Author’s response to reviews

Title: Methylene tetrahydrofolate reductase C677T polymorphism in patients with gastric and colorectal cancer in a Korean population

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Authors: Lian-Hua Cui, Min-Ho Shin, Sun-Seog Kweon, Hee Nam Kim, Hye-Rim Song, Jin-Mei Piao, Jin-Su Choi, Hyun Jeong Shim, Jun Eul Hwang, Hyeong-Rok Kim, Young-Kyu Park, Soo-Hyun Kim

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Thank you for the opportunity to revise our manuscript, and also thank the reviewers for the useful and insightful comments.

In accordance with reviewers’ suggestions, we have highlighted changes in the revision manuscript by using bold font, below are our responses to the reviewer’s comments. We hope that all the suggestions and corrections have been incorporated appropriately, and hope that it is suitable to be reviewed and considered for publication please.

Thank you for your consideration. We look forward to hearing from you.

Sincerely yours,
Reviewer #1: Nagwa Meguid

My comments and suggestions are:

1- I recommend the authors to study two samples germ cells and tumour cells to compare from part of the studied cases to find out the role of mutation in developing cancer. This could have been better to shed light on the possibility of acquiring mutations at 677 due to rapid cell growth followed by weakened profreezing mechanism. This will be more informative to the study.

Our response: Thank your insightful comments. It's difficult for us to compare the role of the germ cells and tumor cells on mutation in developing cancer due to a lack of corresponding data in our study. However, previous studies have shown the role of mutations at 677 on development of cancer. A change of C to T at nucleotide 677 in MTHFR C677T results in an amino acid substance change of an alanine to valine, and this substance is associated with reduced enzyme activity that leads to reduced plasma folate levels. Low enzyme activity of MTHFR C677T variant genotypes are associated with DNA hypomethylation, which may induce genomic instability and thereby affect the expression of oncogenes or tumor suppressor genes.

2- Authors explain the interaction between MTHFR polymorphisms and smoking and drinking habit and age for gastric and colorectal cancer risk, on the other hand no information is given about life style of Korean diet. The lack of data regarding the plasma folate levels of case group are important data.

Our response: Rapid economic development have led to changes in Korean food consumption patterns: consumption of the staple foods such as rice, barley and potatoes has declined, while consumption of meat, fruit, vegetables and dairy products has increased. According to the report of Korean National Health and Nutrition Examination Survey in 1998, 2001, and 2005, increasing trends in daily vegetable consumption have been shown during those years. It has been known that vegetables and fruits are major source of folate.

Unfortunately, we have no information regarding the plasma folate levels of case group, which is limited for us to evaluate the gene-nutrient interaction in our study. We added this potential limitation in the discussion section.
Reviewer #1: Maria Piazuelo

Minor essential revisions:

1. Page 3: Abstract. In the “Results” section, the second sentence: “The MTHFR 677TT genotype showed a weak positive association with colorectal cancer…” is confusing. I think the authors meant the opposite. Please review it.

   **Our response:** Thank you for pointing out our negligence, we have revised it on revised manuscript.

2. Page 4. Background: In the 1st paragraph: Please use italics for H. pylori. In the 3rd paragraph: I suggest changing the beginning of the sentence: “Methylenetetrahydrofolate reductase (MTHFR) is a circulating form of folate that plays…” for the following: “Methylenetetrahydrofolate reductase (MTHFR) [no italics] is an enzyme that plays…”

   **Our response:** we have revised it on revised manuscript.

3. Page 6: Methods: Please describe in this section the characteristics of the subjects of the “control” group and how they were selected (or provide a reference, if possible, about the Thyroid Disease Prevalence Study mentioned). Somewhere else in the manuscript is stated that they were “healthy” individuals from the general population, but the criteria for selection are not clear.

   **Our response:** we have provided a reference on revised manuscript.

About the describing of our control group as follows:

   The control group (n = 1700) consisted of participants in the Thyroid Disease Prevalence Study. This study was performed in the Yeonggwang and Muan counties of Jeollanam-do Province and Namwon city of Jeollabuk-do province, Korea, between July 2004 and January 2006. A total of 4018 subjects, aged 50.6 ± 14.6 years (range 20–74 years), were randomly selected by 5-year age strata and sex. Of the total number, 3486 were eligible subjects. Of those eligible, 1700 (48.8% of the eligible subjects; 821 men and 879 women), aged 52.2 ± 14.3 years, underwent clinical examinations. At the time of their peripheral blood collections, all case and control subjects provided their informed consent to participate in this study.
4. Page 8: The last sentence of the “Genotyping” section seems to be truncated.

   Our response: we have added a full point on the revised manuscript.

5. Page 14: 2nd paragraph: I would suggest modifying the first sentence. Alcohol consumption is not “recognized as a major risk factor” for gastric cancer.

   Our response: we have revised it on revised manuscript.

6. Table 1: Include the word “mean” in the variable Age. Also, I would suggest including additional rows for the information of Tumor site for Colorectal cancer (separated from Gastric cancer).

   Our response: according to the reviewer’s comments, we have revised Table 1 on revised manuscript.