Reviewer's report

Title: Methylenetetrahydrofolate reductase polymorphisms and interaction with smoking and alcohol consumption in lung cancer risk: a case-control study in a Japanese population

Version: 2 Date: 28 September 2011

Reviewer: Ulrika Ericson

Reviewer's report:

Abstract:
1/ The background section of the abstract should clearly include the aim of the study. The aim of the study is still unclear. I would suggest that you replace the last sentence by We examined if smoking or alcohol modify associations between MTHFR polymorphisms and lung cancer risk. (If there are too many words in the abstract, you could delete the P-values in the result section. My previous intention was to delete some of the results and add P-values, but as it is now the P-values do not give any additional information apart from the CIs.)

2/ The result section of the abstract from line 37
The result section should be clearer in order to give the reader a correct interpretation.

Please replace A gene-environment interaction was suggested,…with “The highest risks were seen for 677TT-carriers with a smoking history or excessive drinking (OR=6.16, 95% CI:3.48-10.9 for smoking; OR=3.09, 95% CI:1.64-5.81 for drinking (compared with C-carriers without history of smoking or excessive drinking)), but no interactions were seen.
The 1298CC genotype (P=0.05) was only associated with increased risk among non-smokers, and smoking (P>0.01) was only associated with increased risks among 1298A-carriers, but no significant interaction was seen. There was a synergistic interaction between the 1298CC genotype and drinking (P=0.05). The highest risk was seen for the CC-carriers with excessive drinking (OR=7.24, CI:1.89-27.7compared with the A-carriers without excessive drinking)”

Discussion
3/ Line 349-350, Please write no “significant” effect modification. After lung cancer: add “(P for interaction=0.05). However, the risk estimates indicated that smoking and the “at-risk genotype did not seem to be associated with increased risk among those already at increased risk due to one of the two factors (smoking/at-risk genotype.)

Minor essential revisions
Background:
4/ Line 92. Please replace …involved in low MTHFR with related to low MTHFR activity.

Additional comment:
The C677T polymorphism is in linked to the A1298C polymorphism. I suppose that the material is too small for analysis of combined genotypes, but especially the C677T SNP may have confounded the results concerning the A1298C SNP, because the C677T is associated with a more pronounced decreased enzyme activity. Please discuss this.

**Level of interest:** An article whose findings are important to those with closely related research interests

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

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests'