0.85** | (0.46-1.56) | 0.39 (0.99) | 0.20 (0.97) |
| **rs4648022** | G/G | 1341/2085 | **1.00** | ref. | | |
| | G/A | 231/406 | **0.88** | (0.68-1.14) | | |
| | A/A | 12/21 | **0.83** | (0.34-2.01) | 0.60 | 0.34 (0.99) |
| **rs4648011** | A/A | 571/893 | **1.00** | ref. | | |
| | A/C | 739/1176 | **0.95** | (0.79-1.16) | | |
| | C/C | 265/437 | **0.98** | (0.75-1.3) | 0.88 | 0.85 |
| **rs4496586** | C/C | 436/662 | **1.00** | ref. | | |
| | C/G | 765/1241 | **0.94** | (0.77-1.15) | | |
| | G/C | 378/604 | **0.99** | (0.76-1.29) | 0.78 | 0.92 |
| **rs3774964** | A/A | 654/1030 | **1.00** | ref. | | |
| | A/G | 703/1103 | **1.02** | (0.85-1.24) | | |
| | G/G | 227/383 | **1.02** | (0.76-1.35) | 0.97 | 0.88 |
| **rs3774934** | G/G | 1294/2037 | **1.00** | ref. | | |
| | G/A | 273/453 | **0.91** | (0.72-1.16) | | |
| | A/A | 17/26 | **1.01** | (0.44-2.36) | 0.73 | 0.52 |
| **rs230525** | A/A | 702/1120 | **1.00** | ref. | | |
| | A/G | 695/1098 | **1.05** | (0.87-1.26) | | |
| | G/G | 182/296 | **1.04** | (0.76-1.41) | 0.89 | 0.71 |
| **rs230521** | G/G | 586/930 | **1.00** | ref. | | |
| | G/C | 740/1152 | **1.01** | (0.84-1.22) | | |
| | C/C | 256/432 | **0.97** | (0.74-1.28) | 0.94 | 0.89 |
| **rs230510** | T/T | 479/792 | **1.00** | ref. | | |
| | T/A | 779/1229 | **1.04** | (0.86-1.26) | | |
| | A/A | 324/495 | **1.04** | (0.79-1.35) | 0.92 | 0.77 |

**Table A.4 continued: Associations between candidate SNPs and tagSNPs in *NFκB1* and risk of colorectal cancer adjusted for age and sex**

| DB SNP ID | Genotype | Cases/ Controls[a] | OR | 95% CI | Global-p[b] ($P_{act}$) | p-trend ($P_{act}$) |
|---|---|---|---|---|---|---|
| **rs230506** | A/A | 1351/2129 | **1.00** | ref. | | |
| | A/G | 218/369 | **0.87** | (0.67-1.13) | | |
| | G/G | 13/16 | **1.42** | (0.55-3.7) | 0.38 (0.99) | 0.53 |
| **rs230490** | G/G | 535/838 | **1.00** | ref. | | |
| | G/A | 757/1238 | **0.92** | (0.76-1.11) | | |
| | A/A | 292/440 | **1.09** | (0.82-1.44) | 0.28 (0.99) | 0.76 |
| **rs230489** | A/A | 1261/1978 | **1.00** | ref. | | |
| | A/G | 302/507 | **0.89** | (0.71-1.12) | | |
| | G/G | 20/30 | **1.17** | (0.58-2.37) | 0.49 (0.99) | 0.54 |
| **rs230488** | G/G | 847/1333 | **1.00** | ref. | | |
| | G/A | 646/1008 | **1.01** | (0.85-1.21) | | |
| | A/A | 90/171 | **0.76** | (0.53-1.08) | 0.22 (0.98) | 0.41 (0.99) |
| **rs230487** | A/A | 808/1255 | **1.00** | ref. | | |
| | A/C | 648/1069 | **0.90** | (0.75-1.08) | | |
| | C/C | 128/192 | **1.04** | (0.74-1.45) | 0.37 (0.99) | 0.64 |
| **rs228619** | G/G | 423/658 | **1.00** | ref. | | |
| | G/A | 760/1227 | **0.97** | (0.79-1.18) | | |
| | A/A | 398/631 | **0.96** | (0.73-1.26) | 0.94 | 0.76 |
| **rs228618** | C/C | 437/710 | **1.00** | ref. | | |
| | C/A | 773/1226 | **1.07** | (0.87-1.3) | | |
| | A/A | 373/580 | **1.10** | (0.84-1.44) | 0.77 | 0.79 |
| **rs2085549** | A/A | 897/1436 | **1.00** | ref. | | |
| | A/G | 591/909 | **1.09** | (0.91-1.31) | | |
| | G/G | 96/171 | **0.96** | (0.67-1.37) | 0.55 | 0.50 (0.99) |
| **rs2085548** | G/G | 772/1236 | **1.00** | ref. | | |
| | G/A | 671/1026 | **1.07** | (0.89-1.29) | | |
| | A/A | 141/252 | **1.00** | (0.73-1.37) | 0.70 | 0.72 |
| **rs1610152** | G/G | 1442/2287 | **1.00** | ref. | | |
| | G/C or C/C | 142/228 | **1.04** | (0.74-1.47) | 0.97 | -- |
| **rs1609798** | G/G | 764/1194 | **1.00** | ref. | | |
| | G/A | 649/1046 | **1.02** | (0.84-1.22) | | |
| | A/A | 170/268 | **1.11** | (0.81-1.53) | 0.79 | 0.60 |
| **rs13117745** | G/G | 1147/1783 | **1.00** | ref. | | |
| | G/A | 395/678 | **0.91** | (0.74-1.12) | | |
| | A/A | 42/54 | **1.27** | (0.76-2.11) | 0.34 (0.99) | 0.85 |
| **rs12509517** | C/C | 791/1244 | **1.00** | ref. | | |
| | C/G | 634/1012 | **1.03** | (0.85-1.23) | | |
| | G/G | 159/260 | **1.08** | (0.78-1.48) | 0.90 | 0.66 |
| **rs10489113** | A/A | 1054/1639 | **1.00** | ref. | | |
| | A/G | 465/782 | **0.87** | (0.72-1.05) | | |
| | G/G | 64/94 | **0.95** | (0.62-1.47) | 0.36 (0.99) | 0.28 (0.99) |
| **rs10014309** | G/G | 1222/1920 | **1.00** | ref. | | |
| | G/A | 337/552 | **1.01** | (0.81-1.26) | | |
| | A/A | 25/42 | **0.96** | (0.51-1.78) | 0.98 | 0.99 |
| **rs997476** | C/C | 1385/2227 | **1.00** | ref. | | |
| | C/A or A/A | 196/289 | **1.16** | (0.88-1.54) | 0.57 | -- |

[a] Unaffected Sibling Controls, [b] No SNP was noteworthy at the 25% or 50% FDR level,

[c] When cases<5, only the dominant model was analyzed, [d] No G/G genotypes

### Table A.5: Associations between candidate SNPs and tagSNPs in *NFκB1* and risk of colon cancer adjusted for age and sex

| DB SNP ID | Genotype | Cases/ Controls[a] | OR | 95% CI | Global-p[b] ($P_{act}$) | p-trend ($P_{act}$) |
|---|---|---|---|---|---|---|
| Candidate SNP | | | | | | |
| **rs4648072** | A/A | 949/1512 | **1.00** | ref. | | |
| **M507V** | A/G[d] | 10/23 | **0.63** | (0.20-1.97) | 0.69 | -- |
| TagSNPs | | | | | | |
| **rs7674640** | A/A | 251/398 | **1.00** | ref. | | |
| | A/G | 458/768 | **0.93** | (0.72-1.20) | | |
| | G/G | 250/372 | **1.03** | (0.73-1.46) | 0.65 | 0.88 |
| **rs765789** | A/A | 640/996 | **1.00** | ref. | | |
| | A/T | 292/484 | **0.89** | (0.69-1.13) | | |
| | T/T | 27/55 | **0.63** | (0.35-1.14) | 0.26 (0.98) | 0.14 (0.88) |
| **rs6833962** | G/G | 760/1183 | **1.00** | ref. | | |
| | G/A | 161/261 | **0.94** | (0.69-1.29) | | |
| | A/A | 7/19 | **0.45** | (0.17-1.20) | 0.28 (0.99) | 0.35 (0.99) |
| **rs6813322** | G/G | 238/392 | **1.00** | ref. | | |
| | G/C | 464/764 | **1.02** | (0.79-1.32) | | |
| | C/C | 241/360 | **1.11** | (0.79-1.56) | 0.80 | 0.56 |
| **rs4698863** | G/G | 454/724 | **1.00** | ref. | | |
| | G/A | 394/650 | **1.03** | (0.81-1.3) | | |
| | A/A | 111/161 | **1.24** | (0.82-1.85) | 0.54 | 0.41 (0.99) |
| **rs4648141** | G/G | 674/1048 | **1.00** | ref. | | |
| | G/A | 263/449 | **0.81** | (0.63-1.06) | | |
| | A/A | 22/38 | **0.72** | (0.37-1.41) | 0.25 (0.98) | 0.11 (0.83) |
| **rs4648135** | A/A | 856/1379 | **1.00** | ref. | | |
| | A/G or G/G[d] | 102/154 | **1.21** | (0.78-1.86) | 0.66 | -- |
| **rs4648110** | T/T | 624/967 | **1.00** | ref. | | |
| | T/A | 307/508 | **0.87** | (0.68-1.11) | | |
| | A/A | 28/60 | **0.59** | (0.33-1.06) | 0.15 (0.90) | 0.08 (0.72) |
| **rs4648090** | G/G | 731/1136 | **1.00** | ref. | | |
| | G/A | 215/370 | **0.86** | (0.66-1.14) | | |
| | A/A | 12/28 | **0.50** | (0.21-1.15) | 0.19 (0.95) | 0.12 (0.86) |
| **rs4648022** | G/G | 811/1274 | **1.00** | ref. | | |
| | G/A or A/A | 148/259 | **0.88** | (0.64-1.22) | 0.73 | -- |
| **rs4648011** | A/A | 340/547 | **1.00** | ref. | | |
| | A/C | 451/730 | **1.03** | (0.80-1.31) | | |
| | C/C | 162/253 | **1.14** | (0.80-1.62) | 0.73 | 0.49 (0.99) |
| **rs4496586** | C/C | 272/398 | **1.00** | ref. | | |
| | C/G | 453/768 | **0.87** | (0.67-1.12) | | |
| | G/C | 233/363 | **0.92** | (0.65-1.31) | 0.52 | 0.64 |
| **rs3774964** | A/A | 390/640 | **1.00** | ref. | | |
| | A/G | 429/669 | **1.15** | (0.91-1.47) | | |
| | G/G | 140/226 | **1.19** | (0.83-1.71) | 0.47 (0.99) | 0.28 (0.99) |
| **rs3774934** | G/G | 785/1244 | **1.00** | ref. | | |
| | G/A | 164/281 | **0.86** | (0.64-1.16) | | |
| | A/A | 10/10 | **1.42** | (0.41-4.91) | 0.46 (0.99) | 0.49 (0.99) |
| **rs230525** | A/A | 423/685 | **1.00** | ref. | | |
| | A/G | 421/677 | **1.10** | (0.86-1.39) | | |
| | G/G | 112/173 | **1.19** | (0.8-1.78) | 0.62 | 0.35 (0.99) |
| **rs230521** | G/G | 350/572 | **1.00** | ref. | | |
| | G/C | 450/705 | **1.09** | (0.86-1.39) | | |
| | C/C | 158/258 | **1.10** | (0.78-1.57) | 0.76 | 0.82 |
| **rs230510** | T/T | 291/471 | **1.00** | ref. | | |
| | T/A | 473/764 | **0.99** | (0.78-1.26) | | |
| | A/A | 195/300 | **1.00** | (0.71-1.42) | 0.99 | 0.99 |
| **rs230506** | A/A | 816/1296 | **1.00** | ref. | | |
| | A/G | 135/232 | **0.82** | (0.59-1.14) | | |
| | G/G | 7/5 | **2.33** | (0.44-12.22) | 0.23 (0.97) | 0.46 (0.99) |

**Table A.5 continued: Associations between candidate SNPs and tagSNPs in *NFκB1* and risk of colon cancer adjusted for age and sex**

| DB SNP ID | Genotype | Cases/ Controls[a] | OR | 95% CI | Global-p[b] ($P_{act}$) | p-trend ($P_{act}$) |
|---|---|---|---|---|---|---|
| **rs230490** | G/G | 319/495 | **1.00** | ref. | | |
| | G/A | 461/768 | **0.96** | (0.76-1.22) | | |
| | A/A | 179/272 | **1.20** | (0.85-1.7) | 0.33 (0.99) | 0.42 (0.99) |
| **rs230489** | A/A | 751/1203 | **1.00** | ref. | | |
| | A/G | 195/318 | **0.98** | (0.73-1.3) | | |
| | G/G | 13/13 | **1.82** | (0.67-4.96) | 0.41 (0.99) | 0.77 |
| **rs230488** | G/G | 526/819 | **1.00** | ref. | | |
| | G/A | 379/617 | **0.93** | (0.74-1.16) | | |
| | A/A | 53/97 | **0.62** | (0.39-0.98) | 0.13 (0.87) | 0.10 (0.81) |
| **rs230487** | A/A | 489/738 | **1.00** | ref. | | |
| | A/C | 388/681 | **0.81** | (0.64-1.02) | | |
| | C/C | 82/116 | **1.09** | (0.71-1.69) | 0.10 (0.79) | 0.48 (0.99) |
| **rs228619** | G/G | 258/392 | **1.00** | ref. | | |
| | G/A | 462/766 | **0.91** | (0.7-1.18) | | |
| | A/A | 238/377 | **0.86** | (0.6-1.23) | 0.67 | 0.40 (0.99) |
| **rs228618** | C/C | 258/426 | **1.00** | ref. | | |
| | C/A | 472/762 | **1.14** | (0.89-1.48) | | |
| | A/A | 228/347 | **1.24** | (0.87-1.77) | 0.46 (0.99) | 0.24 (0.98) |
| **rs2085549** | A/A | 551/896 | **1.00** | ref. | | |
| | A/G | 352/546 | **1.10** | (0.87-1.39) | | |
| | G/G | 56/93 | **0.94** | (0.58-1.53) | 0.62 | 0.73 |
| **rs2085548** | G/G | 471/780 | **1.00** | ref. | | |
| | G/A | 405/615 | **1.15** | (0.91-1.45) | | |
| | A/A | 83/140 | **1.07** | (0.71-1.62) | 0.51 | 0.44 (0.99) |
| **rs1610152** | G/G | 868/1401 | **1.00** | ref. | | |
| | G/C or C/C | 91/133 | **1.30** | (0.82-2.05) | 0.50 | -- |
| **rs1609798** | G/G | 461/743 | **1.00** | ref. | | |
| | G/A | 392/632 | **1.11** | (0.87-1.41) | | |
| | A/A | 106/155 | **1.30** | (0.86-1.96) | 0.42 (0.99) | 0.21 (0.96) |
| **rs13117745** | G/G | 693/1083 | **1.00** | ref. | | |
| | G/A | 248/423 | **0.89** | (0.68-1.16) | | |
| | A/A | 18/29 | **0.82** | (0.40-1.67) | 0.64 | 0.36 (0.99) |
| **rs12509517** | C/C | 480/770 | **1.00** | ref. | | |
| | C/G | 379/613 | **1.09** | (0.86-1.38) | | |
| | G/G | 100/152 | **1.23** | (0.81-1.85) | 0.58 | 0.59 |
| **rs10489113** | A/A | 643/996 | **1.00** | ref. | | |
| | A/G | 289/480 | **0.85** | (0.66-1.08) | | |
| | G/G | 27/59 | **0.53** | (0.29-0.97) | 0.07 (0.70) | **0.038** (0.48) |
| **rs10014309** | G/G | 758/1194 | **1.00** | ref. | | |
| | G/A | 186/320 | **0.92** | (0.7-1.22) | | |
| | A/A | 15/21 | **1.16** | (0.45-2.99) | 0.76 | 0.93 |
| **rs997476** | C/C | 842/1356 | **1.00** | ref. | | |
| | C/A or A/A | 115/179 | **0.97** | (0.68-1.38) | 0.99 | -- |

[a] Unaffected Sibling Controls, [b] No SNP was noteworthy at the 25% or 50% FDR level,

[c] When cases<5, only the dominant model was analyzed, [d] No G/G genotypes

**Table A.6: Associations between candidate SNPs and tagSNPs in *NFκB1* and risk of rectal cancer adjusted for age and sex**

| DB SNP ID | Genotype | Cases/ Controls[a] | OR | 95% CI | Global-p[b] ($P_{act}$) | p-trend ($P_{act}$) |
|---|---|---|---|---|---|---|
| Candidate SNP | | | | | | |
| **rs4648072** | A/A | 499/826 | **1.00** | ref. | | |
| **M507V** | A/G[d] | 6/13 | **0.64** | (0.10-4.12) | 0.84 | -- |
| TagSNPs | | | | | | |
| **rs7674640** | A/A | 127/234 | **1.00** | ref. | | |
| | A/G | 259/402 | **1.10** | (0.78-1.54) | | |
| | G/G | 119/202 | **0.97** | (0.61-1.54) | 0.72 | 0.90 |
| **rs765789** | A/A | 333/551 | **1.00** | ref. | | |
| | A/T | 146/258 | **0.94** | (0.67-1.32) | | |
| | T/T | 26/29 | **2.00** | (0.95-4.22) | 0.12 (0.86) | 0.45 (0.99) |
| **rs6833962** | G/G | 410/656 | **1.00** | ref. | | |
| | G/A or A/A[d] | 80/148 | **0.77** | (0.49-1.2) | 0.49 (0.99) | -- |
| **rs6813322** | G/G | 130/230 | **1.00** | ref. | | |
| | G/C | 249/398 | **0.97** | (0.68-1.38) | | |
| | C/C | 120/201 | **0.98** | (0.62-1.54) | 0.99 | 0.93 |
| **rs4698863** | G/G | 240/383 | **1.00** | ref. | | |
| | G/A | 213/355 | **0.91** | (0.66-1.26) | | |
| | A/A | 51/101 | **0.84** | (0.49-1.44) | 0.78 | 0.78 |
| **rs4648141** | G/G | 349/579 | **1.00** | ref. | | |
| | G/A | 135/233 | **0.95** | (0.66-1.35) | | |
| | A/A | 21/26 | **1.90** | (0.82-4.41) | 0.22 (0.97) | 0.55 |
| **rs4648135** | A/A | 455/742 | **1.00** | ref. | | |
| | A/G or G/G | 50/96 | **0.73** | (0.42-1.26) | 0.48 (0.99) | -- |
| **rs4648110** | T/T | 321/533 | **1.00** | ref. | | |
| | T/A | 154/265 | **0.98** | (0.7-1.37) | | |
| | A/A | 30/41 | **1.55** | (0.77-3.11) | 0.40 (0.99) | 0.52 (1.00) |
| **rs4648090** | G/G | 380/620 | **1.00** | ref. | | |
| | G/A | 114/205 | **0.85** | (0.57-1.25) | | |
| | A/A | 11/14 | **1.53** | (0.52-4.47) | 0.42 (0.99) | 0.69 |
| **rs4648022** | G/G | 425/689 | **1.00** | ref. | | |
| | G/A | 73/141 | **0.83** | (0.53-1.3) | | |
| | A/A | 7/7 | **3.33** | (0.53-20.85) | 0.16 (0.93) | 0.88 |
| **rs4648011** | A/A | 194/307 | **1.00** | ref. | | |
| | A/C | 228/372 | **0.86** | (0.61-1.21) | | |
| | C/C | 81/156 | **0.76** | (0.47-1.23) | 0.50 (0.99) | 0.25 (0.98) |
| **rs4496586** | C/C | 130/225 | **1.00** | ref. | | |
| | C/G | 257/402 | **1.13** | (0.80-1.59) | | |
| | G/C | 115/210 | **1.09** | (0.69-1.74) | 0.78 | 0.69 |
| **rs3774964** | A/A | 216/341 | **1.00** | ref. | | |
| | A/G | 217/359 | **0.90** | (0.64-1.26) | | |
| | G/G | 72/139 | **0.83** | (0.5-1.38) | 0.73 | 0.44 (0.99) |
| **rs3774934** | G/G | 414/681 | **1.00** | ref. | | |
| | G/A | 86/146 | **0.98** | (0.63-1.53) | | |
| | A/A | 5/12 | **0.96** | (0.23-3.91) | 0.99 | 0.92 |
| **rs230525** | A/A | 231/380 | **1.00** | ref. | | |
| | A/G | 220/354 | **0.98** | (0.71-1.36) | | |
| | G/G | 52/103 | **0.83** | (0.51-1.37) | 0.77 | 0.57 |
| **rs230521** | G/G | 197/318 | **1.00** | ref. | | |
| | G/C | 228/367 | **0.91** | (0.65-1.28) | | |
| | C/C | 79/152 | **0.80** | (0.50-1.28) | 0.65 | 0.36 (0.99) |
| **rs230510** | T/T | 151/281 | **1.00** | ref. | | |
| | T/A | 249/387 | **1.18** | (0.85-1.65) | | |
| | A/A | 104/171 | **1.12** | (0.70-1.78) | 0.63 | 0.60 |
| **rs230506** | A/A | 431/715 | **1.00** | ref. | | |
| | A/G | 67/114 | **1.02** | (0.62-1.71) | | |
| | G/G | 6/10 | **1.37** | (0.33-5.63) | 0.90 | 0.78 |

**Table A.6 continued: Associations between candidate SNPs and tagSNPs in *NFκB1* and risk of rectal cancer adjusted for age and sex**

| DB SNP ID | Genotype | Cases/ Controls[a] | OR | 95% CI | Global-p[b] ($P_{act}$) | p-trend ($P_{act}$) |
|---|---|---|---|---|---|---|
| **rs230490** | G/G | 182/290 | **1.00** | ref. | | |
| | G/A | 234/403 | **0.78** | (0.56-1.09) | | |
| | A/A | 89/146 | **0.80** | (0.48-1.33) | 0.35 (0.99) | 0.28 (0.99) |
| **rs230489** | A/A | 408/662 | **1.00** | ref. | | |
| | A/G | 89/162 | **0.82** | (0.54-1.24) | | |
| | G/G | 7/15 | **0.91** | (0.30-2.71) | 0.60 | 0.39 (0.99) |
| **rs230488** | G/G | 257/442 | **1.00** | ref. | | |
| | G/A | 218/331 | **1.25** | (0.91-1.72) | | |
| | A/A | 30/64 | **1.15** | (0.59-2.24) | 0.39 (0.99) | 0.31 (0.99) |
| **rs230487** | A/A | 263/449 | **1.00** | ref. | | |
| | A/C | 204/324 | **1.05** | (0.75-1.47) | | |
| | C/C | 38/66 | **1.07** | (0.59-1.95) | 0.96 | 0.77 |
| **rs228619** | G/G | 131/229 | **1.00** | ref. | | |
| | G/A | 243/385 | **1.15** | (0.82-1.61) | | |
| | A/A | 129/225 | **1.10** | (0.69-1.75) | 0.73 | 0.65 |
| **rs228618** | C/C | 145/249 | **1.00** | ref. | | |
| | C/A | 245/390 | **1.00** | (0.71-1.42) | | |
| | A/A | 115/200 | **0.92** | (0.58-1.45) | 0.88 | 0.71 |
| **rs2085549** | A/A | 282/463 | **1.00** | ref. | | |
| | A/G | 191/308 | **1.06** | (0.76-1.48) | | |
| | G/G | 32/68 | **1.03** | (0.57-1.87) | 0.95 | 0.81 |
| **rs2085548** | G/G | 247/394 | **1.00** | ref. | | |
| | G/A | 208/342 | **0.94** | (0.67-1.32) | | |
| | A/A | 50/101 | **0.94** | (0.55-1.60) | 0.93 | 0.75 |
| **rs1610152** | G/G | 461/754 | **1.00** | ref. | | |
| | G/C or C/C | 44/85 | **0.72** | (0.4-1.28) | 0.49 | -- |
| **rs1609798** | G/G | 243/384 | **1.00** | ref. | | |
| | G/A | 211/354 | **0.92** | (0.66-1.28) | | |
| | A/A | 50/98 | **0.89** | (0.52-1.52) | 0.86 | 0.59 |
| **rs13117745** | G/G | 361/592 | **1.00** | ref. | | |
| | G/A | 125/221 | **0.98** | (0.69-1.4) | | |
| | A/A | 19/25 | **1.78** | (0.74-4.3) | 0.35 (0.99) | 0.54 |
| **rs12509517** | C/C | 251/407 | **1.00** | ref. | | |
| | C/G | 210/340 | **1.00** | (0.71-1.4) | | |
| | G/G | 44/92 | **0.90** | (0.52-1.56) | 0.92 | 0.79 |
| **rs10489113** | A/A | 332/549 | **1.00** | ref. | | |
| | A/G | 145/260 | **0.89** | (0.63-1.26) | | |
| | G/G | 28/29 | **2.13** | (1.02-4.46) | 0.06 (0.63) | 0.49 (0.99) |
| **rs10014309** | G/G | 368/618 | **1.00** | ref. | | |
| | G/A | 129/204 | **1.25** | (0.84-1.88) | | |
| | A/A | 8/16 | **0.91** | (0.35-2.35) | 0.47 (0.99) | 0.46 (0.99) |
| **rs997476** | C/C | 437/740 | **1.00** | ref. | | |
| | C/A or A/A | 68/99 | **1.58** | (0.96-2.61) | 0.19 (0.96) | -- |

[a] Unaffected Sibling Controls, [b] No SNP was noteworthy at the 25% or 50% FDR level,

[c] When cases<5, only the dominant model was analyzed, [d] No G/G genotypes

**Table A.7: Interaction between rs5029748 in *IκBKβ* and SNPs in *IκBKβ* and *NFκB1* on the risk of colon cancer[a]**

| SNP 1 genotype | SNP 2 genotype | Cases | Controls | OR | 95% CI | Global-p | Interaction-p[b] |
|---|---|---|---|---|---|---|---|
| **rs5029748 from *IκBKβ* combined with other *IκBKβ* genotypes** | | | | | | | |
| ***IκBKβ*** | ***IκBKβ*** | | | | | | |
| **rs5029748** | **rs2272733** | | | | | | |
| C/C | G/G | 426 | 629 | **1.00** | ref. | | |
| C/A or A/A | G/G | 331 | 571 | **0.72** | (0.56-0.93) | | |
| C/C | G/A or A/A | 154 | 244 | **0.96** | (0.68-1.34) | | |
| C/A or A/A | G/A or A/A | 48 | 90 | **0.64** | (0.40-1.03) | **0.05** | 0.81 |
| **rs5029748** | **rs3747811** | | | | | | |
| C/C | T/T | 290 | 439 | **1.00** | ref. | | |
| C/A or A/A | T/T | 2 | 3 | n/a | -- | | |
| C/C | T/A or A/A | 290 | 434 | **0.97** | (0.73-1.30) | | |
| C/A or A/A | T/A or A/A | 377 | 658 | **0.71** | (0.54-0.93) | **0.02** | 0.46 |
| **rs5029748** | **rs6474387** | | | | | | |
| C/C | C/C | 473 | 712 | **1.00** | ref. | | |
| C/A or A/A | C/C | 352 | 596 | **0.75** | (0.59-0.96) | | |
| C/C | C/T or T/T | 100 | 145 | **1.11** | (0.73-1.67) | | |
| C/A or A/A | C/T or T/T | 22 | 61 | **0.39** | (0.21-0.75) | **0.004** | 0.07 |
| **rs5029748** | **rs9694958** | | | | | | |
| C/C | A/A | 468 | 691 | **1.00** | ref. | | |
| C/A or A/A | A/A | 341 | 595 | **0.70** | (0.55-0.90) | | |
| C/C | A/G or G/G | 112 | 181 | **0.93** | (0.64-1.35) | | |
| C/A or A/A | A/G or G/G | 38 | 67 | **0.76** | (0.45-1.28) | **0.05** | 0.62 |
| **rs5029748** | **rs10217111** | | | | | | |
| C/C | G/G | 324 | 500 | **1.00** | ref. | | |
| C/A or A/A | G/G | 294 | 511 | **0.73** | (0.55-0.97) | | |
| C/C | G/C or C/C | 256 | 373 | **1.10** | (0.81-1.51) | | |
| C/A or A/A | G/C or C/C | 85 | 150 | **0.79** | (0.54-1.16) | **0.04** | 0.92 |
| **rs5029748** | **rs10958713** | | | | | | |
| C/C | G/G | 451 | 670 | **1.00** | ref. | | |
| C/A or A/A | G/G | 0 | 1 | n/a | -- | | |
| C/C | G/A or A/A | 129 | 203 | **0.82** | (0.57-1.19) | | |
| C/A or A/A | G/A or A/A | 378 | 661 | **0.68** | (0.53-0.88) | **0.01** | 0.26 |
| **rs5029748** | **rs11986055** | | | | | | |
| C/C | A/A | 522 | 791 | **1.00** | ref. | | |
| C/A or A/A | A/A | 365 | 624 | **0.74** | (0.58-0.95) | | |
| C/C | A/C or C/C | 58 | 82 | **1.12** | (0.66-1.92) | | |
| C/A or A/A | A/C or C/C | 14 | 37 | **0.47** | (0.21-1.06) | **0.03** | 0.20 |
| **rs5029748 from *IκBKβ* combined with *NFκB1* genotypes** | | | | | | | |
| ***IκBKβ*** | ***NFκB1*** | | | | | | |
| **rs5029748** | **rs7674640** | | | | | | |
| C/C | A/A | 142 | 224 | **1.00** | ref. | | |
| C/A or A/A | A/A | 109 | 171 | **0.83** | (0.56-1.24) | | |
| C/C | A/G or G/G | 438 | 649 | **1.03** | (0.75-1.41) | | |
| C/A or A/A | A/G or G/G | 270 | 491 | **0.69** | (0.49-0.99) | **0.03** | 0.34 |
| **rs5029748** | **rs765789** | | | | | | |
| C/C | A/A | 392 | 564 | **1.00** | ref. | | |
| C/A or A/A | A/A | 248 | 432 | **0.67** | (0.50-0.90) | | |
| C/C | A/T or T/T | 188 | 309 | **0.80** | (0.60-1.09) | | |
| C/A or A/A | A/T or T/T | 131 | 230 | **0.64** | (0.45-0.92) | **0.02** | 0.40 |
| **rs5029748** | **rs6833962** | | | | | | |
| C/C | G/G | 455 | 665 | **1.00** | ref. | | |
| C/A or A/A | G/G | 305 | 518 | **0.75** | (0.58-0.98) | | |
| C/C | G/A or A/A | 106 | 164 | **1.02** | (0.70-1.46) | | |
| C/A or A/A | G/A or A/A | 62 | 116 | **0.74** | (0.48-1.14) | 0.11 | 0.90 |

