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.

Authors:

Kristiina Tamboom (kristiinatamboom@hot.ee)
Krista Kaasik (kkaasik@yahoo.com)
Jelena Aršavskaja (Jelena@celecure.com)
Mare Tekkel (mare.tekkel@tai.ee)
Aili Lilleorg (aili.lilleorg@regionaalhaigla.ee)
Peeter Padrik (Peeter.Padrik@kliinikum.ee)
Andres Metspalu (andres@ebc.ee)
Toomas Veidebaum (toomas.veidebaum@tai.ee)

Version: 3 Date: 18 December 2009

Author's response to reviews:

Dear Thanagarajan Rajkumar,

Thank you for reading our manuscript: “BRCA1 mutations in women with familial or early-onset breast cancer and BRCA2 mutations in familial cancer in Estonia” again.

Please find the comments to your remarks as follows.

MAJOR COMPULSORY CORRECTIONS

T.R.” The Authors talk about Early onset cancer cases (<45 years) and the Familial cancer cases. Some of the early onset cases have a family history as well. It seems illogical to club them under early onset. It is well known that Hereditary cancers can affect women at an earlier age. They have done this for the BRCA2 case wherein a deleterious mutation was detected (c. 6190C>T) in a lady aged 36 years with breast cancer with 2 first degree and 1 second degree relative with breast cancer.”

K.T.” Please, let me introduce to you the background of grouping the patients as we did; we had two different studies which we put together to get a better overview of BRCA1 and BRCA2 mutations in Estonia. In one study, patients were collected based on family history (analyzed for BRCA1 and BRCA2) and the second group was collected based on early onset (<45 years) (analyzed for BRCA1). That is why we analyzed the data separately. The early onset patients were collected based only on the age of onset and they were asked to fill out questionnaires regarding family history, so some of them had a family history of breast or ovarian cancer and they may be grouped with the familial cases as you...
suggested.

T.R. “Hence, it would be essential to re-analyse the data, including the patients whose onset of disease was <45 years but with a family history as Familial cancers. This results in 6 deleterious mutations being seen in the familial cases (5 with family history of breast / ovarian cancers and <45 years of age; and 1 with family history of breast / ovarian cancers and >45 years of age). One individual had not developed any cancer but only had strong family history and was found to have a deleterious mutation. This is more of predictive testing and can be mentioned separately.”

K.T. “I have re-analyzed the data as you suggested. Now I have removed patients who had breast or ovary cancer in relatives (31 individuals) from the early-onset group and assigned them to the family history group. After that, 64 individuals remained in the early-onset group. Also, I have removed the predictive testing cases (33 individuals without cancer) from the family history group and assigned them to the predictive testing group.”

T.R. “Additionally, I am not still clear about their inclusion of 49 cases under the “Familial cases”. Do all the 49 individuals included have had breast or ovarian cancer? The Result section mentions that from the 28 pedigrees, 49 individuals were tested but only 17 had cancer and that the rest were high risk relatives. Are these high risk relatives, ones whose family member had been detected to have deleterious mutation or are they merely a member of a family which had several members affected? Either way, it is necessary to remove this group from the analysis, and only take patients who had developed cancer. The Predictive testing carried out on unaffected members whose family member carried a deleterious mutation can be mentioned separately”

K.T. “Familial cases were cases wherein the individual tested for BRCA1 and 2 had cancer and also had at least one relative with breast or ovarian cancer and cases where an individual without cancer was tested for BRCA1 and 2 and had at least two cases of breast or ovarian cancer in the family. Now I have removed the cases wherein the individual without cancer was tested for BRCA1 and 2 from the family history group and assigned them to the predictive testing group. The family history group now consists of the following: individuals who had breast or ovarian cancer (16 individuals) and patients from the early-onset group who had relatives with breast or ovarian cancer (31 individuals), a total of 47 individuals.”

T.R.” The authors will need to re-look at the 95 early onset cases and identify those with family history of breast and/or ovarian cancer. These patients will need to be
removed from the early onset group and brought under the familial cancer group.”
K.T." Now I have removed the patients who had relatives with breast or ovarian cancer (31 individuals) from the early-onset group and assigned them to the family history group. There are now 64 individuals remaining in the early-onset group." 

MINOR ESSENTIAL CORRECTIONS
T.R.
1. The terminologies used for relatives can be corrected – for e.g. instead of Mother’s Mother – Maternal Grandmother and so on.
2. There are several grammatical errors in the manuscript which will need to be corrected.
K.T." I have corrected the terminology and grammatical errors”

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