

Reviewer's report

Title: Polymorphisms in Multidrug Resistance 1, Cyclooxygenase-2 and Breast Cancer Resistance Protein Genes and Risk of Colorectal Cancer, a prospective population based case control study.

Version: 1 **Date:** 1 February 2009

Reviewer: Kiyonori Kuriki

Reviewer's report:

Dear Authors;

In a nested-case-control study within a Danish prospective follow-up study, the authors examined genetic susceptibilities of inflammatory response and gut barrier function for colorectal cancer, and then investigated gene-environmental interactions between SNIPs of the following three genes and lifestyle factors (smoking status, alcohol consumption and use of non-steroidal anti-inflammatory drugs (NSAIDs)); i.e., Multi-drug Resistance 1 (MDR1/ABCB1), Breast Cancer Resistance Protein (BCRP)/ABCG2 and Cyclooxygenase-2 (COX-2) genes. The study hypothesis and interesting findings, however, were not clearly shown, and the risk of colorectal cancer was appropriately discussed.

Special comments:

1) In Abstract, interactions between the SNIPs and use of NSAIDs should be clearly described; i.e., incidence rate ratios should be shown along with p values for interaction.

2) Regarding inflammatory response and gut barrier function, relationships between the three genes (or the products) were not appropriately introduced in the text. This reviewer, therefore, strongly suggests excluding the SNIP of the BCRP/ABCG2 gene. Instead, in Background, relationships between the two genes (or the products) and P-glycoprotein should be clearly summarized.

3) In general, NSAIDs are accepted as one of protective factors for the risk of colorectal cancer. In Background, therefore, the estimated findings on gene-environmental and gene-gene interactions should be mentioned, and then, in Discussion, the gaps with the study findings should be clearly summarized.

4) MDR1/ABCB1 has a broad spectrum of carcinogens including polycyclic aromatic hydrocarbon (PAH) compounds (page 9, lines 9-11). Why did not the authors investigate gene-environmental interactions between the SNIPs of the gene and any special foods, e.g., grilled meat rich in PAH compounds? In this manuscript, the findings are very important.

5) Regarding risk estimation for colorectal cancer, how were dietary intakes of fiber and red meat treated as confounding factors? Were there categorized variables for each special criterion or continuous variables?

6) Habitual exercise is a convincing protective factor, but this is not included in one of confounding factors. Why?

7) Excepting Table 5, use of NSAIDs was not also included in one of confounding factors for estimating the risk. Why?

8) In Discussion (2nd paragraph), the sentences were overstated. Please see the above comment.

9) In Table 1, statistical information was not shown between the two groups. Units for age and BMI were also appropriately shown.

10) In Table 3, the findings were not informative because biological activities of the SNIP have not been cleared in vivo studies. The risks were just calculated, so there should be excluded.

11) Finally, the title should be appropriately changed based on the findings of the study.

12) The two keyword, ATP-binding cassette transporters and xenobiotics, were not found in the text.

Minor comment:

1) In Abstract, which genes are related to gut barrier function and inflammatory response, respectively?

2) In page 6 (line 2), “no known functional ...” should be changes as follows: i.e., “unknown functional ...”.

3) In Table 2, what was “c” of “P-value_c” meant?

4) Abbreviations should be appropriately defined in the text (including Abstract), e.g., NSAID.

5) Total number of references was too much.

6) Regarding reference No.25, please show the number of volume.

Sincerely yours.

Dr. Kiyonori KURIKI

Level of interest: An article of limited interest

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.