Author's response to reviews

Title: Methylenetetrahydrofolate reductase C677T polymorphism in patients with lung cancer in a Korean population

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Version: 4 Date: 11 January 2011

Author's response to reviews: see over
Author’s response to reviews:

Title: Methylenetetrahydrofolate reductase C677T polymorphism in patients with lung cancer in a Korean population

Authors: Lian-Hua Cui, Min-Ho Shin, Hee Nam Kim, Hye-Rim Song, Jin-Mei Piao, Sun-Seog Kweon, Jin-Su Choi, Woo-Jun Yun, Young-Chul Kim, In-Jae Oh, Kyu-Sik Kim

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Author’s response to reviews: see over
Dear Editor-in-Chief

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,

Lian-Hua Cui, Min-Ho Shin, Hee Nam Kim, Hye-Rim Song, Jin-Mei Piao, Sun-Seog Kweon, Jin-Su Choi, Woo-Jun Yun, Young-Chul Kim, In-Jae Oh, Kyu-Sik Kim
Reviewer's report

Title: Methylene tetrahydrofolate reductase C677T polymorphism in patients with lung cancer in a Korean population

Version: 2 Date: 21 December 2010

Reviewer: Emanuela Taioli

Reviewer's report:

This is an interesting paper reporting on the role of an MTHFR polymorphism on lung cancer. Although the study is well conducted and the analysis is sound, I am unable to decide on the relevance of this paper, since no information is given on the biological basis for looking at MTHFR in lung cancer. At this point, any gene-disease association can be looked at, but one expects a rational behind the choice of a gene in relation to a certain cancer. Although I understand previous work on gastric cancer, esophageal cancer, folate levels and MTHFR polymorphisms, I don’t see anywhere why lung cancer has been studied and what the premises for this choice are.

Our response: The premise of our study is that many epidemiologic studies have provided evidence that high consumption of vegetables and fruits is associated with a reduced risk of lung cancer[8, 9], and vegetables and fruits are major source of folate. In addition, previous studies have also demonstrated that folate deficiency may result in abnormal DNA methylation and impaired DNA synthesis leading to malignant transformations. Methylene tetrahydrofolate reductase (MTHFR) is a critical enzyme in folate metabolism. A change of C to T at nucleotide 677 in MTHFR C677T is associated with reduced enzyme activity that leads to reduced plasma folate levels [8]. 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. Thus, it was hypothesized that the polymorphism of MTHFR may also influence the development of lung cancer. Although several studies have addressed the polymorphism of MTHFR 677 C>T in relation to lung cancer risk, its results remain conflicting rather than conclusive. Therefore, we conducted a larger single study to evaluate the association between MTHFR C677T polymorphisms and the lung cancer risk in a specific population.

Reviewer's report

Title: Methylenetetrahydrofolate reductase C677T polymorphism in patients with lung cancer in a Korean population

Version: 2 Date: 3 December 2010

Reviewer: Keitaro Matsuo

Reviewer's report:

Cui et al. conducted a large case-control study to evaluate association between MTHFR C677T polymorphism and risk of lung cancer in Korean population. Although the question is interesting and important, several points in the manuscript should be reconsidered according to following points.

1. Genotyping

Describe consistency of result in two genotyping methods.

Our response: As your suggestion, we have added the consistency of result in two genotyping methods in section of methods.
2. Subjects, study design

Describe more detail about control enrollment and their nature and discuss appropriateness about being controls for lung cancer case-control study. Controls were from population and cases are from hospital, therefore, it is difficult to say this is a population-based case-control study unless the hospital substantially covers virtually all patients from population where controls were enrolled. If the condition do not match this, authors should not call the study as 'a population-based case-control study'. Describe detail about this and discuss it as a potential limitation.

Our response: Thank you for providing valuable comments.

As you mentioned, indeed, our hospital patient could not cover all patients of general population, thus, according to your suggestion, we have corrected this sentence as follows: the sentence “population-based case-control study” is modified “case-control study”. In addition, we added this limitation in the section of discuss as follows:

Another limitation of the present study is that the case group was composed of lung cancer patients who were enrolled from hospital, which could not be representative general population.

For the describe more detail about control enrollment, the recruitment of the control subjects has been described in detail elsewhere[19]. 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.
3. Analysis

a. Based on table 2, if 677T dominant model (CT and TT vs. CC) is applied, the association will be significant in the crude estimation. It is questionable why authors did not try dominant model in addition genotype model. Presenting result with a result of dominant model is more compatible with their interpretation and off course with the study question. So, this reviewer recommend to present table 2 and 3 with results by dominant model.

**Our response:** The authors would like to thank you for judicious reading of the manuscript and valuable comments which greatly improved this manuscript. According to reviewer’s suggestion, we have added the information in our revised manuscript. The results were shown in table 2 and 3.

b. Authors disease stage in the analysis; however, it is questionable to analyze this characteristics as a result of genetic polymorphism because stage is a just cross-sectional feature in the disease process. If authors want to say something about disease progressiveness defined by MTHFR polymorphism, they should see survival by the polymorphism. I recommend to remove stage from table 1 and 3 to improve the manuscript.

**Our response:** According to reviewer’s suggestion, we have removed stage from table 1 and 3.

c. Heterogeneity test.

Authors only present results by stratified analysis. It would be informative to have
heterogeneity testing by each stratifying factor.

**Our response:** The authors would like to thank you for judicious reading of the manuscript and valuable comments which greatly improved this manuscript. According to reviewer’s suggestion, we have added the information in our revised manuscript. The results were shown in table 3.

4. discussion

a. Authors discussed lack of serum folate level or dietary folate intake in the case group as limitation; however, this statement does not make sense. Basically, as the study is case-controls study, controls should have same data if authors want to draw inference about causality by MTHFR polymorphism. Moreover, cross-sectional measurement of folate levels in the serum adds only a little about causality.

Fruit/vegetable consumption are one of the important factor for the lung cancer. Family history of lung cancer is also. Lack of these information is a very important limitation. Discuss it.

**Our response:** according to reviewer’s suggestion, we have added these limitations in section of discussion as follows.

It is well known that familial aggregation of lung cancer could increase the risk of lung cancer, and a high consumption of vegetables and fruits is associated with a reduced risk of lung cancer. However, we have no information on the accuracy of reported family history of cancer, dietary folate intake or detailed data on the environmental tobacco exposure risk factors for lung cancer. Thus, we cannot evaluate
the relationship between gene-environment interactions. Another limitation of the present study is that the case group was composed of lung cancer patients who enrolled from hospital, which could not be representative the general population.