Author's response to reviews

Title: Survival of endometrial cancer patients in Germany in the early 21st century: a period analysis by age, histology, and stage

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

Thank you very much for the kind offer to consider a revised version of our manuscript. We are very grateful for the reviewers’ helpful and constructive comments, and we have revised the manuscript accordingly. Below please find each of the reviewers’ comments followed by our response.

Sincerely,

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Reviewer: Timo Hakulinen

Minor essential revisions:

Table 1 The stage column can be omitted ("yes" for every row).
Response: corrected.

Table 4 Footnote c has an extra a.
Response: corrected.

Discretionary revisions:

As the coverage has been extended from Saarland, it is of interest to make a comparison with the Saarland figures in order to see if the previous base had been representative. At least, increased precision could be thereby shown. Also comparisons against the EUROCARE and SEER results would be of great interest and should be included. This comparison, nevertheless, is only meaningful for Table 4, as far as the EUROCARE data are concerned.

Response: Added as suggested (page 12; lines 188-196).
Reviewer: Henry Kitchener

This paper straightforward paper describes survival data for endometrial cancer based on a large German population. The data are of interest to those practising gynaecological oncology, and developing trials in endometrial cancer. It confirms a number of knowns, but provides up to date data relevant to modern practice in a highly developed healthcare system.

The report is well written, and the only comment I would make is that the relative survival relates to age matched populations. Women with endometrial cancer tend to be obese and have more comorbidity hence in the results of trials, deaths from other causes are common; around 30% over five years. I think there should be some acknowledgement and discussion of this.

Response: We agree to the reviewer and added in the discussion that less favorable prognosis of endometrial cancer in the oldest age group might be in part attributable to comorbidities and less access to therapeutic innovations (Sant M et al 2009; Balducci L 2000), as old patients are generally under-represented in cancer clinical trials (Balducci L 2000). (page 14, lines 227-230).
Reviewer: Marjetka U Urji Vrčaj

Table 4 correct: c age-adjusted, incorrect: c age-aadjusted

Response: We corrected the footnote in Table 4.
Reviewer: Laura Woods

General comments

This is a well written, well referenced paper detailing patterns and trends in endometrial cancer survival in Germany. The authors provide a clear outline of the justification for their study, an appropriate analysis, well structured tables and a good discussion.

Major compulsory revisions

1) I was interested that this paper makes no mention of net survival and its relationship to relative survival. Relative survival has been the preferred means of estimating net survival from cancer registry data for a number of decades. However, recently it has been shown to be a biased method of estimating net survival. A case could still be made for using relative survival, including consistency with previous results and the fact that the bias is smaller in some circumstances in comparison to others. Yet this is not done in this paper. I would like to see the recent advances regarding the relationship between net survival and relative survival (as estimated using Ederer II) explained in full in the methods section of the paper, and a full justification of their chosen approach included.

Response: Revised as suggested (page 8, lines 110-112).

2) The proportion of missing data for stage in this study is substantial (44%). Although this is noted, there is very little information given about who these persons might be, or why this information is likely to be missing. No attempt was made to analyse these data using strategies available to adjust for missing values such as multiple imputation. At this level of missingness, it may not be possible to impute appropriately. This means, however, that stage-specific results should be regarded with a good deal of caution. I would like to see the authors consider how to deal with these missing values in the analysis. If they chose to do a complete case analysis only, this should be justified. In either case, a description of who the missing cases are in terms of the other variables in the data set should be included, and the interpretation of the stage-specific results should be appropriately cautious in the light of these associations.

Response: We agree that due to the substantial proportion of missing data for stage these results should be interpreted with caution. We hesitated to impute the stage variables due to the amount of missing information. But as suggested, we now describe differences in the characteristics of patients with and without stage information. Patients with stage information were on average 2.6 years younger and had more often adenocarcinoma than carcinoma NOS, sarcoma or other (mixture) histologies, and had a slightly higher age-adjusted survival than those without stage information (81.1 (0.4) versus 79.5 (0.6))(page 15-16, lines 264-267).

3) The follow up in this study is provided up to 2006. The analysis strategy uses period estimation which gives a more 'up-to-date' estimate of survival. Yet, since we are now
in 2012, it must already be possible to know the vital status of all patients at least 4, if not nearer 5 years after their diagnosis. Most cancer registries have a short time-lag for mortality data: therefore, why did the authors choose to limit the follow-up to 2006, rather than do a complete analysis of patients followed up to the end of 2010? This would be more 'up-to-date' than what has actually been provided. If vital status is now available for patients up to December 2011, a full 5-year cohort analysis could be performed and the results would be fully 'up-to-date' for this particular cohort of patients (those diagnosed up to 2006). Preferably, the data should be updated and the analyses re-run: if this is not possible a full explanation of why these dates have been chosen should be given.

Response: We agree that more up-to-date data would be preferable. However, like in other collaborative cancer survival studies, an update of the database with extensive data quality and plausibility checks could only be performed once at the beginning of the project. An update of the data is planned in the next round of the project, contingent on continued project funding. As no improvement in relative survival was observed throughout the period from 2002 to 2006 and in the absence of breakthroughs in therapy for this cancer, we would though expect rather similar survival rates even in more recent years.

Minor essential revisions

4) Abstract, page 3, Conclusion, line 1: "In this first population-based study" Is this true? How does this statement relate to reference number 11?

Response: the reference 11 did not focus on endometrial cancer and only data from the Saarland cancer registry were used in reference 11. Our study is the first one that uses population-based data for a large part of Germany and the first one that specifically focuses on endometrial cancer. Nevertheless, we now dropped the word “first” to prevent potential misunderstandings (page 3, line 42-43).

5) Introduction, page 4, paragraph 2, line 2: "... and reproductive factors.." Explain what these are (and the direction of the association).

Response: Reproductive factors refer to parity and age at child birth. High parity and late age at last birth are associated with protection from endometrial cancer. We now changed the wording to clarify what is meant (page 4, line 59).

6) Materials and methods, page 7, paragraph 3, line 1: "period analysis (13), model-based period analysis...." Explain in greater detail what this is and how it adds to the simple period analysis results.

Response: Model-based period analysis is used in this manuscript to model trends from 2002 to 2006 in relative survival over time. An advantage to computing simple period analysis estimates for single calendar years is the increased precision of model based period estimates, which results from the use of the whole data set in the estimation of
the survival estimates for 2002 and 2006. In addition, model based period analysis allows to test for significance of time trends. The approach is based on a Poisson regression model as described in detail in reference 14. Age group-specific numbers of patients at risk and of deaths by year of follow-up for each single calendar year between 2002 and 2006 were computed. The numbers of death were then modeled as a function of age at diagnosis, the year of follow-up (entered as a categorical variable) and the calendar year (added as continuous variable) by Poisson regression with the logarithm of the person-years at risk as offset. We now explain the approach and its advantages in more detail (page 8-9; lines 118-126).

Discretionary revisions

7) English: Abstract, page 3, Methods, line 5: "Age adjustment was PERFORMED using five...." [better than 'done']

Response: corrected

8) English: Abstract, page 3, Results, line 3: "...70+ years. FURTHERMORE PROGNOSIS VARIED STRONGLY by histologic subtypes..." [better phrasing]

Response: corrected

9) English: Introduction, page 4, paragraph 2, line 2: "... related to overweight..." Would normally be phrased in relation to 'higher BMI' or 'to obesity'

Response: corrected

10) English: Materials and methods, page 6, paragraph 3, line 1: "Staging was built..." This is awkward English -perhaps "Stage of disease at diagnosis was defined according..."

Response: corrected