Author's response to reviews

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

Authors:

Rikke D Hansen (RHa@nrcwe.dk)
Mette Sorensen (Mettes@cancer.dk)
Anne Tjonneland (Annet@cancer.dk)
Kim Overvad (KO@dce.au.dk)
Hakan Wallin (HWA@nrcwe.dk)
Ole Raaschou-Nielsen (Ole@cancer.dk)
Ulla Vogel (UBV@nrcwe.dk)

Version: 3 Date: 14 January 2008

Author's response to reviews: see over
Coverletter to Editor Dr. Lolu da-Silva

We have addressed each comment by referee 2, giving a point-by-point response.

Best regards,

Rikke Dalgaard Hansen
(on behalf of Ulla Vogel)

1. As suggested, we have now included the word "haplotype" in the title of the manuscript
2. As we see it, there is no conflict in stating that the variant GG genotype is negatively related to CRC risk, meaning that it is protective in relation to CRC risk, and to say that the corresponding wildtype AA genotype is associated with increased risk of cancer, and that the increased risk is strengthened when haplotype analysis is employed.
3. Reviewer 2 concludes on the results in the Norwegian study and the present study. We do not know whether the reviewer wants any changes to be made. Please don’t hesitate to tell us, if any changes are wanted.
4. It was proposed that the results of GE-interactions are shown stratified by gender in Table 3. We now show the stratified risk estimates.
5. Estimation of cancer risk is suggested to be adjusted for age in Table 2, 3 and 4. We estimated IRR by the Cox proportional hazards model with age as the underlying time-axis. This means that for every case, with a certain age at time point for cancer diagnosis, the risk is calculated by using all members of the sub-cohort of the same age at that specific time point as reference. Thus, the risk estimates are adjusted for age in the three Tables according to the Cox proportional hazards model. We chose to use a random sample of the DHC cohort as a reference in order to facilitate comparisons between risk estimates and genotype distributions from different studies that are nested into the DHC cohort.
6. Power calculations were already made for the haplotype. We have now moved the power calculation to the final part of the Method section.
7. The reviewer proposes to rewrite the manuscript as a short communication. The Medical Editors of BMC and we do not share the view that this manuscript would be better published as a short report.
8. The length of the background section was commented. We have now shortened the background section.

Minor comments:
   1. "The findings for the total study population should be deleted" in table 2 and 3. After revision, the two tables only contain the risk estimates stratified by gender
   2. Definition of the high risk haplotype are now included in the text at the first chapter of the introduction
   3. Power calculations are moved to the "Method"-section