Author's response to reviews

Title: Polymorphisms in the xenobiotic transporter Multidrug Resistance 1 (MDR1) gene and interaction with meat intake in relation to risk of colorectal cancer in a Danish prospective case-cohort study.

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Author's response to reviews: see over

Dear Editor

Thank you very much for the good message. In this situation we do not want to withdraw the manuscript. Enclosed please find a revised manuscript and a point-by-point answer to the comments from the referee.

Response to the reviewer

1. We have changed the introduction and discussion in order to discuss the potential functional effect of the MDR1 C3435T polymorphism. Recent studies suggest that the MDR1 C3435T polymorphism affect the folding of the P-glycoprotein and (thereby) change the substrate specificity. We have changed the discussion to clarify that an increased risk was observed among carries of the variant allele **in subgroups** in the two studies (previous ref. No. 17 and 18) and that MDR1 polymorphisms have not been associated with overall risk of CRC, therefore, we have toned down the importance of these two studies. In addition, we have added the expected risk alleles in the introduction as suggested by the referee.
2. In the introduction and discussion, we have added a discussion on the biological mechanisms related to the transport of carcinogen. In order to that we observe association to risk of CRC for both the MDR1 G-rs3789243A and C3435T polymorphisms, we would like to add a table showing the combination of the two genotypes (Table 3). Furthermore, we discuss the possible significance of substrate specificities between P-glycoprotein and BCRP in relation to risk of CRC.
3. COX-2 expression is induced by both alcohol and smoking, and therefore we have adjusted for both of these factors. Physical activity is not a risk factor in the present study, and we therefore have chosen not to adjust for that factor. However, if it is desired, it will take some time because our statistician is unavailable until November.
4. Spearman's rank correlation coefficients for the food items have been added as suggested.

5. We have elaborated on the substrate differences between BCRP and MDR1 which may be important in relation to risk of CRC and therefore we found that the presentation of result regarding BCRP is relevant.
6. We have now included the results regarding COX-2 in the abstract.
7. As suggested, we have added the expected risk alleles in the introduction as suggested.
8. Handling the two genotype with non-NSAID use as each reference group do not change the results; significant higher risk among the CC genotype by NSAID use and no significant effect for the CT and TT genotype by NSAID use.
9. We have searched for interaction between COX-2 polymorphisms and NSAID use, because an interaction would imply that COX-2 and NSAID use are both implicated in CRC carcinogenesis and that the effects of the two are dependent on each other. Thus, an interaction would provide biological plausibility that NSAID and COX-2 function are implicated in CRC, in line with the observed interaction between MDR1 polymorphisms and meat intake. We therefore think that the lack of strong interaction is also an important finding that support the lack of association between COX-2 polymorphisms and CRC risk. We therefore wish to maintain the interaction analysis instead of doing the analysis suggested by the referee. We do agree. We have changes the paragraph. We have changed the abstract as proposed.

Yours sincerely

Vibeke Andersen