Relation between the SNPs in Methylenetetrahydrofolate Reductase Gene C677T and G1793A and the Susceptibility of Sporadic Breast Cancer*

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ABSTRACT: To investigate the relation between C677T and G1793A site SNPs (Single nucleotide polymorphisms) of methylenetetrahydrofolate reductase (MTHFR) gene and the susceptibility of sporadic breast cancer, the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used to analyze the SNPs of MTHFR C677T and G1793A in 200 breast cancer patients and 200 control volunteers, and the logistic regression analysis was performed to investigate the association between different genotypes and susceptibility of breast cancer. The results showed that, the frequency of MTHFR 677TT genotype in the breast cancer group was 25.00%, which was significantly higher than 10.50% in the controls (X^2=14.401, P=0.001); The frequency of MTHFR 677CT genotype was 44.50%, which was lower than 54.50% in the controls; the frequency of MTHFR 677CC genotype was similar in both the cases and the controls; and the frequency of MTHFR 1793GA genotype was 18.50%, which was evidently higher than 8.50% in the controls (X^2=8.563, P=0.003). The allele frequencies of MTHFR 677T and 1793A in the breast cancer patients were 47.25% and 9.25%, respectively, which were significantly greater than 37.75% and 4.25% in the controls. For MTHFR C677T, the MTHFR 677TT genotype was found to be at a significant 2.732-fold increased risk of developing breast cancer (95% CI=1.418~5.051, P=0.001), compared with that in the referent group carrying the MTHFR 677CC genotype. For MTHFR G1793A, the MTHFR1793GA genotype was found to be at a significant 2.444-fold increased risk of developing breast cancer (95% CI=1.325~4.505, P=0.004), compared with the referent group carrying the MTHFR 1793GG genotype. Besides, the polymorphism of MTHFR C677T gene in the breast cancer group was associated with the tumor size (x^2=7.431, P=0.024), while the polymorphism of MTHFR G1793A gene was associated with lymph node metastasis (x^2=8.939, P=0.011) and cancer histological grading (x^2=9.983, P=0.007). The polymorphism of MTHFR genes C677T and G1793A is correlated with the susceptibility of sporadic breast cancer.

Key words: Sporadic breast cancer; Methylenetetrahydrofolate reductase (MTHFR); Single nucleotide polymorphisms; Polymerase chain reaction-restriction fragment length polymorphism(PCR-RFLP)

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Introduction

Breast cancer, as one of the most common malignant tumors in women, shows a continuously increasing trend in morbidity in China. The investigation of tumor pathogenesis becomes a hot topic in the current oncologic research. Tumor is a genetic disease in nature and gene mutation is the molecular foundation that cells develop into tumors. At present, the pathogenesis of breast cancer is still unclear. Folic acid deficiency may damage the normal methylation of DNA and affect DNA synthesis and repair, thus causing cell cancerization[1]. MTHFR is a key enzyme in folic acid metabolism. The studies have found that MTHFR gene is polymorphic and C677T polymorphism influences enzyme activity and thus affects the metabolism of folic acid[2]. Although there are many reports on the relation between the polymorphism of MTHFR C677T gene and breast cancer, the results are not all consistent[3-5]. There are few published reports on the association between the polymorphism of MTHFR G1793A site and the risk of breast cancer. In this paper, we investigated the correlation between MTHFR C677T or G1793A and the susceptibility of breast cancer by a case-controlled study.

1 Materials and Methods

1.1 Materials

The breast cancer group (experimental group) included the female patients with breast cancer who were admitted to Department of Breast Surgery of the Affiliated Hospital of Medical College Qingdao University from December 2010 to April 2011, diagnosed definitely by postoperative pathological examination and received no treatment for breast cancer before operation. There were 200 patients in the breast cancer group, with the age of 28-82 years

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(median age: 49 years). In these 200 patients, 176 cases were infiltrating ductal carcinoma, 2 cases infiltrating lobular carcinoma, and 22 cases other types of carcinoma; 129 cases had a tumor size ≤2 cm and 71 cases had a tumor size > 2 cm; according to the cytological grading, 11 cases were grade I, 106 cases grade II, and 83 cases grade III; 77 cases had axillary lymph node metastasis; 133 cases had positive estrogen receptor (ER); and 115 cases had positive progesterone receptor (PR). The control group included 200 healthy female volunteers aged 26-80 years (median age: 48 years) who received the physical examination in the Affiliated Hospital of Medical College Qingdao University during the same period of time. The subjects in two groups all had no family history of breast cancer with Han ethnicity, and provided informed consent.

