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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

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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 abnormity of folate metabolism will have a negative effect on the methylation and synthesis of DNA. Methylenetetrahydrofolate 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 Methylenetetrahydrofolate 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.

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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).

Table1: Characteristics of the studies included in this meta-analysis.

Author	References	Year	Nationality	Ethnicity	Cancer type	Case/Control	Genotype(Case/Control)			Genotyping method	Source of control	P for HWE
							AA	AC	CC			
Song et al	[13]	2012	China	Asian	OC	202/198	107/112	79/77	16/9	Taqman	HB	0.35
Webb et al	[14]	2011	Australian	Mixed	OC	1638/1278	770/598	693/561	175/119	Mass ARRAY	PB	0.44
Terry et al	[15]	2010	USA	Caucasian	OC	1038/1093	515/534	430/450	93/109	Taqman	PB	0.32
Terry et al	[15]	2010	USA	Caucasian	OC	153/484	68/236	67/200	18/48	Taqman	PB	0.56
Terry et al	[15]	2010	USA	Caucasian	OC	364/412	173/189	149/180	42/43	Taqman	PB	0.99
Lu et al	[16]	2015	China	Asian	BC	560/560	369/352	172/185	19/23	Taqman	HB	0.83
He et al	[17]	2014	China	Asian	BC	310/381	138/173	132/155	40/53	PCR-RFLP	HB	0.06
Huang et al	[18]	2014	China	Asian	BC	1232/1232	787/796	386/391	59/45	PCR-RFLP	HB	0.72
Wang et al	[19]	2014	China	Asian	BC	435/435	206/214	176/172	53/49	PCR-RFLP	HB	0.11
Qiao et al	[20]	2014	China	Asian	BC	535/673	258/351	235/280	42/42	PCR-RFLP	HB	0.25
Zheng et al	[21]	2013	China	Asian	BC	296/306	135/151	129/130	32/25	PCR-RFLP	HB	0.69
Akilzhanova et al	[22]	2013	Kazakhstan	Asian	BC	315/604	138/318	142/242	35/44	Taqman	PB	0.83

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Wu et al	[23]	2012	China	Asian	BC	75/75	37/42	32/28	6/5	PCR-RFLP	HB	0.91
Lajin et al	[24]	2012	Syria	Asian	BC	119/126	44/65	52/48	23/13	PCR-RFLP	HB	0.36
Hua et al	[25]	2011	China	Asian	BC	95/90	50/55	42/32	3/3	PCR-RFLP	PB	0.52
Papandreou et al	[26]	2011	Greece	Caucasian	BC	300/283	129/136	135/116	36/31	PCR-RFLP	HB	0.41
Hosseini et al	[27]	2011	Iran	Caucasian	BC	294/300	36/60	96/135	162/105	PCR-RFLP	Not stated	0.17
Cerne et al	[28]	2011	Slovenia	Caucasian	BC	524/269	258/131	219/117	47/21	Taqman	HB	0.46
Vainer et al	[29]	2010	Russia	Caucasian	BC	831/785	398/379	353/330	80/76	PCRRFLP	PB	0.74
Ma et al	[30]	2009	Brazil	Mixed	BC	458/458	269/279	168/157	21/22	Taqman	HB	0.99
Ericson et al	[31]	2009	Sweden	Caucasian	BC	541/1072	242/487	242/480	57/105	Sequencing	PB	0.40
Ma et al	[30]	2009	Japan	Asian	BC	388/387	254/256	119/116	15/15	Taqman	HB	0.68
Platek et al	[32]	2009	USA	Mixed	BC	928/1781	443/842	402/758	83/181	Taqman	PB	0.59
Gao et al	[33]	2009	China	Asian	BC	624/624	446/425	169/188	9/11	PCR-RFLP	PB	0.06
Kotsopoulos et al	[34]	2008	Canada	Caucasian	BC	941/780	466/398	390/309	85/73	Mass ARRAY	HB	0.25
Inoue et al	[35]	2008	Singapore	Asian	BC	380/662	225/387	139/234	16/41	PCR-RFLP	PB	0.48
Kan et al	[36]	2007	China	Asian	BC	125/101	70/61	41/32	14/8	PCR-RFLP	PB	0.21
Xu et al	[37]	2007	USA	Mixed	BC	1062/1103	558/536	417/457	87/110	Mass ARRAY	PB	0.39
Stevens et al	[38]	2007	USA	Mixed	BC	494/493	224/252	228/201	42/40	PCR-RFLP	PB	0.99
Kalyankumar et al	[39]	2006	Indian	Caucasian	BC	88/95	49/65	33/26	6/4	PCR-RFLP	Not stated	0.50
Chou et al	[40]	2006	China	Asian	BC	142/285	104/172	30/95	8/18	PCR-RFLP	HB	0.32
Justenhoven et al	[41]	2005	Germany	Caucasian	BC	582/634	273/295	256/266	53/73	Taqman	PB	0.27
Shrubsole et al	[42]	2004	China	Asian	BC	1121/1208	768/824	311/344	42/40	PCR-RFLP	PB	0.58
Qi et al	[43]	20	China	Asian	BC	217/218	155/1	58/71	4/3	PCR-RFLP	PB	0.08

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Forsti et al	[44]	2004	Finland	Caucasian	BC	223/298	94/133	102/127	27/38	PCR-RFLP	Not stated	0.38
Le Marchand et al	[45]	2004	USA	Asian	BC	318/410	224/271	83/126	11/13	Taqman	PB	0.72
Le Marchand et al	[45]	2004	USA	Caucasian	BC	320/415	160/211	118/166	42/38	Taqman	PB	0.52
Le Marchand et al	[45]	2004	USA	African	BC	246/639	171/433	68/187	7/19	Taqman	PB	0.83
Le Marchand et al	[45]	2004	USA	Mixed	BC	236/664	146/423	77/212	13/29	Taqman	PB	0.71
Le Marchand et al	[45]	2004	USA	Mixed	BC	69/286	40/155	25/110	4/21	Taqman	PB	0.81
Ergul et al	[46]	2003	Turkey	Caucasian	BC	118/193	50/90	48/85	20/18	PCR-RFLP	HB	0.75
Sharp et al	[47]	2002	England	Caucasian	BC	55/60	27/24	25/25	3/11	PCR-RFLP	HB	0.33

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 ($I^2 \geq 50\%$, 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

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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 1study 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 (Figure1).

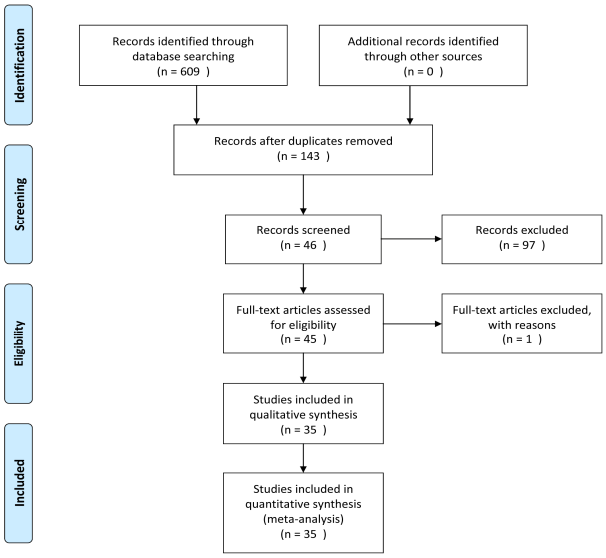

Figure 1: Flow diagram of literature search

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}) (Table2). 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) (Table3). 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 = 0.0 3.), 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.) (Table3).

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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	
	OR/95%CI	P	OR/95%CI	P	OR/95%CI	P	OR/95%CI	P	OR/95%CI	P
Caucasian										
	1.04(0.99-1.10)	0.1	1.12(1.00-1.25)	0.05	1.04(0.97-1.11)	0.32	1.11(1.00-1.23)	0.06	1.01(0.94-1.09)	0.71
Asian										
	1.03(0.98-1.08)	0.34	1.13 (0.99-1.28)	0.07	1.01(0.95-1.07)	0.78	1.13(1.00-1.29)	0.06	0.99(0.93-1.06)	0.76
Mixed										
	1.02(0.96-1.08)	0.51	1.03(0.89-1.18)	0.72	1.03 (0.96-1.11)	0.45	1.01(0.89-1.16)	0.87	1.03 (0.95-1.12)	0.46
BC										
	1.04(1.00-1.07)	0.04	1.10(1.02-1.19)	0.01	1.03 (0.99-1.07)	0.19	1.10(1.01-1.19)	0.02	1.01(0.97-1.06)	0.56
OC										
	1.02 (0.95-1.09)	0.64	1.07(0.91-1.27)	0.41	1.00(0.91-1.10)	0.96	1.08 (0.92-1.27)	0.35	0.99(0.89-1.09)	0.8
HB										
	1.07(1.01-1.12)	0.02	1.16(1.02-1.31)	0.02	1.07(1.00-1.14)	0.05	1.13(1.00-1.28)	0.046	1.05(0.98-1.12)	0.17
PB										
	1.00(0.97-1.04)	0.84	1.02(0.93-1.12)	0.68	1.00(0.95-1.05)	0.99	0.98(0.90-1.07)	0.64	1.00(0.95-1.05)	0.89
Total										
	1.05(1.02,1.08)	0.004	1.11(1.03-1.19)	0.005	1.03(0.99-1.07)	0.13	1.10(1.03-1.18)	0.007	1.01(0.97-1.06)	0.49

OC, ovarian cancer; BC, breast cancer; P, P value for χ^2; 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		A VS C		AA VS CC		AA VS (AC+CC)		(AC+AA) VS CC		AA VS AC	
	Type	OR/95%CI	P	OR/95%CI	P	OR/95%CI	P	OR/95%CI	P	OR/95%CI	P
Caucasian											
	BC	1.06(1.00-1.12)	0.05	1.15(1.01-1.31)	0.03	1.05(0.97-1.13)	0.24	1.14(1.01-1.29)	0.03	1.02(0.94-1.11)	0.63
	OC	0.99(0.89-1.09)	0.78	0.97 (0.77-1.22)	0.8	0.984(0.86-1.12)	0.81	0.98(0.78-1.22)	0.83	0.99(0.86-1.14)	0.86
Asian											
	BC	1.02 (0.97-1.07)	0.44	1.11(0.97-1.27)	0.11	1.00(0.94-1.07)	0.89	1.12(0.98-1.27)	0.09	0.99(0.92-1.05)	0.7
	OC	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

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		5)	6	9)	5	)	7	9)	6	2)	3
HB											
	BC	1.06(1.01-1.12)	0.03	1.14(1.01-1.30)	0.04	1.06(1.00-1.14)	0.07	1.12(0.99-1.27)	0.07	1.05(0.98-1.12)	0.18
	OC	1.20(0.87-1.65)	0.26	1.86(0.79-4.39)	0.15	1.16(0.78-1.72)	0.47	1.81(0.78-4.19)	0.16	1.07(0.71-1.62)	0.73
PB											
	BC	0.98(0.94-1.03)	0.44	0.97(0.87-1.08)	0.55	0.98(0.93-1.04)	0.47	0.97(0.87-1.09)	0.64	0.98(0.93-1.04)	0.54
	OC	1.01(0.94-1.09)	0.82	1.05(0.89-1.24)	0.58	1.00 (0.90-1.10)	0.91	1.06(0.90-1.25)	0.5	0.98(0.89-1.09)	0.73
Mixed											
	BC	0.99 (0.92-1.06)	0.74	0.92(0.78-1.09)	0.32	1.01(0.92-1.10)	0.84	0.91(0.77-1.07)	0.24	1.03(0.94-1.13)	0.55
	OC	1.03(0.92-1.15)	0.64	1.14(0.88-1.48)	0.31	0.99(0.86-1.15)	0.91	1.17 (0.91-1.49)	0.22	0.96(0.82-1.12)	0.6

OC, ovarian cancer; BC, breast cancer; P, P value for χ^2; OR, odds ratio; CI, confidence interval; Mixed, mixed population.

Heterogeneity and Sensitivity Analysis

No significant heterogeneity was found in the meta-analysis. (Figure2, Figure3) 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' test and Egger' 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) (Figure4). The random effect model was carried out in the case of $P < 0.05$, $I^2 \geq 50\%$, while the fixed effect model was applied to calculate the ORs value and 95%CI in the genetic models of $P > 0.05$, $I^2 < 50\%$. In addition, the results were stable after sensitivity analysis.

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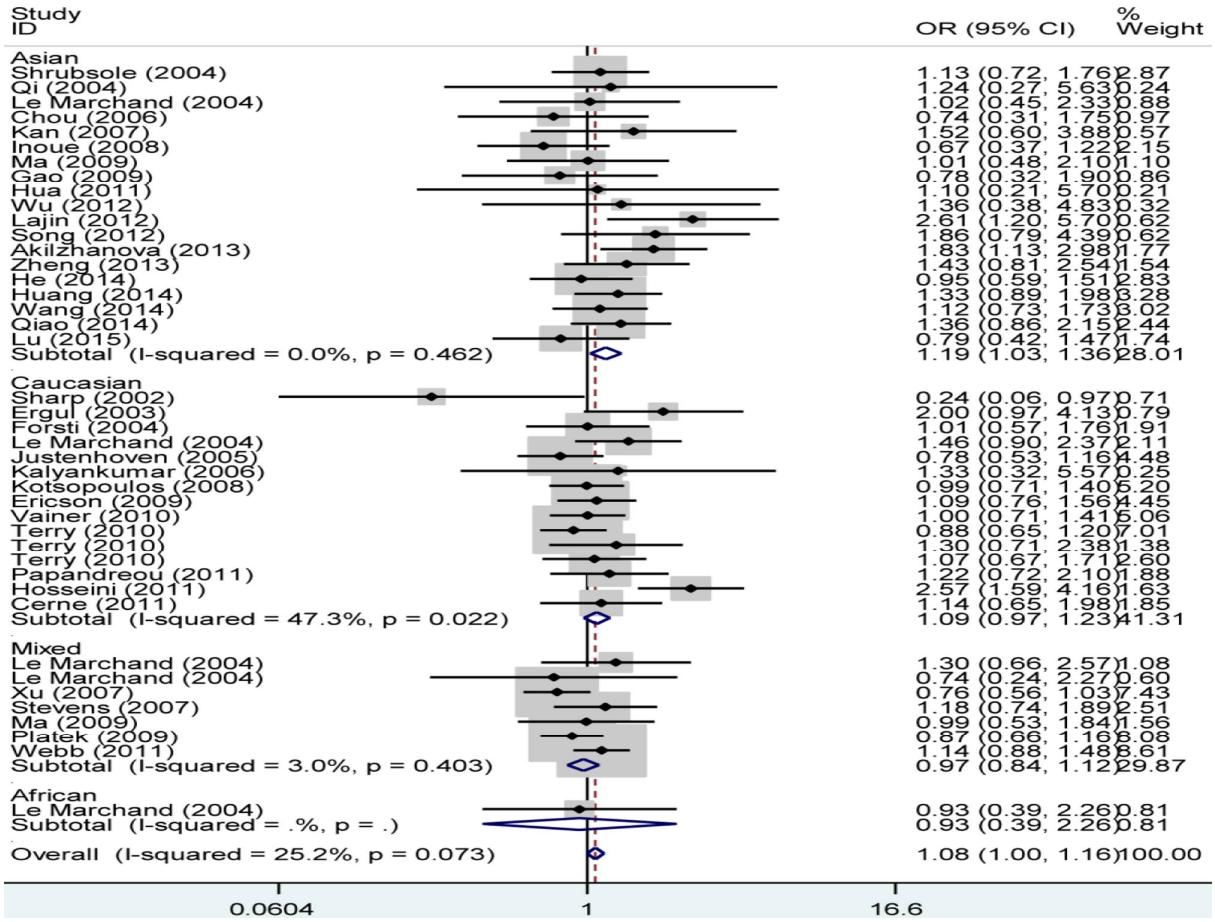

Figure 2: Forest plot of MTHFR A1298C (AA VS CC) for breast cancer and/or ovarian cancer (Ethnicity)

OR, odds ratio; 95%CI, 95% confidence interval; Mixed, mixed population

doi:10.21010/ajtcam.v13i5.11

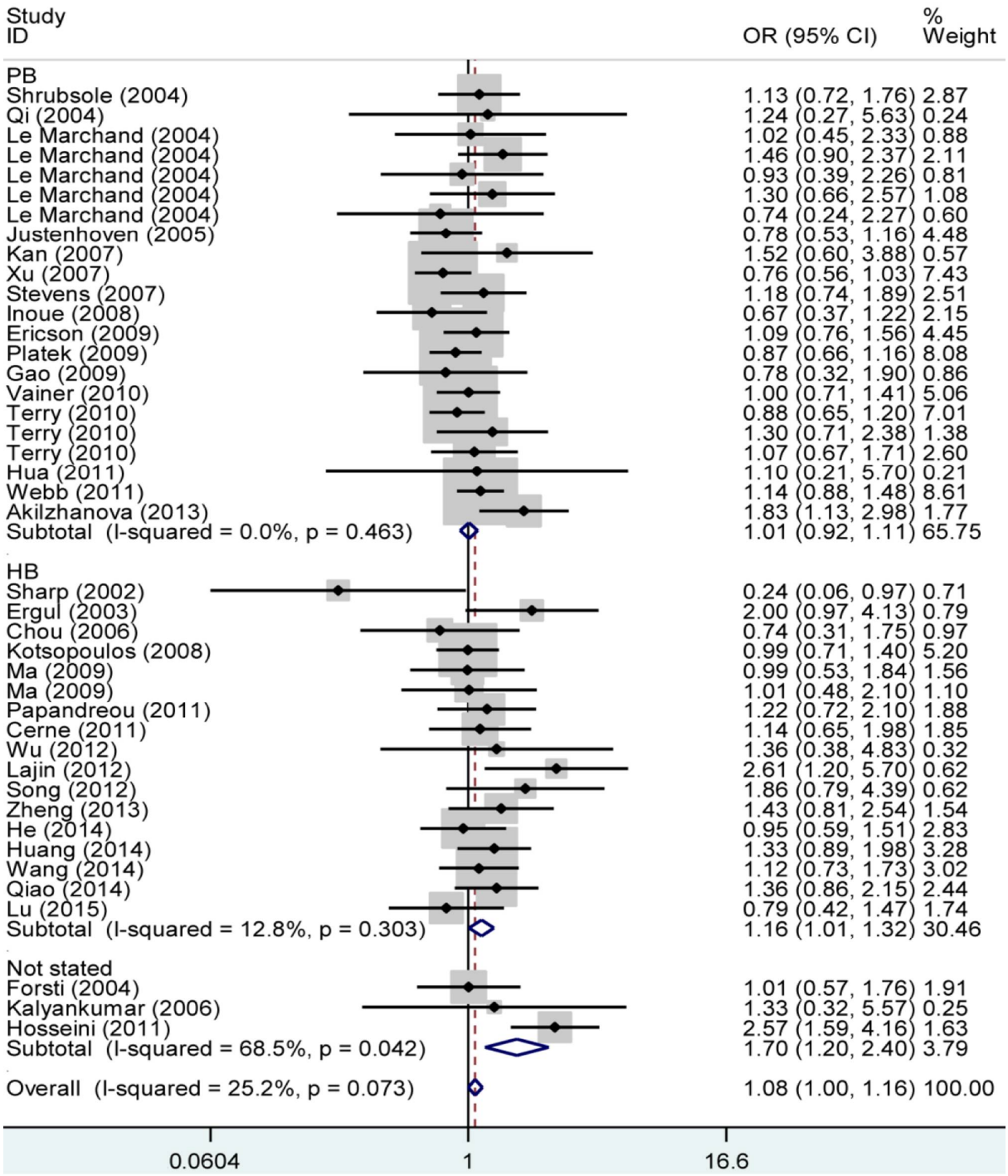

Figure 3: Forest plot of MTHFR A1298C (AA VS CC) for breast cancer and/or ovarian cancer (Source of control). OR, odds ratio; 95% CI, 95% confidence interval

doi:10.21010/ajtcam.v13i5.11

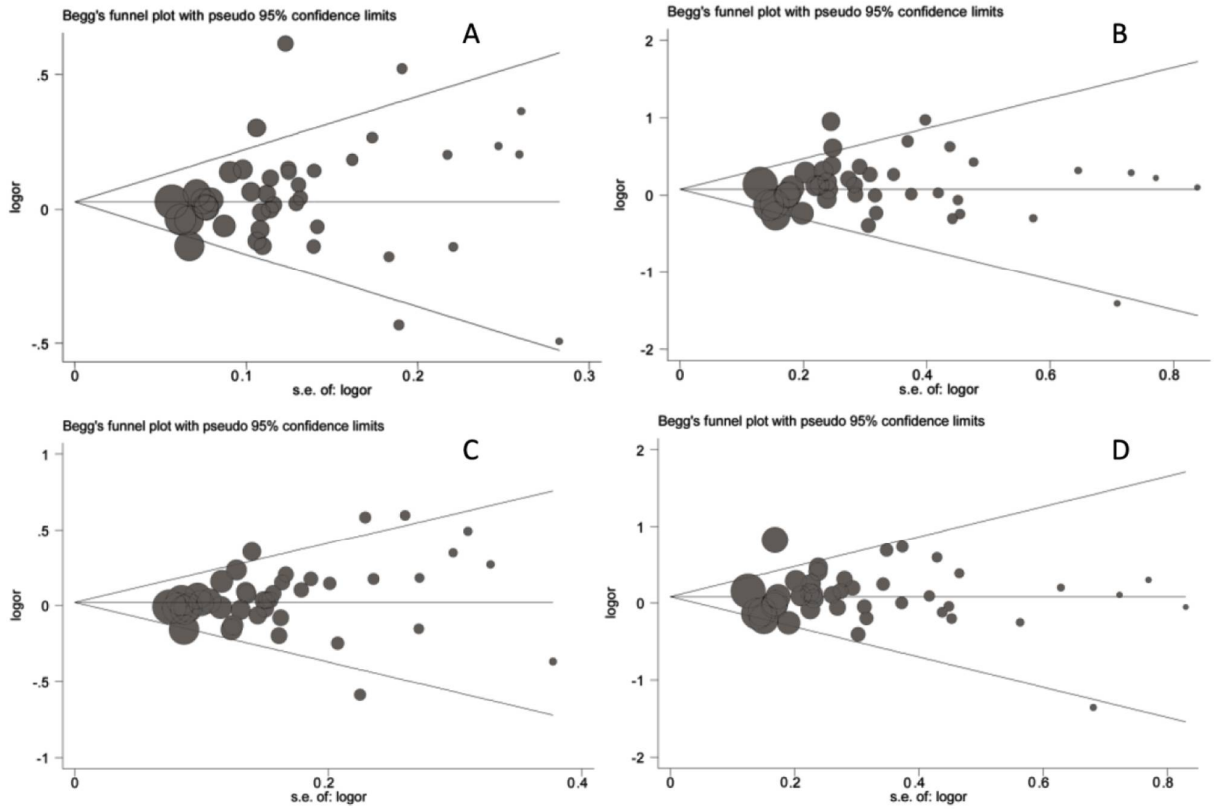

Figure 4: Begg funnel plot for publication bias test of association between MTHFR A1298C polymorphism and breast cancer and/or ovarian cancer. A, A VS C; B, AA VS CC; C, AA VS (AC + CC); D, (AA + AC) VS CC

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)

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.

References

1. Akilzhanova A, Nurkina Z, Momynaliev K, Ramanculov E, Zhumadilov Z, Rakhypbekov T, Hayashida N, Nakashima M, Takamura N. (2013). Genetic profile and determinants of homocysteine levels in Kazakhstan patients with breast cancer. Anticancer Res. Sep 1;33(9):4049-4059.
2. Balmana J, Diez O, Rubio IT, Cardoso F. (2011). BRCA in breast cancer: ESMO Clinical Practice Guidelines. ANN ONCOL. Sep 1;22(Suppl 6):i31-i34.
3. Cancer Genome Atlas Network. (2012). Comprehensive molecular portraits of human breast tumours. NATURE. Oct 4;490(7418):61-70.
4. Chou YC, Wu MH, Yu JC, Lee MS, Yang T, Shih HL, Wu TY, Sun CA. (2006). Genetic polymorphisms of the methylenetetrahydrofolate reductase gene, plasma folate levels and breast cancer susceptibility: a case-control study in Taiwan. CARCINOGENESIS. Jun 15;27(11): 2295-2300.
5. Dersimonian R, Laird N. (1986). Meta-analysis in clinical trials. Control Clin Trials. Sep 1;7(3): 177-188.
6. Ergul E, Sazci A, Utkan Z, Canturk NZ. (2003). Polymorphisms in the MTHFR gene are associated with breast cancer. Tumour Biol. Nov 1;24(6):286-290.
7. Ericson U, Sonestedt E, Ivarsson MI, Gullberg B, Carlson J, Olsson H, Wirfalt E. (2009). Folate intake, methylenetetrahydrofolate reductase polymorphisms, and breast cancer risk in women from the Malmo Diet and Cancer cohort. Cancer Epidemiol Biomarkers Prev.

Apr 1;18(4):1101-1110.

8. Forsti A, Angelini S, Festa F, Sanyal S, Zhang Z, Grzybowska E, Pamula J, Pekala W, Zientek H, Hemminki K, Kumar R. (2004). Single nucleotide polymorphisms in breast cancer. Oncol Rep. Apr 1;11(4):917-922.
9. Gao CM, Tang JH, Cao HX, Ding JH, Wu JZ, Wang J, Liu YT, Li SP, Su P, Matsuo K, Takezaki T, Tajima K. (2009). MTHFR polymorphisms, dietary folate intake and breast cancer risk in Chinese women. J Hum Genet. Jul 1;54(7):414-418.
10. Gayther SA, Pharoah PD. (2010). The inherited genetics of ovarian and endometrial cancer. Curr Opin Genet Dev. Jun 1;20(3):231-238.
11. He JM, Pu YD, Wu YJ, Qin R, Zhang QJ, Sun YS, Zheng WW, Chen LP. (2014). Association between dietary intake of folate and MTHFR and MTR genotype with risk of breast cancer. GENET MOL RES. Jan 20;13(4):8925-8931.
12. Hosseini M, Houshmand M, Ebrahimi A. (2011). MTHFR polymorphisms and breast cancer risk. ARCH MED SCI. Feb 1;7(1):134-137.
13. Hua Z, Wang YB, Ni J, Ge F, Zou TN. (2011). Serum folate, vitamin b12 concentration and mthfr, ms gene polymorphism associated with risk of breast cancer research. Mod Oncol. May 1;19(03):428-431.
14. Huang CY, Chang WS, Shui HA, Hsieh YH, Loh CH, Wang HC, Ji HX, Hsiao CL, Hsu CM, Tsai CW, Bau DT. (2014). Evaluation of the contribution of methylenetetrahydrofolate reductase genotypes to Taiwan breast cancer. ANTICANCER RES. Aug 1;34(8):4109-4115.
15. Jemal A, Siegel R, Xu J, Ward E. (2010). Cancer statistics, 2010. CA Cancer J Clin. Sep 1;60(5): 277-300.
16. Jiang Hua Q, De Chuang J, Zhen Duo L, Shu de C, Zhenzhen L. (2014). Association of methylenetetrahydrofolate reductase and methionine synthase polymorphisms with breast cancer risk and interaction with folate, vitamin B6, and vitamin B 12 intakes. Tumour Biol. Sep13;35(12): 11895-11901.
17. Jing C, Huang Z, Duan Y, Xiao X, Zhang R, Jiang J. (2012). Folate intake, methylenetetrahydrofolate reductase polymorphisms in association with the prognosis of esophageal squamous cell carcinoma. Asian Pac J Cancer Prev. Jan 20;13(2):647-651.
18. Justenhoven C, Hamann U, Pierl CB, Rabstein S, Pesch B, Harth V, Baisch C, Vollmert C, Illig T, Bruning T, Ko Y, Brauch H. (2005). One-carbon metabolism and breast cancer risk: no association of MTHFR, MTR, and TYMS polymorphisms in the GENICA study from Germany. Cancer Epidemiol Biomarkers Prev. Dec 1;14(12):3015-3018.
19. Kalyankumar C, Jamil K. (2006). Methylene tetrahydofolate reductase (MTHFR) C677T and A1298C polymorphisms and breast cancer in South Indian population. Int J Cancer Res. Feb 1;2(2):143–51, 2006.
20. Kamangar F, Dores GM, Anderson WF. (2006). Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. May 10;24(14):2137-2150.
21. Kan XX, Zou TN, Wu XY, Wang X. (2007). Association between MTHFR genotype polymorphism and breast cancer susceptibility in human population from Yunnan. Cancer Res Prev Treat. Oct 9;34(9):716–718.
22. Kotsopoulos J, Zhang WW, Zhang S, McCready D, Trudeau M, Zhang P, Sun P, Narod SA. (2008). Polymorphisms in folate metabolizing enzymes and transport proteins and the risk of breast cancer. Breast Cancer Res Treat. Jan 19;112(3):585-593.
23. Lajin B, Alhaj SA, Ghabreau L, Alachkar A. (2012). Association of polymorphisms in one-carbon metabolizing genes with breast cancer risk in Syrian women. Tumour Biol. Feb 29;33(4):1133-1139.
24. Le Marchand L, Haiman CA, Wilkens LR, Kolonel LN and Henderson BE. (2004). MTHFR polymorphisms, diet, HRT, and breast cancer risk: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev. Dec 1;13(12):2071-2077, 2004.
25. Lu Q, Jiang K, Li Q, Ji YJ, Chen WL, Xue XH. (2015). Polymorphisms in the MTHFR gene are associated with breast cancer risk and prognosis in a Chinese population. Tumour Biol. May 1;36(5): 3757-3762.
26. Inoue M, Robien K, Wang R, Van Den Berg DJ, Koh WP, Yu MC. (2008). Green tea intake, MTHFR/TYMS genotype and breast cancer risk: the Singapore Chinese Health Study. CARCINOGENESIS. Jul 31;29(10):1967-1972.
27. Ma E, Iwasaki M, Kobayashi M, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, Tsugane S. (2009). Dietary intake of folate, vitamin B2, vitamin B6, vitamin B12, genetic polymorphism of related enzymes, and risk of breast cancer: a case-control study in Japan. Nutr Cancer. Jan 20;61(4):447-456.
28. Mantel N, Haenszel W. (1959). Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. Apr 1;22(4):719-748.

29. Morita M, Yin G, Yoshimitsu S, Ohnaka K, Toyomura K, Kono S, Ueki T, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Maekawa T, Yasunami Y, Takenaka K, Ichimiya H, Terasaka R: Folate-related nutrients, genetic polymorphisms, and colorectal cancer risk: the fukuoka colorectal cancer study. (2013). Asian Pac J Cancer Prev. Jan 20;14(11):6249-6256.
30. Papandreou CN, Doxani C, Zdoukopoulos N, Vlachostergios PJ, Hatzidaki E, Bakalos G, Ziogas DC, Koufakis T, Zintzaras E. (2012). Evidence of association between methylenetetrahydrofolate reductase gene and susceptibility to breast cancer: a candidate-gene association study in a South-eastern European population. DNA Cell Biol. Feb 1;31(2):193-198.
31. Platek ME, Shields PG, Marian C, McCann SE, Bonner MR, Nie J, Ambrosone CB, Millen AE, Ochs-Balcom HM, Quick SK, Trevisan M, Russell M, Nochajski TH, Edge SB, Freudenheim JL. (2009). Alcohol consumption and genetic variation in methylenetetrahydrofolate reductase and 5-methyltetrahydrofolate-homocysteine methyltransferase in relation to breast cancer risk. Cancer Epidemiol Biomarkers Prev. Aug 25;18(9):2453-2459.
32. Qi J, Miao X, Tan W, Yu CY, Liang G, Lv WF, Lin DX. (2004). Methylenetetrahydrofolate reductase gene single nucleotide polymorphisms and breast cancer risk. Chin J Oncol. May 1;26(5):287–9.
33. Rizzolo P, Silvestri V, Tommasi S, Pinto R, Danza K, Falchetti M, Gulino M, Frati P, Ottini L. (2013). Male breast cancer: genetics, epigenetics, and ethical aspects. Ann Oncol. Nov 1;24 (Suppl 8):i75-i82.
34. Ruark E, Snape K, Humburg P, Loveday C, Bajrami I, Brough R, Rodrigues DN, Renwick A, Seal S, Ramsay E, Duarte SV, Rivas MA, Warren-Perry M, Zachariou A, Campion-Flora A, Hanks S, Murray A, Ansari PN, Douglas J, Gregory L, Rimmer A, Walker NM, Yang TP, Adlard JW, Barwell J, Berg J, Brady AF, Brewer C, Brice G, Chapman C, Cook J, Davidson R, Donaldson A, Douglas F, Eccles D, Evans DG, Greenhalgh L, Henderson A, Izatt L, Kumar A, Lalloo F, Miedzybrodzka Z, Morrison PJ, Paterson J, Porteous M, Rogers MT, Shanley S, Walker L, Gore M, Houlston R, Brown MA, Caufield MJ, Deloukas P, McCarthy MI, Todd JA, Turnbull C, Reis-Filho JS, Ashworth A, Antoniou AC, Lord CJ, Donnelly P, Rahman N. (2013). Mosaic PPM1D mutations are associated with predisposition to breast and ovarian cancer. Nature. Jan 17;493(7432):406-410.
35. Sharp L, Little J, Schofield AC, Pavlidou E, Cotton SC, Miedzybrodzka Z, Baird JO, Haites NE, Heys SD, Grubb DA. (2002). Folate and breast cancer: the role of polymorphisms in methylenetetrahydrofolate reductase (MTHFR). Cancer Lett. Jul 8;181(1):65-71.
36. Shrubsole MJ, Gao YT, Cai Q, Shu XO, Dai Q, Hebert JR, Jin F, Zheng W. (2004). MTHFR polymorphisms, dietary folate intake, and breast cancer risk: results from the Shanghai Breast Cancer Study. Cancer Epidemiol Biomarkers Prev. Feb 1;13(2):190-196.
37. Song CX, Lei P, Wang T. (2012). Folate, MTHFR C677T and A1298C polymorphisms with the relationship with ovarian cancer risk among Chinese females. African Journal of Microbiology Research Vol. Jun 14;21(5):4761-4766.
38. Song H, Ramus SJ, Tyrer J, Bolton KL, Gentry-Maharaj A, Wozniak E, Anton-Culver H, Chang-Claude J, Cramer DW, DiCioccio R, Dork T, Goode EL, Goodman MT, Schildkraut JM, Sellers T, Baglietto L, Beckmann MW, Beesley J, Blaakaer J, Carney ME, Chanock S, Chen Z, Cunningham JM, Dicks E, Doherty JA, Durst M, Ekici AB, Fenstermacher D, Fridley BL, Giles G, Gore ME, De Vivo I, Hillemanns P, Hogdall C, Hogdall E, Iversen ES, Jacobs IJ, Jakubowska A, Li D, Lissowska J, Lubinski J, Lurie G, McGuire V, McLaughlin J, Medrek K, Moorman PG, Moysich K, Narod S, Phelan C, Pye C, Risch H, Runnebaum IB, Severi G, Southey M, Stram DO, Thiel FC, Terry KL, Tsai YY, Tworoger SS, Van Den Berg DJ, Vierkant RA, Wang-Gohrke S, Webb PM, Wilkens LR, Wu AH, Yang H, Brewster W, Ziogas A, Houlston R, Tomlinson I, Whittemore AS, Rossing MA, Ponder BA, Pearce CL, Ness RB, Menon U, Kjaer SK, Gronwald J, Garcia-Closas M, Fasching PA, Easton DF, Chenevix-Trench G, Berchuck A, Pharoah PD, Gayther SA. (2009). A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. Nat Genet. Sep 1;41(9):996-1000.
39. Stevens VL, McCullough ML, Pavluck AL, Talbot JT, Feigelson HS, Thun MJ, Calle EE. (2007). Association of polymorphisms in one-carbon metabolism genes and postmenopausal breast cancer incidence. Cancer Epidemiol Biomarkers Prev. Jun 1;16(6):1140-1147.
40. Terry KL, Tworoger SS, Goode EL, Gates MA, Titus-Ernstoff L, Kelemen LE, Sellers TA, Hankinson SE, Cramer DW. (2010). MTHFR polymorphisms in relation to ovarian cancer risk. GYNECOL ONCOL. Nov 1;119(2):319-324.
41. Turnbull C, Rahman N. (2008). Genetic predisposition to breast cancer: past, present, and future. Annu Rev Genomics Hum Genet. Jan 20;9:321-345.
42. Vainer AS, Boiarskikh UA, Voronina EN, Selezneva IA, Sinkina TV, Lazarev AF, Petrova VD, Filipenko ML. (2010). [Polymorphic

variants of folate metabolizing genes (C677T and A1298C MTHFR, C1420T SHMT1 and G1958A MTHFD) are not associated with the risk of breast cancer in West Siberian Region of Russia]. Mol Biol (Mosk). Sep 1;44(5):816-823.

43. Wang ZG, Cui W, Yang LF, Zhu YQ, Wei WH. (2014). Association of dietary intake of folate and MTHFR genotype with breast cancer risk. GENET MOL RES. Jul 24;13(3):5446-5451.
44. Webb PM, Ibiebele TI, Hughes MC, Beesley J, van der Pols JC, Chen X, Nagle CM, Bain CJ, Chenevix-Trench G, Australian Cancer Study (Ovarian Cancer), Australian Ovarian Cancer Study Group. (2011). Folate and related micronutrients, folate-metabolising genes and risk of ovarian cancer. EUR J CLIN NUTR. Jun 1;65(10):1133-1140.
45. Weiwei Z, Liping C, Dequan L. (2014). Association between dietary intake of folate, vitamin B6, B12 & MTHFR, MTR Genotype and breast cancer risk. PAK J MED SCI. Jan 1;30(1):106-110.
46. Wu XY, Ni J, Xu WJ, Zhou T, Wang X. (2012). Interactions between MTHFR C677T-A1298C variants and folic acid deficiency affect breast cancer risk in a Chinese population. Asian Pac J Cancer Prev. Jan 20;13(5):2199-2206.
47. Xu X, Gammon MD, Zhang H, Wetmur JG, Rao M, Teitelbaum SL, Britton JA, Neugut AI, Santella RM, Chen J. (2007). Polymorphisms of one-carbon-metabolizing genes and risk of breast cancer in a population-based study. Carcinogenesis. Jul 1;28(7):1504-1509.
48. Yang Z, Zhang XF, Liu HX, Hao YS, Zhao CL. (2012). MTHFR C677T polymorphism and colorectal cancer risk in Asians, a meta-analysis of 21 studies. Asian Pac J Cancer Prev Jan 20;13(4): 1203-1208.
49. Zhao P, Lin F, Li Z, Lin B, Lin J, Luo R. (2011). Folate intake, methylenetetrahydrofolate reductase polymorphisms, and risk of esophageal cancer. Asian Pac J Cancer Prev. Jan 20;12(8): 2019-2023.
50. Ziva CJ, Stegel V, Gersak K, Novakovic S. (2011). Lack of association between methylenetetrahydrofolate reductase genetic polymorphisms and postmenopausal breast cancer risk. MOL MED REP. Nov 30;4(1):175-179.