Author's response to reviews

Title: Assessment of the effect of iris colour and having children on 5-year risk of death after diagnosis of uveal melanoma: a follow-up study.

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

We would like to thank you and the reviewers for the helpful comments. We revised our manuscript accordingly and believe that the quality of the manuscript has increased. We therefore would like to thank the reviewers and extended our acknowledgement. Below please find point by point our reactions to the reviewers’ comments. The original reviewers’ comments are printed in capital letters. We hope that the revised version of the manuscript meets your and the reviewers’ expectations. If there is anything we can do to facilitate the Journal’s consideration of our paper, please do not hesitate to let me know.

With kind regards

Andrea Schmidt-Pokrzywniak on the behalf of all authors

GENERAL COMMENTS:

(1) ACKNOWLEDGMENTS
- BY WAY OF A SECTION 'ACKNOWLEDGMENTS', PLEASE ACKNOWLEDGE ANYONE WHO CONTRIBUTED TOWARDS THE ARTICLE BY MAKING SUBSTANTIAL CONTRIBUTIONS TO CONCEPTION, DESIGN, ACQUISITION OF DATA, OR ANALYSIS AND INTERPRETATION OF DATA, OR WHO WAS INVOLVED IN DRAFTING THE MANUSCRIPT OR REVISING IT CRITICALLY FOR IMPORTANT INTELLECTUAL CONTENT, BUT WHO DOES NOT MEET THE CRITERIA FOR AUTHORSHIP. PLEASE ALSO INCLUDE THE SOURCE(S) OF FUNDING FOR EACH AUTHOR, AND FOR THE MANUSCRIPT PREPARATION. AUTHORS MUST DESCRIBE THE ROLE OF THE FUNDING BODY, IF ANY, IN DESIGN, IN THE COLLECTION, ANALYSIS, AND INTERPRETATION OF DATA; IN THE WRITING OF THE MANUSCRIPT; AND IN THE DECISION TO SUBMIT THE MANUSCRIPT FOR PUBLICATION. PLEASE ALSO ACKNOWLEDGE ANYONE WHO CONTRIBUTED MATERIALS ESSENTIAL FOR THE STUDY. IF A LANGUAGE EDITOR HAS MADE SIGNIFICANT REVISION OF THE MANUSCRIPT, WE RECOMMEND THAT YOU ACKNOWLEDGE THE EDITOR BY NAME, WHERE POSSIBLE.

THE ROLE OF A SCIENTIFIC (MEDICAL) WRITER MUST BE INCLUDED IN THE ACKNOWLEDGEMENTS SECTION, INCLUDING THEIR SOURCE(S) OF FUNDING. WE SUGGEST WORDING SUCH AS 'WE THANK JANE DOE WHO PROVIDED MEDICAL WRITING SERVICES ON BEHALF OF XYZ PHARMACEUTICALS LTD.' AUTHORS SHOULD OBTAIN PERMISSION TO ACKNOWLEDGE FROM ALL THOSE MENTIONED IN THE ACKNOWLEDGEMENTS SECTION.

- WE INSIST YOU TO INCLUDE THIS IN THE MANUSCRIPT EVEN THOUGH YOU DIDN'T HAVE FUNDING.

(2) WE NOTICE THAT YOU HAVE INCLUDED TABLES AS ADDITIONAL FILES. IF YOU WANT THE TABLES TO BE VISIBLE WITHIN THE FINAL PUBLISHED MANUSCRIPT PLEASE INCLUDE THEM IN THE MANUSCRIPT IN A TABLES SECTION FOLLOWING THE REFERENCES.

Point 1: We have add the acknowledgements section
Point 2: We include the table in the table section
REFEREE 1:

MAJOR COMPULSORY REVISIONS

1. IN THE ABSTRACT, PARTICULARLY THE METHODS AND RESULTS SECTION, HAVING CHILDREN AS A PROGNOSTIC FACTOR DOES NOT APPEAR. THIS IS IN CONFLICT WITH THE TITLE OF THE PAPER AND NEEDS TO BE ADDRESSED.

We have added sentences about “having children in the methods and results section.

2. MATERIAL AND METHODS SECTION ON EXPOSURE AND OUTCOME FINAL SENTENCE: THE SOURCES OF CAUSE OF DEATH INFORMATION ARE RATHER VARIABLE. PLEASE STATE EXACTLY WHICH PERCENTAGE WAS BASED ON THE OFFICIAL DEATH CERTIFICATES, AND CORRESPONDINGLY ON PHYSICIAN INFORMATION. IT IS NOT CLEAR IN THE METHODS HOW THIS INFORMATION WAS RETRIEVED: BY QUESTIONNAIRE TO PHYSICIANs, BY PERSONAL INTERVIEW, ANY OTHER WAY. PLEASE CLARIFY. THIS IS LATER DISCUSSED AS A STRENGTH OF THE STUDY, WHICH MAY BE TRUE OF THERE WERE VARIOUS SOURCES OF INFORMATION FOR INDIVIDUAL CASES, BUT THIS IS NOT CLEAR.

We added the percentages and the information how it was retrieved.

MINOR ESSENTIAL REVISIONS

1. BACKGROUND, FIRST PARAGRAPH: MORTALITY RATE SHOULD BE FATALITY (RATE); THE MORTALITY RATE (IN ABSOLUTE TERMS) FOR UVEAL MELANOMA IS LOW, IT BEING A RARE TUMOUR.

We have changed the term.

2. MATERIAL AND METHODS FINAL SENTENCE UNDER THE HEADING “PATIENTS”: ADD WHEN THE INFORMED CONSENT WAS OBTAINED, BECAUSE IT SEEMS IMPLAUSIBLE THAT FOR THOSE FOLLOWED-UP VIA REGISTRATION OFFICES AN INDIVIDUAL CONSENT WAS OBTAINABLE AT THAT TIME. ALTERNATIVELY IT WAS OBTAINED FROM ALL RESPONDING PATIENTS (NOT ALL PATIENTS).

3. RESULTS SECOND PARA: PLEASE CHECK THE NUMBERS: 357 PATIENTS SHOULD BE 457 EQUATING TO 99.5% OF THE TOTAL COHORT.

We changed all above-quoted points accordingly.
4. RESULTS FINAL PARA: WHY SHOULD THE HR INCREASE WITH INCREASING NUMBER OF CHILDREN? YOU ARE ADDRESSING A POTENTIAL "DOSE-RESPONSE" ISSUE HERE, AND HR COULD PERHAPS BE EXPECTED TO DECREASE WITH INCREASING NUMBER OF CHILDREN IF I AM NOT MISTAKEN, HOWEVER, THIS IS NOT THE CASE.

That’s correct, this is a mistake, we changed it in “decrease”.

DISCUSSION, SECTION ON RISK SCORE PRIOR TO SECTION ON STRENGTHS: IS IT PROBABLY CORRECT TO SPEAK OF SINGLE RISK SCORE HERE GIVEN THAT VARIOUS FACTORS WERE ENTERED INTO THE MODEL. FOR CLARITY, PLEASE SPECIFY "THE RISK FACTORS" AND PROVIDE SOME INFORMATION ON WHAT IS CONSIDERED GOOD, MODERATE OR WEAK PREDICTION BASED ON THE STATISTICS EMPLOYED AS NOT ALL READERS WILL BE OVERLY FAMILIAR WITH C STATISTICS (COULD BE DONE HERE OR AS AN ADDITIONAL SENTENCE IN THE METHODS).

We have added some sentences in the methods.

DISCRETIONARY REVISIONS 1.

2. GENERAL COMMENT: ARE THERE ANY SURVIVAL DIFFERENCES RELATED TO TYPE OF TREATMENT REPORTED IN THE LITERATURE? CONSIDER ADDING SOME INFORMATION IN THE BACKGROUND SECTION ABOUT THIS.
3. RESULTS: TABLE 2 IS PRESENTED AS SUPPL. FILE. I SUGGEST IT TO BE PART OF THE MAIN MANUSCRIPT, SINCE QUANTITATIVE DATA ON THE ISSUE OF HAVING CHILDREN IS FOUND ONLY HERE. ALTERNATIVELY, AND GIVEN THE MAJOR COMMENT BELOW, CONSIDER CHANGING THE TITLE OF THE PAPER TO FOCUS ON IRIS COLOUR (PERHAPS ADDING: AND OTHER PROGNOSTIC FACTORS)

Point 1 and 3: We changed all above-quoted points accordingly.
Point 2: There are no survival differences related to the type of treatment

MINOR ESSENTIAL REVISIONS NOT FOR PUBLICATIONS
1. ABSTRACT: FIRST SENTENCE METHODS: A COHORT … WAS RECRUITED
2. ABSTRACT CONCLUSION: IRIS COLOUR IS (MORE OR LESS) NEWLY ADDED TO THE PROGNOSTIC FACTORS. I SUGGEST REPLACING "AMONG" WITH "BEYOND".
3. BACKGROUND FIRST PARA: REMOVE HYPHEN IN … SURVIV AL AFTER 5 AND 10 YEARS
4. BACKGROUND SECOND PARA, SENTENCE STARTING WITH " SEVERAL STUDIES …": REMOVE S FROM FACTORS
5. BACKGROUND FINAL PARA: PROGNOSIS CAN BE BASED …. – CONSIDER ADDING: ESTIMATES OF PROGNOSIS ….
6. BACKGROUND FINAL PARA: REMOVE INSERT….., WHETHER THIS IS GOOD OR BAD, … . APPEARS UNNECESSARY!
8. DISCUSSION FIRST PARA: SENTENCE STARTING WITH: ANOTHER REASON – REMOVE THE COMMA AND ADD A "THAT". CHECK THE WORDING OF THE SUBSEQUENT SENTENCE (EVOLVED TOO DRAMATICALLY?)
9. DISCUSSION SECTION ON HAVING CHILDREN AS PROGNOSTIC FACTOR: CHECK THE SECOND SENTENCE WHICH
INCLUDES BOTH HOWEVER AND BUT.
10. CONCLUSION: PLEASE REVISIT WORDING.
11. GRAMMAR IN THE COMPETING INTERESTS AND CONTRIBUTIONS SECTION: REPLACE HAVE WITH HAS IN ALL
INSTANCES, BETTER: CHANGE TO SIMPLE PAST TENSE. IT APPEARS THAT NOBODY ACTUALLY DRAFTED THE
MANUSCRIPT, ONLY ASP HELPED TO DO SO. PLEASE CHECK SECTION AND REVISE.
12. FIGURE 1: DELIMIT DIGITS BY POINT, NOT COMMA

We changed all 12 points accordingly.

REFEREE 2:

MAJOR COMPULSORY REVISIONS
I SUGGEST THE CONCLUSION REGARDING THE FINDINGS ON IRIS COLOUR AND PARITY ARE LESS STRONG (E.G. MAY BE... RATHER THAN ...ARE), DUE TO THE BORDERLINE STATISTICAL SIGNIFICANCE, AND THE NEED OF A CONFIRMATION IN FURTHER STUDIES OR IN A META-ANALYSIS OF RISK FACTORS. PARTICULARLY, THERE ARE ONLY 62 CASES WITH DARK IRIS, WHO SUFFERED FROM 4 OR 5 DEATHS. THERE MAY BE MORE VARIABILITY THAN EXPECTED IN THESE ESTIMATES, AS THEY ARE BASED ON ONLY FEW EVENTS.

We changed the sentence.
Although we agree with the referee that our findings are not statistically significant to a significance level of 0.05, one has to bear in mind that the RIFA study originally was designed for examining associations between radiofrequency radiation and the risk of developing uveal melanoma. The number of required participants is based on a power calculation that addresses this main study question. Therefore, the interpretation of statistical tests for secondary study questions, for which the study has lower power, should be done very cautiously (if at all). The association between having children and uveal melanoma death, for example, is only analysed in women, who contribute about only one half of the total study population.

MINOR COMPULSORY REVISIONS
IN THE LAST PARAGRAPH AT PAGE 10 AND FIRST AT PAGE 11, YOU REPORT ON 5-YEAR PREDICTED PROBABILITIES OF SURVIVAL FOR COVARIATES SUBGROUP. IT WOULD BE USEFUL TO REPORT THEIR DIFFERENCE AND 95%CI IN BRACKETS.
DISCRETIONARY REVISIONS

PLEASE REPORT ON ETHNICITY IN RELATION TO IRIS COLOUR, IF AVAILABLE.

We have added the 95% CI.

In our study there are only people from Germany with white skin colour.