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Original Article

Single nucleotide polymorphism rs10889677 in miRNAs Let-7e and Let-7f binding site of IL23R gene is a strong colorectal cancer determinant: Report and meta-analysis

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ABSTRACT

Single nucleotide polymorphisms (SNPs) in the recognition sites of microRNAs (miRNAs), located at 3′ untranslated region (UTR) of mRNAs, interfere with posttranslational gene regulation. Deregulation of genes may contribute to some disease susceptibility including colorectal cancer (CRC). In the present study, in a case-control setup, 167 CRC patients and 161 control subjects were studied for allele and genotype frequency of rs10889677 polymorphism in miRNAs Let-7e and Let-7f binding sites at 3′ UTR of IL23R gene using PCR–RFLP assay. Also, related articles were retrieved from MEDLINE, Cochrane review, Google Scholar and Scopus databases for meta-analysis study. According to our results, AA genotype of SNP rs10889677 was significantly correlated with increased risk of CRC (OR = 3.10; 95% CI [1.86–5.18]; P: < 0.001). In a meta-analysis on 10 risk estimates for the CC versus AA genotype, we found an inverse association between CC SNPs and risk of all cancer (OR = 0.59; 95% CI [0.49–0.71]; $P < 0.001$). In conclusion, our results demonstrate that rs10889677 polymorphism is significantly associated with CRC risk.

Introduction

Colorectal cancer (CRC) rated as the third diagnosed malignancy and the fourth most common cause of cancer mortality worldwide, with an estimated 1.2 million new cases and 608,700 related death in 2008 [1,2]. Although the incidence of CRC is lower in Asian than Western countries, recent studies have shown increasing rates of CRC in Iran [3–6]. Genetic syndromes like Lynch and FAP, together with positive family history constituting up to 30% of CRC susceptibility; however common genetic variants present in individuals' genome considered as the main genetic risk of CRC. Recent genome-wide association studies (GWAS) determined multiple CRC-related single nucleotide polymorphisms (SNPs) [7–9]. Many important mammalian genes, including those regulating cell cycle progression, apoptosis and tumor biogenesis inhibitors are subjected to posttranscriptional regulation via interaction with microRNAs (miRNAs) that bind to their specific recognition elements known as seed sequences located at 3′untranslated region (UTR) of mRNAs [10,11]. Each mRNA can simultaneously possess conserved seed sequences for several miRNAs where the occurrence of any SNPs could disturb thermodynamic features of miRNA-mRNA hybridization site [12–14]. Actually, growing number of studies have suggested that miRSNPs constitute a promising novel class of polymorphic variations worth investigation, with the potential of opening new areas of research in cancer biology and clinical oncology [15,16]. Moreover, it has been suggested that miRSNPs could be employed as useful biomarkers in the study of disease progression, patient prognosis, and treatment efficacy of cancer [17,18].

Association between inflammation and tumor biogenesis especially in CRC is well-characterized. Inflammation is stimulated by cytokines and chemokines, which can be produced often by the cells such as macrophages, B and T lymphocytes that recruited to the tumor microenvironment [19,20]. Several studies reported that the interleukin-23 receptor (IL23R) interact with IL-23 which is essential for retaining the T-helper 17 (Th17) response. Th17 induces the release of proinflammatory cytokines mostly through IL17 secretion. There is a growing body of evidence to suggest that IL-23 inhibits the immunesurveillance activity mediated by

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$CD8^+$ T cells and accelerate tumor proliferation as well. Therefore, deregulation of IL23R may affect an individual's cancer risk [20–23]. As previously mentioned, SNPs in miRNA binding site can alter the miRNA regulatory function affecting target mRNA expression [10,24,25]. Based on previous studies and evaluation of SNP and miRNA databases (e.g., miRBase, miRanda and mirdSNP), rs10889677 variant located at 3′UTR of IL23R gene was selected for this study. This variant is in miRNAs Let-7e and Let-7f binding site [26]. Previous studies indicated that this SNP is correlated with IL23R gene expression [26,27]. Also, rs10889677 is reported to be associated with colorectal, bladder and breast cancer risks and inflammatory bowel disease, but the conflict of results are evident [20,21,26,28,29]. Here we evaluated the correlation of SNP rs10889677 with sporadic CRC. Correlation between environmental and lifestyle risk factors with CRC incidence and interrelationship between some of these risk factors and genotypes were evaluated. Also, current study would provide information on the pathological findings (167 items). Finally, we carried out a meta-analysis for the association between SNP rs10889677 with all cancer risk.

Materials and methods

Study population

For this case control study, during 2-year period from mid-2014 to mid-2016, totally 328 participants were selected amongst patients referred to the colonoscopy centers of the University Hospitals, Isfahan, Iran. All CRC cases (167) were first diagnosed by colonoscopy and then followed their pathology report for the ultimate confirmation of their colonoscopy based CRC diagnosis. For the controls (161), also selections have been made based on colonoscopy examination. All participants have signed an informed consent form based on the Isfahan University of Medical Sciences Ethical Committee instructions. To eliminate any established genetic risk factor for CRC, patients were individually interviewed to select cases with sporadic CRC without positive history of familial cancers. Anthropometric characteristics as well as other parameters believe to influence the CRC susceptibility risk including gender, age, BMI, physical activity, smoking status and NSAIDs consumption were registered by a structured questionnaire. Also information about pathological and clinical characteristics such as location, type, grade, stage, tumor size and lymph node status collected from documented pathology report.

SNP selection

Fig. 1 summarizes the course of SNP selection in IL23 and IL23R gene. As it is evident, SNPs located at 3′UTR of the target genes were considered for this study. Minor allele frequency higher than 0.05 and being located at miRNAs regulatory elements (MREs) constituted other two criteria considered for SNP selection. According to these criteria only SNP rs10889677 located within the miRNAs Let-7e and Let-7f binding site of IL23R gene showed our defined characteristics and hence selected for this study.

Genotyping of the selected polymorphism

Genomic DNA was extracted from peripheral blood using PrimePrep Genomic DNA Isolation Kit (GeNetBio, Korea). The quality and quantity of the extracted DNA was assessed by agarose gel electrophoresis and spectrophotometry. SNP genotyping performed by polymerase chain reaction– restriction fragment length polymorphism (PCR–RFLP) method. PCR was performed in a total volume of 25 μL, including 2.5 μL 10x PCR buffer, 1 mM $MgCl_2$, 200 μM each dNTPs, 0.2 μM each primer (forward 5′-CATGTTTTCATTTCCCTTGGA −3′) and (reverse 5′- TGTGCCTGTATGTGTGACCA −3′), 100 ng of genomic DNA, and 1.5 U of Taq DNA polymerase. Thermal cycling was included an initial denaturation of 94 °C for 5 min and then 34 cycles including 94 °C, 57 °C, and 72 °C, all for 30 s and a final extension at 72 °C for 5 min. RFLP was carried out using the *MnlI* restriction endonuclease enzyme. Subsequently digestion products were differentiated on the agarose gel in order to determine the genotype of the samples. Fragment sizes of 189 and 60 bp indicated the presence of CC homozygous, a single 249 bp fragment displayed the AA homozygous and three fragments of 249, 189 and 60 bp indicated the presence of AC heterozygous. Confirmation of the RFLP based genotyping was done by direct sequencing of randomly selected samples (10% of samples) with different genotypes. All mandatory applicable laboratory health and safety procedures related to this research have been fully observed and practiced.

Statistics

Genotype frequencies in case and controls were tested for Hardy–Weinberg equilibrium using χ^2 test. Associations between IL23R (rs10889677) polymorphism with susceptibility to sporadic CRC was examined by logistic regression analysis. Correlation among this polymorphism and CRC was evaluated using odds ratios (ORs) and 95% confidence intervals (CIs). The significance level was set at $P < 0.05$. The difference in demographic and lifestyle characteristics distribution such as age, gender, smoking status, BMI and NSAIDs consumption, assessed by Pearson χ^2 test for categorical variables and *t*-test for continuous variables. Mann–Whitney test was used to compare physical activity between CRC and control groups. All statistical analyses were performed using $SPSS_{22}$ (SPSS, Chicago, IL., USA).

Meta-analysis

Methods and search strategy

We had intended to summarize data on correlation between single nucleotide polymorphism rs10889677 in miRNAs Let-7e and Let-7f binding site of IL23R gene and cancer risk.

In this field, we conducted a literature search, of MEDLINE, Cochrane review, Google Scholar and Scopus databases for related studies. The search terms were "Neoplasms" (MeSH) AND "Single Nucleotide Polymorphisms" (MeSH) AND "IL23R" (tiab) AND "miRNAs Let-7e" (tiab) AND "miRNAs Let-7f" (tiab). Studies were eligible for inclusion in the current analysis if: (i) single nucleotide polymorphism rs10889677 in miRNAs Let-7e and Let-7f binding site of IL23R gene was assessed; (ii) their final outcome was cancer risk; and (iii) estimates of relative risks (RR), hazard ratios (HR) or odds ratio (OR) with corresponding 95% CI for the cancer risk among SNP genotypes were provided. Two investigators extracted data independently, and any discrepancies were resolved by discussion.

Statistical analysis

Odds ratio were used as the measure correlation between single nucleotide polymorphism rs10889677 in miRNAs Let-7e and Let-7f binding site of IL23R gene and cancer risk. Meta-analyses were performed using the random-effects model that was presented as forest plots with 95% CI. The statistical heterogeneity of the studies was calculated with the Cochran's Q and I-squared index (I-squared > 50% was considered as significant heterogeneity). To assess the impact of possible factors on pooled effect size and heterogeneity, subgroup analyses were performed. Publication bias was assessed using the funnel plot method and Begg's test.

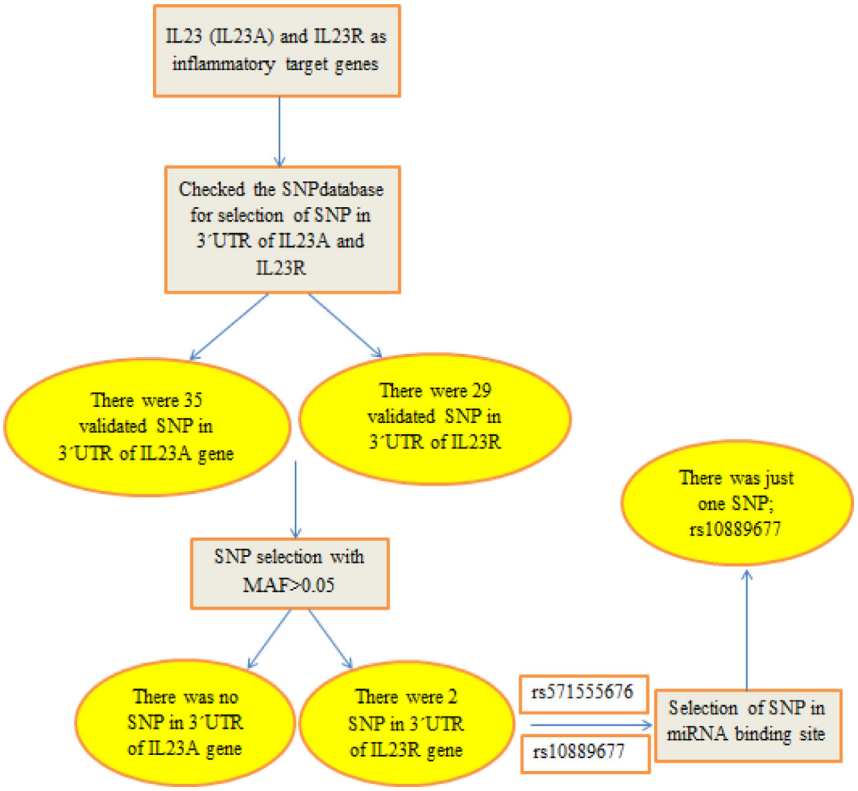

Fig. 1. SNP selection algorithm.

Statistical analyses were conducted using the statistical software package Stata version 11.2. P values less than 0.05 were considered statistically significant.

Result

Demographic, lifestyle and tumor characteristics

Our study was intended to evaluate the relationship between rs10889677 single nucleotide polymorphism located at 3′ UTR of IL-23R gene and CRC susceptibility. In this case control study 167 confirmed CRC patients (85 male and 82 female) and 161 (67 male and 94 female) unaffected individuals were selected amongst those referred to colonoscopy units of our university hospitals. Mean age in case and control groups were 56.8 ± 11.24 and 56.3 ± 10.94 respectively. Statistically no difference was exist between the cases and controls in terms of sex (*P*: 0.09) and age (*P*: 0.68). There is considerable difference between case and control groups regarding physical activity and BMI (*P*: < 0.001 and *P*: 0.04 respectively). Also we found that healthy subjects in control group have more NSAIDs consumption compared with CRC patients group (*P*: 0.003). However there was no statistically significant difference between patients and controls in terms of smoking status (*P*: 0.76). Distribution of patients by the site of the primary tumor revealed that 38(22.8%) of the tumors were right-sided, 10(6%) originated from the transverse colon, and 27(16.2%) originated from the descending colon, whereas 56 patients (33.5%) were found to have a cancer that originated from the sigmoid colon. Study population and tumor characteristics are summarized in Tables 1 and 2 respectively.

Genotype and allele distribution

Genotype distribution of rs10889677 polymorphism in cases and control group was in agreement with Hardy–Weinberg equilibrium. Significant association was found between AA genotype and CRC risk (*P*: < 0.001). The frequency of AA, CC and AC genotypes were 17.4%, 29.8% and 52.8% in controls and 39.5%, 20.4% and 40.1% in cases respectively. Regarding allele distribution, A allele was more frequent in case group compared to that of controls (*P*: < 0.001). The details of genotypes and allele frequency are shown in Table 3.

Table 1
Characteristics of CRC patients and controls selected for present study.

	Controls (*N*: 161)	Cases (*N*: 167)	*P* value
Age (mean ± SD)	56.3 ± 10.94	56.8 ± 11.24	0.68
Gender			
Male	67(41.6%)	85(50.9%)	0.09
Female	94(58.4%)	82(49.1%)	
Smoking			
Yes	26(16.1%)	29(17.4%)	0.76
No	135(83.9)	138(82.6)	
NSAIDs			
Irregular	124(77%)	149(89.2%)	0.003*
Regular	37(23%)	18(10.8%)	
Physical activity			
Low	93(57.8%)	125(74.9%)	<0.001*
Moderate	43(26.7%)	36(21.6%)	
High	25(15.5%)	6(3.6%)	
BMI (mean ± SD) kg/m^2	25.4 ± 4.00	26.4 ± 4.26	0.04*

* : *P* value < 0.05.

Findings from meta-analysis

We identified 10 database from 6 studies including gastric cancer [30], esophageal squamous cell carcinoma [31], breast [21,32], lung (*n* = 2) [32], nasopharyngeal (*n* = 2) [32], ovarian [33] and bladder [20] that met the inclusion criteria of this meta-analysis. The association between CC and CA rs10889677genotypes in miRNAs Let-7e and Let-7f binding site of IL23R gene compared to the AA SNPs and cancer risk was assessed. In this meta-analysis on 10

Table 2
Patients' demographics and tumor characteristics.