**Table A.7 continued: Interaction between rs5029748 in *IκBKβ* and SNPs in *IκBKβ* and *NFκB1* on the risk of colon cancer[a]**

| SNP 1 genotype | SNP 2 genotype | Cases | Controls | OR | 95% CI | Global-p | Interaction-p[b] |
|---|---|---|---|---|---|---|---|
| **rs5029748** | **rs6813322** | | | | | | |
| C/C | G/G | 142 | 229 | **1.00** | ref. | | |
| C/A or A/A | G/G | 96 | 163 | **0.78** | (0.53-1.15) | | |
| C/C | G/C or C/C | 429 | 630 | **1.09** | (0.81-1.47) | | |
| C/A or A/A | G/C or C/C | 276 | 494 | **0.73** | (0.53-1.01) | **0.02** | 0.43 |
| **rs5029748** | **rs4698863** | | | | | | |
| C/C | G/G | 276 | 416 | **1.00** | ref. | | |
| C/A or A/A | G/G | 178 | 308 | **0.71** | (0.51-0.99) | | |
| C/C | G/A or A/A | 304 | 457 | **1.03** | (0.77-1.39) | | |
| C/A or A/A | G/A or A/A | 201 | 354 | **0.74** | (0.53-1.05) | **0.05** | 0.96 |
| **rs5029748** | **rs4648141** | | | | | | |
| C/C | G/G | 412 | 582 | **1.00** | ref. | | |
| C/A or A/A | G/G | 262 | 466 | **0.65** | (0.49-0.87) | | |
| C/C | G/A or A/A | 138 | 291 | **0.72** | (0.52-0.99) | | |
| C/A or A/A | G/A or A/A | 117 | 196 | **0.63** | (0.43-0.90) | **0.01** | 0.17 |
| **rs5029748** | **rs4648135** | | | | | | |
| C/C | A/A | 518 | 782 | **1.00** | ref. | | |
| C/A or A/A | A/A | 338 | 597 | **0.71** | (0.55-0.91) | | |
| C/C | A/G or G/G | 61 | 89 | **1.14** | (0.68-1.90) | | |
| C/A or A/A | A/G or G/G | 41 | 65 | **0.95** | (0.50-1.80) | **0.03** | 0.60 |
| **rs5029748** | **rs4648110** | | | | | | |
| C/C | T/T | 380 | 537 | **1.00** | ref. | | |
| C/A or A/A | T/T | 244 | 430 | **0.66** | (0.50-0.89) | | |
| C/C | T/A or A/A | 200 | 336 | **0.78** | (0.58-1.05) | | |
| C/A or A/A | T/A or A/A | 135 | 232 | **0.62** | (0.44-0.89) | **0.01** | 0.35 |
| **rs5029748** | **rs4648090** | | | | | | |
| C/C | G/G | 436 | 632 | **1.00** | ref. | | |
| C/A or A/A | G/G | 295 | 504 | **0.71** | (0.54-0.93) | | |
| C/C | G/A or A/A | 143 | 241 | **0.83** | (0.60-1.14) | | |
| C/A or A/A | G/A or A/A | 84 | 157 | **0.61** | (0.42-0.90) | **0.03** | 0.81 |
| **rs5029748** | **rs4648072** | | | | | | |
| C/C | A/A | 573 | 857 | **1.00** | ref. | | |
| C/A or A/A | A/A | 376 | 655 | **0.71** | (0.56-0.91) | | |
| C/C | A/G or G/G | 7 | 16 | **0.62** | (0.16-2.46) | | |
| C/A or A/A | A/G or G/G | 3 | 7 | **0.36** | (0.06-2.04) | **0.03** | 0.85 |
| **rs5029748** | **rs4648022** | | | | | | |
| C/C | G/G | 484 | 709 | **1.00** | ref. | | |
| C/A or A/A | G/G | 327 | 565 | **0.70** | (0.54-0.90) | | |
| C/C | G/A or A/A | 96 | 163 | **0.83** | (0.56-1.23) | | |
| C/A or A/A | G/A or A/A | 52 | 96 | **0.69** | (0.44-1.08) | **0.03** | 0.50 |
| **rs5029748** | **rs4648011** | | | | | | |
| C/C | A/A | 210 | 312 | **1.00** | ref. | | |
| C/A or A/A | A/A | 130 | 235 | **0.68** | (0.47-0.97) | | |
| C/C | A/C or C/C | 367 | 557 | **0.98** | (0.73-1.33) | | |
| C/A or A/A | A/C or C/C | 246 | 426 | **0.71** | (0.50-1.01) | **0.04** | 0.90 |
| **rs5029748** | **rs4496586** | | | | | | |
| C/C | C/C | 166 | 222 | **1.00** | ref. | | |
| C/A or A/A | C/C | 106 | 176 | **0.67** | (0.44-1.02) | | |
| C/C | C/G or G/G | 413 | 648 | **0.83** | (0.60-1.15) | | |
| C/A or A/A | C/G or G/G | 273 | 483 | **0.62** | (0.43-0.90) | **0.04** | 0.60 |
| **rs5029748** | **rs3774968** | | | | | | |
| C/C | G/G | 168 | 276 | **1.00** | ref. | | |
| C/A or A/A | G/G | 132 | 225 | **0.81** | (0.56-1.16) | | |
| C/C | G/A or A/A | 412 | 597 | **1.13** | (0.84-1.52) | | |
| C/A or A/A | G/A or A/A | 247 | 437 | **0.76** | (0.54-1.06) | **0.03** | 0.38 |

**Table A.7 continued: Interaction between rs5029748 in *IκBKβ* and SNPs in *IκBKβ* and *NFκB1* on the risk of colon cancer[a]**

| SNP 1 genotype | SNP 2 genotype | Cases | Controls | OR | 95% CI | Global-p | Interaction-p[b] |
|---|---|---|---|---|---|---|---|
| **rs5029748** | **rs3774964** | | | | | | |
| C/C | A/A | 242 | 365 | **1.00** | ref. | | |
| C/A or A/A | A/A | 148 | 275 | **0.64** | (0.46-0.90) | | |
| C/C | A/G or G/G | 338 | 508 | **1.05** | (0.78-1.42) | | |
| C/A or A/A | A/G or G/G | 231 | 387 | **0.82** | (0.58-1.16) | **0.02** | 0.35 |
| **rs5029748** | **rs3774934** | | | | | | |
| C/C | G/G | 472 | 705 | **1.00** | ref. | | |
| C/A or A/A | G/G | 313 | 539 | **0.72** | (0.56-0.93) | | |
| C/C | G/A or A/A | 108 | 168 | **0.90** | (0.61-1.31) | | |
| C/A or A/A | G/A or A/A | 66 | 123 | **0.60** | (0.39-0.94) | **0.03** | 0.78 |
| **rs5029748** | **rs230525** | | | | | | |
| C/C | A/A | 262 | 397 | **1.00** | ref. | | |
| C/A or A/A | A/A | 161 | 288 | **0.70** | (0.51-0.98) | | |
| C/C | A/G or G/G | 316 | 476 | **1.08** | (0.80-1.44) | | |
| C/A or A/A | A/G or G/G | 217 | 374 | **0.77** | (0.54-1.08) | **0.03** | 0.98 |
| **rs5029748** | **rs230521** | | | | | | |
| C/C | G/G | 217 | 326 | **1.00** | ref. | | |
| C/A or A/A | G/G | 133 | 246 | **0.67** | (0.47-0.96) | | |
| C/C | G/C or C/C | 362 | 547 | **1.03** | (0.76-1.39) | | |
| C/A or A/A | G/C or C/C | 246 | 416 | **0.77** | (0.54-1.09) | **0.04** | 0.64 |
| **rs5029748** | **rs230510** | | | | | | |
| C/C | T/T | 163 | 261 | **1.00** | ref. | | |
| C/A or A/A | T/T | 128 | 210 | **0.80** | (0.55-1.15) | | |
| C/C | T/A or A/A | 417 | 612 | **1.06** | (0.78-1.44) | | |
| C/A or A/A | T/A or A/A | 251 | 452 | **0.72** | (0.51-1.01) | **0.04** | 0.45 |
| **rs5029748** | **rs230506** | | | | | | |
| C/C | A/A | 491 | 736 | **1.00** | ref. | | |
| C/A or A/A | A/A | 325 | 560 | **0.73** | (0.57-0.93) | | |
| C/C | A/G or G/G | 89 | 136 | **0.89** | (0.59-1.35) | | |
| C/A or A/A | A/G or G/G | 53 | 101 | **0.56** | (0.35-0.90) | **0.03** | 0.62 |
| **rs5029748** | **rs230490** | | | | | | |
| C/C | G/G | 192 | 289 | **1.00** | ref. | | |
| C/A or A/A | G/G | 127 | 206 | **0.77** | (0.53-1.12) | | |
| C/C | G/A or A/A | 388 | 584 | **1.02** | (0.76-1.38) | | |
| C/A or A/A | G/A or A/A | 252 | 456 | **0.71** | (0.50-1.01) | **0.05** | 0.63 |
| **rs5029748** | **rs230489** | | | | | | |
| C/C | A/A | 458 | 694 | **1.00** | ref. | | |
| C/A or A/A | A/A | 293 | 509 | **0.73** | (0.56-0.94) | | |
| C/C | A/G or G/G | 122 | 178 | **1.04** | (0.73-1.48) | | |
| C/A or A/A | A/G or G/G | 86 | 153 | **0.69** | (0.46-1.05) | **0.05** | 0.71 |
| **rs5029748** | **rs230488** | | | | | | |
| C/C | G/G | 316 | 452 | **1.00** | ref. | | |
| C/A or A/A | G/G | 210 | 367 | **0.69** | (0.52-0.93) | | |
| C/C | G/A or A/A | 263 | 420 | **0.89** | (0.68-1.16) | | |
| C/A or A/A | G/A or A/A | 169 | 294 | **0.67** | (0.48-0.94) | **0.04** | 0.64 |
| **rs5029748** | **rs230487** | | | | | | |
| C/C | A/A | 308 | 413 | **1.00** | ref. | | |
| C/A or A/A | A/A | 181 | 325 | **0.62** | (0.45-0.84) | | |
| C/C | A/C or C/C | 272 | 460 | **0.72** | (0.54-0.97) | | |
| C/A or A/A | A/C or C/C | 198 | 337 | **0.60** | (0.43-0.84) | **0.01** | 0.14 |

**Table A.7 continued: Interaction between rs5029748 in *IκBKβ* and SNPs in *IκBKβ* and *NFκB1* on the risk of colon cancer**[a]

| SNP 1 genotype | SNP 2 genotype | Cases | Controls | OR | 95% CI | Global-p | Interaction-p[b] |
|---|---|---|---|---|---|---|---|
| **rs5029748** | **rs228619** | | | | | | |
| C/C | G/G | 157 | 213 | **1.00** | ref. | | |
| C/A or A/A | G/G | 101 | 179 | **0.60** | (0.39-0.92) | | |
| C/C | G/A or A/A | 422 | 660 | **0.81** | (0.59-1.13) | | |
| C/A or A/A | G/A or A/A | 278 | 483 | **0.62** | (0.43-0.90) | **0.02** | 0.30 |
| **rs5029748** | **rs228618** | | | | | | |
| C/C | C/C | 154 | 247 | **1.00** | ref. | | |
| C/A or A/A | C/C | 104 | 179 | **0.82** | (0.56-1.22) | | |
| C/C | C/A or A/A | 425 | 626 | **1.27** | (0.93-1.74) | | |
| C/A or A/A | C/A or A/A | 275 | 483 | **0.86** | (0.61-1.21) | **0.02** | 0.35 |
| **rs5029748** | **rs2085549** | | | | | | |
| C/C | A/A | 339 | 513 | **1.00** | ref. | | |
| C/A or A/A | A/A | 212 | 383 | **0.69** | (0.52-0.92) | | |
| C/C | A/G or G/G | 241 | 360 | **1.04** | (0.77-1.40) | | |
| C/A or A/A | A/G or G/G | 167 | 279 | **0.78** | (0.56-1.10) | **0.04** | 0.65 |
| **rs5029748** | **rs2085548** | | | | | | |
| C/C | G/G | 290 | 443 | **1.00** | ref. | | |
| C/A or A/A | G/G | 181 | 337 | **0.67** | (0.49-0.91) | | |
| C/C | G/A or A/A | 290 | 430 | **1.06** | (0.79-1.43) | | |
| C/A or A/A | G/A or A/A | 198 | 325 | **0.82** | (0.58-1.15) | **0.03** | 0.49 |
| **rs5029748** | **rs1610152** | | | | | | |
| C/C | G/G | 527 | 797 | **1.00** | ref. | | |
| C/A or A/A | G/G | 341 | 604 | **0.70** | (0.54-0.90) | | |
| C/C | G/C or C/C | 53 | 75 | **1.18** | (0.68-2.03) | | |
| C/A or A/A | G/C or C/C | 38 | 58 | **1.06** | (0.54-2.07) | **0.02** | 0.49 |
| **rs5029748** | **rs1609798** | | | | | | |
| C/C | G/G | 282 | 428 | **1.00** | ref. | | |
| C/A or A/A | G/G | 179 | 315 | **0.73** | (0.53-1.00) | | |
| C/C | G/A or A/A | 298 | 444 | **1.13** | (0.84-1.51) | | |
| C/A or A/A | G/A or A/A | 200 | 343 | **0.84** | (0.60-1.19) | 0.05 | 0.83 |
| **rs5029748** | **rs13117745** | | | | | | |
| C/C | G/G | 423 | 603 | **1.00** | ref. | | |
| C/A or A/A | G/G | 270 | 480 | **0.66** | (0.50-0.87) | | |
| C/C | G/A or A/A | 157 | 270 | **0.78** | (0.56-1.08) | | |
| C/A or A/A | G/A or A/A | 109 | 182 | **0.69** | (0.48-1.01) | **0.02** | 0.17 |
| **rs5029748** | **rs12509517** | | | | | | |
| C/C | C/C | 295 | 448 | **1.00** | ref. | | |
| C/A or A/A | C/C | 185 | 322 | **0.70** | (0.51-0.96) | | |
| C/C | C/G or G/G | 285 | 425 | **1.07** | (0.80-1.43) | | |
| C/A or A/A | C/G or G/G | 194 | 340 | **0.78** | (0.56-1.10) | **0.04** | 0.83 |
| **rs5029748** | **rs10489113** | | | | | | |
| C/C | A/A | 394 | 560 | **1.00** | ref. | | |
| C/A or A/A | A/A | 249 | 436 | **0.67** | (0.50-0.90) | | |
| C/C | A/G or G/G | 186 | 313 | **0.76** | (0.56-1.03) | | |
| C/A or A/A | A/G or G/G | 130 | 226 | **0.61** | (0.43-0.87) | **0.01** | 0.42 |
| **rs5029748** | **rs10014309** | | | | | | |
| C/C | G/G | 458 | 676 | **1.00** | ref. | | |
| C/A or A/A | G/G | 300 | 518 | **0.69** | (0.53-0.90) | | |
| C/C | G/A or A/A | 122 | 197 | **0.87** | (0.63-1.21) | | |
| C/A or A/A | G/A or A/A | 79 | 144 | **0.69** | (0.46-1.03) | **0.04** | 0.58 |

[a] Adjusted for age and sex

[b] No SNP was noteworthy at the 25% or 50% level

**Table A.8: Interaction between rs10958713 in *IκBKβ* and SNPs in *IκBKβ* and *NFκB1* on the risk of colon cancer[a]**

| SNP 1 genotype | SNP 2 genotype | Cases | Controls | OR | 95% CI | Global-p | Interaction-p[b] |
|---|---|---|---|---|---|---|---|
| **rs10958713 from *IκBKβ* combined with other *IκBKβ* genotypes** | | | | | | | |
| ***IκBKβ*** | ***IκBKβ*** | | | | | | |
| **rs10958713** | **rs2272733** | | | | | | |
| G/G | G/G | 317 | 467 | **1.00** | ref. | | |
| G/A or A/A | G/G | 439 | 733 | **0.75** | (0.58-0.97) | | |
| G/G | G/A or A/A | 134 | 204 | **1.05** | (0.73-1.51) | | |
| G/A or A/A | G/A or A/A | 68 | 130 | **0.61** | (0.40-0.93) | **0.03** | 0.32 |
| **rs10958713** | **rs3747811** | | | | | | |
| G/G | T/T | 286 | 435 | **1.00** | ref. | | |
| G/A or A/A | T/T | 6 | 7 | **2.58** | (0.30-22.20) | | |
| G/G | T/A or A/A | 165 | 236 | **1.11** | (0.79-1.57) | | |
| G/A or A/A | T/A or A/A | 501 | 856 | **0.74** | (0.57-0.96) | **0.03** | 0.19 |
| **rs10958713** | **rs6474387** | | | | | | |
| G/G | C/C | 358 | 532 | **1.00** | ref. | | |
| G/A or A/A | C/C | 466 | 776 | **0.76** | (0.60-0.97) | | |
| G/G | C/T or T/T | 86 | 127 | **1.14** | (0.73-1.77) | | |
| G/A or A/A | C/T or T/T | 36 | 79 | **0.51** | (0.29-0.87) | **0.01** | 0.17 |
| **rs10958713** | **rs9694958** | | | | | | |
| G/G | A/A | 351 | 520 | **1.00** | ref. | | |
| G/A or A/A | A/A | 457 | 766 | **0.73** | (0.57-0.94) | | |
| G/G | A/G or G/G | 100 | 151 | **1.04** | (0.70-1.55) | | |
| G/A or A/A | A/G or G/G | 50 | 97 | **0.65** | (0.40-1.06) | **0.05** | 0.58 |
| **rs10958713** | **rs10217111** | | | | | | |
| G/G | G/G | 231 | 341 | **1.00** | ref. | | |
| G/A or A/A | G/G | 386 | 670 | **0.69** | (0.52-0.93) | | |
| G/G | G/C or C/C | 220 | 330 | **1.00** | (0.71-1.40) | | |
| G/A or A/A | G/C or C/C | 121 | 193 | **0.78** | (0.53-1.13) | **0.04** | 0.59 |
| **rs10958713** | **rs11986055** | | | | | | |
| G/G | A/A | 398 | 597 | **1.00** | ref. | | |
| G/A or A/A | A/A | 488 | 818 | **0.74** | (0.58-0.95) | | |
| G/G | A/C or C/C | 53 | 74 | **1.18** | (0.68-2.07) | | |
| G/A or A/A | A/C or C/C | 19 | 45 | **0.50** | (0.23-1.06) | **0.02** | 0.17 |
| **rs10958713 from *IκBKβ* combined with *NFκB1* genotypes** | | | | | | | |
| ***IκBKβ*** | ***NFκB1*** | | | | | | |
| **rs10958713** | **rs7674640** | | | | | | |
| G/G | A/A | 108 | 171 | **1.00** | ref. | | |
| G/A or A/A | A/A | 143 | 224 | **0.81** | (0.54-1.21) | | |
| G/G | A/G or G/G | 343 | 500 | **1.04** | (0.72-1.49) | | |
| G/A or A/A | A/G or G/G | 364 | 640 | **0.71** | (0.49-1.02) | **0.04** | 0.45 |
| **rs10958713** | **rs765789** | | | | | | |
| G/G | A/A | 304 | 439 | **1.00** | ref. | | |
| G/A or A/A | A/A | 335 | 557 | **0.69** | (0.52-0.91) | | |
| G/G | A/T or T/T | 147 | 232 | **0.82** | (0.58-1.15) | | |
| G/A or A/A | A/T or T/T | 172 | 307 | **0.63** | (0.45-0.89) | **0.03** | 0.57 |
| **rs10958713** | **rs6833962** | | | | | | |
| G/G | G/G | 355 | 516 | **1.00** | ref. | | |
| G/A or A/A | G/G | 404 | 667 | **0.77** | (0.60-0.99) | | |
| G/G | G/A or A/A | 79 | 122 | **1.00** | (0.66-1.53) | | |
| G/A or A/A | G/A or A/A | 89 | 158 | **0.80** | (0.54-1.18) | 0.20 | 0.64 |
| **rs10958713** | **rs6813322** | | | | | | |
| G/G | G/G | 107 | 177 | **1.00** | ref. | | |
| G/A or A/A | G/G | 131 | 215 | **0.80** | (0.54-1.19) | | |
| G/G | G/C or C/C | 336 | 484 | **1.13** | (0.81-1.58) | | |
| G/A or A/A | G/C or C/C | 368 | 640 | **0.76** | (0.55-1.06) | **0.03** | 0.32 |

**Table A.8 continued: Interaction between rs10958713 in *IκBKβ* and SNPs in *IκBKβ* and *NFκB1* on the risk of colon cancer[a]**

| SNP 1 genotype | SNP 2 genotype | Cases | Controls | OR | 95% CI | Global-p | Interaction-p[b] |
|---|---|---|---|---|---|---|---|
| **rs10958713** | **rs4698863** | | | | | | |
| G/G | G/G | 214 | 315 | **1.00** | ref. | | |
| G/A or A/A | G/G | 239 | 409 | **0.69** | (0.50-0.95) | | |
| G/G | G/A or A/A | 237 | 356 | **0.98** | (0.71-1.37) | | |
| G/A or A/A | G/A or A/A | 268 | 455 | **0.73** | (0.51-1.03) | **0.04** | 0.72 |
| **rs10958713** | **rs4648141** | | | | | | |
| G/G | G/G | 317 | 446 | **1.00** | ref. | | |
| G/A or A/A | G/G | 356 | 602 | **0.67** | (0.51-0.89) | | |
| G/G | G/A or A/A | 134 | 225 | **0.73** | (0.51-1.04) | | |
| G/A or A/A | G/A or A/A | 151 | 262 | **0.60** | (0.42-0.86) | **0.01** | 0.35 |
| **rs10958713** | **rs4648135** | | | | | | |
| G/G | A/A | 404 | 605 | **1.00** | ref. | | |
| G/A or A/A | A/A | 451 | 774 | **0.71** | (0.56-0.91) | | |
| G/G | A/G or G/G | 46 | 64 | **1.21** | (0.65-2.23) | | |
| G/A or A/A | A/G or G/G | 56 | 90 | **0.89** | (0.52-1.53) | **0.03** | 0.86 |
| **rs10958713** | **rs4648110** | | | | | | |
| G/G | T/T | 292 | 413 | **1.00** | ref. | | |
| G/A or A/A | T/T | 331 | 554 | **0.68** | (0.51-0.90) | | |
| G/G | T/A or A/A | 159 | 258 | **0.78** | (0.56-1.09) | | |
| G/A or A/A | T/A or A/A | 176 | 310 | **0.61** | (0.43-0.85) | **0.02** | 0.48 |
| **rs10958713** | **rs4648090** | | | | | | |
| G/G | G/G | 338 | 486 | **1.00** | ref. | | |
| G/A or A/A | G/G | 392 | 650 | **0.70** | (0.53-0.92) | | |
| G/G | G/A or A/A | 112 | 185 | **0.81** | (0.56-1.16) | | |
| G/A or A/A | G/A or A/A | 115 | 213 | **0.62** | (0.43-0.90) | **0.03** | 0.66 |
| **rs10958713** | **rs4648072** | | | | | | |
| G/G | A/A | 447 | 657 | **1.00** | ref. | | |
| G/A or A/A | A/A | 501 | 855 | **0.71** | (0.56-0.89) | | |
| G/G | A/G or G/G | 4 | 14 | **0.36** | (0.07-1.78) | | |
| G/A or A/A | A/G or G/G | 6 | 9 | **0.69** | (0.17-2.75) | **0.02** | 0.26 |
| **rs10958713** | **rs4648022** | | | | | | |
| G/G | G/G | 376 | 545 | **1.00** | ref. | | |
| G/A or A/A | G/G | 434 | 729 | **0.70** | (0.54-0.90) | | |
| G/G | G/A or A/A | 75 | 125 | **0.82** | (0.53-1.26) | | |
| G/A or A/A | G/A or A/A | 73 | 134 | **0.67** | (0.46-1.02) | **0.03** | 0.52 |
| **rs10958713** | **rs4648011** | | | | | | |
| G/G | A/A | 161 | 242 | **1.00** | ref. | | |
| G/A or A/A | A/A | 178 | 305 | **0.70** | (0.49-1.00) | | |
| G/G | A/C or C/C | 288 | 425 | **1.01** | (0.72-1.41) | | |
| G/A or A/A | A/C or C/C | 325 | 558 | **0.71** | (0.49-1.01) | **0.03** | 0.86 |
| **rs10958713** | **rs4496586** | | | | | | |
| G/G | C/C | 133 | 172 | **1.00** | ref. | | |
| G/A or A/A | C/C | 138 | 226 | **065** | (0.43-0.97) | | |
| G/G | C/G or G/G | 317 | 496 | **0.80** | (0.56-1.14) | | |
| G/A or A/A | C/G or G/G | 369 | 635 | **0.61** | (0.42-0.89) | **0.03** | 0.31 |
| **rs10958713** | **rs3774968** | | | | | | |
| G/G | G/G | 127 | 215 | **1.00** | ref. | | |
| G/A or A/A | G/G | 173 | 286 | **0.83** | (0.57-1.21) | | |
| G/G | G/A or A/A | 324 | 456 | **1.19** | (0.85-1.66) | | |
| G/A or A/A | G/A or A/A | 334 | 578 | **0.79** | (0.56-1.11) | **0.03** | 0.28 |
| **rs10958713** | **rs3774964** | | | | | | |
| G/G | A/A | 192 | 284 | **1.00** | ref. | | |
| G/A or A/A | A/A | 197 | 356 | **0.63** | (0.46-0.88) | | |
| G/G | A/G or G/G | 259 | 387 | **1.02** | (0.73-1.42) | | |
| G/A or A/A | A/G or G/G | 310 | 508 | **0.80** | (0.56-1.13) | **0.02** | 0.33 |

**Table A.8 continued: Interaction between rs10958713 in *IκBKβ* and SNPs in *IκBKβ* and *NFκB1* on the risk of colon cancer**[a]

| SNP 1 genotype | SNP 2 genotype | Cases | Controls | OR | 95% CI | Global-p | Interaction-p[b] |
|---|---|---|---|---|---|---|---|
| **rs10958713** | **rs3774934** | | | | | | |
| G/G | G/G | 364 | 542 | **1.00** | ref. | | |
| G/A or A/A | G/G | 420 | 702 | **0.74** | (0.57-0.95) | | |
| G/G | G/A or A/A | 87 | 129 | **0.96** | (0.63-1.46) | | |
| G/A or A/A | G/A or A/A | 87 | 162 | **0.60** | (0.40-0.90) | **0.03** | 0.54 |
| **rs10958713** | **rs230525** | | | | | | |
| G/G | A/A | 204 | 302 | **1.00** | ref. | | |
| G/A or A/A | A/A | 218 | 383 | **0.66** | (0.47-0.92) | | |
| G/G | A/G or G/G | 245 | 369 | **1.00** | (0.71-1.39) | | |
| G/A or A/A | A/G or G/G | 288 | 481 | **0.75** | (0.52-1.06) | **0.03** | 0.61 |
| **rs10958713** | **rs230521** | | | | | | |
| G/G | G/G | 168 | 253 | **1.00** | ref. | | |
| G/A or A/A | G/G | 181 | 319 | **0.68** | (0.48-0.97) | | |
| G/G | G/C or C/C | 282 | 418 | **1.03** | (0.74-1.44) | | |
| G/A or A/A | G/C or C/C | 326 | 545 | **0.76** | (0.53-1.08) | **0.04** | 0.76 |
| **rs10958713** | **rs230510** | | | | | | |
| G/G | T/T | 122 | 200 | **1.00** | ref. | | |
| G/A or A/A | T/T | 169 | 271 | **0.81** | (0.56-1.19) | | |
| G/G | T/A or A/A | 329 | 471 | **1.10** | (0.78-1.56) | | |
| G/A or A/A | T/A or A/A | 338 | 593 | **0.74** | (0.52-1.06) | **0.03** | 0.37 |
| **rs10958713** | **rs230506** | | | | | | |
| G/G | A/A | 381 | 570 | **1.00** | ref. | | |
| G/A or A/A | A/A | 434 | 726 | **0.74** | (0.58-0.95) | | |
| G/G | A/G or G/G | 70 | 100 | **0.97** | (0.61-1.55) | | |
| G/A or A/A | A/G or G/G | 72 | 137 | **0.57** | (0.37-0.87) | **0.02** | 0.41 |
| **rs10958713** | **rs230490** | | | | | | |
| G/G | G/G | 146 | 218 | **1.00** | ref. | | |
| G/A or A/A | G/G | 173 | 277 | **0.79** | (0.55-1.13) | | |
| G/G | G/A or A/A | 305 | 453 | **1.07** | (0.77-1.49) | | |
| G/A or A/A | G/A or A/A | 334 | 587 | **0.73** | (0.51-1.03) | **0.04** | 0.48 |
| **rs10958713** | **rs230489** | | | | | | |
| G/G | A/A | 358 | 535 | **1.00** | ref. | | |
| G/A or A/A | A/A | 392 | 668 | **0.71** | (0.55-0.92) | | |
| G/G | A/G or G/G | 93 | 135 | **0.98** | (0.66-1.44) | | |
| G/A or A/A | A/G or G/G | 115 | 196 | **0.72** | (0.49-1.05) | **0.048** | 0.90 |
| **rs10958713** | **rs230488** | | | | | | |
| G/G | G/G | 252 | 350 | **1.00** | ref. | | |
| G/A or A/A | G/G | 273 | 469 | **0.66** | (0.49-0.88) | | |
| G/G | G/A or A/A | 198 | 320 | **0.82** | (0.61-1.11) | | |
| G/A or A/A | G/A or A/A | 234 | 394 | **0.67** | (0.49-0.92) | **0.03** | 0.25 |
| **rs10958713** | **rs230487** | | | | | | |
| G/G | A/A | 230 | 310 | **1.00** | ref. | | |
| G/A or A/A | A/A | 259 | 428 | **0.70** | (0.52-0.96) | | |
| G/G | A/C or C/C | 221 | 361 | **0.81** | (0.59-1.11) | | |
| G/A or A/A | A/C or C/C | 248 | 436 | **0.58** | (0.42-0.81) | **0.01** | 0.92 |
| **rs10958713** | **rs228619** | | | | | | |
| G/G | G/G | 125 | 162 | **1.00** | ref. | | |
| G/A or A/A | G/G | 132 | 230 | **0.59** | (0.39-0.89) | | |
| G/G | G/A or A/A | 325 | 509 | **0.78** | (0.55-1.12) | | |
| G/A or A/A | G/A or A/A | 375 | 634 | **0.60** | (0.41-0.88) | **0.02** | 0.26 |
| **rs10958713** | **rs228618** | | | | | | |
| G/G | C/C | 119 | 192 | **1.00** | ref. | | |
| G/A or A/A | C/C | 139 | 234 | **0.79** | (0.53-1.16) | | |
| G/G | C/A or A/A | 332 | 479 | **1.27** | (0.89-1.82) | | |
| G/A or A/A | C/A or A/A | 367 | 630 | **0.86** | (0.61-1.22) | **0.02** | 0.46 |

