Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 546–550

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Methylenetetrahydrofolate reductase gene polymorphism in endometrial cancer: A systematic review and meta-analysis

Xian-jun Wang [a,*], Li-hui Xu [a], Yue-ming Chen [a], Li Luo [b], Qiao-feng Tu [a], Jin Mei [c]

[a] Department of Laboratory Medicine, Hangzhou First People's Hospital, Hangzhou, China
[b] School of Laboratory Medicine & Life Science, Wenzhou Medical University, Wenzhou, China
[c] Department of Obstetrics/Gynaecology and Genetics, Hangzhou First People's Hospital, Hangzhou, China

ARTICLE INFO

Article history:
Accepted 24 February 2015

Keywords:
endometrial cancer
methylenetetrahydrofolate reductase
MTHFR
polymorphisms
risk

ABSTRACT

Objective: We conducted a meta-analysis of case-controlled prospective or retrospective studies to assess the effect of *MTHFR* polymorphisms on the risk of developing endometrial cancer.
Materials and methods: PubMed, Cochrane, EMBASE, and ISI Web of Knowledge were searched (up to March 2014) for prospective or retrospective case-controlled studies that investigated the association of three *MTHFR* polymorphisms (rs180113 [C677T], rs1801131 [A1289C], and rs2274976 [G1793A]) with endometrial cancer.
Results: The patient population included subjects from three separate countries: China, Spain, and the USA. Only one study reported quantitative findings for *MTHFR* G1793A and, consequently, this polymorphism was not evaluated in our analysis. There were no significant associations of any *MTHFR* C677T or *MTHFR* A1298C alleles or genotypes with endometrial cancer (all $p > 0.300$).
Conclusion: This meta-analysis does not support the association of endometrial cancer with two common *MTHFR* polymorphisms from this patient population.

Introduction

Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme controlling the metabolism of methionine and folate which are essential components for nucleotide synthesis and DNA methylation, respectively [1]. Several single nucleotide polymorphisms (SNPs) in the *MTHFR* gene have been identified. The *MTHFR* C677CT (rs180113) polymorphism results in an alanine-to-valine substitution at amino acid 222 and is associated with reduced enzyme activity and increased thermolability [2]. This polymorphism is thought to play an important role in the etiology of cancer [3,4] and has been associated with increased risk for the development of cardiovascular disease, Alzheimer's disease, adult depression, neural tube defects in the fetus, thyroid cancer, ovarian cancer in Asians, colorectal cancer, and hematological malignancy [1,5–8]. The polymorphism *MTHFR* A1289C (rs1801131) is a missense mutation that causes a glutamate-to-alanine change at amino acid 429 in the C-terminal region of the protein that may affect enzyme activity [9] and has been associated with leukemia, lymphoma, and multiple myeloma risk [5,8,10]. A third polymorphism, *MTHFR* G1793A (rs2274976), results in an arginine to glutamic acid change at amino acid 594. The functional significance of this change is unknown [11]. There are conflicting results if the different polymorphisms are protective of or increase the risk of certain cancers [1,7–9,12–14].

Endometrial cancer is a common invasive gynecologic cancer and, among gynecologic malignancies, is the second-leading cause of death worldwide [15]. A number of factors have been associated with increased risk of endometrial cancers, including hormonal factors, inflammation, familial predisposition, genetic alterations, growth factors, diet, altered immune system, environmental factors, and oxidative stress [16–18]. Few studies have evaluated the association of genetic polymorphisms in *MTHFR* and endometrial cancer, with the findings being inconsistent [10,11,19–22]. We conducted a meta-analysis of case-controlled prospective or retrospective studies to assess the effect of *MTHFR* polymorphisms on the risk of developing endometrial cancer.

* Corresponding author. Department of Laboratory Medicine, Hangzhou First People's Hospital, Huansha Road Number 261, Hangzhou, 310006, China.
E-mail address: wangxj0525@126.com (X.-j. Wang).

http://dx.doi.org/10.1016/j.tjog.2015.08.005

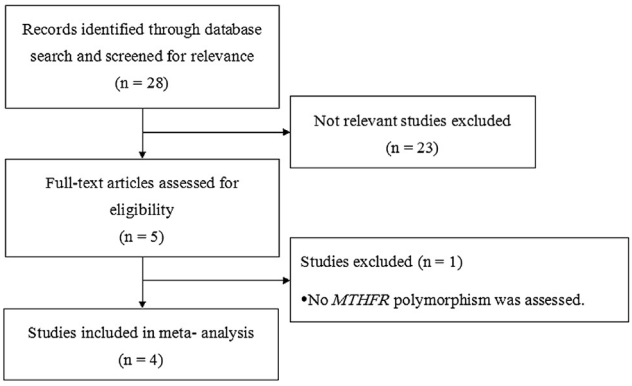

Figure 1. Flow diagram of study selection. *MTHFR* = methylenetetrahydrofolate reductase.