Characteristics	Total patients no (%)	Male no (%)	Female no (%)
Total patient	167(100%)	85(50.9)	82(49.1)
Mean age ± SD	64.11 ± 12.62	63.40 ± 12.71	64.84 ± 12.56
Location 1			
Cecume	4(2.4%)	3(3.5%)	1(1.2%)
Ascending	38(22.8%)	21(24.7%)	17(20.7%)
Transverse	10(6%)	7(8.2%)	3(3.7%)
Descending	27(16.2%)	17(20%)	10(12.2%)
Sigmoid	56(33.5%)	22(25.9%)	34(41.5%)
Rectum	32(19.2%)	15(17.6%)	17(20.7%)
Location 2			
Proximal[1]	52(31.1%)	31(36.5%)	21(25.6%)
Distal[2]	83(49.7%)	39(45.9%)	44(53.7%)
Rectal[3]	32(19.2%)	15(17.6%)	17(20.7%)
Grade			
Well	78(46.7%)	41(48.2%)	37(45.1%)
Moderate	69(41.3%)	30(35.5%)	39(47.6%)
Poorly	20(12%)	14(16.5%)	6(7.3%)
Mean size ± SD	4.92 ± 2.03	5.13 ± 2.02	4.69 ± 2.03
Lymph node status			
0	122(73.1%)	63(74.1%)	59(72%)
1–3	31(18.6%)	15(17.6%)	16(19.5%)
≥4	14(8.4%)	7(8.2%)	7(8.5%)
Stage			
I	59(35.3%)	33(38.8%)	26(31.7%)
II	50(29.9%)	25(29.4%)	25(30.5%)
III	32(19.2%)	17(20%)	15(18.3%)
IV	**26(15.6%)**	**10(11.8%)**	**16(19.5%)**

[1] : Ascending + Cecume + Transverse.
[2] : Descending + Sigmoid.
[3] : Rectum.

risk estimates for the CC versus AA genotype, we found an inverse association between CC SNPs and risk of all cancer (OR = 0.63; 95% CI [0.48–0.78]; $P < 0.001$; Fig. 2). Publication bias was not observed by Begg's test ($P = 0.14$). There were not asymmetries in funnel's plots in the current analyses. However, a significant between-study heterogeneity was found (I-squared = 67.5%, $p = 0.001$).

We used subgroup analysis to find out sources of heterogeneity (Fig. 3) through fixed effects. The subgroup analysis by cancer type resulted in resolve the heterogeneity and the test of between-subgroup heterogeneity was significant ($P = 0.001$). Through subgroup analysis by 4 studies in gastro-intestinal cancer, we found that a significant protective effect in CC compared to AA polymorphism in the mentioned cancers risk. (OR = 0.56; 95% CI [0.43–0.69]; $P < 0.001$). Same results was obtained by subgroup analyses based on breast and ovarian cancer, (OR = 0.61; 95% CI [0.49–0.74]; $P < 0.001$) and lung cancer, (OR = 0.48; 95% CI [0.31–0.64]; $P < 0.001$). However, the CC genotype was significantly associated with bladder cancer in the Tielong Tang study (CC vs AA OR = 1. 82; 95% CI [1.20 −2.44]; $P < 0.001$). similarly, individuals with CA variant of rs10889677 in miRNAs Let-7e and Let-7f binding site of IL23R gene compared with AA had a significant less odd for cancer among 7 database. (OR = 0.79; 95% CI [0.73–0.85]; $P < 0.001$; Fig. 4). Test of between-studies heterogeneity was not significant (I-squared = 0.0%, $P > 0.05$). Funnel plots and Begg's test ($P = 0.54$) indicated no publication bias in studies.

Discussion

It is a well-known fact that chronic inflammation contributes to cancer development [19,22]. Persistent exposure to inflammatory factors such as cytokines and chemokines lead to increased cell proliferation, mutagenesis, oncogene activation and angiogenesis [20,34]. Interleukin 23 (IL-23) being proinflammatory cytokine has a great impact on tumor development by inducing inflammation in the tumor microenvironment [35,36]. Several studies reported that interactions between IL23 with its receptor (IL-23R) play an important role in Th17 response maintenance. Th17 induces release of proinflammatory cytokines mostly through IL17 secretion and finally this path increases inflammation. IL23R considered as an important contributor in chronic inflammatory diseases by triggering the differentiation of Th17. The Th17 pathway is important for the acute microbial infections [37], and any irregularity in the pathway is associated with inflammatory bowel disease (IBD) [38–40]. IL23R signaling pathway involved interaction between IL23Rα and IL12Rβ1 at cell surface which is activated by binding IL23 cytokine [41,42] (Fig. 6). There are plenty of evidences that suggest a pivotal role for IL23R in chronic inflammation [37,43,44]. The mouse studies clearly indicate that inflammatory cytokines including TNF, IL-6, IL-11, IL-17, IL-21, IL-22, and IL-23 is of great importance in the pathogenesis of mainly CRC as well as other cancers [36,45]. These studies also suggest that inhibitors of inflammatory cytokine production, receptor binding, or receptor signaling are quite efficient in the treatment or even prevention of CRC. Also previous reports demonstrated that antitumor and antimetastatic functions of natural killer cells (NK cells) are repressed by IL-23 and consequently IL-23R [21–23]. There are several lines of evidences for deregulation of IL23 and IL23R in multiple malignancies [27,29]. Two main pathways are usually considered for gene aberrant expression; genetics and epigenetics determinants. One of the important epigenetic regulators in human genome are microRNAs [46]. Several miRNAs including Let-7e and Let-7f have putative miRNA binding sites in 3′UTR of IL23R. These two miRNAs can down-regulate IL-23R gene expression [21,26,47]. miR-let-7f can block IL-23R expression, resulting in the down-regulation of the IL-23/IL-23R pathway and downstream IL-17 production.

Previous studies indicated that rs10889677 A>C SNP is correlated with genetic susceptibility to various tumors such as lung, bladder, breast, colorectal and ovarian [20,33,48]. Here we report our findings about the correlation of SNP rs10889677 and sporadic CRC in Iranian population conducted in a case control setup. Homozygous AA genotypes (Adjusted OR: 3.10, 95% CI: 1.86–5.18) and A allele (Adjusted OR: 1.89, 95% CI: 1.38–2.58) were more frequent in CRC patients. However there are instances like bladder and ovarian cancers that CC genotypes and C alleles proposed to act as risk allele [20,33]. On the other hand our results were consistent with several previous studies conducted in Tunisia and

Table 3
Association between genotypes and allele frequency with CRC risk.

	Case no (%)	Control no (%)	*P* value	OR (95%CI)
Genotype frequency				
CC	34(20.4%)	48(29.8%)	<0.001*	3.10 (1.86–5.18)
AA	66(39.5%)	28(17.4%)		
AC	67(40.1%)	85(52.8%)		
Allele frequency				
A	199 (59.6%)	141(43.8%)	<0.001*	1.89(1.38–2.58)
C	135(40.4%)	181(56.2%)		

* : *P* value < 0.05.

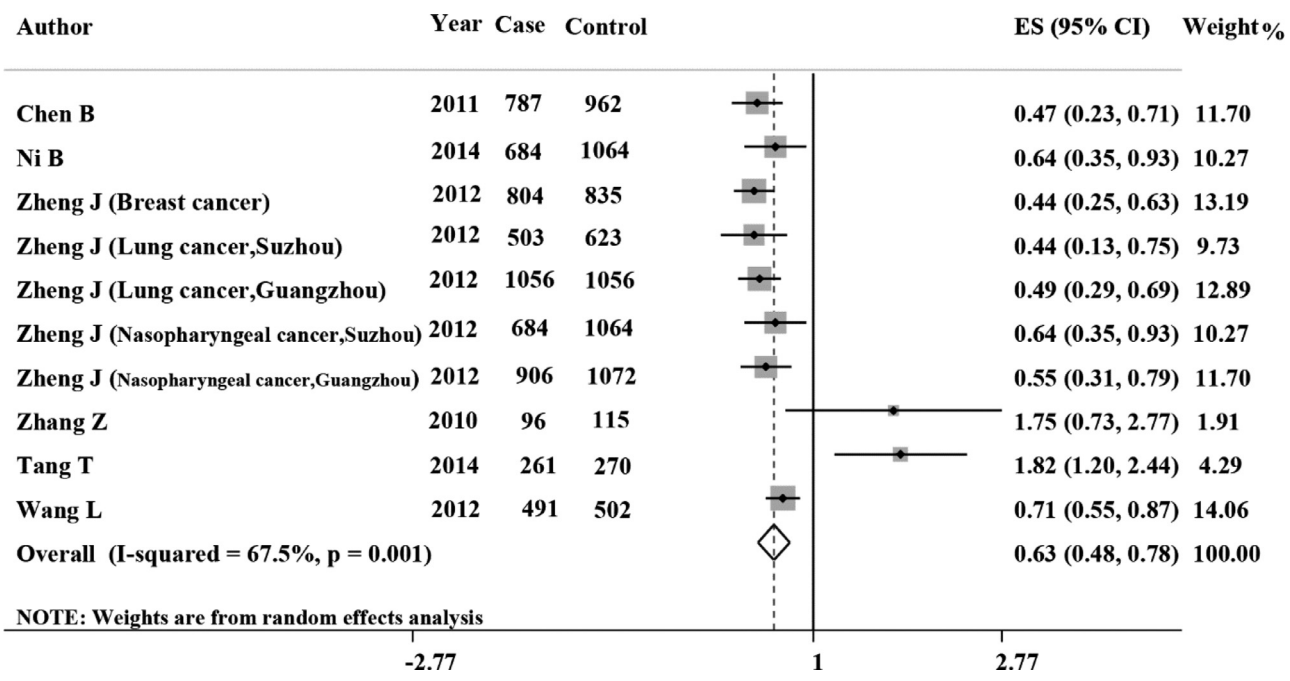

Fig. 2. Odds ratio of cancer among individuals with CC genotype compared those with AA genotype.

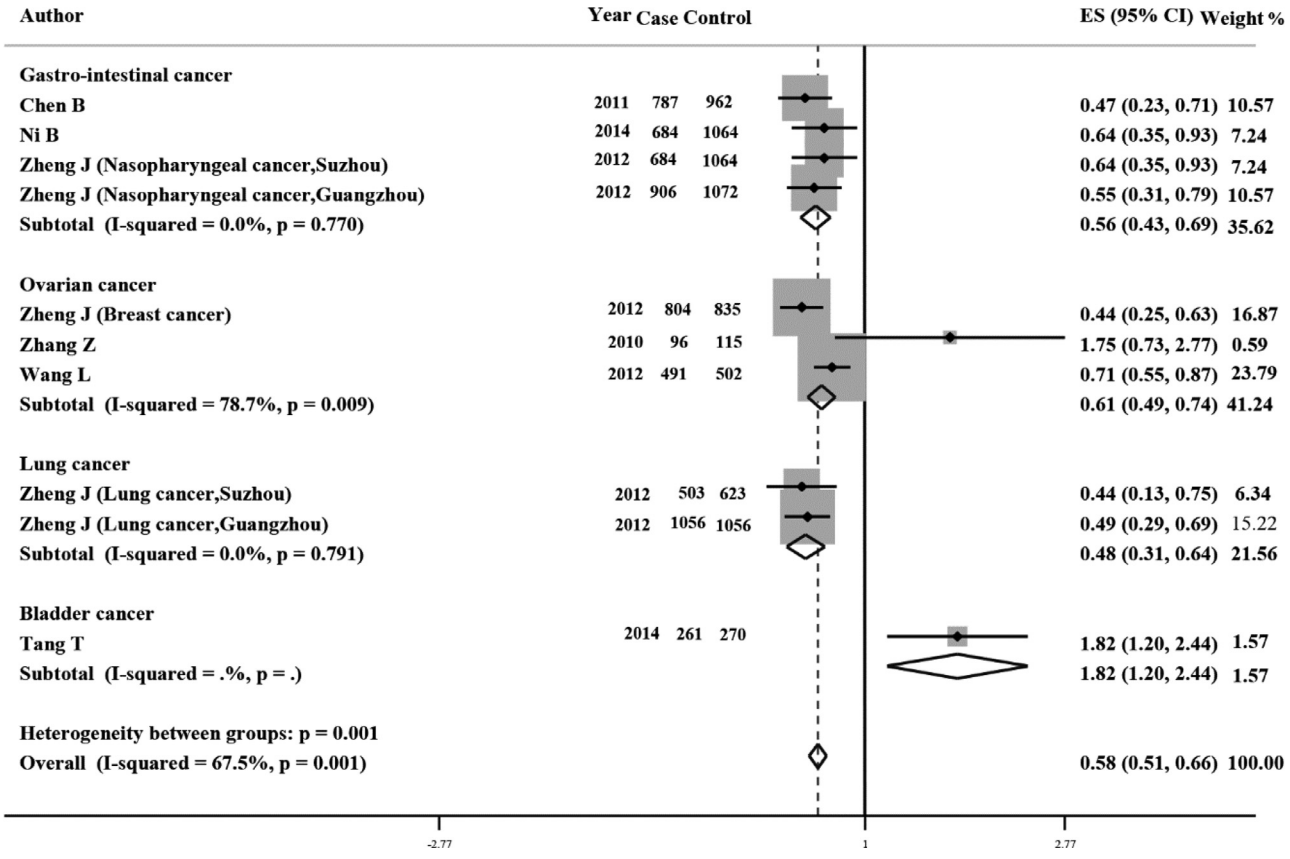

Fig. 3. Odds ratio of cancer among individuals with CC genotype compared those with AA genotype by cancer type subgroup.

Chinese populations on CRC, breast and lung cancers [21,28,49]. These results also were coordinate with Zwiers et al. that A allele can modulate the binding capacity of miRNAs [26]. Sivanesan et al. worked out three protective variants of IL23R and stated that R381Q and V362I variants have lower protein stability leading to reduced expression levels, while the G149R variant is retained in the endoplasmic reticulum (ER) as unfolded polypeptides and concluded that reduces IL23R expression protect against malignancies [50]. Underexpression of let-7a-5p and let-7f-5p microRNAs in plasma and stool samples of early stage colorectal carcinoma reported by Ghanbari et al. indicating the role as tumor suppressor for these miRNAs [51]. Destruction of miRNA binding sites on the

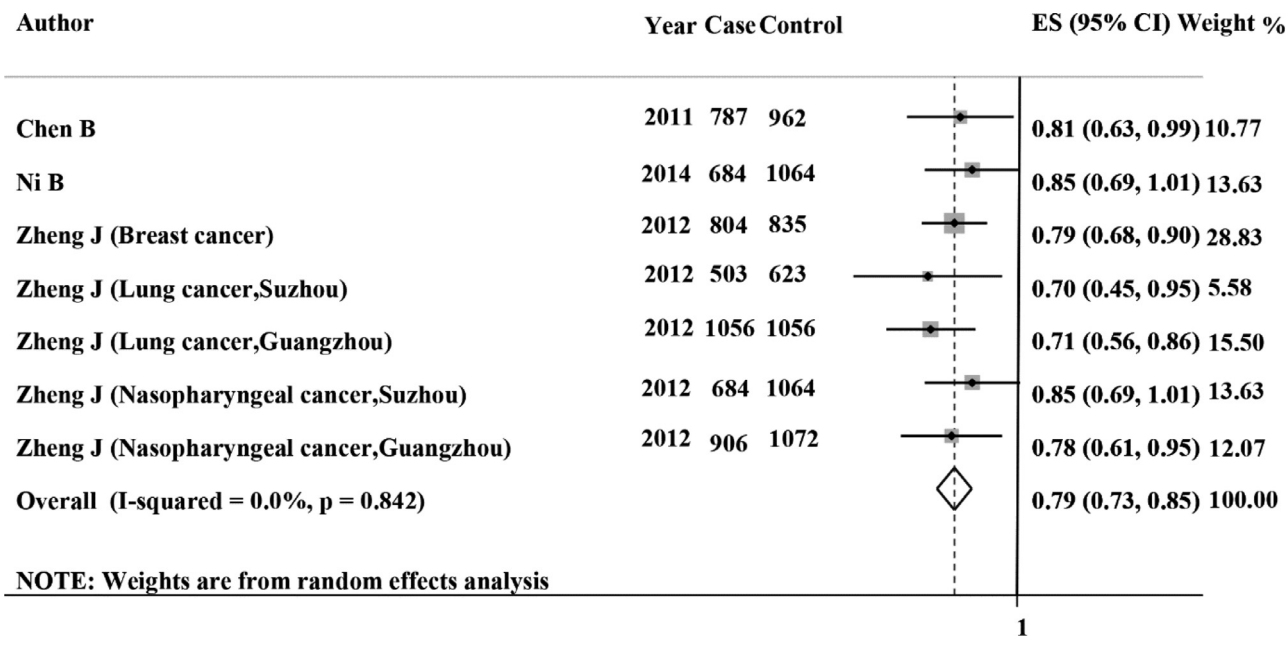

Fig. 4. Odds ratio of cancer among individuals with CA genotype compared with those with AA genotype.

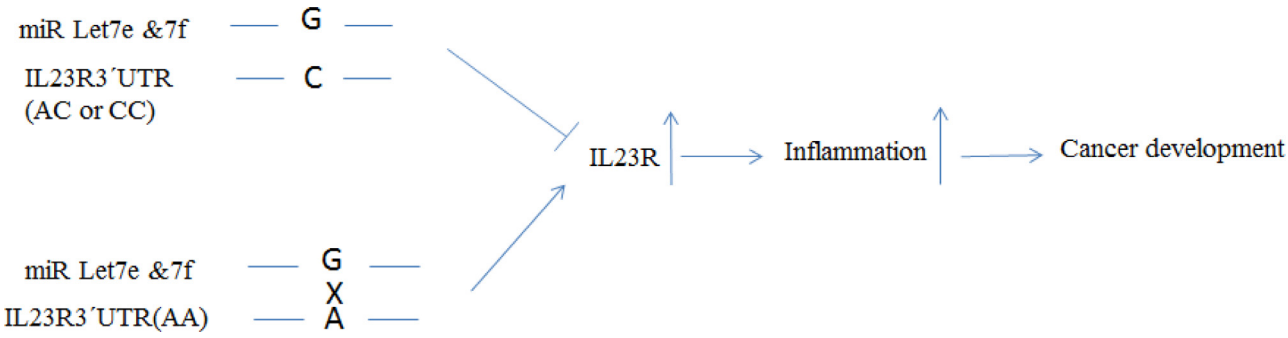

Fig. 5. Proposed mechanistic relationship of the Let-7e, f binding site polymorphism in the IL23R 3′UTR region with inflammation and cancer development.

target mRNAs due to the occurrence of SNPs exerting the same effects as of miRNA downregulation because the consequence of both is overexpression of the target genes. Since presence of A allele disrupt the interaction between Let-7e, f and IL23R mRNA, elevation of IL23R protein expression would prepare suitable ground for tumor biogenesis through pathways discussed above (Fig 5). The results obtained in our study were confirmed by the meta-analysis study we performed. There is an association between AA SNPs and risk of all studied cancers. We also assessed association between some of the demographic and lifestyle characteristics of participants with CRC incidence (Table 1).

Several studies conducted to find out whether miRSNPs could regarded as prognosis markers that enabling us to assess aggressive types of CRC. rs61764370 located in let-7 miRNA binding site in the KRAS 3′ UTR was shown to identify early-stage CRC cases. This polymorphism also proved useful in making decision about the therapy [52]. Two miRSNPs within 3′ UTR of base excision repair genes, SMUG1 (rs223392) and NEIL2 (rs1534862) manipulate activity of these genes with significant modulation of clinical outcomes [53]. Reports of some genetic variants of inflammatory mediators are comparable to our present study. For instance, C allele of rs10082466 in mannose-binding lectin 2 (MBL2) gene is associated with higher susceptibility to CRC due to production of a novel binding site for miR-27a and miR-27b. The increased binding affinity predicted for the C allele of rs10082466 was associated with lower plasma MBL levels and activity [54]. Our previous studies revealed that miRSNPs in COX2 gene (765G>C) and NOD2 gene (rs3135500) could modify the protective effect of NSAIDs and modify individual risks to CRC risk [55,56]. SNPs within the 3′-UTR of NFkBIA (rs696) and NOD2 (rs3135500) genes are important in CRC susceptibility by disturbing inflammatory network balance [1,55,57]. SNPs located near the target site of let-7 also demonstrated to be effective in gene expression of target gene. For example it is l shown that CC and TC genotype of rs3811463 in LIN28 gene is effective in breast cancer susceptibility. The reason is due to the demolition of miRNA Binding site and hence overexpression of LIN28 gene. [58]. Several studies reveled that polymorphisms such as rs712 in the let-7 binding site on KRAS gene is associated with increased risk of breast cancer [59], non-small-cell lung cancer [60], gastric cancer [61] and oral cancer [62]. JB Kjersem et al. demonstrated that rs61764370 polymorphism in let-7 microRNA binding site in 3′ UTR of KRAS gene is associated with clinical outcome of CRC treated with cetuximab [63]. Q Xu et al. reported that rs6458238 in 3′ UTR of pepsinogen C gene (PGC) near the let-7 microRNA binding site in H. pylori infected individuals increased gastric cancer risk [64]. Based on previous studies and our analysis in meta-analysis segment, we carried out a repetitive study in Iranian population. Our result was compatible with our analysis on previous studies. These results demonstrate that this polymorphism is a good marker in cancer prognosis especially in CRC. Although it's essential to have a panel of SNPs as a biomarker for precise determination of prognosis, especially in inflammatory pathway.

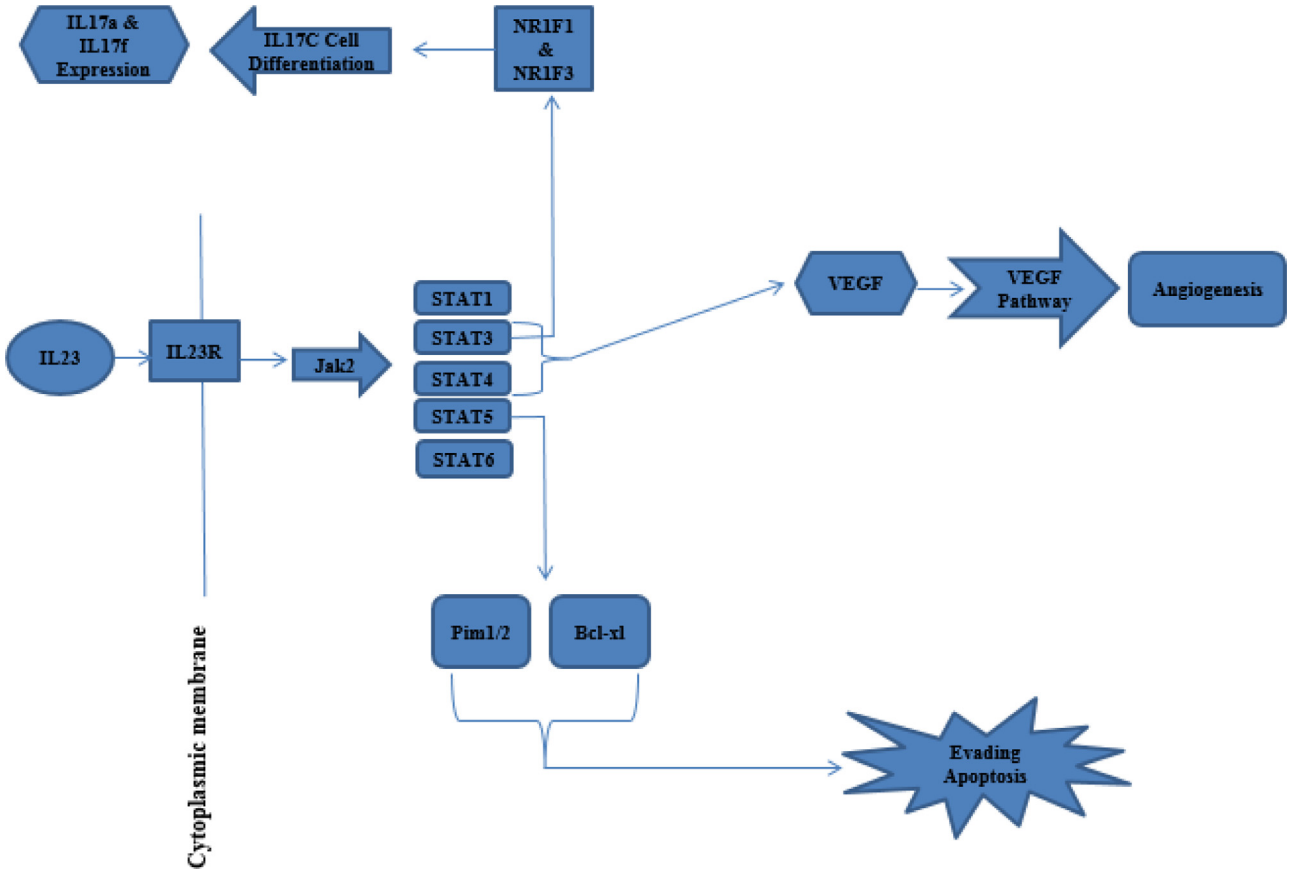

Fig. 6. IL23 pathway.

Conclusion

As a results further evaluation of the role of rs10880677 A>C polymorphism in let-7 microRNA binding site of IL23R in other population with an expanded population size would help to reach a definite conclusion regarding the role of this polymorphism and may prove its utility as a CRC screening biomarker.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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