Original Article

Evaluation of SEPP1 and Selenoprotein S Gene Polymorphisms (rs7579 and rs34713741) in Relation to Colorectal Cancer Susceptibility in Subset of Iranian Population: A Case–control Study

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Abstract

Background: Colorectal cancer (CRC) is rated as the second cause of cancer death worldwide. Selenium (Se) has antioxidant activity and antitumor effect, especially in colon cancer. This important role occurs through selenoproteins. Low Se intake or low plasma Se and selenoproteins concentrations are associated with higher risk of CRC. rs7579 polymorphism in 3' untranslated region of the *SEPP1* gene can effect on selenocysteine incorporation during protein synthesis and also effect on microRNA –messengerRNA interaction and sequentially change in *SEPP1* expression. rs34713741 polymorphism as a promoter variant in selenoprotein S *(SELS)* gene can effect on *SEIS* expression and finally lead to increased CRC risk. **Methods:** A case–control study using 60 CRC patients and 74 noncancerous counterparts were undertaken in order to determine rs7579 and rs34713741 genotypes using real-time polymerase chain reaction high-resolution melting method. **Results:** We found an association of borderline statistical significance between allele A for rs7579 in *SEPP*1 and CRC risk (adjusted odds ratio = 1.63; confidential interval = 0.99–2.07; $P = 0.05$). The frequency of genotypes rs34713741 of the mentioned polymorphisms was not significantly different between case and control groups ($P = 0.23$ and $P = 0.93$, respectively). **Conclusions:** The results suggest that these polymorphisms probably has not a substantial role in Iranian CRC risk and is not a serious potential factor in risk assessment of mentioned disease among Iranians.

Keywords: *Colorectal cancer, high-resolution melting, polymorphism, selenium, selenocysteine, selenoprotein S gene, SEPPI gene*

Introduction

Colorectal cancer (CRC) remains a substantial public health problem worldwide. Although the incidence and mortality rates of CRC are low in Iran compared with Western countries, current statistics revealing a rapid increase in the Middle East countries, including Iran.[1,2] Several different factors could affect the risk of CRC. It has been proven that risk of CRC could be modulated by nutritional factors. Selenium (Se) is a dietary micronutrient essential for human health. Low Se intake or low plasma Se concentrations are associated with higher risk of a recurrence of colonic tumors.[3,4] Increased intake of Se has been shown to have anticarcinogenic properties through the prevention of DNA damage and oxidative stresses.[5,6] Se is definitely integrated as the amino acid selenocysteine (Sec) into 25 so-called selenoproteins, which have been demonstrated to confer protection from ROS (function in redox signaling and oxidative stress) and subsequently exert important role in cancer.[5,7] Some studies revealed that increase in Se levels lead to elevated selenoprotein biosynthesis and as a consequence suppressed C-reactive protein (CRP) production, thereby attenuating the inflammatory process. As a result, Se and Selenoproteins may cause inhibition of inflammation, by inhibition of nuclear factor kappa B binding to the promoter genes, attenuation of cytokines release, and as a result suppression of CRP synthesis.[8,9] Sec is incorporated into selenoproteins cotranslationally with two specific conserved stem-loop structure in the 3' untranslated region (3'UTR) of the messengerRNAs (mRNAs), designated the Sec insertion sequence (SECIS) element, that requisite to substitute a UGA codon

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from "stop" to Sec.[10,11] Some of these selenoproteins comprise the family of selenoprotein P (*SEPP)* and selenoprotein S (*SELS*).[6,12]

Selenoprotein P (SELENOP also known as *SEP*, *SELP*, *SEPP*, or *SEPP1*) which serves as a Se transport protein, contains at least 50% of the total Se in plasma.[13,14] Furthermore, it has been implicated in extracellular antioxidant activities.[15] Accordingly, Selenoprotein P expression could be associated with resistance to chemotherapy by preventing the induction of ROS in human pancreatic cancerous cells.[16] Expression of *SEPP1* is also dramatically decreased or diminished in a subset of human prostate, cirrhosis, and also in colon tumors and Crohn's disease, whereas *SEPP1* is abundantly expressed in normal colon mucosa and liver.[16-18] *SELS* (SELENOS; also known as *SELS*, *VIMP, SBBI8*, *or SEPS1*) is a protein localized in the endoplasmic reticulum (ER) and in the plasma membrane.[19,20] It may help to defend cells against oxidative damage and apoptosis. *SELS* is involved in the inflammatory response regulation in the ER by removing of unfolded proteins.[21] There are some variants in 3'UTR or promoter that are associated with altered levels of selenoproteins (*SEPP1* and *SELS*) that could affect antioxidant activity, and as a result, increased the likelihood of cancer development. For example, the rs7579 located in the untranslated region (3'UTR) of the SEPP1 gene, thus potentially could affect Sec incorporation during protein synthesis by affecting on SECIS in 3'UTR of this gene.[22] On the other hand, rs7579 in 3'UTR of mRNA may impact microRNAs functions by influence in the secondary structure of 3'UTR and thermodynamic features of hybridization site.[23,24] These single-nucleotide polymorphisms (*SNPs)* also can deregulate expression of the target gene by a change in binding capacity of microRNAs (miRNAs). Investigate on *miRNA* and *SNP* databases (such as miRBase, miRanda, and mirdsnp) shows that this polymorphism (rs7579) is in the vicinity of hsa-miR-3150a, hsa-miR-676, hsa-miR-450a, and hsa-miR-567 binding site that could influence on miRNA-mRNA interaction and sequentially deregulate SEPP1 expression. In this regards, studies demonstrated that this variant (rs7579) is associated with a change in the proportion of *SEPP1* in plasma and could alter the risk of CRC and prostate cancer.[5,25,26] *SElS* gene polymorphism such as rs34713741 is closely related to a variety of malignant tumors such as colorectal and gastric cancer.[12,27] This *SNP* rs34713741 in the *SELS* promoter is functional in that they affect *SElS* expression and plasma levels of inflammatory cytokines.[19] Possible linkage of rs34713741 could have some changes in inflammatory events in the rectum and lead to increased CRC risk since altered inflammatory processes have been correlated with colon tumor development.[12]

Given that selenoprotein Polymorphisms have not studied yet in Iranian population. The aim of the present study was to analyze the potential influence of two functional SNPs, present within selenoprotein genes; *SEPP1* and *SELS* gene in subset of the Iranian population and the risk of sporadic CRC.

Materials and Methods

Study population and sample preparation

This case–control study conducted on 60 patients (33 men and 27 women), [Table 1] and 74 healthy participants (30 men and 44 women), [Table 1]. Participants with no histologically confirmed CRC and no familial history of related cancers were randomly selected from the colonoscopy units of Al-Zahra hospital. Controls were individuals with no evidence of colonoscopy signs of CRC. They were recruited from the same residential areas. Informed consent was obtained from all the participants approved by Isfahan University of Medical Sciences Ethics Committee. The participants were interviewed and data on gender, age, smoking status, nonsteroidal anti-inflammatory drug (NSAID) usage, and physical activity were obtained using a structured questionnaire. Genomic DNA was extracted from 5-ml ethylenediaminetetraacetic acid-anticoagulated peripheral blood samples obtained from the participants by Prime Prep Genomic DNA Isolation Kit (GeNetBio, Korea). The quality and quantity of the extracted DNA was determined by agarose gel electrophoresis and spectrophotometer.

Genotyping of SNP rs7579 (A/G) and rs34713741 (C/T) polymorphism

Genotype analysis of rs7579 and rs34713741 was analyzed by real-time polymerase chain reaction high-resolution

Table 1: Baseline characteristics of colorectal cancer patients and controls in the study

variable	Controls (*n*=74), *n* (%)	Cases (*n*=60), *n* (%)	*P*
Age (mean±SD)	48.35±12.24	57.45±13.18	<0.001*
Gender			
Male	30 (40.5)	33 (55)	0.09
Female	44 (59.5)	27 (45)	
Smoking			
Yes	23 (31.1)	18 (30)	0.89
No	51 (68.9)	42 (70)	
NSAIDs			
Irregular	37 (50)	45 (75)	0.003*
Regular	37 (50)	15 (25)	
Physical activity			
Very low	23 (31.1)	30 (50)	0.04*
Low	29 (39.2)	18 (30)	
Moderate	18 (24.3)	8 (13.3)	
High	4 (5.4)	4 (6.7)	
BMI (kg/m^2), mean±SD	25.58±43.61	26.62±4.81	0.16

*Significant level of less than 0.05. SD: Standard deviation, NSAID: Nonsteroidal anti-inflammatory drug, BMI: Body mass index

melting method (HRM) using HOT FIREPol® EvaGreen® HRM Mix (Solis BioDyne) and Rotor-Gene 6000 analyzer device. The forward sequence primers of rs7579 have 5'-TTATACCCACAGAAGCCAGTC-3' and the reverse have 5'-AGTAGATTTCTCCATGTTTGC AC-3'. The forward sequence primers of rs34713741 have 5'-CTTCCGGTGCGCTCCTAC-3', and the reverse have 5'-GGCGACCACTGACTTCCTT-3'.

