Reviewer's report

Title: Contribution of germline BRCA1 and BRCA2 sequence alterations in to breast cancer in Northern India.

Version: 1 Date: 17 February 2006

Reviewer: Fernando Schmitt

Reviewer's report:

General

Identification of BRCA1 and BRCA2 has led to major changes in the treatment and follow up of patients with an inherited predisposition to breast and ovarian cancer. The genetic approach has allowed the identification of high risk patients what makes this study biologically and medically relevant. However the authors should clarify the points that I addressed in the review.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The authors claim that both BRCA1 and BRCA2 genes have been found more prevalent among early onset cases compared to older onset and familial breast cancer patients, however its important to stress that the study included 105 early onset cases and only 34 cases with a family history of breast and/or ovarian cancer. So it is not surprising that we observe more mutations in the early onset cases than in the ones with a family history (also the difference is not that striking, 15 out of 105 compared to 4 out 34);

2. In the case selection section, the 204 breast cancer cases are well described, still the authors did not mention the control group. Actually I could only find the number of controls in Tables 2 and 3. I assumed it was 65, was that correct (and which criteria was used to select them ?) If so, it was a very small number of controls compared to the breast cancer population studied. The authors should include a larger number of controls (bigger than the population studied) and try to match it with the population in analysis in terms of, for example, age.

3. The description made in the missense mutations in BRCA1/2 genes is not precise. The authors should refer that although they haven?t found this alterations in the control group, some of them are considered, according to the BIC database, polymorphisms, like for example S1613G and A2951T. In the case of this last alteration the explanation given for the substitution of a non polar hydrophobic aminoacid for a polar hydrophobic one is, in the opinion of this reviewer, a little wishful thinking for a possible deleterious mutation. And what about D47E? Do the authors have any possible explanation for a probable role?

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. - Reference [2] used for the estimation of breast cancer deaths in India is a bit old (1996). The authors should find a more recent statistic (for example in the International Agency for Research on Cancer; www.iarc.fr);

2. - How many times was the sequencing performed? How did the authors ruled out the possibility of PCR fidelity artefacts?
3. The journals in the references are not in the BMC requested form. They should be presented in italic.

Discretionary Revisions (which the author can choose to ignore)

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

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

Statistical review: No

Declaration of competing interests:

'I declare that I have no competing interests'