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REVIEW PAPER

Correlation of a well-known genetic variation in one-carbon metabolism pathway with breast cancer susceptibility in Iranian population

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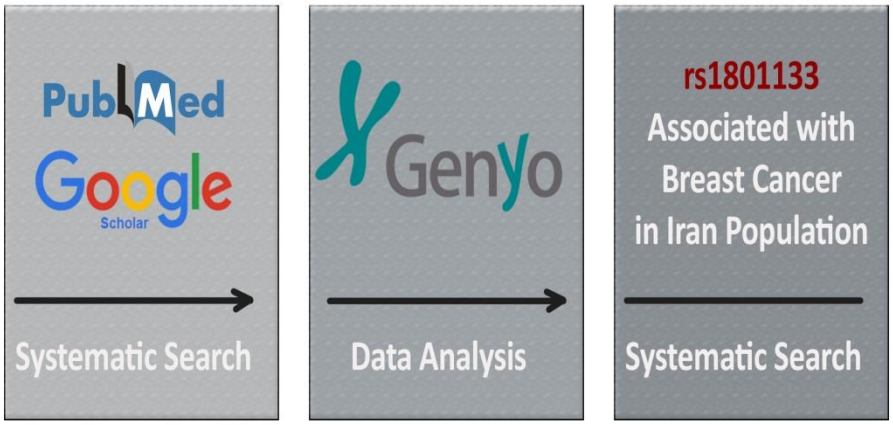
Highlights

- MTHFR is an essential gene for cell procedures and tumor pathways.
- rs1801133 is associated with breast cancer in the Iranian population.
- rs1801133 is associated with breast cancer in studies with a sample size greater than 250 subjects.

Graphical Abstract



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Abstract

The one-carbon metabolism pathway is an essential cycle in cellular reactions. Methylenetetrahydrofolate reductase is a critical gene in this pathway. This gene contains numerous variations in which the rs1801133 is considered the most common polymorphism. This study was aimed to examine the correlation of the above-mentioned genetic variation with the risk of breast cancer in the Iranian population through a meta-analysis procedure. In this search, valid electronic databases such as PubMed and Goggle scholar were used to gather eligible studies. Finally, five useful articles were included in our meta-analysis. The odds ratio (OR) and 95% confidence interval (CI) were examined by http://bioinfo.genyo.es/metagenyo online software to evaluate the strength of association values. The data from the meta-analysis illustrated that the rs1801133 genetic variation is correlated with breast cancer in TT vs. CC and TT vs. CC+CT hereditary models within Iranian women. Also, the OR analysis revealed that the studies with a sample size > 250 were associated with breast cancer. According to these findings, the studied single nucleotide polymorphism could be considered a molecular genetic variation for breast cancer in Iranian women.

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Introduction

In Iran, breast cancer accounts for 16% of all cancers and is still ranked first. The incidence of breast cancer in almost all provinces of Iran is very high (1). Identifying the causative agents of this disease, including its genetic factors, will provide valuable information to researchers and physicians to find a way to prevent, treat, or at least increase the life expectancy of patients. Some researchers have examined the cellular and molecular aspects of breast cancer, but many of the risk factors for breast cancer are unknown (2).

Methylenetetrahydrofolate reductase (MTHFR) is a rate-limiting enzyme in the methyl cycle, encoded by the MTHFR gene (3). Methylenetetrahydrofolate reductase catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. 5-Methyltetrahydrofolate is a common substrate for the re-methylation of homocysteine to methionine (4). Folate is important for the synthesis and methylation of DNA as well as for protein synthesis. Homocysteine is a sulfur-consisting amino acid metabolite of the crucial amino acid methionine (5). This enzyme is involved in an essential biochemical interaction in the folate cycle between methionine and S-adenosyl methionine. Folate plays a crucial role in regulating homocysteine homeostasis (6). Researchers have reported that folate deficiency increases DNA failure (7). Many mechanisms might elucidate the correlation between serum folate levels and breast cancer. Serum folate levels are inversely related to serum homocysteine (Hcy) concentrations (8). Decreased serum vitamin B levels increase homocysteine concentration and thus disrupt the re-methylation cycle, which ultimately disrupts DNA synthesis, repair, and methylation (9). The MTHFR gene has polymorphisms at several points, but there are three prevalent single nucleotide polymorphisms (SNPs), A1298C (rs1801131), C677T (rs1801133), and G1793A (rs2274976) in this gene that the frequency of these variations is geographically different. C677T and A1298C polymorphisms reduce folate metabolism and hyperhomocysteinemia by 70% (10, 11).

Some previous studies studied the correlation of polymorphism *MTHFR*-C677T with the risk of breast cancer. Sohn et al. in 2004 found that C677T single nucleotide polymorphism has a role in the risk of breast tumor (12). A meta-analysis in 2017 determined that *MTHFR*-C677T variation might be a genetic risk factor for breast cancer, especially in Asians (13). Another meta-analysis in 2016 concluded that *MTHFR*-A1298C variation might increase the risk of breast tumor (14). Another meta-analysis in 2019 indicated that the C677T variation is correlated with a substantial risk for development of breast cancer in Latino ethnicity, whereas they did not report this association for A1289C polymorphism (15). However, some studies investigate the correlation of C677T variation in the *MTHFR* sequence with risk of breast cancer in the Iranian population, but the outcomes are questionable (16, 17). Therefore, the purpose of this study is to determine the association of C677T SNP of the *MTHFR* with the risk of breast cancer in Iran by a meta-analysis.

Materials and methods

Search approach and paper selection standards

The papers were obtained by exploring the Google Scholar, PubMed, and valid Persian databases using the following keywords “C677T”, “677C>T”, “methylenetetrahydrofolate reductase” and “MTHFR”, “breast cancer”, published up to the end of 2020. Also, the search was done in the Persian language. The inclusion principles for the current quantitative synthesis meta-analysis were: (1) papers must examine the correlation between *MTHFR*-C677T SNP and breast tumor in Iran; (2) papers must include complete information on genotype frequencies of controls and cases; (3) papers must be case-control design with human origin. Exclusion principles were: (1) paper design contrary to case-control; (2) papers with other cancers or men breast cancer; (3) papers in countries other than Iran; and (3) review, case report, meta-analysis and other similar papers. Duplicated publications were also excluded.

Data extraction

Two researchers independently isolated the features of the included papers. The following information from each paper was extracted: name of the author, city in Iran, sample size, age mean of cases and controls, lymph

node metastasis, genotype frequencies of C677T variation in the case and healthy controls, a p-value of Hardy-Weinberg equilibrium (HWE) in control groups, and genotyping method. Outcomes were compared, and possible differences were solved by argument. If critical data was lost from the paper, the investigator of the particular papers were contacted by email or telephone and requested to provide further data.

Statistical analysis

The strength of correlation of the *MTHFR*-C677T SNP and risk of breast cancer was assessed by odds ratios (OR) with the 95% confidence intervals (95% CI). We calculated the risk of MTHFR-C677T gene variation using the following six genetic models: T vs. C, TT vs. CC, CT vs. CC, CT+TT vs. CC, TT vs. CC+CT, CT vs. TT+CC. We estimated the heterogeneity among studies by the Cochran's chi-square Q test and I^2 score. When the heterogeneity was low (P heterogeneity> 0.1), the fixed-effects model was used to calculate OR; otherwise, a model of random-effects was used. Statistical assessments in the meta-analysis procedure were carried out by http://bioinfo.genyo.es/metagenyo/ online software.

Results and Discussion

Eligible articles and study characteristics

By searching in databases, 113 potentially relevant studies were found for C677T variation. After screening the papers according to the inclusion and exclusion principles, 5 eligible papers (16-20) were finalized for our meta-analysis. The complete procedure of selecting the studies is presented in Figure 1, and the detailed data of each qualified paper is illustrated in Table 1. These articles were published between 2016 and 2019. Three publications were from Fars ethnicity, and two remainders were from Arab and Kurd ethnicities. No deviation from HWE was found for control groups of all included studies. Four papers used the PCR-RFLP method to genotyping SNP, and one of them used the TaqMan method. The quality assessment of the included papers was also provided in Table 1 that three of them were of high quality, and two others were moderate to high quality. Concerning A1298C polymorphism, we found just one paper that did not meet the inclusion criteria for definitive cancer diagnosis.

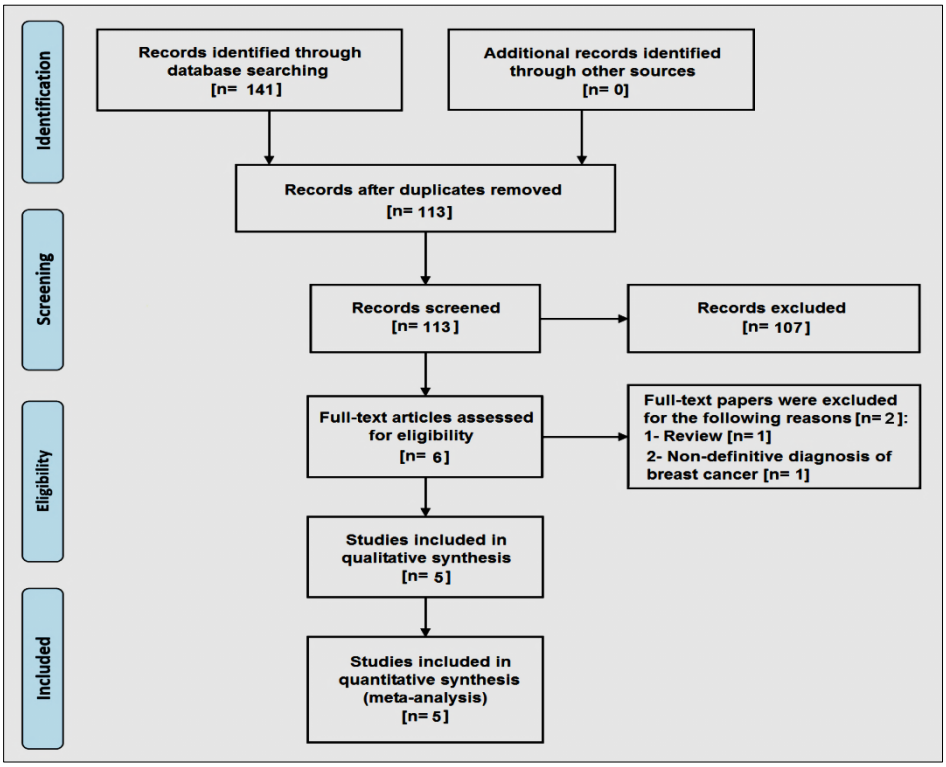

Figure 1. PRISMA flow diagram of the Iranian populations' studies: The chart shows a systematic review of the literature for inclusion/exclusion of the Iranian populations' studies in meta-analysis.

Meta-analysis results

After pooling all data, the overall number of case and control subjects from five eligible studies were calculated 527 and 659, respectively. The genetic correlation outcomes of meta-analysis are detailed in Table 2. Overall, a meaningfully correlation was found between C677T variation an increased risk of breast cancer under TT *vs*. CC (OR= 3.64, 95%CI= 1.14-11.62, *p*= 0.029) and TT *vs*. CC+CT (OR= 3.05, 95%CI= 1.07-8.70, *p*= 0.037) genetic models (Table 2, Figure 2). Stratified examination by ethnicity showed no significant correlation between C677T genetic variation and breast cancer risk for Fars ethnicity in all genetic models. After subgroup analysis by sample size, we detected substantial associations between the C677T variation and breast cancer risk in papers with sample size> 250 subjects for T *vs*. C (OR= 1.89, 95%CI= 1.44-2.48, *p*< 0.001), TT *vs*. CC (OR= 3.38, 95%CI= 1.69-6.76, *p*= 0.001), CT+TT *vs*. CC (OR= 2.11, 95%CI= 1.03-4.32, *p*= 0.041), TT *vs*. CC+CT (OR= 2.52, 95%CI= 1.28-4.96, *p*= 0.007) genetic models. Besides, significant associations were observed for studies with STREGA score between 18-22 in TT *vs*. CC (OR= 2.80, 95%CI= 1.52-5.14, *p*= 0.001) and TT *vs*. CC+CT (OR= 2.28, 95%CI= 1.25-4.13, *p*= 0.007) genetic models. As well, we found noteworthy associations in studies that used PCR-RFLP method in TT *vs*. CC (OR= 2.35, 95%CI= 1.33-4.15, *p*= 0.003) and TT *vs*. CC+CT (OR= 2.00, 95%CI= 1.14-3.48, *p*= 0.015) genetic models (Tables 2).

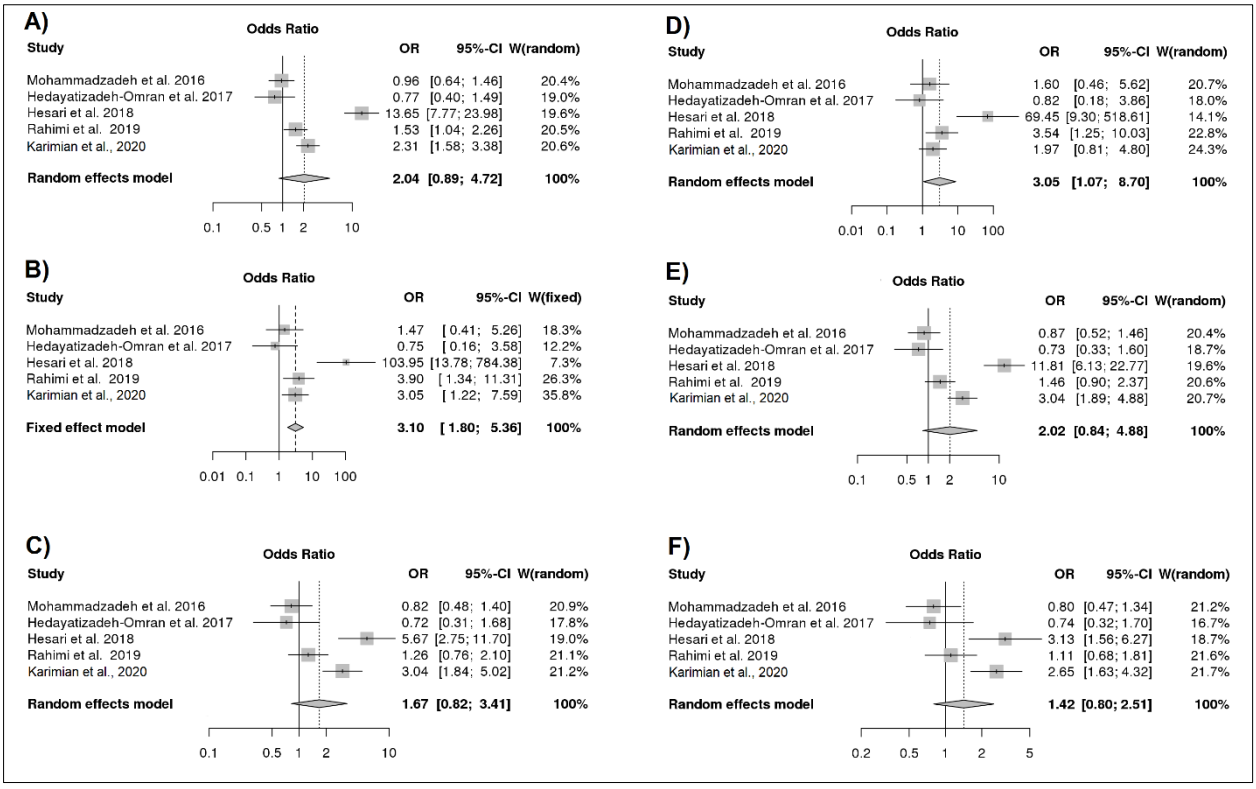

Figure 2. Forest plot of the meta-analysis for *MTHFR*-C677T in allelic, heterozygote, homozygote, recessive, dominant, and overdominant models.

Heterogeneity and publication bias

The outcomes of heterogeneity and publication bias were summarized in Table 3. Overall heterogeneity analysis showed that there are true heterogeneities in all five genetic models, which are remained in the Fars ethnicity subgroup. Stratified analysis by sample size revealed that the heterogeneities disappeared in studies with sample sizes more than 250 subjects in T *vs*. C (P_h= 0.137, I^2= 0.55), TT *vs*. CC (P_h= 0.730, I^2= 0), and TT *vs*. CC+CT (P_h= 0.404, I^2= 0) genetic models. Besides, this was observed after stratification in studies with STREGA score between 18-22 in TT *vs*. CC (P_h= 0.500, I^2= 0) and TT *vs*. CC+CT (P_h= 0.580, I^2= 0) and also in studies employing PCR-RFLP method in TT *vs*. CC (P_h= 0.289, I^2= 0.201) and TT *vs*. CC+CT (P_h= 0.468, I^2= 0) genetic models. Possible publication bias of the current meta-analysis was evaluated by funnel plot (Figure 3), which

showed no noteworthy publication bias in total and stratified subgroup analyses. Egger's test approved this analysis, and we did not observe any publication bias (P_{Egger}> 0.05).

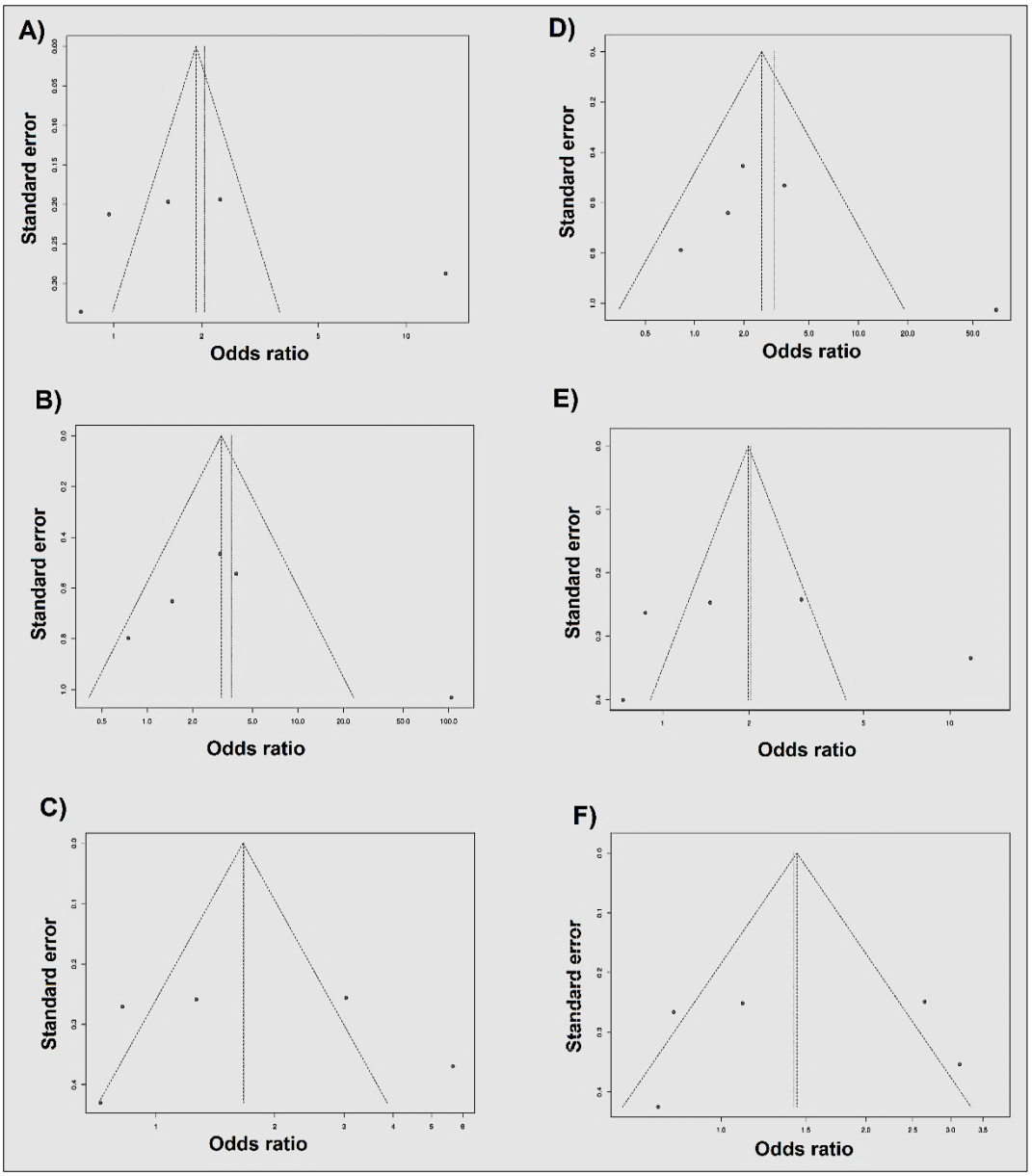

Figure 3. Funnel plot of the meta-analysis for *MTHFR*-C677T in allelic, heterozygote, homozygote, recessive, dominant, and over dominant models.

Breast cancer is one of the most malignant and invasive cancers and is the second leading cause of cancer-related mortality worldwide (21). Various factors such as hormones, lifestyle, environmental factors, and genetic factors are essential in carcinogenic effects. Some genes that are essential candidates in susceptibility to breast cancer include hOGG, GSM1, CYP19, and CASP8 (22). Some studies have focused on the genetic variants of enzymes involved in one-carbon metabolism with breast cancer risk (21, 23). Variations in enzymes involved in metabolism of one-carbon such as methylene tetrahydrofolate reductase (MTHFR), methionine synthase (MTR) thymidylate synthetase (TS), methionine synthase reductase (MTRR) and play an vital role in the folate metabolism (24, 25). Folate metabolism is a cycle in which enzymes interact with each other through their substrates (23). Single nucleotide polymorphisms in the MTHFR gene can be a risk factor for breast cancer (26, 27, 28). This paper investigated the correlation of C677T variation in the MTHFR sequence with the risk of breast tumor in Iran by a meta-analysis process. We observed that the C677T polymorphism could be considered a risk factor for breast tumors in Iranian women (29).

Table 1. Characteristics of included studies in meta-analysis.

City in Iran (Ethnicity)	Sample size (Case/Control)	Age mean (Case Control)	Lymph node metastasis	Genotype frequencies						*P* HWE	Genotyping method	Author, Year (Reference)
				Case			Control					
				CC	CT	TT	CC	CT	TT			
Ahvaz (Arab)	233 (123/110)	48.56 ± 11.32 48.96 ± 07.81	-	68	48	7	57	49	4	0.093	PCR-RFLP	Mohammadzadeh et al., 2016
Mazandaran (Fars)	114 (54/60)	47.90 ± 11.40 35.80 ± 12.90	35.20%	38	13	3	38	18	4	0.368	PCR-RFLP	Hedayatizadeh-Omran et al., 2017
Arak (Fars)	242 (100/142)	48.50 ± 09.97 46.71 ± 08.09	18.00%	40	27	33	126	15	1	0.464	TaqMan	Hesari et al., 2018
Kermanshah (Kurd)	297 (100/197)	49.50 ± 10.20 51.20 ± 10.90	72.00%	50	40	10	117	74	6	0.157	PCR-RFLP	Rahimi et al., 2019
Kashan (Fars)	300 (150/150)	43.45 ± 6.31 44.80 ± 6.21	58.67%	64	71	15	104	38	8	0.082	PCR-RFLP	Karimian et al. 2020

Table 2. Association results in the meta-analysis for C677T polymorphism.

Group	T *vs.* C		TT *vs.* CC		CT *vs.* CC		CT+TT *vs.* CC		TT *vs.* CC+CT		CT *vs.* TT+CC	
	OR (95% CI)	*p*	OR (95% CI)	*P*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Total	2.04 (0.89-4.72)	0.094	3.64 (1.14-11.62)	0.029	1.67 (0.82-3.41)	0.154	2.02 (0.84-4.88)	0.118	3.05 (1.07-8.70)	0.037	1.42 (0.80-2.51)	0.233
Fars ethnicity	2.92 (0.68-12.46)	0.149	2.18 (0.45-10.56)	0.331	2.39 (0.85-6.66)	0.097	3.01 (0.76-11.97)	0.117	4.21 (0.52-34.43)	0.180	1.92 (0.89-4.16)	0.096
Sample size< 250	2.17 (0.37-12.66)	0.391	4.42 (0.33-59.75)	0.264	1.50 (0.42-5.38)	0.537	1.96 (0.34-11.29)	0.452	4.05 (0.40-41.24)	0.237	1.23 (0.49-3.06)	0.661
Sample size> 250	1.89 (1.44-2.48)	< 0.001	3.38 (1.69-6.76)	0.001	1.96 (0.83-4.63)	0.124	2.11 (1.03-4.32)	0.041	2.52 (1.28-4.96)	0.007	1.71 (0.73-4.03)	0.216
PCR-RFLP method	1.33 (0.83-2.10)	0.233	2.35 (1.33-4.15)	0.003	1.27 (0.66-2.44)	0.473	1.34 (0.71-2.52)	0.364	2.00 (1.14-3.48)	0.015	1.18 (0.65-2.16)	0.580

Table 3. Results of heterogeneity and publication bias in the meta-analysis.

Group	T *vs.* C			TT *vs.* CC			CT *vs.* CC			CT+TT *vs.* CC			TT *vs.* CC+CT			CT *vs.* TT+CC		
	Ph	I^2	P_E	*Ph*	I^2	P_E	*Ph*	I^2	P_E	*Ph*	I^2	P_E	*Ph*	I^2	P_E	*Ph*	I^2	P_E
Total	1e-04	0.94	0.733	0.003	0.75	0.543	1e-04	0.86	0.955	1e-04	0.92	0.907	0.009	0.71	0.413	7e-04	0.79	0.900
Fars ethnicity	1e-04	0.96	0.991	7e-04	0.86	0.700	0.001	0.85	0.705	1e-04	0.93	0.845	0.002	0.84	0.613	0.017	0.75	0.520
Sample size< 250	1e-04	0.97	0.816	3e-04	0.88	0.402	1e-04	0.90	0.798	1e-04	0.96	0.873	0.002	0.85	0.414	0.004	0.82	0.830
Sample size> 250	0.137	0.55	-	0.730	0	-	0.016	0.83	-	0.035	0.78	-	0.404	0	-	0.014	0.84	-
PCR-RFLP method	0.004	0.77	0.326	0.289	0.201	0.106	0.001	0.81	0.508	0.001	0.81	0.398	0.468	0	0.336	0.003	0.78	0.538

Some previous examination has stated that MTHFR-C677T and MTHFR-A1298C correlate with an elevated risk of breast tumours (24, 26). Some studies have described no correlation between these polymorphisms and breast cancer (23, 27, 28). The discrepancies in the results of different studies may be due to differences in population backgrounds, environmental and genetic factors. Methyltetrahydrofolate has a prominent role in the balance of methyl groups between DNA synthesis and DNA methylation (29, 30). This enzyme plays a chief role in the metabolism of one-carbon by accelerating the permanent conversion of 5, 10-methylene tetrahydrofolate (required for DNA synthesis) to 5-methyl-tetrahydrofolate (required for DNA methylation). This is a form of carbon donor folate to convert homocysteine to methionine. The methyl methionine group is used to form S-adenosyl methionine. S-adenosyl methionine is a methyl donor for DNA and protein methylation (31-35). 5, 10-methylene tetrahydrofolate is similarly vital for the synthesis of purine and thymidylate. Thus, MTHFR activity and folate accessibility might both influence gene regulation. A form that has little activity leads to a decrease in S-adenosyl methionine and consequently hypomethylation. This phenomenon raises the breast tumor risk. The possible impact of MTHFR activity on methylation of DNA and the accessibility of thymidylates and uridylates for the synthesis of DNA and its repair is one of the important candidates for cancer (36-38).

Conclusion

One of the research fields in breast cancer genetics is the study of polymorphism in genes involved in breast cancer. Genetic polymorphisms in these genes can be a risk factor for some disorders, including breast cancer. There are many genes in which polymorphisms affect the incidence of breast cancer. One of the crucial genes in which polymorphism causes breast cancer is methylenetetrahydrofolate reductase gene. Statistical analysis of this study shows that people containing the T allele of C677T polymorphism are at high risk for breast cancer. Therefore, this mutation may be a genetic risk factor for breast cancer among Iranian women. As a result, these gene polymorphisms could be considered a potential biomarker for screening people prone to breast cancer.

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