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ORIGINAL PAPER

The effects of polymorphisms in methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), and methionine synthase reductase (MTRR) on the risk of cervical intraepithelial neoplasia and cervical cancer in Korean women

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Abstract The purpose of the study was to investigate the association between cervical cancer risk and single-nucleotide polymorphisms (SNPs) in three one-carbon metabolism genes, *methylenetetrahydrofolate reductase* (*MTHFR*), *methionine synthase* (*MTR*), and *methionine synthase reductase* (*MTRR*) in Korean women. Twelve SNPs were identified in *MTHFR*, *MTR*, and *MTRR* in the 927 case–control samples, which included 165 cervical intraepithelial neoplasia 1 (CIN1), 167 cervical intraepithelial neoplasia 2 and 3 (CIN2/3), 155 cervical cancer patients, and 440 normal controls. The frequencies of the genotypes and haplotypes were assessed in the controls, CINs, and cervical cancers. Individual carriers of the variant allele C of *MTHFR* A1298C (rs1801131) had a 0.64-fold [95% confidence interval (CI): 0.42–0.98] decreased risk for CIN2/3 compared with common homozygotes. However, no significant association was found between most other variants and cervical cancer risk. The results also identified an increased CIN1 risk in carriers with at least one copy of haplotype 3 in the MTHFR gene (odds ratio, 1.88; 95% CI: 1.03–3.42). In conclusion, there was no significant association between most SNPs in *MTHFR*, *MTR*, or *MTRR* and the risk of CIN and cervical cancer in Korean women. In addition, there was no significant association of *MTHFR* haplotypes with risk of CIN2/3 and cervical cancer.

Keywords Cervical intraepithelial neoplasia · Cervical cancer · Genetic polymorphisms · Methylenetetrahydrofolate reductase · Methionine synthase · Methionine synthase reductase

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Introduction

Although the incidence of uterine cervical cancer has been decreasing in Korea because of the increased availability of screening tests, it is the fourth most common malignant disease in Korean women, accounting for 9.8% of total malignancies in 2002 [1].

Folate and methionine metabolisms play an important role in carcinogenesis due to their involvement in DNA methylation and repair [2–4]. Several epidemiological studies have suggested the importance of folate in the risk of cervical cancer, although the results are not consistent [5–7]. *5,10-Methylenetetrahydrofolate reductase* (*MTHFR*), *methionine synthase* (*MTR*), and *methionine synthase reductase* (*MTRR*) play important roles in one-carbon metabolism. Polymorphisms in the genes for *MTHFR* C677T (rs1801133) and A1298C (rs1801131), *MTR* A2756G (rs1805087), and *MTRR* A66G (rs1801394) are known to have functional relevance [4]. Genetic variants of these genes alter their respective enzyme activities [4, 8–11], with consequent abnormalities in DNA methylation and synthesis, and therefore influence susceptibility to cancer [4]. Most studies of cervical cancer have focused on two putative functional polymorphisms in *MTHFR* C677T and A1298C; however, the findings are inconsistent [12–18]. Variations in other genes in the one-carbon metabolic pathway could affect cervical cancer risk, but have been evaluated less thoroughly in published studies [15, 19].

Therefore, a hospital-based case–control study was conducted to evaluate whether 12 genetic polymorphisms in three folate-metabolizing genes (*MTHFR*, *MTR*, and *MTRR*) and the *MTHFR* haplotypes are associated with cervical cancer risk in Korean women.

Methods

Study population

The subjects enrolled were adults (age range, 20–75 years) with a histologically proven diagnosis of cervical intraepithelial neoplasia (CIN) or cervical cancer between February 2006 and July 2007 at seven tertiary medical centers in Korea. CIN lesions were subdivided according to clinical meaningfulness into CIN1 and CIN2/3 based on the American Society for Colposcopy and Cervical Pathology 2006 guidelines [20]. The histopathological diagnoses included 165 cases of CIN1, 167 cases of CIN2/3, and 155 cases of cervical cancer. Control subjects ($n = 440$), who had a normal Pap smear on the day of recruitment without any history of abnormal Pap smears, were randomly selected from the divisions of gynecologic oncology of the same hospitals during the same study period. After informed consent was obtained, each subject was asked to fill out questionnaires regarding lifestyle and to provide 10 ml blood samples. The research protocol was approved by the institutional review boards of each institute.

