Reviewer’s report

Title: Polymorphisms in ASE-1, RAI and ERCC1 and the effects of tobacco smoking and alcohol consumption on risk of colorectal cancer: A Danish prospective case-cohort study

Version: 1 Date: 30 July 2007

Reviewer: Henk van Kranen

Reviewer’s report:

General

Although clearly written, a number of arguments used to justify the importance of the chromosomal 19q13.2-3 region are questionable (see below).

All critical remarks in the genetics literature about the limited power of small studies are also applicable to this study, although I am also aware of how difficult it is to publish (sound) null associations.

In conclusion the analysis, presentation and interpretation of the data are OK but the underlying biological hypotheses are less adequately formulated.

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

I do not agree with the argument that involvement of a chromosomal region in breast and lung cancer warrants further investigation. It is becoming increasingly clear that many genes are acting in a tissue-specific context (see for example results from the cancer genome sequencing project and the 'driver and passengers in cancer' discussion in Nature, March 2007).

Because the three candidate-genes are not pathway driven, separate arguments about different processes are put forward but not always clear. For example, in line with arguing it would be suspected that increased expression of RAI should enhance apoptosis. In my opinion a reference to the expression of RAI in lymphocytes here is not valid (see first comment).

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

I would strongly recommend to adhere to gene symbols from HUGO Gene Nomenclature Committee (HGNC) database, so PPP1R13L instead of RAI and CD3EAP instead of ASE-1 or alternatively include both the official gene symbol and the alias.

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: Needs some language corrections before being published

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