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Original Article

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

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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.

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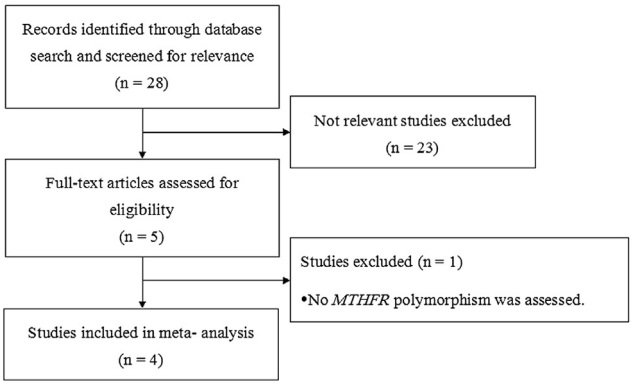

Figure 1. Flow diagram of study selection. *MTHFR* = methylenetetrahydrofolate reductase.

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.