Author's response to reviews

Title: Prevalence of the BRCA1 founder mutation c.5266dup in Brazilian individuals at-risk for the Hereditary Breast and Ovarian Cancer Syndrome

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Author's response to reviews: see over
Porto Alegre, October 11th, 2011.
To: The Hereditary Cancer in Clinical Practice Editorial Team


Dear Editors,
As corresponding author and in response to the referees of the above mentioned manuscript we hereby present a point-by-point response of the questions and suggestions presented. A revised version of the manuscript has been attached to this document.
Yours sincerely,

Patricia Ashton-Prolla
Corresponding author
REFEREE 1 - Cezary Cybulski
This is an important paper that shows a significant frequency (5%) of 5382insC founder mutation in BRCA1 among 137 unrelated Brazilian cancer-affected women from HBOC families.

Comments:
1. A BRCA1 mutation causes BC and OC. Eleven probands with cancers other than ovarian-breast cancer should be excluded.
Response: We thank the reviewer for this suggestion. The sample studied here includes a vast majority of breast or ovarian cancer affected probands. The five patients that were not affected by at least one breast or one ovarian cancer had a significant family history of these tumors in first and second degree relatives, and thus, we have decided to include them. We have included a comment in the methods section as well as in the discussion, to further clarify this point. In addition, we have added a sentence indicating the mutation frequency when only breast or ovarian cancer-affected probands are considered.

2. The paper would benefit from a table describing the cohort (table 1 may be extended) – i.e. how many BC and OV were present in these families in I-st, II-nd degree relatives, (per family) what was the mean age of diagnosis (for BC and OC) in these families. These were only HBOC families?
Response: We have expanded Table 1 to include the information suggested by the referee. We have also expanded the description of inclusion criteria in the methods section of the manuscript.

3. The authors underestimate their results. The prevalence of 5382insC in the cases is significant. Given the simplicity and low costs of testing for one founder mutation (i.e. ASO PCR) such testing is deeply justified, before full screening of BRCA1. However the sensitivity of 5382insC testing in BRCA1 mutation detection needs to be established (in this population). Can you estimate this based on your data?
Response: We have modified the discussion to consider this important comment of referee 1, regarding the significance of 5382insC in the series of cases studied here. We consider that the methodology used for BRCA1 testing in this case (BRCA1 sequencing) is currently the gold standard for genotyping regardless of the population studied. Since very few studies contained comprehensive information on the full
mutation spectrum of Brazilian HBOC families have been published, we can not provide precise information on the prevalence of this particular mutation in relation to all mutation-positive HBOC families in Brazil.

4. 5382insC is more Slavic than AJ founder allele, please see the papers on Polish population.
Response: We thank the reviewer for this observation and have included a comment and references regarding this important information in the introduction of the manuscript.

REFEREE 2 - Pål Møller

One word-wide BRCA1 founder mutation (c.5266) is allledgedely reported twice in Brazil. The report validate this finding and report a prevalence of 5% in a highly selected set of patients. The cohort was not defined with respect to family history nor ethnicity besides the statement that they were not Ashkenazi. The cohort was tested for the three Ashkenazi mutations only, and the report follwingly have no bearing on the possiblible existence of additional frequent Brazilian mutations. The mns uses too many words to describe breast cancer and inherited breast cancer in general, and without proper references (it is not documented that 5-10% of breast cancers are hereditary, and such a figure may have no meaning without reference to population examined).
Response: We thank the referee for this comment and have reorganized the introduction to contemplate the comments of both referees. We have included a reference to the affirmative of the estimate about the prevalence of hereditary cancer in general.

An important information is given in last sentence in first section in Discussion: BRCA testing is not available in Brazil besides for a few who may pay privately. As cost is dramatically dropping, and as results of full sequencing may be difficult to interpret and above all so in a distinct population where normal variation is unknown, to me the conclusion of this study should be that prevalent mutations should be looked for by cheap tests in all immigrant populations the last 500 years, and the test panel should include the founder mutations in the populations the immigrants were coming from. This will give no difficult answers to interpert, an the reported figure of 5% prevalence of
one such mutation in the cohort examined, is actually high and indicates that there is much more to gain through this path.

Response: We have reconsidered the results in light of the comments of both referees and have indicated in the discussion the significance of the results presented for this subset of Brazilian HBOC families.

Secondary, there is an obvious need to search for founder mutation(s) in the native Brazilian populations.

Response: We are very grateful to the referee for this suggestion and will consider this approach in future research endeavors. Since we and others (da Costa et al., 2008; Hamel et al., 2011) have demonstrated that the BRCA1 c.5266dup mutation that occurs in Brazil shares the same haplotype as the mutation encountered in Ashkenazi Jews and in several other European population groups, we infer in the discussion that the mutation was likely introduced in Brazil by one or more of these population groups. However, we conclude that further studies should indeed be conducted to detail the history of the mutation and its origin in Brazil.