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JAK/STAT/SOCS-signaling pathway and colon and rectal cancer

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Abstract

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway is involved in immune function and cell growth. We evaluated the association between genetic variation in *JAK1* (10 SNPs), *JAK2* (9 SNPs), *TYK2* (5 SNPs), *SOCS1* (2 SNPs), *SOCS2* (2 SNPs), *STAT1* (16 SNPs), *STAT2* (2 SNPs), *STAT3* (6 SNPs), *STAT4* (21 SNPs), *STAT5A* (2 SNPs), *STAT5B* (3 SNPs), *STAT6* (4 SNPs) with risk of colorectal cancer. We used data from population-based case-control studies (colon cancer n=1555 cases, 1956 controls; rectal cancer n=754 cases, 959 controls). *JAK2*, *SOCS2*, *STAT1*, *STAT3*, *STAT5A*, *STAT5B*, and *STAT6* were associated with colon cancer; *STAT3*, *STAT4*, *STAT6*, and *TYK2* were associated with rectal cancer. Given the biological role of the JAK/STAT-signaling pathway and cytokines, we evaluated interaction with *IFNG, TNF,* and *IL6;* numerous statistically significant associations after adjustment for multiple comparisons were observed. The following statistically significant interactions were observed: *TYK2* with aspirin/NSAID use; *STAT1*, *STAT4*, and *TYK2* with estrogen status; and *JAK2*, *STAT2*, *STAT4*, *STAT5A*, *STAT5B*, and *STAT6* with smoking status and colon cancer risk; *JAK2*, *STAT6*, and *TYK2* with aspirin/NSAID use; *JAK1* with estrogen status; *STAT2* with cigarette smoking and rectal cancer. *JAK2*, *SOCS1*, *STAT3*, *STAT5*, and *TYK2* were associated with colon cancer survival (HRR of 3.3 95% CI 2.01, 5.42 for high mutational load). *JAK2*, *SOCS1*, *STAT1*, *STAT4*, and *TYK2* were associated with rectal cancer survival (HRR 2.80 95 %CI 1.63, 4.80). These data support the importance of the JAK/STAT-signaling pathway in colorectal cancer and suggest targets for intervention.

Keywords

JAK; STAT; SOCS; colon cancer; rectal cancer; estrogen; NSAIDs; cigarette smoking

Introduction

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway is involved in immune function and cell growth and differentiation[1, 2]. The JAK family consists of four non-receptor protein tyrosine kinases, JAK1, JAK2, JAK3, and TYK2. Of these, JAK1, JAK2, and TYK2 are expressed ubiquitously in mammals, while JAK3 is expressed mainly in hematopoietic cells[3]. Once activated by cytokines, JAKs serve as docking sites for signaling molecules such as STATs. Activated STATs translocate from

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the cytoplasm to the nucleus where they increase the transcription rate of several genes. STAT1 and STAT2 were first identified as contributing to activation of genes involved in immune response[4]. Five additional STATs have been identified: STAT3, STAT4, STAT5A, STAT5B, and STAT6. Cytokines, as part of a feedback loop, up-regulate suppressors of cytokine signaling (SOCS) that inhibit the activity of JAKs and STATs[5]. Several studies have implicated components of the JAK/STAT/SOCS-signaling pathway in colorectal adenomas and cancer, [1, 2, 6] which is biologically plausible given that the gut contains the largest collection of lymphoid tissue in the body[4].

Research focused on understanding the JAK/STAT/SOCS-signaling pathway often has involved their interaction and relationship with cytokines. STAT1 and STAT2 were first identified from work involving downstream events of receptor binding of IFNγ on transcriptional activation of genes involved in immune response[4]. Pro-inflammatory cytokines, such as TNFα, IL-6, and INFγ have been shown to up-regulate STAT proteins[4, 7, 8]. Both JAK1 and JAK2 are important for cytokines through use of the shared receptor subunits, γ chain (γc) and gp130; IFNs and IL-6 are two important pro-inflammatory cytokines that use these receptors that are essential for cytokine signaling[9]. JAK2 is essential for hormone-like cytokine signaling, including prolactin signaling[9]. Thus, the JAK/STAT/SOCS-signaling pathway is an important regulator of the ultimate cellular response to cytokines.

The influence of genetic variation in the JAK/STAT/SOCS-signaling pathway on colon and rectal cancer risk is unknown. It is biologically plausible that JAK/STAT/SOCS-signaling pathway risk would be associated with genetic variation in cytokine genes such as *TNF* and its receptors, *IFNG* (IFNγ) and its receptors, and *IL6* which are important cytokines associated with inflammatory processes, aspirin/NSAIDs that influence inflammation, cigarette smoking that can influence inflammation through oxidative stress, and estrogen which has many biological functions including anti-inflammatory properties. In this study we evaluate genetic variation in the JAK/STAT/SOCS-signaling pathway and assess if that variation is associated with key cytokine and inflammation-related factors and risk of developing colon and rectal cancer. Because the JAK/STAT/SOCS-signaling pathway influences cell growth, we also evaluate if genetic variation in this pathway is associated with survival after diagnosis with colon and rectal cancer.

Methods

Data for the study come from a population-based case-control study of colon cancer (cases n=1,555; controls n=1,956) and rectal cancer (cases n=754; controls n=959) The colon cancer study case identification was between October1, 1991 and September 30, 1994 and included people living in the Twin Cities Metropolitan Area, Kaiser Permanente Medical Care Program of Northern California (KPMCP) and a seven-county area of Utah [10]. The rectal study used identical data collection methods as the colon study, it included population-based cases with cancer of the rectosigmoid junction or rectum who were identified between May 1997 and May 2001 in Utah and KPMCP [11]. Eligible cases were between 30 and 79 years old at time of diagnosis with adenocarcinoma, English speaking, mentally competent to complete the interview, had no previous history of CRC, and no known (as indicated on the pathology report) familial adenomatous polyposis, ulcerative colitis, or Crohn's disease. Controls were matched to cases by sex and by 5-year age groups. At KPMCP, controls were randomly selected from membership lists. In Utah, controls 65 years and older were randomly selected from the Health Care Financing Administration lists and controls younger than 65 years were randomly selected from driver's license lists. Controls were selected from driver's license and state-identification lists in Minnesota. Study details have been previously reported [10, 11].

