Reviewer's report

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

Version: 2 Date: 24 December 2005

Reviewer: JaeYong Park

Reviewer's report:

General

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. More detailed information about the cases and controls populations and the method of recruiting cases and control is needed, namely: 1) whether control subjects were representative of the target population (participation rate and comparison of participants to non-participants); 2) how the cases and controls were matched (462 cases: 511 controls in this study) – the reason for such a matching must be provided; and 3) why the gender ratio was different between the cases and controls even though they matched the cases and controls based on the age and gender (339:123 in the cases and 252:292 in the controls). In addition, the age distributions of cases and controls should be presented.

2. How do the authors conclude the XRCC1 polymorphisms jointly contribute to risk of NPC? The risk estimate (adjusted OR = 0.48, P = 0.01, if considering multiple comparison, P = 0.02) of 194Trp/Trp was similar to that (adjusted OR = 0.44, P = 0.01, if considering multiple comparison, P = 0.05) of Trp/Trp-Arg/Arg. Generally, the combined genotype has greater power than any individual single nucleotide polymorphism (SNP) when the contributing SNPs are not all directly observed, as long as they are within linkage units defined by haplotype loci, whereas combined genotype analysis can decrease the statistical power of an association study if a contributing SNP is directly observed and acts by itself (the causative SNP). The observed effect of the combined genotypes on the risk of cancer seems to be attributed to one of the both polymorphisms (that is, codon 194 polymorphism) - the Trp allele was in LD with the Arg allele. The authors should discern the relative contribution of each polymorphism to the observed association.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. The authors’ description about the results of previous studies mentioned in the 3rd paragraph of the introduction section is relatively unclear.

Examples
1) In the study by Shen et al. [13]
194Trp allele: associated with decreased risk of gastric cancer
399Gln allele: associated with increased risk of gastric cancer (adjusted OR = 1.53) compared to the Arg399Arg genotype.
2) In the study by Olshan et al. [15]
Codon 194 polymorphism: associated with increased risk of SCCHN
Codon 399 polymorphism: associated with decreased risk of SCCHN
2. Genotyping analysis for XRCC1 codons 194 and 399 polymorphisms have previously well described in the reference 17. Therefore, genotyping section (with figures 1 and 2) would be better to describe or cut back. In addition, it would be better to mention how to verify the results of genotyping analysis.

3. Significant associations might arise by chance when multiple comparisons are made. However, this was not fully recognized and clearly stated. Some form of correction of P-value for multiple testing is required.

4. The reasons why 417 cases and 495 controls were eligible for testing codon 194 polymorphism and why 425 cases and 501 controls were eligible for testing codon 399 polymorphism should be explained.

5. The authors need to present the crude odds ratios before they present the adjusted values.

6. The data of stratification analysis according to age, gender and smoking status are also needed.

7. The effect of XRCC1 polymorphisms on the risk of cancer may be different among various cancers due to different etiologies and pathogenesis. Therefore, the data of this study should first be compared to the data of previous study regarding the role of these polymorphisms on the risk of NPC.

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**Discretionary Revisions (which the author can choose to ignore)**

**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:** Needs some language corrections before being published

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests.