Reviewer’s report

Title: Polymorphisms in metabolic genes, their combination and interaction with tobacco smoke and alcohol consumption and risk of gastric cancer: a case-control study in an Italian population

Version: 1 Date: 16 August 2007

Reviewer: Francois Sichel

Reviewer’s report:

General
It’s a rather good paper dealing with gene-environment interaction in gastric cancers. The main limitations of this study are, as stated by authors themselves, the sample size and the lack of data about Helicobacter pylori infection. Methodology for this case-control study looks good, however the main conclusions about GSTT1 and SULT1A1 modulation of gastric cancer susceptibility and their interaction with tobacco consumption should be confirmed by a larger study. I am more cautious in my opinion about CYP2E1-alcohol interaction as discuss below.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Abstract, results section: OR and CI for GSTT1 null genotype and SULT1A1 His/His genotype are different from those showed in table 2 (2.17 instead of 2.10 for GSTT1; 2.28 [0.90-5.74] instead of 2.46 [1.03-5.90] for SULT1A1, respectively).

Materials and methods, genotyping section. Authors should mention current nomenclature for CYP1A1 and CYP2E1 alleles, according to CYP alleles nomenclature committee (see http://www.cypalleles.ki.se/index.htm). MspI alleles of CYP1A1 are CYP1A1*2A and *2B. Furthermore, m2 nomenclature is unclear, corresponding usually to Ile462Val polymorphism in exon 7, not to MspI. CYP2E1 Rsal polymorphism (c2 allele) corresponds to *5A and *5B alleles and Dral (C allele) to *5A and *6 alleles.

Discussion
1. Helicobacter pylori infection is now recognized as a major etiological factor for gastric cancers. As these data were not available in this study, it could lead to a strong bias in the results. This should be mention in the second paragraph of the
2. Interaction between alcohol consumption and CYP2E1 Dral polymorphism is shown in a very weak sample (15 cases and 27 controls, e.g. only one case never drinker bearing this polymorphism), so I suggest to shorten the 4th paragraph of the discussion and authors to be more cautious about this result. Furthermore, whether Dral alleles increase gene expression or not is unclear. A study from Inoue and al. (2000) showed no effect of this polymorphism on protein expression and enzyme activity in human liver microsomes. (Inoue K et al. Characterization of liver microsomal 7-ethoxycoumarin O-deethylation and chlorzoxazone 6-hydroxylation activities in Japanese and Caucasian subjects genotyped for CYP2E1 gene. Arch. Toxicol. 2000;74(7):372-8.)

Some minor misspellings:
Abstract section, result paragraph, line 6: in respect to....
Materials and methods, statistical analysis section, page 9 line 5: In order to assess
Discussion, page 12, line 4: homozygotes; page 14 line 4: 1-hydroxyacetyl

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

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