Author's response to reviews

Title: BRCA1 mutations in women with familial or early-onset breast cancer and BRCA2 mutations in familial cancer in Estonia.

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Author's response to reviews:

Dear Hereditary Cancer in Clinical Practice Editorial Team,

please find my answers to the reviewers: Arvids Irmejas and Thanagarajan Rajkumar as follows:

Dear Arvids Irmejas,

Thank you for reading my manuscript: BRCA1 Mutations in Women with Familial or Early-Onset Breast Cancer in Estonia. Please find the answers to your questions and comments, as follows:

1. A.R.:“ Discussion and comparison with Finnish BRCA1 studies results is lacking (Ethnically closest neighbours!!!)

K.T.:“ Now I have included the Finnish studies. I have originally discussed more about the neighbours: russians, because the cohort for BRCA1 mutation analyses included also russians. Also, recent study demonstrate that Latvians, Lithuuenians and Nort-Western Russians are genetically even close to Estonians than Finns (Nelis M.et al PLoSOne. 2009;4(5):e5472) “

2. A.R.:“ Criteria for familial cases are very unspecific and therefore this is very heterogeneous group of individuals/families. Very low percentage of pathogenic mutations confirms the low specificity of selection criteria. The same percentage of clinical mutations probably will be detected also in consecutive breast cancer group.“

K.T.:“ I agree that the selection criteria for familial cases are not perfect. I have discussed the reasons in the article „

3. A.R.:“ BRCA2 gene testing study could be done in young breast cancer group and in families with 3 or more cases of breast/ovarian cancer, in order to
increase knowledge about hereditary cancer etiology in Estonia, because Estonia is geographically very close to Finland, where there are BRCA2 gene founder mutations confirmed.

K.T.: “We have data for BRCA2 mutations in familial cases, now I have included these to the article.”

With kind regards,
Kristiina Tamboom
Corresponding author on behalf of the all co-authors.

Dear Thanagarajan Rajkumar,

Thank you for reading my manuscript: BRCA1 Mutations in Women with Familial or Early-Onset Breast Cancer in Estonia. Please find the answers to your questions and comments, as follows:

Major compulsory revision

1. T.R.: “Table 2 is confusing. While the text mentions that 28 pedigrees (49 individuals) were included in the study, the Table has only 44 patients included. While the Table mentions that it provides information on mutation results in patients with family history, there are 16 patients in whom there is no family history at all of cancer. In addition, 11 patients have a family history of cancers other than breast and ovary.”

K.T.: “Concerning the question about Table 2, I shall start from the headline of Table 2 Individuals with alterations in BRCA1 gene and cancer incidence in their relatives from Estonia. I meant that the table contains only individuals with genetic alterations in the BRCA1 gene (44 individuals had some kind of alterations, 5 did not have). Also the table includes two groups of individuals (early-onset and familial), in column two (patient ID) is mentioned the familial cases (fam and number), all other cases are early-onset cases (number). Now I have remade the Table 2 as you suggest in point 4.”

2. T.R.: “Further, 4 subjects had no evidence of cancer but had BRCA1 mutation analysis done since family history of breast or ovarian cancers was present in their first or second degree relatives. Among these 4, only one has a pathogenic mutation (c.5385dupC) while the rest are all polymorphisms of no or unknown significance. Normally Predictive testing (testing an unaffected member in a family which has another member/members affected by cancer and carrying a deleterious mutation) is usually limited to the pathogenic mutation only. It does not seem clinically relevant to check for polymorphisms when they are of no or unknown clinical significance.”

K.T.: “In these 4 cases when the subject had no cancer and the relatives had cancer the mutation status was not known before the study. That is why we could not make predictive testing. These patients were included in the study and analyzed with the method of choice (SSCP-HD and sequencing).
3. T.R.:” Additionally, a new mutation c.5385dupC is mentioned in the Table for the first time. This mutation is not described in the BIC database as well. I am not sure whether this refers to c.5382insC.
K.T.: “c.5385dupC refers to c.5382insC, now I constantly use c.5382insC name.”

4. T.R.:“I would suggest a Table which lists only the clinically significant mutations along with other information such as family history, clinico-pathologic features of relevance. All the polymorphisms as mentioned earlier can be given separately excluding the family history, providing the frequency of detection only. The low rate of mutation detection in families is likely to be due to poor selection/eligibility criteria.”
K.T.:”I abide with your advise and I made new table from existing table 2. As the table 2 was confusing as you mentioned in your first question. New table 2 lists only the clinically significant mutations along with other information such as family history, clinico-pathologic features of relevance.

Minor Essential Revisions

T.R.:”The mutation/polymorphisms are not consistently named using the HUGO recommendation. This needs to be done both in the Text and in the Table”
K.T.:”I have corrected the mutation/polymorphisms names.”
T.R.:”The discussion can focus more on the pathogenic mutations, including clinico-pathological information on these patients.”
K.T.:”I have, included clinico-pathological information on these patients in the article text.”

I also shall bring to attention that reviewer Arvids Irmejas point out the following: “BRCA2 gene testing study could be done in young breast cancer group and in families with 3 or more cases of breast/ovarian cancer, in order to increase knowledge about hereditary cancer etiology in Estonia, because Estonia is geographically very close to Finland, where there are BRCA2 gene founder mutations confirmed." My answer to A.R. was:“We have data for BRCA2 mutations in familial cases I included these to the article. “
So, now I have included also the data about BRCA2 mutations in familial cases.

With kind regards,
Kristiina Tamboom
Corresponding author on behalf of the all co-authors.