Author’s response to reviews

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

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Author’s response to reviews:

Reviewer reports:

> Reviewer #1: 1. There are two key questions to be addressed in the review. One is what the markers are, the other is the frequency. The latter needs be answered by studies with a control group, such as cohort and case-control. The authors may need to specify the control group in the inclusion criteria and the metrics such as RR, OR they plan to use in data synthesis.

Reply:

- The candidate markers according to preliminary search and references are mentioned in the manuscript, at the end of the background section (page 4 line 117 and 118)

- The OBJECTIVE, REVIEW QUESTIONS, INCLUSION CRITERIA and STRATEGY FOR DATA SYNTHESIS are revised in the manuscript based on the reviewer's comments. If the primary studies will be comparative form, the meta- analysis will be performed accordingly. (page 4 line125, line 131, line 146 and page 6 line 190)

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> 2. This is a relatively broad topic. In order to exhaust all the markers reported so far, the authors would need to make their search strategies sensitive enough. The authors might need to justify further the sensitivity and inclusiveness of the search terms they use for "cancer cells" and "markers" respectively.

Reply:
- According to reviewer's comments, and after consult with expert librarians, the word “marker” was added by "OR" in “pubmed search strategy”, so regardless of what marker is reported in the article, the related article will be included in search, therefor this will be sensitive enough and we do not miss any study. On the other hand, if we add just known markers to the search strategy by “AND”, new markers may not be entered into the search.

- For the sensitivity based on cancer cells, each study in cancer field has at least one of the following terms.

  \[(\text{tumor cell} \ OR \ \text{cancer stem cell} \ OR \ \text{initiating stem cell} \ OR \ \text{tumor initiating cell})\]

  However, we added the word “cancer cell” to the search strategy in the manuscript (page 5 line 163). In addition; we will conduct hand searching in key journals to find all relevant studies.

> 3. The authors should also describe more about the model they plan to use in data synthesis, such as fixed effect or random effect model along with the metrics as mentioned in point 1, as well as the criteria of using each of them.

Reply:

To reply the above comment, the following part has been revised in the manuscript, “STRATEGY FOR DATA SYNTHESIS”, (page 6 lines 194-196, page 6 line 201-205)

For studies with control group, we are planning to use meta-analysis to combine the results. We will present dichotomous outcomes as odds ratios with 95% confidence intervals (CI). Heterogeneity will be evaluated to determine the extent of variation in effect estimates due to heterogeneity rather than chance. The heterogeneity among the primary studies will be evaluated by a visual inspection of the forest plots, \(\chi^2\) test (with significance defined at \(\alpha\)-level of 10%) and \(I^2\) statistic. Categories of heterogeneity will be: \(\leq\)25% low, 26%–50% moderate, 51%–75% substantial, and \(\geq\)76% as considerable heterogeneity as defined by Higgins. For low and moderate level of heterogeneity we will use fixed-effect model and a random-effects model will be used in situations where the level of heterogeneity is substantial. If there is a considerable level of heterogeneity and the number of studies is enough, we will try to identify potential sources of heterogeneity by investigating individual studies and using meta-regression. Publication bias will be assessed by funnel plots and Egger’s test. Sensitivity analysis will be performed according to languages, quality of the studies, and differences in countries when appropriate.

> 4. It is noted that the authors mentioned the criteria they use to define statistical Heterogeneity. Nevertheless, the authors should be reminded that there are three types of heterogeneity, clinical,
methodological, and statistical heterogeneity. They should assess all the three aspects when evaluating the heterogeneity across the included studies.

Reply: In line with this valuable reviewer's comment, we will assess all of the three aspects of heterogeneity (clinical, methodological, and statistical) across the included studies in systematic review article.

> 5. The authors plan to use Begg's funnel plot and test to detect publication bias. Although this is still a widely used method, people who use it should be aware of its limitations and be cautious in their interpretations and conclusions. For example, change of metrics would change the shape of the plot; true heterogeneity and poor methodological quality could also lead to an asymmetric plot; statistical test for potential publication bias is usually lack of power (see Lau et al. The case of the misleading funnel plot. BMJ, 2006. Sterne et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analysis of randomized controlled trials.). The authors would need to reconsider these points when interpreting the funnel plot.

Reply:

In agreement with this valuable reviewer's comment, we will consider the limitations of Begg's funnel plot and its interpretations and conclusions in systematic review article.