ASSOCIATION OF MTHFR A1298C POLYMORPHISM WITH BREAST CANCER AND/OR OVARIAN CANCER RISK: AN UPDATED META-ANALYSIS

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Abstract

Background: Recent years have witnessed the discovery of similar gene variations between breast cancer and ovarian cancer, inherited breast and ovarian cancer in particular. A large number of case-control studies have been conducted to explore the association of Methylenetetrahydrofolate Reductase (MTHFR) A1298C polymorphism with breast cancer and/or ovarian cancer risk. However, the results are still inconsistent and inconclusive. Consequently, we performed a meta-analysis to evaluate the association between MTHFR A1298C polymorphism and breast, ovarian cancer risk.

Materials and Methods: A comprehensive retrieval was conducted in the electronic database of PubMed, Web of Science and Chinese National Knowledge Infrastructure (CNKI) until June 2015 to identify eligible studies. A total of 35 studies which examined the association of MTHFR A1298C polymorphism with breast cancer and/or ovarian cancer were identified. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the effect of gene polymorphism. And allele model, homozygous model, co-dominant model, dominant model, recessive model were applied.

Result: In the overall analysis, significantly increased breast cancer and/or ovarian cancer risk was found (for allele model A VS C OR = 1.05, CI: 1.02-1.08, P = 4×10⁻³; for homozygous model AA VS CC OR = 1.11, CI: 1.03-1.19, P = 5×10⁻³; for recessive model (AC +AA) VS CC: OR = 1.10, CI: 1.03-1.18, P = 7×10⁻³).

Conclusion: In the subgroup analysis, significantly increased breast cancer risk was identified among Caucasians. MTHFR A1298C polymorphism might contribute to an increased risk of breast cancer and/or ovarian cancer susceptibility. In addition, MTHFR A1298C polymorphism had a significant association with breast cancer in Caucasians.

Key words: Breast cancer, Ovarian cancer, MTHFR A1298C, Polymorphism, Meta-analysis
Introduction

Breast cancer is one of the most common cancer among women in the world, accounting for 411093 cancer deaths per year, while ovarian cancer is the leading cause of gynecologic cancer death worldwide (Kamangar et al., 2006; Jemal et al., 2010). There are many risk factors such as genetic, hormonal and environmental factors involved in the pathogenesis of breast cancer and/or ovarian cancer in women (Rizzolo et al., 2013). Over the last few years, there was strong evidence that rare gene mutations played an important role in breast and ovarian cancer predisposition (Tumbull et al., 2008). For instance, the variation in the BRCA1 and BRCA2 genes is the most common genetic cause of hereditary forms of both breast cancer and ovarian cancer; and the prevalence of BRCA1 or BRCA2 mutation is different among ethnic groups, countries and regions (Gayther et al., 2010). In addition, a lot of rare variants that confer the risks of breast, ovarian cancer are discovered with many case-control studies. More recently, some rare gene mutations such as PPM1D, PALB2, ATM, CHEK2, BRIP1 and RAD51C gene involved in DNA repair were found in sporadic breast, ovarian cancer (Ruark et al., 2013). Women who carried mutations in these genes had a high risk of breast cancer and/or ovarian cancer. Furthermore, many molecular commonalities which were conducive to exploring related aetiology and similar therapeutic opportunities of breast cancer and/or ovarian cancer were found (Kobolot et al., 2012). The finding of these similar Molecular mutations was helpful for providing new molecular therapeutic targets (Balmana et al., 2011).

Folate metabolism plays a crucial role in nucleic acid synthesis, methionine regeneration, oxidation and reduction reactions of one carbon units (Morita et al., 2013). And adequate folate intake is benefit for cell division and homeostasis. Moreover, Folates can mediate the transfer of one carbon units which is vital for the synthesis of S-adenosylmethionine (SAM) which offers the methyl group in the methylation reaction of DNA, RNA and protein (Yang et al., 2012). Therefore, the abnormality of folate metabolism will have a negative effect on the methylation and synthesis of DNA. Methyleneetetrahydrofolate reductase (MTHFR) gene is located on the chromosome 1, which mediates the irreversible conversion of 5, 10-methylenetetrahydrofolate (5, 10-MTHF) to 5-methyltetrahydrofolate (5-MTHF) which is the predominant form of folate in plasma and provides the methyl group for de novo methionine synthesis (Zhao et al., 2011). C677T in exon 4 and A1298C in exon7 are the most common nucleotide polymorphisms (SNPs) in MTHFR gene. Studies have found the two polymorphisms can reduce amount of 5-MTHF and increase amount of 5, 10-MTHF (Jing et al., 2012).

In recent years, several studies have been conducted to evaluate the association of gene polymorphisms with the breast cancer and/or ovarian cancer. But the evidence was not enough to explain the molecule origin of breast cancer and ovarian cancer. At the same time, many studies concerning the association of the MTHFR A1298C polymorphism with breast and/or ovarian cancer have been conducted, but the association between sporadic breast, ovarian cancer and Methyleneetetrahydrofolate Reductase (NADPH2) gene A1298C (rs1801131) polymorphism remained controversial and ambiguous. Thus, to further clarify the molecule origin of breast cancer and ovarian cancer and offer a molecular target for molecular detection of breast cancer and/or ovarian cancer, the meta-analysis of evaluating the association between MTHFR A1298C polymorphism and breast, ovarian cancer was performed.

Materials and Methods

Publication Search Strategy

Genetic association studies between breast, ovarian cancer and the MTHFR A1298C polymorphism, up to June, 2015, were retrieved by searching PubMed, Web of Science and CNKI (Chinese National Knowledge Infrastructure) database with combinations of the following terms: “MTHFR”, “A1298C”, “rs1801131”, “polymorphism”, “SNP”, “mutation”, “breast carcinoma”, “breast cancer”, “breast neoplasm”, “breast malignance”, “ovarian carcinoma”, “ovarian cancer”, “ovarian neoplasm”, “ovarian malignance”, “breast and ovarian carcinoma”, “breast and ovarian cancer”. In addition, only published studies with full text articles were included. And full text of the retrieved articles was scrutinized to confirm that the data included could be used to perform meta-analysis.
Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) evaluation about the association of MTHFR A1298C polymorphism with breast cancer and/or ovarian cancer risk; (b) case-control studies; (c) genotype data were available for cases and controls; (d) genotype distribution of control must be fit in Hardy–Weinberg equilibrium (HWE).

The exclusion criteria were as follows: (a) no detailed information of genotype data; (b) duplicate of a previously published study; (c) deviation from HWE in controls.

Data Extraction

Information was extracted from the included publications according to the inclusion criteria and the exclusion criteria. The following data were collected: author’s surname, year of publication, country, racial descent, cancer type, source of the control population, genotyping method and the frequency of genotype. Two authors independently extracted this information from all eligible studies (Table1).

| Author        | Year | Nationality | Ethnicity | Cancer Type | Case/Control | Genotype(Case/Control) | Genotyping Method | Source of control | P for HWE |
|---------------|------|-------------|-----------|-------------|--------------|------------------------|------------------|------------------|----------|
| Song et al    | 2012 | China       | Asian     | OC          | 202/198      | 107/1 12            | Taqman           | HB               | 0.35     |
| Webb et al    | 2011 | Australia   | Mixed     | OC          | 1638/12 78   | 770/5 98 61         | Mass             | PB               | 0.44     |
| Terry et al   | 2010 | USA         | Caucasian | OC          | 1038/10 93   | 515/5 34 50         | Taqman           | PB               | 0.32     |
| Terry et al   | 2010 | USA         | Caucasian | OC          | 153/484 68/23| 67/20 9            | Taqman           | PB               | 0.56     |
| Terry et al   | 2010 | USA         | Caucasian | OC          | 364/412 173/1| 149/1 42/43        | Taqman           | PB               | 0.99     |
| Lu et al      | 2015 | China       | Asian     | BC          | 560/560 369/3| 172/1 19/23        | Taqman           | HB               | 0.83     |
| He et al      | 2014 | China       | Asian     | BC          | 310/381 138/1| 132/1 40/53        | PCR-RFLP         | HB               | 0.06     |
| Huang et al   | 2014 | China       | Asian     | BC          | 1232/12 32  | 787/7 386/3 59/45  | PCR-RFLP         | HB               | 0.72     |
| Wang et al    | 2014 | China       | Asian     | BC          | 435/435 206/2| 176/1 53/49        | PCR-RFLP         | HB               | 0.11     |
| Qiao et al    | 2014 | China       | Asian     | BC          | 535/673 258/3| 235/2 42/42        | PCR-RFLP         | HB               | 0.25     |
| Zheng et al   | 2013 | China       | Asian     | BC          | 296/306 135/1| 129/1 32/25        | PCR-RFLP         | HB               | 0.69     |
| Akilzhanova et al | 2013 | Kazakhstan | Asian     | BC          | 315/604 138/3| 142/2 35/44        | Taqman           | PB               | 0.83     |
| Authors          | Year | Country | Ethnicity | Breed Type | Samples | PCR/RFLP | Notation | Nucleotide Similarity |
|------------------|------|---------|-----------|------------|---------|----------|----------|----------------------|
| Wu et al         | 2012 | China   | Asian     | BC         | 75/75   | 37/42    | 32/28    | 6/5                  | 0.91     |
| Lajin et al      | 2011 | Syria   | Asian     | BC         | 119/126 | 44/65    | 52/48    | 23/13                | 0.36     |
| Hua et al        | 2011 | China   | Asian     | BC         | 95/90   | 50/55    | 42/32    | 3/3                  | 0.52     |
| Papandreou et al | 2011 | Greece  | Caucasian | BC         | 300/283 | 129/1    | 135/1    | 36/16                | 0.41     |
| Hosseini et al   | 2011 | Iran    | Caucasian | BC         | 294/300 | 36/60    | 96/13    | 162/1                | 0.17     |
| Cerne et al      | 2011 | Slovenia| Caucasian | BC         | 524/269 | 258/1    | 219/1    | 47/21                | 0.46     |
| Vainer et al     | 2010 | Russia  | Caucasian | BC         | 831/785 | 398/3    | 353/3    | 80/76                | 0.74     |
| Ma et al         | 2009 | Brazil  | Mixed     | BC         | 458/458 | 269/2    | 168/1    | 21/22                | 0.99     |
| Ericson et al    | 2009 | Sweden  | Caucasian | BC         | 541/107 | 242/4    | 242/4    | 57/10                | 0.40     |
| Ma et al         | 2009 | Japan   | Asian     | BC         | 388/387 | 254/2    | 119/1    | 15/15                | 0.68     |
| Platek et al     | 2009 | USA     | Mixed     | BC         | 928/178 | 443/8    | 402/7    | 83/18                | 0.59     |
| Gao et al        | 2009 | China   | Asian     | BC         | 624/624 | 446/4    | 169/1    | 9/11                 | 0.06     |
| Kotsopoulos et al| 2008 | Canada  | Caucasian | BC         | 941/780 | 466/3    | 390/3    | 85/73                | 0.25     |
| Inoue et al      | 2008 | Singapore| Asian     | BC         | 380/662 | 225/3    | 139/2    | 16/41                | 0.48     |
| Kan et al        | 2007 | China   | Asian     | BC         | 125/101 | 70/61    | 41/32    | 14/8                 | 0.21     |
| Xu et al         | 2007 | USA     | Mixed     | BC         | 1062/11 | 558/5    | 417/4    | 87/11                | 0.39     |
| Stevens et al    | 2007 | USA     | Mixed     | BC         | 494/493 | 224/2    | 228/2    | 42/40                | 0.99     |
| Kalyankumar et al| 2006 | India   | Caucasian | BC         | 88/95   | 49/65    | 33/26    | 6/4                  | 0.50     |
| Chou et al       | 2006 | China   | Asian     | BC         | 142/285 | 104/1    | 30/95    | 8/18                 | 0.32     |
| Justenhoven et al| 2005 | Germany | Caucasian | BC         | 582/634 | 273/2    | 256/2    | 53/73                | 0.27     |
| Shrubsole et al  | 2004 | China   | Asian     | BC         | 1121/12 | 768/8    | 311/3    | 42/40                | 0.58     |
| Qi et al         | 2007 | China   | Asian     | BC         | 217/218 | 155/1    | 58/71    | 4/3                  | 0.08     |
OC, ovarian cancer; BC, breast cancer; HB, hospital based control; PB, population based control; Mixed, mixed population; PCR-RFLP, Polymerase Chain Reaction- Restriction Fragment Length Polymorphism.

### Statistical Analysis

HWE was tested by the Chi-square test only in control groups of each study included. Crude odds ratios (ORs) with 95% confidence intervals (95%CIs) were used to evaluate the strength of association between MTHFR A1298C and breast cancer and/or ovarian cancer susceptibility. In the overall and subgroup analysis, the associations of MTHFR A1298C polymorphism with breast cancer and/or ovarian cancer risk were evaluated with five genetic models: homozygous model (AA VS CC), co-dominant model (AA VS AC), dominant model (AA VS (AC + CC), recessive model ((AC + AA) VS CC) and allele model (A VS C ). Subgroup analysis based on tumor type, ethnicity and source of control were performed. Heterogeneity was detected by the Chi-square based on Q test (P < 0.05, the significant level of statistical heterogeneity) and I^2 index (I^2 ≥ 50%, the significant level of statistical heterogeneity). The random-effect model (DerSimonian et al., 1986) would be used if moderate or high heterogeneity existed. Otherwise, the fixed effects model (the Mantel-Haenszel method) was used (Mantel et al., 1959). Egger’s test and Begg’s funnel plots were performed to examine the publication bias. Sensitivity analysis was conducted by removing each study and observed the stability of the conclusion. Statistical analysis was carried out with STATA (Version 12.0, College Station, TX, USA) software. All the tests were two-sided.

### Results

#### Study Characteristics

A total of 609 relevant publications were retrieved from our initial electronic search with 5 letters, 3 case reports, 14 meta-analyses, 6
reviews. 143 publications were included after eliminating meta-analysis, review and scanning the title and abstract. By reading full-text, 97 articles were excluded because they were not associated with MTHFR A1298C polymorphism and breast, ovarian cancer susceptibility or didn’t contain available data. 1 study was removed because of the same data in two studies. Moreover, 9 case-control studies were deviated from HWE and the data of 1 study was inaccuracy which the number of 1298AA carriers was larger than 1298CC carriers. As a consequence, 35 studies with 19,527 cases and 23,123 controls were finally identified in this meta-analysis. The method of literature retrieval was shown in Figure 1. Of all the eligible studies, there were 3 studies for ovarian cancer and 32 studies for breast cancer, while 19 researches were conducted in Asian populations, 15 were performed in Caucasian populations. Furthermore, the genotyping methods included TaqMan, Mass ARRAY, PCR-RFLP (Polymerase chain reaction- Restriction fragment length polymorphism) and Sequencing in these studies were extracted (Figure 1).

Quantitative Analysis

Overall analysis and subgroup analysis by tumor type, ethnicity and control sources were performed to evaluate the association between MTHFR A1298C polymorphism and breast, ovarian cancer risk with five genetic models. In the overall analysis, statistically significant association between MTHFR A1298C polymorphism and breast cancer and/or ovarian cancer susceptibility was detected in three genetic models (allele model, A VS C OR = 1.05, CI: 1.02 - 1.08, P = 4×10^-3; homozygous model, AA VS CC OR = 1.11, CI: 1.03 - 1.19, P = 5×10^-3; recessive model, (AC + AA) VS CC OR = 1.10, CI: 1.03 - 1.18, P = 7×10^-3) (Table 2). In the stratified analysis by racial descent, no increased risk of breast cancer and/or ovarian cancer was found, while subgroup analysis by cancer type indicated a significant association between MTHFR A1298C polymorphism and breast cancer risk (allele model, A VS C OR = 1.04, CI: 1.00 - 1.07, P = 4×10^-3; recessive model, (AC + AA) VS CC OR = 1.10, CI: 1.01 - 1.19, P = 0.02; homozygous model, AA VS CC OR = 1.10, CI: 1.02 - 1.19, P = 0.01). In subgroup meta-analysis by cancer type in different ethnicity, the 1298A allele yielded a significantly increased risk for breast cancer compared to the 1298C allele in Caucasians. Meanwhile, no significant association with a higher breast cancer and/or ovarian cancer risk in Asian populations was found. The stratified analysis by control source was also conducted, significant statistical difference was found in the subgroup of control based hospital (allele model, A VS C OR = 1.07, CI: 1.01 - 1.12, P = 0.02; recessive model, (AC + AA) VS CC OR = 1.13, CI: 1.00 - 1.28, P = 4.6×10^-3; homozygous model, AA VS CC OR = 1.16, CI: 1.02 - 1.31, P = 0.02) (Table 3). Furthermore, there is significant association between breast cancer and A1298C polymorphism in Caucasians (AA VS CC OR = 1.15, CI: 1.01 – 1.31, P = 0.03; (AC + AA) VS CC OR = 1.14, CI: 1.01 – 1.29, P = 0.03), while significant association of breast cancer risk with A1298C polymorphism was revealed in the subgroup of control based hospital (A VS C OR = 1.06, CI: 1.01 – 1.12, P = 0.03; AA VS CC OR = 1.14, CI: 1.01 – 1.30, P = 0.04.) (Table 3).
Table 2: Results of Genetic Models for MTHFR A1298C Polymorphisms and breast cancer and/or ovarian cancer

| MTHFR A1298C | A VS C | AA VS CC | AA VS (AC+CC) | (AC+AA) VS CC | AA VS AC |
|--------------|--------|----------|---------------|----------------|---------|
| Caucasian    |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.04(0.99-1.10) | 0.1   | 1.12(1.00-1.25) | 0.05 | 1.04(0.97-1.11) | 0.3 | 1.11(1.00-1.23) | 0.06 | 1.01(0.94-1.09) | 0.7 |
| Asian        |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.03(0.98-1.08) | 0.34  | 1.13(0.99-1.28) | 0.07 | 1.01(0.95-1.07) | 0.7 | 1.13(1.00-1.29) | 0.06 | 0.99(0.93-1.06) | 0.7 |
| Mixed        |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.02(0.96-1.08) | 0.51  | 1.03(0.89-1.18) | 0.72 | 1.03(0.96-1.11) | 5  | 1.01(0.89-1.16) | 0.87 | 1.03(0.95-1.12) | 6 |
| BC           |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.04(1.00-1.07) | 0.04  | 1.10(1.02-1.19) | 0.01 | 1.03(0.99-1.07) | 9  | 1.10(1.01-1.19) | 0.02 | 1.01(0.97-1.06) | 0.5 |
| OC           |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.02(0.95-1.09) | 0.64  | 1.07(0.91-1.27) | 0.41 | 1.00(0.91-1.10) | 0.9 | 1.08(0.99-1.09) | 0.35 | 0.99(0.89-1.09) | 0.8 |
| HB           |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.07(1.01-1.12) | 0.02  | 1.16(1.02-1.31) | 0.02 | 1.07(1.00-1.14) | 0.0 | 1.13(1.00-1.28) | 0.04 | 1.05(0.98-1.12) | 0.1 |
| PB           |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.00(0.97-1.04) | 0.84  | 1.02(0.93-1.12) | 0.68 | 1.00(0.95-1.05) | 0.9 | 0.98(0.90-1.07) | 0.64 | 1.00(0.95-1.05) | 0.8 |
| Total        |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.05(1.02-1.08) | 0.00  | 1.11(1.03-1.19) | 0.00 | 1.03(0.99-1.07) | 0.1 | 1.10(1.03-1.18) | 0.00 | 1.01(0.97-1.06) | 0.4 |

OC, ovarian cancer; BC, breast cancer; P, P value for χ²; OR, odds ratio; CI, confidence interval; Mixed, mixed population.

Table 3: Subgroup analysis results based type of cancer, ethnicity and source of control for breast cancer and/or ovarian cancer.

| MTHFR A1298C | Typ e | A VS C | AA VS CC | AA VS (AC+CC) | (AC+AA) VS CC | AA VS AC |
|--------------|-------|--------|----------|---------------|----------------|---------|
| Caucasian    |       |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.06(1.00-1.1) | 0.0   | 1.15(1.01-1.03) | 0.0 | 1.05(0.97-1.13) | 0.2 | 1.14(1.01-1.2) | 0.0 | 1.02(0.94-1.11) | 0.6 |
| BC           |       |        |          |               |                 |         |
| 0.99(0.89-1.0) | 0.7   | 0.97    | 0.8     | 0.984(0.86-1.1) | 0.8 | 0.98(0.78-1.2) | 0.8 | 0.99(0.86-1.1) | 0.8 |
| OC           |       |        |          |               |                 |         |
| 1.02(0.97-1.07) | 4    | 7      | 1       | 1.00(0.94-1.07) | 0.8 | 1.12(0.98-1.2) | 0.0 | 0.99(0.92-1.0) | 0.7 |
| Asian        |       |        |          |               |                 |         |
| OR/95%CI     | P      | OR/95%CI | P             | OR/95%CI       | P       |
| 1.20(0.87-1.6) | 0.2   | 1.86(0.79-4.3) | 0.1 | 1.16(0.78-1.72) | 0.4 | 1.81(0.78-4.1) | 0.1 | 1.07(0.71-1.6) | 0.7 |
Mixed physiopathological models were used to assess the association between the disease and the studied genetic models.

### Heterogeneity and Sensitivity Analysis

No significant heterogeneity was found in the meta-analysis. (Figure 2, Figure 3) Begg’s funnel plot and Egger’s test were used to evaluate the publication bias of the studies. No significant publication bias was found after Begg’s test and Egger’s test (for breast cancer: A VS C Begg’s test P=0.34, Egger’s test P=0.29; AA VS CC Begg’s test P=0.74, Egger’s test P=0.46; AA VS AC Begg’s test P=0.13, Egger’s test P=0.29; AA VS (AC+CC) Begg’s test P=0.09, Egger’s test P=0.14; (AC+AA) VS CC Begg’s test P=0.59, Egger’s test P=0.97; for ovarian cancer: A VS C Begg’s test P=0.33, Egger’s test P=0.21; AA VS CC Begg’s test P=0.62, Egger’s test P=0.37; AA VS AC Begg’s test P=0.14, Egger’s test P=0.35; AA VS (CA+CC) Begg’s test P=0.33, Egger’s test P=0.22; CC VS (CA+AA) Begg’s test P=0.33, Egger’s test P=0.35; for breast and/or ovarian cancer: A VS C Begg’s test P=0.16, Egger’s test P=0.18; AA VS CC Begg’s test P=0.59, Egger’s test P=0.30; AA VS AC Begg’s test P=0.07, Egger’s test P=0.17; AA VS (AC+CC) Begg’s test P=0.04, Egger’s test P=0.07; (AC+AA) VS CC Begg’s test P=0.53, Egger’s test P=0.75) (Figure 4). The random effect model was carried out in the case of P < 0.05, I² ≥ 50%, while the fixed effect model was applied to calculate the ORs value and 95%CI in the genetic models of P > 0.05, I² < 50%. In addition, the results were stable after sensitivity analysis.
Figure 2: Forest plot of MTHFR A1298C (AA VS CC) for breast cancer and/or ovarian cancer (Ethnicity)

OR, odds ratio; 95%CI, 95% confidence interval; Mixed, mixed population
**Figure 3:** Forest plot of MTHFR A1298C (AA VS CC) for breast cancer and/or ovarian cancer (Source of control). OR, odds ratio; 95% CI, 95% confidence interval.
Discussion

MTHFR is a key enzyme in the intracellular folate homeostasis and metabolism. A1298C (rs1801131) is one of the most common polymorphism of MTHFR gene, which leads to the changing of Glutamate (Glu) to Alanine (Ala). This polymorphism has been considered to affect the enzyme activity of MTHFR (Jing et al., 2012). Studies have suggested that the folate deficiency can influence the genetic stability of DNA which might increase the risk of cancer (Le et al., 2004). The small sample size of case–control studies might be a limiting factor to evaluate the most convinced associated loci. Studies included enough data could provide an obvious solution to increase the statistical power. A study performed by Gao et al. indicated that all genotype analysis showed lack of association between folate intake and MTHFR A1298C polymorphism in Chinese female. There was a significant association between MTHFR A1298C polymorphism and breast cancer was found after age adjustment (Gao et al., 2009). And the same conclusion was also displayed in Japanese population which a statistically significant interaction between the MTHFR A1298C polymorphism and breast cancer risk. Interestingly, vitamin B6 intake had a significant association with MTHFR A1298C polymorphism (Ma et al., 2009). Moreover, in the research done by Sharp et al., breast cancer risk of 1298CC carrier was significantly lower compared to 1298AA carrier (OR = 0.24, 95% CI: 0.06–0.97, P = 0.04) (Sharp et al., 2002).

In contrast, the opposite result was also found in Caucasians (Forsti et al., 2004). At the same time, the contradictory conclusions also were exhibited in ovarian cancer. For instance, significant higher ovarian cancer risk in MTHFR 1298CC than MTHFR 1298AA was detected from the studies of Song et al (Song et al., 2012). Though, Terry et al. found that MTHFR SNPs A1298C were not associated with ovarian cancer risk in Caucasians. This study included 1642 cases and 2068 controls from three study populations and the age was corrected (Terry et al., 2010). And no association of MTHFR A1298C (rs1801131) with ovarian cancer risk was displayed from the UK-based GWAS (Song et al., 2009).
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These studies got different results according to their own researches. But many environmental factors and clinical information, for example the sample size, disease subtype, age, hormone level and so on, would reduce the statistical power. Hence, we can’t get a convictive answer if MTHFR A1298C mutation will happen both in breast cancer and in ovarian cancer. So, the meta-analysis and systematic review was needed to resolve the problem.

In the overall data, the results indicated that MTHFR A1298C polymorphism might be a significant risk factor for breast cancer and/or ovarian cancer risk. In the stratified analysis of ethnicity, compared with A allele, a significantly increased breast cancer risk was associated with C allele in Caucasians. Moreover, significantly increased risk was also pronounced for breast cancer in Caucasians and Asians. Meta-analysis has great power for analyzing cumulative data in cancer. It can investigate a large number of samples and assess the effect of genetic factors on disease risk. But heterogeneity often existed among studies included. So we continued to perform the subgroup analysis based cancer type after the subgroup analysis based ethnicity or source of control. The results revealed the significant relevance of MTHFR A1298C polymorphism with breast cancer risk also existed in the study which the control sample derived from hospital. In addition, the sensitivity analysis shown the results was stable. As a consequence, MTHFR A1298C might contribute to breast cancer risk from the subgroup analysis.

In recent years, a lot of researches displayed that the same molecular mutations existed both in breast cancer and in ovarian cancer. In the meta-analysis, the carrier of MTHFR 1298CC have a higher breast cancer risk than MTHFR 1298AA carrier, especially in Caucasians. But the same results were not found in the studies of ovarian cancer risk. Though MTHFR A1298C is not the same molecular variation between breast cancer and ovarian cancer, MTHFR A1298C might be a risk factor for breast cancer risk in Caucasians.

Cancer is one of complicated multi-genetic diseases, and different genetic background could produce obvious heterogeneity. Many factors could affect the precision of experimental conclusion. There are many restrictions in this study. For instance, selection criteria are different in the selection of control group. And many other factors such as age, tumor grade, smoking, drinking, obesity and diet could influence the occurrence of cancer risk. In order to eliminate the heterogeneity, we used the random-effect model and performed the subgroup analysis. In the meantime, we removed the studies which the genotype distribution was not consistent with the HWE to ensure the validity of the statistical results. In this study, the amount of ovarian cancer sample is too small. So, many comprehensive case-control studies concerning ovarian cancer are still to be performed in the future.

In conclusion, MTHFR A1298C polymorphism is significantly associated with risk of breast cancer and/or ovarian cancer. Further studies with a large scale and considering gene-gene and gene-environment interactions should be conducted to investigate the association.

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