Original Article
http://mjiri.iums.ac.ir
Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2020(7 Jul);34.75. https://doi.org/10.47176/mjiri.34.75

The independent and combined effects of selected risk factors and Arg399Gln XRCC1 polymorphism in the risk of colorectal cancer among an Iranian population

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Received: 30 Jul 2019 Published: 7 Jul 2020

Abstract

Background: Several environmental and genetic factors have contributed to the development of colorectal cancer (CRC). We aimed to investigate the independent and combined effects of some selected risk factors and Arg399Gln XRCC1 polymorphism on CRC.

Methods: A total of 180 patients with CRC and 160 healthy individuals who were matched for sex, age, and place of residence (Northeast of Iran) participated in this case-control study. Before collecting blood samples and filling out questionnaires, a written consent form was obtained from all participants. Genotypes were determined by RFLP-PCR. The comparison of genotype and allele frequencies was performed using p value based on the results of chi-square test. The odds ratios (OR) and 95% confidence intervals (CI) were calculated by employing a logistic regression model. All statistical calculations were performed using SPSS. Each of the 2-sided p values less than 0.05 were considered statistically significant.

Results: The level of literacy, physical activity, consumption of vegetables and fruits, and tea intake of the patients were significantly lower than healthy individuals, but gastrointestinal disorders, family history of cancer, BMI, and fast food consumption were significantly higher in cases than in controls. No significant difference was observed between the 2 groups regarding smoking, opioid addiction, alcohol consumption, diet, fish consumption, and liquid intake, using the kitchen hood, diabetes, and cardiovascular disease. Arg/Gln + Gln/Gln and Arg/Gln genotypes were involved in increased CRC risk (The crude OR =1.781 with a 95% CI of 1.156-2.744 and OR = 1.690 with a 95% CI of 0.787-3.630). Also, Gln/Gln genotype was more frequent in CRC group than in control group. However, none of the risk factors interacted with polymorphism, and thus did not have an effect on CRC.

Conclusion: Some risk factors, such as reducing the consumption of vegetables and fruits or reducing physical activity as well as polymorphism of the XRCC1 Arg399Gln alone, increase the risk of CRC, but they do not interact with each other.

Keywords: Risk factors, Polymorphism, XRCC1, Colorectal cancer

Conflicts of Interest: *None declared*
Funding: *None*

Cite this article as: Mehrzad J, Dayyani M, Erfanian-Khorasani M. The independent and combined effects of selected risk factors and Arg399Gln XRCC1 polymorphism in the risk of colorectal cancer among an Iranian population. *Med J Islam Repub Iran.* 2020 (7 Jul);34:75. https://doi.org/10.47176/mjiri.34.75

Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide. Its prevalence in developed world regions is still higher than in developing countries (1). However, in recent years, due to changes in lifestyle, diet,

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↑What is "already known" in this topic:
Some factors such as red meat, especially its processed varieties, inactivity, and low consumption of vegetables and fruits are effective in causing colorectal cancer. However, the impact of the genetic factor XRCC1 Arg399Gln is contradictory.

→What this article adds:
First, it was found that XRCC1 Arg399Gln polymorphism is associated with colorectal cancer in Khorasan Razavi province. Second, the effects of this genetic factor and environmental factors on the development of this cancer are independent of each other.

[DOI: 10.47176/mjiri.34.75]

or many other factors, the incidence of CRC in developing countries such as Iran has increased. Genetic, demographic, environmental, lifestyle, and type of diet alone or in combination have contributed to this cancer. The effects of these factors on cancer development vary according to individual genetics or metabolic enzymes involved in the detoxification of carcinogens or activation of procarcinogens (2).

Some risk factors for CRC such as age, family history, and genetic differences cannot be changed by the individual and are not controlled, but other factors can be changed and controlled. It has been recognized that diet high in red meats like beef and lamb and processed meats such as sausages play major roles in increasing the risk of CRC. Also, reduced consumption of vegetables and fruits play important roles in increasing the incidence of CRC. Other factors that increase the risk of developing CRC include high-fat foods, obesity, physical inactivity, smoking, and heavy alcohol consumption. Also, the possibility of CRC in people with diabetes mellitus or inflammatory bowel diseases and ulcerative colitis is more than other people (3-9).

One of the most important genetic differences among populations is single-nucleotide polymorphism (SNP). Whenever these SNPs exist in the exons of a DNA repair gene, it may be possible to substitute one amino acid and the protein cannot perform the desired task. Therefore, an SNP may ultimately lead to cancer (10, 11). Of course, genome-wide association studies (GWAS) have demonstrated the relationship between SNPs with several cancers (12). Therefore, researchers have a great interest in finding interactions between carcinogenic risk factors and SNPs associated with cancers, including CRC, and have done some studies in this field (13).

One of the genes and proteins that have been studied for the association of their polymorphisms with cancer is the scaffolding protein X-ray repair cross-complementing group 1 (XRCC1). This protein forms a complex with some other proteins to facilitate DNA repair through base excision repair (BER) mechanism and single-strand break repair processes. One of the important polymorphisms is Arg399Gln XRCC1 (rs25487). The association of Arg399Gln polymorphism with CRC and its interaction with cancer risk factors has been studied in some investigations; however, the results have been contradictory (14-17).

Although relatively large studies have been conducted to investigate the impact of some environmental and demographic factors on CRC, comprehensive studies dealing with the interaction of these factors with the genetics of this cancer are limited (18). Therefore, considering the importance of this topic that can be used to make appropriate decisions and determine the appropriate strategy for preventing CRC, in this study, the independent and combined effects of a large number of risk factors and Arg399Gln XRCC1 polymorphism in CRC were studied in the densely populated areas of Khorasan Razavi province, Iran, including Mashhad, Neyshabur, and their neighboring cities.

Methods

Participants

In this case-control study, 180 individuals with CRC and 160 healthy controls participated. The mean (± SD) age of patients and the control group was 57.9 ± 14.9 and 59.2 ± 13.5 years, respectively. Patients were randomly selected from those with CRC who referred to the Radiotherapy Center and Radiology Center of Reza hospital in Mashhad and hospital of 22 Bahman in Neyshabur. Healthy people were selected from volunteers whose age, sex, and area of residence were matched to patients (Khorasan Razavi province in northeastern Iran). Before collecting blood samples and filling out the questionnaire, the necessary explanations were provided to the participants; then, a written consent form was prepared from all participants. Demographic data and lifestyle factors were collected from all patients and healthy participants through conducting personal interviews (Table 1).

Genotyping

Genomic DNA was isolated from 5 mL whole blood and used for XRCC1 Arg399Gln genotype using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis. For PCR in 20 µL reaction, the following materials were used: 0.5 µL dNTPs (25mM), 2.5 µL PCR buffer (2mM), 1.5 µL $MgCl_2$ (1.5 mM), 1 µL DNA (˜80-100 ng/µL), 0.5 µL of each primer (12.5 pmol), and 0.5 µL Taq DNA polymerase (5 U/µL). The 615 bp XRCC1 PCR products were amplified with the primers 5'- TTGTGCTTTCTCTGTGTCCA -3' (forward) and 5'- TCCTCCAGCCTTTTCTGATA -3' (reverse). PCR products were incubated with 10 U of MspI for 3 hours at 37°C in a mixture of 20 µL. The Gln allele was not digested by this restriction enzyme, while the Arg allele revealed 374 and 241 bp fragments following digestion and agarose gels electrophoresis (Fig. 1) (17).

Fig. 1. Representative gel of XRCC1 Arg399Gln polymorphism, showing MspI digested amplicons. The Arg allele is represented by 374 and 241-bp fragments, while the Gln allele is represented by a 615-bp band. Lane 1, 100-bp ladder; lanes 4, 6, 9, and 11, homozygous (Gln/Gln) genotype (615 bp); lanes 3, 7, 10, and 13, homozygous (Arg/Arg) genotype (374 and 241 bp); lanes 2, 5, 8, and 12, heterozygous (Gln/Arg) genotype (615, 374 and 241 bp).

[DOI: 10.47176/mjiri.34.75]

Statistical analysis

The frequency of genotypes and alleles in different groups were compared using Pearson's p value based on the chi-square test. The crude odds ratios (OR) and 95% confidence intervals (CI) were calculated by employing a logistic regression model. SPSS software (SPSS Inc, Chicago, Illinois) was used for statistical analysis. Each of the 2-sided p values less than 0.05 were considered statistically significant.

Hardy-Weinberg's equilibrium tests were performed in the control group using gene frequency and chi-square test with one degree of freedom. To do so, a software in the following website was used: http://www.oege.org/software/hwe-mr-calc.shtml (19).

Results

The demographic and environmental factors of patients and controls are summarized in Table 1. The level of literacy, physical activity, consumption of vegetables and fruits, and tea intake of patients with cancer were significantly lower than the healthy control, but gastrointestinal disorders, family history of cancer, BMI, and fast food consumption were significantly higher in the cases than the controls. No significant difference was observed between the 2 groups in smoking, opioid addiction, alcohol consumption, diet, fish consumption, and liquid intake, hood in the kitchen, diabetes, and cardiovascular disease.

Frequency distribution of XRCC1 Arg399Gln polymorphism in patients with CRC and controls are presented in Table 2. Given that the p-value was less than 0.05, there

Table 1. Comparison of demographic and environmental factors among 180 patients with colorectal cancer and 160 healthy participants

Factors	Level	Patients (n/%)	Healthy (n/%)	[a]*p* value
Age (years)	≤50	49(27.2)	45(28.1)	1.000
	51-64	63(35.0)	59(36.9)	
	≥65	60(33.3)	56(35.0)	
Gender	Male	77(42.8)	70(43.8)	0.930
	Female	103(57.2)	90(56.2)	
Dwelling	Mashhad	95(52.7)	85(53.1)	0.878
	Neyshabur	34(18.8)	33(20.6)	
	Adjacent areas	51(28.3)	42(26.2)	
Literacy Rate (years)	0	44(26.7)	19(11.9)	0.001*
	1-9	54(32.7)	71(44.4)	
	10-12	46(27.9)	48(30.0)	
	>12	21(12.7)	22(13.8)	
Physical Activity (Type of job)	Inactive	110(70.8)	94(58.8)	0.021*
	Active	50 (29.2)	66(41.2)	
Body Mass Index (kg/m2)	<18.5	13(10.6)	14(8.7)	<0.001
	18.5–24.9	60(48.8)	114(71.2)	
	25–29.9	43(35.0)	28(17.5)	
	≥30	7(5.7)	4(2.5)	
Diet	Vegetarian	10(5.8)	14(8.8)	0.568
	Most Animal foods	56(32.6)	51(31.9)	
	Varied	106(61.6)	95(59.4)	
Kitchen Hood	Yes	78(43.3)	75(46.9)	0.741
	No	95(54.9)	85(53.1)	
Fish (intake/week)	Never	39(24.4)	35(19.9)	0.601
	<1.0	78(48.8)	74(42.0)	
	1.0-1.99	19(11.9)	25(14.2)	
	≥2.0	24(15.0)	42(23.9)	
Vegetable (servings/day)	<1.0	92(75.5)	60(37.5)	<0.001*
	1.0-2.99	30(18.8)	63(39.4)	
	≥3.0	38(23.8)	37(23.1)	
Fruit (servings/day)	<1.0	41(24.7)	93(58.1)	<0.001*
	1.0-2.99	81(48.8)	54(33.8)	
	≥3.0	44(26.5)	13(8.1)	
Fluid (cups/day)	<2	31(18.5)	30(18.8)	0.987
	2-7.99	99(58.9)	93(58.1)	
	≥8	38(22.6)	37(23.1)	
Tea (cups/day)	<4	35(44.9)	89(55.6)	0.049*
	4-6.99	35(44.9)	46(28.8)	
	≥7	8(10.2)	20(12.5)	
Fast Food (servings/week)	0	63(35.4)	107(66.9)	<0.001*
	>1	34(19;1)	41(25.6)	
	1-2.99	25(14.0)	7(4.4)	
	≥3	56(31.5)	5(3.1)	
Smoking	Yes	35(19.4)	30(18.8)	0.900
Opioids Addiction	Yes	16(8.9)	14(8.8)	1.000
Alcohol Drinking	Yes	4(2.2)	5(3.1)	0.740
Gastrointestinal Disorders	Yes	29(17.8)	4(2.5)	<0.001*
Family History of Cancer	Yes	13(9.4)	2(1.2)	<0.001*
Diabetes	Yes	5(2.8)	7(4.4)	0.561
Cardiovascular Disease	Yes	18(10.0)	9(5.6)	0.160

[a]Pearson's p value based on chi-square test. *Statistically significant.

[DOI: 10.47176/mjiri.34.75]

was a relationship between this polymorphism and CRC (This polymorphism causes bowel cancer.).

