Reviewer’s report

Title: Testing for BRCA1 mutations using a combination of homogeneous selection criteria and immunohistochemical characteristics of breast cancers

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Reviewer: Petra Nederlof

Reviewer’s report:

The authors present a study to evaluate the use of immunochemical analysis of breast tumors to determine which patients are eligible for DNA molecular screening for BRCA1 mutations. They analyzed tumors from 93 patients by IHC and mutational analysis.

In itself the question is legitimate, as only in a relative small proportion of patients from breast cancer families indeed BRCA1/2 mutations are found. As is known from many publications, most BRCA1 tumors are ER negative. So it is not surprising that application of this criterion will yield in higher mutation frequencies. The question they do not address is how to increase the yield in BRCA2 mutation carriers. Since these breast tumors can be both ER+ and ER-, a similar approach is not possible. So in fact, all hereditary tumors must be screened for BRCA2 mutations, and only the additional screening for BRCA1 could be omitted.

Minor Essential Revisions

The writing is not acceptable. Many sentences are difficult to understand, abbreviations are used in the abstract without explanation, and there are inconsistencies in the numbers.

Examples:
Abstract

94 FBCs deriving from patients enrolled by specific conditions of eligibility….. Do the authors mean: primary breast tumors from breast cancer families defined by specific eligibility criteria? If so, what criteria were used? In the results the number 93 patients is used, must this be 94?

Results

Overall, excluding the cancers characterized by double hormonal positive receptorial status, the mutation screening could be performed only in 29 patients. I don’t think that the authors mean to say that in the other cases mutational screening was not possible. Do the authors mean: From the 93 cases, 29 tumors did not show a positive staining for both hormone receptors ER and PR; of which 10 showed a BRCA1 mutation.

Title:
It is unclear what the “homogeneous selection criteria” are, this is not further specified in the text.

One does not “test for BRCA1 mutations” using the criteria and IHC, one “selects” eligible patients for testing. The title is therefore not acceptable and misleading.

Methods
The Allred method should be described in more detail. How is the scoring done? In tables 1-3 values are given without any explanation. What does ER score – (2) mean? And +(6)?
What does HER2 score – mean? Negative (IHC 0) of “not done”.
Which methods/antibodies were used for the ER and PR staining?

Results
The IHC score of the mutations or UV carriers are given, but not the results for the other cases. They should be added.

According to the tables all BRCA1 mutations found were ER negative. Could use of that criterion not be enough? Why use ER- and/or PR-? Since the results for the remaining tumors are not given, it is unclear what the effect of one marker (ER) would be.

Table 4/5 are “other cases” all non-BRCA1 mutation carriers?

Conclusion
BRCA1 immunohistochemistry, a rapid and easy performing test…… This suggests the use of an antibody against the BRCA1 protein…. An easy to perform test???

About 90% of BRCA1 related cancers showed ER negative….. In fact all 10 BRCA1 cases showed ER- staining. Or do the authors discuss the literature?

… with the possible limitation of loosing one rue BRCA1….. The authors mean “miss” But more importantly, there may be a way around this problem in many families. If there are more family members with breast cancer, one could select the case with an ER negative breast tumor. It is very unlikely that all tumors in a BRCA1 mutated family are ER positive.

Finally, the dataset is rather small. Given that we already know that BRCA1 tumors are in general ER negative (~90%), one would like to test many more cases (several hundreds) to really get a feel for what one would miss and what the advantage of this approach would be.

Level of interest: An article of limited interest

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