Materials and methods

PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Cochrane (http://www.cochrane.org), EMBASE (http://www.elsevier.com/solutions/embase), and ISI Web of Knowledge (www.webofknowledge.com) were searched (up to March 2014) using a combination of the following terms: MTHFR, methylenetetrahydrofolate reductase, endometrial carcinoma, endometrial cancer, genetic polymorphisms. Case-control, prospective, or retrospective studies that investigated *MTHFR* polymorphisms in patients with endometrial cancer were included in the analysis. All studies had to be published in English and must have reported the quantitative primary outcome for *MTHFR* polymorphism and endometrial cancer as an odds ratio (OR). Letters, comments, editorials, case reports, proceedings, or personal communications were not included in the analysis. The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) [23,24].

Data extraction

Data extracted from the included studies were: name of the first author, year of publication, geographic region in which the study was performed, study design, number of patients in the treatment and control arms, patient demographics, associated *MTHFR* genetic polymorphism, whether the polymorphisms were in Hardy-Weinberg equilibrium, and the reported OR and 95% confidence intervals (CI) for the associations of *MTHFR* with endometrial cancer. The list of potential studies were reviewed and the data extraction performed by two independent reviewers, and a third reviewer resolved any disagreement between the two reviewers.

Statistical analysis

Heterogeneity among the studies was assessed by the Cochran Q and the I^2 statistics. The heterogeneity was considered significant if either the Q statistic had $p < 0.1$ or $I^2 > 50\%$. When heterogeneity was considered significant, the random-effects model (DerSimonian-Laird approach) was performed. Otherwise, the fixed-effects model (Mantel-Haenszel approach) was used. The pooled estimates for OR of endometrial cancer in *MTHFR* 677C-to-T allele and genotypes CT vs. CC, TT vs. CC, and CT+TT vs. CC, and for the 1298A-to-C allele and genotypes CA vs. AA, CC vs. AA, and CA+CC vs. AA were performed using Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, NJ, USA). A two-sided $p < 0.05$ was considered statistically significant. Publication bias was not evaluated in this study, as five or fewer studies are insufficient to detect funnel-plot asymmetry [25]. Sensitivity analysis was performed based on the leave-one-out approach.

Results

The database search identified 28 potential studies (Figure 1). Twenty-three were considered irrelevant and were excluded. Five were further evaluated and one was excluded because it did not report findings regarding *MTHFR* polymorphisms. Four studies were included in the meta-analysis [11,19–21].

All four studies were case-controlled in design and were published between 1997 and 2013. The studies were performed in three separate countries: USA [20,21], China [11], and Spain (Table 1) [19]. Together the studies included 1915 endometrial cancer cases (range, 80 to 1041) and 2328 (range, 60 to 1030) control cases. Two studies reported that the frequency of the

Table 1
Summary of basic characteristics of the included studies.

First author (y)	Type of study	Region	Number of patients,	Age (y)	Study population		Hardy-Weinberg equilibrium test		
			EC/Control	EC/Control	EC	Control	*MTHFR* 677	*MTHFR* 1298	*MTHFR* 1793
Liu, J.J. (2013)	Nested case-control	USA	572/572	30-55/30-55	Nurses aged 30–55, diagnosed with invasive type-1 EC	Nurses randomly selected from non-EC pool and matched menopause status as EC subjects	NR	NR	NR
Xu, W.H. (2007)	Population-based case-control	China	1041/1030	30-69/30-69	Female permanent residents of urban Shanghai, China, EC diagnosed	Female permanent resident of urban Shanghai, China, randomly selected from resident registry; did not have EC or hysterectomy	None of the genotype frequencies for the polymorphisms deviated significantly from Hardy-Weinberg equilibrium among cases or controls		
Paynter, R.A. (2004)	Nested case-control	USA	222/666	NR	NR	NR	Both MTHFR polymorphisms were in Hardy-Weinberg equilibrium in the cases and the controls		NR
Esteller, M. (1997)	Hospital-based case-control	Spain	80/60	45–82/44–76	Female aged 45–82, selected at Valld'Hebron Hospital of Barcelona, Spain, with proven diagnosis of EC and no radiation or hormonal therapy prior to surgery	Female selected at Valld'Hebron Hospital of Barcelona, Spain, with no clinical or histological malignancy and no history of any other cancer	NR	NR	NR

EC = endometrial cancer; *MTHFR* = methylenetetrahydrofolate reductase; NR = not reported.

Table 2
Summary for the reported associations between *MTHFR* and *EC* from the included studies.

1st author (year of publication)	*MTHFR* 677 − CC/ CT/ TT or OR (95% CI)		*MTHFR* 1298 − AA/ AC/ CC or OR (95% CI)		*MTHFR* 1793 − GG/ GA/ AA or OR (95% CI)	
	EC	Control	EC	Control	EC	Control
Liu, J.J. (2013)	OR (T to C): 1.06 (0.89, 1.27)		OR (C to A): 1.03 (0.87, 1.23)		NR	NR
Xu, W.H. (2007)	356/506/167	337/521/158	699/300/37	705/280/34	856/174	855/158
	OR (CT to CC): 0.9 (0.8−1.1)[b]		OR (AC to AA): 1.1 (0.9−1.3)[b]		OR (AG+AA to GG): 1.1 (0.9−1.4)	
	OR (TT to CC): 1.0 (0.8−1.3)[b]		OR (CC to AA): 1.1 (0.7−1.8)[b]			
Paynter, R.A. (2004)	97/99/22	299/296/68	102/88/29	302/285/78	NR	NR
	OR (CT to CC): 1.10 (0.75−1.60)[a]		OR (AC to AA): 0.85 (0.59−1.22)[a]			
	OR (TT to CC): 1.11 (0.62−1.99)[a]		OR (CC to AA): 0.88 (0.51−1.52)[a]			
Esteller, M. (1997)	25/43/12	34/20/6	NR	NR	NR	NR
	OR (CT+TT to CC): 2.8 (1.36, 6.14)					

CI = confidence interval; EC = endometrial cancer; *MTHFR* = methylenetetrahydrofolate reductase; NR = not reported; OR = odds ratio.
[a] Additionally adjusted for body mass index prior to diagnosis, weight gain since age 18, age at menarche, ages at first birth and last birth, age at menopause, parity, pack-years of smoking, and first-degree family history of endometrial cancer or colon cancer.
[b] Adjusted for age.

