Reviewer’s report

Title: Methylenetetrahydrofolate reductase rs1801133 and rs1801131 polymorphisms and lung cancer risk in a Japanese population

Version: 1 Date: 25 August 2011

Reviewer: Ulrika Ericson

Reviewer’s report:

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Minor essential revisions

Abstract:
1/ The background section of the abstract should clearly include the purpose of the study. (MTHFR polymorphisms and lung cancer and interactions between MTHFR genotypes and smoking/alcohol on lung cancer risk). Exclude the first sentence, because fruits and vegetables are not examined in this study. Include at least one sentence about smoking and alcohol.

2/ In the result section of the abstract, it could be more informative to report p-values and directions for important associations between genotypes and lung cancer in strata of smoking/alcohol and associations between smoking/alcohol and lung cancer in strata of genotypes and finally the observed interaction. The presented ORs only show that the highest risks are seen among smokers/alcohol-consumers homozygous for the minor alleles, but does not indicate if there is an interaction.

3/..., compared with non-smokers with at least one minor...should read ..., compared with non-smokers with at least one major...

4/ Replace (genotype or drinking status) with (genotype and drinking status) in the result section of the abstract

Background:
5/ The Back ground section is well written and gives a good introduction, but it could be shortened down.

6/ In the last part of the third paragraph it should be clarified why genotypes connected to low MTHFR activity may be associated with increased risk. Since enhanced availability of 5,10-methylene THF may reduce misincorporation of uracil, it would be logical to expect a decreased risk in individuals with these genotypes. Therefore it is probably the decreased availability of 5-methyl THF for DNA methylation that is the crucial mechanism behind the expected increased risk of lung cancer in individuals with genotypes connected to low enzyme activity.

7/ The background section could end with a more precise statement concerning the aim of the study. Report in short what is examined in tables 2-4 and not only
a case-control study… with special attention to…

Statistical methods:
8/ Please clarify which variables were included in the multiplicative factor in the interaction analysis.

Results:
9/ Concerning results from tables 3 and 4.
Please report the P values for interaction even if they were non-significant.
In addition, it would be more informative to report directions and P-values for associations in different strata (e.g. association between genotype and lung cancer in strata of smoking status and association between smoking and lung cancer in strata of genotypes.) (e.g. the 1298CC genotype was associated with increased risk of lung cancer among never smokers but not among smokers. Smoking was only significantly associated with lung cancer among subjects with at least one 1298A-allele. However, no significant interaction was seen between the A1298C genotype and smoking.) This would give a better understanding of potential interactions.

Discussion:
10/ Please add a short summary of the main findings from tables 2-4 at the beginning of the discussion.
11/ The discussion could be shortened to become more concise and easier to follow. Only matters of importance to the findings in this paper should be discussed in detail. The discussion would profit of being more structured.
12/ Please discuss the risk of selection bias. According to table 1 the controls seem very different from the cases with regard to several variables (e.g. age). It is possible that they also differ with regard to other unmeasured factors, which could not be included in the statistical models. What about ionizing radiation?
13/ Please discuss the risk of recall bias. The cases and controls may have recalled and reported their alcohol consumptions more or less accurate.
14/ End of third paragraph: The lower prevalence…Is the lower prevalence among those with the 1298CC genotype meant?
15/ Fifth paragraph, concerning ref 33. Ever drinkers do not seem to have a significantly higher risk than never drinkers (the CIs overlap). If possible give the p-value in the genotype strata or only the text without ORs and CIs.
16/ Since folate intake probably is inversely related to smoking, please discuss if the observed interaction could reflect an interaction between folate intake and MTHFR genotype. The weaknesses and possible consequences of not having data on folate intake/status should at least be addressed more in the discussion.

Table 1:
17/ Is 0 correct for pack years among the controls?

Table 2:
18/ Explain in the footnotes: Which genotypes were compared in the recessive and dominant models?

Tables 3 and 4:
19/ I suggest that the results for the genotypes are presented in the columns and smoking/alcohol results are kept in the rows, so that P-values for associations in different strata easier could be incorporated in the table, but please keep the ORs from the joint effect model. In addition P-values for interactions could be added to the tables.

Discretionary revisions

20/ Title: I suggest that the title is changed to include the interactions and the type of study.
Example: Methylenetetrahydrofolate reductase polymorphisms, smoking, alcohol intake and lung cancer risk in a Japanese case control study.

21/ I suggest that the names MTHFR C677T and MTHFR A1298C are used throughout the paper, because it will then be easier to distinguish between the SNPs. The rs numbers could be mentioned in the introduction.

Background:

22/ Second paragraph: an L is missing in (5-methyl THF)

Methods:

23/ In the study subjects and data collection section, end of first paragraph: The abbreviation ETS and the brackets could be deleted. Add spouse after exposure. (The abbreviation does not seem to be used in the paper.)

Discussion:

24/ Second paragraph: Is rice really considered an important folate source in Japan? Despite the high rice intake, that is not my conclusion from the cited reference (ref 51).

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

Quality of written English: Acceptable

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