**Table A.8 continued: Interaction between rs10958713 in *IκBKβ* and SNPs in *IκBKβ* and *NFκB1* on the risk of colon cancer**[a]

| SNP 1 genotype | SNP 2 genotype | Cases | Controls | OR | 95% CI | Global-p | Interaction-p[b] |
|---|---|---|---|---|---|---|---|
| **rs10958713** | **rs2085549** | | | | | | |
| G/G | A/A | 264 | 397 | **1.00** | ref. | | |
| G/A or A/A | A/A | 286 | 499 | **0.70** | (0.52-0.93) | | |
| G/G | A/G or G/G | 187 | 274 | **1.03** | (0.74-1.43) | | |
| G/A or A/A | A/G or G/G | 221 | 365 | **0.77** | (0.54-1.08) | **0.04** | 0.76 |
| **rs10958713** | **rs2085548** | | | | | | |
| G/G | G/G | 227 | 347 | **1.00** | ref. | | |
| G/A or A/A | G/G | 243 | 433 | **0.70** | (0.51-0.94) | | |
| G/G | G/A or A/A | 224 | 324 | **1.08** | (0.7-1.50) | | |
| G/A or A/A | G/A or A/A | 264 | 431 | **0.80** | (0.57-1.13) | **0.03** | 0.77 |
| **rs10958713** | **rs1610152** | | | | | | |
| G/G | G/G | 410 | 620 | **1.00** | ref. | | |
| G/A or A/A | G/G | 457 | 781 | **0.72** | (0.57-0.92) | | |
| G/G | G/C or C/C | 41 | 51 | **1.41** | (0.73-2.71) | | |
| G/A or A/A | G/C or C/C | 50 | 82 | **0.91** | (0.51-1.60) | **0.03** | 0.75 |
| **rs10958713** | **rs1609798** | | | | | | |
| G/G | G/G | 222 | 325 | **1.00** | ref. | | |
| G/A or A/A | G/G | 238 | 418 | **0.69** | (0.50-0.95) | | |
| G/G | G/A or A/A | 229 | 345 | **1.05** | (0.76-1.46) | | |
| G/A or A/A | G/A or A/A | 269 | 442 | **0.83** | (0.58-1.17) | **0.04** | 0.46 |
| **rs10958713** | **rs13117745** | | | | | | |
| G/G | G/G | 327 | 464 | **1.00** | ref. | | |
| G/A or A/A | G/G | 365 | 619 | **0.67** | (0.51-0.88) | | |
| G/G | G/A or A/A | 124 | 207 | **0.79** | (0.55-1.12) | | |
| G/A or A/A | G/A or A/A | 142 | 245 | **0.66** | (0.46-0.95) | **0.02** | 0.31 |
| **rs10958713** | **rs12509517** | | | | | | |
| G/G | C/C | 233 | 344 | **1.00** | ref. | | |
| G/A or A/A | C/C | 246 | 426 | **0.67** | (0.43-0.91) | | |
| G/G | C/G or G/G | 218 | 327 | **1.00** | (0.72-1.39) | | |
| G/A or A/A | C/G or G/G | 261 | 438 | **0.77** | (0.55-1.09) | **0.03** | 0.51 |
| **rs10958713** | **rs10489113** | | | | | | |
| G/G | A/A | 305 | 432 | **1.00** | ref. | | |
| G/A or A/A | A/A | 337 | 564 | **0.68** | (0.51-0.90) | | |
| G/G | A/G or G/G | 146 | 239 | **0.76** | (0.54-1.06) | | |
| G/A or A/A | A/G or G/G | 170 | 300 | **0.60** | (0.43-0.84) | **0.01** | 0.47 |
| **rs10958713** | **rs10014309** | | | | | | |
| G/G | G/G | 359 | 515 | **1.00** | ref. | | |
| G/A or A/A | G/G | 398 | 679 | **0.67** | (0.52-0.87) | | |
| G/G | G/A or A/A | 92 | 156 | **0.79** | (0.54-1.15) | | |
| G/A or A/A | G/A or A/A | 109 | 185 | **0.69** | (0.47-1.01) | **0.02** | 0.27 |

[a] Adjusted for age and sex

[b] No SNP was noteworthy at the 25% or 50% level

**Table A.9: Association between NSAID use and colorectal cancer risk stratified by *IκBKβ* SNP genotypes[a]**

| | | Never or Former NSAID Use | | | Current NSAID use | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases/ Controls[b]** | **OR** | **95% CI** | **Cases/ Controls[b]** | **OR** | **95% CI** | **Global-p** | **Interaction-p** |
| **rs2272733** | G/G | 978/1511 | **1.00** | ref. | 273/449 | **0.89** | (0.73-1.08) | | |
| **(G>A intron 5)** | G/A or A/A[c] | 256/403 | **1.03** | (0.80-1.32) | 70/128 | **0.77** | (0.51-1.15) | 0.33 | 0.43 |
| **rs3747811 (T>A intron 1)** | T/T | 352/567 | **1.00** | ref. | 98/155 | **0.86** | (0.61-1.21) | | |
| | T/A | 603/948 | **0.90** | (0.72-1.13) | 178/283 | **0.86** | (0.65-1.14) | | |
| | A/A | 278/400 | **0.98** | (0.73-1.32) | 67/139 | **0.69** | (0.46-1.03) | 0.42 | 0.40 |
| **rs5029748 (C>A intron 2)** | C/C | 704/1086 | **1.00** | ref. | 200/313 | **0.89** | (0.70-1.12) | | |
| | C/A | 458/725 | **0.84** | (0.68-1.04) | 127/225 | **0.74** | (0.55-0.99) | | |
| | A/A | 72/105 | **0.85** | (0.54-1.32) | 16/39 | **0.54** | (0.27-1.09) | 0.24 | 0.71 |
| **rs6474387** | C/C | 1052/1649 | **1.00** | ref. | 306/488 | **0.92** | (0.76-1.11) | | |
| **(C>T intron 19)** | C/T or T/T | 166/246 | **1.09** | (0.79-1.50) | 33/80 | **0.57** | (0.32-1.00) | 0.08 | ***0.04***[e] |
| **rs9694958** | A/A | 1046/1619 | **1.00** | ref. | 293/482 | **0.90** | (0.74-1.09) | | |
| **(A>G intron 5)** | A/G or G/G | 188/296 | **1.09** | (0.82-1.43) | 50/95 | **0.75** | (0.48-1.18) | 0.29 | 0.28 |
| **rs10217111 (G>C 5' outside UTR)** | G/G | 815/1256 | **1.00** | ref. | 211/385 | **0.78** | (0.63-0.97) | | |
| | G/C | 356/584 | **0.98** | (0.78-1.22) | 117/174 | **0.99** | (0.71-1.36) | | |
| | C/C | 62/75 | **1.36** | (0.83-2.24) | 15/18 | **1.95** | (0.84-4.51) | 0.10 | 0.22 |
| **rs10958713 (G>A intron 19)** | G/G | 535/846 | **1.00** | ref. | 154/244 | **0.87** | (0.67-1.14) | | |
| | G/A | 553/865 | **0.89** | (0.72-1.10) | 157/243 | **0.83** | (0.63-1.11) | | |
| | A/A | 145/204 | **0.82** | (0.58-1.17) | 32/89 | **0.52** | (0.32-0.85) | 0.20 | 0.39 |
| **rs11986055** | A/A | 1138/1778 | **1.00** | ref. | 328/532 | **0.90** | (0.75-1.08) | | |
| **(A>C intron 1)** | A/C or C/C | 96/137 | **1.16** | (0.77-1.75) | 15/45 | **0.48** | (0.23-0.98) | 0.06 | ***0.03***[d] |

[a] Adjusted for age, sex, BMI, physical activity and smoking

[b] Unaffected Sibling Controls

[c] When cases<5, only the dominant model was analyzed

[d] *Noteworthy at the 25% FDR level*

[e] *Noteworthy at the 50% FDR level*

**Table A.10: Association between NSAID use and colon cancer risk stratified by *IκBKβ* SNP genotypes[a]**

| dbSNP ID | genotype | Never or Former NSAID Use | | | Current NSAID use | | | Global-p | Interaction-p |
|---|---|---|---|---|---|---|---|---|---|
| | | Cases/ Controls[b] | OR | 95% CI | Cases/ Controls[b] | OR | 95% CI | | |
| **rs2272733** | G/G | 575/895 | **1.00** | ref. | 180/292 | **0.89** | (0.70-1.14) | | |
| **(G>A intron 5)** | G/A or A/A[c] | 161/252 | **1.16** | (0.85-1.60) | 38/81 | **0.69** | (0.40-1.20) | 0.17 | 0.16[e] |
| **rs3747811 (T>A intron 1)** | T/T | 224/331 | **1.00** | ref. | 66/107 | **0.69** | (0.46-1.05) | | |
| | T/A | 358/578 | **0.75** | (0.56-1.01) | 112/182 | **0.72** | (0.49-1.03) | | |
| | A/A | 154/238 | **0.69** | (0.47-1.01) | 40/84 | **0.52** | (0.31-0.86) | 0.15 | 0.42 |
| **rs5029748 (C>A intron 2)** | C/C | 445/648 | **1.00** | ref. | 133/217 | **0.75** | (0.56-1.01) | | |
| | C/A | 248/435 | **0.65** | (0.49-0.86) | 75/132 | **0.65** | (0.44-0.96) | | |
| | A/A | 43/65 | **0.63** | (0.34-1.16) | 10/24 | **0.44** | (0.21-0.93) | **0.02** | 0.45 |
| **rs6474387** | C/C | 625/979 | **1.00** | ref. | 198/315 | **0.91** | (0.72-1.15) | | |
| **(C>T intron 19)** | C/T or T/T | 102/155 | **1.22** | (0.80-1.86) | 18/51 | **0.45** | (0.21-1.01) | **0.04** | ***0.02[d]*** |
| **rs9694958** | A/A | 617/961 | **1.00** | ref. | 189/312 | **0.88** | (0.69-1.12) | | |
| **(A>G intron 5)** | A/G or G/G | 119/186 | **1.22** | (0.86-1.74) | 29/61 | **0.72** | (0.40-1.32) | 0.19 | 0.20[e] |
| **rs10217111 (G>C 5' outside UTR)** | G/G | 480/759 | **1.00** | ref. | 134/244 | **0.77** | (0.58-1.01) | | |
| | G/C | 216/347 | **1.07** | (0.80-1.44) | 73/114 | **0.98** | (0.65-1.48) | | |
| | C/C | 40/41 | **1.61** | (0.88-2.93) | 11/15 | **1.79** | (0.65-4.94) | 0.22 | 0.66 |
| **rs10958713 (G>A intron 19)** | G/G | 346/497 | **1.00** | ref. | 103/168 | **0.71** | (0.51-0.98) | | |
| | G/A | 310/535 | **0.64** | (0.49-0.84) | 98/155 | **0.66** | (0.46-0.96) | | |
| | A/A | 79/116 | **0.56** | (0.35-0.90) | 17/50 | **0.36** | (0.19-0.68) | **0.006** | *0.20[e]* |
| **rs11986055** | A/A | 676/1058 | **1.00** | ref. | 207/343 | **0.87** | (0.69-1.09) | | |
| **(A>C intron 1)** | A/C or C/C | 60/89 | **1.28** | (0.76-2.17) | 11/30 | **0.47** | (0.19-1.20) | 0.09 | *0.05[d]* |

[a] Adjusted for age, sex, BMI, physical activity and smoking

[b] Unaffected Sibling Controls

[c] When cases<5, only the dominant model was analyzed

[d] *Noteworthy at the 25% FDR level*

[e] *Noteworthy at the 50% FDR level*

**Table A.11: Association between NSAID use and rectal cancer risk stratified by *IκBKβ* SNP genotypes[a]**

| | | Never or Former NSAID Use | | | Current NSAID use | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases/ Controls[b]** | **OR** | **95% CI** | **Cases/ Controls[b]** | **OR** | **95% CI** | **Global-p** | **Interaction-p[d]** |
| **rs2272733** | G/G | 328/533 | **1.00** | ref. | 72/134 | **0.89** | (0.70-1.14) | | |
| **(G>A intron 5)** | G/A or A/A[c] | 84/125 | **1.00** | (0.65-1.54) | 20/39 | **0.69** | (0.34-1.40) | 0.70 | 0.54 |
| **rs3747811 (T>A intron 1)** | T/T | 113/200 | **1.00** | ref. | 23/41 | **0.95** | (0.50-1.81) | | |
| | T/A | 201/316 | **0.94** | (0.65-1.36) | 47/86 | **0.87** | (0.53-1.45) | | |
| | A/A | 98/143 | **1.18** | (0.70-1.99) | 22/46 | **0.79** | (0.79-1.60) | 0.78 | 0.66 |
| **rs5029748 (C>A intron 2)** | C/C | 214/374 | **1.00** | ref. | 52/81 | **1.12** | (0.71-1.77) | | |
| | C/A | 174/251 | **1.14** | (0.80-1.63) | 34/78 | **0.75** | (0.44-1.27) | | |
| | A/A | 24/34 | **1.39** | (0.66-2.93) | 6/14 | **0.74** | (0.19-2.89) | 0.56 | 0.24 |
| **rs6474387** | C/C | 350/578 | **1.00** | ref. | 79/145 | **0.90** | (0.63-1.29) | | |
| **(C>T intron 19)** | C/T or T/T | 56/75 | **1.13** | (0.68-1.88) | 11/26 | **0.64** | (0.27-1.49) | 0.60 | 0.32 |
| **rs9694958** | A/A | 351/568 | **1.00** | ref. | 79/146 | **0.90** | (0.63-1.27) | | |
| **(A>G intron 5)** | A/G or G/G | 61/91 | **1.11** | (0.69-1.77) | 13/27 | **0.69** | (0.31-1.53) | 0.68 | 0.41 |
| **rs10217111** | G/G | 281/433 | **1.00** | ref. | 58/119 | **0.77** | (0.51-1.15) | | |
| **(G>C 5' outside UTR)** | G/C or C/C | 130/226 | **0.83** | (0.56-1.23) | 34/54 | **0.82** | (0.47-1.46) | 0.60 | 0.46 |
| **rs10958713 (G>A intron 19)** | G/G | 157/298 | **1.00** | ref. | 39/64 | **1.12** | (0.68-1.86) | | |
| | G/A | 206/285 | **1.28** | (0.90-1.81) | 40/75 | **0.92** | (0.55-1.55) | | |
| | A/A | 49/75 | **1.17** | (0.63-2.17) | 13/33 | **0.81** | (0.36-1.81) | 0.58 | 0.39 |
| **rs11986055** | A/A | 381/620 | **1.00** | ref. | 88/160 | **0.90** | (0.64-1.26) | | |
| **(A>C intron 1)** | A/C or C/C | 31/39 | **1.35** | (0.72-2.53) | 4/13 | **0.54** | (0.17-1.73) | 0.45 | 0.20 |

[a] Adjusted for age, sex, BMI, physical activity and smoking

[b] Unaffected Sibling Controls

[c] When cases<5, only the dominant model was analyzed

[d] No SNP was noteworthy at the 25% or 50% FDR level

**Table A.12: Association between NSAID use and colorectal cancer risk stratified by *NFκB1* SNP genotypes[a]**

| | | Never or Former NSAID Use | | | | Current NSAID use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Global-p** | **Interaction-p[c]** |
| Candidate SNP | | | | | | | | | | | |
| **rs4648072** | A/A | 1216 | 1883 | **1.00** | ref. | 342 | 569 | **0.87** | (0.73-1.04) | | |
| **M507V** | A/G[e] | 18 | 33 | **0.71** | (0.26-1.9) | 1 | 8 | **0.26** | (0.02-2.8) | 0.24 | 0.41 |
| TagSNPs | | | | | | | | | | | |
| **rs7674640** | A/A | 320 | 517 | **1.00** | ref. | 93 | 143 | **1.00** | (0.71-1.4) | | |
| | A/G | 602 | 935 | **0.98** | (0.78-1.23) | 163 | 293 | **0.81** | (0.61-1.09) | | |
| | G/G | 312 | 463 | **1.00** | (0.74-1.35) | 87 | 141 | **0.81** | (0.54-1.22) | 0.57 | 0.62 |
| **rs765789** | A/A | 826 | 1253 | **1.00** | ref. | 225 | 376 | **0.83** | (0.67-1.04) | | |
| | A/T | 360 | 591 | **0.91** | (0.73-1.13) | 102 | 182 | **0.81** | (0.6-1.11) | | |
| | T/T | 48 | 71 | **1.01** | (0.59-1.73) | 16 | 19 | **1.18** | (0.56-2.49) | 0.51 | 0.73 |
| **rs6833962** | G/G | 984 | 1485 | **1.00** | ref. | 274 | 449 | **0.90** | (0.74-1.1) | | |
| | G/A or A/A[d] | 212 | 346 | **0.93** | (0.7-1.24) | 58 | 103 | **0.73** | (0.48-1.12) | 0.43 | 0.55 |
| **rs6813322** | G/G | 307 | 511 | **1.00** | ref. | 94 | 138 | **1.13** | (0.81-1.58) | | |
| | G/C | 602 | 928 | **1.01** | (0.81-1.27) | 162 | 294 | **0.83** | (0.62-1.11) | | |
| | C/C | 308 | 456 | **1.07** | (0.8-1.44) | 83 | 136 | **0.79** | (0.52-1.19) | 0.30 | 0.19 |
| **rs4698863** | G/G | 586 | 888 | **1.00** | ref. | 163 | 276 | **0.82** | (0.63-1.06) | | |
| | G/A | 507 | 819 | **0.93** | (0.75-1.16) | 145 | 236 | **0.88** | (0.66-1.17) | | |
| | A/A | 140 | 209 | **1.05** | (0.74-1.49) | 35 | 65 | **0.89** | (0.51-1.56) | 0.62 | 0.76 |
| **rs4648141** | G/G | 874 | 1326 | **1.00** | ref. | 236 | 396 | **0.84** | (0.68-1.04) | | |
| | G/A | 322 | 532 | **0.90** | (0.71-1.15) | 94 | 169 | **0.80** | (0.58-1.1) | | |
| | A/A | 38 | 57 | **0.86** | (0.47-1.57) | 13 | 12 | **1.44** | (0.62-3.35) | 0.40 | 0.42 |
| **rs4648135** | A/A | 1107 | 1711 | **1.00** | ref. | 308 | 514 | **0.88** | (0.73-1.06) | | |
| | A/G or G/G | 126 | 205 | **0.92** | (0.64-1.3) | 35 | 60 | **0.75** | (0.42-1.35) | 0.43 | 0.82 |
| **rs4648110** | T/T | 810 | 1218 | **1.00** | ref. | 214 | 364 | **0.82** | (0.65-1.02) | | |
| | T/A | 376 | 619 | **0.90** | (0.72-1.12) | 110 | 192 | **0.83** | (0.61-1.12) | | |
| | A/A | 48 | 79 | **0.89** | (0.54-1.46) | 19 | 21 | **1.10** | (0.53-2.29) | 0.49 | 0.56 |
| **rs4648090** | G/G | 942 | 1420 | **1.00** | ref. | 256 | 428 | **0.87** | (0.71-1.06) | | |
| | G/A | 269 | 462 | **0.86** | (0.67-1.1) | 81 | 140 | **0.75** | (0.53-1.06) | | |
| | A/A | 22 | 33 | **0.85** | (0.42-1.73) | 6 | 9 | **0.60** | (0.13-2.66) | 0.49 | 0.96 |
| **rs4648022** | G/G | 1048 | 1591 | **1.00** | ref. | 288 | 478 | **0.87** | (0.71-1.05) | | |
| | G/A or A/A | 186 | 322 | **0.87** | (0.64-1.18) | 55 | 98 | **0.75** | (0.5-1.13) | 0.30 | 0.98 |

**Table A.12 continued: Association between NSAID use and colorectal cancer risk stratified by *NFκB1* SNP genotypes[a]**

| | | Never or Former NSAID Use | | | | Current NSAID use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Global-p** | **Interaction-p[c]** |
| **rs4648011** | A/A | 444 | 671 | **1.00** | ref. | 123 | 211 | **0.82** | (0.61-1.09) | | |
| | A/C | 567 | 905 | **0.89** | (0.72-1.11) | 170 | 260 | **0.89** | (0.66-1.19) | | |
| | C/C | 216 | 334 | **1.05** | (0.77-1.43) | 48 | 102 | **0.71** | (0.44-1.13) | 0.33 | 0.28 |
| **rs4496586** | C/C | 343 | 508 | **1.00** | ref. | 93 | 150 | **0.80** | (0.57-1.13) | | |
| | C/G | 597 | 932 | **0.96** | (0.77-1.21) | 162 | 297 | **0.77** | (0.58-1.03) | | |
| | G/C | 290 | 469 | **0.94** | (0.7-1.27) | 87 | 128 | **1.05** | (0.7-1.57) | 0.39 | 0.31 |
| **rs3774964** | A/A | 501 | 766 | **1.00** | ref. | 148 | 251 | **0.83** | (0.63-1.09) | | |
| | A/G | 549 | 861 | **0.97** | (0.78-1.2) | 152 | 233 | **0.97** | (0.72-1.3) | | |
| | G/G | 184 | 289 | **1.07** | (0.78-1.47) | 43 | 93 | **0.68** | (0.41-1.12) | 0.36 | 0.24 |
| **rs3774934** | G/G | 1010 | 1533 | **1.00** | ref. | 278 | 483 | **0.81** | (0.67-0.99) | | |
| | G/A or A/A | 224 | 383 | **0.83** | (0.64-1.09) | 65 | 94 | **0.96** | (0.64-1.43) | 0.13 | 0.13 |
| **rs230525** | A/A | 544 | 844 | **1.00** | ref. | 154 | 265 | **0.82** | (0.63-1.07) | | |
| | A/G | 541 | 845 | **1.03** | (0.83-1.27) | 151 | 242 | **0.97** | (0.72-1.3) | | |
| | G/G | 148 | 226 | **1.11** | (0.79-1.57) | 34 | 69 | **0.79** | (0.46-1.37) | 0.49 | 0.59 |
| **rs230521** | G/G | 454 | 698 | **1.00** | ref. | 128 | 221 | **0.84** | (0.63-1.12) | | |
| | G/C | 568 | 887 | **0.96** | (0.77-1.19) | 170 | 254 | **0.94** | (0.7-1.26) | | |
| | C/C | 210 | 330 | **1.04** | (0.76-1.42) | 45 | 101 | **0.67** | (0.41-1.08) | 0.40 | 0.27 |
| **rs230510** | T/T | 373 | 609 | **1.00** | ref. | 104 | 176 | **0.93** | (0.68-1.27) | | |
| | T/A | 606 | 930 | **1.02** | (0.82-1.27) | 168 | 287 | **0.84** | (0.63-1.12) | | |
| | A/A | 254 | 377 | **1.03** | (0.76-1.39) | 70 | 114 | **0.89** | (0.58-1.36) | 0.70 | 0.83 |
| **rs230506** | A/A | 1051 | 1599 | **1.00** | ref. | 293 | 510 | **0.81** | (0.67-0.98) | | |
| | A/G or G/G | 181 | 316 | **0.78** | (0.58-1.04) | 50 | 67 | **1.04** | (0.66-1.65) | 0.06 | **0.046** |
| **rs230490** | G/G | 434 | 632 | **1.00** | ref. | 98 | 198 | **0.62** | (0.46-0.85) | | |
| | G/A | 586 | 940 | **0.88** | (0.71-1.1) | 168 | 286 | **0.81** | (0.61-1.07) | | |
| | A/A | 214 | 344 | **0.92** | (0.67-1.25) | 77 | 93 | **1.19** | (0.77-1.83) | **0.04** | **0.02** |
| **rs230489** | A/A | 971 | 1502 | **1.00** | ref. | 284 | 457 | **0.89** | (0.73-1.09) | | |
| | A/G or G/G | 262 | 413 | **0.90** | (0.69-1.17) | 59 | 120 | **0.68** | (0.47-0.98) | 0.20 | 0.44 |
| **rs230488** | G/G | 658 | 1020 | **1.00** | ref. | 186 | 304 | **0.90** | (0.71-1.14) | | |
| | G/A | 499 | 767 | **1.05** | (0.85-1.28) | 143 | 228 | **0.93** | (0.71-1.24) | | |
| | A/A | 77 | 125 | **0.92** | (0.61-1.38) | 13 | 45 | **0.40** | (0.19-0.86) | 0.12 | 0.18 |
| **rs230487** | A/A | 624 | 948 | **1.00** | ref. | 180 | 297 | **0.87** | (0.68-1.12) | | |
| | A/C | 506 | 815 | **0.89** | (0.72-1.1) | 139 | 243 | **0.76** | (0.57-1.02) | | |
| | C/C | 104 | 153 | **1.06** | (0.72-1.57) | 24 | 37 | **0.89** | (0.5-1.6) | 0.41 | 0.99 |

**Table A.12 continued: Association between NSAID use and colorectal cancer risk stratified by *NFκB1* SNP genotypes**[a]

| | | Never or Former NSAID Use | | | | Current NSAID use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases** | **Controls**[b] | **OR** | **95% CI** | **Cases** | **Controls**[b] | **OR** | **95% CI** | **Global-p** | **Interaction-p**[c] |
| **rs228619** | G/G | 332 | 501 | **1.00** | ref. | 91 | 153 | **0.79** | (0.56-1.12) | | |
| | G/A | 595 | 924 | **0.98** | (0.78-1.23) | 159 | 292 | **0.79** | (0.59-1.06) | | |
| | A/A | 304 | 491 | **0.91** | (0.67-1.23) | 93 | 132 | **1.01** | (0.68-1.5) | 0.41 | 0.26 |
| **rs228618** | C/C | 333 | 552 | **1.00** | ref. | 103 | 149 | **1.14** | (0.83-1.57) | | |
| | C/A | 608 | 925 | **1.14** | (0.91-1.43) | 159 | 291 | **0.89** | (0.66-1.2) | | |
| | A/A | 292 | 439 | **1.16** | (0.85-1.57) | 81 | 137 | **0.89** | (0.59-1.35) | 0.26 | 0.15 |
| **rs2085549** | A/A | 687 | 1084 | **1.00** | ref. | 205 | 336 | **0.87** | (0.69-1.10) | | |
| | A/G | 472 | 703 | **1.10** | (0.89-1.36) | 117 | 200 | **0.97** | (0.72-1.31) | | |
| | G/G | 75 | 129 | **0.97** | (0.64-1.47) | 21 | 41 | **0.73** | (0.37-1.41) | 0.51 | 0.91 |
| **rs2085548** | G/G | 592 | 931 | **1.00** | ref. | 177 | 289 | **0.89** | (0.70-1.13) | | |
| | G/A | 530 | 792 | **1.06** | (0.86-1.31) | 137 | 228 | **0.94** | (0.70-1.26) | | |
| | A/A | 112 | 192 | **1.05** | (0.73-1.50) | 29 | 59 | **0.71** | (0.40-1.26) | 0.58 | 0.70 |
| **rs1610152** | G/G | 1127 | 1743 | **1.00** | ref. | 309 | 521 | **0.87** | (0.72-1.05) | | |
| | G/C or C/C | 107 | 173 | **0.94** | (0.64-1.36) | 34 | 55 | **0.76** | (0.42-1.37) | 0.41 | 0.81 |
| **rs1609798** | G/G | 593 | 901 | **1.00** | ref. | 166 | 284 | **0.82** | (0.63-1.05) | | |
| | G/A | 504 | 806 | **0.99** | (0.80-1.23) | 144 | 228 | **0.98** | (0.73-1.31) | | |
| | A/A | 137 | 202 | **1.16** | (0.81-1.65) | 33 | 64 | **0.84** | (0.47-1.49) | 0.46 | 0.47 |
| **rs13117745** | G/G | 904 | 1364 | **1.00** | ref. | 240 | 407 | **0.82** | (0.67-1.02) | | |
| | G/A | 301 | 510 | **0.92** | (0.73-1.18) | 90 | 159 | **0.87** | (0.63-1.20) | | |
| | A/A | 29 | 42 | **0.95** | (0.52-1.77) | 13 | 10 | **1.85** | (0.76-4.53) | 0.33 | 0.29 |
| **rs12509517** | C/C | 608 | 935 | **1.00** | ref. | 177 | 296 | **0.83** | (0.65-1.07) | | |
| | C/G | 498 | 783 | **1.01** | (0.82-1.25) | 135 | 220 | **0.97** | (0.72-1.31) | | |
| | G/G | 128 | 198 | **1.13** | (0.79-1.60) | 31 | 61 | **0.82** | (0.46-1.48) | 0.56 | 0.62 |
| **rs10489113** | A/A | 829 | 1247 | **1.00** | ref. | 224 | 377 | **0.82** | (0.65-1.02) | | |
| | A/G | 356 | 595 | **0.85** | (0.68-1.06) | 103 | 181 | **0.81** | (0.59-1.10) | | |
| | G/G | 48 | 73 | **0.92** | (0.55-1.56) | 16 | 19 | **0.97** | (0.46-2.07) | 0.42 | 0.66 |
| **rs10014309** | G/G | 950 | 1470 | **1.00** | ref. | 266 | 436 | **0.89** | (0.73-1.09) | | |
| | G/A or A/A | 284 | 444 | **1.06** | (0.83-1.36) | 77 | 141 | **0.83** | (0.58-1.19) | 0.39 | 0.53 |
| **rs997476** | C/C | 1088 | 1699 | **1.00** | ref. | 292 | 508 | **0.82** | (0.67-0.99) | | |
| | C/A or A/A | 143 | 217 | **1.14** | (0.82-1.57) | 51 | 69 | **1.40** | (0.90-2.16) | 0.06 | 0.12 |

[a] Adjusted for age, sex, BMI, physical activity and smoking , [b] Unaffected Sibling Controls, [c] No SNP was noteworthy at the 25% or 50% FDR level

Table A.13: Association between NSAID use and colon cancer risk stratified by ***NFκB1*** **SNP genotypes**[a]

| | | Never or Former NSAID Use | | | | Current NSAID use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases** | **Controls**[b] | **OR** | **95% CI** | **Cases** | **Controls**[b] | **OR** | **95% CI** | **Global-p** | **Interaction-p**[c] |
| Candidate SNP | | | | | | | | | | | |
| **rs4648072** | A/A | 727 | 1130 | **1.00** | ref. | 217 | 368 | **0.83** | (0.66-1.04) | | |
| **M507V** | A/G[e] | 9 | 18 | **0.57** | (0.16-2.01) | 1 | 5 | **0.57** | (0.05-6.13) | 0.32 | 0.89 |
| TagSNPs | | | | | | | | | | | |
| **rs7674640** | A/A | 196 | 304 | **1.00** | ref. | 55 | 88 | **0.98** | (0.63-1.5) | | |
| | A/G | 350 | 562 | **0.94** | (0.7-1.26) | 103 | 198 | **0.74** | (0.51-1.07) | | |
| | G/G | 190 | 282 | **1.03** | (0.69-1.52) | 60 | 87 | **0.84** | (0.5-1.4) | 0.51 | 0.74 |
| **rs765789** | A/A | 488 | 742 | **1.00** | ref. | 151 | 244 | **0.82** | (0.62-1.08) | | |
| | A/T | 226 | 365 | **0.88** | (0.66-1.18) | 62 | 115 | **0.75** | (0.5-1.11) | | |
| | T/T | 22 | 41 | **0.64** | (0.31-1.32) | 5 | 14 | **0.38** | (0.12-1.27) | 0.33 | 0.87 |
| **rs6833962** | G/G | 579 | 885 | **1.00** | ref. | 181 | 289 | **0.90** | (0.7-1.15) | | |
| | G/A or A/A[d] | 134 | 208 | **1.01** | (0.7-1.47) | 32 | 70 | **0.60** | (0.34-1.05) | 0.24 | 0.17 |
| **rs6813322** | G/G | 184 | 304 | **1.00** | ref. | 54 | 85 | **1.09** | (0.7-1.69) | | |
| | G/C | 356 | 558 | **1.07** | (0.8-1.43) | 104 | 198 | **0.84** | (0.58-1.2) | | |
| | C/C | 184 | 275 | **1.15** | (0.78-1.7) | 57 | 82 | **0.86** | (0.51-1.45) | 0.51 | 0.43 |
| **rs4698863** | G/G | 351 | 542 | **1.00** | ref. | 99 | 176 | **0.74** | (0.53-1.02) | | |
| | G/A | 296 | 487 | **0.96** | (0.73-1.27) | 97 | 157 | **0.91** | (0.64-1.3) | | |
| | A/A | 89 | 119 | **1.19** | (0.76-1.85) | 22 | 40 | **1.02** | (0.52-2.02) | 0.42 | 0.57 |
| **rs4648141** | G/G | 517 | 785 | **1.00** | ref. | 155 | 253 | **0.85** | (0.65-1.11) | | |
| | G/A or A/A | 219 | 363 | **0.83** | (0.61-1.12) | 63 | 120 | **0.65** | (0.44-0.97) | 0.16 | 0.76 |
| **rs4648135** | A/A | 662 | 1029 | **1.00** | ref. | 190 | 336 | **0.80** | (0.63-1.01) | | |
| | A/G or G/G | 73 | 119 | **1.00** | (0.62-1.6) | 28 | 35 | **1.18** | (0.54-2.55) | 0.30 | 0.29 |
| **rs4648110** | T/T | 480 | 722 | **1.00** | ref. | 143 | 236 | **0.81** | (0.61-1.07) | | |
| | T/A | 233 | 379 | **0.86** | (0.64-1.14) | 70 | 124 | **0.75** | (0.51-1.1) | | |
| | A/A | 23 | 47 | **0.60** | (0.3-1.19) | 5 | 13 | **0.42** | (0.12-1.48) | 0.28 | 0.93 |
| **rs4648090** | G/G | 558 | 853 | **1.00** | ref. | 171 | 275 | **0.87** | (0.67-1.12) | | |
| | G/A or A/A | 177 | 294 | **0.89** | (0.64-1.23) | 47 | 98 | **0.62** | (0.39-0.99) | 0.20 | 0.39 |
| **rs4648022** | G/G | 621 | 957 | **1.00** | ref. | 187 | 307 | **0.85** | (0.67-1.08) | | |
| | G/A or A/A | 115 | 189 | **0.90** | (0.61-1.32) | 31 | 66 | **0.61** | (0.36-1.04) | 0.24 | 0.46 |
| **rs4648011** | A/A | 264 | 404 | **1.00** | ref. | 73 | 136 | **0.64** | (0.44-0.93) | | |
| | A/C | 340 | 554 | **0.89** | (0.67-1.19) | 110 | 170 | **0.93** | (0.64-1.37) | | |
| | C/C | 127 | 188 | **1.16** | (0.77-1.74) | 34 | 64 | **0.88** | (0.5-1.56) | 0.15 | 0.12 |

**Table A.13 continued: Association between NSAID use and colon cancer risk stratified by *NFκB1* SNP genotypes[a]**

| | | Never or Former NSAID Use | | | | Current NSAID use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Global-p** | **Interaction-p[c]** |
| **rs4496586** | C/C | 209 | 303 | **1.00** | ref. | 63 | 92 | **0.81** | (0.53-1.25) | | |
| | C/G | 345 | 563 | **0.89** | (0.66-1.20) | 103 | 197 | **0.70** | (0.48-1.01) | | |
| | G/C | 181 | 277 | **0.90** | (0.61-1.34) | 52 | 83 | **0.90** | (0.53-1.53) | 0.48 | 0.69 |
| **rs3774964** | A/A | 302 | 469 | **1.00** | ref. | 85 | 163 | **0.67** | (0.48-0.95) | | |
| | A/G | 324 | 512 | **0.99** | (0.75-1.32) | 103 | 152 | **1.03** | (0.71-1.50) | | |
| | G/G | 110 | 167 | **1.15** | (0.76-1.73) | 30 | 58 | **0.89** | (0.49-1.61) | 0.22 | 0.19 |
| **rs3774934** | G/G | 604 | 918 | **1.00** | ref. | 177 | 314 | **0.78** | (0.61-1.00) | | |
| | G/A or A/A | 132 | 230 | **0.81** | (0.58-1.14) | 41 | 59 | **0.89** | (0.54-1.47) | 0.18 | 0.22 |
| **rs230525** | A/A | 322 | 508 | **1.00** | ref. | 98 | 170 | **0.73** | (0.53-1.02) | | |
| | A/G | 323 | 512 | **1.03** | (0.78-1.36) | 96 | 159 | **1.00** | (0.69-1.45) | | |
| | G/G | 90 | 128 | **1.28** | (0.82-2.01) | 22 | 44 | **0.94** | (0.48-1.83) | 0.30 | 0.47 |
| **rs230521** | G/G | 270 | 422 | **1.00** | | 77 | 143 | **0.69** | | | |
| | G/C | 340 | 532 | **0.98** | (0.74-1.29) | 109 | 167 | **0.96** | (0.66-1.39) | | |
| | C/C | 125 | 194 | **1.10** | (0.73-1.65) | 32 | 63 | **0.86** | (0.48-1.54) | 0.39 | 0.34 |
| **rs230510** | T/T | 224 | 361 | **1.00** | ref. | 66 | 108 | **1.00** | (0.67-1.5) | | |
| | T/A | 361 | 560 | **0.99** | (0.75-1.31) | 108 | 195 | **0.77** | (0.54-1.11) | | |
| | A/A | 151 | 227 | **1.05** | (0.71-1.56) | 44 | 70 | **0.79** | (0.46-1.36) | 0.53 | 0.57 |
| **rs230506** | A/A | 627 | 956 | **1.00** | ref. | 184 | 329 | **0.77** | (0.61-0.98) | | |
| | A/G or G/G | 108 | 191 | **0.75** | (0.51-1.09) | 34 | 44 | **0.98** | (0.56-1.70) | 0.09 | 0.08 |
| **rs230490** | G/G | 252 | 371 | **1.00** | ref. | 65 | 120 | **0.67** | (0.45-0.99) | | |
| | G/A | 348 | 570 | **0.95** | (0.71-1.26) | 111 | 191 | **0.82** | (0.57-1.17) | | |
| | A/A | 136 | 207 | **1.08** | (0.72-1.60) | 42 | 62 | **1.17** | (0.67-2.04) | 0.28 | 0.31 |
| **rs230489** | A/A | 567 | 894 | **1.00** | ref. | 180 | 298 | **0.88** | (0.69-1.13) | | |
| | A/G or G/G | 169 | 253 | **0.97** | (0.70-1.35) | 38 | 75 | **0.62** | (0.39-1.00) | 0.22 | 0.26 |
| **rs230488** | G/G | 411 | 615 | **1.00** | ref. | 113 | 199 | **0.77** | (0.57-1.05) | | |
| | G/A | 282 | 456 | **0.95** | (0.73-1.23) | 94 | 152 | **0.85** | (0.60-1.20) | | |
| | A/A | 43 | 75 | **0.63** | (0.37-1.08) | 10 | 22 | **0.49** | (0.19-1.29) | 0.23 | 0.80 |
| **rs230487** | A/A | 369 | 539 | **1.00** | ref. | 118 | 192 | **0.85** | (0.62-1.17) | | |
| | A/C | 295 | 519 | **0.79** | (0.60-1.03) | 90 | 156 | **0.70** | (0.49-1.02) | | |
| | C/C | 72 | 90 | **1.32** | (0.79-2.21) | 10 | 25 | **0.60** | (0.27-1.37) | 0.06 | 0.34 |

**Table A.13 continued: Association between NSAID use and colon cancer risk stratified by *NFκB1* SNP genotypes[a]**

| | | Never or Former NSAID Use | | | | Current NSAID use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Global-p** | **Interaction-p[c]** |
| **rs228619** | G/G | 197 | 294 | **1.00** | ref. | 61 | 95 | **0.80** | (0.51-1.24) | | |
| | G/A | 358 | 566 | **0.97** | (0.71-1.31) | 99 | 193 | **0.71** | (0.49-1.04) | | |
| | A/A | 180 | 288 | **0.84** | (0.56-1.25) | 58 | 85 | **0.93** | (0.56-1.55) | 0.41 | 0.33 |
| **rs228618** | C/C | 196 | 330 | **1.00** | ref. | 62 | 92 | **1.20** | (0.79-1.82) | | |
| | C/A | 366 | 558 | **1.29** | (0.96-1.73) | 101 | 197 | **0.90** | (0.62-1.32) | | |
| | A/A | 173 | 260 | **1.29** | (0.86-1.93) | 55 | 84 | **1.00** | (0.58-1.7) | 0.18 | 0.14 |
| **rs2085549** | A/A | 417 | 672 | **1.00** | ref. | 130 | 216 | **0.81** | (0.61-1.07) | | |
| | A/G | 277 | 411 | **1.09** | (0.82-1.44) | 74 | 130 | **0.97** | (0.66-1.44) | | |
| | G/G | 42 | 65 | **0.94** | (0.54-1.64) | 14 | 27 | **0.70** | (0.3-1.64) | 0.54 | 0.88 |
| **rs2085548** | G/G | 360 | 582 | **1.00** | ref. | 108 | 190 | **0.77** | (0.57-1.04) | | |
| | G/A | 315 | 464 | **1.10** | (0.84-1.46) | 88 | 146 | **1.00** | (0.68-1.46) | | |
| | A/A | 61 | 102 | **1.02** | (0.63-1.64) | 22 | 37 | **0.91** | (0.45-1.86) | 0.50 | 0.77 |
| **rs1610152** | G/G | 673 | 1046 | **1.00** | ref. | 191 | 341 | **0.80** | (0.63-1) | | |
| | G/C or C/C | 63 | 102 | **1.06** | (0.64-1.75) | 27 | 31 | **1.23** | (0.55-2.78) | 0.26 | 0.32 |
| **rs1609798** | G/G | 355 | 552 | 1.00 | ref. | 102 | 185 | **0.73** | (0.53-1.01) | | |
| | G/A | 296 | 479 | 1.05 | (0.79-1.39) | 95 | 147 | **1.05** | (0.73-1.52) | | |
| | A/A | 85 | 113 | 1.32 | (0.84-2.07) | 21 | 40 | **1.00** | (0.50-2.00) | 0.24 | 0.39 |
| **rs13117745** | G/G | 534 | 811 | **1.00** | ref. | 157 | 263 | **0.82** | (0.63-1.07) | | |
| | G/A | 189 | 314 | **0.89** | (0.65-1.22) | 56 | 104 | **0.74** | (0.49-1.11) | | |
| | A/A | 13 | 23 | **0.64** | (0.27-1.5) | 5 | 6 | **1.02** | (0.27-3.83) | 0.52 | 0.71 |
| **rs12509517** | C/C | 368 | 571 | **1.00** | ref. | 108 | 191 | **0.73** | (0.53-1.00) | | |
| | C/G | 288 | 465 | **1.01** | (0.77-1.34) | 90 | 143 | **1.01** | (0.70-1.47) | | |
| | G/G | 80 | 112 | **1.24** | (0.79-1.96) | 20 | 39 | **0.97** | (0.48-1.96) | 0.32 | 0.41 |
| **rs10489113** | A/A | 493 | 742 | **1.00** | ref. | 149 | 243 | **0.80** | (0.61-1.06) | | |
| | A/G or G/G | 243 | 406 | **0.80** | (0.60-1.07) | 69 | 130 | **0.70** | (0.48-1.02) | 0.17 | 0.77 |
| **rs10014309** | G/G | 582 | 901 | **1.00** | ref. | 171 | 283 | **0.83** | (0.65-1.07) | | |
| | G/A or A/A | 154 | 247 | **0.92** | (0.67-1.27) | 47 | 90 | **0.75** | (0.48-1.17) | 0.39 | 0.92 |
| **rs997476** | C/C | 650 | 1013 | **1.00** | ref. | 188 | 329 | **0.80** | (0.63-1.02) | | |
| | C/A or A/A | 84 | 135 | **0.91** | (0.60-1.38) | 30 | 44 | **1.03** | (0.58-1.81) | 0.33 | 0.32 |

[a] Adjusted for age, sex, BMI, physical activity and smoking, [b] Unaffected Sibling Controls, [c] No SNP was noteworthy at the 25% or 50% FDR level

[d] When cases<5, only the dominant model was analyzed, [e] No G/G genotypes

## Table A.14: Association between NSAID use and rectal cancer risk stratified by *NFκB1* SNP genotypes[a]

| | | Never or Former NSAID Use | | | | Current NSAID use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Global-p** | **Interaction-p[c]** |
| Candidate SNP | | | | | | | | | | | |
| **rs4648072** | A/A | 406 | 647 | **1.00** | ref. | 92 | 172 | **0.86** | (0.61-1.2) | | |
| **M507V** | A/G[e] | 6 | 12 | **0.62** | (0.11-3.64) | 0 | 1 | **0.00** | (0-0) | 0.51 | 0.31 |
| TagSNPs | | | | | | | | | | | |
| **rs7674640** | A/A | 98 | 182 | **1.00** | ref. | 28 | 49 | **0.94** | (0.52-1.71) | | |
| | A/G | 213 | 318 | **1.16** | (0.79-1.7) | 46 | 81 | **0.99** | (0.59-1.68) | | |
| | G/G | 101 | 158 | **1.00** | (0.6-1.66) | 18 | 43 | **0.71** | (0.32-1.58) | 0.78 | 0.84 |
| **rs765789** | A/A | 279 | 437 | **1.00** | ref. | 54 | 110 | **0.77** | (0.50-1.19) | | |
| | A/T | 115 | 199 | **0.92** | (0.63-1.35) | 30 | 58 | **0.83** | (0.46-1.48) | | |
| | T/T | 18 | 22 | **1.94** | (0.80-4.70) | 8 | 5 | **2.40** | (0.84-6.87) | 0.27 | 0.78 |
| **rs6833962** | G/G | 338 | 520 | **1.00** | ref. | 71 | 133 | **0.85** | (0.58-1.25) | | |
| | G/A or A/A[d] | 62 | 117 | **0.72** | (0.43-1.18) | 18 | 30 | **0.76** | (0.36-1.64) | 0.50 | 0.61 |
| **rs6813322** | G/G | 99 | 178 | **1.00** | ref. | 30 | 49 | **1.02** | (0.58-1.80) | | |
| | G/C | 205 | 315 | **1.00** | (0.68-1.48) | 44 | 80 | **0.88** | (0.52-1.48) | | |
| | C/C | 103 | 157 | **1.01** | (0.62-1.64) | 17 | 43 | **0.59** | (0.26-1.33) | 0.80 | 0.52 |
| **rs4698863** | G/G | 195 | 298 | **1.00** | ref. | 45 | 82 | **0.89** | (0.56-1.41) | | |
| | G/A | 174 | 282 | **0.88** | (0.61-1.28) | 38 | 69 | **0.74** | (0.43-1.27) | | |
| | A/A | 42 | 79 | **0.82** | (0.44-1.54) | 9 | 22 | **0.68** | (0.23-1.99) | 0.91 | 0.98 |
| **rs4648141** | G/G | 292 | 461 | **1.00** | ref. | 57 | 115 | **0.75** | (0.50-1.14) | | |
| | G/A or A/A | 120 | 197 | **0.97** | (0.66-1.44) | 35 | 58 | **1.04** | (0.58-1.84) | 0.62 | 0.35 |
| **rs4648135** | A/A | 367 | 583 | **1.00** | ref. | 87 | 152 | **0.92** | (0.65-1.3) | | |
| | A/G or G/G | 45 | 76 | **0.78** | (0.44-1.40) | 5 | 20 | **0.37** | (0.12-1.19) | 0.27 | 0.25 |
| **rs4648110** | T/T | 271 | 424 | **1.00** | ref. | 50 | 106 | **0.75** | (0.49-1.16) | | |
| | T/A | 123 | 205 | **1.01** | (0.69-1.46) | 30 | 59 | **0.88** | (0.49-1.56) | | |
| | A/A | 18 | 30 | **1.21** | (0.51-2.87) | 12 | 8 | **1.98** | (0.74-5.30) | 0.59 | 0.49 |
| **rs4648090** | G/G | 318 | 487 | **1.00** | ref. | 61 | 130 | **0.77** | (0.52-1.14) | | |
| | G/A or A/A | 94 | 172 | **0.82** | (0.53-1.26) | 31 | 43 | **0.89** | (0.49-1.63) | 0.54 | 0.35 |
| **rs4648022** | G/G | 351 | 543 | **1.00** | ref. | 73 | 142 | **0.82** | (0.57-1.18) | | |
| | G/A or A/A | 61 | 115 | **0.78** | (0.47-1.30) | 19 | 30 | **0.84** | (0.40-1.76) | 0.60 | 0.52 |
| **rs4648011** | A/A | 158 | 237 | **1.00** | ref. | 35 | 66 | **0.95** | (0.55-1.66) | | |
| | A/C | 178 | 295 | **0.82** | (0.55-1.21) | 50 | 74 | **0.82** | (0.49-1.39) | | |
| | C/C | 74 | 124 | **0.87** | (0.50-1.49) | 7 | 32 | **0.25** | (0.08-0.78) | 0.23 | 0.11 |

Table A.14 continued: Association between NSAID use and rectal cancer risk stratified by *NFκB1* SNP genotypes[a]

| | | Never or Former NSAID Use | | | | Current NSAID use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Global-p** | **Interaction-p[c]** |
| **rs4496586** | C/C | 109 | 179 | **1.00** | ref. | 21 | 45 | **0.73** | (0.37-1.45) | | |
| | C/G | 212 | 313 | **1.16** | (0.79-1.7) | 45 | 85 | **0.95** | (0.56-1.63) | | |
| | G/C | 88 | 166 | **1.01** | (0.6-1.68) | 26 | 42 | **1.11** | (0.55-2.24) | 0.80 | 0.67 |
| **rs3774964** | A/A | 169 | 262 | **1.00** | ref. | 46 | 74 | **1.04** | (0.63-1.69) | | |
| | A/G | 180 | 287 | **0.91** | (0.63-1.33) | 37 | 70 | **0.77** | (0.44-1.34) | | |
| | G/G | 63 | 110 | **0.92** | (0.52-1.61) | 9 | 29 | **0.39** | (0.14-1.14) | 0.57 | 0.35 |
| **rs3774934** | G/G | 339 | 527 | **1.00** | ref. | 74 | 147 | **0.76** | (0.53-1.09) | | |
| | G/A or A/A | 73 | 132 | **0.80** | (0.48-1.35) | 18 | 26 | **1.19** | (0.57-2.49) | 0.36 | 0.13 |
| **rs230525** | A/A | 191 | 296 | **1.00** | ref. | 39 | 80 | **0.88** | (0.52-1.48) | | |
| | A/G | 175 | 279 | **1.00** | (0.69-1.43) | 45 | 72 | **0.86** | (0.52-1.43) | | |
| | G/G | 46 | 83 | **0.88** | (0.50-1.54) | 6 | 20 | **0.42** | (0.11-1.57) | 0.79 | 0.70 |
| **rs230521** | G/G | 160 | 246 | **1.00** | ref. | 36 | 68 | **0.97** | (0.56-1.68) | | |
| | G/C | 179 | 292 | **0.89** | (0.61-1.3) | 49 | 72 | **0.89** | (0.53-1.49) | | |
| | C/C | 72 | 120 | **0.95** | (0.56-1.61) | 7 | 32 | **0.25** | (0.08-0.77) | 0.21 | 0.07 |
| **rs230510** | T/T | 122 | 216 | **1.00** | ref. | 28 | 62 | **0.73** | (0.42-1.27) | | |
| | T/A | 202 | 310 | **1.15** | (0.79-1.67) | 47 | 74 | **1.10** | (0.65-1.87) | | |
| | A/A | 87 | 133 | **1.09** | (0.65-1.84) | 17 | 37 | **0.89** | (0.4-1.99) | 0.77 | 0.76 |
| **rs230506** | A/A | 351 | 552 | **1.00** | ref. | 79 | 156 | **0.78** | (0.55-1.11) | | |
| | A/G or G/G | 60 | 107 | **0.83** | (0.46-1.49) | 13 | 17 | **1.45** | (0.61-3.48) | 0.33 | 0.11 |
| **rs230490** | G/G | 157 | 222 | **1.00** | ref. | 24 | 65 | **0.50** | (0.27-0.91) | | |
| | G/A | 194 | 315 | **0.76** | (0.53-1.09) | 40 | 84 | **0.66** | (0.39-1.11) | | |
| | A/A | 61 | 122 | **0.63** | (0.36-1.11) | 28 | 24 | **1.32** | (0.6-2.87) | 0.08 | **0.017** |
| **rs230489** | A/A | 331 | 519 | **1.00** | ref. | 76 | 137 | **0.81** | (0.56-1.18) | | |
| | A/G or G/G | 80 | 140 | **0.78** | (0.49-1.24) | 16 | 36 | **0.76** | (0.38-1.51) | 0.57 | 0.67 |
| **rs230488** | G/G | 202 | 352 | **1.00** | ref. | 55 | 86 | **1.14** | (0.75-1.74) | | |
| | G/A or A/A | 210 | 305 | **1.35** | (0.95-1.92) | 37 | 87 | **0.79** | (0.45-1.37) | 0.11 | **0.04** |
| **rs230487** | A/A | 217 | 354 | **1.00** | ref. | 45 | 92 | **0.80** | (0.51-1.27) | | |
| | A/C | 167 | 247 | **1.04** | (0.70-1.53) | 37 | 73 | **0.84** | (0.50-1.41) | | |
| | C/C | 28 | 58 | **0.78** | (0.39-1.56) | 10 | 8 | **2.89** | (0.89-9.38) | 0.38 | 0.11 |
| **rs228619** | G/G | 110 | 182 | **1.00** | ref. | 21 | 46 | **0.72** | (0.36-1.42) | | |
| | G/A | 198 | 298 | **1.10** | (0.75-1.61) | 45 | 83 | **0.95** | (0.56-1.62) | | |
| | A/A | 102 | 179 | **0.99** | (0.60-1.64) | 26 | 44 | **0.96** | (0.48-1.91) | 0.88 | 0.82 |

**Table A.14 continued: Association between NSAID use and rectal cancer risk stratified by *NFκB1* SNP genotypes[a]**

| | | Never or Former NSAID Use | | | | Current NSAID use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **dbSNP ID** | **genotype** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Cases** | **Controls[b]** | **OR** | **95% CI** | **Global-p** | **Interaction-p[c]** |
| **rs228618** | C/C | 113 | 194 | **1.00** | ref. | 31 | 52 | **0.94** | (0.54-1.64) | | |
| | C/A | 201 | 309 | **1.01** | (0.69-1.49) | 44 | 78 | **0.91** | (0.53-1.55) | | |
| | A/A | 98 | 156 | **1.00** | (0.61-1.65) | 17 | 43 | **0.64** | (0.28-1.43) | 0.88 | 0.68 |
| **rs2085549** | A/A | 230 | 355 | **1.00** | ref. | 51 | 101 | **0.80** | (0.50-1.29) | | |
| | A/G | 153 | 249 | **0.98** | (0.67-1.42) | 38 | 59 | 0.98 | (0.57-1.67) | | |
| | G/G | 29 | 55 | **1.08** | (0.55-2.12) | 3 | 13 | 0.49 | (0.12-2.06) | 0.85 | 0.57 |
| **rs2085548** | G/G | 200 | 302 | **1.00** | ref. | 47 | 85 | **0.87** | (0.52-1.43) | | |
| | G/A or A/A | 212 | 356 | **0.89** | (0.62-1.29) | 45 | 87 | **0.74** | (0.45-1.23) | 0.70 | 0.89 |
| **rs1610152** | G/G | 373 | 595 | **1.00** | ref. | 87 | 152 | **0.92** | (0.65-1.31) | | |
| | G/C or C/C | 39 | 64 | **0.81** | (0.43-1.51) | 5 | 21 | **0.37** | (0.12-1.13) | 0.25 | 0.23 |
| **rs1609798** | G/G | 285 | 444 | **1.00** | ref. | 55 | 114 | **0.76** | (0.5-1.17) | | |
| | G/A | 110 | 195 | **0.98** | (0.66-1.44) | 28 | 54 | **0.86** | (0.47-1.57) | | |
| | A/A | 17 | 20 | **2.27** | (0.84-6.10) | 9 | 5 | **2.75** | (0.99-7.67) | 0.18 | 0.79 |
| **rs13117745** | G/G | 303 | 473 | **1.00** | ref. | 58 | 116 | **0.76** | (0.51-1.15) | | |
| | G/A or A/A | 109 | 186 | **0.99** | (0.66-1.47) | 34 | 56 | **1.08** | (0.61-1.92) | 0.61 | 0.32 |
| **rs12509517** | C/C | 200 | 315 | **1.00** | ref. | 50 | 87 | **0.95** | (0.60-1.51) | | |
| | C/G | 175 | 270 | **1.02** | (0.70-1.47) | 35 | 68 | **0.79** | (0.45-1.38) | | |
| | G/G | 37 | 74 | **0.90** | (0.49-1.68) | 7 | 18 | **0.66** | (0.19-2.32) | 0.92 | 0.83 |
| **rs10489113** | A/A | 277 | 433 | **1.00** | ref. | 55 | 112 | **0.76** | (0.50-1.16) | | |
| | A/G | 117 | 204 | **0.91** | (0.62-1.33) | 27 | 55 | **0.79** | (0.43-1.47) | | |
| | G/G | 18 | 21 | **2.26** | (0.87-5.90) | 10 | 6 | **2.24** | (0.82-6.12) | 0.18 | 0.89 |
| **rs10014309** | G/G | 301 | 487 | **1.00** | ref. | 67 | 128 | **0.88** | (0.61-1.29) | | |
| | G/A or A/A | 111 | 171 | **1.27** | (0.81-1.99) | 25 | 45 | **0.99** | (0.51-1.93) | 0.55 | 0.73 |
| **rs997476** | C/C | 362 | 585 | **1.00** | ref. | 75 | 149 | **0.71** | (0.50-1.00) | | |
| | C/A or A/A | 50 | 74 | **1.33** | (0.79-2.24) | 17 | 24 | **1.30** | (0.62-2.71) | 0.11 | 0.44 |

[a] Adjusted for age, sex, BMI, physical activity and smoking

[b] Unaffected Sibling Controls

[c] No SNP was noteworthy at the 25% or 50% FDR level

[d] When cases<5, only the dominant model was analyzed

[e] No G/G genotypes