Reviewer's report

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

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Reviewer: Keitaro Matsuo

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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.

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.

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.

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.

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

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.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.