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# Polymorphisms in insulin pathway genes and cancer risk

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ABSTRACT

**Background:** Insulin is a big hormone (5808 Da) generally produced with the aid of the pancreas. Insulin receptors (IR) are found in neurons and glial cells. Insulin resistance has been related to increased plasma insulin levels, glucose intolerance, elevated insulin-like growth factor-1 (IGF-I), glucose and free fatty acids, body mass index, and an elevated risk for colorectal cancers. Proinflammatory cytokines, boom components, and hormones secreted by adipocytes play a key role in colorectal cancer etiology. Acetyl-CoA acetyltransferase (ACAT1) mediates insulin-precipitated cell proliferation and metastatic outcomes in colorectal cancer cells. Therefore, miRNAs might serve as a biological connection between metabolic changes linked to obesity and the beginning and progression of Colorectal Cancer Cancer (CRC). Furthermore, these findings shed new light on weight problems as a CRC danger component in which miRNA dysregulation may be involved. The function of IGFs in CRC is investigated by examining the association of two genetic polymorphisms in IGFBP-3 (a G → C single nucleotide polymorphism) and IGF-1 (a cytosine-adenosine dinucleotide repeat) with CRC risk in addition to the possibility of the other interventions, including physical activity, body mass index (BMI), and the use of postmenopausal hormones. These factors can exert their effects by modifying IGF-1 and the related binding proteins (IGFBP). Furthermore, the IGFBP-3 genotype can lead to a substantial effect modifier in the association between CRC and risk factors. It has been found that functional polymorphisms in the pathway of insulin genes, including IGFBPI, INSR, INS, and insulin receptor substrates 1 and 2 (IRS1 and IRS2), can be related to CRC.

**Keywords: Cancer, CRC, Genotype, Insulin, Variant.**

## INTRODUCTION:

### Insulin secretion

The pancreas produces the big hormone insulin (5,808 Da), and blood-brain barrier saturable insulin transporters regulate its entry into the brain (BBB). Insulin receptors (IR) are found in neurons and glia throughout the brain and are responsible for insulin transmission (1).

### Insulin and colorectal cancer

Although insulin is thought of for its metabolic effects, it also performs an important function in colorectal carcinogenesis and cancer progression. It increases the range of receptors of IGF-1 and growth hormone, which stimulates the synthesis of ovarian androgens and inhibits the synthesis of sex hormone-binding globulin and IGFBP-1 (1). Excessive energy consumption, a bodily state of no activity, and weight problems result in insulin resistance. Consequently, plasma insulin concentrations tend to increase. Insulin resistance has been linked to increased plasma insulin levels, glucose intolerance, increased IGF-I, glucose and free fatty acid levels, body mass index, and an increased risk of colorectal cancer. In another meta-analysis take a look at, it was said that in non-Asian societies, excessive ranges of c-peptide and insulin were drastically associated with a drastically increased chance of colorectal cancer (2). Meta-analysis studies performed also propose that hyperinsulinism, excessive c-peptide degrees, and insulin resistance (HOMA-IR) are associated with an expanded chance of colorectal cancer (2). Therefore, this study aimed to investigate the metabolic changes associated with obesity and its relationship with the genotype or frequency of alleles in the onset and progression of CRC.

### Insulin resistance

Insulin resistance, necessarily connected with obesity, type 2 diabetes mellitus, and metabolic syndrome, has been diagnosed as a dangerios element in numerous situations, including tumor development. We can say that the Western diet has caused the deadly diseases of obesity, insulin resistance, metabolic syndrome, and cardiovascular disease, and that it is now causing an epidemic of colon cancer. Records and pathophysiology that hyperlink insulin, insulin growth factor-1, insulin resistance, and adipocytokines with colon cancers. Insulin resistance, an essential mechanism that hyperlinks obesity, diabetes mellitus kind 2, and metabolic syndrome, is a condition in which the ordinary response of cells to insulin is reduced, which leads to hyperglycemia and hyperinsulinemia. Weight problems are a disease characterized by insulin resistance (IR) and persistent low-grade inflammation. Leptin, adiponectin, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-) are only a few of the substances secreted by adipose tissue, which serves as an endocrine organ and controls metabolism, strength intake, and fat accumulation (3). The chronic inflammatory state induced by elevated cytokine levels creates a pro-tumorigenic milieu that promotes angiogenesis. Similarly, proinflammatory cytokines, which are mostly produced by macrophages, can cause IR. According to the definition of IR, a known amount of exogenous or endogenous insulin cannot raise glucose uptake and utilization in a person as much as it does in a normal population (3).

### Factors affecting CRC

Despite this, the molecular pathways through which obesity leads to CRC remain unknown. However, in addition to inherited factors and a poor diet, a few pathophysiological processes, such as IR (as explained above) and persistent low-grade inflammation, have been identified as probable causes of CRC in obesity. Hyperinsulinemia, adipokines, pro-inflammatory cytokines, enhanced IGF-I bioavailability, and sex-steroid hormones have all been linked to the development of CRC, (Fig. 1) (4).

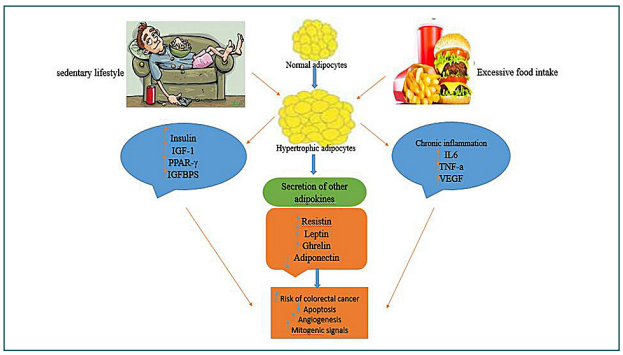


**Figure 1.** Overweight and the causes of colon cancer. VEGF: Vascular endothelial growth factor; PPAR-γ: Peroxisome proliferator-activated receptor-γ; TNF-α: Tumor necrosis factor-α; IGFBPs: Insulin-like growth factor binding protein; IGF-1: Insulin-like growth factor-1; IL-6: Interleukin-6

### The two main mechanisms of adipokine that lead to CRC cancer

Obesity-related diseases are a significant public health concern, and obesity is linked to colorectal cancer. Adipocitis-related diseases and pathogenic adipocyte formation can be triggered by adipocyte hypertrophy and visceral adipose tissue accumulation. Adipose tissue plays a critical and active part in the immunological response of the organism (5). Cytokines/adipokines, which are released by adipose tissue, play a crucial role in adipocyte-macrophage communication. As a result, low-grade chronic systemic inflammation is linked to visceral adipocytes. Adipocytes are crucial to understanding the causes of colorectal cancer due to proinflammatory cytokines, growth factors, and hormones. Adiponectin, resistin, and ghrelin are the most prominent cytokines. Insulin resistance, glucose intolerance, high plasma insulin levels, body mass index, insulin-like growth factor (IGF-1), glucose, and fatty acid ranges have also been linked to the etiology of colorectal cancer. The term "cancer" describes numerous malignant tumors that can affect almost all organs and tissues. With changing life patterns and increased interaction with various carcinogens, the incidence of cancer has gradually increased (5). In addition, colorectal cancers are the third maximum type of cancer amongst men (10% of all cancers), it ranks as the second among girls (9.2% of all cancers). The underlying mechanism of the correlation between colorectal cancers and obesity has now not been understood; adipokines and insulin are taken into consideration to play a key function in this relationship. The primary mechanism amongst these is that weight problems lead to insulin resistance and hyperinsulinism, causing a reduction in insulin-binding protein 1 (IGFBP-1) degrees. This reduction results in a boom in insulin-like growth factors (IGF-1 cell proliferation and inhibiting apoptosis). Obesity affects the levels of adipokines released by adipose tissue (adiponectin, leptin, resistin, and proinflammatory cytokines such as interleukin-6 and tumor necrosis factor -α). Apart from adiponectin, an increased level of these adipokines can contribute to tumor formation, development, and metastasis (6).

### Colorectal cancer (CRC) and IGF-I

IGFBPs have a role in regulating IGF1 bioactivity. As a result, IGFBPs play a role in colorectal carcinogenesis by directing downstream signaling pathways (Fig. 2). IGF1 induces cell proliferation by activating protein kinase and mitogen-activated 3-kinase pathways. In colorectal tissue, IGF1 has been demonstrated to enhance cell proliferation, while monoclonal antibodies that target IGF1 receptors reduce cell proliferation. The findings imply that dietary/lifestyle or pharmacologic 1) interventions targeting the IGF gadget may also provide a promising approach to lowering the risk of colorectal cancer (7). Studies have shown that the role of IGF-1 in carcinogenesis is through inhibition of apoptosis and stimulation of proliferation. Weight problems are another reason for the link between IGF-1 and CRC, so body weight increases stimulate this link. Currently, it has been shown that IGF-1 is inversely related to E-cadherin in various kinds of cancer. E-cadherin is a member of the cadherin superfamily and plays an important role in the formation and upkeep of intercellular adhesion (8). It has previously been shown that E-cadherin deficiency leads to the removal of cell-to-cell adhesion, thus enhancing epithelial-mesenchymal transmission (EMT), which is an important and effective factor in tumor formation. Hence, E-cadherin expression decreased and was found to be associated with CRC progression (9).

### Role of Insulin-like growth factor binding protein-7 (IGFBP-7)

Protein-7 bound to insulin growth factor (IGFBP-7) is a tumor adhesion factor and vasomodulin, which is a secreted protein and is known to be one of several proteins associated with IGFBP. IGFBP7 is an essential binding protein for an insulin-like growth factor that is found throughout the body. It is involved in cell proliferation, differentiation, and growth, as well as insulin distribution (10). Among members of the IGFBP family, IGFBP7 is the protein with the strongest insulin-binding capacity ever discovered. Compared to IGFBP1-6, its ability to bind to insulin is 500 times stronger. The IGFBP7 protein binds to insulin excessively, so insulin cannot bind to its receptor, thus producing insulin resistance by inhibiting

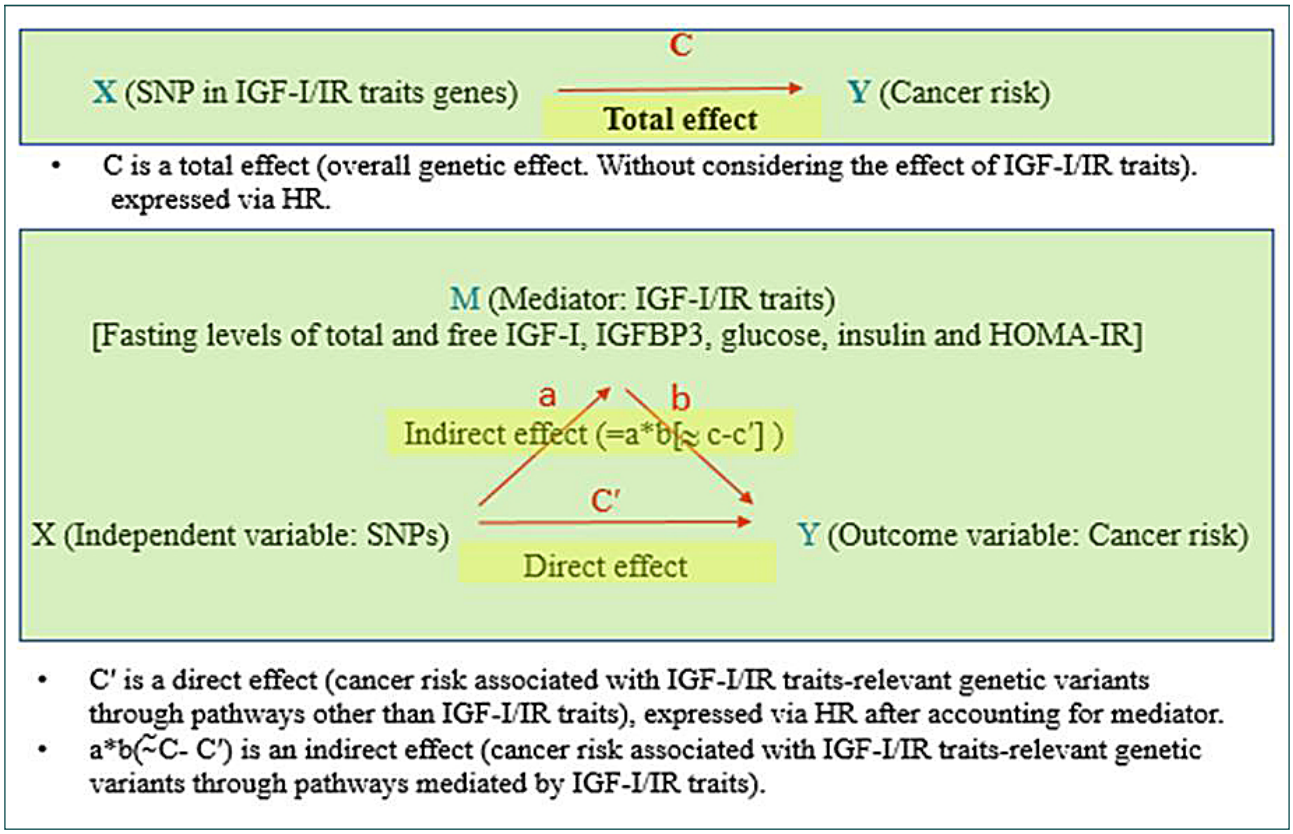


**Figure 2. Diagrams showing the relationship between IGF-I/IR features, IGF-I/IR genes, and the risk of colorectal cancer.** (HOMA-IR, homeostatic model assessment-insulin resistance; IGF-I, insulin-like growth factor-I; HR, hazard ratio; IGFBP3, IGF binding protein 3; IR, insulin resistance; SNP, single-nucleotide polymorphism.) C' is a direct impact (cancer risk linked to IGF-I/IR characteristics-relevant genetic variations through pathways other than IGF-I/IR traits), expressed through HR after mediator is taken into account. C is an overall effect (genetic influence without taking into account the impact of IGF-I/IR characteristics), indicated as HR. As a result of pathways regulated by IGF/IR characteristics, a*b (_C-C') is an indirect impact (cancer risk related wih IGF-I/IR traits-relevant genetic variations).

autophosphorylation in insulin receptor β and stimulating IRS-1 phosphorylation (11).

## Association of insulin with ACAT and colorectal cancer

Colorectal cancer tissues have greater ACAT1 expression than normal ones. As a result, ACAT1 may have a role in colon cancer etiology. According to this research, ACAT1 mediates the effects of insulin on most colorectal cancer cells' ability to proliferate and spread. Colon cancer is the second most prevalent cancer among women and the third most prevalent. Cancer among males in the world. Meanwhile, insulin, by activating its receptors, IGF-I receptors, or hybrid insulin/IGF-I receptors, can induce colorectal carcinogenesis without delay. These findings show that insulin may also play a role in colorectal cancer development (12). Cellular proliferation and survival can be triggered when insulin binds to its receptor, causing cellular proliferation and survival. Numerous studies on insulin gene polymorphism have shown its association with colorectal cancer (13). In previous research, we observed that an increase in insulin causes overexpression of ACAT mRNA and protein expression in macrophages, so the accumulation of large amounts of cholesterol ester leads to atherosclerosis and the two ERK / p38MAPK / JNK signaling pathways are associated with this. The two forms of cellular cholesterol are free cholesterol (FC) and cholesterol esters (CE). ACAT converts FC to CE using cholesterol and acyl-coenzyme. Cholesterol ester hydrolase (CEH) reverses the conversion of CE to FC. ACAT and CEH act in contradistinct ways to preserve the dynamic equilibrium between FC and CE (14). ACAT1 and ACAT2 are the two ACAT isoenzymes that have been found so far. ACAT1 is found mostly in

nerve cells, endothelial cells, and macrophages. Whereas ACAT2 is primarily found in epithelial cells, intestinal villus, and liver cells. ACAT is also strongly associated with atherosclerosis and Alzheimer's disease. Studies have shown that ACAT / cholesterol ACAT / cholesterol ester can be a starting point for the strengthening and growth of tumor cells. The ACAT-1 inhibitor has been shown to limit colon cancer growth and apoptosis by decreasing cholesterol ester accumulation in fat droplets while raising free cholesterol levels (15).

### Changes in insulin-sensitive miRNAs

Changes in miRNAs associated with insulin sensitivity, lipid metabolism, and glucose tolerance have been investigated in weight disorders and CRC. All of the metabolic modifications have been proven to be related to the danger of CRC in obesity, and a number of the defined miRNAs have been found to be similarly dysregulated in obesity, IR, and CRCA. As a result, miRNAs may serve as a biological connection between metabolic alterations linked to obesity and the initiation and progression of CRC. These findings suggest obesity is a risk factor for CRC, which is associated with impaired miRNA regulation. Also in CRC cells, a decrease in miR-497 leads to an increase in IGF1R, while overexpression of miR-497 leads to a decrease in the endogenous IGF1R protein (16). This incident causes CRC malignancy (such as increased sensitivity to apoptosis and inhibition of cell survival due to chemotherapy pills). Studies of human subjects with body mass index and waist-to-hip ratio (WHR) records have confirmed that the miR-497 gene is linked to WHR, suggesting that it is also involved in weight problems (17). In addition, the miR-497 overexpression range causes IR in the liver of mice that have an overly fatty diet, inhibiting insulin receptor gene expression. non-alcoholic fatty liver disease (NAFLD) and Obesity can be triggered by alterations in miR-155 in obese mice and bring about an enhancement in resisting, which regulates insulin sensitivity (18). According to recent research, miR-21, which is associated with weight problems and T2D in mice (19), also has a tumorigenic function in CRC because CRC is significantly upregulated by colon adenoma and neoplastic mucosa (20). An analysis of CRC patients with and without weight issues represents a turning point in the study of how circulating miRNAs affect CRC linked to obesity. According to this, three circulating miRNAs (miR-27b, miR-130b, and miR-138) have been located to be elevated and negatively associated with peroxisome proliferator-activated receptor gamma (PPARγ), investigated in peripheral blood mononuclear cells (PBMC). PPAR is known to have tumor-suppressing properties, and an augmentation of these miRNAs has been linked to the risk of CRC in obese people (21), In light of these CRC results, overexpression of miR-27b-3p increases visceral fat storage and accelerates browning inhibition in white adipose tissue and epidermal adipose tissue, (fig. 3) (22).

### Role of IGF-1 and IGFBP-3

Colorectal cancer risk has been linked to a variety of modifiable lifestyle factors, including postmenopausal hormone use, obesity, and physical activity. There has been a hypothesis that the manipulation of insulin-like growth factor-1 (IGF-1) and the related binding proteins (IGFBP) can mediate the effects of a range of these factors. The normal cells of colorectal epithelial cells express IGF-1 receptors (23, 24). These receptors stimulate mitogenesis while they are activated by IGF-1 in vitro (25). Cyclin D1 stimulation increases DNA synthesis and, as an important protein in the cell cycle, exerts the mitogenic effects of IGF-1 (26). In addition, IGF-1 leads to the prevention of apoptosis by adjusting the expression of Bax and Bcl proteins as well as preventing the trigger of the apoptotic pathway (27, 28). The action of IGF-1 is regulated through interacting with the IGFBPs, especially IGFBP-3, established as the independent ap-

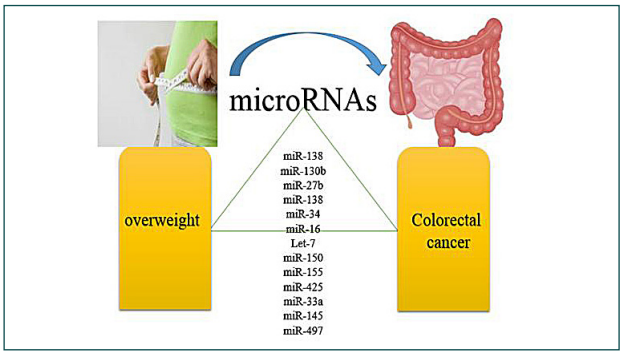


**Figure 3.** micro RNAs in common between obesity and colorectal cancer.

optotic agent, which prevents the activity of IGF-1 (29-32) which has been shown to have several growth-promoting effects, including potential IGF-1–induced cell growth (32). It also mediates the effects of growth stimulation to transform growth factor-h (33, 34).

### Relationship between colorectal cancer risk and two genetic variants in IGFBP-3 (a G → C single nucleotide polymorphism) and IGF-1 (a cytosine adenosine dinucleotide repeat)

In comparison to the common genotypes (homozygous for the 19 repeat allele), the IGF-1 genotype is moderately linked to increased colorectal cancer risk, while the IGFBP-3 genotype is weakly linked to such risk; additionally, the GG genotype is associated with an OR of 1.3 (1.0-1.8) compared to the CC genotype (30, 31).

IGFBP-3 shows a similar relationship with colorectal cancer for the genotype of GG in comparison with the CC genotype (35). Although women with the 19/19 IGF-1 genotype showed a relationship of high BMI with a risk of colorectal cancer, it was observed in both genders with the IGFBP-3 GG genotype (14). The decrease in colorectal cancer risk related to vigorous exercise in males may only apply to those who carry the C-IGFBP-3 allele. Only women with the GG genotype showed a link between lower colorectal cancer risk and current postmenopausal hormone. The increased colorectal cancer risk in both genders is independently related to the high levels of IGF-1 as well as the low levels of IGFBP-3 (36). The following relationship exists between levels of circulating IGFBP-3 and this polymorphism:

As compared to the CC genotype, the GG genotype has been related to highly increased levels of circulating IGFBP-3. Besides the IGF-1 polymorphism, the GG genotype has been associated with a higher risk of colorectal cancer. It was observed that the interaction between lifestyle factors and IGF genes is considerable. (37, 38) The evidence shows that the modified IGF physiology can lead to the relationship between colorectal cancer risk and BMI, which emerged in women modified by IGF-1 genotype (19).

### INSR gene and 603G polymorphism

The risk of CRC has been related to the INSR A-603G promoter SNPs placed within an Sp1-binding area with carriers of the G allele having a reduced risk based on the OR (odds ratio) of 0.71, and 95% CI (confidence interval) of 0.54–0.93 (39). Although the risk of CRC and INSR

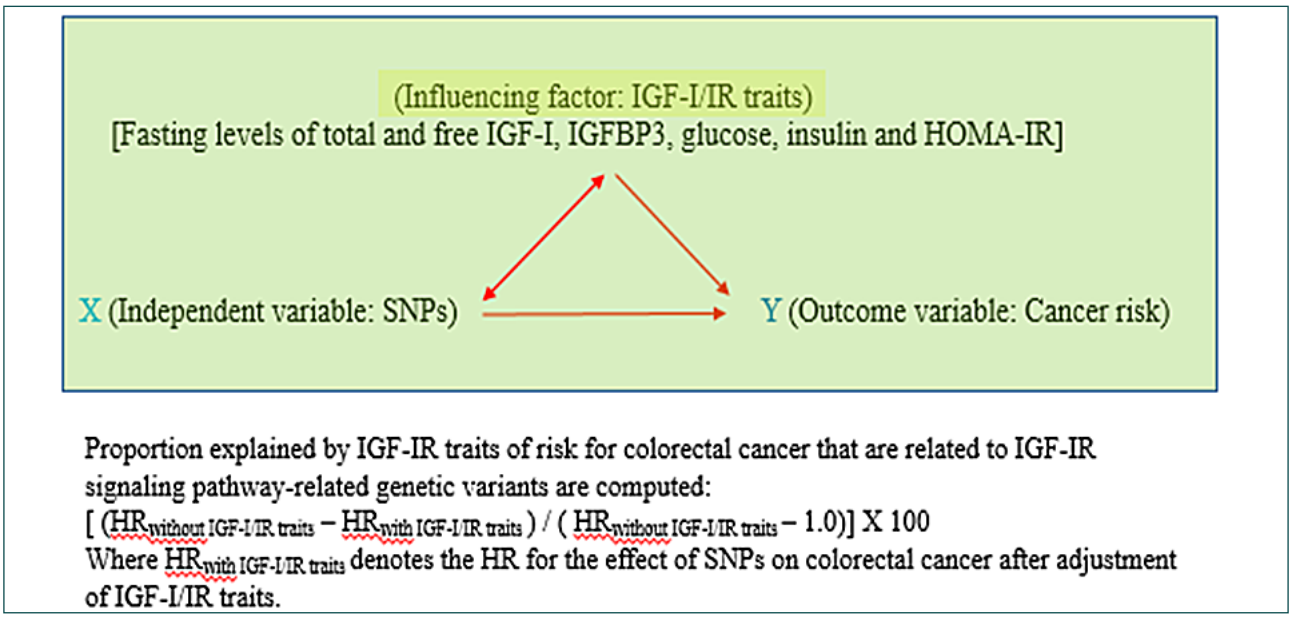


**Figure.4. Pathways of SNPs in genes associated with IGF-I/IR signalling pathways, IGF-I/IR characteristics, and colorectal cancer.** (IR, insulin resistance; IGFBP3, IGF binding protein 3; factor-I; SNP, single-nucleotide polymorphism) Calculated as follows: [(HRwithout IGF-I/IR traitsHRwith IGF-I/IR traits) / (HRwithout IGF-I/IR traits1.0)] X 100, where HRwith IGF-I/IR characteristics stands for the HR for the impact of SNPs on colorectal cancer following adjustment for IGF-I/IR traits.

(A-603G) genotypes has been significant, the variant allele carriers in the INSR gene showed highly reduced CRC risk (40).

### Association between IRS1 Gly972Arg polymorphism and risk of CRC

The polymorphism of IRS1 Gly972Arg placed between two tyrosine residues that are on phosphorylation has been engaged in interaction with downstream signaling molecules (40). Insulin-stimulated signaling is hampered by the Arg variant's reduced binding to the PI-3 kinase p85 regulatory subunit (41). Furthermore, the allele of Arg has been linked to a higher CRC risk (42). Although the Gly972Arg SNP has not been highly related to the CRC risk, the carriers' risk of the protective INSR allele has been reduced in people who are carrying the IRS1 Arg allele (43).

### Association between IRS2 Gly1057Asp polymorphism and risk of CRC

Although the IRS2 Gly1057Asp polymorphism is located near two areas of putative phosphorylation tyrosine, no effects on the capability of the p85 subunit of PI-3 kinase have been observed (44). In addition to IRS1, much research on insulin resistance-related disorders has reported the IRS2 SNP inconsistent effects (44). As opposed to the homozygotes, the heterozygotes of the Asp allele have contributed to the decreased risk of CRC (42). However, no correlation has been found between CRC risk and IRS2 Gly1057Asp (43).

### Association between C1127INSPstI and risk of CRC

The C1127INSPstI is placed on the 30-UTR (30-untranslated region) of the INS gene that plays a significant part in the stability of mRNA and can modify the production of insulin (39) According to the available data, there is no significant relationship between CRC risk and SNP (43). It has been indicated that the INSR-603G allele carriers reduce the CRC risk. In addition, both the IRS1 972Arg allele and the INSR-603G have shown stronger protective effects, but they are still to be proved through other sets of independent samples. SNPs in insulin pathway genes may have a stronger impact on CRC risk in both obese and diabetic patients as a result of the link between CRC and insulin-related disorders, but more research is needed to achieve reliable results (Fig.4) (43).

### Relationship between CRC and LEPR Gln223Arg polymorphism in the Iranian population

There is a lack of evidence supporting the considerable difference in the frequencies of genotype and allele following adaptation for confounders (i.e., BMI, age, sex, and smoking) between the patients with controls for the Gln223Arg polymorphism of LEPR and CRC. The results have indicated that the cases controlled by BMI, sex, and smoking have no substantial difference from the CRC cases. It has been concluded that the CRC risk in the Iranian population has not been related to the LEPR Gln223Arg polymorphism (45).

### Association between polymorphism (-23HphI) in Insulin Gene and colorectal cancer

The difference in the INS gene and the-23HphI variant between controls and cases in both genotype or allele frequencies is negligible; even after adjusting for BMI, age, smoking status, sex, CRC family history, and regular NSAID use, it remained the same. There is also no evidence confirming the effect adjustment of the relationship between CRC and the -23HphI variant by sex, BMI, or area of the tumor. As a result, there is no evidence to support the effect of the INS gene-23HphI variant on the risk of CRC (46).

### Risk of colorectal cancer and types of type 2 diabetes

rs864745 (JAZF1), rs7578597 (THADA), rs7961581 (TSPAN8), and rs5219 (KCNJ11) that are usually related to colorectal cancer risk, modified for sex, age, race, and ethnicity. Although the T2D risk allele of rs5219 (KCNJ11) has been shown to increase colorectal cancer risk, the T2D risk allele is associated with a lower risk of this cancer (47). The heterogeneous effects of sex have been observed in the THADA and KCNJ11. Their effects on the increase of CRC have been substantially related to the colorectal cancer risk in women. The same pattern with lower intensity has been found in men as well. Although the risk of colorectal cancer in men has been related to KCNJ11, rs5219, it has not been found in women (47).

### THADA (rs7578597) and KCNJ11(rs5219)

A significant relationship to colorectal cancer has been

observed in the missense variants in the THADA and KCNJ11 loci, including rs7578597 and rs5219. The link between THADA and KCNJ11 variants and colorectal cancer risk has been established in cases without diabetes. The variant of THADA has been dominant in cases with normal weight, while it has been also observed in overweight cases (47). The most considerable relationships of KCNJ11 (rs5219) and THADA (rs7578597) with the colorectal cancer risk were in cases without diabetes, which can indicate the decreased study power in the diabetic subgroup (i.e., colorectal cancer cases/controls is 538/1328). Regarding THADA (rs7578597), the high-risk allele of diabetes (T) has been related to a decreased colorectal cancer risk, indicating this polymorphism has different effects concerning colorectal cancer and diabetes (48).

### T allele of rs7578597 associated with risk of T2D

Although the T allele has been linked to a lower risk of colorectal cancer in a multiethnic population [51], the T allele of rs7578597 has been related to a 15% rise in the risk of T2D (49), it has also been associated with reduced levels of insulin during the examination of oral glucose tolerance in the Chinese population (50). The difference in the relationship between T2D and colorectal cancer can be associated with the differences in the biological effects of THADA in cases with poorly characterized biological activity (51).

### TSPAN8/LGR5 (rs7961581) and JAZF1 (rs864745) and

TSPAN8/LGR5 (rs7961581) and JAZF1 (rs864745) genes have profound biological implications for colorectal cancer risk development phenotypes, but they have a weak relationship with colorectal cancer risk (47). As substantial relationships between rs5219 (KCNJ11), rs7578597 (THADA), rs7961581 (TSPAN8), and rs864745 (JAZF1) remained the same following the change in diabetes status, diabetes can associate these T2D variants with the risk of colorectal cancer (47).

### INS gene rs689 variant

Although most epidemiologic studies have indicated that genes related to the insulin signaling pathway are CRC-related genes because the metabolic and clinical aspects of subjects with CRC include elevated obesity risk and IR, little research has tested the relationship between CRC risk and INS gene variants. Furthermore, previous research has found no link between advanced colorectal adenoma and gene variants (43). There is no considerable relationship between the risk of CRC and the INS gene rs689 variant. As the rs689 variant is placed in the INS gene promoter, the promoter sequence alterations can affect the protein expression. The major deviations from HWE have been found for the variant in both control and case populations. The HWE deviations can be found due to various causes, such as population, small sample size, stratification, inbreeding, or genotyping error. Therefore, it is not recommended that INS is a predisposing gene for the risk of CRC in the Iranian population. However, it should be considered that the HWE deviation can influence the interpretation of the relationship between the risk of CRC and the INS gene rs689 variant and Although it has been concluded that the gene is unrelated to CRC pathogenesis, other variants of the INS gene should be thoroughly studied (52).

### INSR gene rs1799817 variant

The examination of the relationship between the risk of CRC and the variant of His 1085 C/T in the exon 17 of the INSR gene has been in good agreement with other studies (43, 53, 54) and indicates a considerable relationship between the risk of CRC and the INSR gene variant, whereas null relationships have also been found (52). The genotypes of INSR rs1799817 TT+CT and CT compared with the genotype of CC showed 1.86 and 2.18 higher increased risks for CRC in females, respectively. While this study shows the relationship between the risk of CRC and the variant of INSR gene rs1799817, previous studies have shown that other variants of the INSR gene, including rs1864010 and rs1051690, are associated with the risk of CRC. The synonymous polymorphism (His1085His) rs1799817 at exon 17 indicates that there is no change in the INSR amino acid sequence. However, the precise molecular mechanism accountable for the variation in biological effects is yet to be largely investigated.

### Gene types IRS1 rs1801278 and IRS2 rs1805097

The two genes, including IRS2 and IRS1, have interac-

tions with the cell growth and signaling pathways that modulate glucose metabolism. The IRS1 gene variant rs1801278 (Gly972Arg) has an association with type 2 diabetes (55). Furthermore, it has been observed that obesity has a substantial association with the IRS2 gene rs1805097 (Gly1057Asp) variant (56). However, the effects of the gene variants of IRS1 and IRS2 on the risk of CRC risk have been unclear (40, 42, 43, 57, 58). Also, a significant relationship between the risk of CRC risk and the IRS1 gene rs1801278 variant has not been observed, which is similar to the previous study (43). Likewise, most previous researchers have reported no relationship between the IRS2 gene rs1805097 variant and the risk of CRC (43, 57, 58). However, associations between the risk of CRC and both the rs1801278 and rs1805097 variants have been significant (40, 42). The inconsistent findings in different studies can be attributed to several causes, including the differences in genetic makeup, false-positive results, genotyped markers, nutritional factors, disease definition, or statistical methods. Alternatively, the rs1805097 and rs1801278 variants could be in link disequilibrium with the unfamiliar functional variants of the IRS2 and IRS1 genes, indicating the observed difference.

### Gene types IGF1 rs5742612 and IGFBP3 rs2854744

The relationship between the gene variants of IGFBP3 rs2854744 and IGF1 rs5742612 and the risk of CRC has been studied. These two polymorphisms have been placed in the promoter region, and protein expression is affected by modifying the promoter sequence. In addition, available epidemiologic investigations have shown that CRC cases have lower serum levels of IGFBP3 and greater serum levels of IGF1 as compared to controls (59, 60). On the contrary, considerable relationships have been found between the gene variants of IGF1 and IGFBP3 and the risk of CRC (61). Furthermore, the findings coincide with those studies showing a negligible relationship between the gene variants of IGF1 and IGFBP3 and the risk of CRC (42, 52, 62, 63).

The results do not support the idea that the IGFBP3 rs2854744 and IGF1 rs5742612 gene types may have a role in the etiology of colorectal cancer in the Iranian population, even though there is no obvious explanation for these contradictions.

## Conclusion

ACAT1 is involved in insulin-precipitated cell proliferation and metastatic outcomes in colorectal cancer cells. Therefore, miRNAs may serve as a biological connection between metabolic changes linked to obesity and the start and progression of CRC. Among females, the genotype of IGF-1 has adjusted the association between colorectal cancer and BMI. It was found that the GG genotype in both genders has led to the relationship between colorectal cancer and BMI. By the recent results, the INSR-603G allele carriers can diminish the CRC risk. Based on the outcomes of the case-control investigation, there is a negligible difference found in genotype and allele frequencies regarding the cases with controls for the Gln223Arg polymorphism of LEPR and CRC after or before modifying confounders including BMI, gender, age, and smoking habits. For the INS gene variant 23HphI, there was no discernible change in genotype or allele frequencies between the patients and controls, and after adjusting for age, sex, BMI, regular NSAID usage, family history of CRC and smoking habits, this lack of difference continued to be insignificant. In addition, the -23HphI variant has shown no impact on the obesity risk in controls and cases with CRC. Colorectal cancer risk was linked to four SNPs in type 2 diabetes: rs864745 (JAZF1), rs7578597 (THADA), rs7961581 (TSPAN8, LGR5), rs5219 (KCNJ11). The strongest association was for the rs7578597 (THADA) Thr1187Ala missense polymorphism (Ptrend= 0.004 adjusted for multiple testing), with the high-risk allele for colorectal cancer being the low-risk allele for diabetes. The results have demonstrated that the risk variants of diabetes influence the probability of the risk of cancer through different mechanisms in those suffering from diabetes. The rs1805097 (Gly1057Asp) variant of the IRS2 gene shows a substantial relationship with obesity. However, the IRS2 gene rs1805097 variant has no link to CRC. investigations have shown that the risk of CRC is related to other INSR gene variants, including rs1864010 and rs1051690. The INSR gene can lead to CRC development. In females,

the genotypes of CT and INSR rs1799817 TT+CT have caused higher risks of CRC as compared to the CC genotype.

**Conflict of Interest**

In this work, the authors state that they have no conflicts of interest.

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