Reviewer's report

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

Version: 2 Date: 24 October 2007

Reviewer: Kiyonori Kuriki

Reviewer's report:

Dear Dr. Hansen,

Considering the reviewers' comment and questions, this manuscript was revised. In this population based cohort study, the subjects were randomly selected and the sample size was not small. The study hypothesis and the estimated results were mentioned in the text. The power calculation was accounted for reliability for risk assessment. The design of this study was well-established, but the authors filed to find gene-environmental interactions between the haplotype and lifestyle factors (tobacco smoking and drinking consumption) for colorectal cancer risk. Therefore, this reviewer proposes that the authors rewrite the manuscript as a short communication and a brief report.

Special comments

1. Considering study backgrounds, most important findings were shown in Table 4. The authors examined gene-environmental interactions between “a previously identified high risk haplotype” and the two lifestyle factors for colorectal cancer risk [line (L) 2-7, paragraph (PG) 2, page (p) 3; L 1-3, PG 3, p 3; L 1-4, PG 2, p 4; L 1-3, PG 3, p 5; and L 5-8, PG 1, p 6]. In the title, therefore, a key word “haplotype” should be used.

2. The haplotype (included in the “AA” genotype of the RAI polymorphism) was reported as a “possible” risk factor of cancers on several sites (L 2-7, PG 2, p 3; L 1-3, PG 3, p 3). Of the three SNIPs, the authors hypothesized that colorectal cancer risk “negatively” related to the “GG” genotype (Skjelbred et al, BMJ Cancer 2006;6:175-), but not “AA”, of the RAI polymorphism, and then that the increased risk for the AA genotype was enhanced by the other two neighboring SNIPs, the ERCC1 and ASE-1 polymorphisms (L 2, PG 2, p 3; L 1-3, PG 1, p 6). This was difficult to understand. To facilitate understanding by readers, this should be clearly explained in the text.

3. In Skjelbred's report, OR and 95% CI were 0.49 and 0.21-1.13 for women with the GG +AG genotype (BMJ Cancer 2006;6:175-). In contrast to previous studies (L 1-4, PG 4, p 11), moreover, colorectal cancer risk was positively related to the “GG” genotype of the RAI polymorphism (IRR=1.94, 95% CI, 0.71-5.32, not significant for p-value) in this study. This was inconsistent with the hypothesis.
4. In study backgrounds, “gender” and “age”- specific differences between the haplotype and colorectal cancer risk were stressed (L 1-10, PG 2, p 4, L 5-11, PG 2, p 5). Cases and controls were matched on gender in this study. Therefore, this reviewer strongly proposes to show gene-environmental interactions stratified by gender in Table 3.

5. In Tables 2, 3 and 4, colorectal cancer risk should be adjusted for age at baseline. Why were not the controls matched on both age and gender? This point should be discussed in the text.

6. Although the power calculation was mentioned in the text, this should be done for the high risk haplotype, considering the study hypothesis and the backgrounds.

7. First, in Table 2, colorectal cancer risk was not linked to both the high risk haplotype and the GG genotype of the RAI polymorphism in each gender. Compared with the latter, the risk for the former was attenuated in women. Second, in Table 4, among women without the haplotype, smoking intensity and alcohol intake were “marginally” linked to the increased risk. The interactions for each lifestyle factor were not observed. These findings were inconstant with the study hypothesis. In this study, the authors failed to find new or significant findings. This reviewer strongly proposes that the authors rewrite the manuscript a short communication and a brief report, considering the journal policy.

8. Background section has been very long. In the same journal, Skjelbred et al (BMJ Cancer 2006;6:175-) had briefly summarized the three SNIPs and their study purpose. As described above, the authors failed to find new or significant findings in this study. To facilitate understanding by the readers, the section should be briefly summarized.

Minor comment
1. The findings for total (i.e., all) in Tables 2 and 3 should be deleted.
2. “High risk haplotype” should be defined in the text at the first use (page 3) and Table 2 (and 4).
3. The power calculation should be moved on a section of “Materials and Methods”.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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.