Author's response to reviews

Title: Pre-Invasive And Invasive Disease In Women With A Cytological Diagnosis Of High-Grade Lesion And High Grade Lesion Can Not Exclude Microinvasion

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Author's response to reviews: see over
Covering Letter

Dear Ms. April Rada,

Regarding the paper named Pre-Invasive and Invasive Disease in Women With a Cytological Diagnosis of High-Grade Lesion And High Grade Lesion Can Not Exclude Microinvasion, we are resubmitting a new version with the issues addressed in your e-mail dated Dec 9th, as follows.

Regards,
Nina Kuperman.

REFEREE 1:

Major Compulsory Revisions

1. The last sentence of the ‘methods’ section of the abstract is not mentioned in the article, though there is a relevant section of table 1 that is not discussed at all in the results section of the article. I’m not sure that this last sentence reflects the results in the table, but it may just be that the wording is unclear – the abstract says the ‘presence of lesions’, but the table seems to compare HSIL/HSIL-micro with colposcopic findings and possibility of vision of squamo-columnar junction.

The authors: The last sentence of the ‘methods’ section of the abstract is mentioned on line 121 of the new version of the article.

Table 1 is a purely descriptive table. It describes the characteristics of our sample, not results. That is why the table was not detailed on the “Results” section, although it was mentioned. The p-value refers only to difference between the groups In the new version, we added some comments on patient
characteristics (lines 175-180) according to the cytologic result. This table does not show the prevalence of disease after the diagnostic investigation.

2. When there is an expected value of less than 5 in a cell, a Fisher’s exact test can be carried out instead of a chi-squared test, rather than not doing a test.

The authors: Done. Please, see Table 1 in the new version.

3. More information is needed in the Background section – for example, is there cervical screening in Rio de Janeiro? That cervical cancer is the 3rd most common cancer in Brazil (as stated in the abstract). What are the current recommendations for HSIL and HSIL-micro/what are the pathways to diagnosis? (This is especially important, as I could only find them in Portuguese online.)

The authors: Done. Please, see lines 79-99 in the new version.

4. The methods section does not contain a statistical methods section. Some of the necessary information is given in the last paragraph of the results section – this should be moved to the methods section. However more information is needed, for example how the PR was calculated and should be interpreted.

The authors: Done. Please, see lines 148-155 in the new version.

5. It would be useful to know what proportion of HSIL-micro are seen at the named collaborating secondary units – 68 cases over 6.5 years seems very low.

The authors: Done. Please, see lines 163-166 in the new version.

6. Results section – Tables 1 and 2 need explaining in the text, rather than just saying the tables exist. This is especially true for results that are picked out in the abstract, but are currently not mentioned anywhere in the text.

The authors: Done. Please, see lines 175-192 in the new version.

7. The results for Tables 3 and 4 are currently given in the Discussion section (paragraph 6 of the discussion), but are not given in the results section – this should be moved to the results section.

The authors: Done. Please, see lines 193-201 in the new version.

8. The age categories for Tables 3 and 4 are not sensible, as they do not
split up the HSIL-micro women (42/47 are in the 35+ category). As a broader point, I am concerned about the selection of controls, and the fact they have such a different age distribution. In my opinion it would be preferable to match on age (and possibly year of cytology, if you are concerned that the quality of cytology has changed during your study) rather than selecting the 2 previous and 2 following women with HSIL.

The authors: The cut-point for the age categories was calculated based on a ROC curve to find the best cut-off point. There are no issues regarding the quality of cytology during the years. What we suppose that may have happened is that experts may have gained more expertise over the years. That is the reason why we chose controls based on the date of the exams, choosing the closest dates as possible.

9. You must say that the sample is a symptomatic sample in the methods section, instead of only mentioning it in the discussion.

The authors: Although we discuss this point in the Discussion section, our sample is not of symptomatic women. It is composed of women who attended the primary care unit for routine cervical cancer screening. The patient being symptomatic is only a hypothesis which could explain the differences found between our results and the ones in the literature, since the reality in Brazil is that many women do not attend screening regularly, as recommended, and do so only when they are symptomatic. But we do not have this information. This is clearer now on lines 233-241 in the new version.

10. The discussion would benefit from following STROBE guidelines. In particular, there is no ‘strengths and limitations’ section of the discussion.

The authors: Indeed, this article was not written following the STROBE guidelines, although most of its recommendations were followed in our article. We improved the new version in order to meet more of these guidelines.

11. Paragraph 1 of the discussion should include the search terms used if they are claiming there’s no prior research on the topic.

The authors: The terms used were “HSIL microinvasion”, “microinvasion”, “cannot exclude microinvasion”, “cannot exclude micro invasion”, “cannot exclude invasion”, “Cervical Intraepithelial Neoplasia” and “Papanicolaou Test”. In Pubmed, they were used in the following strategy: (((((HSIL microinvasion) OR microinvasion) OR "cannot exclude microinvasion") OR "cannot exclude micro invasion") OR "cannot exclude invasion") AND ("Cervical Intraepithelial Neoplasia"[Mesh]) AND "Papanicolaou Test"[Mesh]). In other databases, they were used in the same way, using their own tools. Please, see lines 211-220 in the new version.
12. In Table 1, it is not clear to me how women pap smear findings of normal were included in the study – I assume that these are not the smears that got the woman into the study, but I don’t know when they are from. Similarly, for ‘procedure made’, is this the first, or the most severe, or most recent, or diagnostic?

The authors: The "normal" result is a histological result, not a cytological one. All women studied received a cytological diagnosis of either HSIL or HSIL-micro. None had a normal cytological diagnosis. The procedure was the only diagnostic procedure performed after an abnormal Pap smear result. This is already explained at the end of Table 2, footnote.

13. In tables 3 and 4, is age adjusted for as a categorical or continuous variable?

The authors: It’s adjusted as a categorical variable using the cut-off point of “less than 25 years old”, “25 to 34 years old” and “35 years old or more”.

Minor Essential Revisions

1. In the abstract, methods section, the dates are given as June 2006-June 2012, whereas in the paper and figure it’s June 2006 – December 2012.

The authors: Done. Please, see line 62 in the new version.

2. The word ‘once’ is regularly used instead of the word ‘since’.

The authors: Done

3. I would remove ‘mass screening’ from your keywords, given that your sample is symptomatic women.

The authors: The sample is not of symptomatic women. It is composed of women who attended the primary care unit for screening. As mentioned above, the patient being symptomatic is only a hypothesis, since the reality in Brazil is that many women do not attend screening regularly and do so only when they are symptomatic. But we do not have this information. The kind of screening performed is indeed a “mass screening”. This is clearer now on lines 233-241 in the new version.

4. In paragraph 5 of the discussion, you have said that 100% of women with HSIL-micro had preinvasive or invasive disease, but according to your figure 1, there were 2 women (out of 47) with HPV/CIN1 – your earlier
definition of preinvasive is CIN2+ (for Table 3).

The authors: Corrected. Please, see lines 245-249 in the new version.

5. Table 1 – clarify what ‘gesta’ and ‘para’ refer to.

The authors: Changed. Please, see Table 1 in the new version.

6. Table 4 – for ages 25-34, the total for HSIL-micro should be 4, not 7.

The authors: Corrected. Please, see Table 4 in the new version.

7. The manuscript needs to be edited by an English speaker before publication

The authors: An English speaker will edit the manuscript once it is accepted for publication.

Discretionary Revisions

1. In paragraph 3 of the results section, I would give the total number as well as the observed number alongside the percentages – for example, in the second line of the third paragraph of results, I would have 63.8% (30/47).

The authors: Done. Please, see line 188-192 in the new version.

2. In the discussion, paragraph 4, I would mention that the sample in the Massad paper was based on a screening sample, to make clear the comparison to a symptomatic sample.

The authors: Our sample is not of symptomatic women, as explained before.

3. In paragraph 4 of the discussion, I would change the order of the points regarding difference in age, and the symptomatic sample, as the symptomatic sample is likely to be more important in explaining the difference in results.

The authors: There are no symptomatic women in our study, as explained before.
REFEREE 2:

1. **The discussion lacks sufficient references to the literature. Many articles report on the number of LSIL, HSIL, carcinoma histology in case of HSIL cytology, so this has to be added.**

   **The authors:** That was not our intention. Our objective was only to compare differences in the prevalence of disease between these two groups, HSIL-micro and HSIL cytology. We compared our findings with important articles that show the prevalence of disease in patients with HSIL cytology, because our aim was to found out if the prevalence of disease is so different in HSIL-micro group that would justify such a different approach and management. The recommendation of management of women with a cytological diagnosis of HSIL-micro nowadays in Brazil is similar to the microcarcinoma ones. This is now better explained in lines 93-105 in the new version.

2. **The authors suggest a more invasive approach in case of HSIL Micro. What is meant with this more invasive approach? And is it indeed advisable, or should you be less invasive by only taking some biopsies first to get a proper histological diagnosis. Also this needs to be discussed with literature references in the discussion.**

   **The authors:** The recommended approach for women with an HSIL-micro cytology in Brazil is conization and was based in expert opinion. In our opinion, the percentage of histologically confirmed disease found in our sample justifies such approach. The biopsies are not advisable, since we found almost 100% of disease in those patients and directed biopsies proved to be less accurate do discard invasive disease. Please, see lines 93-105 and 188-192 in the new version.