Interview Data Collection

Data were collected by trained and certified interviewers using laptop computers. All interviews were audio-taped and reviewed for quality control purposes [12]. The referent period for the study was two years prior to diagnosis for cases and prior to selection for controls. Detailed information was collected on diet, physical activity, medical history, and cigarette smoking history, regular use of aspirin and non-steroidal anti-inflammatory drugs, use of hormone replacement therapy, menopausal history, and body size.

Tumor Registry Data

Tumor registry data were obtained to determine disease stage at diagnosis and months of survival after diagnosis. Disease stage was categorized centrally by one pathologist in Utah using the sixth edition of the American Joint Committee on Cancer (AJCC) staging criteria. Local tumor registries also provided information on patient follow-up including vital status, cause of death, and contributing cause of death. Follow-up was obtained for all study participants for at least five years and was terminated for the Colon Cancer Study in 2000 and for the Rectal Cancer Study in 2007.

TagSNP Selection and Genotyping

TagSNPs were selected using the following parameters: LD blocks were defined using a Caucasian LD map and an r^2=0.8; minor allele frequency (MAF) >0.1; range= −1500 bps from the initiation codon to +1500 bps from the termination codon; and 1 SNP/LD bin. All markers were genotyped using a multiplexed bead-array assay format based on GoldenGate chemistry (Illumina, San Diego, California). A genotyping call rate of 99.85% was attained. Blinded internal replicates represented 4.4% of the sample set; the duplicate concordance rate was 100%. Individuals with missing genotype data were not included in the analysis for that specific marker. We evaluated associations with candidate genes, including *JAK1* (10 SNPs), *JAK2* (9 SNPs), *TYK2* (5 SNPs), *SOCS1* (2 SNPs), *SOCS2* (2 SNPs), *STAT1* (16 SNPs), *STAT2* (2 SNPs), *STAT3* (6 SNPs), *STAT4* (21 SNPs), *STAT5A* (2 SNPs), *STAT5B* (3 SNPs), *STAT6* (4 SNPs). Table 1 details SNPs associated with colon or rectal cancer, either by independent associations or through interactions; online Supplement 1 contains information about all SNPs included on the platform.

Statistical Methods

Statistical analyses were performed using SAS® version 9.2 (SAS Institute, Cary, NC). We report odds ratios (ORs) and 95% confidence intervals (95%CIs) assessed from multiple logistic regression models adjusting for age, center, race/ethnicity, and sex. To summarize risk associated with multiple variants across the pathway we created a summary polygenic score that was based on all at-risk genotypes for colon and rectal cancer. The score for each SNP was based on the inheritance model and its associated risk. For the co-dominant or additive model a score of zero, one, or two was assigned which directly as correlated to the number of high-risk alleles; scores of zero or two were assigned for the dominant and recessive models. After assigning a score for each SNP previously identified as being significant, the scores were summed across SNPs to generate an individual polygenic summary score. Individuals missing SNP data were dropped from the analysis. The continuous score variable was redefined as a categorical variable based on the frequency distribution within the study population.

Analysis for interaction was based on tagSNPs within each gene. We tested interaction with targeted genes including tumor necrosis factor and its receptors (*TNF, TNFRSF1A, TNFRSF1B),* interferon gamma and its receptors *(IFNG*, *IFNGR1*, *IFNGR2*), and *IL6* which we hypothesized would modify the effect of candidate genes given the importance of

cytokines in regulating the pathway. Lifestyle variables were selected because of their biological plausibility for involvement in this candidate pathway. In these analyses we focused on interaction between estrogen status (defined as currently using hormone replacement if post-menopausal or being pre/peri menopausal), cigarette smoking status, and use of aspirin/NSAIDs. These factors were targeted because of their influence on estrogen, inflammation, and oxidative stress. *P* values for interaction were determined using a likelihood-ratio test comparing a full model that included an ordinal interaction term with a reduced model without an interaction term.

Survival-months were calculated based on month and year of diagnosis and month and year of death or date of last contact. Associations between SNPs and risk of dying of colorectal cancer were evaluated using Cox proportional hazards models to obtain multivariate hazard rate ratios (HRRs) and 95% confidence intervals. We adjusted for age at diagnosis, study center, race, sex, tumor molecular phenotype, and AJCC stage to estimate HRRs.

Adjusted multiple-comparison p values, taking into account tagSNPs within the gene, were estimated using the methods of Conneely and Boehnke [13] via R version 2.12.0 (R Foundation for Statistical Computing, Vienna, Austria). Wald p values (1 df) from the main effect models and interaction p values based on likelihood-ratio tests were used in the calculation of multiple comparisons. We consider a pACT of <0.20 as potentially important given the underlying candidate pathway approach of this study and the need to consider both type 1 and type 2 errors. We believe that findings at this level would merit replication, especially when evaluating interactions.

Results

Evaluation of the associations with SNPs in genes in the JAK/STAT signaling pathway showed more significant associations for colon cancer than for rectal cancer (Table 2). *JAK2* (4 SNPs), *SOCS2* (1 SNP), *STAT1* (2 SNPs), *STAT3* (2 SNPs), *STAT5A* (1 SNP), *STAT5B* (2 SNPs), and *STAT6* (1 SNP) were significantly associated with colon cancer. After adjustment for multiple testing, all but five SNPs remained significant at the 0.10 level and all but one had a pACT value of <0.20. Only four SNPs in four separate genes, *STAT3*, *STAT4*, *STAT6*, and *TYK2,* were associated with rectal cancer. The adjusted p values for *STAT3*, *STAT6*, and *TYK2* were 0.0552, 0.0623, and 0.1255 respectively. Assessment of mutational load from having multiple at-risk alleles showed only minimal increased risk for colon cancer. However, for rectal cancer having all four at-risk alleles (score of 8) versus none (score of 0–2) was associated with an almost four-fold increased risk (OR 3.90 95 %CI 2.02, 7.52), which was considerably greater than the combined independent risk.

Given the biological role of the *JAK/STAT* signaling pathway and its involvement with *IFNG, TNF*, and other cytokines, we evaluated interaction with *IFNG* and its receptors, *TNF* and its receptors, and *IL6*. We observed numerous statistically significant associations; those with pACT values of <0.20 are shown in Table 3 while those with unadjusted p values of <0.05 but adjusted p values of >0.20 are available in the online Supplement 2. We observed more associations with colon cancer than with rectal cancer. For colon cancer, we observed significant interaction and adjusted pACTs of <0.2 between *IFNG* and *STAT4*, *JAK1*, *JAK2*, and *SOCS1*; between *IFNGR1* and *STAT6* and *TYK2; IFNGR2* and *STAT1*, *STAT5B*, *SOCS2*, *SOCS1*, and *STAT4. TNF* interacted significantly with *JAK2*, *STAT1*, *STAT6*, *JAK1,* and *STAT4; TNFRSF1A* and *STAT3*, *STAT6*, *STAT5A*, *STAT5B*, *TYK2*, and *JAK1. IL6* interacted with *STAT5B, JAK1*, *JAK2*, *STAT3*, *STAT6*, and *STAT4*. For rectal cancer we observed that *IFNG* interacted with *JAK2*, *IFNGR1* interacted with STAT5B and *SOCS2*, and *IFNGR2* interacted with *JAK1, JAK2*, *STAT3*, and *STAT5A. TNF* interacted with *TYK2* and *TNFRSF1A* interacted with *JAK2*, *SOCS2*, *SOCS1*, and

STAT4. *IL6* interacted with *JAK2*, *STAT1*, *STAT4* and with *TYK2*. For both colon and rectal cancer several SNPs within each gene interacted with the targeted pathway genes, i.e. *IFNG*, *TNF*, and *IL6*.

Assessment of interaction between genes in the JAK/STAT-signaling pathway and use of aspirin/NSAIDs, estrogen status, and cigarette smoking showed several significant interactions (Table 4). For colon cancer, *TYK2* interacted significantly with aspirin/NSAID use; *STAT1*, *STAT4*, and *TYK2* interacted with estrogen status; and *JAK2*, *STAT2*, *STAT4*. *STAT5A*, *STAT5B*, and *STAT6* interacted with smoking status. Several significant associations also were detected with rectal cancer. *JAK2*, *STAT6*, and *TYK2* interacted significantly with aspirin/NSAID use; *JAK1* interacted with estrogen status and *STAT2* with cigarette smoking. Of potential importance, is the observation that five *STAT1* SNPs interacted with estrogen status for colon cancer and four *JAK1* SNPs interacted with estrogen status for rectal cancer. Also, three *JAK2* SNPs interacted with smoking status. The associations involving the variant genotype with either estrogen or NSAID use resulted in reduced risk of colon cancer below that observed for the variant without the lifestyle exposure, which is also true for NSAID use and rectal cancer. For colon cancer, having the variant genotype in the presence of smoking typically increased risk beyond that observed for being a smoker and not having the variant or having the variant and not smoking cigarettes.

Several SNPs were associated with survival after diagnosis for both colon and rectal cancer (Table 5). For colon cancer, *JAK2* (5 SNPs), *SOCS1* (1 SNP), *STAT3* (3 SNPs), *STAT5* (1 SNP), and *TYK2* (2 SNPs) were associated with survival. For rectal cancer, *JAK2* (1 SNP), *SOCS1* (1 SNP), *STAT1* (4 SNPs), *STAT4* (2 SNPs), and *TYK2* (1 SNP) were associated with survival. In Table 5, we summarize the combined effect of these at-risk SNPs in relation to survival. For both colon and rectal cancer the hazard of dying increases with mutational load after adjusting for disease stage and molecular phenotype of the tumor. For colon cancer the estimate of risk of dying is HRR of 3.3 (95% CI 2.01, 5.42) for the highest category of mutational load, while for rectal cancer it is 2.80 (95 % CI 1.63, 4.80).

Discussion

Genetic variation in the JAK/STAT/SOCS-signaling pathway appears to be associated with both colon and rectal cancer risk. We observed associations with several SNPs for development of both colon and rectal cancer as well as with survival after diagnosis. The impact of the genetic variation in this signaling pathway goes beyond that observed for main effects and encompasses additional risk associated with interaction of genetic and lifestyle factors.

Evaluation of genetic variation in this pathway with risk of colon and rectal cancer has not previously been reported to our knowledge, however genetic associations between *JAK2*, *TYK2*, and *STAT3* have been reported with Crohn's disease and ulcerative colitis.[14] The JAK/STAT/SOCS-signaling pathway plays a critical role in immune response and regulation of inflammation given its essential affiliation with cytokine signaling. Additionally, components of the pathway, such as STAT3, have been shown to promote uncontrolled cell growth and survival through dysregulation of gene expression involved in apoptosis, cell-cycle regulation, and angiogenesis.[15] JAK1, JAK2, and STAT3 have been associated with colorectal cancer progression[2]. Thus, our observation that mutational load associated with the pathway influences survival is consistent with previous reports of biological effects of this pathway.

While the pathway appeared to be associated with both colon and rectal cancer, the magnitude of the association identified with each independent SNP was generally weak for both colon and rectal cancer. Key differences between colon and rectal cancer were observed. First, the number of SNPs and genes associated with colon cancer was greater than that observed for rectal cancer. However, evaluation of mutational load derived from these SNPs and the corresponding associations implied that for colon cancer the composite effect of having multiple variant alleles was only marginally greater than the risk associated with the individual SNPs themselves, while for rectal cancer, having all high-risk alleles, resulted in considerably greater risk than would be expected from addition of the independent risk. Likewise, differences also were observed in the SNPs associated with colon and rectal cancer. It is unclear why these differences exist. It could stem from the relative importance of different biological mechanisms for colon and rectal cancer, despite the overlap of importance for the pathway for both cancers, including genes targeted by various STATs. While we acknowledge that these differences could stem from chance findings, many associations remained significant after adjusting for multiple comparisons. These findings are supported by other reports showing differences in both genetic and lifestyle factors for colon and rectal cancer [11, 16–19]. We have reported that miRNA expression profile of normal tissue from colon and rectal cancer are different[20], further supporting the hypothesis that colon and rectal cancer represent two distinct diseases.