Arg/Gln+Gln/Gln and Arg / Gln heterozygote genotype were particularly associated with an increased risk of CRC (OR=1.781, with a 95% CI of 1.156-2.744, and OR=1.690, with a 95% CI of 0.787-3.630, respectively).

Table 2. Frequency distribution of XRCC1 Arg399Gln polymorphism in patients with CRC and controls

Genotype	CRC (n = 180)	Controls (n = 160)	CRC versus control	
	n (%)	n (%)	OR (95% CI)	[a]p-value
GG(wild)	83(46.1)	96(60.0)	1	0.037*
AG	78(43.3)	51(31.9)	1.690(0.787-3.630)	
AA(variant)	19(10.6)	13(8.1)	0.956(0.434-2.103)	
AG +AA	97(53.9)	64(40.0)	1.781(1.156-2.744)	0.009*

[a]Pearson's p value based on chi-square test. *Statistically significant.

Table 3. Combined effects of XRCC1 Arg399Gln polymorphism and environmental factors upon colorectal cancer risk

Factors	Level	Arg/ Gln	Arg/ Gln	Gln/ Gln	[a]p-value
Gender	Female	57	32	8	0.930
	Male	46	46	11	
Age (years)	<50	24	22	3	0.734
	50-65	28	26	9	
	>65	29	24	7	
Literacy (years)	0	22	17	5	0.859
	1-9	25	25	4	
	10-12	22	19	5	
	>12	7	12	2	
Dwelling	Mashhad	47	40	8	0.591
	Neyshabur	13	15	6	
	Adjacent areas	23	23	5	
Physical Activity (Type of job)	Inactive	60	52	9	0.077
	Active	18	23	9	
Body Mass Index (kg/m^2)	<18.5	6	6	1	0.592
	18.5–24.9	34	22	4	
	25–29.9	18	18	7	
	≥30	4	3	0	
Diet	Vegetarian	3	4	3	0.208
	Most animal foods	30	22	4	
	Varied	49	47	10	
Kitchen Hood	Yes	35	36	7	0.796
	No	44	40	11	
Edible Oil	Vegetable	8	21	4	0.521
	Animal	14	10	2	
	Varied	61	47	13	
Fish (intake / week)	Never	14	16	5	0.946
	<1.0	12	11	2	
	1.0-1.99	34	31	9	
	≥2.0	21	18	3	
Vegetable (servings/day)	<1.0	30	24	6	0.313
	1.0-2.99	22	31	10	
	≥3.0	20	14	3	
Fruit (servings/day)	<1.0	24	19	4	0.309
	1.0-2.99	31	39	11	
	≥3.0	21	13	4	
Liquid (cups/day)	<2	18	12	1	0.350
	2-7.99	40	46	13	
	≥8	19	15	4	
Tea (cups/day)	<4	18	15	2	0.251
	4-6.99	20	12	3	
	≥7	7	0	1	
Fast Food (servings/week)	0	29	26	8	0.888
	>1	13	17	4	
	1-2.99	13	12	1	
	≥3	26	23	6	
Smoking	Yes	14	16	5	0.636
Opioids Addiction	Yes	9	6	1	0.650
Alcohol Drinking	Yes	3	1	0	0.261
Gastrointestinal Disorders	Yes	65	56	13	0.699
Family History of Cancer	Yes	6	5	2	0.914
Diabetes	Yes	2	3	0	0.684
Cardiovascular Disease	Yes	11	7	0	0.202

[a]Pearson's p value based on chi-square test.

[DOI: 10.47176/mjiri.34.75]

Also, Gln/Gln genotype was more frequent in the CRC group than the control group. The distribution of Arg399Gln polymorphism genotype in the control group was in accordance with Hardy-Weinberg equilibrium ($\chi 2$=1.61; p=0.204).

The combined effects of Arg399Gln polymorphism and environmental factors on the risk of CRC are presented in Table 3. Since all the p values for the selected risk factors were greater than 0.05, none of them interacted with polymorphism, and thus were not effective in the development of CRC.

Discussion

Because age, sex, and area of residence of the control group were matched to those of the case group, the 2 groups were not significantly different with regards to these factors. However, the difference in literacy levels between the 2 groups was significant, as the literacy level of patients with cancer was lower than that of healthy controls. Therefore, low education levels might have influenced the lifestyle and consumption of appropriate food or other factors and have contributed to the development of CRC.

