Author’s response to reviews

Title: Colon cancer risk and different HRT formulations: A case-control study.

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Author’s response to reviews:

The Journal BMC Cancer
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Dr. J.A LeGood,
Assistant Editor

Dear Dr. Le Good

I like to submit the revised version of our manuscript on behalf of all co-authors

MS: 1639770584124726
Use of various HRT formulations is not associated with increased risk of colon cancer: A case-control study
Juergen C Dinger, Lothar AJ Heinemann, Sabine Moehner, Thai DoMinh and Anita Assmann

This letter shows how we respond to the referees and complied with the suggestions in the revised manuscript.

We appreciate the thoughtful comments and useful suggestions of the reviewers that led to the revision of the manuscript

In the following we list the questions/remarks of reviewer I (italic) and our response:

(1)...the title somewhat implies that the paper findings are surprising... vast majority of the studies reported a decrease or a null effect of HRT on Colon Cancer risk... a more neutral title is more appropriate...

We agree with the critical remark of the referee and changed the title to "colon cancer risk and different HRT formulations: A case-control study". We hope this is neutral and clear enough. If not, we ask for another, more appropriate phrase. Thanks.

(2)...CEE and SEE : The AA should give details of these abbreviations...

Sorry, SEE was a spelling error in the text and is corrected now to CEE. All abbreviations are explained throughout the text when used the first time.

(3)....The effects of CEE alone and CEE+MPA should be discussed on more details, discussing the interpretations given by the WHI....

We expanded the discussion (page 6, 2nd para). Our findings do not contradict the result of the WHI study, although the numbers are small in our observational research. WHI reported a 37% reduction of the relative risk of colon cancer in user of combined CEE and MPA, we found 36% reduction. The confidence intervals of the adjusted risk estimates were almost identical in both studies, and not statistically significant. In general, the magnitude of risk reduction meets the results of several observational studies. It is new in our study that we tried to compare the risk between CEE/MPA and other combination HRTs common in Europe.
The value of this comparison however is limited due to small numbers and other potential problems explained under "limitation of the study".

(4)...Norethindrone acetate (NETA: the European definition noretisterone acetate should be added....

Thank you for making us aware of this mistake: Actually, we mean norethisterone acetate and not norethindrone acetate. This was corrected on page 3 and table 4.

(5)...in table 1 the breast feeding and OC use were reported to be associated to a decrease risk...the AA should discuss these findings ...

We explained this observation somewhat more explicit in the result section. Breast feeding, higher number of children point in the same direction - a seemingly lower risk of CoC. Regardless whether this is a statistical artefact or an indicator for a true issue - it was not the objective of this study to answer this question with relative small numbers and other limitations of the study (see discussion part of the manuscript). Like OC ever-use, this information was obtained in a search for other differences between cases and controls that possibly could explain different risk of HRT user (potential confounding). Thus, we hesitate to discuss this as "results" of the study. Although OC ever-use is closer to the research question of an effect of hormones on colon cancer risk, the study was not designed to analyse the impact of OCs on CoC. Fortunately - take at face-value - the point estimates of OC use and HRT use (irrespective of formulation) point in a similar direction, i.e. toward lower risk of colon cancer, mainly non-significant. For this reason, we explained the findings under results more detailed and added a few more words to the discussion part but did not discuss it in detail with literature. Are these revisions an acceptable compromise?

Here are the questions/remarks of reviewer II and our responses

(a)...General remarks:.... The possible protective role of estrogens in colon carcinogenesis has been long debated..... Methylation of DNA is equivalent to gene silencing, with inactivation of a number of genes downstream......

Although we did not intend to discuss this important field of pathogenesis in detail, we expanded the relevant part of the discussion (3rd para of discussion) and referenced with two articles with more detailed information (9,10). I hope this is an agreeable compromise.

(b).....small numbers of cases in many sub-analyses, the authors failed to detect meaningful differences in colon cancer risk according to different hormone preparations or ways of administration....

This was discussed under "limitations of the study" in the revised manuscript. We tried to stress this problem even more than in the previous manuscript and start this section with such a short statement. The remaining description of limitations was not altered.

(c)......ever -oral contraceptive users had a significant reduced colon cancer risk when compared to never users (OR = 0.64, 95% CI, 0.46-0.89) . Conversely, no significant difference in colon cancer risk was detected between ever- HRT users and never users...

As stated above, the apparently inverse association between ever-use of OCs and colon cancer risk was not considered as a particular study result but information used to identify possible confounding. Moreover, the non-significant association between HRT use and colon cancer does not exclude a reduced risk in many formulation sub-groups or time intervals (see non-significantly reduced risk estimates in tables 2 and 3).

(d)....Have the authors found any difference in right colon cancer and left colon cancer risk associated with HRT use ?

Unfortunately, we did not collect the information about right- or left colon cancer from the tumour centres/registers. Thus, we cannot answer this question.
(e)....Have the authors found any correlation between HRT use and colon cancer mortality?

It was part of the study protocol that only alive cancer cases were asked for participation in the study. We have the information about hormone use only from the study participants. Again, we cannot answer this question.

Many thanks for kind assistance and helpful suggestions

Yours sincerely

Lothar A.J. Heinemann, MD, PhD, MSc, DSc