MicroRNA-binding site polymorphisms and risk of colorectal cancer: A systematic review and meta-analysis

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Abstract
Genetic variations in miRNAs binding site might participate in cancer risk. This study aimed to systematically review the association between miRNA-binding site polymorphisms and colorectal cancer (CRC). Electronic literature search was carried out on PubMed, Web of Science (WOS), Scopus, and Embase. All types of observational studies till 30 November 2018 were included. Overall 85 studies (21 SNPs) from two systematic searches were included analysis. The results showed that in the Middle East population, the minor allele of rs731236 was associated with decreased risk of CRC (heterozygote model: 0.76 [0.61-0.95]). The minor allele of rs3025039 was related to increased risk of CRC in East Asian population (allelic model: 1.25 [1.01-1.54]). Results for rs3212986 were significant in overall and subgroup analysis (P < .05). For rs1801157 in subgroup analysis the association was significant in Asian populations (including allelic model: 2.28 [1.11-4.69]). For rs712, subgroup analysis revealed a significant (allelic model: 1.41 [1.23-1.61]) and borderline (allelic model: 0.92 [0.84-1.00]) association in Chinese and Czech populations, respectively. The minor allele of rs17281995 increased risk of CRC in different genetic models (P < .05). Finally, rs5275, rs4648298, and rs61764370 did not show significant associations. In conclusion, minor allele of rs3025039, rs3212986, and rs712 polymorphisms increases the risk of CRC in the East Asian population, and heterozygote model of rs731236 polymorphism shows protective effect in the Middle East population. In Europeans, the minor allele of rs17281995 may increase the risk of CRC, while rs712 may have a protective effect. Further analysis based on population stratifications should be considered in future studies.

KEYWORDS
colorectal cancer, meta-analysis, microRNAs, polymorphism
INTRODUCTION

Colorectal cancer is one of the most serious illnesses in both sexes. It has been recognized as the second and third common cancers in females and males, respectively. Incidence and mortality of colorectal cancer (CRC) was about 6.1% of new cancer cases and was around 9.2% of cancer death based on Global Cancer Statistics 2018. Its incidence is three times higher in developed countries than developing counters. CRC imposes enormous global burden which could be related to aging and population growth, socioeconomic status, diet, lifestyle, and habits including smoking, western diet, and physical activity. Early diagnosis of CRC leads to lesser treatment cost besides better survival and prognosis. Early prognosis or diagnosis of CRC is also important in cancer survival. Nine of 10 people with CRC would have more than 5 years of survival, if the diagnosis is performed at the stage one while diagnosis in the last stage leads to merely 1 year of survival. For this purpose, finding novel biomarkers for noninvasive early diagnosis of CRC will be crucial in disease treatment.

Some risk factors of CRC including diet and smoking could be modified in contrast to genetic factors. MicroRNAs (miRNAs) are important genetic factors which are regulating around 60% of human protein-coding genes. It is believed that miRNAs play an important role in the pathogenesis of CRC. miRNA polymorphisms might participate in cancer prognosis through their effect on miRNA gene transcription, processing, expression, and target selection. A meta-analysis in 2016 has been implemented on the association between miR-27a rs895819 in the loop of pre-miRNA and shows that this SNP may be a risk factor for CRC (for instance in allelic model OR = 1.21 [1.11-1.31]). A systematic review and meta-analysis has been published in 2014 based on the role of two polymorphisms in miR-146a and in miR-196a2 on the susceptibility towards CRC. The results revealed that miR-196a2 polymorphism rs11614913 is associated with the risk of CRC. Another review paper in 2015 described the association of miRNA variants (in miR-146a, hsa-miR-149, and hsa-miR-196a2) and CRC and showed that rs2910164 (1.24 [1.03-1.49]) and rs2292832 (1.18 [1.08-1.38]) may increase the risk of CRC, and rs11614913 and rs3746444 (0.57 [0.34-0.95]) may decrease the risk of CRC. In 2017, a review article was published on the risk of CRC and polymorphisms in microRNA gene. Based on these results let-7, miR-149, miR-603, miR-34b/c, and miR-146a gene SNPs were associated with CRC.

Polymorphisms in miRNA-binding sites may also alter the risk and survival of a variety of human complex diseases including CRC. miRNA-binding sites are conserved through evolution and contain lesser polymorphisms. Polymorphisms in these sites can affect miRNA:mRNA interactions and target mRNA expression. In one study, the association between let-7 miRNA-binding site polymorphisms and CRC outcome has been described, based on one miRNA, one database (PubMed), and also CRC risk was not investigated. miRNAs’ target site polymorphisms may potentially play a role in the interaction between miRNAs and their target mRNA, which is dependent on the effect of polymorphism on miRNA:mRNA interactions. There was also a meta-analysis on 3'UTR polymorphisms and the risk of cancers, but the results were only for two polymorphisms and were not specific for CRC or miRNA-binding sites. To the best of our knowledge, there is no previous systematic review on the association between miRNA-binding site polymorphisms and CRC. Therefore, the lack of a comprehensive systematic review focusing on miRNA-binding site polymorphisms and CRC is obvious.

Because of importance and economic burden of CRC, and regarding the significant role of miRNA-binding site polymorphisms on CRC according to the previous studies besides lack of a systematic review on this subject, the necessity of such study on association between miRNA-binding site polymorphisms and CRC, as prognostic markers, is quite clear. For this purpose, the main objective of the current systematic review was to explore and reveal the association of 3'UTR and miRNA-binding site polymorphisms with the risk of CRC. The secondary specific objective was to determine the effect of ethnicity on these associations.

METHODS AND ANALYSIS

The methods of this study have been developed according to the PRISMA-P 2015 checklist. PRISMA 2009 flow diagram was used to display the flow of document number through the different phases of the study (Figure 1). The protocol of this systematic review is registered in International Prospective Register for Systematic Reviews (PROSPERO) on January 11, 2018 (Registration ID = CRD42018084094).

2.1 Eligible studies and participants

This study imposed a restriction on the study design. Observational studies (case-control, cohort, and cross-sectional), describing the association between miRNA-binding site polymorphisms and CRC, were eligible for inclusion. Primary documents will be screened according to the PECO criteria (Participants, Exposure, Comparisons, and Outcomes) and objectives of this study. Studies with deviation from Hardy-Weinberg equilibrium and with the lack of required primary data or data for estimating genotype numbers were excluded. This study also applied a restriction on publication date. Only documents published from January 1, 1992 to November 30, 2018 were searched. This restriction was based on...
on two reasons; first: miRNA discovery date, and second: most recent publications were relevant to our study subject. There was no restriction about the language of documents related to the topic of this study. Non-English languages articles were translated by free language translation services or by a translator. There was also no limitation on age, gender, ethnicity, and method of genotyping. The study did not impose a restriction on colorectal cancer stages (I, II, III, and IV). Colorectal polyps and family-based case-control studies were not considered for inclusion.

2.2 MicroRNAs binding site polymorphism

Polymorphisms in miRNA-binding sites have been reported to be associated with cancers.31,32 These SNPs are conserved through evolution.23 These sites act as diagnostic and prognostic biomarkers associated with cancer risk and outcome.33 Their association with susceptibility, outcome, treatment, prognosis, and progression of CRC has also been reported.20,34-36 In this systematic review, studies that evaluated the relationship between miRNA-binding site polymorphisms and CRC were included and the primary outcome of this review was finding association between miRNA-binding site polymorphisms and CRC susceptibility. Moreover, subgroup analysis for ethnicity was carried out on association of CRC risk with microRNA-binding site polymorphisms.

2.3 Search methods for studies identification

In order to identify the relevant papers on miRNA-binding site polymorphisms and colorectal cancer, online systematic search (electronic searches) of literature was performed in PubMed, Embase, Scopus, and Web of Science. We developed PubMed search syntax, as the main database, this syntax was adapted to other database. PubMed search syntax was performed by combined medical subject headings (MeSH), Emtree terms, keywords of related papers, also free text words. Key search terms were “colorectal neoplasms,” “miRNA,” “Polymorphism, Single Nucleotide,” and their equivalents (Table S1). To identify more results, we also manually checked references from included primary articles and relevant reviews, conference papers, gray literature, as well as contact with corresponding authors for missing data.
| References | Study design | rsID (target miRNA) |
|------------|--------------|---------------------|
| 37         | Case-control | rs10082466 (miR-27a) |
| 38         | Case-control | rs11466537 (miR-1193) |
| 39         | Case-control | rs12904 (miR-200 family: miR-200c, miR-429, and miR-200b) |
| 40         | Case-control | rs12915554 (miR-185-3p) |
| 41         | Case-control | rs141178472 (miR-520a) |
| 42         | Case-control | rs16917496 (miR-502) |
| 43         | Case-control | rs1710 (miRNA-binding site polymorphism*) |
| 44         | Case-control | rs2015 (miR-376a-5p) |
| 45         | Case-control | rs2737 (miR-379) |
| 46         | Case-control | rs3135500 (miR-158, miR-215, miR-98, miR-573) |
| 47         | Case-control | rs11169571 (miR-1283, miR-520d-5p) |
| 48         | Case-control | rs34149860 (miR-29b) |
| 49         | Case-control | rs4648298 (miR-21, miR590) |
| 50         | Case-control | rs3814058 (miR-129-5p) |
| 51         | Case-control | rs4245739 (miR-191) |
| 52         | Case-control | rs4804800 (miR-622, miR-1238) |
| 53         | Case-control | rs4939827 (miR-375) |
| 54         | Case-control | rs5275 (miR-542-3p) |
| 55         | Case-control | rs61764370 (let-7) |
| 56         | Case-control | rs61764370 (let-7) |
| 57         | Case-control | rs696 (miR449a) |
| 58         | Case-control | rs696 (miR-449a, miR-34b) |
| 59         | Case-control | rs712 (let-7) |
| 60         | Case-control | rs712 (miR-200b, miR-429, miR-200c, miR-193b) |
| 61         | Case-control | rs8679 (miR-145) |
| 62         | Case-control | rs964778 (miR-300-3p), rs1043784 (miR-584), rs10038999 (miR-629), rs1129976 (miR-150) |
| 63         | Case-control | rs712 (let-7), rs61764370 (let-7) |
| 64         | Case-control | rs12997 (miR-130-3p), rs13347 (miR-509-3p), rs10836347, rs11821102 (miRNA-binding site polymorphisms) |
| 65         | Case-control | rs17468, rs2317676 (miRNA-binding site polymorphisms) |
| 66         | Case-control | rs3135500, rs1368439 (miRNA-binding site polymorphisms) |
| 67         | Case-control | rs847 (miR-98, let-7 if/g), rs848 (miR-558, miR-621, let-7i), rs1295685 (miR-621) |
| 68         | Case-control | rs1590 (miR-532-5p, miR-768-3p), rs1434536, rs17023107 (miRNA-binding site polymorphisms) |
| 69         | Case-control | rs1434536, rs413815 (miR-570), rs1059293, rs27194, rs43216 (miRNA-binding site polymorphisms) |
| 70         | Case-control | rs1062044 (miR-423-5p), rs17477864 (miR-186-5p), rs3824998 (miR-221-3p), rs4768914 (miR-200c-3p), rs1046165 (miR-451a) |
| 71         | Case-control | rs108621 (miR-193a-3p, miR-338-3p), rs3212986 (miR-15a) |
| 72         | Case-control | rs3660, rs1044129, rs1053667, rs4901706, rs11337 (miRNA-binding site polymorphisms) |
| 73         | Case-control | rs1131445 (miR-135a/135b), rs1051208 (miR-213), rs1435554, rs16870224, rs11515 (miRNA-binding site polymorphisms) |
| 74         | Case-control | rs1126547 (hsa-miR-141, hsa-miR-200a), rs2229090 (miR-1225-3p, miR-3123, miR-3619), rs9914073 (miR-548c-3p, miR-605), rs17339395 (miR-4299), rs7356 (miR-3149, miR-1183), rs1803541 (miR-568, miR-802), rs4956 (miR-518a-5p, miR-527, miR-1205), rs1271563 (miR-2355-3p, miR-4288), rs45522131 (miR-26a/b, miR-374a) |

(Continues)
2.4 | Data collection

2.4.1 | Screening for eligible studies

Screening and eligibility checking was performed in three following steps. First, duplicate documents were removed. Second, for screening, two reviewers independently scrutinize remaining documents by checking title and/or abstract. Third, full texts’ eligibility was independently scrutinized by two reviewers. Any disagreements between two reviewers were resolved by consensus strategy and third-person strategy.

2.4.2 | Data extraction and management

A data extraction form was created and then piloted by two reviewers. This form included the following data: the name of first author, country of study, year of publication, study design, age, gender, ethnicity, names of 3’UTR or binding site SNPs, genotyping methods, minor allele frequency (MAF), HWE, sample size, matching criteria (such as age and sex), source of controls (HB, hospital base or PB, population base), odds ratio (OR), confidence interval (95% CIs), and other related raw data. In the next step, two reviewers independently extracted data based on the extraction form. Disagreements were resolved by strategies listed above.

2.5 | Analysis

2.5.1 | Meta-analysis

Meta-analysis was performed by using R (3.5.2). Odds ratio and 95% CI were used to investigate the associations between each polymorphism in miRNA-binding site and CRC. The meta-analysis was performed based on different genetic models (allelic model (A vs a), homozygous model (AA vs aa), heterozygote model (Aa vs aa), dominant model (AA + Aa vs aa), recessive model (AA vs Aa + aa), and overdominant model (Aa vs AA + aa)). All included studies were at the risk of various types of heterogeneity. For exploring possible sources of heterogeneity, included studies were divided according to the type of polymorphisms. For each polymorphism, if sufficient studies were included,
subgroup analysis (based on ethnicity) was applied. Odds ratios were estimated by fixed effects model (FEM) or random effects model (REM), according to the heterogeneity level. Level of heterogeneity between primary studies was obtained by the Cochran’s Q test ($P < .05$ is statistically significant) and the $I^2$ statistic in forest plots. We used the following guide to interpret the amount of heterogeneity: $I^2 < 25\% = \text{low heterogeneity}; 25 \geq I^2 < 50\% = \text{moderate heterogeneity}; 50 \geq I^2 < 75\% = \text{severe heterogeneity}; 75\% \geq I^2 = \text{highly severe heterogeneity}.$

**TABLE 2** 3'UTR polymorphisms and colorectal cancer risk (included from first search strategy)

| Reference | Study design | rsID |
|-----------|--------------|------|
| 82        | Case-control | rs1058881 |
| 83        | Case-control | rs1059234 |
| 84        | Case-control | rs731236 |
| 85        | Case-control | rs108621 |
| 86        | Case-control | rs142559064 |
| 40        | Case-control | rs146588909 |
| 87        | Case-control | rs17281995 |
| 88        | Case-control | rs1801157 |
| 89        | Case-control | rs1801157 |
| 90        | Case-control | rs1801157 |
| 91        | Case-control | rs2075786 |
| 44        | Case-control | rs2241703 |
| 92        | Case-control | rs3025039 |
| 93        | Case-control | rs3025039 |
| 94        | Case-control | rs3025039 |
| 95        | Case-control | rs3025039 |
| 96        | Case-control | rs3212986 |
| 50        | Case-control | rs3732360 |
| 97        | Case-control | rs3742330 |
| 98        | Nested case-cohort | rs5275 |
| 99        | Case-control | rs78378222 |
| 100       | Case-control | rs5275 |
| 101       | Case-control | rs5275 |
| 102       | Case-control | rs57898959 |
| 103       | Case-control | rs8176318 |
| 104       | Case-control | rs696 |
| 105       | Case-control | rs713041 |
| 106       | Case-control | rs7579 |
| 107       | Case-control | rs8878 |
| 108       | Case-control | rs9138 |
| 109       | Case-control | rs9138 |
| 110       | Case-control | CDX2-G1312T |
| 111       | Case-control | rs868, rs7591 |
| 112       | Case-control | rs5275, rs4648298 |
| 113       | Case-control | rs67085638, rs77628730 |
| 114       | Case-control | rs4648298, rs5276, rs13306035 |
| 115       | Case-control | rs1205, rs3093075 |
| 116       | Case-control | rs7975232, rs1544410 |
| 117       | Case-control | rs16930073, rs8491, rs854551 |
| 118       | Case-control | rs11875, rs1042669, rs4149206 |
| 119       | Case-control | rs3025040, rs10434, rs3025053 |
| 72 | Case-control | rs735482, rs2336219, rs1052133 |