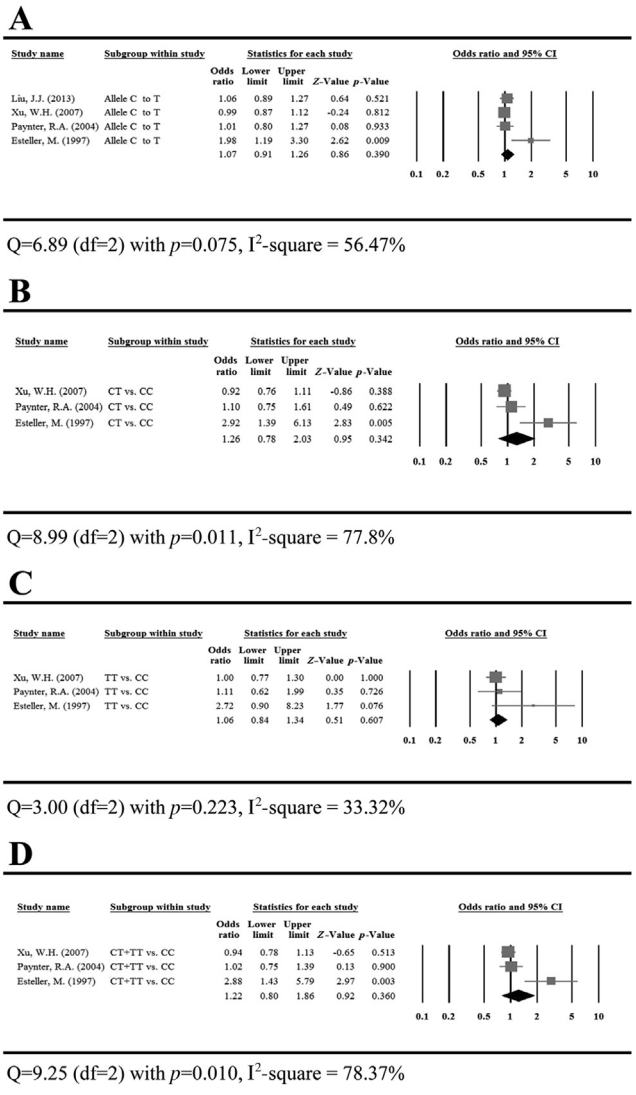

Figure 2. Meta-analyses for the odds ratios of *MTHFR* 677 (A) C-to-T allele, (B) genotype CT vs. CC, (C) genotype TT vs. CC, and (D) genotype CT+TT vs. CC. The random-effects model was performed if either the Q statistic with $p < 0.1$ or $I^2 > 50\%$. Otherwise, the fixed-effect model was performed. CI = confidence interval.

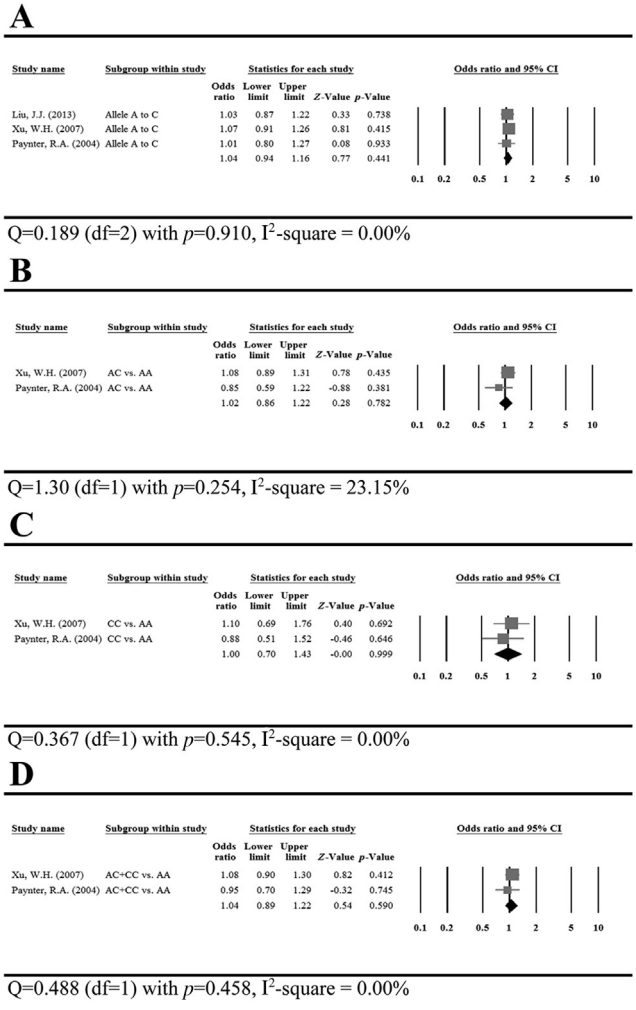

Figure 3. Meta-analysis for the odds ratio of *MTHFR* 1298 (A) A-to-C allele, (B) genotype AC vs. AA, (C) genotype CC vs. AA, and (D) genotype AC+CC vs. AA. The random-effects model was performed if either the Q statistic with $p < 0.1$ or $I^2 > 50\%$. Otherwise, the fixed-effect model was performed. CI = confidence interval.

genetic polymorphisms *MTHFR* C677T, *MTHFR* A1298C, and *MTHFR* G1793A were in Hardy-Weinberg equilibrium [11,20].

The OR for the association of *MTHFR* polymorphisms and endometrial cancer was reported in four studies for *MTHFR* C677T and in three studies for *MTHFR* A1298C (Table 2). Only the study of Xu et al [11] reported the association of *MTHFR* G1793A with endometrial cancer. Therefore, the meta-analysis did not include this polymorphism in the analysis (Figures 2 and 3).

The pooled data for both *MTHFR* C677T and *MTHFR* A1298C showed heterogeneity ($p < 0.01$ and $I^2 > 50\%$), hence a random-effects model was used for the analyses. There was no significant association of any of the alleles or genotypes of *MTHFR* C677T or *MTHFR* A1298C with endometrial cancer [all $p > 0.300$, (Figures 2 and 3)]. Sensitivity analysis using the leave-one-out approach found that no single study overly influenced the findings and that the results were reliable (Table 3).

Using the NOS for case-control studies, the quality of the design of each study, regarding selection of the study groups, comparability of the groups, and ascertainment of exposure, was assessed (Table 4) [23]. The study of Panter et al [20] was of high quality, having the maximum score for all three criteria (4 stars for selection, 2 for comparability, and 3 for exposure), and that of Esteller et al [19] was of lower quality relative to the other studies, with two stars for selection and one star for comparability.

Table 3
The corresponding sensitivity-analyses for the meta-analyses of *MTHFR* 677 and 1298.

	Study name, first author (y)	The pooled estimates and related statistics with one study removed		
		OR (95% CI)	*Z*	*p*
MTHFR 677 Allele C to T	Liu, J.J. (2013)	1.12 (0.86–1.46)	0.863	0.388
	Xu, W.H. (2007)	1.16 (0.89–1.52)	1.124	0.261
	Paynter, R.A. (2004)	1.12 (0.89–1.41)	0.989	0.322
	Esteller, M. (1997)	1.01 (0.92–1.11)	0.193	0.847
	Overall pooled estimate (random)	1.07 (0.91–1.26)	0.859	0.390
MTHFR 677 genotype CT vs. CC	Xu, W.H. (2007)	1.70 (0.66–4.39)	1.091	0.275
	Paynter, R.A. (2004)	1.55 (0.50–4.77)	0.759	0.448
	Esteller, M. (1997)	0.95 (0.80–1.13)	−0.551	0.581
	Overall pooled estimate (random)	1.26 (0.78–2.03)	0.949	0.342
MTHFR 677 genotype TT vs. CC	Xu, W.H. (2007)	1.35 (0.81–2.26)	1.137	0.256
	Paynter, R.A. (2004)	1.05 (0.82–1.36)	0.408	0.683
	Esteller, M. (1997)	1.02 (0.80–1.29)	0.144	0.886
	Overall pooled estimate (fixed)	1.06 (0.84–1.34)	0.514	0.607
MTHFR 677 genotype CT+TT vs. CC	Xu, W.H. (2007)	1.63 (0.59–4.49)	0.948	0.343
	Paynter, R.A. (2004)	1.56 (0.52–4.65)	0.799	0.424
	Esteller, M. (1997)	0.96 (0.82–1.13)	−0.496	0.620
	Overall pooled estimate (random)	1.22 (0.80–1.86)	0.916	0.360
MTHFR 1298 Allele A to C	Liu, J.J. (2013)	1.05 (0.92–1.20)	0.715	0.475
	Xu, W.H. (2007)	1.02 (0.89–1.17)	0.318	0.750
	Paynter, R.A. (2004)	1.05 (0.93–1.18)	0.823	0.410
	Overall-pooled estimate (fixed)	1.04 (0.94–1.16)	0.771	0.441

CI = confidence interval; OR = odds ratio.

Table 4
Quality assessment of included studies.

	Liu, J.J.	Xu, W.H.	Esteller, M.	Paynter, R.A.
Selection	***	***	**	****
Comparability	*	*	*	**
Exposure	***	***	***	***

Discussion

Although endometrial cancer is a common female malignancy, little is known regarding genetic susceptibility factors. We performed a meta-analysis to evaluate the association of endometrial cancer with two common polymorphisms in the *MTHFR* gene: *MTHFR* C677T and *MTHFR* A1298C. Four case-controlled studies were included in the meta-analysis, encompassing 1915 endometrial cancer cases and 2328 controls. Our meta-analysis found no significant association of any of the alleles or genotypes of *MTHFR* C677T and *MTHFR* A1298C with endometrial cancer (all $p > 0.300$).

The four studies included in this meta-analysis differed in their findings with regard to the relationship of *MTHFR* C677T and *MTHFR* A1298C with endometrial cancer. Liu et al [21] performed a prospective cohort analysis that investigated whether SNPs that are involved in one-carbon metabolism influence the association of dietary factors with endometrial cancer in women from the USA. They genotyped 572 endometrial cancer cases and matched controls and examined 29 mostly nonsynonymous SNPs in genes involved in one-carbon metabolism. For *MTHFR*, they evaluated *MTHFR* C677T and *MTHFR* A1298C. They found that *MTHFR* C677T and *MTHFR* A1298C SNPs were significantly associated with endometrial cancer ($p \geq 0.05$), however, there was a suggestion that the 677-TT or 1298-CC genotypes had a protective effect for folate, vitamin B2, vitamin B6, vitamin B12, and alcohol intake and endometrial cancer.

Xu et al [11] also did not find a relationship between *MTHFR* SNPs and endometrial cancer. Their study was a population-based case-controlled study that investigated the individual and joint effects of *MTHFR* C677T, *MTHFR* A1298AC, and *MTHFR* G1793A polymorphisms with dietary folate and other methyl-related nutrients on endometrial cancer risk. They genotyped 1041 newly diagnosed endometrial cancer cases and 1030 controls from women aged 39 to 69 years from Shanghai, China. They found no association between the risk of endometrial cancer and the derived haplotypes of the *MTHFR* SNPs. However, they did find that folate intake may modify the effect of *MTHFR* polymorphisms on endometrial cancer risk, as women carrying the *MTHFR* A1298C or *MTHFR* G1793A allele and having high folate intake had the lowest risk of endometrial cancer (p-$_{\text{interaction}} = 0.08$ and p-$_{\text{interaction}} = 0.03$, respectively).

Similarly, Paynter et al [20] investigated 201 endometrial cancer cases and 603 controls from the USA and found little or no association between the *MTHFR* genotype and endometrial cancer. For *MTHFR* C677T, the adjusted OR (95% CI) for comparing the presence of the T allele to the CC homozygotes was 1.10 (0.77–1.57) and for *MTHFR* A1298C, the adjusted OR (95% CI) for the presence of the C allele compared to the AA homozygotes was 0.85 (0.61–1.20).

In contrast, the study of Esteller et al [22] did find an association of *MTHFR* C677T with endometrial cancer in a Spanish population. The study of Esteller et al [19] included 80 patients with endometrial cancer and 60 controls. They found that a significant increase in endometrial cancer in patients carrying the 677-C/T or 677-T/T genotypes {alanine-to-valine substitution, [OR (95% CI); 2.88 (1.36-6.14)]; $p = 0.002$}. They also found a significant association of the 677-T allele and undifferentiated cellular grade endometrial cancer ($p = 0.03$).

The difference between the studies may reflect the different populations investigated, as geographical regions may have different genetic and environmental factors that might affect the findings [10]. For example, Pu et al [7] found that the *MTHFR* C667T polymorphism was associated with ovarian cancer in Asian, but not in Caucasian women [7]. Additionally, the etiology of endometrial cancer is not well understood and multiple risk factors can

influence its development. The presence of risk factors, including dietary intake, may also be geographically dependent, which could also influence findings. Xu et al [11] found that women with the lowest risk of endometrial cancer carried the *MTHFR* A1298C allele and had the highest intake of both folate and riboflavin. The type of cancer may also influence findings, as Esteller et al [19] found the greatest association of MTHFR C677T with endometrial cancer in women with poorly or moderately differentiated tumors as compared with those having well-differentiated tumors [19]. The three studies that found no association of the two *MTHFR* polymorphisms with endometrial cancer were also of higher quality in design than the study of Paynter et al [20].

There are several limitations to this study that should be considered when interpreting the results. Only four studies were included in the meta-analysis. There was insufficient information in the four studies to perform subgroup analysis to investigate the effect of folate consumption and ethnicity on outcomes. This meta-analysis only investigated the effect of two polymorphisms (C677T and A1298C) and did not evaluate the effect of other polymorphisms or the joint effect of the two included polymorphisms on risk of developing endometrial cancer. Our findings point to the need for additional controlled studies to examine the relationship of *MTHFR* polymorphisms and endometrial cancer.

In conclusion, this meta-analysis is consistent with *MTHFR* C677T and *MTHFR* A1298C polymorphisms not being significantly associated with an increased risk of endometrial cancer. Larger well-designed studies are needed to investigate the association of these MTHFR polymorphisms with susceptibility for endometrial cancer.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

This study was supported by the Medical Research and Special Disease Projects of the Bureau of Science and Technology, Hangzhou, Zhejiang province, China (20110733Q02).

References

[1] Trimmer EE. Methylenetetrahydrofolate reductase: biochemical characterization and medical significance. Curr Pharm Des 2013;19:2574–93.
[2] Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995;10:111–3.
[3] Kim YI. Role of the *MTHFR* polymorphisms in cancer risk modification and treatment. Future Oncol 2009;5:523–42.
[4] Toffoli G, De Mattia E. Pharmacogenetic relevance of *MTHFR* polymorphisms. Pharmacogenomics 2008;9:1195–206.
[5] Jiang N, Zhu X, Zhang H, Wang X, Zhou X, Gu J, et al. The relationship between methylenetetrahydrofolate reductase polymorphism and hematological malignancy. Clin Lab 2014;60:767–74.
[6] Yan Y, Han F, Fu H, Xia W, Qin X. Association between *MTHFR* C677T polymorphism and thyroid cancer risk: a meta-analysis. Tumour Biol 2014;35:7707–12.
[7] Pu D, Jiang SW, Wu J. Association between *MTHFR* gene polymorphism and the risk of ovarian cancer: a meta-analysis of the literature. Curr Pharm Des 2014;20:1632–8.
[8] Zhao M, Li X, Xing C, Zhou B. Association of methylenetetrahydrofolate reductase C677T and A1298C polymorphisms with colorectal cancer risk: a meta-analysis. Biomed Rep 2013;1:781–91.
[9] van der Put NM, Gabreels F, Stevens EM, Smeitink JA, Trijbels FJ, Eskes TK, et al. A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? Am J Hum Genet 1998;62:1044–51.
[10] Izmirli M. A literature review of *MTHFR* (C677T and A1298C polymorphisms) and cancer risk. Mol Biol Rep 2013;40:625–37.
[11] Xu WH, Shrubsole MJ, Xiang YB, Cai Q, Zhao GM, Ruan ZX, et al. Dietary folate intake, *MTHFR* genetic polymorphisms, and the risk of endometrial cancer among Chinese women. Cancer Epidemiol Biomarkers Prev 2007;16:281–7.
[12] Pereira AC, Schettert IT, Morandini Filho AA, Guerra-Shinohara EM, Krieger JE. Methylenetetrahydrofolate reductase (*MTHFR*) c677t gene variant modulates the homocysteine folate correlation in a mild folate-deficient population. Clin Chim Acta 2004;340:99–105.
[13] Shannon B, Gnanasampanthan S, Beilby J, Iacopetta B. A polymorphism in the methylenetetrahydrofolate reductase gene predisposes to colorectal cancers with microsatellite instability. Gut 2002;50:520–4.
[14] Yin G, Kono S, Toyomura K, Hagiwara T, Nagano J, Mizoue T, et al. Methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and colorectal cancer: the Fukuoka Colorectal Cancer Study. Cancer Sci 2004;95:908–13.
[15] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29.
[16] Verit FF, Yucel O. Endometriosis, leiomyoma and adenomyosis: the risk of gynecologic malignancy. Asian Pac J Cancer Prev 2013;14:5589–97.
[17] Group SGOCPECW, Burke WM, Orr J, Leitao M, Salom E, Gehrig P, et al. Endometrial cancer: a review and current management strategies: part II. Gynecol Oncol 2014;134:393–402.
[18] Group SGOCPECW, Burke WM, Orr J, Leitao M, Salom E, Gehrig P, et al. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol 2014;134:385–92.
[19] Esteller M, Garcia A, Martinez-Palones JM, Xercavins J, Reventos J. Germ line polymorphisms in cytochrome-P450 1A1 (C4887 *CYP1A1*) and methylenetetrahydrofolate reductase (*MTHFR*) genes and endometrial cancer susceptibility. Carcinogenesis 1997;18:2307–11.
[20] Paynter RA, Hankinson SE, Hunter DJ, De Vivo I. No association between *MTHFR* 677 C->T or 1298 A->C polymorphisms and endometrial cancer risk. Cancer Epidemiol Biomarkers Prev 2004;13:1088–9.
[21] Liu JJ, Hazra A, Giovannucci E, Hankinson SE, Rosner B, De Vivo I. One-carbon metabolism factors and endometrial cancer risk. Br J Cancer 2013;108:183–7.
[22] Esteller M, Garcia A, Martinez-Palones JM, Xercavins J, Reventos J. Clinicopathologic features and genetic alterations in endometrioid carcinoma of the uterus with villoglandular differentiation. Am J Clin Pathol 1999;111:336–42.
[23] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. PLoS Negl Trop Dis 2013;7(5):e2195. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [accessed 27.08.15].
[24] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[25] Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000;320:1574–7.