1.2 Reagents and Methods

1.2.1 DNA extraction: A 2 ml peripheral venous blood sample was collected under fasting from the breast cancer group and the control group using a tube containing EDTA as the anticoagulant, then the human genomic DNA extract kit N1121/N1122 (Dongsheng Biotech Co., Ltd., Guangzhou) was used to extract genomic DNA from 500 μl whole blood, finally the concentration and purity of DNA were measured and the extracted DNA was preserved at -20℃ for use.

1.2.2 Polymorphism analy sis of MTHFR C677 T and G1793A genes The primer design was performed referring to the reference [6] (the primers were synthesized by Shanghai Sunny Biotech Co., Ltd.), and the PCR-RELP method was used to analyze the polymorphism of MTHFR C677T and G1793A genes.

The primer containing C677T polymorphic site was amplified into 5'-TGAAGGAGAAGGTGTCTGCGGGA-3'and 5'-AGGACGGTGCGGTGAGAGTG-3', with the product length of 198 bp. The PCR system had a total volume of 10μl, and contained Premix Taq5.0 μl [provided by TaKaRa Biotechnology(Dalian)Co., Ltd.], distrand DNA template 1μl, double distilled water 3.2 μl, forward primer 0.4 μl and reverse primer 0.4 μl. The PCR amplification conditions were shown below: 5 min at 94 ℃; 30 s at 94 ℃, 30 s at 62 ℃, and 30 s at 72 ℃, 35 cycles; 7 min at 72 ℃. The products were digested for 16 h (at 37 ℃) using the specific restriction endonuclease HinfI (BioLabs, New England), then the electrophoresis with 3% agarose gel and EB staining were performed, and finally the digestion results were displayed in the imaging system.

The primer containing G1793A polymorphic site was amplified into 5'-CTCTGTGTGTGTGTGCATGTGTGCG-3' and 5'-GGGACAGGAGTGGCTCCAACGCAGG-3', with a product length of 310 bp. The PCR system had a total volume as same as the abovementioned. The PCR amplification conditions were seen below: 5 min at 94 ℃; 30 s at 94 ℃, 30 s at 64 ℃, and 30 s at 72 ℃, 40 cycles; 7 min at 72 ℃. The products were digested for 16 h (at 37 ℃) by using the specific restriction endonuclease BsrbI (BioLabs, New England), then the electrophoresis with 3% agarose gel and EB staining were performed, and finally the digestion results were displayed in the imaging system.

1.2.3 Statistic analysis Hardy-Weinberg equilibrium test was used to confirm the group representativeness of study samples. SPSS 17.0 software was applied to create a database, and X^2 test was employed to analyze the allele frequency, distribution difference between different genotypes, and relationship with the clinical pathological characteristics of breast cancer. The relative risk (RR) was assessed by calculating odds radios (ORs). The logistic regression analysis was performed for correlation. A statistically significant difference was considered if $P<0.05$.

2 Results

2.1 Electrophoretograms of MTHFR C677T and G1793A polymorphic sites:

For MTHFR C677T, the normal CC genotype had no digestion site and only produced a complete fragment of 198 bp, while the hybrid genotype CT produced three fragments of 198 bp, 175 bp and 23 bp, and the mutant genotype TT produced two fragments of 175 bp and 23 bp. For MTHFR G1793A, the normal GG produced two fragments of 233 bp and 77 bp, while the hybrid genotype GA produced three fragments of 310 bp, 233 bp and 77 bp, and the mutant genotype AA produced a complete fragment of 310 bp.

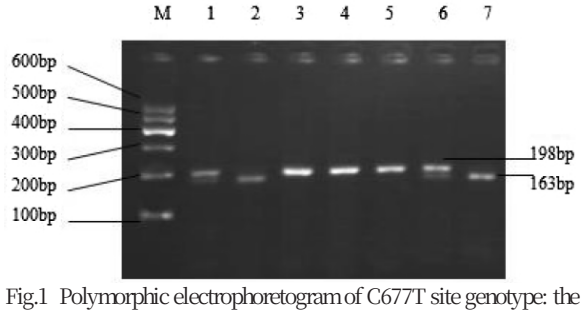

Fig.1 Polymorphic electrophoretogram of C677T site genotype: the specimens 3, 4 and 5 were CC genotype, the specimens 1 and 6 were CT genotype, and the specimens 2 and 7 were TT genotype (the 23bp fragment was not shown in 3% agarose gel)

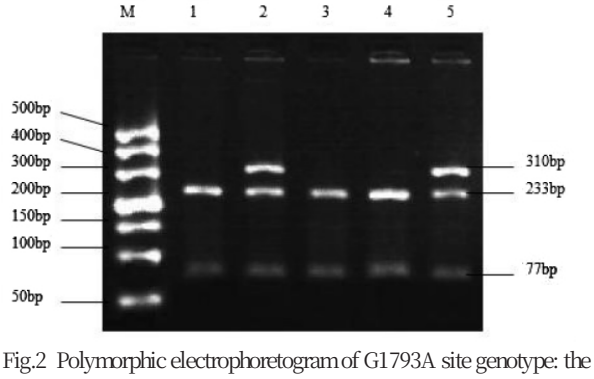

Fig.2 Polymorphic electrophoretogram of G1793A site genotype: the specimens 1, 3 and 4 were GG genotype, and the specimens 2 and 5 were GA genotype

2.2 Distribution frequency of MTHFR genotypes

The distribution of MTHFR C677T and G1793A genotypes in the breast cancer group and the control group met Hardy-Wein-

berg equilibrium law (P>0.05), thus there was group representativeness. The age difference between the breast cancer group (49± 11.46) and the control group (48± 10.84) was not significant statistically (P>0.05).

There was significant difference in the distribution of MTHFR C677T genotype between the breast cancer group and the control group (X^2=14.484, P=0.001). The further analysis showed that the frequency of MTHFR 677TT genotype in the breast cancer group was significantly greater than that in the control group (X^2=14.401, P=0.001); No MTHFR 1793AA mutant homozygote was observed in both the cases and the controls; a significant difference was seen in the distribution of MTHFR 1793GG and GA genotypes between the cases and the controls (X^2=8.563, P=0.003); the difference in the allele frequency distribution of MTHFR C677T and MTHFR G1793A sites was significant between the cases and the controls (Table 1).

Table 1 Genotype and allele frequency distribution of MTHFR C677T and G1793A (case, %)

	Cases	Controls	x^2	P
Genotype frequency (%) of C677T				
CC	61(30.50)	70(35.00)	0.919	0.338
CT	89(44.50)	109(54.50)	4.000	0.045
TT	50(25.00)	21(10.50)	14.401	0.001
Allele frequency (%)				
C	211(52.75)	249(62.25)	7.386	0.007
T	189(47.25)	151(37.75)	7.386	0.007
Genotype frequency (%) of G1793A				
GG	163(81.50)	183(91.50)	8.563	0.003
GA	37(18.50)	17(8.50)	8.563	0.003
Allele frequency (%)				
G	363(90.75)	383(95.75)	7.944	0.005
A	37(9.25)	17(4.25)	7.944	0.005

Table 2 Correlation between different MTHFR C677T genotypes and the clinical pathological characteristics of breast cancer (case, %)

		CC	CT	TT	x^2	P
Tumor size (cm)	≤2	37(18.50)	66(33.00)	26(13.00)	7.431	0.024
	>2	24(12.00)	23(11.50)	24(12.00)		
Histological grading	I	3(1.50)	7(3.50)	1(0.50)	3.404	0.493
	II	36(18.00)	44(22.00)	26(13.00)		
	III	22(11.00)	38(19.00)	23(11.50)		
Lymph node metastasis	0	41(20.50)	54(27.00)	28(14.00)	4.191	0.381
	1~3	13(6.50)	16(8.00)	14(7.00)		
	≥4	7(3.50)	19(9.50)	8(4.00)		
ER	(-)	23(11.50)	24(12.00)	20(10.00)	3.138	0.208
	(+)	38(19.00)	65(32.50)	30(15.00)		
PR	(-)	26(13.00)	37(18.50)	22(11.00)	0.078	0.962
	(+)	35 (17.50)	52(26.00)	28(14.00)		
C-erbB-2	(-)	44(22.00)	68(34.00)	36(18.00)	0.482	0.786
	(+)	17(8.50)	21(10.50)	14(7.00)		
P53	(-)	29(14.50)	40(20.00)	23(11.50)	0.098	0.952
	(+)	32(16.00)	49(24.50)	27(13.50)		

2.3 Correlation between the polymorphism of MTHFR gene and the clinical pathological factors of breast cancer

The data from Table 2 showed that the polymorphism of MTHFR C677T gene was associated with the tumor size. The data from Table 3 revealed that the polymorphism of MTHFR G1793A gene was associated with lymph node metastasis and cancer histological grading.

Table 3 Correlation between different MTHFR G1793A genotypes and the clinical pathological characteristics of breast cancer (case, %)

		GG	GA	x^2	P
Tumor size (cm)	≤2	102(51.00)	27(13.50)	1.423	0.233
	>2	61(30.50)	10(5.00)		
Histological grading	I	9(4.50)	2(1.00)	9.983	0.007
	II	78(39.00)	28(14.00)		
	III	76(38.00)	7(3.50)		
Lymph node metastasis	0	102(51.00)	21(10.50)	8.939	0.011
	1~3	39(19.50)	4(2.00)		
	≥4	22(11.00)	12(6.00)		
ER	(-)	56(28.00)	11(5.50)	0.290	0.590
	(+)	107(53.50)	26(13.00)		
PR	(-)	72(36.00)	13(6.50)	1.008	0.315
	(+)	91(45.50)	24(12.00)		
C-erbB-2	(-)	119(59.50)	29(14.50)	0.452	0.501
	(+)	44(22.00)	8(4.00)		
P53	(-)	76(38.00)	16(8.00)	0.139	0.709
	(+)	87(43.50)	21(10.50)		

2.4 Correlation between MTHFR genotypes and breast cancer risk

The logistic regression analysis showed that, the MTHFR 677TT genotype was found to be at a significant 2.732-fold increased risk of developing breast cancer (95% CI=1.418~5.051, P=0.001), compared with that in the referent group carrying the MTHFR 677 CC genotype, while the heterozygote MTHFR 677CT did not increase the breast cancer risk significantly (OR=0.937,95% CI=0.602~1.459, P=0.773). For MTHFR G1793A, the MTHFR1793GA genotype was found to be at a significant 2.444-fold increased risk of developing breast cancer (95% CI=1.325~4.505, P=0.004), compared with the referent group carrying the MTHFR 1793GG genotype.

3 Discussion

MTHFR is a key enzyme in methionine-folic acid metabolism, and catalyzes 5, 10-methylene tetrahydrofolic acid to transform into 5-methyl tetrahydrofolic acid irreversibly. 5-methyl tetrahydrofolic acid serves as the raw material of S-adenosyl methionine (SAM) synthesis and is involved in the synthesis of purine and pyrimidine, while SAM is a common methyl donor for various methylation reactions in cells. A study has found that MTHFR C677T polymorphism evidently increases the breast cancer risk, suggesting folic acid deficiency and/or dysbolism may involve the carcinogenesis process. In this study, the mutation allele frequency of MTHFR C677T significantly increased in the breastcancerpatients (P<0.05), the genotype frequency of MTHFR 677TT was evidently higher than that in the control patients (P<0.05), and compared with men with a homozygous (677CC) allele, men with a homozygous (677 TT) allele had a 2.732-fold increased risk of developing breast cancer. These findings were consistent to the study results of Maruti SS et al [3].

The mechanism of MTHFR gene mutation increasing the risk of developing breast cancer may be related to the resultant DNA methylation abnormality. MTHFR gene 677C→T mutation causes the thermal instability and decreased activity of MTHFR, thus resulting in the decreased yield of SAM and affecting DNA methylation. Frosst reported that the enzyme activity of 677CT and 677TT genotypes was only 65% and 30% of that of 677CC genotype [7], and the low-activity MTHFR genotypes were associated with the development risks of acute lymphoblastic leukemia (ALL), lung cancer, gastric cancer, rectal cancer and other cancers [8, 9]. A study has revealed that whole-genome hypomethylation is often coexisting with the regional hypermethylation of anti-oncogene CpG island [10]. Genomic DNA hypomethylation is usually seen in the early stage of many human tumors including breast cancer and cancerization,

which is generally accompanied by the over-expression of c-myc and c-Ha-ras [11] and the abnormal change of anti-oncogene p53[12]. In this study, the carriers of 677TT genotype with the most significant decrease of enzyme activity were more susceptible of developing breast cancer than those of 677CC genotype, while 677CT genotype had no effect on the risk of breast cancer. This may suggest that only a certain degree of methyl donor failure caused by folic acid deficiency or dysbolism can result in cell cancerization.

The relationship between MTHFR gene polymorphism and the risk of developing breast cancer also may be influenced by folic acid intake. When there is full intake of folic acid, the carriers of MTHFR mutant genes have a low risk of developing cancer; in this case, methyl donor is assured and the increased content of 5, 10-methylene tetrahydrofolic acid provides raw materials for de novo synthesis of nucleotide. However when folic acid intake is insufficient, the individuals carrying MTHFR mutant genes have a high risk of developing cancer; in this case, the main mechanism is DNA methylation abnormality. Stern found that the genomic DNA methylation level of MTHFR 677TT genotype carriers was significantly lower than that of MTHFR 677CC genotype carriers [13], which was directly and evidently associated with the folic acid content in red blood cells. The effect of this MTHFR polymorphism depending on folic acid nutritional status on the risk of developing cancer was confirmed in this study, though no data of plasma folic acid level were available for further analysis [14]. The previous studies have shown that insufficient folic acid intake is very common in Chinese population, which may be an important cause for MTHFR gene polymorphism increasing the susceptibility of breast cancer [15].

Rady reported a race difference in MTHFR G1793A gene polymorphism, the allele frequency of MTHFR 1793A was 1.3% in German Jews, 3.1% in African-Americans, 5.8% in Spanish-Americans, and 6.9% in American-Caucasians[16]. This study showed the allele frequency of MTHFR 1793A was 4.25% in the healthy Han population, and there was a significant difference between different races. A study has reported that MTHFR G1793A gene polymorphism may increase the development risks of endometrial cancer and squamous cell carcinoma of the head and neck [17,18]. Few available reports are about the relationship between MTHFR G1793A gene polymorphism and breast cancer. It was found in this study that the mutation allele frequency and genotype frequency of G1793A in the breast cancer patients were significantly higher than those in the control patients ($P<0.05$), and MTHFR G1793A genotype carriers had a breast cancer risk 2.444 fold greater than MTHFR 1793GG genotype carriers. The clinical pathological analysis showed that C677T gene polymorphism was correlated with the tumor size, while G1793A gene polymorphism was associated with tumor histological grading and lymph node metastasis. These results have indicated that MTHFR G1793A gene polymorphism may increase the susceptibility of breast cancer. It is inferred theoretically that G1793A polymorphism is demonstrated by the 594th codon of MTHFR gene and this region is critical to maintain the structural stability of protein, when the mutation of G→A takes place in this site, the charged arginine will be transformed into the neutral glutamic acid (R594Q), causing the changed stability and function of MTHFR and eventually affecting the folic acid metabolism process. However, the specific mechanism is still unknown and needs to be studied further.

In conclusion, this study has proven the correlation between the mononucleotide polymorphism of MTHFR genes and the susceptibility of breast cancer, which provides a genetic basis for the hypothesis that insufficient folic acid intake and (or) folic acid dysbolism may play a role in the development of breast cancer. If this relationship is further confirmed, a new idea concerning the prevention of breast cancer will become available.

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亚甲基四氢叶酸还原酶基因 C677T、G1793A 单核苷酸多态性与散发性乳腺癌易感性的关系*

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摘要 目的：研究亚甲基四氢叶酸还原酶(MTHFR)基因 C677T、G1793A 位点单核苷酸多态性与散发性乳腺癌易感性关系。**方法：**采用聚合酶链反应-限制性片段长度多态性(PCR-RFLP)方法，对 200 例乳腺癌患者及 200 例正常对照者 MTHFR 基因 C677T、G1793A 位点单核苷酸多态性进行分析，logistic 回归分析不同基因型与乳腺癌风险的关系。**结果：**乳腺癌组 MTHFR 677TT 基因型频率为 25.00%显著高于正常对照组的 10.50%(X^2=14.401，P=0.001)，CT 基因型频率为 44.50%低于正常对照组的 54.50%，CC 基因型频率在乳腺癌组和正常对照组中无差别；MTHFR 1793GA 基因型频率为 18.50%显著高于正常对照者的 8.50%(X^2=8.563，P=0.003)。乳腺癌患者 MTHFR 677T 和 1793A 等位基因频率分别为 47.25%、9.25%，显著高于对照组中的 37.75%、4.25%。MTHFR 677TT 基因型携带者罹患乳腺癌的风险是 677CC 基因型携带者的 2.732 倍(95%CI=1.418～5.051，P=0.001)，MTHFR 1793GA 基因型携带者罹患乳腺癌的风险是 1793GG 基因型携带者的 2.444 倍(95%CI=1.325～4.505，P=0.003)。另外，乳腺癌组中 MTHFR C677T 基因多态性与肿瘤大小相关(x^2=7.431，P=0.024，MTHFR G1793A 基因多态性与淋巴结转移情况(x^2=8.939，P=0.011)、癌组织学分级(x^2=9.983，P=0.007)相关。**结论：**MTHFR C677T、G1793A 基因多态性与散发性乳腺癌的易感性相关。

关键词：散发性乳腺癌；亚甲基四氢叶酸还原酶；单核苷酸多态性；PCR-RFLP

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