Selection of polymorphisms and genotyping

Single-nucleotide polymorphism (SNP) information was retrieved from the National Center for Biotechnology Information database (www.ncbi.nlm.nih.gov/SNP). The SNPs selected as polymorphic markers were in the region between 5 kb upstream and 5 kb downstream of the following three genes: *MTHFR*, *MTR*, and *MTRR*. The SNPs were genotyped in 48 independent samples from Koreans of the general population (data not shown). Based on these genotype results, SNPs were chosen whose minor allele frequencies were >0.1. Then, the tag SNPs among the chosen SNPs were determined through the linkage disequilibrium (LD) bin approach implemented in the Tagger program (http://www.broad.mit.edu/mpg/tagger; accessed May 31 2007). The LD bin approach defines the bins of SNPs that are in very strong LD with a specified γ^2 threshold, and then one SNP is selected which represents the remaining SNPs in each bin [21]. A γ^2 threshold of 0.8 was used.

Genotyping with fluorescence polarization detection

Genomic DNA was extracted from the EDTA-treated blood samples using a QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, CA, USA).

Genotype identification was performed with the GenomeLab SNPstream (ultra-high throughput; UHT [22]) system, which uses multiplexed polymerase chain reaction (PCR) in conjunction with tag array single-base extension genotyping (Beckman Coulter, Fullerton, CA, USA). This system and its accompanying SNPstream software has been described by Demomme and Van Oene [23]. PCR was performed on an ABI Gene Amp 9700 thermal cycler (Applied Biosystems, Foster City, CA, USA) using Taq Gold DNA polymerase. Multiplexed PCR and genotyping were performed in homogeneous reactions, and assay results were read by direct two-color fluorescence on a SNPstream UHT Array Imager. In order to ensure quality control, genotyping was blinded to case–control status, and a 10% masked random sample of subjects was repeatedly tested; the results were concordant for all masked duplicated sets.

Statistical analysis

Chi-square tests were used to determine whether individual variants were in Hardy–Weinberg equilibrium (HWE) at each locus in the samples. The allelic frequency and

genotypic distribution of the SNPs among the groups were compared. A p value < 0.05 was considered to be significant. Odds ratios (ORs) were estimated using the logistic regression procedure in the SAS program, while age, menopausal status, parity, use of oral contraceptives, smoking status, alcohol consumption status, and use of multivitamins were used as adjusting covariates. Haplotypes for polymorphic sites of *MTHFR* were reconstructed via a Bayesian approach using PHASE software [24]. Analyses for the association between the haplotype and cervical carcinogenesis risk were performed using unconditional logistic regression at the individual level, where the covariate was defined by the number of copies (0, 1, or 2) of each haplotype that a subject carried. All analyses were performed using SAS 8.0 software (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 shows the distribution of cases and controls by background characteristics. Four hundred and forty controls and 487 cases (CIN1 = 165; CIN2/3 = 167; cancer = 155) were compared with regard to age, menopausal state, body mass index (BMI), parity, education, use of oral contraceptives, monthly income, smoking status, drinking, and intake of multivitamins. Cervical cancer patients were significantly more likely to be postmenopausal, have an older age at diagnosis and a higher BMI. Cases overall tended to have a lower education and monthly income, higher proportion of drinking and passive smoking, and lower consumption of multivitamins. No differences for parity, oral contraceptive use, or smoking status were observed between cases and controls.

Table 1 General characteristics of the study subjects

Variables	Control (n = 440)	CIN1 (n = 165)	CIN 2/3 (n = 167)	Cervical cancer (n = 155)	p[a]
Age (years), n (%)					
<40	124 (28.2)	81 (49.1)	82 (49.1)	28 (18.1)	
40–49	160 (36.4)	47 (28.5)	58 (34.7)	53 (34.2)	
50–59	112 (25.4)	26 (15.7)	19 (11.4)	35 (22.6)	
>60	44 (10.0)	11 (6.7)	8 (4.8)	39 (25.1)	<0.001
Post-menopause (%)	39.4	22.6	19.8	65.2	<0.0001
BMI (kg/m^2), n (%)					
<18.5	19 (4.3)	18 (10.9)	16 (9.6)	7 (4.5)	
18.5–22.9	246 (55.9)	80 (48.5)	95 (56.9)	60 (38.7)	
23–24.9	86 (19.6)	33 (20.0)	31 (18.5)	35 (22.6)	
>25	89 (20.2)	34 (20.6)	25 (15.0)	53 (34.2)	<0.001
Parity, mean (SD)	2.25 (0.91)	2.26 (0.82)	2.19 (0.85)	2.63 (1.25)	NS
Education					
≥University (%)	31.5	33.5	24.7	9.0	<0.0001
Oral contraceptive use (%)	15.5	20.0	21.6	20.7	NS
Household income (KRW)					
≥4,000,000 (%)	36.3	33.1	19.9	10.4	<0.0001
Smoking status, n (%)					
Non-smoker	399 (91.1)	138 (83.6)	143 (85.6)	136 (87.7)	
Former	13 (3.0)	8 (4.9)	8 (4.8)	6 (3.9)	
Current	26 (5.9)	19 (11.5)	16 (9.6)	13 (8.4)	NS
Passive smoking (%)	40.0	51.5	49.7	42.6	<0.05
Alcohol drinking, n (%)					
Never	233 (53.2)	49 (29.7)	58 (34.7)	82 (52.9)	
Former	15 (3.4)	6 (3.6)	14 (8.4)	20 (12.9)	
Current	190 (43.4)	110 (66.7)	95 (56.9)	53 (34.2)	<0.0001
Ever use multivitamins (%)	38.8	29.3	20.1	17.8	<0.0001

CIN cervical intraepithelial neoplasia, *BMI* body mass index

[a] p Values are from the chi-square test for categorical variables or from the ANOVA or ANCOVA (age adjusted) test for continuous variables. All p values are two-sided

Table 2 shows genotype distributions with ORs and 95% confidence intervals (CIs) for cervical dysplasia and cancer risk. The 12 SNPs from the three genes (*MTHFR*, *MTR*, and *MTRR*) were genotyped for the case–control samples. The *MTHFR* rs1801131 (A1298C) SNP showed significantly different frequencies between the CIN2/3 patients and the controls; cases with the *MTHFR* 1298CA/CC genotype had a significantly lower risk for CIN2/3 (OR 0.64; 95% CI: 0.42–0.98), but not for CIN1 or cervical cancer compared to those with the *MTHFR* 1298AA

Table 2 The effects of polymorphisms in MTHFR, MTR, and MTRR on CIN and cervical cancer

Genotypes	Control	CIN1		CIN2/3		Cervical cancer	
	n (%)	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]
MTHFR rs1476413							
GG	207 (68)	64 (68)	1.00[b]	66 (67)	1.00[b]	56 (59)	1.00[b]
GA/AA	97 (32)	30 (32)	0.96 (0.57–1.60)	32 (33)	0.96 (0.58–1.60)	39 (41)	1.36 (0.82–2.25)
MTHFR rs1801131							
AA	280 (65)	107 (67)	1.00[b]	117 (73)	1.00[b]	89 (60)	1.00[b]
CA/CC	150 (35)	53 (33)	0.87 (0.58–1.30)	43 (27)	0.64 (0.42–0.98)	59 (40)	1.10 (0.73–1.64)
MTHFR rs1801133							
CC/CT	352 (82)	134 (84)	1.00[b]	128 (80)	1.00[b]	118 (81)	1.00[b]
TT	77 (18)	25 (16)	0.81 (0.48–1.36)	32 (20)	1.11 (0.69–1.78)	28 (19)	1.17 (0.71–1.93)
MTHFR rs2066462							
CC	258 (84)	79 (84)	1.00[b]	82 (83)	1.00[b]	79 (83)	1.00[b]
CT/TT	49 (16)	15 (16)	0.88 (0.46–1.69)	17 (17)	0.95 (0.50–1.80)	16 (17)	1.02 (0.53–1.96)
MTHFR rs2274976							
GG	259 (84)	79 (84)	1.00[b]	82 (83)	1.00[b]	79 (83)	1.00[b]
AG/AA	48 (16)	15 (16)	0.89 (0.46–1.71)	17 (17)	0.95 (0.50–1.81)	16 (17)	1.08 (0.56–2.08)
MTHFR rs3737964							
GG	350 (84)	128 (83)	1.00[b]	134 (87)	1.00[b]	113 (78)	1.00[b]
AG/AA	67 (16)	27 (17)	1.13 (0.67–1.88)	20 (13)	0.77 (0.44–1.35)	31 (22)	1.33 (0.81–2.19)
MTR rs1805087							
GA/GG	120 (28)	35 (22)	1.00[b]	38 (24)	1.00[b]	31 (21)	1.00[b]
AA	309 (72)	124 (78)	1.43 (0.91–2.26)	121 (76)	1.28 (0.82–1.98)	116 (79)	1.50 (0.94–2.40)
MTRR rs1801394							
AA/GA	407 (95)	149 (94)	1.00[b]	143 (89)	1.00[b]	137 (93)	1.00[b]
GG	23 (5)	10 (6)	1.02 (0.46–2.28)	17 (11)	1.82 (0.92–3.61)	11 (7)	1.47 (0.67–3.23)
MTRR rs2303080							
AT/AA	80 (19)	32 (21)	1.00[b]	30 (20)	1.00[b]	30 (21)	1.00[b]
TT	340 (81)	119 (79)	0.98 (0.61–1.59)	121 (80)	1.04 (0.64–1.70)	113 (79)	0.92 (0.56–1.51)
MTRR rs162036							
GA/GG	143 (33)	52 (33)	1.00[b]	49 (31)	1.00[b]	44 (30)	1.00[b]
AA	284 (67)	104 (67)	0.91 (0.61–1.38)	108 (69)	1.04 (0.69–1.57)	102 (70)	1.16 (0.76–1.77)
MTRR rs16879334							
GC/GG	154 (37)	61 (40)	1.00[b]	52 (34)	1.00[b]	47 (34)	1.00[b]
CC	264 (63)	91 (60)	0.90 (0.60–1.34)	103 (66)	1.22 (0.81–1.82)	92 (66)	1.19 (0.78–1.81)
MTRR rs10380							
CT/TT	115 (27)	43 (27)	1.00[b]	39 (25)	1.00[b]	34 (23)	1.00[b]
CC	312 (73)	116 (73)	0.89 (0.58–1.38)	119 (75)	1.04 (0.67–1.61)	114 (77)	1.24 (0.78–1.96)

CIN cervical intraepithelial neoplasia, *MTHFR* methylenetetrahydrofolate reductase, *MTR* methionine synthase, *MTRR* methionine synthase reductase

[a] ORs and 95% CIs calculated using unconditional logistic regression, adjusted for age, menopausal status (pre-menopause vs. post-menopause), parity (one vs. two vs. three or more), oral contraceptive use, smoking status (ever vs. never), alcohol consumption status (ever vs. never), and HPV infection status

[b] Reference category

Table 3 The studied MTHFR polymorphisms

Listed in dbSNP	Location	Nucleotide location	Sequence change	Amino acid change	Minor allele frequency	HWE
rs3737964	5′ Flanking	−3871	G/A		0.087	0.548
rs1801133	Exon 4	665	C/T	Ala222Val	0.413	0.374
rs2066462	Exon 6	1056	C/T		0.084	0.440
rs1801131	Exon 7	1286	A/C	Glu429Ala	0.185	0.836
rs1476413	IVS 9	+35	G/A		0.181	0.671
rs2274976	Exon 11	1781	G/A	Arg594Gln	0.082	0.672

MTHFR methylenetetrahydrofolate reductase, *HWE p* values from the chi-square test for Hardy–Weinberg equilibrium

genotype after adjusting for age, menopausal status, parity, use of oral contraceptives, smoking status, alcohol consumption, and use of multivitamins. However, none of the other *MTHFR* polymorphisms showed any significant association with the risk of CINs and cervical cancer based on genotype. In addition, no notable effects were found for polymorphisms in the *MTR* or *MTRR* gene, although cases carrying the common homozygous A allele in *MTR* rs1805087 (A2756G) for CIN1 (OR, 1.43; 95% CI: 0.91–2.26) and cervical cancer (OR, 1.50; 95% CI: 0.94–2.40) or the homozygous G allele in *MTRR* rs1801394 (A66G) for CIN 2/3 (OR, 1.82; 95% CI: 0.92–3.61) were each related to a borderline increased risk.

Additionally, associations between haplotypes in the *MTHFR* gene and CINs and cervical cancer risk were evaluated. Table 3 shows marker information for *MTHFR*, including the dbSNP id, the chromosomal position, the sequence change, and the minor allele frequency. All SNPs were in HWE ($p > 0.05$). Among six SNPs of the *MTHFR* gene, 10 haplotypes were identified (Table 4). The four common haplotypes with >5% frequency were categorized as Hap1–Hap4 and the other rare haplotypes were grouped in the analysis (Table 5). Subjects carrying a copy of the Hap3 haplotype, which contains variant alleles at rs3737964 (5′ flank), rs1801131 (A1298C), and rs1476413 (IVS 9), had an increased risk of CIN1 compared to the controls (OR; 1.88, 95% CI: 1.03–3.42). However, no significant association was observed between any of the other haplotypes and CIN or cervical cancer risk.

Table 4 Distribution of haplotype frequencies for MTHFR and the estimated frequency of each haplotype

	5′ Flanking −3871	Exon 4 665	Exon 6 1056	Exon 7 1286	IVS 9 +35	Exon 11 1781	Frequency (%)
Hap1	G	T	C	A	G	G	632 (41.25)
Hap2	G	C	C	A	G	G	590 (38.51)
Hap3	A	C	C	C	A	G	127 (8.29)
Hap4	G	C	T	C	A	A	125 (8.16)
Hap5	G	C	C	C	G	G	27 (1.76)
Hap6	G	C	C	A	A	G	20 (1.31)
Hap7	A	C	C	A	G	G	7 (0.46)
Hap8	G	C	T	C	A	G	2 (0.13)
Hap9	G	C	T	C	G	G	1 (0.07)
Hap10	G	T	C	C	G	G	1 (0.07)

Discussion

The aim of this study was to evaluate one-carbon metabolism gene polymorphisms as risk factors for cervical carcinogenesis. The frequencies of common variants in the *MTHFR*, *MTR*, and *MTRR* genes were investigated, and the results showed that most genotypes and haplotypes did not alter the risk for cervical dysplasia or cervical cancer. Only the *MTHFR* A1298C genotypes in the present study showed a decreased risk for CIN2/3 in carriers of the variant C allele. In addition, the analysis of frequent haplotypes of *MTHFR* revealed that Hap3 showed a significant association with a higher risk of CIN1.

Although one-carbon metabolism is highly regulated by several enzymes, most studies have reported controversial results with respect to associations between *MTHFR* polymorphisms and the risk of cervical cancer. In previous reports, *MTHFR* C677T polymorphisms have been suggested to be associated with a risk of early-onset cervical carcinogenesis in Korean women [25]. However, a more recent study in Korea could not confirm a linkage between the *MTHFR* C677T and A1298C or the *MTR* A2756G genotypes and risk of cervical cancer [15]. The results of the present study correspond well with those of the earlier study which reported that polymorphisms of *MTHFR* C677T and *MTR* A2756G are not associated with risk of cervical cancer [19]. Gerhard et al. [16] and Rao et al. [26] also reported no significant association between *MTHFR* C677T or A1298C and cervical carcinogenesis. In contrast, two studies reported the *MTHFR* C677T polymorphism to be an increased risk factor for CIN with the T allele [17, 18]. On the other hand, Zoodsma et al. [14] reported that the *MTHFR* C677T genotype is associated with a decreased risk of cervical cancer in women carrying at least one T allele, whereas no association was seen with CIN.

Table 5 Association between MTHFR haplotypes and CIN and cervical cancer

Haplotype		Control ($n = 299$)	CIN1 ($n = 109$)		CIN2/3 ($n = 101$)		Cervical cancer ($n = 96$)	
		n	*n*	OR (95% CI)[a]	*n*	OR (95% CI)[a]	*n*	OR (95% CI)[a]
Hap1	0 Copies	108 (36)	37 (34)	1[b]	39 (39)	1[b]	34 (35)	1[b]
	1 Copy	140 (47)	56 (51)	1.17 (0.70–1.94)	41 (41)	0.74 (0.43–1.26)	47 (49)	1.09 (0.64–1.86)
	2 Copies	51 (17)	17 (15)	0.91 (0.46–1.82)	21 (20)	0.98 (0.51–1.89)	15 (16)	1.10 (0.53–2.28)
Hap2	0 Copies	113 (38)	41 (37)	1[b]	38 (38)	1[b]	41 (43)	1[b]
	1 Copy	138 (46)	54 (49)	1.13 (0.69–1.86)	46 (46)	0.99 (0.59–1.65)	40 (42)	0.79 (0.47–1.34)
	2 Copies	48 (16)	15 (14)	0.97 (0.48–1.97)	17 (17)	1.23 (0.61–2.47)	15 (15)	0.82 (0.40–1.69)
Hap3	0 Copies	256 (86)	88 (80)	1[b]	90 (89)	1[b]	77 (80)	1[b]
	1 Copy	38 (13)	22 (20)	1.88 (1.03–3.42)	11 (11)	0.85 (0.41–1.78)	18 (19)	1.46 (0.76–2.79)
	2 Copies	5 (1)	0 (0)	–	0 (0)	–	1 (1)	0.58 (0.06–5.65)
Hap4	0 Copies	252 (84)	93 (85)	1[b]	84 (83)	1[b]	79 (82)	1[b]
	1 Copy	45 (15)	16 (14)	0.95 (0.45–1.61)	15 (15)	0.90 (0.46–1.74)	16 (17)	1.14 (0.59–2.20)
	2 Copies	2 (1)	1 (1)	2.27 (0.19–27.12)	2 (2)	4.43 (0.56–35.01)	1 (1)	1.34 (0.10–17.44)
Others	0 Copies	275 (92)	106 (96)	1[b]	92 (91)	1[b]	89 (93)	1[b]
	1 Copy	23 (8)	4 (4)	0.45 (0.15–1.39)	9 (9)	1.47 (0.63–3.40)	7 (7)	0.76 (0.30–1.91)
	2 Copies	1 (0)	0 (0)	–	0 (0)	–	0 (0)	–

CIN cervical intraepithelial neoplasia, *MTHFR* methylenetetrahydrofolate reductase

[a] ORs and 95% CIs calculated using unconditional logistic regression, adjusted for age, menopausal status (pre-menopause vs. post-menopause), parity (one vs. two vs. three or more), oral contraceptive use, smoking status (ever vs. never), alcohol consumption status (ever vs. never), and HPV infection status

[b] Reference category

The effects of *MTRR* polymorphisms have not been previously investigated in relation to cervical carcinogenesis risk. Studies investigating the *MTRR* A66G (rs1801394) polymorphism with breast cancer, gastric cancer, head and neck squamous cell carcinomas, and multiple myeloma have yielded inconsistent results [27–31]. In the present study, no clear evidence of a link between the *MTRR* A66G polymorphism and cervical carcinogenesis risk was found.

These conflicting results may be associated with variable sample size and racial variation. The present study has several strengths. Possible confounding effects of cervical carcinogenesis-related lifestyle factors were comprehensively considered. More importantly, oncogenic HPV infection was also adjusted as a confounder in the multivariate model, which is a significant cause of cervical cancer. Furthermore, minor allele frequencies were similar to previously published Korean studies [15, 25]. The genotyping rates in the present study were also very high for each locus, and the haplotype analysis provided a better basis for evaluating the interaction between genetic polymorphisms and cervical carcinogenesis risk. Prior studies of the *MTHFR* haplotype and cervical cancer were limited to only two candidate polymorphisms (C655T and A1298C) [14, 32]. In the present study, Hap3 showed a significant association with CIN1. It is unclear whether Hap3 functionally affects CIN risk. However, *MTHFR* A1298C is a functional variant and 5′ flank polymorphism may have functional significance by affecting mRNA stability or regulation of translation [33, 34].

The present study also has its limitations. Even though this study had a relatively large total sample size, the minor allele frequency was somewhat low for statistically evaluating potential interactions. A larger study with greater statistical power would be needed to detect associations of the magnitude observed in the present study, and this issue is particularly relevant to subgroup analyses for interaction tests in the present study, with its small strata sizes. Not all key enzymes in the one-carbon metabolism pathway were studied. Therefore, the possibility remains that additional genetic variations in this metabolic pathway may be related to cervical carcinogenesis risk.

In summary, this study dose not support a substantial association between the evaluated genetic polymorphisms and cervical cancer risk, with the possible exception of the *MTHFR* A1298C (rs1801131) variant and one haplotype in *MTHFR*. Therefore, the role of genetic polymorphism in cervical cancer susceptibility in Korean women should be evaluated using further studies with larger cohorts of patients and controls.

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