Author's response to reviews

Title: Protecting the underscreened women in developed countries. The value of HPV test

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Author's response to reviews: see over
Dear Editor,

Thank you very much for your interest in our article. We do appreciate the referee’s comments that certainly help to improve our manuscript. Please find our responses to the referee 2 point-by-point.

Referee 2:

• Answer to the discretionary revisions:

1. I suggest that the authors rewrite the discussion to follow strobe, it will aid the reader through their arguments to support their results.

Response: We have reviewed the discussion extensively. See our edited copy with all the changes.

2. The authors state that 7% of women underwent colposcopy and biopsies for unknown reasons. Is it possible that these women have been regularly screened through the private sector? I don’t think this is a major issue but perhaps should be mentioned in the discussion.

Response: The referee is right in the sense that it is surprising that double negative women have a biopsy taken. Unfortunately we did not have any more details on the medical reasons of why these women were biopsied. More likely these women underwent a thorough exam including biopsies because they had a history of poor screening. It is unlikely that they were derived from the private clinics. We suspect this referral happens when women are diagnosed with cancer.

We have rewritten the paragraph for its better compression: “We could not correct for a potential verification bias as HPV-negative women were not referred to colposcopy and biopsy. But in our study, about 7% of women with negative screening results had histological data for unknown reasons to the investigators. Unfortunately we did not have any more details on other medical reason of why these women were biopsied. However, none of these women were diagnosed with CIN2+. In Kulasingam et al study, in which random biopsies were performed in all double negative women, no CIN2+ was reported [19]. Thus, the data support that if there is any identification bias the weight of it must be small”.

3. Is the HPV positivity rate among women with cytology negative high (14.5%)? In fact can the authors comment on the HPV positivity found in the study compared to the general population?

Response: The 14.5% is not the HPV positivity percent among women with negative cytology (this percent was 5.5%). Ours text says: “At 36 months, the cumulative detection of CIN2+ in women with normal cytology and HPV positive at baseline was 14.5% and 39.3% in women with both tests being positive (Figure 2)”.

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We cannot compare the HPV positivity found in our study (6.7%) with that of the general population because the HPV test was only introduced as primary test combined with cytology among poorly screened women. In the rest of women undergoing screening, the HPV test is not performed.

4. The small number of women who were cytology positive, HPV negative and the fact that there was no disease among them suggested that the quality of cytology in Spain is poor. This may also be the reason why no additional gains were observed with co-testing.

Response: Among the HPV negative women with a positive cytology result included mostly ASC-US. It is well known that this a diagnosis subject to error and poor reproducibility. Our data was however small and thus the interpretation of the estimates should take this into account.

Based in our data, we think co-testing does not offer any advantage with respect to HPV test because the HPV test detected all but one CIN2 case at baseline.

Answer to the minor essential revisions - "Minor issues not for publication"

1. First paragraph of the introduction: “This it is well accepted that the success of any screening programme will markedly rely if it reaches a high coverage”. I wasn’t quite sure what they meant – do they mean that successful screening programmes rely on high coverage to achieve success?

Response: For clarification we have rewritten the sentence: “Historically, organized screening using cytology at regular intervals with a high coverage has reduced the incidence of invasive CC in many countries [2,3]”.

2. Results second to last paragraph: “Among the HPV positive one, 15 women had a persistent....” I would remove the word ‘one’.

Response: It has been removed.

Finally, the revised manuscript was also uploaded following the instructions.

I would like to request, on behalf of all the authors, that you consider finally, this manuscript for publication in your journal.

Yours sincerely,

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