Professor Yaron Niv – letter of revision

Dear Editor,
Thank you for accepting my paper for publication.
Enclosed please find my "step-by-step" answers for the reviewers' comments.

Sincerely yours,

Yaron

Professor Yaron Niv
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Reviewer 1.

This is a very good paper, with a large amount of interesting data and work. The analysis is conducted respecting the protocols of meta-analysis.

Thank you.

The Authors may write a comment in the discussion also on the expression of Mucin in PanIN and as marker of possible pre-neoplastic lesion (not only IPMN but also PanIN) highlighting more this concept.

Added in page 13, line 4-6.

Reviewer 2.

The manuscript by Yaron Niv presents a systematic review and meta-analysis of mucin expression in the pancreas. This is an interesting and well-written review of mucin expression in the pancreas.

Thank you.

1. There is obviously heterogeneity regarding detection of mucin expression (e.g. different antibodies for IHC, protein vs. mRNA detection etc.) and disease classification (e.g. classification of intraductal papillary mucinous neoplasms). I would recommend to further discuss this.

See "limitations", page 12, last paragraph, and page 13, line 1-6.

2. The author should follow the PRIMSA guidelines for systematic reviews.

See page 6, line 12.

3. Which criterion was used for the analysis of publication bias?

See page 7, line 9-10.

4. In the context of expression analysis, what does the OR represent? Obviously it makes a difference comparing quantitative e.g. RT-PCR data to qualitative e.g. IHC data. In other words, what does an OR of 10 mean? 10-fold higher expression? That would not make much sense for IHC?

See page 7, line 3-5.

5. The authors should group the included studies according to their relevance. Did any of the studies followed the STARD guidelines?

All the studies.

Did the studies validate their antibodies prior to IHC analysis?

Not mentioned.

6. It would be interesting to perform an additional analysis with the best/most relevant studies.

Done – see studies on MUC1, MUC2 and MUC5AC.

Reviewer 3.

The authors are to be congratulated on their efforts in preparing this manuscript.

Thanks you.

I have several thoughts:
1. The use of the word "lesion" is discouraged. What is a "lesion"? Separate pre-malignant from malignant

We separated pre-malignant from malignant - see figures 4a and 4b.

2. The English could be improved. Style too.

Done.

3. There is no stated hypothesis.

See page 5 last paragraph.

4. A better description of the publications involved in the meta-analysis should be discussed in more detail. A good meta-analysis of badly described studies leads to inadequate statistical analyses.

See page 9-11, "studies description". I choose only good studies (20 of 949) according to inclusion criteria.

5. Publication bias must be discussed in detail.

See page 7, last paragraph.

6. What is a benign lesion? Is this confused with neoplastic tumors? Pre-malignant tumors?

Changed to "pre-malignant" – page 7, line 2.

7. Are there differences among gastric vs. intestinal vs. pancreaticobiliary IPMN?

Yes – see Discussion

There is enough herein to encourage the authors to improve this manuscript for publication.

Reviewer 4.

Mucin expression and the pancreas – a systematic review and meta-analysis
Summary This was a meta-analysis of studies on mucin and pancreas that were published up to May 31, 2016. After various criteria were applied, 20 studies were adjudged to be suitable for this purpose. The studies looked at normal pancreas and various pancreatic lesions including but not limited to intraductal papillary mucinous tumors (IPMNs), mucinous noncystic carcinomas, and pancreatic ductal adenocarcinoma (PDAC). The techniques used to analyse the mucin varied over time (as is to be expected) and included histochemistry, immunohistochemistry and PCR. The study concludes that mucin expression may be a useful prognostic marker in the transformation of IPMN to PDAC, as a prognostic marker and as a target for therapy.

Comments
The subject of mucin expression in pancreatic neoplasia is interesting and topical. I therefore find this article to be quite meritorious.

Thanks you.

However, I think that it could be improved in several areas, as follows:

1. In the Results and Discussion, one gets the impression that the findings from each of the cited papers are just summarized one after another. So this kind of robs the paper of flow and readability. I think there should be a better attempt to synthesize the findings and come up with clearer take home messages for the readership (taking into consideration the biology of the disease). For example, **after reading the Refs. provided by the author, some of the common themes are:**
1. i) There are various pathways for the development of pancreatic cancer e.g. a) from IPMNs and b) pancreatic intraepithelial neoplasia (PanIN)

ii) For IPMN, there are various classifications e.g. a) large duct IPMN and side-branch IPMN b) gastric or intestinal IPMN (dark cell vs clear cell IPMN)
iii) a) Gastric IPMNs are MUC1 negative and MUC2, and rarely develop into cancer. These IPMNs are usually located in the branch ducts b) Intestinal IPMNs are MUC1 negative but MUC2 positive. However, when they transforms into cancer, the MUC1 becomes positive. They are mostly located in the main duct
iv) MUC4 expression in IPMNs may help to distinguish the worrisome intestinal IPMNs from the safer gastric-type IPMNs.
Etc……..I do not want to belabour the point, but there are many such generalizations that can be made from the selected papers. This helps to weave a story within the biological context, and stimulates the readership to see what the next steps are in this evolving field.

See page 12, last paragraph.

2. The paper's English needs improvement to provide flow of ideas and readability

Done

3. There are many typographical errors e.g.
i) page2, Abstr, Search till May 31, 2016. …….p6, Methods. Search till May 31, 2015
ii) p2, Conclusion, IMPN, should be IPMN
iii) p8, Immunohistochemistry (IHC). etc

Done

4. Please note that I do not have expertise in the meta-analysis part of the paper. Overall, I like the concept of the paper but would suggest improvements along the lines indicated above. Thank you.