Reviewer's report

Title: HPV seropositivity synergizes with susceptibility loci identified in GWASs at apoptosis associated genes to increase the risk of esophageal squamous cell carcinoma (ESCC)

Version: 2 Date: 15 January 2014

Reviewer: Hong Cai

Reviewer's report:

This is a straight case-control study evaluating the potential interactions of three susceptible loci and HPV-16 L1 seropositivity on the risk of ESCC in China. While this study might be potential interesting, the paper is preliminary in current form. My comments are as follows:

1. The ESCC cases and normal controls in this study were recruited from different departments of one hospital. More detailed information about the recruitment of the study subjects should be provided, particularly the controls. As a typical hospital-based study, crucial demographic characteristics in cases and controls, such as social economic status (SES) and the place of origin etc., should be compared carefully to ensure the comparability between the two groups. If these data are not available, the potential impact (selection bias and limited representativeness of the sample) should be discussed.

2. The layout of table 1 should be revised and odds ratios (95%CI) of the demographic and HPV sero-status variables should be added.

3. In table 2, the genotype categories should be reordered from low risk to high risk. For example, the genotypes of rs738722 should be presented as CC (ref.), CT and TT. And the trend tests should also be re-conducted.

4. The ORs and 95%CIs of the gene-HPV interaction term by smoking and drinking status should be presented in the figure or in the text.

5. A combined variable can be constructed using the genotypes of rs2074356 and rs2274223 to further evaluate the gene-gene interaction as well as their interaction with HPV sero-status on ESCC. This new variable could be categorized into 4 groups, namely, CC/A, (TC+TT)/A, CC/ (G+AG) and (TC+TT)/(G+AG). The gene-gene interaction could be evaluated in the typical way. And the interaction between the combined genotype variable and HPV sero-status could be assessed by constructing a 2×8 table or adding 1 more panel in the figure.

6. The 1st limitation should be deleted from the discussion as one single study cannot answer all the questions. The 3rd limitation should also be revised since the current analyses are not limited by the statistical power notably. If other crucial variables should also be analyzed but limited by the sample size, the authors should definitely present the results first. The limitation induced by a hospital-based sampling should be discussed here.
7. The “conclusions” should be reorganized to be more logical and clearer by focusing on the positive results and conclusions. The following structure could be considered, “the independent roles of susceptibility loci and HPV sero-status …the gene-gene and gene-HPV interactions on ESCC… the effect modification induced by smoking and drinking”.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests