Reviewer's report

**Title:** Interaction between polymorphisms of the Human Leukocyte Antigen and HPV-16 Variants on the risk of invasive cervical cancer

**Version:** 1  **Date:** 21 April 2008

**Reviewer:** Margaret Madeleine

Reviewer's report:

Discretionary and Minor Essential Revisions

This well conceived and analyzed study builds on prior work examining HLA and HPV16 variants associations with cervical cancer and makes new observations. Extension of this work to include more samples would be important to separate chance findings from true associations due to the small number of cases in each subgroup. That said, this study has strongly elevated/reduced ORs that suggest real associations. The most interesting findings are when the type of variant in the tumor seems to completely change the direction of the associations.

Here are some suggestions for the authors:

1. Describe what is known about HPV16 variants and their associations with ICC in the introduction.

Methods

1. Are response proportions for the case and control groups available?
2. Describe source of DNA for HLA testing in the methods section.
3. How did you choose which HLA/HPV16 variants associations to report? Were all the associations present above a certain % in the case subgroups or control group presented? Were they chosen a priori or based on frequency? This could be addressed in the Methods section or elsewhere, but seems essential.

Results

1. One-third of the 107 cases described in the results are not used in the main analysis; consider restricting Table 1 to the singly infected n=69 cases. Also, present the branch variants separately from the E6 substitutions in Table 1, since they constitute the case groups for Tables 3 and 4.
2. In Table 2, it would be very helpful to include the control N/C prevalence, otherwise the reader has to look up your previous paper.
3. In Table 3 and 4, please explain grouping DQA1*0101/0104 (*0104 has 3 different AA from *0101) separately from DQA1*0102 (2 different AA from *0101)?
4. In Table 3, ICC-EP=24, but it looks like EP=23 in Table 1.
5. In Table 4, ICC-E6 38L variant has n=29, but 83L=23 in Table 1.

Discussion
1. Second sentence is unclear, similar frequencies compared to what group?
2. The *1302 allele, and lack of carriage among AA tumors, is a striking finding and could be emphasized more strongly in the abstract. Since the other nearly universal finding between HLA and Cx Ca besides DRB1*13 being reduced risk is of increased risk associated with DQB1*0301, I was hoping to see the DQB1*0301 allele associations by HPV16 variant type in the tumor. Could that be added or are the numbers too small?

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests.