original article

Polymorphisms in RETN gene and susceptibility to colon cancer in Saudi patients

Rowyda N. Alharithy

From the Department o f Biochemistry, King Abdulaziz University, Jeddah, Saudi Arabia

Correspondence: Dr. Rowyda N. Alharithy · Department of Biochemistry, King Abdulaziz University, PO Box 40288 Jeddah 21499 Saudi Arabia · T: 0505444238 F: 0126393640 · ralharithy@kau.edu.sa

Ann Saudi Med 2014; 34(4): 334-339

DOI: 10.5144/0256-4947.2014.334

BACKGROUND AND OBJECTIVES: Resistin is an adipocytokine, which has been studied for its role in insulin resistance and recently in inflammation. Several single-nucleotide polymorphisms (SNPs) have been identified in the human resistin gene (RETN). This study aims to investigate the association of RETN rs1862513 (C-420G) and rs3745367 (G+299A) SNPs with the colon cancer risk in Saudi patients.

DESIGN AND SETTINGS: This is a case-control study conducted among Saudi adult colon cancer patients recruited from King Abdulaziz Hospital and Oncology Center in Jeddah, Saudi Arabia.

SUBJECTS AND METHODS: In this study, 120 Saudi volunteers (60 colon cancer patients and 60 disease-free controls) were studied. The SNPs were determined by polymerase chain reaction (PCR) and genotyping using PCR- restriction fragment length polymorphism analysis.

RESULTS: In comparing the result obtained for the patient group with that of the controls, colon cancer group displayed different genotype distribution of the RETN C-420G and G+299A SNPs. The study indicated that the SNP-420 heterozygous (CG) genotype (odds ratio [OR]=2.48, 95% CI 1.07-5.74, *P*=.03) and the SNP +299 heterozygous (GA) genotype (OR=6.5, 95% CI 1.77-24.18, *P*=.002) significantly increased the risk of colon cancer. A further analysis of the genotype combination of SNPs RETN C-420G and G+299A showed a larger increase in the colon cancer risk.

CONCLUSION: These preliminary results suggested a potential role for RETN C-420G and G+299A polymorphisms in the genetic predisposition to colon cancer disease.

Colon cancer is a heterogeneous disease arising in association with abnormalities in different molecular pathways. Epidemiological studies have revealed that genetic susceptibility and environmental factors place certain individuals at a higher risk of developing colon cancer.[1-3] To reduce colon cancer-related deaths, many studies aimed at identifying more genes linked to colon cancer and finding novel screening- and prognosis-related biomarkers.[4-9] To date, there are no biomarkers that precisely predict the presence of the disease. Therefore, genetic variation analysis might provide a window into the genetic landscape of human colon cancer to identify new genes. The most frequent type of variation in the human genome and excellent genotypic markers for research are single-nucleotide polymorphisms (SNPs). They serve as potential and unique genetic markers for association-based approaches to discover genetic components bearing complex traits. SNP profiles and patterns may find immense utility in identifying a comprehensive collection of genes that contribute to the development and susceptibility of complex diseases such as cancer. The presence of SNPs in several genes (MLH1, MSH2, PMS2, APC, MUTYH, SMAD7, STK11, XRCC3, DNMT1, MTHFR, RAD51, XRCC2, EXO1, XRCC1, VDR, and RETN) was reported to be associated with colon cancer.[7,10-17] Therefore, identifying these SNPs is important for scientists to ascertain the gene or genes that predispose individuals to the colon cancer risk.

Resistin gene (RETN) codes a peptide hormone called resistin, which is a 12.5–kDa, C-terminal, cysteine-rich signaling peptide. Former researches suggested that resistin in humans is secreted predominantly by adipose tissue, in particular, from adipocytes and macrophages.[18,19] Subsequent studies suggested that resistin may not come directly from adipocytes, and may rather originate from inflammatory cells infiltrating fat tissue.[20-22] The release of resistin appears to be stimulated

by inflammation, lipopolysaccharide, interleukin--6, hyperglycemia, growth, and gonadal hormones. While released within the fat tissue, resistin acts on adipocytes themselves leading to insulin resistance. Resistin exists in 3 forms: a trimer, a hexamer, and a monomer; the lower molecular weight form is the most active.[23] Since the discovery of resistin in 2001, there has been controversy regarding the role of resistin in humans. There has been strong data for rodent (mice) on the pathophysiological effects of resistin in mediating a multitude of metabolic impairments, including insulin resistance and type II diabetes.[24] Unfortunately, these findings have not been necessarily translatable to humans. A clear finding regarding resistin physiology in humans suggests that resistin adipose tissue expression and resistin serum levels increase in obese subjects.[25-27] Consistent with this, there are strong positive correlations between plasma resistin levels and increases in both body mass index (BMI) and the quantity of abdominal visceral adipose tissue.[25,28-31]

Given the importance of obesity in colon cancer development and the fundamental role of resistin in obesity, it is reasonable to hypothesize that RETN gene SNPs may play a role in colon cancer susceptibility. SNPs rs1862513 (C-420G) and rs3745367 (G+299A) in the RETN gene were selected because of their previous association with resistin circulating levels.[15,32] The rs1862513 (C-420G) SNP, in the promoter region of the RETN gene, has been associated with obesity, insulin sensitivity, and insulin resistance.[33-35] Here, the study investigated the effect of rs1862513 (C-420G) and rs3745367 (G+299A) SNPs in RETN gene on the risk of colon cancer.

SUBJECTS AND METHODS

Participants

A case-control study was conducted among Saudi adult patients (n=60) with a diagnosis of colon cancer. The patients were recruited from King Abdulaziz Hospital and Oncology Center in Jeddah, Saudi Arabia. They had positive colonoscopic results for malignancy, histologically confirmed as colon cancer. Unrelated subjects (controls) (n=60) were recruited in the same period as the cases from the family clinic of King Abdulaziz Hospital, and they were judged to be in good health according to their medical history and colonoscopy preventive examination. Both colon cancer patients and controls were excluded if they had diabetes or high blood pressure, or if they were under any treatment course. All volunteers and patients signed an informed consent for participation. The ethical committees of the King Abdulaziz University had approved the study.

Anthropometric analyses

Anthropometric parameters represented by weight and height were measured for each patient included in the study. The BMI was calculated by applying the following formula: BMI=weight (kg)/height (m^2). Data about the medical history of each patient was also collected.

Genotyping

The SNP rs1862513 (C-420G), the one that showed an association with colorectal cancer in the study by Pechlivanis and his team, was selected for the analysis.36 Furthermore, SNP rs3745367 (G+299A) was selected from dbSNP (http://www.ncbi.nlm.nih.gov). Total genomic DNA was extracted from peripheral blood (5 mL) samples using a DNA extraction kit (QIAamp DNA Blood Mini Kit; Hilden, Germany), applying the manufacturer's protocol. The polymorphisms were identified using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Two sets of primers (5.0 nmol) from TIB (TIB Molbiol Inc., Germany) were used. For promoter region amplification, the forward primer 5'-TTTTGTCATGTTTGCATCAGC-3' and reverse primer 5'-GGGCTCAGCTAACCAAAT-3'were used. For 3'-untranslated region amplification, the forward primer 5'-AGAGTCCACGCTCCTGTGTT-3' and reverse primer 5'-CATCTCCAGGTTTATTTCCAG-3'were used. The amplification was performed in a volume of 25 µL, containing 0.2 µg genomic DNA, 1X PCR buffer, 2.5 mM $MgCl_2$, 0.2 mM of each dNTP, 0.1 µM of each primer, and 0.5 U Taq DNA poly-

Table 1. The characteristics of the patient and the control groups.

Variables	Patients n=60 Mean (SD)	Controls n=60 Mean (SD)	*P* value
Age (y)	50.5 (12.1)	54.3 (12.3)	.08
Height (cm)	163.2 (9.1)	160.8 (9.0)	.14
Weight (kg)	77.4 (10.1)	66.4 (13.3)	.001[b]
Waist (cm)	80.1 (31.1)	67.1 (24.8)	.01[a]
Hip (cm)	88.6 (35.6)	66.0 (30.2)	.0001[b]
WHR	0.96 (0.3)	1.08 (0.3)	.19
BMI	28.6 (6.1)	25.3 (5.4)	.005[b]

Z-test was used in the comparison.

BMI: body mass index; SD: standard deviation; WHR: waist-to-hip ratio.

[a]Significant; [b]Highly significant.

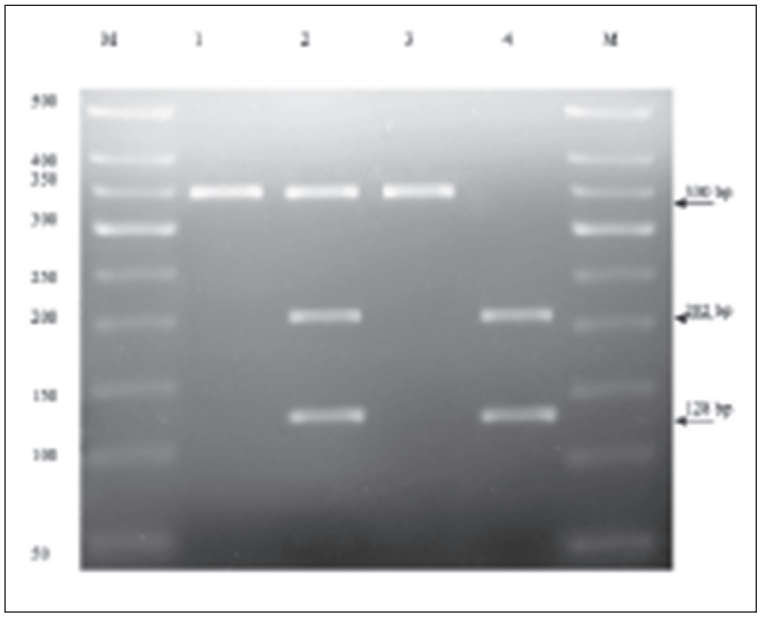

Figure 1. Photograph of a 2% agarose gel showing the result of BbsI digest. Lane M: DNA marker. Lane 1: uncut PCR product of size 330 bp. Lane 2:heterozygous (CG) genotype that shows 3 bands of size 330, 202, and 128 bp. Lane 3: homozygous (GG) genotype that shows an uncut band of size 330 bp. Lane 4: normal (CC) genotype that shows 2 bands of size 202 and 128 bp.

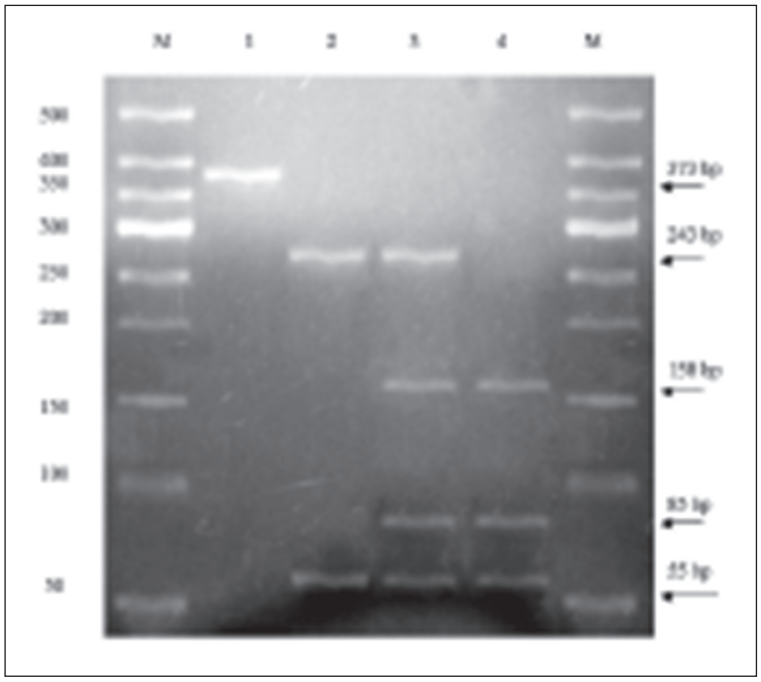

Figure 2. Photograph of a 2% agarose gel showing the result of AluI digest. Lane M: DNA marker. Lane 1: uncut PCR product of size 373 bp. Lane 2: normal (GG) genotype that shows 2 bands of size 243 and 55 bp. Lane 3: heterozygous (GA) genotype that shows 4 bands of size 243,158, 85, and 55. Lane 4: homozygous (AA) genotype that shows 3 bands of size 158, 85, and 55 bp.

merase (Promega Corporation, Madison, WI, USA). The PCR initial denaturation was done at 96°C for 5 minutes, 40 cycles at 96°C for 35 seconds and at 51°C for 35 seconds (SNP C-420G), 55°C for 30 seconds (SNP G+299A), 72°C for 35 seconds, and a final elongation step at 72°C for 4 minutes. A total of 5 µL of the PCR products was digested with restriction endonucleases (BpiI for SNP C-420G and AluI for SNP G+299A) for 2 hours at 37°C. The PCR products of digestion were analyzed by electrophoresis on 2% agarose gels stained with ethidium bromide.

Statistical analysis

The statistical analyses were performed using the SPSS version 16.0 (SPSS Inc.,Chicago, USA). Continuous variables were expressed as the means (standard deviation [SD]). In addition, Mann-Whitney U/Wilcoxon Rank Sum test (Z-test) was used to compare between the 2 groups. The Hardy-Weinberg equilibrium (HWE) was tested for genotype distributions and allele frequencies. The differences in genotype distributions and allelic frequencies between colon cancer patients and controls were examined using the Fisher exact and the chi-square tests. The odds ratios (OR) and 95% confidence interval (95% CI) ranges were calculated by using logistic regression. Significance was considered at a *P* value <.05.

RESULTS

Subjects' characteristics

The mean age was 50.5 years for colon cancer patients and 54.3 years for controls. No significant difference was found for body height, waist-to-hip ratio, and age between the 2 groups. However, the body weight (*P*=.001), waist (*P*=.01), hip (*P*=.0001), and BMI (P=.005) were significantly higher in the colon cancer patients than in the controls. The characteristics of the patient and the control groups are shown in **Table 1**.

PCR-RFLP analysis

The amplified fragment that contains C-420G SNP showed a size of 330 bp. The wild (CC) genotype showed 2 bands of sizes 202 and 128 bp. The heterozygous (CG) genotype showed 3 fragments of sizes 330, 202, and 128 bp. The homozygous (GG) genotype produced 1 fragment of size 330 bp (**Figure 1**). The other amplified fragment that contains G299A showed a size of 373 bp. The genotype for the wild (GG) individuals produced 2 bands of sizes 243 and 55 bp. The heterozygous (GA) genotype produced 4 bands of sizes 243, 158, 85, and 55 bp. The homozygous (AA) genotype

produced 3 bands of sizes 158 85, and 55 bp (**Figure 2**).

In the recruited control group, the genotype distribution of C-420G was out of HWE (X^2= 6.18, df=1, *P*=.01). In the patients, the genotype distribution of C-420G was in HWE (X^2= 0.67, df=1, *P*=.41). When the C-420G genotype frequencies were compared between the healthy control and patient groups, the CC genotype occurred with a lower frequency in colon cancer patients than in controls, thus suggesting its protective effect against colon cancer (see **Table 2**). However, CG heterozygosity and G alleles were more prevalent in patients and might, therefore, convey susceptibility for the disease.

In regard to G299A SNP, the genotype distributions for the controls (X^2= 6.55, df=1, *P*=.01) and the patients (X^2= 29.83, df=1, *P*=.0001) were out of HWE, which is possibly because of the small sample size. As shown in **Table 3**, the wild GG genotype occurred with a lower frequency in patients (5%) than in controls (25%). The prevalence of GA genotype was 85% in patients and 65% in healthy individuals (OR=6.5, *P*=.002). A further association analysis was conducted to identify the interactions of the 2 SNPs, C-420G and G299A, and their impact on the colon cancer risk. The genotype combinations CC/GA, CG/GA, and GG/GA for C-420G and G299A were associated with a higher risk of colon cancer (**Table 4**).

DISCUSSION

Adipokines, secreted by the adipose tissue, are strong candidates for the link between obesity and colon cancer risk.[37,38] To investigate the influence of rs1862513 (C-420G) and rs3745367 (G+299A) SNPs in RETN gene on the colon cancer risk, the SNPs were genotyped in a cohort of cases and controls from Saudi Arabia. In the single SNP analysis, the data of the present study showed that both rs1862513 (C-420G) and rs3745367 (G+299A) SNPs had an association with the colon cancer risk (OR 2.48, 95% CI 1.07-5.74 and OR 6.33, 95% CI 1.77-24.18, respectively).

The promoter SNP rs1862513 (C-420G) has been investigated by many groups; some researchers examined its association with resistin levels[39-43] and a few others studied its relationship with diabetes[32,44] or adiposity.[33,45-47] However, only 3 publications with contradicting findings have addressed the question of an association between rs1862513 (C-420G) SNP and colorectal cancer (CRC) risk.[17,36,48] The present study confirms the results of the 2 studies that reported an association between RETN SNP rs1862513 (C-420G) and colon cancer risk.[17,36]

Table 2. Genotypes and allele frequencies of RETN C-420G SNP for patients and controls.

Genotypes	Frequencies %		P value[a]	OR (95% CI)[b]	Risk ratio (95% CI)
	Patients (n=60)	Controls (n=60)			
CC	25.0 (n=15)	40.0 (n=24)		1.00 (Reference)	1.00 (Reference)
CG	55.0 (n=33)	33.3 (n=20)	.03	2.48 (1.07-5.74)	1.48 (1.02-2.16)
GG	20.0 (n=12)	26.7 (n=16)	.95	1.03 (0.38-2.79)	1.02 (0.56-1.84)
CG + GG	75.0	60.0	.12	1.83 (0.85-3.96)	1.22 (1.08-1.58)
Alleles					
C	55.0	56.5		1.00 (Reference)	1.00 (Reference)
G	45.0	43.5	.12	1.11 (0.67-1.84)	1.06 (0.79-1.40)

Two-sided X^2 test; [a]*P* value <.05 was considered significant; [b]Odds ratio (OR) 95% confidence interval (CI). SNP: Single-nucleotide protein.

Table 3. Genotypes and allele frequencies of RETN gene G299A for patients and controls.

Genotypes	Frequencies %		P value[a]	OR (95% CI)[b]	Risk ratio (95% CI)
	Patients (n=60)	Controls (n=60)			
GG	5.0 (n=3)	25.0 (n=15)		1.00 (Reference)	1.00 (Reference)
GA	85.0 (n=51)	65.0 (n=39)	.002[c]	6.5 (1.77-24.18)	1.31 (1.09-1.56)
AA	10.0 (n=6)	10.0 (n=6)	.11[d]	5.0 (0.93-26.79)	2.33 (1.03-5.29)
GA + AA	95.0	75.0	0002[c]	6.33 (1.73-23.23)	1.27 (1.08-1.48)
Alleles					
G	47.5	57.5		1.00 (Reference)	1.00 (Reference)
A	52.5	42.5	.12[a]	1.49 (0.89-2.49)	1.24 (0.94-1.62)

[a]*P* value <.05 was considered significant; [b]Odds ratio (OR) 95% confidence interval (CI); [c]Two-sided X^2 test; [d]Two-sided Fisher exact test.

Although a few studies were performed on the association of rs1862513 (C-420G) SNP with CRC, no study has been reported on the association of rs3745367 (G+299A) SNP in RETN gene with CRC risk. The present study observed that carriers of the heterozygous (GA) genotype of SNP 299 (OR=6.5, 95% CI 1.77-24.18, *P*=.002) had a significantly higher colon cancer risk than carriers of the wild (GG) geno-

Table 4. Genotype combination of SNPs C-420G and G299A in RETN gene.

C-420G/G299A	Frequencies %		OR (95% CI)	Risk ratio (95% CI)	*P* value
	Patients (n=60)	Controls (n=60)			
Genotypes					
Wild/ Wild CC/GG	0.02 (n=1)	0.18 (n=11)	1.00 (Reference)	1.00 (Reference)	
Wild/ Hetero CC/GA	0.25 (n=15)	0.23 (n=14)	11.78 (1.34-103.52)	1.67 (1.16-2.42)	.01[b]
Wild/ Homo CC/AA	0	0	0	0	1[b]
Hetero/Wild CG/GG	0.03 (n=2)	0.02 (n=1)	22 (0.94-515.90)	8 (1.04-61.53)	.08[b]
Hetero/ Hetero CG/GA	0.48 (n=29)	0.28 (n=17)	18.76 (2.22-158.36)	1.59 (1.17-2.16)	.0007[a]
Hetero/ Homo CG/AA	0.03 (n=2)	0.02 (n=1)	22 (0.94-515.90)	8 (1.04-61.53)	.08[b]
Homo/Wild GG/GG	0	0.05 (n=3)	0	0	1[b]
Homo/ Hetero GG/GA	0.12 (n=7)	0.13 (n=8)	9.63 (0.98-94.54)	2.07 (1.15-3.74)	.04[b]
Homo/Homo GG/AA	0.07 (n=4)	0.08 (n=5)	8.8 (0.77-100.26)	2.56 (1.09-5.98)	.12[b]

[a]Two-sided X^2 test; [b]Two-sided Fisher exact test; SNP: Single-nucleotide protein.

type. To the best of our knowledge, this study is the first to describe the association of RETN rs3745367 (G+299A) SNP with colon cancer risk.

Cancer is a multigenic disease in which single SNP may only have a modest independent effect, and multiple SNPs may provide a more accurate representation of the risk. The present study explored the interaction of RETN G299A and C-420G SNPs in 60 controls and 60 cases of colon cancer. The odds ratio (OR) was used to evaluate the colon cancer risk in terms of the best combination of SNP-SNP interactions. Compared to their corresponding non-SNP combinations, the estimated OR of the patients with CG/GA (OR=18.76; CI: 2.22–158.36; *P*=.0007) and GG/GA (OR=9.63; CI: 0.98- 94.54; *P*=.04) combinations were characterized by a higher colon cancer risk. This combination effect could be explained by the additive effect of the 2 genotypes.

Although a single SNP may have a moderate effect on the development of cancer, several SNPs together can exert a significant influence. The pondering question is "how many SNPs are needed?". The answer to this question is not simple due to the fact that the effect of genotype on disease phenotype varies between diseases and populations, owing this to genetic and environmental heterogeneity. A strategy utilizing biomarkers to stratify patients into appropriate screening programs can potentially prevent colon cancer. Future work approaching epistatic relationships from the SNP level is a need for a preventive strategy.

Although the number of subjects was small in this study limiting the statistical power, the finding of this study should be considered. Despite this limitation, the design of this study was relatively strong because the controls were recruited from the same cohort as the colon cancer patients. Also the cases and controls were matched by age and sex.

In summary, the present data indicates a potential role for RETN G299A and C-420G polymorphisms in the genetic predisposition to colon cancer disease in the Saudi population. It also demonstrated a combined effect of SNPs RETN C-420G and G+299A and showed an increased chance of the colon cancer risk. The interaction was not previously reported. Future research should be conducted with a larger sample population and a combination approaches to further test SNP-SNP interactions in adipocytokine genes associated with the colon cancer risk.

REFERENCES

1. Kruk J, Czerniak U. Physical activity and its relation to cancer risk: updating the evidence. Asian Pac J Cancer Prev. 2013; 14(7): 3993-03.
2. Peters U, Jiao S, Schumacher FR, Hutter CM, Aragaki AK, Baron JA, et al. Identification of genetic susceptibility loci for colorectal tumors in a genome-wide meta-analysis. Gastroenterology. 2013; 144(4): 799-07.
3. Tse G, Eslick GD. Cruciferous vegetables and risk of colorectal neoplasms: a systematic review and meta-analysis. Nutr Cancer. 2014; 66(1): 128-39.
4. Fishel R, Lescoe MK, Rao MR, Copeland NG, Jenkins NA, Garber J, et al. The human mutator gene homology MSH2 and its association with hereditary nonpolyposis colon cancer. Cell. 1993; 75(5): 1027-38.
5. Uthoff SM, Eichenberger MR, McAuliffe TL, Hamilton CJ, Galandiuk S. Wingless-type frizzled protein receptor signaling and its putative role in human colon cancer. Mol Carcinog. 2001; 31(1): 56-62.
6. Gunter MJ, Leitzmann MF. Obesity and colorectal cancer: epidemiology, mechanisms and candidategenes. J Nutr Biochem. 2006; 17(3): 145-56.
7. Krupa R, Sliwinski T, Wisniewska-Jarosinska M, Chojnacki J, Wasylecka M, Dziki L, et al. Polymorphisms in RAD51, XRCC2 and XRCC3 genes of the homologous recombination repair in colorectal cancer--a case control study. Mol Biol Rep. 2011; 38(4): 2849-54.
8. Lurje G, Zhang W, Lenz HJ. Molecular prognostic markers in locally advanced colon cancer. Clin Colorectal Cancer. 2007; 6(10): 683-90.
9. Peltekova VD, Lemire M, Qazi AM, Zaidi SH, Trinh QM, Bielecki R, et al. Identification of genes expressed by immune cells of the colon that are regulated by colorectal cancer-associated variants. Int J Cancer. 2014; 134(10): 2330-41.
10. Tomlinson I, Houlston R. Is EXO1 a colon cancer predisposition gene? Gastroenterology. 2001; 120(7): 1860-62.
11. Slattery ML, Herrick JS, Lundgreen A, Fitzpatrick FA, Curtin K, Wolff RK. Genetic variation in a metabolic signaling pathway and colon and rectalcancer risk: mTOR, PTEN, STK11, RPKAA1, PRKAG2, TSC1, TSC2, PI3K and Akt1. Carcinogenesis. 2010; 31(9): 1604-11.
12. Gündüz M, Cacına C, Topta? B, Yaylım-Eraltan ?, Tekand Y, ?sbir T. Association of vitamin D receptor gene polymorphisms with colon cancer. Genet Test Mol Biomarkers. 2012; 16(9): 1058-61.
13. Kim J, Cho YA, Kim DH, Lee BH, Hwang DY, Jeong J, et al. Dietary intake of folate and alcohol, MTHFR C677T polymorphism, and colorectal cancer risk in Korea. Am J Clin Nutr. 2012; 95(2): 405-12.
14. Dowty JG, Win AK, Buchanan DD, Lindor NM, Macrae FA, Clendenning M, et al. Cancer risks for MLH1 and MSH2 mutation carriers. Hum Mutat. 2013; 34(3): 490-97.
15. Jiang X, Castelao JE, Vandenberg D, Carracedo A, Redondo CM, Conti DV et al. Genetic variations in SMAD7 are associated with colorectal cancer risk in the colon cancer family registry. PLoS One. 2013; 8(4): e60464.
16. Al-Harithy RN, Al-Ghafari AB. Resistin in human colon cancer. Increased expression independently of resistin promoter C-180G genotype. Saudi Med J. 2010; 31(5):495-500.
17. Mahmoudi T, Karimi K, Arkani M, Farahani H, Vahedi M, Dabiri R, et al. Resistin-420C>G promoter variant and colorectal cancer risk. Int J Biol Markers. 2014; 27: doi: 10.5301/jbm.5000079.
18. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature. 2001; 409: 307-12.
19. Steppan CM, Brown EJ, Wright CM, Bhat S, Banerjee RR, Dai CY, et al. A family of tissue-specific resistin-like molecules. Proc Natl Acad Sci USA. 2001; 98(2): 502-06.
20. Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. Vitam Horm. 2006; 74: 443-77.
21. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw. 2006; 17 (1): 4-12.
22. Wasim H, Al-Daghri NM, Chetty R, McTernan PG, Barnett AH, Kumar S. Relationship of serum adiponectin and resistin to glucose intolerance and fat topography in South-Asians. Cardiovasc Diabetol. 2006; 5:10.
23. Patel SD, Rajala MW, Rossetti L, Scherer PE, Shapiro L. Disulfidedependent multimeric assembly of resistin family hormones. Science. 2004; 304:1154-58.
24. Qatanani M, Szwergold NR, Greaves DR, Ahima RS, Lazar MA. Macrophage-derived human resistin exacerbates adipose tissue inflammation and insulin resistance in mice. J Clin Invest. 2009; 119: 531-39.
25. Degawa-Yamauchi M, Bovenkerk JE, Juliar BE, Watson W, Kerr K, Jones R, et al. Serum resistin (FIZZ3) protein is increased in obese humans. J Clin Endocrinol Metab. 2003; 88(11): 5452-55.
26. Vendrell J, Broch M, Vilarrasa N, Molina A, Gómez JM, Gutiérrez C, et al. Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. Obes Res. 2004; 12 (6): 962-71.
27. Schäffler A, Büchler C, Müller-Ladner U, Herfarth H, Ehling A, Paul G, et al. Identification of variables influencing resistin serum levels in patients with type 1 and type 2 diabetes mellitus. Horm Metab Res. 2004; 36 (10): 702-07.
28. Azuma K, Katsukawa F, Oguchi, S, Murata M, Yamazaki H, Shimada A, et al. Correlation between serum resistin level and adiposity in obese individuals. Obes Res. 2003; 11(8): 997-1001.
29. Yannakoulia M, Yiannakouris N, Blüher S, Matalas AL, Klimis-Zacas D, Mantzoros CS. Body fat mass and macronutrient intake in relation to circulating soluble leptin receptor, free leptin index, adiponectin, and resistin concentrations in healthy humans. J Clin Endocrinol Metab. 2003; 88(4): 1730-36.
30. Vozarova de Courten B, Degawa-Yamauchi M, Considine RV, Tataranni PA. High serum resistin is associated with an increase in adiposity but not a worsening of insulin resistance in Pima Indians. Diabetes. 2004; 53:1279-84.
31. Piestrzeniewicz K, ?uczak K, Komorowski J, Maciejewski M, Jankiewicz Wika J, Goch JH. Resistin increases with obesity and atherosclerotic risk factors in patients with myocardial infarction. Metabolism. 2008; 57: 488-93.
32. Osawa H, Yamada K, Onuma H, Murakami A, Ochi M, Kawata H, et al. The G/G genotype of a resistin single-nucleotide polymorphism at -420 increases type 2 diabetes mellitus susceptibility by inducing promoter activity through specific binding of Sp1/3. Am J Hum Genet. 2004; 75 (4): 678–86.
33. Engert JC, Vohl MC, Williams SM, Lepage P, Loredo-Osti JC, Faith J, et al. 5? flanking variants of resistin are associated with obesity. Diabetes. 2002; 51(5):1629 –34.
34. Wang H, Chu WS, Hemphill C, Elbein SC. Human resistin gene: molecular scanning and evaluation of association with insulin sensitivity and type 2 diabetes in Caucasians. Journal of Clinical Endocrinology and Metabolism. 2002; 87: 2520–24.
35. Smith SR, Bai F, Charbonneau C, Janderova L, Argyropoulos GA. Promoter genotype and oxidative stress potentially link resistin to human insulin resistance. Diabetes. 2003; 52: 1611–18.
36. Pechlivanis S, Bermejo JL, Pardini B, Naccarati A, Vodickova L, Novotny J, et al. Genetic variation in adipokine genes and risk of colorectal cancer. Eur J Endocrinol. 2009; 160(6): 933-40.
37. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nature Reviews. Cancer 2004; 4(8): 579–91.
38. Trujillo ME, Scherer PE. Adipose tissue-derived factors: impact on health and disease. Endocrine Reviews. 2006; 27:762–78.
39. Cho YM, Youn BS, Chung SS, Kim KW, Lee HK, Yu KY, et al. Common genetic polymorphisms in the promoter of resistin gene are major determinants of plasma resistin concentrations in humans. Diabetologia. 2004; 47(3): 559 –65.
40. Osawa H, Onuma H, Ochi M, Murakami A, Yamauchi J, Takasuka T, et al. Resistin SNP-420 determines its monocyte mRNA and serum levels inducing type 2 diabetes. Biochem Biophys Res Commun. 2005; 335: 596–02.
41. Menzaghi C, Coco A, Salvemini L, Thompson R, De Cosmo S, Doria A, et al. Heritability of serum resistin and its genetic correlation with insulin resistance-related features in nondiabetic Caucasians. J Clin Endocrinol Metab. 2006; 91(7): 2792 –5.
42. Osawa H, Tabara Y, Kawamoto R, Ohashi J, Ochi M, Onuma H, et al. Plasma resistin, associated with single nucleotide polymorphism-420, is correlated with insulin resistance, lower HDL cholesterol, and high-sensitivity C-reactive protein in the Japanese general population. Diabetes Care. 2007; 30:1501– 06.
43. Yamauchi J, Osawa H, Takasuka T, Ochi M, Murakami A, Nishida W, et al. Serum resistin is reduced by glucose and meal loading in healthy human subjects. Metabolism. 2008; 57:149 –56.
44. Ochi M, Osawa H, Hirota Y, Hara K, Tabara Y, Tokuyama Y, et al. Frequency of the G/G genotype of resistin single nucleotide polymorphism at -420 appears to be increased in younger-onset type 2 diabetes. Diabetes. 2007; 56 (11): 2834 –8.
45. Bouchard L, Weisnagel SJ, Engert JC, Hudson TJ, Bouchard C, Vohl MC, et al. Human resistin gene polymorphism is associated with visceral obesity and fasting and oral glucose stimulated C-peptide in the Quebec Family Study. J Endocrinol Invest. 2004; 27(11): 1003 –9.
46. Mattevi VS, Zembrzuski VM, Hutz MH. A resistin gene polymorphism is associated with body mass index in women. Hum Genet. 2004;115: 208 –12.
47. Norata GD, Ongari M, Garlaschelli K, Tibolla G, Grigore L, Raselli S, et al. Effect of the ?420C/G variant of the resistin gene promoter on metabolic syndrome, obesity, myocardial infarction and kidney dysfunction. J Intern Med. 2007; 262 (1): 104 –12.
48. Wågsater D, Mumtaz M, Lofgren S, Hugander A, Dimberg J. Resistin in human colorectal cancer: increased expression independently of resistin promoter -420C > G genotype. Cancer Invest. 2008; 26(10): 1008-14.