

Reviewer's report

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

Version: 2 Date: 11 September 2009

Reviewer: Gareth Evans

Reviewer's report:

The referee initially mentions that summing up the annual incidence rates gives more than 100% penetrance. This is already discussed in detail in the mns (discussion, section 4), and is about the difference between annual incidence rates by age, and cumulative risk by age. The cumulative risk by age may, of course, never exceed 100%. The sum of annual incidence rates may very well exceed 100%.

Although the authors discuss how they derived annual rates they do not explicitly state that these add up to >100%. I agree with their arguments but they need to make it explicit.

Our results for the frequent BRCA1 mutations are the prospectively observed annual incidence rates in the same families in which we previously have reported the cumulative risk by age, and as discussed, the figures match. The observed overall annual incidence rates in our series reflect the ages of the patients included, it is not an estimate of average life-time penetrance.

-OK

Major points 1 & 4 seem to be the same argument. We agree that when not all women included were tested for all rare mutations, there may have been an artificial high fraction of affected with rare mutations, and have modified discussion, section 2 accordingly.

-These are not the same point. The authors must explicitly state that all women had their prevalence examination as a known unaffected (by breast cancer) individual. OR

State that ALL women in their surveillance program receiving a prevalence screen including those still unaffected have been tested. The latter cannot be true as they admit that not all women have undergone predictive testing

Major point 2 & Discretionary revisions: The references suggested are now

included and specifically mentioned in introduction, section 2.

-good

Major point 3. We have expanded the discussion on modifiers in introduction, section 3. We do not trivialise modifiers: in contrast we approach both the concepts and the facts critically. One major conceptual/nomenclature problem is that a modifier should modify, an independent additive risk factor is not a modifier. We do not want to engage in this debate at the moment, and did the least possible: briefly mentioning the concept of modifiers with one up-to-date reference, and referenced King et al for validation of retrospective ascertainment biases to produce artificial results. We have previously in HCCP published that there is no sib-pair association for having ovarian or breast cancer in BRCA mut carrying kindreds, indicating no major modifier of expression. We may, if the editor so wishes, participate in a debate on facts and fiction with respects to modifiers, but that is outside the current report on our prospective findings.

-OK

Minor point 1 & 2: Corrected as suggested.

-Good

Minor point 3: We prefer to calculate annual incidence rates based on those having had no cancer before inclusion and having had no cancer at prevalence round. This gives a clean analytic model, and we have numbers of affecteds large enough to do so. Findings at first control and findings after last control, are difficult to interpret – cfr the MARIBS report.

-OK

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'