

Reviewer's report

Title: High penetrances of BRCA1 and BRCA2 mutations confirmed in a prospective series.

Version: 1 **Date:** 17 July 2009

Reviewer: Gareth Evans

Reviewer's report:

The authors present a prospective analysis of breast cancer rates by age in mutation carriers with BRCA1 and BRCA2 mutations. The main focus is on unaffected carriers but affected carriers are also presented. The authors rightly state that prospective follow up will provide a much more accurate answer than any modelling carried out on retrospective series. I am concerned though that the rates of cancer are a little too high as the addition of the annual rates would exceed a lifetime risk of 100%. This is nonetheless an important study.

Major Compulsory Revisions

1. There needs to be greater clarity as to the date of entry of a woman into the study. In a true prospective study of unaffected women they must test positive for the BRCA1/2 mutation then have a normal mammogram. From the description it is not clear that this is the case. Women could have been followed prospectively had a normal mammogram at prevalence round and subsequently developed breast cancer and only then tested for BRCA1/2. This could be called a prospective study for outcome of their breast cancer but not for a penetrance assessment. The only alternative to this is to test all women in surveillance at the outset. The authors must make this absolutely clear.
2. The authors may have missed the recent publication of the UK MARIBS study (CEBP) which was able to establish a study population of 837 women and follow them prospectively, in this case nearly all women provided a sample and were tested. This prospective study should be referenced
3. The authors rather trivialise the possible effects of modifier genes based on the only publication to date establishing their role. As there are further publications in press it is probably best for the authors to avoid contesting the potential role of these modifiers in altering penetrance.
4. The authors point out a difference in the rates of breast cancer in less common BRCA1 mutations. Again this is subject to bias as to which women get full testing. If all women entering the study had the common mutations tested but only those from proven families or prospective cancers get tested for uncommon mutations this would increase the apparent risks. Indeed modifiers could play a role here. Again the methods need to be clearly stated.

Minor Essential Revisions

1. page 2 Methods line line 9 alter 'strongly giving' to 'giving strong'

2. page 5 para 5 line 2 '..draw (a) firm..'

3. The headings could be clearer to the tables - prevalence round would be preferred to control

Discretionary Revisions

1. The authors could report Evans et al penetrance analysis in BMC cancer that has a prospective element and also Meijers-Heijboer EJ et al N Engl J Med 2001

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests