RESEARCH ARTICLE

The Methylenetetrahydrofolate Reductase C677T Polymorphism and Breast Cancer Risk in Asian Populations

Vandana Rai

Abstract

**Background:** Methylenetetrahydrofolate (MTHFR) is the key enzyme of the folate metabolic pathway and several studies have pointed to association between the MTHFR C677T polymorphism and breast cancer risk. Although significant association was observed in some studies, in others no clear link could be established. **Objective:** A meta-analysis of published Asian case control studies was therefore carried out to shed further light on any C677T breast cancer association. **Materials and Methods:** PubMed, Springer Link, Google Scholar and Elsevier databases were searched for case control studies of associations between MTHFR C677T polymorphism and breast cancer risk. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess the association. A total of 36 studies including 8,040 cases and 10,008 controls were included in the present meta-analysis. **Results:** Overall, a significantly elevated breast cancer risk was associated with the T allele and TT genotype in homozygote comparison and dominant genetic models when all studies were pooled into the meta-analysis (T vs C (allele contrast model): OR=1.23, 95% CI=1.13-1.37, p=0.000; TT vs CC (homozygote model): OR=1.38, 95% CI=1.16-1.63, p=0.0003; TT+CT vs CC (dominant model): OR=1.12, 95% CI=1.01-1.23, p=0.02). **Conclusions:** The present meta-analysis strongly suggested a significant association between the MTHFR C677T polymorphism and risk of breast cancer in Asian populations.

**Keywords:** Meta-analysis - breast cancer - polymorphism - MTHFR - C677T - polymorphism

Introduction

Breast cancer is a primary cause of cancer death among women worldwide. Global breast cancer incidence has been increasing by more than one million new cases every year; the incidence is significantly higher in developed countries than in developing countries (Ferlay, 2000; Sturgeon et al., 2004; Liang et al., 2013). The cumulative lifetime risk for the development of the disease in the general population is estimated to be 10% (Yang and Lippman, 1999). The etiology of breast cancer is not fully understood. Besides age at menarche and menopause, diet, reproductive history, estrogen administration and genetic factors have been suggested as risk factors (Kelsey, 1993; Hulka and Stark, 1995; Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Langsenlehner et al., 2003). Approximately 25% of breast cancers are inherited by germ-line mutations in functional and/or oncogenes (Ozen et al., 2013). Only a small part of familial breast cancer cases can be explained by inherited mutations, the majority being most probably explained by a combination of common low-penetrance gene polymorphisms (Antoniou et al., 2001; Langsenlehner et al., 2003).

Dietary folate deficiency of an individual along with methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms leads to DNA hypomethylation (Friso et al., 2002). Methylation is genetically predetermined, either by imprinting or by inheritance of genes which influence methylation, such as MTHFR and other genes involved in the 1-carbon cycle. Methyl groups required for methylation are synthesized de novo or are supplied in the diet, primarily from folate. Thus, methylation may be modified by gene-exposure interactions occurring during development. Breast cancer is a manifestation of abnormal genetic and epigenetic changes. Interruption of folate metabolism may contribute to disease etiology as it facilitates cross-talk between genetic and epigenetic processes by effecting gene expression through DNA methylation and genome integrity through DNA synthesis and repair (Kim, 1999; Choi and Mason, 2002; Jakubowska et al., 2007).

Methylenetetrahydrofolate is an important enzyme in folate metabolism. It irreversibly converts 5,10-methylene tetrahydrofolate (THF) to 5-methyl THF which provides the methyl group for the de novo synthesis of methionine synthase and DNA methylation (Matthews et al., 1998). It also helps determine the folate levels available for DNA synthesis and repair (Bailey and Gregory, 1999). The C677T polymorphism codes for an alanine to valine
substitution in the N-terminal catalytic domain and results in an allozyme with approximately 65 and 30% of the activity of the wild-type protein for heterozygotes and homozygotes, respectively (Frosst et al., 1995) Allele frequencies for the 677T variant range approximately from 0.24 to 0.44 in European and Caucasian populations, 0.06 in an African population, and 0.35 to 0.41 in Asian populations (Botto and Yang, 2000; Song et al., 2001; Rai et al., 2012). The frequency of homozygosity (TT) ranges from 1% in US African-American populations to more than 20% in US Latinos; 5% to 30% in White populations in Europe and North America; 32.2% in Mexico; 5.8% in White Canadians in Alberta to 14.3% in those in Quebec, Canada; 0.0% in Sub-Saharan Africa; 10.7% in Oceania; and 11.5% in Japanese and 16% in Chinese (Botto and Yang, 2000; Wilcken et al., 2003 Boccia et al., 2007). The C677T variant has been associated with an increased risk for various cancers including endometrial cancer (Esteller et al., 1997), cervical intraepithelial neoplasia (Piyathilake et al., 2000), esophageal squamous cell carcinoma (Song et al., 2001), gastric cancer (Shen et al., 2001), bladder cancer (Lin et al., 2004) and squamous cell carcinoma of the head and neck (Neumann et al., 2005). Many studies investigated the association between the MTHFR C677T polymorphism and breast cancer incidence but results were controversial. Although significant association was observed in some studies (Liu et al., 2013; Ozen et al., 2013; Weiwei et al., 2013) whereas a clear association between MTHFR polymorphisms and the risk to develop breast cancer has not been established in other studies (Shrubsole et al., 2004; Chen et al., 2005; Le Marchand et al 2004; Wu et al., 2012).

Materials and Methods

Literature search

The literature included in the analysis was selected using PubMed, Elsevier, Google Scholar and Springer Link databases with keywords ‘methylenetetrahydrofolate reductase’ or ‘MTHFR’, ‘C677T’ and ‘breast cancer’. All extracted articles read completely and carefully. The control group included individuals without any family history of breast cancer.

Inclusion and exclusion criteria

Eligible studies had to meet all of the following criteria: (1) they were published in a peer-reviewed journal, (2) they contained independent data, (3) they presented sufficient data to calculate the odds ratio (OR) with a confidence interval and a P-value, (4) they were case-control association studies, (5) they described the relevant genotyping protocols or provided reference to them, (6) they used healthy individuals as controls.

Data extraction

Relevant information’s were extracted from all selected studies like- author family name, journal name, year of publication, country name and number of cases and controls for each C677T genotypes (CC,CT and TT genotypes). Allelic number for the cases and controls were calculated from corresponding genotypes.

Meta-analysis

Present meta-analysis examined the overall association for the allele contrast, the contrast of homozygotes, and the recessive, codominant and dominant models. Statistical analysis of MTHFR C677T polymorphism and BC risk was estimated by Odds ratio (ORs) with 95% confidence intervals (CIs). Cochran’s Q statistic was used for heterogeneity test, and heterogeneity between studies was quantified with the I² metric (I²= (Q - df)/Q), which is independent of the number of studies in the meta-analysis. I² takes values of between 0 and 100%, with higher values denoting a greater degree of heterogeneity (Zintzaras and Hadjigeorgiou, 2004) (I²=0% to 25%: no heterogeneity; I²=25% to 50%: moderate heterogeneity; I²=50% to 75%: large heterogeneity; I²=75% to 100%: extreme heterogeneity) (Higgins and Thompson, 2002; Zintzaras, 2007). The pooled OR was estimated using fixed effects (FE) (Mantel and Haenszel, 1959) and random effects (RE) (DerSimonian and Laird, 1986) models. Where large heterogeneity existed, the random effects model, which yields wider confidence intervals (CIs), should be adopted; otherwise both the fixed effects and random effects models should be deemed appropriate. All statistical analysis were performed using MIX version 1.7 (Bax et al., 2006) and Meta-Disc (Zamora et al., 2006), using two-sided P-value.

Publication bias

An estimate of potential publication bias was carried out by the funnel plot, Begg’s and Egger’s test. The significance of the intercept was determined by the t-test suggested by Egger (p>0.05 was considered representative of statistically significant publication bias) (Egger et al.,1997).

Results

Characteristics of included studies

Following these exclusions, 36 individual case-control studies with a total of 9,025 cases and 11,251 controls were included into this meta-analysis (Ergul et al., 2003; Lee et al., 2004; Le Marchand et al., 2004; Lin et al., 2004; Qi et al., 2004; Shrubsole et al., 2004; Deligezer et al., 2005; Chou et al., 2006; Kalyankumar et al., 2006; Hekim et al., 2007; Kan et al., 2007; Yu et al., 2007; Inoue et al., 2008; Suzuki et al., 2008; Cheng et al., 2008; Mir et al., 2008; Gao et al., 2009; Ma et al., 2009; Cam et al., 2009; Li et al., 2009; Yuan et al., 2009; Jin et al., 2009; Alshatwi et al., 2010; Sangrajrang et al., 2010; Wu et al., 2010; Hosseini et al., 2011; Hua et al., 2011; Mohammad et al., 2011; Nausad et al., 2011; Prasad et al., 2011; Akram et al., 2012; Lajin et al., 2012; Wu et al., 2012; Liu et al., 2013; Ozen et al., 2013; Weiwei et al., 2014). Twenty six studies were carried out in different countries/population like- Mixed Asian population (Le Marchand et al., 2004; Mohammad et al., 2011), Arab (Alshatwi et al., 2010), China (Qi et al., 2004; Shrubsole et al., 2004; Chou et al., 2006; Kan et al., 2007; Gao et al., 2009; Li et al., 2009; Yuan et al., 2009; Jin et al., 2009; Wu et al., 2010; Hua et al., 2011; Wu et al., 2012; Liu et al., 2013; Weiwei et al., 2014 ), India (Kalyankumar, et al.2006; Mir et al., 2008; Sangrajrang et al., 2010; Nausad et al., 2011; Prasad et al., 2011 ). Iran
(Hosseini et al., 2011), Japan (Suzuki et al., 2008; Ma et al., 2009), Korea (Lee et al., 2004), Pakistan (Akram et al., 2012), Singapore (Inoue et al., 2008), Syria (Lajin et al., 2012), Taiwan (Lin et al., 2004; Yu et al., 2007; Cheng et al., 2008), Turkey (Ergul et al., 2003; Deligezer et al., 2005; Hekim et al., 2007; Cam et al., 2009; Ozen et al., 2007), China (Chou et al., 2006; Inoue et al., 2008; Cheng et al., 2008; Mir et al., 2008; Ma et al., 2009; Hosseini et al., 2011; Hua et al., 2011; Prasad et al., 2011; Wu et al., 2012) and odds ratio was above one in other twenty five studies.

**Meta-analysis**

Table 3 summarizes the ORs with corresponding 95%CIs for association between C677T polymorphism and risk of breast cancer in allele contrast, homozygote, dominant, recessive and co-dominant models. The pooled Odds Ratios were estimated by both fixed effects (Mantel and Haenszel, 1959) and random effects (Der Simonian and Laird, 1986) models.

**Allele contrast meta-analysis:**

Meta-analysis with allele contrast showed significant association with both fixed effect (OR\textsubscript{tot}=1.1 , 95%CI: 1.05-1.14; \(p<0.001\); OR\textsubscript{homo}=0.77; \(I^2=0.05\) and random effect model (OR\textsubscript{tot}=1.23, 95%CI: 1.13-1.37; \(P=0.000\)). Breast cancer patients with showed a significantly increased frequency of the T allele (Table 3, Figure 1).

In cumulative analysis using fixed and random effect models, the association of mutant ‘T’ allele with breast cancer turned statistically insignificant with the addition

<table>
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<tr>
<th>Study</th>
<th>Country</th>
<th>Case</th>
<th>Control</th>
<th>Reference</th>
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<tr>
<td>Ergul et al., 2003</td>
<td>Turkey</td>
<td>118</td>
<td>193</td>
<td>Tumour Biol, 24, 286-290.</td>
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<tr>
<td>Shrubsole et al., 2004</td>
<td>China</td>
<td>1112</td>
<td>1160</td>
<td>Cancer Epidemiol Biomarkers Prev, 13, 190-196.</td>
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<td>Lee et al., 2004</td>
<td>Korea</td>
<td>186</td>
<td>147</td>
<td>Exp Mol Med 36, 116-121.</td>
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<tr>
<td>Lin et al., 2004</td>
<td>Taiwan</td>
<td>88</td>
<td>342</td>
<td>Anticancer Res 2004, 24, 3863-3868.</td>
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<td>Le Marchand et al., 2004</td>
<td>E.As.</td>
<td>318</td>
<td>410</td>
<td>Cancer Epidemiol Biomarkers Prev 13, 2071-2077</td>
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<tr>
<td>Qi et al., 2004</td>
<td>China</td>
<td>217</td>
<td>218</td>
<td>Chin J Oncol, 26, 287-289.</td>
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<td>Deligezer et al., 2005</td>
<td>Turkey</td>
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<td>Yu et al., 2007</td>
<td>Taiwan</td>
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<td>Cheng et al., 2008</td>
<td>Taiwan</td>
<td>349</td>
<td>530</td>
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<td>Mir et al., 2008</td>
<td>India</td>
<td>35</td>
<td>33</td>
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<td>China</td>
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<td>642</td>
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<td>Ma et al., 2009</td>
<td>Japan</td>
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<td>Nutr Cancer, 61, 447-456.</td>
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<td>Cam et al., 2009</td>
<td>Turkey</td>
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<td>95</td>
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<td>Food Chem Toxicol 2010, 48, 881-1885.</td>
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<td>Hosseini et al., 2011</td>
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<td>300</td>
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<td>Hua et al., 2011</td>
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<td>90</td>
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<td>Wu et al., 2012</td>
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<td>37</td>
<td>Asian Pac J Cancer Prev, 13, 2199-206.</td>
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<td>Liu et al., 2013</td>
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<td>Ozen et al., 2013</td>
<td>Turkey</td>
<td>51</td>
<td>106</td>
<td>Asian Pacific J Cancer Prev, 14 (5), 2903-2908</td>
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of study of Lee et al (2004) and became significant after addition of Kalyankumar et al. (2006) and remained significant till the addition of Ma et al. (2009). After addition of study of Yuan et al. (2009) association turned significant and stayed significant thereafter (result not shown).

**Genotype contrast meta-analysis**

Table 3 summarizes the ORs with corresponding 95% CIs for association between C677T polymorphism and risk of breast cancer in dominant, recessive, homozygote and co-dominant models. Thirty six studies allowed author to make all planned comparisons of genotypes. With primary analysis, there was an increased risk of breast cancer among mutant homozygote variants (TT), with both fixed (OR\textsubscript{TT,CC}=1.24; 95%CI=1.13-1.36; p=0.0001; I^2=58.28%; P\textsubscript{heterogeneity} <0.0001; P\textsubscript{res}=0.04) and random (Random-effects OR\textsubscript{TT,CC}=1.38; 95%CI: 1.16-1.63; p=0.0003) effect models with high statistical heterogeneity between-study. Association of mutant heterozygous genotype (CTvCC) with fixed (OR\textsubscript{CTvCC}=1.03; 95%CI=0.97-1.1;p=0.28; I^2=33.73%; P\textsubscript{heterogeneity}=0.02; P\textsubscript{res}=0.63) and random (OR\textsubscript{CTvCC}=1.05; 95%CI=0.96-1.14;p=0.29) effect models were observed insignificant. Similarly combined mutant genotypes (TTvCTvsCC) showed positive association with schizophrenia using both fixed (OR\textsubscript{TTvCTvCC}=1.08; 95%CI=1.02-1.159 p=0.002; I^2=51.57%; P\textsubscript{heterogeneity}=0.0001; P\textsubscript{res}=0.20) and random (OR\textsubscript{TTvCTvCC}=1.12; 95%CI: 1.01-1.23; p=0.02) effect models. Association between recessive genetic model (TT vs CT+CC) were also found significant with both fixed (OR\textsubscript{TTvCTvCC}=1.22;95%CI=1.12-1.33;p<0.0001; I^2=50.35%; P\textsubscript{heterogeneity}=0.003; P\textsubscript{res}=0.03) as well as random (OR\textsubscript{TTvCTvCC}=1.33; 95%CI: 1.15-1.43; p=0.0001) effects model,(Table 3).

**Publication bias**

Funnel plots, Begg’s and Egger’s test were performed to estimate the risk of publication bias. The shape of funnel plots in all contrast models showed obvious evidence of symmetry (Figure 2). In addition, all the P values of Egger’s test were more than 0.05, which provided
The C677T MTHFR Polymorphism as a Risk Factor for Breast Cancer

Deficiency of nutrients, such as vitamins and microelements, were observed to be correlated with breast cancer (Norat et al., 2014; Weiwei et al., 2014). Folate is as an important nutritional factor which may have a role as a cancer-preventing agent (Kim, 1999; Kotsopoulos et al., 2008). It plays an integral role in DNA synthesis and methylation, and as an epigenetic regulator of gene expression, DNA integrity and stability (Wagner, 1995; Kim, 1999; Kotsopoulos et al., 2008). Folate deficiency may result in increased numbers of DNA strand breaks, impaired DNA repair, enhanced mutagenesis and alterations in DNA methylation patterns. All of these events have been implicated in neoplastic transformation (Baylin et al., 1999; Duthie, 1999; Jones and Laird, 1999; Kim, 2004; Kotsopoulos et al., 2008). This link between folate, folate metabolism, and DNA methylation therefore provides a plausible biologic mechanism for the observed association between MTHFR and breast cancer.

Table 3. Summary Estimates for the Odds Ratio (OR) of MTHFR C677T in Various Allele/Genotype Contrasts, the Significance Level (p value) of Heterogeneity test (Q test), and the I² Metric and Publication Bias p-value (Egger test).

<table>
<thead>
<tr>
<th>Genetic Models</th>
<th>Fixed effect OR (95%CI), p</th>
<th>Random effect OR (95%CI), p</th>
<th>Heterogeneity p-value (Q test)</th>
<th>I² (%)</th>
<th>Publication Bias (p of Egger’s test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele Contrast (T vs C)</td>
<td>1.12 (1.05-1.14), &lt;0.0001</td>
<td>1.23 (1.13-1.37), 0.0000</td>
<td>&lt;0.0001</td>
<td>77.3</td>
<td>0.05</td>
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<tr>
<td>Co-dominant (CT vs CC)</td>
<td>1.03 (0.97-1.1) , 0.28</td>
<td>1.05 (0.96-1.14), 0.29</td>
<td>0.02</td>
<td>33.7</td>
<td>0.63</td>
</tr>
<tr>
<td>Homozygote (TT vs CC)</td>
<td>1.24 (1.13-1.36), &lt;0.001</td>
<td>1.38 (1.16-1.63), 0.0003</td>
<td>&lt;0.0001</td>
<td>58.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Dominant (TT+CT vs CC)</td>
<td>1.08 (1.02-1.15), 0.009</td>
<td>1.12 (1.01-1.23), 0.02</td>
<td>0.0001</td>
<td>51.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Recessive (TT vs CT+CC)</td>
<td>1.22 (1.12-1.33), &lt;0.0001</td>
<td>1.33 (1.15-1.43), 0.0001</td>
<td>0.003</td>
<td>50.3</td>
<td>0.03</td>
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**Discussion**

Deficiency of nutrients, such as vitamins and microelements, were observed to be correlated with breast cancer (Norat et al., 2014; Weiwei et al., 2014). Folate is as an important nutritional factor which may have a role as a cancer-preventing agent (Kim, 1999; Kotsopoulos et al., 2008). It plays an integral role in DNA synthesis and methylation, and as an epigenetic regulator of gene expression, DNA integrity and stability (Wagner, 1995; Kim, 1999; Kotsopoulos et al., 2008). Folate deficiency may result in increased numbers of DNA strand breaks, impaired DNA repair, enhanced mutagenesis and alterations in DNA methylation patterns. All of these events have been implicated in neoplastic transformation (Baylin et al., 1999; Duthie, 1999; Jones and Laird, 1999; Kim, 2004; Kotsopoulos et al., 2008). This link between folate, folate metabolism, and DNA methylation therefore provides a plausible biologic mechanism for the observed association between MTHFR and breast cancer.

The C677T MTHFR polymorphism has been associated with risk for many different types of cancer, including esophageal, colorectal, gastric, pancreatic, prostate, cervical, lung, and leukemia (Boccia et al., 2007; Tu et al., 2012; Mei et al., 2012; Zhang et al., 2012; Wen et al., 2012). Folate deficiency may result in increased numbers of DNA strand breaks, impaired DNA repair, enhanced mutagenesis and alterations in DNA methylation patterns. All of these events have been implicated in neoplastic transformation (Baylin et al., 1999; Duthie, 1999; Jones and Laird, 1999; Kim, 2004; Kotsopoulos et al., 2008). This link between folate, folate metabolism, and DNA methylation therefore provides a plausible biologic mechanism for the observed association between MTHFR and breast cancer.

MTHFR 677TT polymorphism has been associated with risk for many different types of cancer, including esophageal, colorectal, gastric, pancreatic, prostate, cervical, lung, and leukemia (Boccia et al., 2007; Tu et al., 2012; Mei et al., 2012; Zhang et al., 2012; Wen et al., 2012). Folate deficiency may result in increased numbers of DNA strand breaks, impaired DNA repair, enhanced mutagenesis and alterations in DNA methylation patterns. All of these events have been implicated in neoplastic transformation (Baylin et al., 1999; Duthie, 1999; Jones and Laird, 1999; Kim, 2004; Kotsopoulos et al., 2008). This link between folate, folate metabolism, and DNA methylation therefore provides a plausible biologic mechanism for the observed association between MTHFR and breast cancer.

Limitations of the meta-analysis should also be acknowledged like: (i) crude odds ratio was used, (ii) studies with small sample size were included and (iii) publication bias was observed. Publication bias was observed in the present meta-analysis. Publication bias is an important problem particularly in relation to meta-analyses of genetic association studies. Negative results, especially smaller ones, may not be submitted for publication, let alone accepted, rendering any systematic review of published results misleading (Colhoun et al., 2003; Lewis et al., 2005). Despite of several limitations, present meta-analysis provided evidence of the association between the MTHFR C677T polymorphisms and breast cancer risk in Asian population, supporting the hypothesis that MTHFR C677T polymorphism is contributed to overall BC risk.
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References


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