**Author's response to reviews**

**Title:** Polymorphisms of XRCC1 genes and risk of nasopharyngeal carcinoma in the Cantonese population

**Authors:**

- Yun Cao (yunsirsums@163.com)
- Xiao-Ping Miao (Miaoxp@sina.com)
- Ma-Yan Huang (hmy220@sina.com)
- Ling Deng (dengling81@yahoo.com.cn)
- Li-Fu Hu (Lifu.Hu@mtc.ki.se)
- Ingemar Ernberg (Ingemar.Ernberg@mtc.ki.se)
- Yi-Xin Zeng (yxzeng@gzsums.edu.cn)
- Dong-Xin Lin (dlin@public.bta.net.cn)
- Jian-Yong Shao (jyshao@gzsums.edu.cn)

**Version:** 3  **Date:** 28 February 2006

**Author's response to reviews:** see over
Dear Editor:

Here we send you the revised manuscript MS 6734268418496577, which entitled “Polymorphisms of XRCC1 genes and risk of nasopharyngeal carcinoma in the Cantonese population”. This manuscript is not under consideration by another journal and has not been previously published.

Firstly, we appreciate you for your kindly help for managing this manuscript. We are also feel very sorry for delaying to revise this manuscript due to several reasons. According to the questions and comments of reviewers on this manuscript, we discussed the data and text about this manuscript with epidemiologist and statistician, we reanalyzed the data and rewrote the text of this manuscript in parts of result, discussion, as well as abstract. We also describe more information in part of materials and methods in this revised manuscript. I will send you (attach file by email) the original copy of this revised manuscript in which all the changes was labeled in detail, so that you can clearly know what changed compare to the former version of the manuscript.

We also would like to appreciate the reviewers for their help in improving the quality of this manuscript, their good comments as well as their questions to this manuscript. The answers to the reviewers questions is attached to the next page of this letter. Text of this manuscript (not the revision copy) has been copyedited for improving the quality of written English by a professional scientist from Biomedes Office recommended by BMC edit office.

Again, we would appreciate your consideration of this manuscript for publication as a research article in BMC Cancer.

Best regards

Sincerely yours

Jian-Yong Shao, M.D., Ph.D., Professor
Dept. of Pathology
Sun Yat-Sen University Cancer Center
651 Dong Feng Road East
**Answers to the questions and comments of reviewers of this manuscript**

**Answers to Reviewer Allan Hildesheim:**

**Comment 1.** The selected criteria for cases were histologically confirmed, untreated cases, and Cantonese, the selected criteria for controls included cancer-free individuals and Cantonese. For each eligible case subject, we tried to match one control subject by age (±5 years) and ethnicity (Cantonese). Overall, 520 eligible cases and 520 eligible controls agreed to a detailed risk factor interview administered by a trained nurse-interviewer. During interview, among the 520 eligible NPC cases, thirty-three cases were ever accepted radiation treatment, and 15 cases couldn’t collect detailed smoking information, 10 cases refused to blood sample collection, so these 58 cases were wiped off. Among the 520 eligible controls, nine controls were wiped off due to deficient smoking information. Finally, 462 cases (88.8% of eligible) and 511 controls (98.3% of eligible) were included finally.

We notice that the controls are not matched to cases on gender ratio (339:123 in the cases and 252:292 in the controls) and smoking status (298 in the cases and 158 in the controls). Since the gender frequency and smoking status are not matched between cases and controls in this study, we further analyzed the association of \( XRCC1 \) Arg194Trp and Arg399Gln polymorphism and risk of NPC separately by stratification by gender and smoking status in the revision of this study.

**Comment 2.** The effect of codon 399 polymorphism on NPC risk are clearly described in parts of Abstract, Results and Discussion in this revision.

**Comment 3.** The author’s original idea was to observe the joint effect of two \( XRCC1 \) polymorphisms and the risk of NPC, but the term is misused as ‘interaction’. We evaluated the joint effect of polymorphisms at \( XRCC1 \) condon 194 and condon 399, and the \( P \)-values were performed Bonferroni’s correction for multiple comparison analysis. The significance of the \( P \) values was labeled under each table.
Comment 4. Further analysis about association between XRCC1 codon 194 and 399 polymorphisms and NPC risk stratified by smoking status was performed in this revised manuscript (Table 5). Among smokers, compared to XRCC1 194Arg/Arg genotype, subjects carrying the XRCC1 194Trp/Trp genotype had an OR of 0.34 (95% CI, 0.14-0.82; P = 0.01), that was significantly lower than the OR among nonsmokers carrying the Trp/Trp (OR = 0.77; 95% CI, 0.35-1.70) or Arg/Trp genotype (OR = 0.73; 95% CI, 0.48-1.11) (P < 0.01, test for homogeneity). However, no any association of Arg399Gln variant genotypes and risk of NPC in both smokers and nonsmokers was observed in this study (Table 5).

Comment 5. We are so sorry to make the mistake in Table 1, the number of $\geq$20 pack-years smoker were 195 in case group; the number of smoker is 158 in controls. The number of the mean pack-years smoked in the controls should be 22.8. We made a mistake to calculate it for all controls, but not those who were smokers among controls. The Table legends has been corrected in the revision.

Comment 6. Since Cheo EY et al. have investigated the association between NPC risk and polymorphism at codon 280 and codon 399 in XRCC1, we think it is not necessary to repeatedly evaluate the codon 280 in this study. In fact, we report a very similar result of the association between XRCC1 codon 399 variant genotype and risk of NPC compare to Cheo EY’s study.
**Answers to Reviewer JaeYong Park:**

**Comments 1.** The selected criteria for cases were histologically confirmed, untreated cases, and Cantonese, the selected criteria for controls included cancer-free individuals and Cantonese. For each eligible case subject, we tried to match one control subject by age (±5 years) and ethnicity (Cantonese). Overall, 520 eligible cases and 520 eligible controls agreed to a detailed risk factor interview administered by a trained nurse-interviewer. During interview, among the 520 eligible NPC cases, thirty-three cases were ever accepted radiation treatment, and 15 cases couldn’t collect detailed smoking information, 10 cases refused to blood sample collection, so these 58 cases were wiped off. Among the 520 eligible controls, nine controls were wiped off due to deficient smoking information. Finally, 462 cases (88.8% of eligible) and 511 controls (98.3% of eligible) were included finally.

We notice that the controls were not matched to cases on gender ratio (339:123 in the cases and 252:292 in the controls) and smoking status (298 in the cases and 158 in the controls). We tried to match the cases and controls on bases of gender and smoking status, but if gender or smoking status factors were matched to cases, the controls need more individuals to recruit, it is difficult for us, so we remain the controls to conduct the study. Since the gender frequency and smoking status are not matched between cases and controls in this study, we further analyzed the association of XRCC1 Arg194Trp and Arg399Gln polymorphism and risk of NPC separately by stratification by gender and smoking status in the revision of this study.

**Comments 2.** The author’s original idea was to observe the joint effect of two XRCC1 polymorphisms and the risk of NPC, but the term was misused as ‘interaction’. Combination analysis indicate that individuals with the Trp194Trp and Arg399Arg or the Arg194Trp and Arg399Gln genotypes present, respectively, a 0.44-fold (OR = 0.44, 95% CI, 0.23-0.83) and 0.58-fold (OR = 0.58, 95% CI, 0.36-0.93) decreased risk of NPC development compared to individuals with the Arg194Arg and Arg399Arg genotypes. The P value (0.01) for Trp194Trp and Arg399Arg genotypes is statistically significant after Bonferroni’s correction. We can not exclude the joint effect of Trp194Trp and Arg399Arg genotypes in risk of NPC. Since the OR value does not reduce significantly, it is considered that the joint protective effects is mainly contributed by the polymorphism of XRCC1 Trp194Trp genotype.
Answer to Minor Essential Revisions:

Comment 1. Description of the previous studies results is rewritten in a clear way.

Comment 2. Figure 1 and figure 2 are cut back in the revision. In addition, to verify the results, 15% of the random sample were repeated for genotyping, it included 63 cases and 74 controls in codon 194 polymorphism, and 64 cases and 75 controls in codon 399 polymorphism. This was added in the section of methods.

Comment 3. All the data were recalculated and Bonferroni’s correction of $P$-value was evaluated when multiple comparison used.

Comment 4. For genotyping, 417 cases and 495 controls were able to perform analysis of XRCC1 codon 194; 425 cases and 501 controls were able to perform codon 399 polymorphism analysis. The problems for this difference may due to DNA quality or other technique problems.

Comment 5. The unadjusted OR has been added to the Table 2 and Table 3.

Comment 6. The data of stratification analysis according to age, gender and smoking status was performed in this revision. The results of this analysis are described in sections of results and are presented in Table 4, Table 5 and Table 6.

Comment 7. The data of this study has been compared to the data of previous study regarding the role of these polymorphisms on the risk of NPC conducted by Choe EY et al. in section of discussion. Both studies reported a similar result, the XRCC1 399 genotypes was not associated with risk of NPC.