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Dietary influence on MAPK-signaling pathways and risk of colon and rectal cancer

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Abstract

Mitogen-activated protein kinase (MAPK) pathways regulate cellular functions including cell proliferation, differentiation, migration, and apoptosis. Associations between genes in the DUSP, ERK1/2, JNK, and p38 MAPK-signaling pathways and dietary factors associated with growth factors, inflammation, and oxidative stress and risk of colon and rectal cancer were evaluated. Data include colon cases (n=1555) and controls (n=1956) and rectal cases (n=754) and controls (n=959). Statistically significant interactions were observed for the MAPK-signaling pathways after adjustment for multiple comparisons. *DUSP* genes interacted with carbohydrates, mutagen index, calories, calcium, vitamin D, lycopene, dietary fats, folic acid, and selenium. *MAPK1, MAPK3, MAPK1 and RAF1* within the ERK1/2 MAPK-signaling pathway interacted with dietary fats and cruciferous vegetables. Within the JNK MAPK-signaling pathway, interactions between *MAP3K7 and* protein, vitamin C, iron, folic acid, carbohydrates, and cruciferous vegetables; *MAP3K10* and folic acid; *MAP3K9* and lutein/zeaxanthin; *MAPK8* and calcium; *MAP3K3 and* calcium and lutein; *MAP3K1* and cruciferous vegetables. Interaction within the p38-signaling pathway included: *MAPK14* with calories, carbohydrates saturated fat, selenium, vitamin C; *MAP3K2* and carbohydrates, and folic acid. These data suggest that dietary factors involved in inflammation and oxidative stress interact with *MAPK*-signaling genes to alter risk of colorectal cancer.

Keywords

Colorectal Cancer; MAPK; JNK; p38; ERK1/2; diet; inflammation; stress

Introduction

Mitogen-activated protein kinase (MAPK) pathways regulate many cellular functions including cell proliferation, differentiation, migration, and apoptosis [1]. They are activated by a variety of stimuli and phosphorylate transcription factors, kinases and other enzymes, and influence gene expression, metabolism, cell division, morphology, and survival. Each MAPK pathway is a three-tiered cascade that includes a MAP kinase kinase kinase (MAP3K, MEKK, or MKKK), Map kinase kinase (MAP2K, MEK, or MKK), and the MAP kinase (MAPK). MAPK are attenuated by dual specificity MAPK phosphatases (MKPs or DUSP). Three of the major MAPK pathways are extracellular regulated kinases 1 and 2 (ERK1/2), c-Jun-N-terminal kinases (JNKs), and p38. Other less well-studied MAPK pathways are ERK5 and ERK3/ERK4 [2].

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MAPK pathways are activated by various stimuli. For instance, ERK1 and ERK2 are activated by stimuli such as growth factors and cytokines. *Raf*, a MAP kinase kinase kinase, involved in the ERK1/ERK2 pathway responds to growth factors and cytokines [1]. The JNK pathway is involved in regulating responses to stress, inflammation, and apoptosis and are activated by radiation, environmental stresses, and growth factors. The *p38* MAPKs are involved in autoimmunity in humans and are activated by chemical stresses, hormones, cytokines including IL-1 and TNF, and shock [1, 2]. Diet plays a role in many of these pathways through their antioxidant and pro-oxidant properties as well as to possibly influencing growth factors through energy-contributing nutrients.

Few epidemiological studies have evaluated risk associated with genetic variation in MAPK-signaling pathways and cancer. However, the MAPK-signaling pathways have been identified as one of the most strongly associated gene markers to colorectal cancer (CRC) from a GWAS conducted in Germany [3]. Seven *MAPK* genes were identified as being important for CRC in that study. In our previous work, we identified several *MAPK* genes associated with cancer overall, specific tumor molecular phenotype, and survival [4].

In this study we evaluate the associations between diet and the MAPK–signaling pathways as they influence risk of colon and rectal cancer. We do this my evaluating interaction between dietary factors that are associated with colorectal cancer and those that have anti- and pro-oxidant properties. Data for this study come from a large case-control study of colon and rectal cancer.

Materials and Methods

Two study populations are included in these analyses. The first study, a population-based case-control study of colon cancer, included cases (n=1,555 with complete genotype data) and controls (n=1,956 with complete genotype data) identified between October 1, 1991 and September 30, 1994 living in the Twin Cities Metropolitan Area or a seven-county area of Utah or enrolled in the Kaiser Permanente Medical Care Program of Northern California (KPMCP) [5]. The second study, with identical data collection methods, included cases with cancer of the rectosigmoid junction or rectum (n=754 cases and n=959 controls with complete genotype data) who were identified between May 1997 and May 2001 in Utah and at the KPMCP [6]. Eligible cases were between 30 and 79 years of age at the time of diagnosis, living in the study geographic area, English speaking, mentally competent to complete the interview, and with no previous history of CRC, and no previous diagnosis of familial adenomatous polyposis, ulcerative colitis, or Crohn's disease. Cases who did not meet these criteria were ineligible as were individuals who were not black, white, or Hispanic for the colon cancer study. A rapid-reporting system was used to identify cases within months of diagnosis.

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. In Minnesota, controls were selected from driver's license and state-identification lists. Eligibility for controls was the same as those outlined for cases; additionally, controls could not have had a previous colorectal cancer. Study details have been previously reported [5, 6]. All study participants provided informed consent prior to completing the study questionnaire; the study was approved by the Institutional Review Board on Human Subjects at all institutions.

Interview Data Collection

Data were collected by trained and certified interviewers using laptop computers. All interviews were audio-taped as previously described and reviewed for quality control purposes [7]. The referent period for the study was two years prior to diagnosis for cases and selection for controls. Detailed information was collected on diet, physical activity, medical history, reproductive history, family history of cancer, regular use of aspirin and non-steroidal anti-inflammatory drugs, cigarette smoking history, and body size. Dietary information was obtained from an extensive diet history questionnaire that obtained information on food items, the frequency of consumption, the amount usually consumed, and method of preparation; this questionnaire was adapted from the validated CARDIA diet history [8] for computerized administration [9]. Additional questions were asked about meat consumption and preparation. From these questions we created a mutagen index that took into account frequency of red and white meat consumed, method of preparation such as frying, micro-wave, baking or grilling, and how well done the meat was when consumed.

TagSNP Selection and Genotyping

TagSNPs were selected for DUSP1 (2), DUSP2 (1), DUSP4 (6), DUSP6 (4), DUSP7 (1), MAPK1 (6), MAPK3 (1), RAF1 (8), MAPK8 (6), MAP3K1 (8), MAP3K3 (3), MAP3K7 (6), MAP3K9 (19), MAP3K10 (3), MAP3K11 (4), MAPK12 (3), MAPK14 (12), MAP2K1 (7), MAP3K2 (3), MAPK7 (1) using the following parameters: linkage disequilibrium (LD) blocks using a Caucasian LD map with 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. Online supplement 1 has a list of all SNPs assessed, their location, major and minor allele, and Hardy Weinberg Equilibrium (HWE) p value. LD maps are included in an online supplement. All markers were genotyped using a multiplexed bead-array assay 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 samples. The duplicate concordance rate was 100%. Two DUSP6, one MAPK8, one MAPK12, and the single MAPK7 tagSNP failed.

Statistical Methods

Statistical analyses were performed for each study independently using SAS® version 9.2 (SAS Institute, Cary, NC). The linkage disequilibrium (LD) measure, minor allele frequency (MAF) and test for Hardy-Weinberg Equilibrium (HWE) were calculated among white controls using the ALLELE procedure. Dietary variables were evaluated because of their potential involvement in MAPK-signaling pathways. We evaluated interactions between nutrients that could influence by inflammation, oxidative stress, hormones, and growth factors. Dietary medians and interquartile range values adjusted for age using quantile regression [10] are presented in Table 1 along with p values based on the age-adjusted log transformed means. We report odds ratios (ORs) and 95% confidence intervals (CIs) assessed from multiple logistic regression models adjusting for total caloric intake and the matching variables for the original studies: age, center, race/ethnicity, and sex. P values for interaction were determined using a 1-df likelihood-ratio test comparing a full model that included an interaction term to a reduced model without an interaction term.

Multiple comparison adjustments were made taking into account tagSNPs within the gene using the step-down Bonferroni correction (i.e., Holm method) based on the effective number of independent SNPs as determined using the SNP spectral decomposition method proposed by Nyholt [11] and modified by Li and Ji [12] on the full sample of cases and controls. Tables 2 through 5 present interactions between dietary factors and *MAPK* genes that remained significant at the 0.05 level after adjustment for multiple comparisons; an

online supplement has those interactions that were significant at the 0.05 level prior to adjustment for multiple comparisons but the adjusted p values were greater than 0.05.

Results

A description of the study population is shown in Table 1. The majority of the population was over 60 years of age, male, and non-Hispanic white. Significant age-adjusted differences in mean levels of dietary intake were observed for total energy, protein, all types of dietary fat, and selenium for colon cancer. For rectal cancer we observed differences in age-adjusted mean levels of total energy, saturated, mono-unsaturated, and trans-fatty acids, and dietary selenium.

DUSP genes interacted with numerous dietary factors (Table 2), although there was a pattern of both important genes and SNPs. All but three significant interactions between DUSP genes and dietary factors were observed for rectal cancer. *DUSP2* rs1724120 interacted with carbohydrates and *DUSP6* rs10744 and rs770087 interacted with mutagen index to alter risk of colon cancer. For rectal cancer, there also were patterns of association. *DUSP6* rs10744 interacted significantly with calories, calcium, vitamin D, and lycopene where a reduced risk of rectal cancer was observed for the AT/TT genotypes versus AA genotype in the lowest level of intake. *DUSP4* rs2056025 and rs474824 interacted with monounsaturated fat, polyunsaturated fat, trans-fatty acids, folic acid, vitamin D, selenium, and mutagen index. The pattern of these associations was similar to that described above where the homozygote variant genotype has the greatest reduced risk among those with the lowest level of intake.

Seven significant interactions (p_{adj} <0.05) were identified between colon cancer and the genes in the *ERK1* and *ERK2* pathway while three significant interactions were observed for rectal cancer (Table 3). *MAPK1* rs9610470 interacted significantly with saturated and monounsaturated fat; *MAPK3* rs7698 interacted significantly with polyunsaturated fat, and trans-fatty acid. For *MAPK1* rs9610470 the increased risk associated with increasing levels of fat were modified by the CC genotype. For the other SNPs, risk was more associated by level of nutrient intake than genotype. *RAF1* rs3773353, rs4684871 and rs904453 interacted significantly with cruciferous vegetables to alter rectal cancer risk.

Interaction between dietary variables and genes in the JNK pathway was more common for colon cancer than for rectal cancer (Table 4). Several genes, including MAP3K1, MAP3K3, and MAP3K7 are also involved in the p38 signaling pathway, although associations are shown on Table 4. *MAP3K7* was associated with protein, vitamin C, and folic acid. The rs150117 SNP was associated with vitamin C, and folic acid where the variant allele had an opposite effect on risk by level of intake than the wildtype genotype. *MAP3K10* was associated with folic acid (rs3746006). Five SNPs in *MAP3K9* interacted significantly with lutein/zeaxanthin, while *MAPK8* interacted with calcium. For rectal cancer *MAP3K7* rs379912 interacted significantly carbohydrate intake, and cruciferous vegetables. *MAP3K7* rs711267 also interacted with cruciferous vegetables. *MAP3K3* interacted with calcium (rs3785574) and lutein (rs1165832). *MAP3K1* rs43184 interacted significantly with cruciferous vegetables. In all instances the risk associated with rectal cancer was in an opposite direction for the wildtype and variant genotypes with increasing levels of nutrient intake.

Six of the 13 significant interactions for the *p38* pathway were with *MAPK14* (Table 5). *MAPK14* rs10807156 interacted with calories and carbohydrates to alter colon cancer risk, while *MAPK14* rs851011 interacted with saturated fat and selenium and rs851006 interacted with vitamin C to alter rectal cancer risk. Several significant interactions were associated

with *MAP3K2*, including carbohydrates and folic acid with rs6732279 and rs3732209 with lycopene and rectal cancer. *MAP3K2* is also associated with the JNK pathway. One other significant interactions were noted for rectal cancer, *MAPK12* rs742184 with calcium. The patterns of associations were similar as noted above, where level of intake had an opposite effect of risk depending on genotype.

Discussion

MAPK which are activated by environmental stimuli are involved in numerous cellular properties that could influence cancer risk. We observed numerous statistically significant interactions between dietary factors and genes in MAPK-signaling pathways after adjustment for multiple comparisons suggesting that dietary factors are involved in activation and regulation of the key MAPK-signaling pathways.

DUSP4 (rs2056025 and rs474824) and *DUSP6* (primarily rs10744 and 770087) were associated with dietary fats which could have inflammatory and pro-oxidant properties and dietary antioxidants such as selenium, and lycopene. Additionally we observed associations with folic acid, calcium, and vitamin D other nutrients that have been previously associated with colorectal cancer and have anti-oxidant properties [13, 14]. Mutagen index, which takes into account meat preparation methods and represents potential increases of heterocyclic amines and polycyclic aromatic hydrocarbons [15] signal increases in reactive oxygen species [16], interacted with *DUSP6* and colon cancer and *DUSP4* and rectal cancer. *DUSP* genes and SNPs interacted with dietary factors to alter risk associated with rectal cancer to a greater extent than they did with colon cancer. DUSPs negatively regulate the activity of mitogen-activated kinases that are associated with tumor growth and progression [17, 18]. Studies have shown that oxidative stress can mediate loss of *DUSP6* (also known as MPK3) that can subsequently lead to increased tumorigenicity [17]. Dietary factors that could influence levels of oxidative stress could interact with *DUSP* genes to further influence this process.

ERK1 and ERK2-signaling pathway genes have been associated previously with growth factors. For colon cancer we observed interactions with *MAPK1* (rs9610470 and rs11913721) and *MAPK3* (rs7698) genes and dietary fats. The pattern of associations suggests that dietary factors that are associated with lipid hydroperoxides are important in this pathway of MAPK and colon cancer risk. However, the only significant interaction detected for rectal cancer was between *Raf1* (3 SNPs) and cruciferous vegetables. Studies have shown that cruciferous vegetables may have chemo-preventive properties through inactivating ERK1/2 and p38 [19–22]. Raf, a MAP kinase kinase kinase, is involved in the ERK1/ERK2 pathway as the initial responder to growth factors and cytokines [1]. While the literature does not address Raf1 specifically, we believe that our data support the previous work that shows cruciferous vegetables regulate ERK1/2 signaling.

JNK, also known as stress-activated protein kinase 1 (SAPK1), and p38, also known as SAPK2, pathways are activated by pro-inflammatory cytokines and oxidative stress. JNK and ERK have been shown to be modulated by obesity and insulin resistance. A study by Hardwick and colleagues observed that both p38 and JNK were highly expressed in colonic adenomatous polyps [23]. Several genes that relate to both the JNK and p38 signaling pathways, showed interactions with dietary factors. Although we list associations with *MAP3K1*, MAP3K3, and *MAP3K7* on Table 4 and *MAP3K2* on Table 5, there is overlap in their involvement with both pathways. Given the number of interactions from pro-oxidants (i.e. iron and saturated fat) and antioxidants (i.e. vitamin C, folic acid, calcium lutein/zeaxanthin, tochoperol, beta carotene, selenium, and lycopene), it is suggestive that dietary factors that influence oxidative stress and inflammation may have properties that influence

the risk associated with these signaling pathways. The patterns in the data show similar associations for several genes and SNPs within those genes for multiple anti-oxidants which we believe further supports the possibility that associations are real. For instance *MAP3K7*, mainly rs150117 and rs3799912, were associated with altered colon and rectal cancer risk for vitamin C, folic acid, and cruciferous vegetables. Six SNPs in *MAP3K9* were associated with lutein/zeaxanthin and risk of colon cancer. *MAP3K10* rs3746006 was associated with folic acid to alter colon cancer risk. Additionally, *MAP3K1* (1 SNP) and *MAP3K7* (2 SNPs) interacted with cruciferous vegetables to alter rectal cancer risk. We have previously reported associations between *MAPK14* and aspirin interacting to influence colon cancer risk [4].

There are strengths and limitations to our study. The sample size is large and allows us to examine risk factors in colon and rectal cancer separately. The dietary data were obtained from a detailed questionnaire that had previously been validated. Given the detailed data and the extensive nutrient database, we have been able to evaluate several nutrients that could relate to important pathways involved in MAPK signaling. While our analysis was hypothesis driven, others have not evaluated these genes with diet and therefore it also was somewhat exploratory. Thus, we have made numerous comparisons although we have adjusted for those comparisons. Only those at the 0.05 level after adjustment are presented in the text of this manuscript although those <0.15 after adjustment are available online. While we view the consistency we observed across genes and SNPs within those genes as adding support for the observed associations, little is known about the functionality associated with these SNPs. Work to illuminate altered functionality in the genes containing these SNPs is needed.