The thermal profile of the reaction is as follows: hold phase at 95°C for 15 min, 40 cycles of 95° C for 15 s, 57°C for 30 s (for rs7579), 60°C for 30 s (for rs34713741), and 72°C for 20 s, Finally, for HRM analysis, the temperature profile was increased from 60°C to 95°C at the rate of 0.2°C/s. Melting curves were normalized between the two temperature ranges defining the samples with known genotypes as standard. To assess sample genotypes to utilize them in HRM analysis as standard genotypes, some samples were subjected to direct sequencing for further confirmation.

Statistical analysis

SPSS Windows software (version 22.0; SPSS, Chicago, IL, USA) was used for statistical analysis. Hardy–Weinberg equilibrium was tested among cases and controls using Pearson's Chi-square (χ^2) test. Logistic regression analysis was accomplished to investigate genotype and allele frequency differences between cases and controls and calculate specific odds ratios (ORs), 95% confidential intervals (CIs), and *P* values. The differences in demographic characteristics distributions between CRC patients and the control group were compared with the *t*-test and the χ^2 test.

Results

Our study population consisted of 60 CRC patients and 74 CRC-free individuals. Demographic characteristics data of the participants, including age, gender, body mass index (BMI), physical activity, smoking, and (NSAIDs) consumption are summarized in Table 1. There were no statistically significant differences between patients and controls in terms of sex, BMI, and smoking status ($P = 0.09$, $P = 0.16$, and $P = 0.89$, respectively). A statistically significant difference was observed for physical activity ($P = 0.04$). Furthermore, individuals in the control group were more NSAID user compared with sporadic CRC cases ($P < 0.003$).

Genotyping data were in Hardy–Weinberg equilibrium for both SNPs in the tested groups. There was no significant difference for the genotype frequencies of rs7579 and rs34713741 between patients and controls ($P = 0.23$ and $P = 0.93$, respectively). The frequencies of GG, AG, AA genotypes of rs7579 in the control group were 54.1%, 31.1%, and 14.9%, respectively, and the genotype frequencies in the case group were 40%, 36.7%, and 23.3%, respectively. The frequencies of CC, CT, TT genotypes of rs34713741 in the control group were 54.1%, 32.4%, and 13.5%, respectively, and the genotype frequencies in the case group were 56.7%, 31.7%, and 11.7%, respectively.

Table 2 in allele distribution analysis, we found an association of borderline statistical significance between allele A for rs7579 in SEPP1 and CRC risk (adjusted OR = 1.63; CI (0.99–2.07); $P = 0.05$). Furthermore, we studied the allelic frequency distribution of rs34713741 C/T polymorphism among the control and case participants. We could not find any association between allele distribution and risk of CRC; $P = 0.69$. The distributions of genotype and allele frequency are shown in Tables 2 and 3.

Discussion

The results presented here show that for two *SNP*s in selenoprotein genes, rs7579 in *SEPP1* gene, and rs34713741 in SELS gene, there were no differences in genotype frequency between patients with CRC and healthy controls in an Iranian population. For rs7579 in *SEPP1*, the allele frequencies analysis indicated that the allele frequency of the A was higher in patients than in controls, there was an association of borderline statistical significance.

Despite of our nonsignificant results, it is could not underestimate that selenoprotein genes polymorphism is thoroughly related to a variety of malignant neoplasms,[28] especially CRC that could be modulated by nutritional factors principally Se.[29] Se, through the selenoproteins,

Table 2: Association between genotypes and allele frequency with colorectal cancer risk (rs7579)

variable	Case, *n* (%)	Control, *n* (%)	*P*	OR (95%CI)
Genotype frequency				
GG	24 (40)	40 (54.1)	0.23	1.76 (0.88-3.51)
AG	22 (36.7)	23 (31.1)		
AA	14 (23.3)	11 (14.9)		
Allele frequency				
G	70 (58.3)	103 (69.6)	0.05	1.63 (0.99-2.07)
A	50 (41.7)	45 (30.4)		