The results of the present study and those of other studies, including the study by Zheng et al (20), showed that the body mass index of people with CRC before their illness was significantly higher than those who did not have cancer. This suggests that patients may have consumed too much high-fat and high-sugar foods and have not had much exercise or activity. In terms of physical activity, most of the patients in the present study had low mobility (inactive) jobs, such as office work or housekeeping, and people with these occupations who had regular physical activity were included in the active group. Therefore, there was a significant difference between the 2 groups in this regard. In general, physical inactivity and overweight were 2 of the main causes of CRC in this area. Various reasons can be noted for overweight and obesity related to CRC. Obesity and even physical inactivity can lead to insulin resistance and hyperinsulinemia, which cause colon cancer (21). Also, physical inactivity increases fecal bile acid concentrations and increases gastrointestinal transit time, and thus can cause CRC (22).

Moreover, the results of this study showed that smoking, opioid addiction (mainly opium), and drinking alcohol did not differ significantly between the 2 groups and did not correlate with the risk of CRC. However, several studies have found a direct relationship between smoking, use of opioids, and alcohol with CRC (3, 23, 24). In this study, the sample size was not large, so the findings may not be very accurate. However, alcohol consumption is low in the country due to legal restrictions and religious reasons. On the one hand, according to a report by an official Iranian news agency (Fars), a senior official at the Iranian Drug Control Headquarters said that Khorasan Razavi is ranked tenth in provincial drug use. On the other hand, another agency (IRNA) reported that about 2.8 million (3%) of the Iran's population are opioid addicts. In addition, the majority of patients and healthy people studied in this study were women; in general, the statistics of women using these substances are low in Iran and according to unofficial reports, the ratio of women to men addicts is 1 to 9. Therefore, to obtain more accurate results, a larger population should be studied.

The diet of the 2 groups was not very different, and most of them ate different kinds of meals. In fact, the number of people with a vegetarian diet was not high in the 2 groups, and it did not differ significantly. However, fruit and vegetable consumption is significantly higher in healthy people than in cancer patients. Therefore, it can be concluded that the high consumption of fruits and vegetables could prevent colorectal cancer. Also, in several other studies, the association between the consumption of fruits and vegetables, in particular legumes, with colorectal cancer, has been inversed (25). Studies have shown that consuming fish reduces gastrointestinal cancers, including colorectal cancer (26). However, due to the fact that Khorasan province is far from the sea and does not have any permanent rivers, the fish are not abundant, and thus fish consumption is low. Therefore, there were no significant differences between the 2 groups in fish consumption. However, fast food consumption has been significantly higher among cancer patients. Almost all other studies have shown that high consumption of red meat, and especially processed meat, leads to CRC due to various causes, including oxides of nitrogen, haem iron, polycyclic aromatic hydrocarbons (PAHs), and heterocyclic amines (27, 28).

The use of a hood is not common in Iranian kitchens, but newly built houses have a hood. However, even those households that have hoods usually do not use it much. Thus, use of hood at home did not differ between the 2 groups. In fact, in our community, there is not much information about the dangers of home-made air pollution and the benefits of using the kitchen hood. Due to the flame of the stove itself and cooking, especially meat, toxic and polluting gases, such as oxides of nitrogen and PAHs, fill the kitchen and home space that must be removed by the hood, especially in apartments (29, 30).

The findings of this study showed no significant difference between the amount of fluids used by patients and healthy controls. Therefore, the amount of fluid used in preventing cancer has not played a role. These results are consistent with those of the study by Simons et al (31) in the Netherlands. However, the use of fluids, especially water, is intended to protect against CRC due to reduced bowel transit time and, the time when carcinogens are in contact with colonic mucosa (32). However, in the case of drinking tea, which is the main drink of the people in the area, the results showed that there is an inverse relationship between tea consumption and CRC, which is consistent with some other studies (33). In fact, cancer patients had consumed less tea. And this reflects the importance of flavonoid antioxidants in tea to prevent cancer. However, in some other studies, the correlation between tea consumption and CRC prevention has not been proven (34).

Various diseases in the gastrointestinal tract can contribute to the development of cancer, including ulcerative colitis (UC) and Crohn colitis, which increase the risk of

[DOI: 10.47176/mjiri.34.75]

colorectal cancer (35). The present study also confirmed the direct correlation between gastrointestinal diseases and CRC. It has been suggested that the increase in the expression of CL-1, a tight junction specific protein, is likely to contribute to CRC in UC (36). Also, results of this study showed that having a family history of cancer is one of the reasons for disease development. It has been scientifically proven that some of the people with CRC may have inherited a mutated allele in a tumor suppressor gene (37). It has been found that approximately 70% of CRC cases are sporadic and the remaining cases are inherited (38). Nevertheless, according to the present results, about 10% of patients had a family history of cancer and had a significant difference with healthy people.

Concerning the association of diabetes with CRC, some studies have estimated that the risk for this type of cancer in type 2 diabetics is 27% higher than in nondiabetic controls (39). However, in this study, which evaluated the number of diabetic patients among CRC patients and compared them with noncancer individuals, there were not many diabetic individuals (about 3%). Even this number was slightly higher among controls (about 4.5%). Therefore, diabetes and CRC did not interact with each other. The reason for this lack of dependency is not clear. Metformin, which has an inhibitory effect on CRC, has been used extensively. It has been mentioned that metformin and (to an extent) thiazolidinediones may prevent the risk of CRC because of their pharmacological effect of increasing insulin sensitivity (40, 41).

Some studies have shown that one of the complications of patients with CRC is cardiovascular disease that occurs due to treatment with materials such as 5-fluorouracil, which may lead to impaired endothelial function (42). However, other studies have indicated that the use of anti-inflammatory substances such as aspirin or statins to treat and prevent cardiovascular disease can prevent CRC (43). Thus, in this study, this interaction was taken into consideration and investigated. The results showed that the number of people with cardiovascular disease was more in the cancer group than in the control group (10% versus 5.6%), although this difference was not significant. Based on the explanation given in the preceding sentences, the findings of this study were predictable and reasonable.

In the present study, based on the results of genotyping, it was determined that XRCC1 Arg399Gln polymorphism is associated with CRC in Khorasan Razavi province. Similarly, in other previous studies, the XRCC1 Arg399Gln polymorphism was associated with an increased risk of CRC (44, 45). The findings of several comprehensive meta-analysis studies also revealed this relationship (46-48). Therefore, it can be assumed that the structure of XRCC1 protein has been altered by the replacement of L-arginine with L-glutamine, and could not repair DNA damage and ultimately contributed to the risk of CRC. The results of an in-silico study also showed that the mutation (Arg399Gln) significantly altered the structural and functional properties of the XRCC1 protein and caused its malfunction (49). However, other studies found no association between this polymorphism and CRC risk (50, 51). Contradictory results of studies can have different reasons, such as differences in genotyping methods, in matching criteria, and in sample sizes, and the presence of other polymorphisms, interaction with environmental factors, and the specific diet of each region, and other differences.

The interaction of risk factors with the gene, the combined effect of the XRCC1 Arg399Gln polymorphism, and any of the risk factors for CRC development, were also studied. According to the results presented in Table 3, none of the selected risk factors were alone in interaction with this polymorphism. In the present study, the effects of several risk factors and polymorphism were not analyzed simultaneously. A study in Japan also reported no positive interaction between the Arg399Gln polymorphism and alcohol abuse or smoking in the development of CRC, although it has been shown that alcohol and Arg280His polymorphism interact with this cancer (17). In another study that investigated this issue in non-small-cell lung cancer, there was no significant interaction between Arg399Gln polymorphism and factors such as age, education level, and average monthly income, family history of cancer, and smoking, but this interaction existed with type of cooking oils (52). In the study of Sujitha et al (49), environmental factors and schizophrenia, despite the fact that individuals showed a tendency to use nicotine, genotype analysis did not reveal a significant relationship between smoking and genotype distribution.

Conclusion

It is generally concluded that some of the selected risk factors such as reducing the consumption of vegetables and fruits or reducing physical activity as well as polymorphism of the XRCC1 Arg399Gln alone increase the risk of CRC, but they do not interact with each other. In fact, these observations indicated that the mutation in the DNA repair system (Arg399Gln) is inherent in the patients and is not related to the risk factors.

Acknowledgments

The results are from a research project approved by Neyshabur Branch, Islamic Azad University. The study protocol was approved by the Islamic Azad University Ethics Committee (approval number: IR.IAU. NEYSHABUR.REC.1395.9). This study was funded by the Neyshabur Branch, Islamic Azad University.

Conflict of Interests

The authors declare that they have no competing interests.

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[DOI: 10.47176/mjiri.34.75]

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[DOI: 10.47176/mjiri.34.75]