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The Correlation Between Single Nucleotide Polymorphism Patterns and Colorectal Cancer in the Iranian Population

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Abstract

Context: The incidence of colorectal cancer has significantly increased in Iran during the last decade. Accumulating evidence suggests that there is a significant correlation between genetic variations such as polymorphisms and colorectal cancer. Therefore, identification of critical polymorphisms related to colorectal cancer can contribute to find individuals at high risk of CRC.
Evidence Acquisition: The focus of this review was on published articles in English about the association between different single nucleotide polymorphisms and colorectal cancer in the Iranian population. Evidences were gathered by searching online medical databases including Google scholar, Pubmed, Scopus and Science Direct.
Conclusions: Various single nucleotide polymorphisms of critical genes indicated significant association with colorectal cancer in the Iranian population. New polymorphism markers for high risk individuals have been recognized through further investigations to reduce the incidence and mortality of colorectal cancer.

Keywords: Single Nucleotide Polymorphism, Colorectal Cancer, Iranian Population

1. Context

Colorectal cancer (CRC) is one of the most common cancers worldwide with increasing trends of incidence in Eastern countries such as Iran (1-3). Although Asian countries traditionally experience low incidence of CRC, their rapid rise in incidence was significant compared with western populations in the last decade (4). Based on the annual reports of the Cancer Institute, colorectal cancer has been identified as the third and the fifth most common cancer in Iranian females and males, respectively (5, 6). Changes in lifestyle and environmental factors along with genetic predispositions lead to this considerable surge of incidence (4). Three forms of CRC include sporadic, familial and hereditary. Overall, 25% of cases have positive family history of disease; however, CRCs frequently occurs sporadically without family history (7). There are four classified groups of sporadic CRC including; hypermutated, non-hypermutated, CpG island methylator phenotype and elevated microsatellite alterations at tetranucleotide repeats with metastatic behavior (7, 8). Two forms of hereditary CRC include familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). Familial Adenomatous Polyposis and HNPCC occur due to inherited mutations and are observed in about 1% and 5 to 7% of CRC cases, respectively (9). It is now clear that accumulation of genetic and epigenetic alterations leads to dysregulation of the homeostatic functions and consequently neoplastic transformation of CRC (10). In this regard, molecular carcinogenesis of colorectal cancer has been extensively investigated around the world such as Iran and its pathogenesis has been far better known than any other cancer (6).

2. Evidence Acquisition

A search of Google scholar, Pubmed, Scopus and Science Direct was performed. All studies on the association between various single nucleotide polymorphisms and colorectal cancer in the Iranian population were retrieved and reviewed for this review article.

3. Results

3.1. Single Nucleotide Polymorphism (SNP)

During the sequencing process of the human genome, it became clear that the amount of genetic variation is much greater than prior estimations (11). There are different types of variations including microsatellites, variable nucleotide repeats, and complete copies of genes or regions of a chromosome. However, the most frequent sequence variation in the human genome (more than 90%)

is single nucleotide polymorphisms (SNPs). Single Nucleotide Polymorphism is the stable replacement of a single base at a specific position in the genome with a frequency of about one in 1000 bp (12, 13). These SNPs may occur within coding or non-coding sequences and also intergenic regions. Although most of the SNPs are silent (synonymous) and do not modify the protein sequences, some of them change the amino acid sequence of proteins (non-synonymous) as well as gene expression and functions through influencing promoter/enhancer/silencer activity and also mRNA stability. Therefore, they may play an important role in genome evolution and also diversity among individuals such as susceptibility to disorders or drug response. Recognition and evaluation of numerous genetic variations may result in better understanding of their effects on gene function and health of individuals. Knowledge improvement in this area provides a starting point for finding new SNP markers, which can be effectively used in personalized medicine (13). In this regard, extensive studies have been conducted around the world to find the potential relationship between genetic variations and different disorders such as colorectal cancer. This review focused on published articles, which studied the correlation between different SNPs in Iranian populations and colorectal cancer incidence. Table 1 summarizes the results of 55 studies from 2007 to 2016.

3.1.1. DNA Repair Genes

The association between polymorphisms of several DNA repair genes and CRC has been investigated in Iranian populations. In this regard, Khatami et al. (14) demonstrated a significant correlation between O6-methylguanine DNA methyltransferase (*MGMT*) SNPs (*Arg128Gln*, *Gly160Arg* and *Pro58Ser*) and sporadic CRC in Tehran. Three different studies evaluated exonuclease 1 (*EXO-1*) SNPs. Montazer Haghighi et al. (15) indicated the correlation between Leu/Leu genotype of EXO-1 (*Pro757Leu*) and reduced risk of CRC. However, based on two other studies, rs1047840 and rs1635498 had no significant correlation with CRC (16, 17). The association between SNPs of MutL homolog 1 (*MLH1*), including rs1799777 (16) and rs1799977 (17), and CRC was significant. However, no significant relationship was observed for rs2286940 of this gene (17). X-ray repair cross-complementing protein 1 (*XRCC1*) (18), DNA-dependent protein kinase catalytic subunit (*DNA-PKcs or XRCC7*) (19) and xeroderma pigmentosum group D (XPD) (20) are three other DNA repair genes, which have been evaluated. However, the only significant gene among them was XRCC7 (*rs7003908*), which was investigated by Saadat et al. in Shiraz (19).

3.1.2. Immune System Related Genes

According to the results obtained from different studies, it has been demonstrated that there may be significant correlations between SNPs of several genes involved in the immune system and CRC incidence. This significant relationship was observed for Programmed cell death protein 1 gene (*PD1.5* and *PD1.3*) (21, 22), cluster of differentiation 86 (*CD86*) (23), nucleotide-binding oligomerization domain-containing protein 2 (*NOD-2*) (24), Transforming Growth Factor beta 1 (*TGF- β1*) (*-509 C/T*) (25), Interleukin 17 (*IL-17*) (26) and IL-18 (*-137 G/C*) (27) (A A significant association was also shown between IL-16 TG genotype (*rs11556218*) and 1.75 fold increased risk of CRC (P = 0.005) and inverse association between Il-16 CC genotype (*rs4778889*) and CRC in male subjects (P = 0.045) (28). In another study in Shiraz, Mojtahedi et al. (29) indicated an association between Forkhead box P3 (*FoxP3* or *scurfin*) C-2383T SNP and metastatic CRC. No correlation was observed for SNPs of some other genes such as, tumor necrosis factor alpha (*TNF-α*) (-238 G/A) (30), stromal cell-derived factor-1 (*SDF-1α*) (*G801A*) (31), IL-18 (*-607C/A*) (27), IL-22 (*rs1179251*) (34), IL-23 (*rs11209026*, *rs1088967*) (26), TGF- β1 (*-800 G/A*) (25), C-C chemokine receptor type 4 (CCR4) (*rs2228428*) (32), C-C motif chemokine 22 (*CCL22*) (*rs4359426*) (32) and cytotoxic T-lymphocyte-associated protein 4 (*CTLA-4*) (*-1722T/C*, *-1661A/G*, *+49A/G* and *-318C/T*) genotypes (33).

3.1.3. Oncogenes and Tumor Suppressor Genes

Given the critical role of the oncogenes and tumor suppressor genes, their SNPs may play an important role in various cancers, such as CRC. In this regard, SNPs of three tumor suppressor genes including tumor protein p53 (*p53*) (34, 35), cyclin-dependent kinase inhibitor 2A (*CDKN2A* or *p16*) (36) and Axin2 (2) were investigated in Iranian populations. Conflicting results were obtained in two separate studies for p53 (*Arg72Pro*). Although Doosti et al. (35) found a significant association between p53Arg/Arg genotype and susceptibility to CRC among the populations of Isfahan and Chaharmahal Va Bakhtiari; however Mojtahedi et al. (34) found that this correlation was not significant in a sample from Shiraz. No relationship was also observed between CDKN2A (*rs11515*) in microRNA binding site (36) and Axin2 (*Pro50Ser*) SNPs (2), and CRC. On the other hand, an evaluation in Tehran by Azimzadeh et al. (36) demonstrated no correlation between microRNA binding site polymorphism located in oncogene serine/threonine-protein kinase (*c-RAF* or *RAF-1*) and CRC.

3.1.4. Other Genes

Polymorphisms of some other genes have been evaluated in CRC patients and normal Iranian population. For instance, SNPs of DNA Methyltransferase 3B (*DNMT3B*)

(37, 38), glutathione s-transferase theta-1 (*GSTT1*) (39), matrix metalloproteinase-1 (*MMP-1*) (2G/2G) (40), MMP-3 (5A/5A) (41), methylene tetrahydrofolate reductase (*MTHFR*) (C677T) (42, 43), Vitamin D Receptor (VDR) (*ApaI*) (44), multiple drug resistance 1 (*MDR1*) (*G2677T/A*) (45), epidermal growth factor (*EGF*) (rs6983267) (46), cyclooxygenase 2 (*Cox-2*) (*-765G > C*) (47), insulin receptor (*INSR*) (rs1799817) (48) and mothers against decapentaplegic homolog 7 (*SMAD7*) (*rs4464148*) (49) showed a significant correlation with CRC. However, this association was not observed for other genes such as leptin receptor (*LEPR*) (50), prostaglandin E2 receptor 4 (*PTGER4*) (36), integrin beta 4 (*ITGB4*) (36), cytochrome P450 2E1 (*CYP2E1*) (39), Insulin-like growth factor 1 (*IGF1*) (48, 51), insulin-like growth factor-binding protein 3 (*IGFBP3*) (48, 51), parathyroid hormone (*PTH*) (52), calcium-sensing receptor (*CaSR*) (52), prostaglandin-endoperoxide synthase 2 (*PTGS2 or COX-2*) (53) and DNMT1 (14).

3.1.5. Meta-analysis studies

There are several studies in the meta-analysis related to some of the genes mentioned above. As mentioned above, according to Iranian studies, *MMP1/MMP3* (40, 41), *GSTT1* (39), *MTHFR* (42, 43), *EGF* (rs6983267) (37) and *TGFβ1* (25) indicated significant relationships with CRC. Similar results were obtained by other meta-analysis reports, based on 50, 23, 71 and 33 case-control studies, for *MMP1/ MMP3* (54), *GSTT1* (55), *MTHFR* (56) and *EGF* (57), respectively. Another meta-analysis demonstrated similar results for TGF- β1 using 4440/6785 cases/controls (58). No significant association was observed for *MDR1rs1045642* (*C3435T*) SNP by Samanian et al. (45) and these results were confirmed by Wang et al. (59), in a meta-analysis of 34 case-control studies. However, Khedri et al. (60) found it significant in Mashhad. Inconsistency can be also observed between the results of some studies in the meta-analysis and Iranian population. For instance, in the Iranian population *ApaI* and *BsmI* SNPs of VDR gene showed significant and non-significant correlations in CRC, respectively (44, 61). However, quite opposite results were achieved in a meta-analysis based on 23 case-control studies by Yong-Heng Bai et al. (62).

4. Conclusions

Polymorphisms of different crucial genes have been evaluated in CRC patients and the normal population. However, as illustrated in Table 1, most Iranian studies have been undertaken in Tehran and a smaller number of researches have been done in other cities like Shiraz, Isfahan, Mashhad, Chaharmahal Va Bakhtiari and Neyshabur. Given the extent of the Iranian population and possible genetic differences among them, investigations in different cities can be extremely helpful for a better understanding of the association between variations of these genes and colorectal cancer in Iran. On the other hand, due to contradictory results, further investigations are required to obtain more accurate and comprehensive results and also find new potential biomarkers for colorectal cancer.

Footnote

Authors' Contribution: Mozhdeh Zamani: primary idea, data collection, writing and design of the manuscript; Pooneh Mokarram: revision and final approval; Seyed Vahid Hosseini: revision and final approval.

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Table 1. Evaluated Single Nucleotide Polymorphisms in the Iranian Population From 2007 to 2016

Evaluated Gene SNPs	Assay	Sample Size	City	The Relationship Between Genotypes and CRC	Significant P Value OR (95% CI)	Year
CTLA-4						
-1722T/C	PCR-RFLP	109 patients; 190 control	Tehran	Non-significant for genotypes; Significant correlation between TACG haplotype (-1722T, -1661A, -318C, +49G) and CRC	P = 0.009	2007 (33)
-1661A/G and +49A/G						
-318C/T	ARMS					
MMP-1	PCR-RFLP	150 patients; 100 control	Tehran	Significant in smoker men	P = 0.02, OD = 2.17; 95% CI: (1.23 - 3.63)	2008 (40)
2G/2G						
MMP3					P > 0.05	
5A/5A	PCR-RFLP	120 patients; 60 control	Tehran/Isfahan	Non-significant for 5A/6A; Significant for 5A/5A genotype and CRC development and metastasis through MMP3 over-expression	P = 0.74, OR = 2.91; 95% CI: (0.94 - 8.98)	2008 (44)
5A/6A						
TNF-α-238	PCR-RFLP	51 patients; 46 control	Tehran	Non-significant	P = 0.474	2008 (30)
-238 G/A						
DNMT1						
Ile311Val, Ala147Gly	PCR/Pyrosequencing	208 patients; 213 controls	Tehran	Non-significant for DNMT1	P > 0.05	2009 (14)
His97Arg						
MGMT						
Pro58Ser, Leu84Phe	PCR/Pyrosequencing		Tehran	Significant association between MGMT polymorphisms and CRC: Arg128Gln; Gly160Arg	P = 0.005; OR 5.53; 95%CI: (2.58 - 7.16); OR 3.04; 95%CI: (1.48 - 6.31)	
Arg128Gln, Ile143Val						
Gly160Arg						

IL-18					P> 0.05	
	-607C/A	Allele-specific PCR	143 patients; 312 control	Shiraz	Non-significant for -607C/A; Significant for -137 G/C	2009 (27)
	-137G/C					
TGF-β1		PCR-RFLP	134 patients; 138 control	Shiraz	Non-significant for-800 G/A; Significant for -509 C/T	P> 0.05 2009 (25)
	-509 C/T					P< 0.035
MTHFR		MS-PCR	175 patients; 231 control	Shiraz	Significant for C677T in MSI+ CRC; Non-significant for A1289C	P = 0.01, OR = 2.6; 95%CI: (1.3 - 5.3) 2010 (43)
	C677T and A1298C					
EXO1		PCR-RFLP	90 patients; 98 control	Tehran	Significant inverse association	OR = 0.192; 95%CI: (0.040 - 0.921) 2010 (15)
	Leu757Pro					
VDR		PCR-RFLP	160 patients; 180 control	Tehran	Significant for *ApaI*	P = 0.014, OR = 2.25; 95%CI: (1.18 - 4.28) 2010 (44)
	ApaI and Taq1					
P53		Allele-specific PCR	132 patients; 163 control	Shiraz	Non-significant	P> 0.05 2010 (34)
	Arg72Pro					
MLH1		PCR-RFLP	140 patients; 135 control	Tehran	Significant	P< 0.005, OR = 6.142; 95%CI: (12.543 - 3.236) 2011 (16)
	rs1799777					
IL-16		PCR-RFLP	260 patients; 405 control	Tehran	Significant for rs11556218TG genotype	P = 0.005, OR = 1.759; 95% CI: (1.191 - 2.598) 2011 (28)
	rs4072111, rs11556218, rs4778889				Significant inverse correlation between CC genotype of rs4778889 T/C SNP and CRC in male subjects	P = 0.045, OR = 1.192; 95% CI: (0.038 - 0.967)
MDR1		ARMS	60 patients; 60 control	Tehran	Significant for G2677T/A	P< 0.05 2011 (45)
	C3435T, C1236T, G2677T/A				Non-significant for C3435T and C1236T	P> 0.05
MDR1		PCR-RFLP	118 patients; 137 control	Mashhad	Significant	P = 0.003, OR = 2.2 2011 (60)
	C3435T					

DNMT3B 39179 G > T	PCR-RFLP	125 patients; 135 control	Isfahan	Significant through DNMT3B overexpression	P = 0.001, OR = 3.993; 95% CI:(1.726 - 9.238)	2011 (37)
VDR *FokI* and *BsmI*	PCR-RFLP	452 patients; 452 control	Tehran	Non-significant	P > 0.05	2011 (61)
P53 Arg72Pro	Nested PCR- RFLP	145 patients; 140 control	Isfahan/ Chaharmahal Va Bakhtiari	Significant	P < 0.01	2011 (35)
LEPR Gln223Arg	PCR-RFLP	173 patients; 173 control	Tehran	Non-significant	P > 0.05	2011 (50)
PD-1 *PD-1.5* C/T (+ 7785)	Nested PCR- RFLP	175 colon cancer patients; 200 control	Shiraz	Significant	P = 0.024, OR = 1.74; 95% CI: (1.15 - 2.62)	2012 (12)
MTHFR C677T	PCR/Pyrosequencing	234 patients; 257 control	Tehran	Significant inverse association between MTHFR 677TT genotype with colorectal cancer, especially at high levels of folate	P < 0.05	2012 (42)
microRNA*-binding sites located in 5 genes: *IL-16*, *CDKN2A* (*p16*), *RAF-1*, *PTGER4*, *ITGB4	PCR-RFLP	249 patients; 394 control	Tehran	Significant for IL-16 (rs1131445)	P = 0.004	2012 (36)
MMP3 Stromelysin 1 5A/5A	PCR-RFLP	120 patients; 100 control	Isfahan	Significant	P = 0.0003	2012 (41)
***PTGS2* (COX2)** 2765G > C	PCR-RFLP	110 patients; 120 controls	Isfahan	Non-significant	P > 0.05	2012 (53)
VDR 24817 G > A	PCR-RFLP	327 patients; 327 Controls	Tehran	Significant with a stronger association for female subjects	P = 0.016,OR = 2.09; 95% CI: (1.15 - 3.78)	2012 (63)
Axin2 C148T	PCR-RFLP	110 patients; 179 controls	Shiraz	Non-significant	P > 0.05	2012 (2)

EGF rs6983267 and rs4444903	PCR-RFLP	115 patients; 120 controls	Isfahan	Significant for rs6983267; Non-significant for rs4444903C	P = 0.001 P = 0.149	2012 (46)
GSTM1, GSTT1, GSTP1* and *CYP2E1	PCR/Pyrosequencing	100 patients; 100 controls	Tehran	Significant for GSTT1; Non-significant for GSTP1, GSTM1, CYP2E1	P < 0.0001	2012 (39)
EXO1 rs1047840 G > A	PCR-RFLP	118 patients; 130 control	Tehran	Non-significant	P > 0.05	2013 (16)
MLH1 I219V and IVS12 -169 C > T	PCR-RFLP	219 patients; 248 controls	Tehran	Significant for I219V; Non-significant for IVS12-169 C > T	P = 0.01 P > 0.05	2013 (17)
PD-1 *PD-1.3* G/A	PCR-RFLP	80 patients; 110 controls	Shiraz	Significant	P = 0.015 for G/G P = 0.0004 for A/A	2013 (22)
CD86 rs17281995	AD	150 patients; 150 controls	Tehran	Significant	P = 0.007	2013 (23)
XPD Lys751Gln	PCR-RFLP	88 patients; 88 controls	Tehran	Non-significant	P > 0.05	2013 (20)
EGF rs76189946	PCR-RFLP	30 patients; 95 controls	Tehran	Non-significant	-	2013 (64)
EGF rs4444903	PCR-RFLP	220 patients; 220 controls	Tehran	Non-significant	P > 0.05	2013 (65)
FoxP3/Scurfin *C*-2383T/rs3761549	PCR-RFLP	108 patients; 187 controls	Shiraz	Non-significant between controls and patients Significant association between C-2383T genotype and metastatic CRC	P > 0.05 P = 0.006 in men; P = 0.03 in women	2013 (29)
SDF-1α G801A	PCR-RFLP	109 patients; 262 controls	Shiraz	Non-significant	P > 0.05	2013 (31)

