Author’s response to reviews

Title: Clinical and genetic characterization of hereditary breast cancer in a Chinese population

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Version: 1 Date: 02 Sep 2017

Author’s response to reviews:

Dear Dr. Scott,

Re: Manuscript reference No. HCCP-D-17-00011

Please find attached a revised version of our manuscript “Clinical and genetic characterization of hereditary breast cancer in a Chinese population”, which we would like to resubmit for publication in Hereditary Cancer in Clinical Practice.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages we provide point-by-point responses to each of the reviewer’s comments.

Revisions in the text are marked in red. As suggested by the reviewers we revised Table 3 and Table 4. We hope that the revised version of the manuscript will be suitable for publication in Hereditary Cancer in Clinical Practice.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

Xianming Wang
Reviewer #1:

1) Results, Characteristics of the study population, First sentence: "We recruited for this trial 120 patient diagnosed with breast cancer and 120 controls who had first-degree relatives affected by breast cancer." Please provide a rationale why this particular control group has been selected for the study. Currently, it appears to me that this control group might not be appropriate. The study results could be skewed due to the possibility that there is an increased likelihood that some individuals of the control group may harbour a mutation due to a family history of breast cancer.

Answer: We thank the reviewer for the suggestion. The main goal of our manuscript was to investigate genetic characterization of hereditary/familial breast cancer. We included 120 breast cancer patients with a history of familial breast cancer as a study group and we chose 120 healthy women who had first-degree relatives affected by breast cancer as a high-risk group. Using these two groups, we attempted to determine inherited susceptibility genes and probability of developing familial breast cancer. We compared mutation rates of susceptibility genes with the corresponding susceptibility genes rates of East Asian population in 1000 genomes project database which we chose as a control. All participants in 1000 genomes project declared themselves to be healthy at the time the samples were collected and had no associated medical or phenotype history.

2) The results in regards to the germline variant MUTYH c.892-2A>G is of interest. However, this result is mainly discussed in the context of what is already known from the scientific literature. A follow-up/additional studies on this variant would strengthen the scientific contribution of this paper.

Answer: Thank you for your suggestion. It is surprising that we found a higher mutation rate of MUTYH c.892-2A>G in the high-risk group with a history of familial breast cancer. Previous studies [1-4] have confirmed that MUTYH mutations are associated with the occurrence of multiple cancers. The molecular mechanisms of MUTYH mutation in colorectal cancer and MUTYH-associated polyposis have also been extensively studied. However, a correlation between MUTYH mutations and breast cancer (BC) is still not clear [3,5-10]. A study reported that MUTYH mutation frequency is higher in people with family history of BC and colorectal cancer, and found that heterozygous MUTYH mutation is associated with the phenotype of BC [7]. In contrast, other studies showed that MUTYH mutations were not associated with BC [5,8,10].

The MUTYH c.892-2A>G variant has not been studied in BC. Our study suggests that MUTYH c.892-2A>G is a benign variant in the development of BC. A. Two family pedigrees seem suggest segregation of this variant(Fig 1). The proband did not carry the variant, while their relatives with no BC carried it. We need to enlarge the sample size to confirm this result and to
establish potential relationship between this variant MUTYH c.892-2A>G and the development of BC.

Fig 1 Pedigree maps of two families. stands for MUTYH c.892-2A>G mutation. stands for that MUTYH c.892-2A>G mutation was not tested. stands for man. stands for woman. and stand for non-cancerous death. stands for patient with breast cancer. The black arrow indicates the proband. (BC: Breast cancer)

References


Reviewer #2:

1) This report assess the prevalence of a variety of germline variants in two populations, one that has a family history of breast cancer and a personal history of disease the other a population of health women who come from families with a history of breast cancer. The control population cannot be described as a control population as it is heavily biased in favour of genetic predispositions to breast cancer and as such should not be used for this study as it over-estimates the true incidence of causative variants in the population.

Answer: Please see above Answer one.

2) Much focus is put on the presence of MUTYH variants and little emphasis is placed on the recessive nature of disease associated with this gene.

Answer: Please see above Answer two.

3) All germline changes revealed by panel sequencing should be termed germline causative variants (if they are unequivocally so) and use of the 5-tier rating system should be incorporated into the manuscript.

Answer: We thank the reviewer for the suggestion. The 5-tier rating system contained the terms “pathogenic”, “likely pathogenic”, “uncertain significance”, “likely benign,” and “benign” preferred by ACMG. According to a five-tier terminology system, we have filtrated “likely benign”, “benign” and “uncertain significance” variant from all germline changes. And the specific “pathogenic” variant and “likely pathogenic” variant were listed in Table 3 and Table 4.
4) The authors have too few TNBC patients to make any meaningful statement about causative variant prevalence and as such should not attempt to state that the frequency of BRCA mutations in this group of patients is so high.

Answer: We thank the reviewer for this suggestion. TNBC patients have a poor prognosis with a high risk of distant metastasis and death within the first 3-5 years after the diagnosis [1] and at present there is no effective treatment available. Furthermore, it has been reported that TNBC can arise in BRCA1 mutation carriers [2-5] and the incidence of TNBC is approximately 70% for BRCA1 mutation carriers [6-7]. In our study eight of the 12 BRCA1/2 positive samples were in the TNBC group, consistent with this finding. But we agree with the reviewer that we need to enlarge the sample size.

References:


