Author's response to reviews

Title: Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family

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Author's response to reviews: see over
Response to reviewers

Reviewer's report 1
Title: Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family
Version: 1 Date: 21 December 2007
Reviewer: Michael Patrick Lux

Reviewer's report:
Review Evans et al.
The work of Evans and colleagues and their manuscript â##Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family is a review of 385 families (223 with BRCA1 and 162 with BRCA2 mutations) ascertained through two regional cancer genetic services. The objectives of the work are well and matter of actual interest. The authors confirm the high risk of breast and ovarian cancer in mutation carriers. They also found evidence of a cohort effect with women born after 1940 compared to women born before 1930. This effect reaches a strong significance (p=0.0005).
The introduction is short and informative and gives a good overview. Material and methods are presented in a distinct way. Moreover, methods are well described. The tests are objective, reliable and valid. The conclusions are based on a fundamental knowledge. The quality of written English is acceptable.

Thankyou

In my opinion, the manuscript does not need to be seen by a statistician.

The manuscript has been seen by both Prof Doug Easton and Dr Tim Rebbeck and approved

But the following aspects about the paper should be mentioned and questions should be answered:
- Did the author and colleagues analyse CHEK2 in FDRs with breast cancer tested negative for the family mutation.

Yes and no CHEK2 1100delC mutation was found. We have added a sentence on this

- The Manchester score should be explained in a more detailed way, because this score is not used in every country.

Thankyou for pointing this out. We have explained the Manchester score in more detail.
- The age related estimations of untested FDRs with BRCA1/ BRCA2 mutation are based on small collectives, especially for FDRs age 60+. This should be mentioned and discussed with caution.

**We have added some further text to address this.**

- Did the authors define DCIS cases as breast cancer cases?

**DCIS was included as breast cancer. However, this only amounts to 1% of BRCA1 breast cancers and 2% for BRCA2. It is likely that nearly all of these would have become invasive as only 1/16 occurred after 60 years of age. We have added some text to address this.**

- The authors stated that they have censored cases after risk reducing surgery. This is reasonable. Is there also information about use of chemoprevention available?

**Tamoxifen is not licensed in the UK for prevention. Only 23 mutation carriers took tamoxifen as part of the IBIS1 prevention trial and this is unlikely to have materially changed the penetrance estimates. We have nonetheless inserted a sentence to this effect.**

- It would be interesting to compare the model and calculation results to other accepted risk calculation programs, e.g. BRCAPRO, Tyrer-Cuzick. At least, pros and cons of their review/ model should be discussed regarding the accepted risk calculation models.

**Thankyou. We do not consider that our publication represents a new model and comparisons with BRCAPRO/Tyrer-Cuzick would only be valid prospectively. We have nonetheless referred to the fact that BOADICEA model does factor in degree of family history of breast cancer in assessing penetrance**

Therefore, a minor essential revision should be considered. The results are important for daily clinical work. Therefore, I recommend the publication of the paper after the minor essential revision.

**Thankyou**

**Reviewer's report 2**

**Title:** Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family

**Version:** 1 **Date:** 27 February 2008

**Reviewer:** Antonio Russo
Reviewer’s report:
Discretionary Revisions
In the present paper the authors aim is to determine in BRCA1/2 mutation carriers the cumulative risks of breast and ovarian cancer to 70 and to 80 years of age respectively. Penetration estimates for each gene are shown for breast and ovarian cancer in tables and figures that illustrate the text and resulted very similar to those derived from the Breast Cancer Linkage Consortium (BCLC) cohort of high-risk families. A potential criticism of the study is that the authors have not taken enough account of ascertainment bias and that additional adjustment maybe necessary beyond excluding the index case, as properly reported in the manuscript.

Thankyou

What next?: Accept after discretionary revisions
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer 2 has not really requested any alterations