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
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Reviewer: Giannis Mountzios

Reviewer's report:

The current work examines the interaction between HPV seropositivity, smoking, drinking and presence of three susceptibility loci identified by GWASs to predict the likelihood of ESCC. The authors reported that the interaction between HPV16 aerostats and rs2074356 or rs2274223 significantly increased the risk of ESCC in nonsmokers and nondrinkers. In addition, smoking and drinking synergized with the joint effect of HPV16 aerostats and rs2074356 or rs2274223 to substantially increase ESCC risk. The authors are to be commented for the novelty of their ideas and the experimental design. However, some concerns remain:

Major Compulsory Revision

The authors state in their conclusion (both in the abstract and the main text that HPV16 seropositivity synergized with the susceptibility variants to increase ESCC risk. This is not correct because the study did not prove or demonstrate a synergistic mechanism between these two factors. On the contrary, the study only identified a statistical additive effect of the two conditions. No experiments to prove a causative relation were performed in this study. This should be clear in both the abstract and the text. The title should also change accordingly.

Minor Essential Revisions:

Introduction, Page 8, 3rd paragraph: "Given the effect of HPV......with susceptibility to ESCC (10-12). This sentence does not make sense. The effect of HPV on apoptosis is not associated with susceptibility of these SNPs for ESCC

Methods, Page 8, 1st sentence: Written informed consent is mentioned twice in the text

Results: All "OR" in the text should change to "HR" because they represent true hazard ratios for ESCC

Page 11, lines 3-4: "OR=2.04, 95% CI: 2.66-9.56". There is a mistake. OR value should be between the 95% confidence intervals

Discussion: The whole last paragraph of page 15 and first on page 16 is irrelevant to the study endpoints and should be omitted.
Conclusion: Page 16, there must be a mistake in the one before the last line: "rs2074223" should change to "rs207456"

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**
I declare that I have no competing interests