MAPKs are involved in cellular functions including cell proliferation, differentiation, migration, and apoptosis that are central to the carcinogenic process. MAPK are activated by by various stimuli. In this study we tested the hypothesis that dietary factors are involved in MAPK-signaling pathways. We observed consistencies in the data that suggest dietary factors involved in inflammation and oxidative stress interact with *MAPK* genes to alter risk of colon and rectal cancer. We encourage others to examine these genes and SNPs with dietary factors to replicate and confirm these findings.

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Table 1

Characteristics of the study population

	Colon			Rectal		
	Controls n (%)	**Cases n (%)**	**P Value**	**Controls n (%)**	**Cases n (%)**	**P Value**
Age						
30–39	40 (2.04)	23 (1.48)	NA	21 (2.19)	19 (2.52)	NA
40–49	128 (6.54)	102 (6.56)		101 (10.53)	96 (12.73)	
50–59	326 (16.67)	290 (18.65)		243 (25.34)	196 (25.99)	
60–69	673 (34.41)	538 (34.60)		329 (34.31)	250 (33.16)	
70–79	789 (40.34)	602 (38.71)		265 (27.63)	193 (25.60)	
Center						
Utah	378 (19.33)	249 (16.01)	NA	365 (38.06)	274 (36.34)	NA
KPMCP	787 (40.24)	744 (47.85)		594 (61.94)	480 (63.66)	
Minnesota	791 (40.44)	562 (36.14)				
Race/Ethnicity						
NHW	1828 (93.46)	1428 (91.83)	NA	824 (85.92)	625 (82.89)	NA
Hispanic	75 (3.83)	59 (3.79)		63 (6.57)	61 (8.09)	
Black	53 (2.71)	68 (4.37)		43 (4.48)	29 (3.85)	
Asian	NA	NA		29 (3.02)	39 (5.17)	
Sex						
Male	1047 (53.53)	870 (55.95)	NA	541 (56.41)	451 (59.81)	NA
Female	909 (46.47)	685 (44.05)		418 (43.59)	303 (40.19)	
Dietary Variables	Median (IQR)[1]			Median (IQR)		
Energy (Kcal)	2134 (1615, 2829)	2219 (1700, 2949) 85.29 (65.84, 113.20)	<.01	2380 (1752, 3133)	2476 (1784, 3314)	0.03
Protein (gm)	82.68 (62.59, 109.01)		0.02	85.06 (64.05, 111.55)	87.40 (63.90, 118.73)	0.06
Saturated Fat (gm)	26.83 (18.19, 39.09)	28.94 (19.57, 43.13)	<.01	29.21 (19.66, 44.32)	31.21 (21.12, 46.91)	0.01
Monounsaturated Fat (gm)	26.24 (18.08, 38.00)	28.64 (19.82, 41.84)	<.01	32.23 (21.50, 47.10)	34.02 (23.03, 49.79)	0.02
Polyunsaturated (gm) Fat	13.82 (9.90, 19.98)	14.97 (10.49, 21.08)	<.01	20.40 (13.67, 29.27)	21.54 (14.03, 30.46)	0.06
Trans-Fatty Acid (gm)	4.94 (3.20, 7.51)	5.66 (3.63, 8.48)	<.01	5.09 (3.23, 7.76)	5.55 (3.51, 8.57)	0.01
Carbohyrates (gm)	274 (210, 361)	282 (219, 372)	0.07	297 (218, 390)	304 (221, 402)	0.29

	Colon			Rectal		
	Controls n (%)	Cases n (%)	P Value	Controls n (%)	Cases n (%)	P Value
Vitamin C (mg)	148 (101, 210)	147 (102, 209)	0.86	152 (99, 215)	145 (96, 215)	0.36
Folic Acid (mcg)	354 (267, 469)	354 (268, 465)	0.96	357 (260, 476)	352 (257, 468)	0.90
Calcium (mg)	987 (685, 1393)	975 (675, 1372)	0.43	1020 (715, 1462)	982 (690, 1405)	0.67
Vitamin D (mcg)	5.85 (3.37, 9.05)	5.70 (3.43, 8.91)	0.93	6.57 (4.28, 9.86)	6.89 (4.28, 10.06)	0.28
Lutein/Zeaxanthin(mcg)	2266 (1537, 3383)	2238 (1486, 3424)	0.55	2673 (1738, 3995)	2621 (1703, 3888)	0.52
Lycopene (mcg)	5919 (3211, 9752)	5912 (3235, 10027)	0.32	7845 (4470, 13086)	7838 (4136, 13607)	0.97
Alpha-tocopherol (mg)	7.45 (5.24, 10.58)	7.70 (5.35, 11.03)	0.22	9.25 (6.39, 13.10)	9.20 (6.47, 13.29)	0.38
Selenium (mcg)	126 (96, 165)	129 (99, 168)	0.02	130 (95, 185)	134 (101, 197)	0.04
Beta-carotene (mcg)	3786 (2398, 6302)	3990 (2431, 6354)	0.65	3983 (2538, 6519)	3845 (2353, 6296)	0.48
Mutagen Index	624 (369, 943)	659 (407, 1005)	0.09	648 (366, 1040)	731 (396, 1091)	0.17
Cruciferous Vegetables (serv./day)	0.27 (0.09, 0.59)	0.25 (0.09, 0.59)	0.68	0.23 (0.07, 0.54)	0.22 (0.07, 0.49)	0.91

[1] Medians and inter-quartile range (IQR) adjusted for age; p values are based on age adjusted log transformed means