OR: Odds ratio, CI: Confidence interval

Table 3: Association between genotypes and allele frequency with colorectal cancer risk rs34713741

variable	Case, *n* (%)	Control, *n* (%)	*P*	OR (95%CI)
Genotype frequency				
CC	34 (56.7)	40 (54.1)	0.93	1.18 (0.42-3.32)
CT	19 (31.7)	24 (32.4)		
TT	7 (11.7)	10 (13.5)		
Allele frequency				
C	87 (72/5)	104 (70/3)	0.69	1.12 (0.65-1.90)
T	33 (27/5)	44 (29/7)		

OR: Odds ratio, CI: Confidential interval

might exert a major role in colonic epithelial cells response to oxidative situations and that a combination of low Se intake and SNP in selenoprotein genes can ruin that impress and so cause an increased risk of neoplastic transformation.[30,31] A SNP in the *SELS* promoter at position-105 (rs34713741) is regarded as having functionally substantial roles to change the level of expression of the selenoprotein.[19] Previous studies showed an association between a genetic variant rs34713741 in the *SELS* gene promoter and CRC risk.[12] Since the risk of CRC elevated with gut inflammation,[32] it is possible that the correlation of rs34713741 with CRC risk indicates an effect of *SElS* on inflammation. In accordance, genotyping for rs34713741 SNP in *SELS* in the Czech (832 cases and 705 controls) and Korean (827 cases and 727 controls) participants has shown that T allele is a positive modulator of CRC risk.[12,26] The same results obtained from these two distinct populations firmly suggest that regardless of other genetic and lifestyle factors, this SNP located in *SELS* promoter affects CRC risk. There were other some reports that evaluated the risk of mentioned polymorphism in different malignancies, Mao H and *et al*., indicated the linkage of rs34713741 with gastric cancer risk.[27] Allele T of *SELS* rs34713741 polymorphism is significantly associated with an increased risk of gastric cancer in Chinese population. In Hunan Han population, the relative risk of gastric cancer in T allele was 1.62 times of CC genotype.[27] In another study on the Korean population, the presence of T allele for rs34713741 in *SELS* is associated with higher risk of rectal cancer in female participants, while this polymorphism is not associated with colon cancer risk.[12]

Selenoprotein P (*SEPP*), Se carrying molecule, transports hepatic Se to tissues to provide a synthesis of other selenoproteins,[33] hence genetic variations in *SEPP1* would be expected to lead to altered Se metabolism in various tissues. Furthermore, it is well known that, *SEPP1* is one of the candidate genes involved in oxidative stress responses.[34] Oxidative stress is a common phenomenon in many types of cancer cells and related to oncogenic stimulation. Thus, the genetic variation of this gene could alter the susceptibility to oxidative stress and subsequent cancer incidence. A G/A SNP within the 3'-UTR (rs7579) lead to alanine to threonine amino acid replacement and modified the proportion of 50 and 60 kDa isoforms of *SEPP* in the plasma[35] and lead to alternation of Se metabolism in different organs. The study revealed that participants having at least one A allele for rs7579 subjected to an increased risk for CRC. This SNP was significantly associated with advanced adenoma risk in the US population.[36] A European case–control cohorts, results showed an increased incidence for prostate and CRC in minor alleles (AA) carriers of in *SEPP1* rs7579 genotype.[26] A similar borderline significant result was seen in US physicians for imputed rs7579; the rare allele was associated with increased prostate cancer risk,[37] but the results showed that this SNP is not associated with CRC in the Korean population and breast cancer incidence in the Danish population.[12,38] The results from different previous studies highlight the key role of selenoproteins and Se in colorectal function and in preventing the cells from undergoing malignant transformation. However, we found little association between one of these SNPs and risk of CRC (rs7579 allele frequency; $P = 0.05$). Thus, further evaluation of the role of mentioned SNPs population with an expanded population size would help to reach a decisive conclusion regarding the efficacy of this polymorphism and may demonstrate its utility as a CRC screening biomarker. The failure to discover any association between genotype for rs34713741 and rs7579 and susceptibility to CRC may reflect the small size of the population examined in that study and the results require to be confirmed in different populations and different subgroup in order to attain more trustworthy results.

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Conflicts of interest

There are no conflicts of interest.

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