Author's response to reviews

Title: Detection of infectious organisms in archival prostate cancer tissues

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Version: 2
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Author's response to reviews: see over
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Version: 1 Date: 4th June 2014

Authors’ response to reviews: see over
Reviewer's report

Title: Detection of infectious organisms in archival prostate cancer tissues

Version: Date: 12 May 2014

Reviewer: James Goedert

Reviewer's report:

Minor Essential Revisions

1. Is the question posed by the authors well defined? Not entirely. Interesting approach to compare aggressive prostate cancer with non-aggressive prostate cancer, as these are (at least clinically) quite different conditions. However, it is unclear why Propionibacterium acnes, which has been associated with prostate cancer using various assays, was not included.

   • P. acnes was not the subject of this report, however we do acknowledge the literature relevant to P. acnes and prostate cancer.

2. Are the methods appropriate and well described? Yes.

3. Are the data sound? Unsure. The Abstract reports 128 cases, including 52 aggressive and 76 non-aggressive. So why do results report data for 49 aggressive and 66 non-aggressive? Please reconcile.

   • In total, 128 prostate cancer cases (including 52 aggressive and 76 non-aggressive cases) were initially included in the study. However, of these 128 cases only 115 cases (including 49 aggressive and 66 non-aggressive cases) passed quality assessment (amplification of a 268 bp region of the human beta-globin gene) and were deemed suitable for further analysis (as described in lines 131-135 page 5). Therefore, the results only report data for those samples that passed quality assessment.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes.

5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes, except for the omission of P. acnes.

   • Please refer to the response to point 1 above.

6. Are limitations of the work clearly stated? Not entirely. If hypothesis is that no difference will be found (lines 80-83), then statistical power and likelihood of a Type 2 error must be discussed.

   • Gianluca – please answer this.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes, except for the omission of P. acnes.

   • Please refer to the response to point 1 above.

8. Do the title and abstract accurately convey what has been found? Yes.

9. Is the writing acceptable? Yes.

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: No conflicts of interest.
Reviewer's report:

Title: Detection of infectious organism s in archival prostate cancer tissues

Version: 1 Date: 13 May 2014

Reviewer: Silvia Franceschi

Reviewer's report:

The present paper addresses a very important issue (the possible role of STIs in prostate cancer etiology) on which there is still a substantial uncertainty. The paper is clearly written and the laboratory methods accurate.

Major Compulsory Revisions

My only major request is to add some additional comments in the text on the evaluation and interpretation of the findings about Mycoplasma genitalium. An appropriate statistical test would also be useful in Table 2 (p value required – Gianluca?). Although num bers are small and the article’s conclusions are not challenged, the findings about Mycoplasma genitalium should not be considered, in my view, completely negative and deserve at least some background information on the organism. Some more work on Mycoplasma genitalium would also help elucidating the original statistical analysis plans of the present work: it is a little misleading between a comparison of prostate cancers by Gleason score and a comparison of tumor and non-tumor tissue samples.

- We have added the p-value as requested. However, we regard our text to be a balanced discussion and presentation of the strength of the finding.

Minor Essential Revisions

Page 6, last line: the mention of “hit and run” mechanisms is made in a vacuum: no real hypotheses and evidence. Please take away or expand on what you were afraid of.

The text has been expanded slightly to improve the expression around this aspect of the discussion/conclusions as follows:

"Our study hypothesis and aims assumed persistent infection with the candidate organism allowing for molecular detection in the FFPE material. We cannot exclude the possibility of an initial infection leading to oncogenic sequelae followed by clearance either by natural immunity or administration of antibiotics."

Level of interest: Not stated

Quality of written English: Not stated

Statistical review: Not stated

Declaration of conflicting interests: Not stated
Reviewer's report:

Title: Detection of infectious organisms in archival prostate cancer tissues

Version: 1 Date: 28 May 2014

Reviewer: Silvia de Sanjose

Reviewer's report:

Overall the manuscript is clear and results are well presented. The discussion and conclusions are correct.

Minor Essential Revisions

However I think is in the abstract where I find some wording misplaced:

Abstract
The sentence “This study sought DNA evidence of candidate organisms in archival prostate cancer tissues with the aim of assessing if a subset of these cancers arise as pathological sequela in response to infection” is incorrect. Cross sectional information cannot be used to confirm a pathological sequela to infection. I would suggest that “of these cancers show any association with common genital infections”

• The reviewer’s suggestion has been incorporated in the text of the manuscript.

Conclusion says: “... contribute to anything but a small proportion of prostate cancer risk, regardless of tumour phenotype.” I do not think that the study allow to conclude that small proportion of prostate cancers could be attributable to infection based on these data. The association does not mean etiology.

• The author is correct in stating that “association does not mean etiology”. The relevant sentence in the Abstract (conclusion) has been changed to “The low prevalence of detectable microbial DNA makes it unlikely that persistent infection by the selected candidate microorganisms contribute to prostate cancer risk regardless of tumour phenotype.

I am not sure whether Figure 1 is necessary.

• Figure 1 has been removed.

Level of interest: An article whose findings are important to those with closely related research interests.

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.