This pathway was associated with several key lifestyle factors, including aspirin/NSAID use, cigarette smoking and estrogen status. These lifestyle factors were targeted because of their association with inflammation which appears to be a critical modulator of colon and rectal cancer risk[21]. The role of aspirin and NSAID use in colon and rectal cancer risk is well documented [22–25] and has been hypothesized as stemming from the anti-inflammatory properties of these drugs. Cigarette smoking has been associated with increased nitric oxide (NO) synthesis by activating nitric oxide synthase (NOS2) and inflammation;[26–28] NO has been shown to contribute to chronic inflammation [29]. Estrogens could be operating via an inflammation-related mechanism given their influence on the NFκB pathway.[30, 31] Estrogens also have been shown to activate STAT4.[32] Additionally, JAK2 is essential for hormone-like cytokines such as prolactin[9]; estrogens are key regulators of prolactin. Thus, the observation that estrogen status interacts with genes in the JAK/STAT/SOCS-signaling pathway has a biological basis.

TNF, *IFNG*, and *IL6* also were hypothesized to interact with JAK/STAT/SOCS-signaling pathway genes. The association between JAKs and cytokine signaling was identified when mutant JAK cell lines were shown to lack responsiveness to interferon while adding TYK2 restored IFN signaling[9]. Since then, both JAK1 and JAK2 have been shown to be important for cytokines such as TNF, IFN, and IL6 [9]. STAT1 and STAT2 also were originally discovered as mediators of IFN signaling[8]. JAK1 and JAK2 have been shown to be associated with IFNγ receptors subunits[33]. SOCS interacts directly with the JAK/STAT pathway and has been shown to suppress cellular response to various cytokines including IL6 and IFNγ[34]. Thus, we targeted cytokines thought to be operating in the pathway. We observed numerous statistically significant interactions between genes and SNPs in the JAK/STAT/SOCS signaling pathway and these targeted cytokines. Of these interactions, 10 had an adjusted p value of <0.05 and another 19 had adjusted p values of <0.10, many more had adjusted p values of 0.20 or less. Taken together, our data support the importance of the pathway and that genetic variation in this pathway is associated with colon and rectal cancer both for the independent effects, but also for their effect modification of cytokine genes.

Major strengths of our study were the hypothesis-driven approach, the large and extensive data set that includes information on genetic, lifestyle, and survival data, and our ability to examine colon and rectal cancer separately. While we believe that the data we present is

both thorough and informative, we acknowledge that limitations exist. For instance, while we have detected associations we have minimal information on the functionality of the SNPs evaluated. Additional lab-based experiments are needed to determine functionality. Through our analysis of the JAK/STAT/SOCS-signaling pathway, we have made many comparisons. Although we have provided pACT values to take into account multiple comparisons, chance findings may exist and therefore replication of these findings is critical. A hazard of multiple testing adjustments is the increased likelihood of rejecting a finding that is true. Thus, we believe that adjusted p values of <0.20, especially for interactions, merit replication in other large sample sets to validate these findings.

In summary, these data support the hypothesis that the JAK/STAT/SOCS signaling pathway is associated with colon and rectal cancer because of their independent effects on risk as well as from the modifying effect they have on lifestyle and genetic factors. We hypothesized that this pathway is central to development of colon and rectal cancer because of its role in regulation of inflammation. We also provide data which suggest that this pathway is importantly related to survival after cancer diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of genes and respective tagSNPs associated with colon and rectal cancer.

Symbol	Chromosome	Alias	SNP	Major/Minor Allele	MAF[1]	FDR HWE[2]
JAK1	1p32.3-p31.3	*JAK1A*	rs310211	A /G	0.31	1.00
		JAK1B	rs2256298	C /T	0.25	1.00
			rs3790541	C /T	0.11	1.00
			rs310199	T /C	0.29	1.00
			rs310198	C /T	0.11	1.00
JAK2	9p24		rs1887429	G /T	0.27	1.00
			rs2274471	T /C	0.24	0.96
			rs7043371	A /T	0.50	1.00
			rs10974947	G /A	0.25	0.68
			rs3780379	G /A	0.19	0.62
			rs3780381	A /C	0.28	0.95
			rs10815160	T /G	0.24	0.87
SOCS1	16p13.13	*CIS, CISH, JAB, SOCS-1*	rs4780355	T /C	0.30	0.96
		SSI-1, SSI1, TIP3	rs193779	G /A	0.25	0.85
SOCS2	12q	*CIS2, Cish2, SOCS-2*	rs768775	T /C	0.19	0.68
		SSI-2, SSI2, STATI2	rs3816997	T /G	0.14	1.00
STAT1	2q32.2	*DKFZp686B04100*	rs3771300	A /C	0.49	1.00
		ISGF-3	rs16824035	C /T	0.16	1.00
		STAT91	rs4327257	A /C	0.14	1.00
			rs2280233	A /G	0.47	1.00
			rs2280232	T /G	0.26	1.00
			rs7562024	C /T	0.40	1.00
			rs10199181	A /T	0.38	1.00
			rs10208033	T /C	0.42	1.00
STAT2	12q13.2	*ISGF-3, P113, STAT113, MGC59816*	rs2229363	G /T	0.01	<.000001
STAT3	17q21.31	*APRF*	rs1053005	A /G	0.19	0.94
		FLJ20882	rs2293152	G /C	0.40	0.98
		MGC16063	rs6503695	T /C	0.34	0.96

Symbol	Chromosome	Alias	SNP	Major/Minor Allele	MAF[1]	FDR HWE[2]
			rs12949918	T /C	0.41	0.87
			rs1026916	G /A	0.35	0.97
STAT4	2q32.2-q32.3		rs4853540	G /T	0.21	0.96
			rs3024904	A /T	0.11	1.00
			rs3024861	T /A	0.24	0.99
			rs10168266	C /T	0.19	1.00
			rs6752770	A /G	0.28	0.95
			rs11685878	C /T	0.40	0.95
			rs12327969	G /C	0.21	0.96
STAT5A	17q11.2	*MGF*	rs7217728	T /C	0.28	0.03
		STAT5	rs12601982	A /G	0.17	0.75
STAT5B	17q11.2	*STAT5*	rs9900213	G /T	0.16	1.00
			rs6503691	C /T	0.10	0.99
			rs7218653	A /G	0.29	0.74
STAT6	12q13	*D12S1644*	rs3024979	T /A	0.11	1.00
		IL-4-STAT	rs324015	G /A	0.25	0.97
		STAT6B	rs3024974	C /T	0.10	1.00
		STAT6C	rs324011	C /T	0.39	0.90
TYK2	19p13.2	*JTK1*	rs280519	G /A	0.48	0.98
			rs280521	G /A	0.14	1.00
			rs280523	G /A	0.07	0.87
			rs280500	A /G	0.15	1.00

[1]Minor Allele Frequency (MAF) based on controls for non-Hispanic white population.

[2]FDR (HWE) = False Discovery Rate adjusted p value for Hardy Weinberg Equilibrium test; HWE uses NHW controls.

Table 2

Associations between *JAK/STAT/SOCS*-signaling pathway and colon and rectal cancer

	Controls	Cases				
Colon Cancer	**N**	**N**	**OR[1]**	**(95% CI)**	**Wald p value**	**pACT**
JAK2 (rs10815160)					0.0332	0.1718
TT/TG	1840	1431	1.00			
GG	115	123	1.34	(1.02, 1.76)		
JAK2 (rs10974947)					0.0403	0.1805
GG/GA	1863	1457	1.00			
AA	93	97	1.36	(1.01, 1.82)		
JAK2 (rs1887429)					0.0294	0.1704
GG	1019	866	1.00			
GT/TT	921	686	0.86	(0.75, 0.99)		
JAK2 (rs3780379)					0.0066	0.0479
GG/GA	1905	1489	1.00			
AA	51	65	1.68	(1.16, 2.44)		
SOCS2 (rs768775)					0.0196	0.0384
TT	1303	983	1.00			
TC/CC	652	572	1.18	(1.03, 1.36)		
STAT1 (rs2280232)					0.0116	0.1124
TT	1056	900	1.00			
TG	763	563	0.86	(0.75, 0.99)		
GG	136	91	0.77	(0.58, 1.02)		
STAT1 (rs4327257)					0.0319	0.2489
AA	1462	1213	1.00			
AC/CC	494	341	0.84	(0.72, 0.99)		
STAT3 (rs12949918)					0.0170	0.0651
TT	690	492	1.00			
TC/CC	1266	1063	1.19	(1.03, 1.37)		
STAT3 (rs6503695)					0.0032	0.0148
TT	862	614	1.00			

	Controls	Cases				
Colon Cancer	**N**	**N**	**OR[1]**	**(95% CI)**	**Wald p value**	**pACT**
TC	871	735	1.19	(1.03, 1.37)		
CC	223	206	1.32	(1.07, 1.64)		
STAT5A (rs7217728)					0.0035	0.0065
TT	974	699	1.00			
TC	710	614	1.20	(1.04, 1.39)		
CC	182	174	1.31	(1.04, 1.66)		
STAT5B (rs6503691)					0.0068	0.0187
CC	1555	1172	1.00			
CT	365	336	1.20	(1.01, 1.42)		
TT	36	47	1.59	(1.00, 2.53)		
STAT5B (rs7218653)					0.0092	0.0181
AA	998	727	1.00			
AG	780	658	1.15	(1.00, 1.33)		
GG	178	170	1.30	(1.03, 1.64)		
STAT6 (rs324015)					0.0201	0.0751
GG	1118	946	1.00			
GA/AA	838	609	0.85	(0.74, 0.97)		
Summary Score[2]						
(0 – 5)	271	157	1.00			
(6 – 7)	292	203	1.19	(0.91, 1.55)		
(8 – 9)	436	292	1.17	(0.91, 1.50)		
(10 – 11)	426	341	1.37	(1.08, 1.75)		
(12 – 13)	288	286	1.71	(1.32, 2.21)		
(14 – 23)	243	276	2.00	(1.54, 2.61)		
P Trend	<.0001					
Rectal Cancer						
STAT3 (rs2293152)					0.0138	0.0552
GG/GC	791	655	1.00			
CC	168	99	0.71	(0.54, 0.93)		

	Controls	Cases				
Colon Cancer	**N**	**N**	**OR[1]**	**(95% CI)**	**Wald p value**	**pACT**
STAT4 (rs3024861)					0.0416	0.4679
TT/TA	857	690	1.00			
AA	102	64	0.70	(0.49, 0.99)		
STAT6 (rs3024979)					0.0163	0.0623
TT	772	643	1.00			
TA/AA	187	111	0.73	(0.56, 0.94)		
TYK2 (rs280500)					0.0294	0.1255
AA	708	523	1.00			
AG/GG	250	231	1.27	(1.02, 1.57)		
Summary Score						
(0 – 2)	48	13	1.00			
(4 – 4)	262	167	2.45	(1.28, 4.67)		
(6 – 6)	496	423	3.27	(1.74, 6.14)		
(8 – 8)	153	151	3.90	(2.02, 7.52)		
P Trend	<.0001					

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

[2]Summary Score is based on all SNPs showing independent effects

Table 3

Associations between *JAK, SOCS, STAT, TYK2* genes and *IFNG, TNF,* and *IL6*

JAK, SOCS, STAT, TYK2	SNP (Model)[1]	*INFG, TNF, IL6*	SNP (Model)[1]	Wild type[2] Variant		Variant[3] Wild type		Variant[4] Variant		Interaction P Value	p_ACT
				OR	95% CI	OR	(95% CI)	OR	95% CI		
COLON											
STAT4	rs4853540 A)	*IFNG*	rs2069718 (A)	0.74	(0.58,0.95)	0.52	(0.30,0.90)	1.64	(0.87,3.08)	0.0029	0.0900
JAK1	rs3790541 (D)		rs2069718 (D)	0.99	(0.85,1.17)	1.43	(1.10,1.88)	0.89	(0.71,1.11)	0.0055	0.0701
			rs2069727 (A)	0.98	(0.79,1.22)	0.85	(0.63,1.14)	1.68	(1.21,2.34)	0.0031	0.0453
JAK2	rs1887429 (D)		rs2069727 (D)	1.26	(1.03,1.53)	1.10	(0.87,1.41)	0.97	(0.79,1.18)	0.0146	0.1670
SOCS1	rs193779 (D)			1.22	(1.01,1.48)	1.11	(0.87,1.42)	0.96	(0.78,1.17)	0.0197	0.0744
STAT6	rs3024979 (D)	*IFNGR1*	rs3799488 (D)	1.08	(0.90,1.29)	1.09	(0.90,1.32)	0.69	(0.49,0.96)	0.0100	0.0942
			rs9376267 (D)	0.97	(0.83,1.13)	1.18	(0.94,1.47)	0.69	(0.53,0.90)	0.0050	0.0526
TYK2	rs280523 (D)			0.83	(0.71,0.96)	0.71	(0.54,0.93)	0.96	(0.71,1.29)	0.0175	0.1855
STAT1	rs4327257 (D)	*IFNGR2*	rs1532 (A)	1.17	(0.88,1.55)	1.03	(0.82,1.28)	0.47	(0.27,0.84)	0.0024	0.0876
STAT5B	rs9900213 (D)		rs2834211 (D)	1.21	(1.00,1.48)	1.21	(1.03,1.42)	0.92	(0.69,1.22)	0.0100	0.0798
SOCS2	rs768775 (D)		rs2834215 (D)	1.19	(0.98,1.43)	1.66	(1.27,2.17)	1.23	(1.00,1.51)	0.0031	0.0208
SOCS1	rs4780355 (D)		rs9808753 (D)	0.76	(0.61,0.95)	0.89	(0.76,1.04)	0.99	(0.80,1.23)	0.0150	0.0814
STAT4	rs6752770 (D)			0.73	(0.59,0.92)	0.90	(0.77,1.05)	1.04	(0.84,1.29)	0.0037	0.1578
JAK2	rs2274471 (D)	*TNF*	rs1799964 (D)	1.30	(1.09,1.56)	0.99	(0.83,1.18)	0.92	(0.75,1.12)	0.0182	0.1381
STAT1	rs3771300 (D)			0.72	(0.55,0.95)	0.87	(0.71,1.05)	1.14	(0.93,1.40)	0.0002	0.0037
STAT6	rs3024979 (D)			1.02	(0.88,1.19)	0.79	(0.64,0.99)	1.36	(1.04,1.77)	0.0041	0.0216
	rs324011 (D)			1.36	(1.09,1.71)	1.23	(1.03,1.46)	1.23	(1.01,1.49)	0.0345	0.1247
JAK1	rs2256298 (D)		rs1800630 (D)	1.39	(1.14,1.69)	1.24	(1.06,1.46)	1.22	(0.98,1.51)	0.0190	0.1342
STAT4	rs11685878 (D)			1.54	(1.20,1.97)	1.17	(0.99,1.39)	1.21	(0.99,1.48)	0.0118	0.1810
	rs12327969 (D)			1.39	(1.15,1.67)	1.20	(1.02,1.42)	1.12	(0.90,1.40)	0.0093	0.1500
STAT6	rs3024979 (D)			1.08	(0.92,1.27)	0.83	(0.67,1.01)	1.50	(1.12,2.02)	0.0060	0.0295
STAT3	rs12949918 (A)	*TNFRSF1A*	rs4149570 (A)	0.51	(0.35,0.73)	1.00	(0.73,1.38)	1.09	(0.72,1.66)	0.0146	0.1398
STAT6	rs3024979 (D)		rs4149570 (D)	0.96	(0.82,1.11)	1.29	(0.97,1.72)	0.79	(0.63,0.99)	0.0140	0.1340
STAT3	rs1053005 (D)		rs4149576 (D)	1.22	(1.02,1.46)	1.44	(1.13,1.83)	1.20	(0.98,1.46)	0.0115	0.1173
	rs6503695 (D)			1.31	(1.05,1.63)	1.52	(1.20,1.92)	1.41	(1.15,1.75)	0.0210	0.1832
STAT5A	rs12601982 (D)			1.24	(1.04,1.47)	1.54	(1.20,1.97)	1.20	(0.98,1.47)	0.0027	0.0141

JAK, SOCS, STAT, TYK2	SNP (Model)[1]	*INFG, TNF, IL6*	SNP (Model)[1]	Wild type[2] Variant		Variant[3] Wild type		Variant[4] Variant		Interaction P Value	p_ACT
				OR	95% CI	OR	(95% CI)	OR	95% CI		
	rs7217728 (D)			1.27	(1.03,1.56)	1.48	(1.17,1.88)	1.40	(1.14,1.73)	0.0458	0.1621
STAT5B	rs7218653 (D)			1.26	(1.03,1.55)	1.45	(1.15,1.83)	1.34	(1.09,1.63)	0.0286	0.1728
STAT6	rs3024979 (D)			0.98	(0.84,1.15)	0.69	(0.51,0.93)	1.10	(0.88,1.38)	0.0086	0.0897
STAT3	rs6503695 (A)		rs4149577 (A)	0.66	(0.49,0.89)	1.04	(0.69,1.57)	1.31	(0.86,1.99)	0.0192	0.1711
TYK2	rs280519 (D)		rs4149578 (D)	0.68	(0.49,0.96)	0.92	(0.78,1.09)	1.08	(0.85,1.36)	0.0074	0.0940
JAK1	rs2256298 (D)		rs4149584 (D)	0.61	(0.38,0.96)	1.07	(0.93,1.23)	1.85	(1.13,3.04)	0.0020	0.0411
STAT5B	rs9900213 (D)	*IL6*	rs1800796 (D)	0.75	(0.58,0.97)	1.03	(0.88,1.20)	1.22	(0.87,1.72)	0.0364	0.1926
JAK1	rs2256298 (A)		rs1800797 (A)	1.17	(0.90,1.53)	1.75	(1.16,2.63)	0.94	(0.43,2.03)	0.0040	0.0692
JAK2	rs10815160 (A)			1.10	(0.85,1.43)	1.81	(1.20,2.74)	1.05	(0.54,2.05)	0.0045	0.0739
STAT3	rs12949918 (A)			0.66	(0.46,0.94)	1.01	(0.74,1.38)	1.56	(1.01,2.40)	0.0152	0.1419
	rs6503695 (A)			0.70	(0.51,0.96)	1.09	(0.77,1.54)	1.99	(1.17,3.38)	0.0212	0.1794
STAT6	rs324015 (A)			0.77	(0.59,0.99)	0.77	(0.49,1.22)	1.66	(0.79,3.47)	0.0219	0.1895
JAK2	rs3780379 (D)		rs1800797 (D)	1.10	(0.93,1.31)	1.26	(1.01,1.59)	0.85	(0.70,1.03)	0.0009	0.0175
STAT5B	rs9900213 (D)			1.03	(0.87,1.22)	1.31	(1.05,1.64)	0.99	(0.80,1.21)	0.0347	0.1922
STAT4	rs10168266 (D)		rs2069827 (D)	0.70	(0.56,0.89)	0.89	(0.76,1.04)	1.09	(0.82,1.45)	0.0039	0.1373
	rs3024861 (D)			0.67	(0.52,0.86)	0.91	(0.79,1.06)	1.05	(0.81,1.37)	0.0030	0.1131
RECTAL											
JAK2	rs3780381 (A)	*IFNG*	rs2069727 (A)	0.61	(0.41,0.89)	0.43	(0.19,0.98)	0.9	(0.41,1.96)	0.0124	0.1497
STAT5B	rs9900213 (D)	*IFNGR1*	rs1327474 (D)	0.84	(0.65,1.08)	0.69	(0.48,0.98)	0.92	(0.69,1.24)	0.0342	0.1906
SOCS2	rs3816997 (D)		rs3799488 (D)	0.98	(0.75,1.28)	0.75	(0.59,0.96)	1.23	(0.82,1.84)	0.0474	0.1905
	rs768775 (D)		rs9376267 (D)	1.02	(0.80,1.30)	0.93	(0.72,1.21)	1.49	(1.11,2.01)	0.0285	0.1290
JAK1	rs310198 (D)	*IFNGR2*	rs1532 (D)	1.02	(0.81,1.27)	1.15	(0.84,1.57)	0.64	(0.46,0.91)	0.0100	0.1725
JAK2	rs7043371 (A)		rs2834211 (D)	2.18	(1.39,3.41)	1.32	(0.97,1.79)	1.09	(0.68,1.74)	0.0031	0.0668
STAT3	rs1026916 (A)		rs2834215 (A)	1.65	(1.07,2.53)	1.7	(0.98,2.96)	0.91	(0.51,1.63)	0.0054	0.0683
STAT5A	rs12601982 (D)		rs2834215 (D)	1.22	(0.94,1.58)	1.53	(1.03,2.29)	1.08	(0.81,1.46)	0.0229	0.1098
TYK2	rs280500 (D)	*TNF*	rs1800630 (D)	1.39	(1.08,1.78)	1.48	(1.15,1.91)	1.22	(0.86,1.73)	0.0261	0.1443
JAK2	rs10815160 (D)	*TNFRSF1A*	rs4149570 (D)	1.37	(1.05,1.78)	1.39	(1.02,1.91)	1.08	(0.81,1.42)	0.0048	0.0847
SOCS2	rs3816997 (D)		rs4149576 (D)	1.28	(1.01,1.63)	1.17	(0.83,1.64)	0.87	(0.65,1.18)	0.0150	0.0696
			rs4149578 (D)	0.9	(0.67,1.20)	0.73	(0.57,0.93)	1.28	(0.85,1.94)	0.0114	0.0587
STAT4	rs3024904 (D)			1.34	(1.02,1.76)	1.27	(0.97,1.65)	0.73	(0.45,1.16)	0.0035	0.1397

JAK, SOCS, STAT, TYK2	SNP (Model)[1]	*INFG, TNF, IL6*	SNP (Model)[1]	Wild type[2] Variant		Variant[3] Wild type		Variant[4] Variant		Interaction P Value	p_ACT
				OR	95% CI	OR	(95% CI)	OR	95% CI		
SOCS1	rs193779 (D)			1.39	(1.02,1.91)	1.36	(1.09,1.70)	1.06	(0.74,1.52)	0.0181	0.0792
	rs4780355 (D)			0.66	(0.44,0.99)	0.88	(0.71,1.09)	1.29	(0.94,1.77)	0.0018	0.0102
JAK2	rs3780379 (D)	*IL6*	rs1800797 (D)	1.36	(1.07,1.74)	1.46	(1.07,2.01)	1.14	(0.85,1.54)	0.0088	0.1332
STAT4	rs6752770 (A)		rs2069840 (A)	0.58	(0.37,0.91)	0.55	(0.31,0.95)	1.24	(0.53,2.89)	0.0044	0.1564
STAT1	rs16824035 (D)		rs2069840 (D)	0.71	(0.56,0.89)	0.71	(0.51,0.99)	1.01	(0.76,1.34)	0.0015	0.0475
	rs4327257 (D)			0.74	(0.59,0.92)	0.7	(0.48,1.01)	1.06	(0.78,1.44)	0.0023	0.0694
TYK2	rs280519 (D)			0.57	(0.39,0.83)	0.7	(0.51,0.97)	0.71	(0.52,0.97)	0.0097	0.1123

[1]Models: A - additive or co-dominant; D - dominant

[2]Compares wild type (WT) *JAK/STAT/SOCS* SNP and variant from additive or co-dominant model or heterozygote/variant if dominant model for pathway SNP relative to both WT

[3]Compares variant from additive or co-dominant model or heterozygote/variant if dominant model for *JAK/STAT/SOCS* SNP and wild type (WT) pathway SNP relative to both WT

[4]Compares variant from additive or co-dominant model or heterozygote/variant if dominant model for both *JAK/STAT/SOCS* and pathway SNPs relative to both WT

Table 4

Interaction between cigarette smoking, estrogen status, and NSAID use with *JAK, STAT, TYK* and cancer risk

