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Methylenetetrahydrofolate Reductase *C677T* and *A1298C* Polymorphisms and Gastric Cancer: A Meta-analysis

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Background and Aims. Case/control studies that investigated the association between gastric cancer and the *MTHFR C677T* and *A1298C* polymorphisms so far have provided controversial results. To clarify the effect of *MTHFR* polymorphisms on the risk of gastric cancer, a meta-analysis was performed.

Methods. We performed a computerized search of the PubMed database for relevant reports before September 2009. No language restrictions were added. The associated literature was acquired through a deliberate retrieval strategy and selected based on the established inclusion criteria for publications.

Results. The studies provided 4070/6462 cases/controls for *C677T* and 1923/3561 cases/controls for *A1298C*. There was significant heterogeneity ($p = 0.015$, $I^2 = 44.0\%$) among the 22 studies, and the RE model showed that the *C677T* allele *T* was associated with a 17.3% increased risk of gastric cancer compared with the allele *C* (RE OR = 1.173 [1.051−1.274]). Results from the subgroup analysis showed an increased risk in Asians (fixed-effect, FE OR 1.277 [1.179−1.382]), but not in Caucasians (random-effect, RE OR 1.194 [0.866−1.646]). The contrast of homozygotes (*TT* vs. *CC*) produced significant results in Asians (FE OR 1.611 [1.366−1.901]), whereas, in Caucasians, it was not significant (RE OR 1.385 [0.754−2.544]). In regard to the *A1298C* polymorphism, there was no heterogeneity among the 11 studies comparing the *C* vs. the *A* allele ($p = 0.352$, $I^2 = 9.7\%$), but no significant association was detected.

Conclusions. The evidence from our meta-analysis supports that *TT* genotype of *MTHFR C677T* polymorphism contributes to susceptibility to gastric cancer, but no significant association was detected for *CC* genotype of *MTHFR A1298C*.

Key Words: A1298C, *C677T*, Gastric cancer, Meta-analysis, *MTHFR*.

Introduction

Gastric cancer is now the fourth most common and the second most deadly cancer worldwide, with 5-year survival rates <25% (1). Gastric cancer is a multifactorial disease, and its development appears to be the result of complex factors involving *Helicobacter pylori* infection, lifestyle, and genetic factors.

However, only 3% of *H. pylori* seropositive individuals eventually develop the tumor (2), so the *H. pylori* infection by itself is not a necessary or a sufficient cause. Lifestyle risk factors for gastric cancer include tobacco smoking, high salt intake, and low consumption of certain types of vegetables and fruits. Some genetic factors may potentially alter individual susceptibility to gastric cancer (3). Genes involved in folate metabolism such as methylenetetrahydrofolate reductase (*MTHFR*), methionine synthase (*MTR*), and methionine synthase reductase (*MTRR*) have been considered to be associated with gastric cancer (4).

MTHFR is a key enzyme in folate metabolism, irreversibly catalyzing the 5,10-methylenetetrahydrofolate (CH_2-THF) to

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Table 1. Characteristics of eligible studies considered in the meta-analysis

No.	First author	Year of publication	Ethnicity	Cases	Controls	Polymorphisms studied	Reference
1	Galván-Portillo	2009	Mexicans	248	478	*MTHFR C677T*	41
2	Zuniga-Noriega	2008	Mexicans	51	83	*MTHFR C677T*	42
3	Li	2007	Chinese	170	140	*MTHFR C677T;A1298C*	34
4	Vollset	2007	European	245	619	*MTHFR C677T;A1298C*	44
5	Boccia	2007	Caucasian	102	254	*MTHFR C677T;A1298C*	30
6	Mu	2007	Chinese	194	391	*MTHFR C677T;A1298C*	25
7	Zhang	2007	European	295	399	*MTHFR C677TA1298C*	4
8	Gotze	2007	Caucasian	103	106	*MTHFR C677T*	31
9	Wang	2007	Chinese	467	540	*MTHFR C677T*	35
10	Weng	2006	Chinese	38	34	*MTHFR C677T; A1298C*	36
11	Zeybek	2007	Turkish population	35	144	*MTHFR C677T*	45
12	Si	2005	Chinese	122	101	*MTHFR C677T; A1298C*	37
13	Lacasana-Navarro	2006	Mexicans	201	427	*MTHFR C677T*	43
14	Kim	2005	Korean	133	445	*MTHFR C677T; A1298C*	38
15	Graziano	2006	Caucasian	162	164	*MTHFR C677T*	32
16	Wang	2005	Chinese	129	315	*MTHFR C677T*	39
17	Sarbia	2005	Caucasian	332	255	*MTHFR C677T*	33
18	Stolzenberg-Solomon	2003	Chinese	90	398	*MTHFR C677T; A1298C*	40
19	Miao	2002	Chinese	217	468	*MTHFR C677T; A1298C*	26
20	Gao	2002	Chinese	107	200	*MTHFR C677T*	24
21	Bi	2005	Chinese	309	188	*MTHFR C677T*	28
22	Shen	2005	Chinese	320	313	*MTHFR C677T; A1298C*	27

5-methyltetrahydrofolate (CH_3-THF), the primary circulating form of folate and a cosubstrate for transmethylation of homocysteine to methionine. Methionine is the precursor for S-adenosyl-L-methionine, which is the primary methyl donor in the DNA methylation process, so a less active form of MTHFR may lead to lower S-adenosyl-L-methionine levels and, consequently, to hypomethylation, which would be expected to increase the risk of some cancers including gastric cancer (5).

C677T (rs1801133) and *A1298C* (rs1801131) are two common polymorphisms that have been described for *MTHFR* (6,7). They are present in healthy individuals with lower enzyme activity. Individuals who are homozygous (*TT*) for *C677T* have 30% of the enzyme activity compared with those who are homozygous (*CC*), whereas heterozygous (*CT*) have 65% activity (8). Enzyme activity for individuals who are heterozygous for both *C677T* and *A1298C* is ~50–60% (7). Some studies have reported that individuals with the *TT* genotype for *C677T* have reduced folate concentrations and higher plasma homocysteine levels compared with those with the wild-type genotype, whereas for the *A1298C* the evidence is inconsistent (9–13).

Case/control studies that investigated the association between gastric cancer and the *C677T* and *A1298C*