Author’s response to reviews

Title: Circulating cancer stem cell markers in breast carcinomas: a systematic review protocol

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Reviewer reports:

Reviewer #2: This manuscript is to use systematic analysis to evaluate circulating cancer stem cell markers in breast carcinomas. Below are my comments:

1) Please clarify what CSC markers will be included in the outcome evaluation.

Reply:

-To reply the above comment, selected markers have been inserted in outcome section (page 6 line 195). These markers had been selected based on the preliminary search at the time of protocol registry, the search will be updated according to final search syntax and new markers will be added.

2) Please discuss in detail in the systematic review or/and meta-analysis, how the expression of the CSC markers will be normalized across different studies.

Reply:

-To reply the above comment, the following issues are mentioned for more clarification:

- From the clinical point of view, if we limit the systematic review to certain method, the comprehensiveness of the study and ability to discuss a variety of methods disappear.
- In this study, we identify all methods for identification and isolation of circulating breast CSC and review the results from everyone. This can specify and highlight the exist gap in this context for finding the appropriate methods which are suitable for identification and isolation of circulating cancer stem cell markers but they have not been used yet.

- The evaluation of studies will be performed if the sufficient number of studies of different methods will be available, or the expression of the marker will be verified by several methods.

- We do not insist on combining the results of different methods. The meta-analysis will be performed only about included case-control studies when appropriate as it is mentioned in the “STRATEGY FOR DATA SYNTHESIS” part in the manuscript. (page 7.line 245-246 and page 7 line 257-258)

- There is also some explanation about the case-control studies which are mentioned in the “ABSTRACT” and “RISK OF BIAS (QUALITY) ASSESSMENT” in the manuscript text. (page 1 line 34-36 and page 7 line 228-235)

3) Please discuss in detail the inclusion criteria for the methods of CSC identification and isolation for the included study.

Reply:

According to reviewer's comments, the methods of CSC identification and isolation have been illustrated in the inclusion criteria of the manuscript. (pages 4-6 line 145-190)

4) The goal of this study is to improve the identification of CSC in the cancer patients. However, in order to detect the CSC, different studies might use different methods and criteria. This sounds paradoxical. Please discuss the feasibility and rational of this study.

Reply:

Although there are different methods for identification and isolation of CSC in the breast carcinomas, we will categorize articles based on their methods and compare those which used same method to find out which marker has the higher expression among the reported markers, moreover it is possible to find the most popular method which is used for identification and isolation of CSC, to realize the expression pattern of circulating CSC markers in individual subtypes of breast carcinomas, to understand which method is more popular for detection the markers and to compare the methods with each other to find out which one is better according to their precisions. We will also realize which markers are validated with different techniques.

We also emphasize that we do not insist on combining the results of different methods the meta-analysis will be performed only about included case-control studies when appropriate as it is mentioned in the “STRATEGY FOR DATA SYNTHESIS” part in the manuscript. However it
won’t be possible to do meta-analysis due to the variations of methods unless the sufficient number of studies of different methods will be available