Gene	SNP (Model)[1]	Variant[2]		Wildtype				Interaction P Value	p_ACT
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)		
	Colon Cancer	No Recent Aspirin/NSAID Use			Recent Aspirin/NSAID Use				
TYK2	rs280521 (D)	1.00	(0.82, 1.21)	0.49	(0.38, 0.64)	0.72	(0.61, 0.84)	0.0266	0.1146
		No Recent Estrogen			Estrogen Use				
STAT1	rs10199181 (R)	1.19	(0.85, 1.67)	0.37	(0.23, 0.62)	0.65	(0.50, 0.85)	0.0171	0.1406
	rs10208033 (A)	1.35	(0.93, 1.96)	0.39	(0.23, 0.65)	0.66	(0.44, 0.98)	0.0405	0.2628
	rs2280233 (A)	0.78	(0.54, 1.11)	0.58	(0.37, 0.90)	0.37	(0.25, 0.56)	0.0138	0.1239
	rs3771300 (A)	0.70	(0.49, 1.00)	0.58	(0.37, 0.89)	0.37	(0.24, 0.57)	0.0081	0.0805
	rs7562024 (A)	1.44	(0.97, 2.12)	0.48	(0.29, 0.78)	0.71	(0.48, 1.04)	0.0322	0.2250
STAT4	rs6572770 (A)	1.33	(0.83, 2.11)	0.40	(0.20, 0.79)	0.70	(0.51, 0.98)	0.0345	0.3578
TYK2	rs280519 (R)	1.50	(1.12, 2.01)	0.59	(0.39, 0.89)	0.66	(0.50, 0.87)	0.0403	0.1705
		Non Smoker			Recent Smoker				
JAK2	rs10815160 (R)	1.17	(0.87, 1.58)	3.15	(1.60, 6.22)	1.11	(0.93, 1.32)	0.0166	0.0869
	rs1887429 (D)	0.79	(0.68, 0.92)	1.16	(0.90, 1.48)	0.94	(0.75, 1.19)	0.0131	0.0873
	rs7043371 (A)	1.21	(0.98, 1.49)	1.12	(0.80, 1.57)	1.67	(1.19, 2.34)	0.015	0.0895
STAT2	rs2229363 (D)	1.20	(0.74, 1.95)	0.39	(0.14, 1.07)	1.20	(1.01, 1.43)	0.0156	0.0302
STAT4	rs4853540 (A)	1.21	(0.86, 1.68)	0.79	(0.42, 1.48)	1.33	(1.07, 1.66)	0.0304	0.3310
STAT5A	rs7217728 (A)	1.15	(0.89, 1.49)	2.39	(1.44, 3.96)	0.98	(0.76, 1.26)	0.0098	0.0177
STAT5B	rs7218563 (A)	1.14	(0.88, 1.47)	2.30	(1.39, 3.83)	0.97	(0.76, 1.25)	0.0151	0.0398
STAT6	rs3024974 (D)	0.88	(0.72, 1.06)	1.48	(1.02, 2.15)	1.07	(0.89, 1.30)	0.0465	0.1709
	Rectal Cancer	No Recent Aspirin/NSAID Use			Recent Aspirin/NSAID Use				
JAK2	rs10815160 (A)	1.52	(0.92, 2.51)	0.49	(0.26, 0.91)	0.82	(0.63, 1.07)	0.019	0.1149
STAT6	rs324011 (D)	1.48	(1.14, 1.92)	0.86	(0.65, 1.14)	0.94	(0.68, 1.30)	0.0207	0.0782
TYK2	rs280521 (D)	1.40	(1.05, 1.85)	0.62	(0.44, 0.88)	0.82	(0.65, 1.03)	0.0092	0.0418

Gene	SNP (Model)[1]	Variant[2]		Wildtype				Interaction P Value	p_ACT
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)		
		No Recent Estrogen		Estrogen Use					
JAK1	rs2256298 (A)	0.38	(0.14, 1.05)	0.94	(0.44, 2.02)	0.55	(0.35, 0.85)	0.0427	0.1931
	rs310198 (D)	0.69	(0.40, 1.19)	0.81	(0.49, 1.34)	0.54	(0.37, 0.79)	0.0276	0.1402
	rs310199 (A)	0.75	(0.34, 1.62)	1.01	(0.50, 2.06)	0.44	(0.27, 0.71)	0.0136	0.0837
	rs310211 (A)	0.32	(0.12, 0.80)	0.84	(0.42, 1.69)	0.51	(0.32, 0.82)	0.0138	0.0790
		Non Smoker		Recent Smoker					
STAT2	rs2229363 (D)	1.74	(0.86, 3.54)	0.23	(0.03, 1.92)	1.36	(1.05, 1.76)	0.016	0.0309

[1] Models: A - additive or co-dominant; D - dominant

[2] Heterozygote/variant genotype if dominant model; variant if recessive or additive (or co-dominant); all comparisons are made to non-user/smoker and wildtype genotype

Table 5

HRR from pathway SNPs associated with survival after diagnosis with colon or rectal cancer

Summary Score	Death/Person Years	HRR[1]	(95% CI)
	ColonCancer[2]		
(0–7)	31/1304	1.00	
(8–9)	36/985	2.41	(1.47, 3.94)
(10–11)	42/1487	1.70	(1.06, 2.73)
(12–13)	65/1530	2.49	(1.60, 3.87)
(14–15)	52/1212	2.63	(1.67, 4.16)
(16–18)	47/1061	2.57	(1.61, 4.10)
(19–24)	36/570	3.30	(2.01, 5.42)
P Trend	<.0001		
	Rectal Cancer[3]		
(0–4)	19/729	1.00	
(5–7)	19/695	1.29	(0.67, 2.49)
(8–10)	33/842	1.97	(1.11, 3.49)
(11–13)	47/1074	1.62	(0.94, 2.80)
(14–18)	53/951	2.80	(1.63, 4.80)
P Trend	<0.0001		

[1] Hazard Rate Ratios (HRR) and 95% Confidence Intervals (CI) adjusted for age, center, race, sex, AJCC stage, and tumor molecular phenotype

[2] SNPs in colon cancer summary score: JAK2 rs10815160(A), rs10974947(D), rs1887429(A), rs3780379(A), and rs7043371(R), SOCS1 rs4780355(D), STAT3 rs1053005(D), rs2293152(R), and rs8069645(D), STAT5A rs12601982(D), TYK2 rs280521(D) and rs280523(D)

[3] SNPs in rectal cancer summary score: JAK2 rs1536800(R), SOCS1 rs193779(D), STAT1 rs10199181(D), rs1547550(D), rs2280234(D) and rs7562024(A), STAT4 rs10168266(A) and rs16833260(D), TYK2 rs280519(D)