Table 2

Associations between *DUSP* genes, diet and colon and rectal cancer risk

	Low				Intermediate				High					
	Control	Case	OR[1]	95% CI	Control	Case	OR	95% CI	Control	Case	OR	(95% CI)	P_{int}	P_{adj}
Colon Cancer														
Carbohydrates														
DUSP2 (rs1724120)													0.01	0.01
GG/GA	380	311	1.00		793	592	0.82	(0.67, 1.00)	392	305	0.69	(0.51, 0.92)		
AA	109	71	0.79	(0.56, 1.10)	187	169	1.00	(0.76, 1.30)	95	107	0.98	(0.67, 1.43)		
Mutagen Index														
DUSP6 (rs770087)[2]													0.03	0.03
TT	349	223	1.00		607	467	1.18	(0.96, 1.45)	288	285	1.50	(1.19, 1.91)		
TG/GG	158	132	1.29	(0.96, 1.71)	361	288	1.23	(0.98, 1.54)	192	160	1.24	(0.94, 1.63)		
Rectal Cancer														
Energy Intake														
DUSP6 (rs10744)[3]													0.02	0.02
AA	142	124	1.00		304	230	0.86	(0.64, 1.17)	152	136	1.00	(0.71, 1.41)		
AT/TT	104	55	0.60	(0.40, 0.90)	168	116	0.78	(0.55, 1.09)	88	93	1.16	(0.79, 1.71)		
Monounsaturated Fat														
DUSP4 (rs2056025)													0.01	0.03
TT	169	144	1.00		353	260	0.79	(0.59, 1.06)	186	156	0.75	(0.49, 1.15)		
TG	67	38	0.65	(0.41, 1.02)	113	93	0.88	(0.61, 1.27)	52	54	0.91	(0.53, 1.55)		
GG	8	1	0.14	(<0.01, 0.80)	9	5	0.60	(0.18, 1.80)	2	3	1.20	(0.19, 9.48)		
DUSP4 (rs474824)													0.01	0.03
TT	82	72	1.00		171	125	0.76	(0.51, 1.15)	90	61	0.60	(0.35, 1.04)		
TC	104	87	0.93	(0.61, 1.43)	231	167	0.75	(0.51, 1.10)	102	107	0.90	(0.54, 1.51)		
CC	58	24	0.43	(0.24, 0.77)	73	66	0.90	(0.56, 1.44)	48	45	0.77	(0.42, 1.40)		
Polyunsaturated Fat														
DUSP4 (rs2056025)													0.01	0.03
TT	168	139	1.00		353	260	0.83	(0.62, 1.12)	187	161	0.86	(0.57, 1.30)		

	Low				Intermediate				High					
	Control	Case	OR[1]	95% CI	Control	Case	OR	95% CI	Control	Case	OR	(95% CI)	P_{int}	P_{adj}
TG	69	33	0.56	(0.35, 0.90)	110	97	0.99	(0.68, 1.43)	53	55	1.02	(0.60, 1.71)		
GG	9	2	0.27	(0.04, 1.06)	8	4	0.56	(0.15, 1.82)	2	3	1.35	(0.21, 10.66)		
Trans-Fatty Acid														
DUSP4 (rs474824)													0.01	0.03
TT	87	75	1.00		163	112	0.79	(0.53, 1.19)	93	71	0.84	(0.51, 1.37)		
TC	109	78	0.82	(0.54, 1.26)	223	169	0.86	(0.59, 1.25)	105	114	1.17	(0.73, 1.87)		
CC	52	25	0.52	(0.29, 0.91)	85	61	0.78	(0.49, 1.24)	42	49	1.18	(0.67, 2.09)		
Folic Acid														
DUSP4 (rs2056025)													0.01	0.04
TT/TG	237	208	1.00		467	353	0.73	(0.57, 0.94)	236	184	0.57	(0.39, 0.82)		
GG	10	1	0.11	(<0.01, 0.60)	7	4	0.56	(0.14, 1.88)	2	4	1.39	(0.26, 10.38)		
Calcium														
DUSP6 (rs10744) [3]													<0.01	<0.01
AA	131	138	1.00		314	250	0.65	(0.48, 0.88)	153	102	0.44	(0.29, 0.67)		
AT/TT	111	64	0.54	(0.36, 0.79)	164	120	0.59	(0.42, 0.84)	85	80	0.59	(0.37, 0.93)		
Vitamin D														
DUSP4 (rs474824)													0.01	0.03
TT	81	78	1.00		164	119	0.70	(0.47, 1.04)	98	61	0.52	(0.32, 0.84)		
TC	106	84	0.80	(0.52, 1.22)	225	188	0.79	(0.54, 1.15)	106	89	0.68	(0.43, 1.08)		
CC	56	31	0.53	(0.30, 0.91)	90	72	0.71	(0.45, 1.12)	33	32	0.76	(0.41, 1.40)		
DUSP6 (rs10744) [3]													0.01	0.01
AA	143	133	1.00		302	255	0.85	(0.63, 1.15)	153	102	0.59	(0.40, 0.87)		
AT/TT	99	60	0.66	(0.44, 0.98)	177	124	0.70	(0.50, 0.98)	84	80	0.81	(0.52, 1.25)		
DUSP7 (rs9851576)													<0.01	<0.01
AA/AG	239	183	1.00		457	362	0.95	(0.74, 1.23)	224	179	0.83	(0.59, 1.16)		
GG	3	10	4.17	(1.24, 18.9)	22	17	0.90	(0.46, 1.76)	13	3	0.21	(0.05, 0.70)		
Selenium														
DUSP4 (rs2056025)													0.01	0.03

	Low				Intermediate				High					
	Control	Case	OR[1]	95% CI	Control	Case	OR	95% CI	Control	Case	OR	(95% CI)	P_{int}	P_{adj}
TT	175	147	1.00		344	258	0.80	(0.60, 1.07)	189	155	0.77	(0.52, 1.14)		
TG/GG	68	36	0.62	(0.39, 0.97)	132	97	0.78	(0.54, 1.11)	51	61	1.10	(0.67, 1.82)		
Lycopene														
DUSP1 (rs881150)													0.01	0.02
TT	128	132	1.00		269	217	0.69	(0.51, 0.95)	139	102	0.54	(0.37, 0.81)		
TA/AA	115	71	0.61	(0.41, 0.89)	206	142	0.61	(0.43, 0.85)	102	90	0.67	(0.44, 1.00)		
DUSP6 (rs10744)													0.02	0.03
AA	149	147	1.00		300	232	0.69	(0.51, 0.93)	149	111	0.59	(0.41, 0.86)		
AT/TT	94	56	0.60	(0.40, 0.89)	175	127	0.66	(0.47, 0.92)	91	81	0.67	(0.44, 1.02)		
Mutagen Index														
DUSP4 (rs474824)													<0.01	0.02
TT/TC	193	142	1.00		388	324	1.10	(0.84, 1.43)	199	153	0.98	(0.72, 1.34)		
CC	47	23	0.62	(0.35, 1.06)	93	60	0.80	(0.54, 1.19)	39	52	1.61	(1.00, 2.61)		

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

[2] Similar associations for *DUSP6* rs10744 (r^2=1)

[3] Similar associations for *DUSP6* rs770087 (r^2=1)

Table 3

Associations between *ERK1*/2 genes, diet and colon and rectal cancer risk

	Low				Intermediate				High				P_{int}	P_{adj}
	Control	Case	OR[1]	95% CI	Control	Case	OR	95% CI	Control	Case	OR	95% CI		
Colon Cancer														
Saturated Fat														
MAPK1 (rs9610470)													0.01	0.03
TT	288	185	1.00		578	435	1.13	(0.89, 1.42)	261	269	1.40	(1.03, 1.92)		
TC	174	137	1.24	(0.93, 1.66)	357	269	1.14	(0.89, 1.47)	193	170	1.21	(0.87, 1.70)		
CC	26	23	1.38	(0.76, 2.50)	45	49	1.60	(1.02, 2.51)	34	18	0.70	(0.36, 1.31)		
Monounsaturated Fat														
MAPK1 (rs9610470)													0.01	0.03
TT	281	168	1.00		579	461	1.26	(1.00, 1.60)	267	260	1.36	(0.98, 1.88)		
TC	179	131	1.25	(0.93, 1.68)	361	289	1.28	(0.99, 1.66)	184	156	1.18	(0.83, 1.68)		
CC	26	23	1.51	(0.83, 2.74)	42	47	1.72	(1.08, 2.74)	37	20	0.74	(0.39, 1.35)		
Polyunsaturated Fat														
MAPK3 (rs7698)													0.04	0.04
CC	421	266	1.00		852	674	1.19	(0.98, 1.45)	402	387	1.34	(1.02, 1.75)		
CT/TT	65	53	1.26	(0.85, 1.88)	126	110	1.30	(0.96, 1.76)	83	60	0.97	(0.65, 1.46)		
Trans -fatty acid														
MAPK3 (rs7698)													0.02	0.02
CC	432	238	1.00		836	679	1.51	(1.24, 1.84)	407	410	1.85	(1.43, 2.40)		
CT/TT	57	45	1.42	(0.93, 2.16)	137	116	1.54	(1.15, 2.08)	80	62	1.38	(0.92, 2.07)		
Rectal Cancer														
Cruciferous Vegetables														
RAF1 (rs3773353)													0.01	0.03
TT	152	102	1.00		301	241	1.15	(0.85, 1.57)	137	127	1.26	(0.88, 1.81)		
TC	77	65	1.28	(0.85, 1.95)	164	141	1.29	(0.92, 1.81)	85	53	0.89	(0.58, 1.37)		
CC	7	7	1.55	(0.51, 4.67)	21	15	1.07	(0.52, 2.18)	15	3	0.29	(0.07, 0.92)		
RAF1 (rs4684871)													0.01	0.03
AA/AG	203	145	1.00		397	341	1.17	(0.90, 1.51)	192	167	1.12	(0.83, 1.52)		

	Low				Intermediate				High				P_{int}	P_{adj}
	Control	**Case**	**OR[1]**	**95% CI**	**Control**	**Case**	**OR**	**95% CI**	**Control**	**Case**	**OR**	**95% CI**		
GG	33	29	1.24	(0.72, 2.14)	89	54	0.84	(0.56, 1.26)	45	16	0.46	(0.24, 0.84)		
RAF1 (rs904453)													0.01	0.03
CC	67	59	1.00		151	112	0.83	(0.54, 1.28)	72	36	0.53	(0.31, 0.91)		
CA	117	84	0.82	(0.52, 1.29)	230	196	0.94	(0.63, 1.41)	111	92	0.88	(0.56, 1.38)		
AA	52	31	0.67	(0.38, 1.18)	105	89	0.92	(0.59, 1.45)	54	55	1.03	(0.61, 1.74)		

[1]Odds ratio (OR) and 95% confidence intervals (CI) adjusted for age, center, race, sex, and kcal. Percentiles based on sex and study.

Table 4

Association between *JNK*-pathway genes, diet, and colon and rectal cancer

	Low				Intermediate				High					
	Control	Case	OR[1]	95% CI	Control	Case	OR	95% CI	Control	Case	OR	95% CI	P_{int}	P_{adj}
Colon Cancer														
Protein														
MAP3K7 (rs13208824)													0.01	0.03
CC/CA	479	342	1.00		950	771	1.05	(0.87, 1.26)	490	415	0.92	(0.69, 1.22)		
AA	10	3	0.42	(0.09, 1.39)	24	14	0.75	(0.37, 1.47)	3	10	3.97	(1.18, 18.03)		
Vitamin C														
MAP3K7 (rs150117)													<0.01	0.01
AA	216	197	1.00		458	363	0.85	(0.67, 1.08)	252	176	0.67	(0.50, 0.89)		
AT	217	145	0.74	(0.56, 0.99)	400	368	0.97	(0.76, 1.23)	192	156	0.78	(0.58, 1.05)		
TT	56	37	0.73	(0.46, 1.16)	123	61	0.53	(0.37, 0.76)	42	51	1.16	(0.73, 1.85)		
Folic Acid														
MAP3K10 (rs3746006)													0.02	0.04
GG/GA	431	368	1.00		886	699	0.82	(0.69, 0.99)	445	340	0.66	(0.52, 0.84)		
AA	57	33	0.69	(0.44, 1.08)	95	72	0.80	(0.57, 1.13)	38	42	1.00	(0.62, 1.62)		
MAP3K7 (rs150117)													0.01	0.03
AA	207	187	1.00		485	390	0.79	(0.62, 1.01)	234	159	0.54	(0.40, 0.75)		
AT	222	176	0.87	(0.66, 1.16)	387	322	0.81	(0.63, 1.05)	200	171	0.70	(0.51, 0.96)		
TT	59	38	0.71	(0.45, 1.11)	113	59	0.52	(0.35, 0.75)	49	52	0.89	(0.56, 1.40)		
Calcium														
MAPK8 (rs10857565)													0.02	0.04
GG/GA	471	385	1.00		935	737	0.86	(0.72, 1.03)	464	351	0.70	(0.55, 0.89)		
AA	15	24	2.06	(1.07, 4.07)	44	43	1.11	(0.70, 1.73)	27	15	0.48	(0.24, 0.93)		
Lutein + Zeaxanthin														
MAP3K9 (rs11158881)													<0.01	0.03
TT	284	225	1.00		553	441	0.91	(0.73, 1.14)	256	240	0.92	(0.70, 1.20)		
TC/CC	207	194	1.19	(0.92, 1.55)	432	310	0.83	(0.65, 1.04)	224	144	0.62	(0.46, 0.83)		

	Low				Intermediate				High					
	Control	Case	OR[1]	95% CI	Control	Case	OR	95% CI	Control	Case	OR	95% CI	P_{int}	P_{adj}
MAP3K9 (rs11622989)													<0.01	0.03
CC/CT	377	302	1.00		747	563	0.85	(0.70, 1.03)	353	313	0.85	(0.67, 1.08)		
TT	114	117	1.28	(0.95, 1.73)	237	187	0.90	(0.70, 1.15)	127	71	0.56	(0.40, 0.78)		
MAP3K9 (rs11624934)													0.01	0.04
AA	224	213	1.00		471	343	0.70	(0.55, 0.89)	230	160	0.57	(0.43, 0.77)		
AG	222	170	0.81	(0.61, 1.07)	434	324	0.71	(0.56, 0.91)	216	174	0.65	(0.49, 0.87)		
GG	45	36	0.87	(0.54, 1.41)	79	84	1.04	(0.72, 1.50)	34	51	1.21	(0.75, 1.98)		
MAP3K9 (rs11625206)													<0.01	0.01
CC	210	213	1.00		452	330	0.66	(0.51, 0.84)	232	155	0.51	(0.38, 0.69)		
CT	230	166	0.72	(0.55, 0.95)	448	323	0.65	(0.51, 0.83)	205	177	0.66	(0.49, 0.89)		
TT	51	40	0.81	(0.51, 1.27)	84	98	1.08	(0.76, 1.54)	43	51	0.92	(0.58, 1.46)		
MAP3K9 (rs11844774) [2]													<0.01	0.01
TT	163	128	1.00		320	281	1.01	(0.76, 1.35)	143	154	1.07	(0.76, 1.50)		
TC	243	207	1.08	(0.80, 1.45)	474	338	0.82	(0.62, 1.08)	236	170	0.69	(0.50, 0.96)		
CC	85	84	1.27	(0.87, 1.86)	190	132	0.79	(0.57, 1.10)	101	60	0.57	(0.38, 0.86)		
Rectal Cancer														
Carbohydrates														
MAP3K7 (rs3799912)													<0.01	0.02
AA	191	169	1.00		376	293	0.71	(0.53, 0.94)	195	140	0.44	(0.28, 0.68)		
AG/GG	55	34	0.70	(0.43, 1.12)	98	64	0.60	(0.40, 0.89)	44	54	0.80	(0.47, 1.38)		
Calcium														
MAP3K3 (rs3785574)													0.02	0.05
AA/AG	225	177	1.00		424	322	0.83	(0.64, 1.08)	213	171	0.69	(0.48, 1.00)		
GG	17	25	1.87	(0.99, 3.64)	55	48	0.92	(0.59, 1.45)	25	11	0.40	(0.18, 0.84)		
Lutein + Zeaxanthin														
MAP3K3 (rs11658329)													0.01	0.02
GG/GC	232	173	1.00		430	345	0.96	(0.75, 1.24)	210	176	0.88	(0.63, 1.21)		
CC	13	17	1.72	(0.81, 3.70)	44	32	0.83	(0.50, 1.38)	30	11	0.38	(0.17, 0.77)		
Cruciferous Vegetables														

	Low				Intermediate				High					
	Control	**Case**	**OR[1]**	**95% CI**	**Control**	**Case**	**OR**	**95% CI**	**Control**	**Case**	**OR**	**95% CI**	**P_{int}**	**P_{adj}**
MAP3K1 (rs43184) [3]													0.01	0.04
CC	142	124	1.00		295	246	0.94	(0.70, 1.26)	161	113	0.75	(0.53, 1.06)		
CG	83	43	0.59	(0.38, 0.92)	163	129	0.86	(0.61, 1.21)	69	59	0.87	(0.56, 1.35)		
GG	11	7	0.73	(0.26, 1.91)	28	22	0.86	(0.46, 1.57)	7	11	1.71	(0.65, 4.79)		
MAP3K7 (rs3799912)													<0.01	<0.01
AA	186	151	1.00		386	324	1.00	(0.77, 1.30)	190	127	0.75	(0.54, 1.03)		
AG/GG	50	23	0.56	(0.32, 0.96)	100	73	0.88	(0.60, 1.27)	47	56	1.38	(0.88, 2.17)		
MAP3K7 (rs711267)													<0.01	0.01
AA/AG	224	153	1.00		447	369	1.18	(0.92, 1.51)	211	172	1.10	(0.82, 1.48)		
GG	12	21	2.74	(1.32, 5.92)	39	28	1.02	(0.60, 1.73)	26	11	0.58	(0.27, 1.18)		

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

[2] Similar associations for *MAP3K9* rs8010714 (r^2=0.99)

[3] Similar associations for *MAP3K1* rs832582 (r^2=1)

Table 5

Associations between p38-pathway genes, diet, and colon and rectal cancer risk

	Low				Intermediate				High				P_{int}	P_{adj}
	Control	Case	OR[1]	95% CI	Control	Case	OR	95% CI	Control	Case	OR	(95% CI)		
Colon Cancer														
						Energy Intake								
MAPK14 (rs10807156)													0.01	0.04
TT	314	207	1.00		620	483	1.17	(0.95, 1.45)	288	302	1.55	(1.21, 1.97)		
TA	149	109	1.09	(0.80, 1.48)	325	256	1.18	(0.93, 1.51)	164	134	1.21	(0.91, 1.62)		
AA	21	20	1.46	(0.76, 2.77)	39	28	1.08	(0.64, 1.80)	32	14	0.65	(0.33, 1.23)		
						Carbohydrate								
MAP3K2 (rs6732279)													0.01	0.03
GG	217	146	1.00		377	288	1.02	(0.78, 1.34)	175	171	1.06	(0.73, 1.52)		
GT	222	185	1.25	(0.94, 1.67)	462	362	1.06	(0.81, 1.37)	243	183	0.82	(0.57, 1.17)		
TT	49	51	1.57	(1.01, 2.46)	141	111	1.07	(0.76, 1.49)	69	58	0.87	(0.55, 1.38)		
MAPK14 (rs10807156)													0.01	0.04
TT	318	229	1.00		615	497	1.01	(0.81, 1.26)	289	266	0.93	(0.67, 1.28)		
TA	146	128	1.20	(0.90, 1.61)	326	237	0.91	(0.71, 1.17)	166	134	0.83	(0.58, 1.18)		
AA	23	25	1.53	(0.85, 2.79)	38	26	0.85	(0.49, 1.44)	31	11	0.37	(0.17, 0.74)		
						Folic Acid								
MAP3K2 (rs6732279)													0.01	0.03
GG	214	161	1.00		391	284	0.85	(0.65, 1.11)	164	160	0.96	(0.69, 1.34)		
GT	220	187	1.13	(0.85, 1.51)	459	366	0.95	(0.74, 1.23)	248	177	0.71	(0.52, 0.97)		
TT	54	53	1.30	(0.84, 2.00)	134	121	1.07	(0.77, 1.49)	71	46	0.62	(0.39, 0.96)		
Rectal Cancer														
						Saturated Fat								
MAPK14 (rs851011)[2]													<0.01	0.02
TT/TC	242	166	1.00		472	359	1.06	(0.82, 1.38)	227	218	1.23	(0.83, 1.82)		
CC	3	6	3.12	(0.81, 14.99)	7	4	0.86	(0.22, 2.90)	8	1	0.15	(<0.01, 0.87)		
						Calcium								

	Low				Intermediate				High				P_{int}	P_{adj}
	Control	Case	OR[1]	95% CI	Control	Case	OR	95% CI	Control	Case	OR	(95% CI)		
MAPK12 (rs742184)													0.02	0.04
CC	125	119	1.00		239	191	0.72	(0.52, 1.01)	138	90	0.46	(0.29, 0.71)		
CT/TT	117	83	0.75	(0.51, 1.09)	240	179	0.67	(0.48, 0.93)	100	92	0.66	(0.43, 1.02)		
Vitamin C														
MAPK14 (rs851006)													<0.01	0.02
GG	139	132	1.00		270	221	0.81	(0.59, 1.09)	156	99	0.55	(0.38, 0.80)		
GA	91	70	0.82	(0.55, 1.21)	178	109	0.60	(0.43, 0.85)	69	77	0.97	(0.63, 1.50)		
AA	13	8	0.67	(0.26, 1.65)	30	21	0.70	(0.38, 1.29)	13	17	1.17	(0.54, 2.58)		
Selenium														
MAPK14 (rs851011)[2]													<0.01	0.02
TT/TC	242	177	1.00		467	352	0.92	(0.71, 1.20)	232	214	0.99	(0.69, 1.44)		
CC	1	6	8.97	(1.51, 170.50)	9	3	0.43	(0.09, 1.48)	8	2	0.25	(0.04, 1.07)		
Lycopene														
MAP3K2 (rs3732209)													0.01	0.03
TT	126	114	1.00		233	188	0.78	(0.56, 1.08)	128	84	0.55	(0.36, 0.83)		
TC	93	77	0.91	(0.61, 1.35)	193	144	0.74	(0.53, 1.05)	95	86	0.78	(0.51, 1.19)		
CC	24	12	0.57	(0.27, 1.18)	49	27	0.56	(0.32, 0.96)	18	22	1.03	(0.51, 2.09)		
Alpha-tocopherol														
MAP2K1 (rs17259670)													<0.01	0.02
AA	224	156	1.00		406	319	0.96	(0.73, 1.26)	200	166	0.76	(0.50, 1.13)		
AG/GG	22	40	2.65	(1.53, 4.70)	66	46	0.84	(0.54, 1.31)	41	27	0.65	(0.35, 1.17)		

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

[2] Similar associations for *MAPK14* rs851016 (r^2=0.99)