PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of homologous recombination deficiency biomarkers on outcomes in patients with early breast cancer: a systematic review protocol
AUTHORS	Liao, Hao; Pei, Wendi; Zhong, Jianxin; Li, Huiping

VERSION 1 – REVIEW

REVIEWER	Espina, Virginia George Mason University
REVIEW RETURNED	22-Dec-2021

GENERAL COMMENTS	Homologous recombination repair deficiency promotes DNA damage and contributes to hereditary and non-hereditary breast cancer. BRCA1 and BRCA2 are well known tumor suppressor genes that are often mutated in hereditary breast cancer. This protocol is a systematic review of breast cancer outcomes with a subset of homologous recombination deficiency biomarkers. The goal is to facilitate the use of homologous recombination deficiency biomarkers in primary breast cancer. Comments to authors: 1. The types of studies, interventions/exposures, and evaluation indicators in this protocol are limited to a subset of homologous recombination deficiency (HRD) biomarkers. The interventions and evaluation indicators listed are limited to the HRD score, BRCA1/2 mutational status, and HRD status. However, the protocol title, abstract, and introduction refer generally to the broad category of “homologous recombination deficiency biomarkers”. “Biomarkers” is a general term that encompasses genes, proteins, transcripts (mRNA), protein expression, and protein localization. Furthermore, 15 other genes/proteins are well known to modulate homologous recombination repair, including CHK1, CHK2, ATM, ATR, PALB2, RAD51, and RAD54, all of which are biomarkers. The authors should refine the term “HRD biomarkers” by including the analytes and types of analyses that will be included in their study selection. The authors should also consider including studies analyzing protein biomarkers of homologous recombination repair. Examples where the broad “biomarkers” term is used include: Title Abstract line 39 Line 59 Line 65 2. Please list the dates of the study, specifically, what is the time frame of literature to be searched? The end date is December 2021. What is the beginning date?

	3. The search algorithm does not contain the phrases “biomarker, biomarkers, gene, or protein”. Please comment on the reason for excluding these potentially important phrases. 4. Introduction, line 68-69: The authors state that “Cells must undergo two genetic changes to become cancerous: activation of proto-oncogenes and inactivation of tumor suppressor genes[2]”. Many cancer cells do have multiple genetic mutations. However, this statement is not always true. An example is retinoblastoma in which there is a mutation only in the tumor suppressor gene RB1. Please revise this sentence.

REVIEWER	McIntosh, Stuart Queen's University Belfast, Centre for Cancer Research and Cell Biology
REVIEW RETURNED	02-Feb-2022

GENERAL COMMENTS	Thank you for asking me to review this protocol for a systematic review of biomrkers of HRD in patients with breast cancer. I agree that this is an important topic; there are currently no HRD biomarkers in clinical use to guide patient management in this context. I have a few relatively minor comments on the manuscript as it stands. The authors refer to primary breast cancer (PBC) throughout - however I take their aim to be to look at the use of HRD to guide therapy in the (neo)adjuvant setting in early breast cancer. It would be clearer I think if they referred to early breast cancer (EBC, i.e. non-metastatic disease) throughout. In the introduction they refer to the use of PARPis and platinums in advanced disease in gBRCA mutant cancer - but there is now evidence for a benefit for PARPi in high-risk gBRCA mutant EBC from the OympiA trial (Tutt, NEJM 2021). Given the emphasis on EBC in their systematic review they should probably consider adding this point to the discussion. Could they justify restricting the entry criteria to English language only? They state that "the treatment regimens in all studies included should be reasonable" but it's not clear what constitutes reasonable (or who will decide that they are reasonable) - perhaps this could be clarified? There are varying definitions of pCR in the literature - could they specify what they will use as a definition for the purpose of this review? ypT0/ypTis, ypN0 would appear a reasonable definition as it was considered by Cortazar et al in their meta-analysis of neoadjuvant treatment to be optimal. Data synthesis - what will constitute "sufficient studies" to justify meta-analysis?

VERSION 1 – AUTHOR RESPONSE

nt to the discussion.
Reply: Thanks for your kind reminder. I have added the point of the application of PARPi in high-risk gBRCA mutant EBC, “Moreover, based on the latest data from phase III OlympliaA trial, adjuvant olaparib was shown to significantly improve the primary endpoint of invasive Disease-free Survival (DFS) vs. placebo in patients with germline BRCA1/2-mutated high-risk EBC (3-year invasive DFS

rate: 85.9% vs. 77.1%; hazard ratio 0.58, 95% confidence interval 0.41-0.82, P<0.001)", see page 4 line 97-101 (manuscript without tracks).

3. Could they justify restricting the entry criteria to English language only?
Reply: Thanks for your comment. The reason why we restricted the entry criteria to English language was to improve the quality of literature and the efficiency of literature screening. But your question makes us realize that simply restricting language actually does not guarantee the quality of literature. So I have removed this restriction and stated that "Non-English articles potentially eligible for inclusion will be translated to obtain enough data" as you can see in page 6 line 160-161 (manuscript without tracks).

4. They state that "the treatment regimens in all studies included should be reasonable" but it's not clear what constitutes reasonable (or who will decide that they are reasonable) - perhaps this could be clarified?
Reply: Thanks for your suggestion, this would be helpful in improving the clarity of this protocol. I have revised this sentence to "The rationality of treatment regimens in all included studies will be confirmed by the lead author based on the recommendations of NCCN clinical practice guidelines", see page 6 line 161-163 (manuscript without tracks).

5. There are varying definitions of pCR in the literature - could they specify what they will use as a definition for the purpose of this review? ypT0/ypTis, ypN0 would appear a reasonable definition as it was considered by Cortazar et al in their meta-analysis of neoadjuvant treatment to be optimal.
Reply: Thanks for your advice. I have added this definition (ypT0/ypTis, ypN0) of pCR and cited the meta-analysis by Cortazar et al, see page 7 line 177-178 (manuscript without tracks).

6. Data synthesis - what will constitute "sufficient studies" to justify meta-analysis?
Reply: Sorry for this vague expression. Meta-analysis provides a method for taking advantage of the relevant information comprising the statistical significance tests in the studies, avoids the problems associated with using the statistical conclusions arising from individual tests, and does so in a transparent and replicable way. According to the study by Valentine et al, the minimal number of studies a meta-analysis requires is two [28 in the revised manuscript]. Therefore, I have stated in the Data synthesis section that "If there are more than two studies for one outcome, meta-analysis will be further conducted", see page 8 line 223-224 (manuscript without tracks).

Finally, your suggestions are very inspiring to us and extremely helpful to improve this protocol. Thanks again for your time, patience, and efficient work!

In the end, all authors really appreciate your assistance. It would be great honor if we can publish this protocol in your journal. If there are any questions, please do not hesitate to contact me.

VERSION 2 – REVIEW

REVIEWER	McIntosh, Stuart Queen's University Belfast, Centre for Cancer Research and Cell Biology
REVIEW RETURNED	29-Mar-2022

GENERAL COMMENTS	Thank you for addressing the points raised in my previous review. I am happy that these have been addressed and that the manuscript is suitable for publication.