(Continues)
| Gene   | rsID    | Case       | Control   | References | Sig. in genetic models |
|--------|---------|------------|-----------|------------|------------------------|
| CD86   | rs17281995 | 7 48 137   | 0 55 164  | Yesa       |
|        |         | 24 161 475 | 8 114 434 |            |
|        |         | 12 75 217  | 7 67 181  |            |
| PARP1  | rs8679  | 53 335 687 | 66 482 873| No         |
|        |         | 12 60 111  | 14 86 90  |            |
| VEGF   | rs10434 | 8 57 214   | 9 83 213  | No         |
|        |         | 19 143 209 | 11 93 142 |            |
| MLH3   | rs108621 | 219 562 311| 300 665 428| No         |
|        |         | 14 62 124  | 9 59 132  |            |
| IL-16  | rs1131445| 36 110 103 | 34 159 201| No         |
|        |         | 65 287 308 | 53 240 251|            |
| IL12B  | rs1368439| 2 29 61   | 2 35 68   | No         |
|        |         | 21 188 465 | 15 164 388|            |
| PTGER4 | rs16870224| 11 130 523 | 4 116 439 | No         |
|        |         | 2 68 179  | 14 109 271|            |
| BRCA1  | rs8176318| 127 504 484| 109 504 560| No         |
|        |         | 119 445 509| 144 634 640|            |
| VEGF   | rs3025053| 0 36 243   | 0 27 278  | No         |
|        |         | 6 91 274  | 4 67 175  |            |
| MTHFR  | rs4846049| 79 344 373 | 83 351 371| No         |
|        |         | 17 157 276 | 9 113 278 |            |
| SPP1   | rs9138  | 31 138 99  | 20 102 152| Yesb       |
|        |         | 20 42 38  | 19 43 50  |            |
| NOD2   | rs3135500| 15 37 40   | 19 48 38  | Yesc       |
|        |         | 31 42 15   | 10 43 35  |            |
|        |         | 120 303 243| 81 265 209|            |
| KRAS   | rs61764370| 0 66 375   | 2 35 202  | No         |
|        |         | 1 45 151  | 2 68 288  |            |
|        |         | 6 167 916  | 10 215 1200| 76         |

(Continues)
2.5.2 Reporting biases and sensitivity analysis

We used Begg’s test and Egger’s regression method to assess the potential publication bias in primary studies. Main results were depicted by funnel plots (for visual assessment). Sensitivity analysis was performed by the leave-one-out method.

3 RESULTS

In the systematic search, at the first stage we found 9221 documents, with 222 polymorphisms in 3’UTR and miRNA-binding site of genes that were studied for the risk of CRC. Among them we included main polymorphisms in second search for meta-analysis (these polymorphisms were selected because the meta-analysis for all included polymorphisms was not possible, also in order to decrease the false positive prediction of miRNA-binding sites polymorphisms, only polymorphisms that were mentioned in two studies or more were included, one of these studies should report polymorphism in miRNA-binding site). Twenty-five polymorphisms were included (rs10082466, rs10434, rs8176318, rs17281995, rs3212986, rs1368439, rs1131445, rs5275, rs61764370, rs712, rs108621, rs696, rs3135500, rs8679, rs16870224, rs731236, rs3025039, rs3025040, rs3025053, rs4648298, rs1801157, rs3742330, rs4846049, rs854551, and rs9138). Second search strategy applied for these polymorphisms, which contained 5170 documents. Finally, we included 54 studies on the role of 3’UTR polymorphisms and 52 studies on the role of miRNA-binding site polymorphisms and risk of CRC for all the selected polymorphisms (Tables 1 and 2). Finally, 21 polymorphisms with two or more than two included studies were eligible for final analysis (these studies are shown in detail in Tables 3 and 4). For rs17281995 polymorphism, the pooled analysis based on three included articles (rs731236, rs3025039, rs3212986, rs712, rs5275, rs4648298, and rs1801157). The basic characteristics of studies included in the meta-analysis are shown following (Table 4).

For rs731236 in overall meta-analysis (based on minor allele; t) no significant result for the risk of CRC was observed, but in subgroup analysis in Middle East population the results were significant in heterozygote (Tt vs TT) (0.76 [0.61-0.95]) and overdominant models (Tt vs TT + tt) (0.75 [0.61-0.92]), and borderline significance was observed in dominant model (tt + Tt vs TT) (0.81 [0.66-1.00]) (Figure 2, Figure S2).

For rs3025039 in overall, there was no significant association, but subgroup analysis revealed significant results (based on minor allele; T). In East Asian population, the allelic model (T vs C) (1.25 [1.01-1.54]) significantly increased the risk of CRC and in dominant model (TT + TC vs CC) (1.29 [1.00-1.66]) there was a trend towards significance (Figure 3, Figure S3).

In meta-analysis for rs3212986, there were significant results in both overall and subgroup analysis in different genetic models (based on minor allele; T), including homozygote model (TT vs GG) 1.76 (1.08-2.86) (Figure 4, Figure S4).

Although we did not find any significant result for rs712 in overall models, subgroup analysis revealed significant and borderline association in Chinese and Czech populations, respectively, on six genetic models (based on minor allele; T), including homozygote model (TT vs GG) 2.51 (1.70-3.69) and in Czech 0.85 (0.72-1.01) populations (Figure 5, Figure S5).

The allele (A) of rs1801157 polymorphism increased risk of CRC in Asian population, while we did not find any significant results in Caucasian populations (Table 5).

Finally for rs5275 (based on minor allele; C) and rs4648298 (based on minor allele; G), we performed meta-analysis according to three different subgroup analyses (CRC cases, adenoma, and overall). The results in all different genetic models were not significant except dominant model (0.82 [0.70-0.97]) in adenoma for rs5275, also the allelic model (C vs T) showed borderline association 0.92.
TABLE 4  The basic characteristic of included studies (polymorphisms with at least four eligible studies were included)

| SNP   | First author | Year | Country       | Population subgroup | Case     | Study design    | Gender | Age  | Sample size (case-control) | Genotyping method | Quality score | References |
|-------|--------------|------|---------------|---------------------|----------|----------------|--------|------|---------------------------|------------------|--------------|------------|
| rs731236 | Budhathoki   | 2016 | Japan         | East Asian          | CRC      | Nested case-control | F/M    | 40-69 | 356/708                   | TaqMan            | 8            | 125        |
|       | Takeshige    | 2015 | Japan         | East Asian          | CRC      | Case-control     | F/M    | 20-74 | 685/778                   | PCR-RFLP          | 9            | 131        |
|       | Park         | 2006 | Korea         | East Asian          | CRC      | Case-control     | F/M    | 23-81 | 190/318                   | PCR-RFLP          | 6            | 132        |
|       | Hughes       | 2011 | Czech Republic | European            | CRC      | Case-control     | F/M    | >29   | 717/615                   | KASPar            | 8            | 133        |
|       | Bentley      | 2012 | New Zealand   | European            | CRC      | Case-control     | F/M    | —     | 199/182                   | TaqMan            | 7            | 134        |
|       | Gromowski    | 2016 | Poland        | European            | CRC      | Case-control     | F/M    | —     | 195/390                   | TaqMan            | 4            | 135        |
|       | Laczmanska   | 2014 | Poland        | European            | CRC      | Case-control     | F/M    | 32-87 | 157/175                   | SNaPshot Multiplex Kit | 6            | 84         |
|       | Flügge       | 2007 | Russia        | European            | CRC      | Case-control     | F/M    | 29-85 | 256/256                   | PCR-RFLP          | 6            | 136        |
|       | Mahmoudi     | 2010 | Iran          | Middle East         | CRC      | Case-control     | F/M    | 14-90 | 160/180                   | PCR-RFLP          | 6            | 137        |
|       | Moossavi     | 2017 | Iran          | Middle East         | CRC      | Case-control     | F/M    | —     | 100/100                   | PCR-RFLP          | 6            | 138        |
|       | Safaei       | 2012 | Iran          | Middle East         | CRC      | Case-control     | F/M    | —     | 112/112                   | PCR-RFLP          | 6            | 139        |
|       | Atoum        | 2014 | Jordan        | Middle East         | CRC      | Case-control     | F/M    | —     | 93/102                    | PCR-RFLP          | 6            | 140        |
|       | Alkhayal     | 2016 | Saudi Arabia  | Middle East         | CRC      | Case-control     | F/M    | 21-89 | 100/100                   | Sequencing        | 5            | 141        |
|       | Gunduz       | 2012 | Turkey        | Middle East         | CRC      | Case-control     | F/M    | —     | 43/42                      | PCR-RFLP          | 6            | 142        |
|       | Yaylm-Eraltan| 2007 | Turkey        | Middle East         | CRC      | Case-control     | F/M    | —     | 26/52                      | PCR-RFLP          | 4            | 143        |
|       | Dilmec       | 2009 | Turkey        | Middle East         | CRC      | Case-control     | F/M    | —     | 56/169                    | PCR-RFLP          | 4            | 144        |
|       | Kupfer       | 2011 | USA           | African             | CRC      | Case-control     | F/M    | —     | 938/811                   | Sequenom MassARRAY | 7            | 145        |
|       | Slattery     | 2001 | USA           | Caucasian, African, Hispanic | CRC | Case-control | F/M | 30-79 | 427/366                   | PCR-RFLP          | 9            | 146        |
|       | Ochs-Balcom  | 2008 | USA           | Caucasian, African, Hispanic | CRC | Case-control | F/M | ≥40   | 250/246                   | TaqMan            | 8            | 147        |
|       | Yamaji       | 2011 | Japan         | East Asian          | Adenoma  | Case-control     | F/M    | 40-79 | 684/640                   | TaqMan            | 7            | 148        |
|       | Peters       | 2004 | USA           | European            | Adenoma  | Nested case-control | F/M | 55-74 | 716/727                   | PCR-RFLP          | 7            | 149        |
|       | Peters       | 2004 | USA           | African             | Adenoma  | Nested case-control | F/M | 55-74 | 763/774                   | PCR-RFLP          | 7            | 149        |
(Continues)
| SNPs      | First author | Year | Country          | Population subgroup | Case | Study design  | Gender | Age     | Sample size (case-control) | Genotyping method                  | Quality score | References |
|-----------|--------------|------|------------------|---------------------|------|---------------|--------|---------|---------------------------|------------------------------------|-------------|------------|
| rs30259039| Hofmann      | 2008 | Austria          | Caucasian           | CRC  | Case-control  | F/M    | 29-83   | 427/427                  | TaqMan                               | 7           | 150        |
| Wu        |              | 2009 | Germany          | Caucasian           | CRC  | Case-control  | F/M    | 33-91   | 157/117                   | PCR-RFLP                              | 5           | 151        |
| Ungerback |              | 2009 | Sweden           | Caucasian           | CRC  | Case-control  | —      | —       | 302/336                   | MegaBACE™ SNuPe™ Genotyping Kit     | 5           | 95         |
|           | Bayhan       | 2014 | Turkey           | Caucasian           | CRC  | Case-control  | —      | —       | 43/44                     | PCR-RFLP                              | 4           | 152        |
|           | Jannuzzi     | 2015 | Turkey           | Caucasian           | CRC  | Case-control  | F/M    | —       | 103/129                   | PCR-RFLP                              | 8           | 153        |
|           | Yang         | 2017 | China            | East Asian          | CRC  | Case-control  | F/M    | 20-83   | 371/246                   | iMLDR method                          | 7           | 124        |
|           | Bae          | 2008 | Korea            | East Asian          | CRC  | Case-control  | F/M    | 18-95   | 262/229                   | PCR-RFLP                              | 5           | 154        |
|           | Chae         | 2008 | Korea            | East Asian          | CRC  | Case-control  | F/M    | 21-89   | 465/413                   | PCR/DHPLC                             | 4           | 141        |
