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: 3 Date: 8 July 2010

Reviewer: Kiyonori Kuriki

Reviewer’s report:

Dear the authors;

Thank you very much for re-submitting your revised manuscript. This was revised considering the reviewers’ comment, but there were still serious concerns. Please see the following comment.

Major comment

1. Regarding energy adjustment for the risk estimation, "residual method", "multivariate nutrient density method" and etc were introduced by Willett WC in a book "Nutritional Epidemiology (2nd edition; Oxford University Press, 1998)". In general, dietary energy intake is positively correlated with foods/nutrients consumption. Dietary energy intake is also depended on body mass index (BMI), physical activity, energy metabolism efficiency of individuals. Even if increased risks were found for some foods/nutrients consumption, it would be difficult to distinguish between effects (or affects) of their consumption themselves and dietary energy intake. Even if the risk was statistically adjusted for BMI, the majority of readers would wonder whether each effect of BMI and dietary energy intake was completely adjusted. To facilitate understanding by readers, therefore, this reviewer strongly suggests that dietary energy intake should be adjusted by "residual method", or "multivariate nutrient density method". In Table 1, dietary energy intake (and the adjusted food intake) should be also shown.

2. In Tables 3 and 4, the risk should be also adjusted for dietary energy intakes, as described above (please see Comment No.1).

3. Although the risk is not yet adjusted for dietary energy intake, the significant interaction for the NFkB -94ins/del polymorphism in Table 3 might be "by a chance" because such trend was not found in Table 4.

4. Were the results from Table 3 needed? Why were “the risks for additional intake of 25g red or processed meat” shown? As reason, such significant interaction was not found in Table 4.

5. The title was not matched with the result from Table 4, as well as those from Table 5 and 6 (as pointed out by other reviewer).

6. In Table 4, how was each category (i.e., tertile) defined? The procedure should
be stated in the text because the figures were not equally classified in each
tertile. Why?

7. Regarding confounding factors in Tables 5 and 6, the two variables "dietary
fiber" and "red meat (i.e., dietary intake of red or processed meat?)" were also
not adjusted for dietary energy intake, as described above (please see Comment
No.1).

8. Results from your previous study (Reference No. 20; BMC Cancer
2009;9:407) has already been published. To facilitate understanding by readers,
therefore, the numbers of unknown genotypes and unavailable food frequency
questionnaire in each group should be kindly stated in the text (page 8).

9. This reviewer proposes to show total 12 "p-values for trend" on each genotype
with low intake of all 6 polymorphisms in Tables 4, 5 and 6. In Methods, trend
test was slightly stated, but not completely, and detail procedure should be
described.

10. Because we are human, the terms "wild-type" and "variant" are a feeling of
wrongness. Likewise Tables, each genotype was appropriately stated in the text.

Minor comment;
1. Page No. should be shown.
2. In Abstract, the second "colorectal cancer" should be deleted because CRC
was already defined. In the text, the second "polycyclic hydrocarbons" should be
also done in Background (page 6).
3. What was an abbreviation "NSAID" meant in Abstract?
4. An abbreviation "ins/del" was not defined in Abstract.
5. In the text, "tobacco smoking" was not systematically defined; i.e., "tobacco
smoke" (page 5), "smoking" (page 9), and smoking status.
6. In Abstract, "Incidence rate … 95% Confidence Interval" should be changed as
follows; "incidence rate … 95% confidence interval".
7. In Abstract, "(CI:0.98-1.09)" should be shown as "(95% CI:0.98-1.09)".
8. In Lifestyle variables in Methods, "Pearson correlation …" should be stated as
"Partial Pearson's correlation …".
9. In Methods (page 9), no information was stated on habitual exercise (or
physical activity, in page 11).

Level of interest: An article of limited interest

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.