Reviewer's report

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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Reviewer: Michael Patrick Lux

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Review Evans et al.

The work of Evans and colleagues and their manuscript "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. In my opinion, the manuscript does not need to be seen by a statistician.

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.
- The Manchester score should be explained in a more detailed way, because this score is not used in every country.
- 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.
- Did the authors define DCIS cases as breast cancer cases?
- The authors stated that they have censored cases after risk reducing surgery. This is reasonable. Is there also information about use of chemoprevention available?
- 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. 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.