Reviewer's report

Title: High-risk human papillomavirus (HPV) screening and detection in normal, healthy patient saliva samples: a pilot cluster randomized study.

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Reviewer: Aimee R Kreimer

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The authors collected oral specimens from healthy patients at a US dental school with the goal of evaluating oral HPV infection and risk factors for infection.

- Major Compulsory Revisions

1) How was the sample size decided upon? Given the known rarity of oral HPV 16 infection, it is surprising the investigators did not choose to study more individuals. Please include a confidence interval around the 3.9% point estimate (1.1% to 9.7%). Also, in Table 2, I didn’t get replicate the significant p values for the gender and race variables—how did you obtain these p values?

2) What is a ‘pilot clustered randomized study’? Please elaborate on this design feature, and describe what this is a pilot effort for. Use of the word randomized indicates allocation to an intervention (i.e.: vaccine, drug, etc)

3) The method of oral specimen collection is not standard—please provide references in support of its use.

4) The beta-actin positivity was unusually poor (68%), indicating a problem with the laboratory methodology. Perhaps a new aliquot from the original sample should undergo DNA extraction. There exists published literature on the topic of DNA extraction for the purpose of oral HPV detection- perhaps a new method for DNA extraction should be considered. Additionally, since the investigators choose not to use a standard kit for HPV detection, how was their qPCR assay for HPV16 detection validated? Were cervical samples used?

- Minor Essential Revisions

N/A

- Discretionary Revisions

1) The Introduction is extensive and reads more like a teaching tool than of summary of the pertinent literature relating to this topic.

2) Introduction- the authors point to several publications where HPV has been detected in several tumors, including colorectal and breast. The authors should
use caution in that PCR based detection of HPV in tumors or tissue does not imply causation, and may merely be the result of contamination. Similarly, in the following paragraph, the authors state “Of all HPV types, the high-risk strains HPV16 and HPV18 are the most commonly identified from biopsies of oral cancers [19-21], providing strong evidence that HPV may be an independent risk factor for oral cancer.” Finding HPV DNA in tumor is not indicative of causation—more quantitative assays (such as ISH) are needed.

3) The authors may want to make the concluding paragraph of their introduction more prominent, as it summarizes the literature pertaining to the topic of this investigation. Further, the author say “little evidence has been provided….”, but then go on to reference several publications including a systematic review of the literature.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests