Author’s response to reviews

Title: Impact of body mass index and fat distribution on sex steroid levels in endometrial carcinoma: a retrospective study.

Authors:

Willem Jan van Weelden (willemjan.vanweelden@radboudumc.nl)
Kristine Eldevik Fasmer (Kristine.eldevik.fasmer@helse-bergen.no)
Ingvild L Tangen (Ingvild.Tangen@uib.no)
Joanna Inthout (Joanna.intHout@radboudumc.nl)
Karin Abbink (karinabbink@hotmail.com)
Antionius E van Herwaarden (Teun.vanHerwaarden@radboudumc.nl)
Camilla Krakstad (Camilla.krakstad@uib.no)
Leon FAG Massuger (Leon.Massuger@radboudumc.nl)
Ingfrid S Haldorsen (Ingfrid.helene.salvesen.haldorsen@helse-bergen.no)
Johanna MA Pijnenborg (Hanny.MA.Pijnenborg@radboudumc.nl)

Version: 2 Date: 15 May 2019

Author’s response to reviews:

Dr Georg Pfeiler
Editor, BMC Cancer

Date Page
May 10th, 2019 1 of 3

Your reference Contact
W.J. van Weelden
Subject: resubmission manuscript BCAN-D-18-03

Dear doctor Pfeiler,

Thank you for reviewing our manuscript ‘Impact of body mass index and fat distribution on sex steroids levels in endometrial carcinoma’ (BCAN-D-18-0) and considering our paper for publication in BMC Cancer.

We have revised the manuscript based on the comments from the reviewers. We have carefully addressed all comments point by point which are summarized below. Also, we have revised figure 2 as the correlation coefficients were inadvertently misplaced in the middle panel of this figure. This is corrected in this final version of our manuscript.

We thank you for the chance of improving our manuscript based on the remarks. Should you need any additional information, please do not hesitate to contact us.

On behalf of all co-authors, yours sincerely,

Willem Jan van Weelden

Radboud university medical center
Department of Obstetrics and Gynecology
P.O. Box 9101
6500 HB Nijmegen
The Netherlands
Phone: +31643274577
Fax: +31243619637
Willemjan.vanweelden@radboudumc.nl

Editor, dr Pfeiler,

Thank you for submitting to BMC Cancer. We do apologize for the delay, but it was really hard to find adequate reviewers. I suggest to add the reference from reviewer one, then it can be published as it is.

Dear doctor Pfeiler,

We want to thank you for finding reviewers for a manuscript that is so specific as ours. We have included the reference from dr Schwameis and are happy to know that this manuscript is considered suitable for publication in BMC Cancer.
Reviewer 1, dr Schwameis:

This is a concise and well written manuscript. In the manuscript „Impact of body mass index and fat distribution on sex steroid levels in endometrial carcinoma“ van Weelden and colleagues describe a correlation between serum sex steroid levels/serum lipids and measures of adiposity in endometrial cancer patients.

This subject is intriguing and the data are well presented. The statistical analysis seems sound. Anyhow, the low number of patients included into this retrospective study is a major limitation.

In conclusion I have no questions to the authors.

Anyway, I want to point out that SFA has already been shown to be the adiposity parameter most strongly correlated with the development of endometrial cancer (Oncol Rep. 2011 Jul;26(1):65-71. doi: 10.3892/or.2011.1259. Epub 2011 Apr 13.) - This reference might corroborate the results of the present analysis.

Dear dr Schwameis,

Thank you for your kind words. We fully agree that the low number of patients in our study is an important limitation as is pointed out in the discussion line 229-232. Thank you for the suggestion to add the article by Nakamura et al. We have indeed added this in the introduction of our manuscript in line 82 and changed the text in the following way:

'Previous studies have reported a relation between SAV and development of EC, while VAV was associated with adverse outcome (1-3).'

Reviewer 2, dr Phelps:

Well written. They state what sets their research apart from what is already published.

2 comments but do not need to be added for paper to be recommended.

1. Did the ratio of SAV:VAV get assessed? Page 12 eludes that the common contribution was high 35.9%. This confuses me a bit when I am reading and again makes me wonder does the ratio make any difference, is it just the SAV alone regardless of the VAV etc.

Dear doctor Phelps,

Thank you for your compliment. We did indeed evaluate the ratio of SAV to VAV in our analyses, but did not find any additional information and decided to leave them out of the manuscript. The correlations of SAV:VAV ratio with sex steroids and lipids are added below. In
our patient cohort, SAV appears to be the most important contributor of estradiol production regardless of the volume of the visceral fat compartment.

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th>WC</th>
<th>TAV</th>
<th>VAV</th>
<th>SAV</th>
<th>VAV%</th>
<th>SAV/VAV ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol (pmol/L)</td>
<td>.62**</td>
<td>.64**</td>
<td>.74**</td>
<td>.58**</td>
<td>.74**</td>
<td>-.06</td>
<td>-.07</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>.26</td>
<td>.33*</td>
<td>.37*</td>
<td>.29</td>
<td>.43**</td>
<td>-.17</td>
<td>-.11</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>.17</td>
<td>.31</td>
<td>.29</td>
<td>.19</td>
<td>.31</td>
<td>-.15</td>
<td>-.12</td>
</tr>
<tr>
<td>DHEAS (µmol/L)</td>
<td>.36*</td>
<td>.31</td>
<td>.30</td>
<td>.35*</td>
<td>.34*</td>
<td>-.10</td>
<td>-.06</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>-.07</td>
<td>-.08</td>
<td>-.19</td>
<td>-.08</td>
<td>-.20</td>
<td>.01</td>
<td>.05</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>-.23</td>
<td>-.37*</td>
<td>-.45**</td>
<td>-.39*</td>
<td>-.42**</td>
<td>-.15</td>
<td>-.18</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>-.03</td>
<td>-.03</td>
<td>-.13</td>
<td>-.02</td>
<td>-.12</td>
<td>-.01</td>
<td>.05</td>
</tr>
<tr>
<td>NHDL (mmol/L)</td>
<td>-.00</td>
<td>.01</td>
<td>-.08</td>
<td>.01</td>
<td>-.09</td>
<td>.05</td>
<td>.09</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>-.05</td>
<td>.17</td>
<td>.15</td>
<td>.14</td>
<td>.09</td>
<td>.36*</td>
<td>.32</td>
</tr>
<tr>
<td>Chol/HDL ratio</td>
<td>.17</td>
<td>.27</td>
<td>.29</td>
<td>.30</td>
<td>.27</td>
<td>-.13</td>
<td>.17</td>
</tr>
</tbody>
</table>

2. Would be interesting to comment on why the authors think their data shows no significant difference in fat distribution between EEC and NEEC when that is counter to common knowledge.

Enjoyed reading the paper.

Thank you for the chance to elaborate on this topic as we think this is a very interesting discussion. We agree that NEEC carcinogenesis is considered to be not related to estrogen exposure. Nevertheless, estrogen could be important in a subset of NEECs as suggested by the observation that most NEEC patients have risk factors that are commonly associated with EECs and the presence of estrogen receptor in a selection of NEEC tumors. (4, 5) This could explain the similar fat distribution patterns and similar contribution of SAV to estrogen in EEC and NEEC patients in our cohort. Validation of these results in a larger cohort of patients is warranted.


