Reviewer's report

**Title:** Polymorphisms in NFkB, PXR, LXR, interaction with meat, tobacco smoking, NSAID use, and risk of colorectal cancer in a prospective study of Danes

**Version:** 2  **Date:** 25 March 2010

**Reviewer:** Jing Shen

**Reviewer's report:**

This is a case-cohort study nested in the prospective population-based Danish Diet, Cancer and Health study. Several well selected genes and polymorphisms were investigated for the associations with colorectal cancer (CRC) risk and the potential interactions with smoking, meat consumption, and NSAID use. The authors found that carriers of the del-allele of NFkB -94ins/del polymorphism were at statistically significantly higher risk of CRC than the homozygous wildtype carriers. This result was acceptable. But from another result to conclude that “there was interaction between the polymorphism and intake of red and processed meat” was not convincing. Although the p-value for interaction between genotype and red and processed meat was significant (p=0.03), the IRR (1.03, 95%CI: 0.97-1.08) was much smaller than carrying genotyping (ID and DD) alone (IRR=1.45, 95%CI: 1.10-1.91). How to explain this interaction? Not only the p value but also the IRR were important to indicate potential interactions. Therefore, the major problem of the current study was the misunderstanding and explanation of the results that should be adjusted and discussed based on revised results. Title also need changed because of no interaction found.

**Minor comments:**

1) Genotyping section: please explain how the “known genotype controls” was obtained (sequence results or other methods? From cancer cell lines or human samples?)? How many kinds of “known genotype controls” were used in the current study (three different genotypes for each polymorphism were included or not)? More information about the 10% duplicated samples was needed (how many duplicated samples were detected? What is their genotyping distribution? Is that consistent with overall genotyping results?). Please introduce some details of the method used for measuring NFkB -94ins/del polymorphism because this polymorphism is the positive finding in the current study.

2) Statistical analysis: please explain what is the “unweighted” analysis?

3) No explanation for the results of Table 1. It seems no significant difference observed for those risk factors of CRC between cases and controls. Is this consistent with results from all samples of the cohort? If not, there may be selection bias exist. Please discuss the potential impact of the bias for the current conclusion.

4) Results section: Although the details for the PXR and LXR haplotypes may not
be necessarily showed, it is better to describe certain basic information obtained from haplotype study, such as how many different haplotypes observed? What is the common (top three) haplotypes constitute of? What is the frequency of the top haplotypes?

5) Results section: the description of “Del-allele carriers of NFkB -94ins/del were at 3% higher risk pr 25 g meat/day (CI: 0.97-1.08) whereas among homozygous carriers of the wild type ins-allele, the association was in the opposite direction (IRR pr 25g/day: 0.96, CI: 0.90-1.04, p for interaction= 0.03)” was confusing. The reference group of the comparison was unclear. Please describe it in details with a simple but clear way.

**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:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.