Reviewer's report

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

Version: 2 Date: 16 September 2011

Reviewer: Song Yao

Reviewer's report:

The authors responded generally well to the previous comments. However, I still have some concerns as described below.

1. They provided more details in the recruitment of cases and controls, and provided some arguments in the discussion stating that "it is not that our controls were suffered from selection bias". However, these arguments probably could have been constructed more cautiously. The less educated cases compared to controls may well be due to healthy volunteer bias, i.e., higher educated and health-conscious people may be more likely to participate into the study than the lower educated people. Indeed, the big difference in age between cases and controls (cases were on average 10 years older than controls) make it difficult to believe the control group is appropriate for the case group. The similarity in allele frequency between the controls and the general population does not translate into similarities in non-genetic aspects which may bias the observed relationships. It would help to provide the participation rate of cases and controls in the study separately, and also would be more cautious to disclose the fact that the possibility of selection bias could not be excluded.

2. It was stated that to reduce recall bias, newly diagnosed patients were selected. However, this does not necessarily reduce this bias since patients with cancer may be more likely to over-attribute the reason to smoking etc than those without cancer.

3. I do not quite understand the logic flow from the added sentences at line 311-318 to the subsequent conclusion sentence led by "Therefore". I would suggest the authors to reorganize this paragraph.

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

Quality of written English: Acceptable

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

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