COX-2 -765G > C	PCR-RFLP	131 patients; 122 controls	Tehran	Significant	P = 0.03	2013 (47)
***IGF-I* (rs6214)** ***IGFBP-3* (rs3110697)** ***INSR* (rs1052371)** ***IRS2* (rs2289046)**	PCR-RFLP	167 patients; 277 controls	Tehran	Non-significant	P > 0.05	2013 (51)
EXO1 rs1635498 (C723R)	PCR-RFLP	111 patients; 121 controls	Tehran	Non-significant	P > 0.05	2013 (17)
IL-22 rs1179251	PCR-RFLP	166 patients; 236 controls	Tehran	Non-significant	P > 0.05	2013 (34)
PTH (rs6256) **CaSR** (rs1801725)	PCR-RFLP	350 patients; 510 controls	Tehran	Non-significant	P > 0.05	2013 (52)
XRCC1 Arg194Trp (rs1799782C > T)	T-ARMS	112 patients; 110 controls	Neyshabur	Non-significant	P > 0.05	2014 (18)
NOD2 (rs3135500)	PCR-RFLP	88 patients; 88 controls	Isfahan	Significant	P < 0.001, OR = 3.1; 95% CI: (1.621 - 5.930)	2014 (24)
SMAD7 rs2337104	TaqMan assay	109 patients; 109 control	Tehran	Non-significant	P > 0.05	2014 (66)
CCR4 ***C1014T*** (rs2228428) ***CCL22*** ***C16A*** (rs4359426)	PCR-RFLP	165 patients; 150 controls	Shiraz	Non-significant	P > 0.05	2014 (32)

CDKN1A rs762624 and rs3176336	PCR-RFLP	150 patients; 150 controls	Tehran	Non-significant	P> 0.05	2014 (67)
IL-17A rs2275913(G197A)	PCR-RFLP	202 patients; 203 controls	Shiraz	Significant association between TT genotype of IL-17F and reduced risk of CRC	P = 0.03,OR = 0.44; 95%CI: (0.21 - 0.94)	2015 (26)
IL-17F rs763780 (*T7488C*)				Significant correlation between AG genotype of IL-17A and increased risk of CRC compared to AA genotype	P = 0.001, OR = 3.638; 95%CI: (1.814 - 7.296)	
IL-23R rs11209026 r s1088967				Non-significant for IL-23 SNPs	P> 0.05	
INS (rs689) ***INSR*** (rs1799817) ***IRS1*** (rs1801278) ***IRS2*** (rs1805097) ***IGF1*** (rs5742612) ***IGFBP3*** (rs2854744)	PCR-RFLP	261 patients; 339 controls	Tehran	Non-significant for INS, IRS1, IRS2, IGF1, and IGFBP3	P> 0.05	2015 (48)
				Significant association between TT + CT genotype and CT genotype of INSR compared with the CC genotype and increased risk of CRC among females	For TT + CT genotype: P = 0.007 OR = 1.93; 95 % CI: (1.20 - 3.11); For CT genotype: P = 0.002 OR = 2.15 95 % CI: (1.31 - 3.53)	
SMAD7 rs12953717 rs4464148	PCR-RFLP	234 patients; 253 controls	Tehran	Significant association between rs4464148 AG genotype and decreased risk of CRC; Significant for rs12953717 T allele	P = 0.034, OR = 0.635; 95% CI: (0.417-0.967) P = 0.037, OR = 1.339; 95% CI: (1.017 - 1.764)	2015 (49)
DNMT3B -149C/T	PCR-RFLP	108 patients; 185 controls	Shiraz	Significant for TT genotype	OR = 3.3; 95% CI: (1.6-6.9)	2015 (38)
XRCC7	PCR-RFLP	166 patients; 260 controls	Shiraz	Significant among persons with positive family history	P = 0.001,OR = 6.88; 95% CI: (2.27 - 20.8)	2016 (19)


G6721T
(rs7003908)