|           | Jang         | 2013 | Korea            | East Asian          | CRC  | Case-control  | F/M    | —       | 390/492                   | PCR-RFLP                              | 6           | 155        |
|           | Lau          | 2014 | Malaysia         | South Asian         | CRC  | Case-control  | —      | 40-90   | 130/212                   | TaqMan                                | 5           | 156        |
|           | Credidio     | 2011 | Brazil           | Caucasian, African  | CRC  | Case-control  | F/M    | 25-97   | 261/261                   | PCR-RFLP                              | 4           | 157        |
|           | Wu           | 2011 | China            | East Asian          | Adenoma | Case-control | F/M    | 18-75   | 224/200                   | TaqMan                                | 8           | 158        |
| rs3212986 | Hou          | 2014 | China            | East Asian          | CRC  | Case-control  | F/M    | —       | 204/204                   | MALDI-MS                              | 7           | 159        |
|           | Moreno       | 2006 | Spain            | ...                 | CRC  | Case-control  | F/M    | —       | 349/300                   | APEX                                 | 7           | 160        |
|           | Ni           | 2014 | China            | East Asian          | CRC  | Case-control  | F/M    | —       | 213/240                   | TaqMan                                | 8           | 161        |
|           | Yueh         | 2017 | Taiwan           | East Asian          | CRC  | Case-control  | F/M    | —       | 362/362                   | PCR-RFLP                              | 7           | 162        |
|           | Zhang        | 2018 | China            | East Asian          | CRC  | Case-control  | F/M    | —       | 200/200                   | TaqMan                                | 5           | 72         |
| rs712     | Dai          | 2016 | China            | Chinese             | CRC  | Case-control  | F/M    | 36-75   | 430/430                   | iMLDR                                 | 7           | 62         |
|           | Jiang        | 2015 | China            | Chinese             | CRC  | Case-control  | F/M    | —       | 586/476                   | PCR-RFLP                              | 5           | 36         |
|           | Landi        | 2012 | Czech Republic   | Czechs              | CRC  | Case-control  | F/M    | —       | 717/1171                  | KASPar                                | 7           | 79         |
|           | Pan          | 2014 | China            | Chinese             | CRC  | Case-control  | F/M    | —       | 339/313                   | PCR-RFLP                              | 7           | 59         |
|           | Schneiderova | 2017 | Czech Republic   | Czechs              | CRC  | Case-control  | F/M    | 21-78   | 1057/1405                 | KASPar                                 | 6           | 76         |
| SNPs      | First author | Year | Country       | Population subgroup* | Case  | Study design | Gender | Age | Sample size (case-control) | Genotyping method | Quality score | References |
|-----------|--------------|------|---------------|----------------------|-------|--------------|--------|-----|---------------------------|-------------------|--------------|-----------|
| rs5275    | Makar (DALS) | 2013 | USA           | Caucasian            | CRC   | Case-control | F/M    | 30-79 | 2003/2549                 | Illumina™ GoldenGate assay | 6            | 163       |
| Pereira   |              | 2010 | Portugal      | Caucasian            | CRC   | Case-control | F/M    | 50-75 | 115/256                   | PCR-RFLP          | 5            | 100       |
| Siezen (PHV) | 2006 | Netherlands | Caucasian | CRC | Nested case-control | F/M | —     | 200/388 | PCR-RFLP | 7 | 164 |
| Siezen (DOM) | 2006 | Netherlands | Caucasian | CRC | Nested case-control | F/M | —     | 442/693 | PCR-RFLP | 6 | 164 |
| Vogel     |              | 2014 | Norway        | Caucasian            | CRC   | Case-control | F/M    | 50-64 | 189/399                   | KBioscience       | 8            | 165       |
| Zhang     |              | 2012 | China         | East Asian           | CRC   | Case-control | F/M    | 93-30 | 343/340                   | —                 | 6            | 101       |
| Cox       |              | 2004 | Spain         | Caucasian            | CRC   | Case-control | F/M    | 24-92 | 290/271                   | TaqMan            | 6            | 166       |
| Andersen  |              | 2013 | Denmark       | Caucasian            | CRC   | Case-Cohort Study | F/M    | 50-64 | 931/1738                  | KASPar            | 9            | 167       |
| Thompson  |              | 2009 | USA           | Caucasian, African, Other | CRC | Case-control | F/M    | —     | 421/480                   | TaqMan            | 9            | 168       |
| Gunter    |              | 2006 | USA           | _                    | Adenoma | Case-control | F/M    | 43-74 | 210/197                   | TaqMan            | 8            | 169       |
| Pereira   |              | 2016 | Portugal      | Caucasian            | Adenoma | Case-control | F/M    | 50-75 | 191/474                   | —                 | 6            | 170       |
| Siezen    |              | 2006 | Netherlands   | Caucasian            | Adenoma | Case-control | F/M    | —     | 378/396                   | TaqMan            | 7            | 171       |
| Vogel     |              | 2014 | Norway        | Caucasian            | Adenoma | Case-control | F/M    | 50-64 | 983/399                   | KBioscience       | 8            | 165       |
| Gong      |              | 2009 | USA           | _                    | Adenoma | Case-control | F/M    | 30-74 | 162/211                   | PCR-RFLP          | 8            | 112       |
| Ali       |              | 2005 | USA           | Caucasian            | Adenoma | Nested case-control | F/M    | 55-74 | 749/756                   | TaqMan            | 7            | 172       |
| Ashktorab |              | 2008 | USA           | African              | Adenoma | Case-control | F/M    | —     | 70/136                     | TaqMan            | 7            | 173       |
| rs4648298 | Iglesias     | 2009 | Spain         | Caucasian            | CRC   | Case-control | F/M    | —     | 284/123                   | PCR-RFLP          | 7            | 114       |
| Mosallaei |              | 2018 | Iran          | Caucasian            | CRC   | Case-control | F/M    | —     | 88/88                      | PCR-RFLP          | 5            | 49        |
| Ueda      |              | 2008 | Japan         | East Asian           | Adenoma | Case-control | M      | 47-59 | 455/1051                  | PCR-RFLP          | 5            | 174       |
| Gong      |              | 2009 | USA           | _                    | Adenoma | Case-control | F/M    | 30-74 | 162/211                   | PCR-RFLP          | 8            | 112       |

(Continues)
GHOLAMI et al (0.85–1.00) (Tables 6). For rs4648298 recessive, homozygote, and heterozygote (CG vs GG) models the analysis was not possible, because of zero number in GG genotype in all included studies (Table 7).

4 | DISCUSSION

This study aimed to investigate miRNA-binding site polymorphisms and risk of CRC, which may potentially play roles in various conditions. The effects shown for these polymorphisms associated with miRNA:mRNA interactions. Polymorphisms in miRNA-binding site can negatively or positively influence these interactions by different mechanisms such as effect of hybrid stability, target sites accessibility, local RNA secondary structure, and structural accessibility. Among 222 included polymorphisms, 25 were eligible for inclusion in our secondary search strategy. Fourteen polymorphisms, with less than four eligible studies, were included in the pooled analysis. The rs17281995 polymorphism is located in 3’UTR of CD86 gene and binding site of miR-337 and miR-582.22 The minor allele (C) of rs17281995 polymorphism increased the risk of CRC in different genetic models. Although the results are based on limited number of studies but the strong association is noteworthy. This was also observed in the previous review based on two included articles.129 The nonsignificant results are not conclusive and cannot rule out the association between these polymorphisms and the risk of CRC, because of limited number of included studies and also ethnic differences in studied populations. Further studies need to confirm these results. In addition, seven polymorphisms, with more than four eligible studies, were included in the final meta-analysis.

The rs731236 polymorphism is located in 3’UTR of vitamin D receptor gene. Its downregulation is related to cancer progression.178 There are several previous meta-analyses on the role of rs731236 on CRC risk. Most of the previous meta-analyses179-183 found no significant association between the risk of CRC and rs731236. While Serrano et al in their meta-analysis184 found significant results based on analyzing both of colorectal cancer and adenoma. Therefore, all previous meta-analysis results were according to fewer included studies, the overall CRC population and no subgroup analysis were carried out and in some studies adenoma was also included for calculating the risk of CRC. In our study, we carried out subgroup analysis based on different ethnicity and found that the results were different after stratification according to ethnicity. While in overall analysis our results are in line with the previous meta-analysis, showing no relation between the risk of CRC and rs731236 polymorphism. In Middle East population we observed a significant association between this polymorphism and CRC. This result was not reported previously. We also found a heterozygote advantage for the risk of CRC with
FIGURE 2  Forest plot related to rs731236 and risk of CRC. A, Heterozygote model. B, Overdominant model
heterozygote (Tt) showing protective effects compared with homozygotes (TT, tt). Similarly, in a study on pediatric solid tumor, the heterozygote model decreased the risk of CRC compared to homozygote model. The survival rate of subjects with CRC was significantly decreased in heterozygote model compared to homozygote model. More studies are needed to specify the reason for our interesting observation.

In overall analysis, based on 11 included studies, rs3025039 was not related to the risk of CRC, but is showing association in Caucasian and East Asian populations. Based on subgroup analysis, minor allele in East Asian was related to an increased risk of CRC. This SNP is located in 3'UTR of vascular endothelial growth factor gene which may affect hsa-miR-591 target sites. This gene affects angiogenesis, tumor growth, and metastasis. It is also related to CRC outcomes and treatment. Thus the association between rs3025039 and CRC risk may be related to the effect of this SNP on miRNA:mRNA interactions. However, in the previous meta-analysis with five included studies, no significant association was found between this polymorphism and risk of CRC. This might be due to heterogeneity of their data in different populations requiring further subgroup analysis.

According to the results based on five included studies, rs3212986 increased the risk of CRC in all genetic models, which was similar to previous meta-analysis, we also found to the same results in East Asian population. This polymorphism is located in binding site of miR-15a in 3'UTR of ERCC1. This polymorphism and mRNA level of this gene had previously been investigated in CRC. However, the association between rs3212986 and CRC risk may be related to the effect of this SNP on miRNA:mRNA interactions.
For rs1801157 minor allele (A) increased risk of CRC was observed in Asian population. This result is similar to previous meta‐analysis by Xu,191 which found significant association in non‐Caucasian populations. This polymorphism is located in 3'UTR of CXCL12 in a putative miRNA‐binding site for miR‐941.192 The effect of CXCL12 polymorphisms on CRC was previously observed in different studies. The CXCL12 binds to CXCR4 and affects different clinical features of cancers such as progression, angiogenesis, and metastasis.193 Thus the observed association for rs1801157 A allele and CRC may be related to its effect on miRNA:mRNA interactions and CXCL12 expression.

We also found no significant association between rs712 and risk of CRC, in the overall meta‐analysis of five included studies. However, subgroup analysis revealed remarkable and completely different results in Chinese and Czech Republic populations. In Chinese, we observed a strong risk while in Czech population a protective effect was shown in all various models. There is one study similar to our results which confirm the increase risk of this polymorphism in Chinese population.194 In two other meta‐analyses it has been reported that this polymorphism may increases the overall risk of different types of cancers in the Chinese population.195,196 This variant is within let‐7 KRAS binding site. KRAS, is an important oncogene, which has been previously described to be associated with different types of cancers. This gene influence cancer cells differentiation and proliferation, and is highly mutated in many type of cancers such as CRC.197,198 Based on our results differences between populations should be considered for the effect of this binding site polymorphism in future studies.

In addition, our results (based on 10 eligible studies) showed that rs5275 was not related to the risk of CRC. While the minor allele of rs5275 may have a protective effect on the risk of adenoma. This polymorphism is located in COX‐2 gene at miR‐542‐3p target site. COX‐2 is usually overexpressed in colorectal adenoma patients,199 and has effect on pro‐inflammatory prostaglandins and links between inflammation and cancer progression.200 Therefore, the minor allele of rs5275 may be associated with a decreased risk of colorectal adenoma by downregulating COX‐2 expression.

4.1 | Strength and limitations

Our study had several advantages: First, this is the first systematic review for evaluating the role of miRNA‐binding site polymorphisms on CRC susceptibility, and 25 polymorphisms were included in our pooled analysis. Second, to reduce the publication biases and include all relevant documents we carried out a systematic search on four common
**FIGURE 5** Forest plot related to rs712 and risk of CRC. A, Allelic model. B, Homozygote model. C, Dominant model. D, Recessive model. E, Heterozygote model. F, TT vs TG model.

**TABLE 5** Meta-analysis of association between rs1801157 and risk of CRC

| Classification       | Allelic | Q test P value | OR [95% CI] | P value | OR [95% CI] | OR [95% CI] | OR [95% CI] | Q test P value |
|----------------------|---------|----------------|-------------|---------|-------------|-------------|-------------|----------------|
| Caucasian (n = 3)    | 0.98    | 0.82-1.17      | 0.89        | 1.03    | 0.83-1.27   | 0.90        | 0.75        | 0.44-1.26      | 0.90        |
| Asian (n = 2)        | 2.28    | 1.11-4.69      | 0.02        | 2.20    | 0.66-7.30   | <0.01       | 4.94        | 1.69-14.42     | 0.58        |
| Overall (n = 6)      | 1.56    | 0.97-2.50      | <0.01        | 1.59    | 0.93-2.70   | <0.01       | 2.03        | 0.73-5.63      | 0.65        |

The bold values are statistically significant.
databases, as well as other sources such as references of relevant reviews. Third, there was no language bias, we included all relevant documents without any language restriction. Fourth, our study has high power and strength reliability because of our comprehensive and double search strategies and subgroup analyzing based on different ethnicity. Fifth, to reduce binding site false positive prediction, related to bioinformatics tools, we only included polymorphisms located in miRNA-binding site or 3’UTR (stated at least in two of the included documents).

There are also some limitations in our study. First, based on insufficient data, it was mandatory to exclude some relevant documents. Second, some polymorphisms had two or three included article. Third, CRC is a multifactorial disease and we only included genetic effect.

5 | CONCLUSION

miRNA-binding site polymorphisms in this meta-analysis showed significant association with CRC in different populations. Interestingly, rs731236 polymorphism showed a significant association with CRC in Middle East population with a heterozygote advantage. The minor allele in the East Asian populations for rs3025039, rs3212986, and rs712, and also in Asian population for rs1801157, increased the risk of CRC. The minor allele of rs712 may have a protective effect on the risk of CRC in Czech populations, while rs17281995 showed risk effect in the European population. Finally, it can be concluded that these miRNA-binding site polymorphisms play different roles on the risk of CRC in various populations which should be considered in data analysis and interpretation in the future studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

| TABLE 6 | Meta-analysis of association between rs5275 and risk of CRC (n = 9) and adenoma (n = 7) |
| --- | --- |
| Classification | Allelic | Dominant | Recessive | Overdominant |
| | OR [95% CI] | Q test | P value | OR [95% CI] | Q test | P value | OR [95% CI] | Q test | P value |
| CRC | 1.03 [0.98-1.09] | .16 | | 1.03 [0.92-1.16] | .18 | | 1.04 [0.97-1.12] | .38 | | 0.97 [0.90-1.04] | .70 |
| Adenoma | 0.92 [0.85-1.00] | .78 | | **0.82 [0.70-0.97]** | .19 | | 0.94 [0.83-1.05] | .07 | | 0.90 [0.71-1.15] | <.01 |
| Overall | 1.00 [0.95-1.04] | .16 | | 0.96 [0.87-1.05] | .05 | | 1.01 [0.95-1.08] | .09 | | 0.95 [0.86-1.04] | .01 |

The bold values are statistically significant.

| TABLE 7 | Meta-analysis of association between rs4648298 and risk of CRC (n = 2) and adenoma (n = 2) |
| --- | --- |
| Classification | Allelic | Dominant/Overdominant/Heterozygote |
| | OR [95% CI] | Q test | P value | OR [95% CI] | Q test | P value |
| CRC | **1.93 [0.21-17.52]** | <.01 | | **0.47 [0.04-5.39]** | <.01 |
| Adenoma | 1.02 [0.48-2.18] | .99 | | 0.98 [0.46-2.11] | .99 |
| Overall | 1.41 [0.49-4.05] | <.01 | | 1.47 [0.47-4.63] | <.01 |

*These models had similar results, because of zero number in GG genotype.*
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