Reviewer's report

Title: Case-only study of interactions between metabolic enzymes and smoking in colorectal cancer

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Reviewer: Margreet Lüchtenborg

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General

This is an interesting study assessing gene-gene and gene-environment interactions in a Han Chinese population.

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

It would be helpful if the authors could elucidate the study design in more detail. It was unclear to me whether all subjects were interviewed or only the subjects diagnosed with primary (?) colorectal cancer that were included in this study. The latter may have implications for the possibility of bias with regard to the information obtained for cigarette smoking and alcohol consumption and the authors would need to address this. Also, more detail with respect to the applied questionnaire and what period of exposure it referred to would provide more insight.

Although, as the authors explain, a case-only design provides an efficient way to test for interactions, no data with regard to power are included. Considering the study is limited to 207 subjects, what is the likelihood of missing any interactions that may be present?

What do the authors think the observed interaction between SULT1A1 and CYP1B1 may mean? In particular, with respect to offering an explanation to this and to the smoking and CYP1B1 interaction on page 11, the authors mention hypotheses derived from in vitro studies, but fail to explain these hypotheses in the light of an interaction between genotypes or to reference these.

The authors suggest that colorectal cancer may develop in an estrogen-dependent manner. However, they do not report results from an analysis stratified by sex.

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

Although there is mounting evidence that smoking may be associated with colorectal cancer, recent expert reports (IARC, US Surgeon General reports on tobacco smoking and cancer) have not included colorectal cancer in the list of tobacco related cancers, because of inconsistencies between studies and the potential for confounding by alcohol. Although the authors remark the absence of a clear causal relationship in the Discussion, the authors should rephrase the wording throughout the manuscript, so as not to overstate current evidence.

On page 11, the authors write “Evidence suggests that … risk of CRC.”, I think they omitted a reference.

The case-control study referenced in the second paragraph on page 12 was carried out by Slattery et al. in Northern California and Utah in the United States and not the Netherlands. A cohort study on smoking with a nested case-only study that found a borderline significant interaction between GSTM1 null and cigarette smoking was carried out in the Netherlands (Lüchtenborg et al., AJE, May 2005), and I leave it to the discretion of the authors to include this reference in the manuscript.

Discretionary Revisions (which the author can choose to ignore)

As an explanation for the higher risk of colorectal cancer in women who previously had a gynaecological cancer the authors offer an oestrogen-dependent mechanism, but it is also suggestive of HNPCC, which is
hormone-independent.

The authors correctly addressed the underlying gene-environment and gene-gene independence assumption for a case-only design. However, they may want to include in the Methods and Results section the testing of this assumption, of which the findings are reported in the Discussion.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**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.

Margreet Lüchtenborg