Author's response to reviews

Title: Relationship between Cyclooxygenase 8473T>C Polymorphism and Risk of Lung Cancer: a case-control study

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Dear Editor

We appreciate the review of our manuscript entitled “Relationship between Cyclooxygenase 8473T>C Polymorphism and the Risk of Lung Cancer: a case-control study.” We have revised our manuscript according to the comments of reviewers and statistical adviser.

I am enclosing the revised manuscript addressing all the comments of the reviewers and statistical adviser.

A detailed response to each comment is attached to this letter.

Thank you and the reviewers again for your consideration for publishing our manuscript in BMC Cancer. We look forward to your reply.

Very sincerely yours,

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In response to Reviewer 1 (H. Shen)

As your indication, we have changed the term from “Multiple logistic regression analyses” to “Multivariate logistic regression analyses” in the statistical section. Thank you for your comment.

In response to Review 2 (Wei Zhou)

In response to the comment that the manuscript could be shortened: we have shortened the 4th paragraph of the discussion section.
We have cut back the following non-essential sentences:

“The selection bias in a hospital-based case-control study might also be a relevant issue. Given the fact that most of the lung cancer patients are treated at the University Hospital in Korea, it is reasonable to assume that the case group is representative of the lung cancer cases in our community. Another selection bias may have been derived from the controls that did not participate in this study. However, because the age distribution and the sex distribution of the non-participating controls were similar to those of the participating control subjects in the current study, a self-selection bias is unlikely at best. The fact that the allele and genotype frequencies among our control subjects are consistent with those derived from the Hardy-Weinberg equilibrium further supports the nonbiased sampling of our study.”

Thank you for your comment.
In response to the statistical adviser’s comments:

1. In response to the comment that the sample size calculation regarding the histological types of lung cancer should be omitted because the investigation of the different types of lung cancer is only explanatory:
   As your comment, this study was designed to evaluate the effect of the polymorphism on the risk of overall lung cancer, and therefore we originally calculated the sample size for analyzing the overall lung cancer risk. However, one reviewer raised a question whether the sample size is adequate for different histological types of lung cancer. In order to explain that the numbers of each histological type of lung cancer were adequate, we have mentioned the sample size for histologic types of lung cancer only in the revision letter.

2. In response to the comment that it is better to omit the results of subgroup analysis shown in Table 3 due to following reasons: 1) there is no supporting mechanism that the polymorphism has differential effects on the risk of AC according to gender, age and smoking status; and 2) more importantly, the subgroup analyses according to age, gender and smoking status for AC might have type I error (due to multiple comparison) and/or type II error (due to the small number of subjects in the subgroups):
   Several recent observations that ACs arising in never-smokers and smokers are caused by different etiologies, suggesting that the genetic factors involved in the susceptibility to AC could be different between never-smokers and smokers. In addition, the genetic effect on the risk of lung cancer often pronounced in female and younger aged persons. Therefore, it may be important to evaluate whether the COX-2 polymorphism has differential effects on the risk according to gender, age and smoking status.
   Although, as your comment, the data are not sufficient to reach a conclusion due to statistical limitations, we thought to keeping these data would be better for other groups to design further studies regarding the polymorphism in relation to cancer risk. Since the other two reviewers agreed with the submission of the stratification analysis, we are still submitting the results of stratification analysis.
   To emphasize statistical limitations, we have added following sentences in the conclusion section:
   It is possible that our findings, particularly those findings from stratified analyses, can be attributed to chance because of multiple comparisons and/or the relatively small numbers of subjects in the subgroups. Therefore, additional studies with larger sample
sizes will be required to confirm these findings.

3. In response to the comment that since the study is age-gender matched, there is no need for adjustment with age and gender in investigation for overall cancer; we have corrected data (adjusted with pack-years of smoking), which are shown in Table 2.

4. In response to the request that the odds ratios (and p-value) produced from the logistic regression after adjustment for age, sex and smoking should be provided in investigating the SQ, AD, and SM (then, someone can estimate the risk of SQ (or AD, SM) for a C-carrier, male, elderly, and smoker); we have added the odds ratios for age, gender and pack-years of smoking (for overall lung cancer, the odds ratio for pack-years) in the Table 2.

Thank you for your helpful statistical comments.