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BMJ Open

Impact of homologous recombination deficiency biomarkers on outcomes in patients with primary breast cancer: a systematic review protocol

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SCHOLARONE™
Manuscripts

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6 2 **on outcomes in patients with primary breast cancer: a**
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8 3 **systematic review protocol**

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12 5 **Hao Liao,^{1†} Wendi Pei,^{2†} Jianxin Zhong,¹ Huiping Li^{1*}**
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20 21 **Words count:** 1693

21 22 **Number of figure:** 1
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26 **ABSTRACT**

27 **Introduction** Breast cancer patients with homologous recombination deficiency (HRD)
28 such as germline BRCA1/2 mutations would respond to DNA-damaging drugs. Several
29 clinical studies have revealed that HRD biomarkers were associated with the outcomes
30 of patients with primary breast cancer (PBC). However, no systematic review has
31 determined the prognostic role of HRD biomarkers in PBC patients. Therefore, this
32 study will systematically combine and analyze the results of previous studies, to
33 facilitate the clinical use of HRD detection in PBC.

34 **Methods and analysis** We will search five databases including PubMed, Cochrane
35 Library, EMBASE, OVID, and Web of Science through December 2021, with language
36 restriction of English. Two reviewers will independently screen all records based on
37 pre-established inclusion and exclusion criteria. The main outcomes include
38 pathological Complete Response, Disease-free Survival, and Overall Survival. In
39 addition, all studies included must contain the detection of HRD biomarkers. Data
40 extraction will be carried out by two reviewers independently according to a self-
41 designed template. The Newcastle-Ottawa Quality Assessment Scale and Jadad scale
42 will be used for quality assessment for cohort studies and randomized clinical trials,
43 respectively. Review Manager version 5.3.5 will be utilized to perform meta-analysis.
44 Both the Q test and I^2 statistic will be used to assess heterogeneity. Subgroup and
45 sensitivity analysis will be conducted if significant heterogeneity appears and cannot
46 be reduced by using a random-effect model.

47 **Ethics and dissemination** Ethical approval is not required for a systematic review. The
48 results will be disseminated through international and national conferences or peer-
49 reviewed publications.

50 **PROSPERO registration number** CRD42021286522.

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55 **Strengths and limitations of this study**

56 This systematic review will follow the Preferred Reporting Items for Systematic
57 Reviews and Meta-Analyses guidelines.

58 Stringent inclusion and exclusion criteria will be used to select clinical studies assessing
59 the impact of homologous recombination deficiency biomarkers on outcomes of
60 patients with primary breast cancer.

61 Internationally recognized scales will be used for the quality assessment, to exclude
62 low-quality studies and enhance the credibility of pooled results.

63 Only studies published in English will be included in this systematic review.

64 Differences in patient cohort, sample size, treatment regimen, and measure of
65 homologous recombination deficiency biomarkers may yield significant heterogeneity.

66 **INTRODUCTION**

67 Cancer refers to a disease in which cells divide uncontrollably and invade normal
68 tissues[1]. Cells must undergo two genetic changes to become cancerous: activation of
69 proto-oncogenes and inactivation of tumor suppressor genes[2]. Endogenous
70 (replication stress, oxygen radicals, and cell metabolism) and exogenous (radiation,
71 viral infection, and chemotherapy) damaging factors continually act on the genome of
72 cells and caused different degrees of DNA lesions[3]. And what protects organisms
73 from cancer is that cells have inherent repair mechanisms to eliminate these damaging
74 events. DNA damages that occur on a single strand are to be dealt with by a number of
75 simple repair pathways including base-excision repair (BER), nucleotide-excision
76 repair (NER), direct repair (DR), and mismatch repair (MMR). On the contrary, DNA
77 double-strand break (DSB), which is the most severe DNA lesion and the main driver
78 of cancer, requires sophisticated repair pathways such as NHEJ (non-homologous end
79 joining) and HR (homologous recombination)[4]. The HR system utilizes a
80 homologous sister chromatid (available in the S and G2 phases of cell cycle) as a
81 template to copy and replace damaged DNA in a relatively error-free manner compared
82 with NHEJ[5]. A number of key genes including BRCA1/2, RAD51, and PALB2 will
83 encode functional proteins and get involved in the process of repair[6]. If these genes

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4 84 are mutated, the HR system will fail to perform the repair function, which is so-called
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6 85 HR deficiency (HRD), leading to the accumulation of somatic mutations, chromosomal
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8 86 aberrations, and genomic scars (heritable genomic changes resulted from DNA repair
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10 87 defeat), as well as the development of cancer, especially breast cancer (BC)[7, 8].

11 88 BC is a highly heterogeneous disease and treated mainly based on the receptor
12
13 89 expression status. In recent years, with the development of sequencing technology and
14
15 90 our further understanding of genetic variation of cancer, numerous genes are being used
16
17 91 to screen for available therapeutic targets[9]. For example, DNA-damaging drugs such
18
19 92 as PARP inhibitors and platinums have been shown to significantly improve
20
21 93 Progression-free Survival in patients with advanced triple-negative BC (TNBC) with
22
23 94 germline BRCA1/2 mutations[10, 11]. Therefore, as key genes in the process of HR,
24
25 95 BRCA1/2 are generally detected to determine the HRD status of BC patients. However,
26
27 96 only 4% and 22% HRD can be attributed to germline BRCA1/2 mutations in BC and
28
29 97 TNBC, respectively[12-14]. On this condition, biomarkers with wider coverage are
30
31 98 needed to identify more BC patients with HRD. The HRD score is an algorithmic
32
33 99 assessment of three measures of loss of heterozygosity (LOH), large-scale transition
34
35 100 (LST), and telomeric allelic imbalance (TAI)[15]. This kind of assessment along with
36
37 101 BRCA mutation detection is now widely used to define the HRD status.

38
39 102 Several studies have investigated the prognostic role of HRD score in primary BC
40
41 103 (PBC)[16-19]. Telli et al assessed the HRD score in three neoadjuvant TNBC trials and
42
43 104 found that a HRD score ≥ 42 or the presence of BRCA1/2 mutations were correlated
44
45 105 with the objective response rate to platinum-based therapy[16]. SWOG S9313 is a
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47 106 phase III randomized study, comparing the efficacy of simultaneous anthracycline (A)
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49 107 and cyclophosphamide (C) and sequential A→C in more than 3000 stage I/II BC
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51 108 patients. Sharma et al investigated the prognostic role of HRD status in a subset of
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53 109 patients from SWOG S9313. The results indicated that HRD positive status was
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55 110 associated with better Disease-free Survival (DFS) (hazard ratio 0.72; 95% confidence
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57 111 interval 0.51–1.00; $P=0.049$)[17]. Significant associations between HRD positive
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59 112 status and higher pathological Complete Response (pCR) rates of PBC patients were
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113 also revealed in two studies by Loibl et al and Telli et al, respectively[18, 19]. Despite

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4 114 all the above efforts, the detection of HRD biomarkers has not been incorporated into
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6 115 the clinical practice of BC. In addition, no systematic review has explored the
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8 116 relationship between HRD biomarkers and the prognosis of PBC patients. Therefore,
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10 117 we will firstly systematically combine and analyze the results of previous studies in this
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12 118 study, to facilitate the clinical use of HRD detection in PBC.

13 14 119 **METHODS AND ANALYSIS**

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16 120 This systematic review will be conducted and reported according to the Preferred
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18 121 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020
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20 122 statement[20]. This review's protocol has been registered in the International
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22 123 Prospective Register of Systematic Reviews.

23 24 124 **Search strategy**

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26 125 Five databases including PubMed, Cochrane Library, EMBASE, OVID, and Web of
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28 126 Science will be searched through December 2021, with language restriction of English.
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30 127 Medical Subject Headings and free text will be combined to search for concepts such
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32 128 as 'Breast Neoplasms' and 'Primary' and 'Recombinational DNA Repair'. The detailed
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34 129 example of the search strategy applied in PubMed is available in online **Supplemental**
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36 130 **File 1**. In addition, we will search the reference lists of recognized studies to identify
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38 131 additional papers.

39 40 132 **Study selection**

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42 133 All records identified through database searching will be imported into EndNote
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44 134 version 9.1 software. Firstly, duplicates will be removed using the built-in recognition
45
46 135 function of the software by the lead author. Then, all records will be screened by two
47
48 136 reviewers independently according to the title and abstracts. After that, the potentially
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50 137 relevant full-text articles will be reviewed by the same two reviewers independently
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52 138 based on pre-established inclusion and exclusion criteria. Finally, the remaining full-
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54 139 text articles will be assessed for eligibility by the team. Disagreements between the two
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56 140 reviewers will be settled by discussion. The particular reason for exclusion of each
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58 141 reviewed article will be recorded and presented in the final manuscript. In addition, the
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4 142 reference lists of recognized studies will be searched to make sure that no potentially
5 143 eligible article is missed.

8 144 **Inclusion criteria**

10 145 **Types of studies**

12 146 Clinical studies investigating the impact of HRD biomarkers (HRD score, BRCA1/2
13 147 mutational status, and HRD status) on outcomes in patients with PBC will be included.

15 148 This review will only include articles published in English, with no restriction of date.

17 149 The treatment regimens in all studies included should be reasonable. For studies
18 150 involving grouping, the treatment regimen received by patients in each group should be
19 151 comparable.

23 152 **Types of participants**

24 153 Patients with histologically confirmed PBC.

27 154 **Interventions/exposures**

28 155 High HRD score, positive BRCA1/2 mutational status, and positive HRD status.

30 156 Specifically, the assessment of HRD score should include three measures of tumor
31 157 genomic instability (LOH, LST, and TAI), with a cutoff of 42[16].

33 158 **Comparators/control**

34 159 Low HRD score, negative BRCA1/2 mutational status, and negative HRD status.

37 160 **Main outcomes**

38 161 Each study should contain at least one of the following outcomes:

- 40 162 1. pCR: after neoadjuvant therapy, the lesions disappeared completely, or all symptoms
41 163 and signs of unmeasurable lesions disappeared completely;
- 42 164 2. DFS: the time from randomization to disease recurrence or death due to disease
43 165 progression;
- 44 166 3. Overall Survival (OS): the time from randomization to death from any cause.

47 167 **Exclusion criteria**

48 168 Articles that meet the following criteria will be excluded:

- 49 169 1. Non-clinical studies including reviews, conference abstracts, case reports and series,
50 170 and comments;

- 171 2. Patients with metastatic or advanced BC;
- 172 3. No detection of HRD, wrong evaluation methods of HRD score, or other cutoff
- 173 values;
- 174 4. Non-human experiments.

175 **Data extraction**

176 Two reviewers will independently extract data from the included studies into a self-
177 designed data extraction template. If some important data are not available in the
178 articles, we will make contact with the first or corresponding authors for potential
179 support. Differences in opinion between the two reviewers will be settled by discussion.
180 The study selection process is shown in **Figure 1**. The following study characteristics
181 will be collected:

182 **Study details**

183 First author, year of publication, country/region, study design, and setting (neoadjuvant
184 and adjuvant);

185 **Patients characteristics**

186 Patient subtype (hormone receptor-positive, human epidermal growth factor receptor
187 2-positive, and TNBC), number of patients, and treatment regimen;

188 **Evaluation indicators**

189 Main outcomes (pCR, DFS, and OS), HRD biomarkers (HRD score, BRCA1/2
190 mutational status, and HRD status), and score of quality assessment.

191 **Quality assessment**

192 Two reviewers will independently conduct quality assessment using the Newcastle-
193 Ottawa Quality Assessment Scale (NOS) for cohort studies and Jadad scale for
194 randomized clinical trials, respectively[21, 22]. The NOS consists of three key items:
195 1. Selection; 2. Comparability; and 3. Outcome. One point will be added when there is
196 enough support information for an item. One study that obtains at least 6 points will be
197 considered as high quality, with a full score of 9 points[21]. The Jadad scale includes
198 four key items: 1. Randomization; 2. Double blinding; 3. Concealment of allocation;
199 and 4. Withdrawals and dropouts. If the description of one item is described and

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4 200 appropriate, two points will be added to this item. On the contrary, if the description is
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6 201 not described or inappropriate, the score for this item will be zero. If the rating falls
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8 202 between the two situations, one point will be added. Specially, for the item of
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10 203 withdrawals and dropouts, only 1 and 0 point can be chosen. The full score of Jadad
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12 204 scale is 7 points, and a score of more than 3 points means high quality[22].

13 14 205 **Statistical analysis**

15 16 206 **Data synthesis**

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18 207 All data will be synthesized narratively and quantitatively. If there are sufficient studies,
19
20 208 meta-analysis will be further conducted. Otherwise, we will only carry out systematic
21
22 209 review with descriptive analysis. Review Manager version 5.3.5 (Cochrane
23
24 210 Collaboration, Oxford, UK) will be used to pool the results. Odds ratios and hazard
25
26 211 ratios along with 95% confidence intervals will be calculated using the Mantel–
27
28 212 Haenszel method and inverse variance method, respectively. Forest plots will be used
29
30 213 to present the pooled results. For all statistical tests, a two-tailed *P*-value of <0.05 will
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32 214 be considered statistically significant.

33 34 215 **Heterogeneity assessment**

35
36 216 Before pooling the results, both the *Q* test and *I*² statistic will be used to assess
37
38 217 heterogeneity. A *P*-value of <0.1 and an *I*² value of >50% indicate significant
39
40 218 heterogeneity across studies. A fixed-effect model will be used unless considerable
41
42 219 heterogeneity arises. Alternatively, a random-effect model will be used.

43 44 220 **Subgroup and sensitivity analysis**

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46 221 If significant heterogeneity appears and cannot be reduced by using a random-effect
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48 222 model, subgroup analysis or sensitivity analysis will be conducted to find possible
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50 223 source of heterogeneity. The grouping methods of subgroup analysis will be based on
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52 224 the study characteristics, patient subtypes, chemotherapy regimens, or HRD detection
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54 225 methods, while the sensitivity analysis will be conducted by omitting the data of
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56 226 individual studies. The potential source of heterogeneity can be identified if the
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58 227 heterogeneity decreases significantly when carrying out subgroup analysis based on one
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60 228 factor or discarding data from one study.

229 **Publication bias**

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4 230 Stata version 12.0 (Stata Corporation, College Station, TX, USA) will be used to
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6 231 evaluate potential publication bias using Egger's and Begg's test. A *P*-value of <0.05
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8 232 will be considered a significant publication bias.

233 **Patient and public involvement**

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12 234 Patients and/or the public are not involved in the design, conduct, reporting or
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14 235 dissemination plans of this research.

236 **ETHICS AND DISSEMINATION**

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18 237 Ethical approval is not required in this study because no data are related to an individual
19
20 238 patient. The results will be disseminated through international and national conferences
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22 239 or peer-reviewed publications.

23
24 240 **Author contributions** HaL, WP, and JZ were responsible for the conception of the
25
26 241 study plan, and preparation of the manuscript. HuL reviewed the study plan and
27
28 242 manuscript and offered comments and edits.

29
30 243 **Funding** None.

31
32 244 **Competing interests** None declared.

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34 245 **Patient consent for publication** Not required.

35
36 246 **Data sharing** No additional data available.

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46 251 appropriate credit is given, any changes made indicated, and the use is non-commercial.
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323 **Figure legend**

324 **Figure 1** Flow diagram of study selection process.

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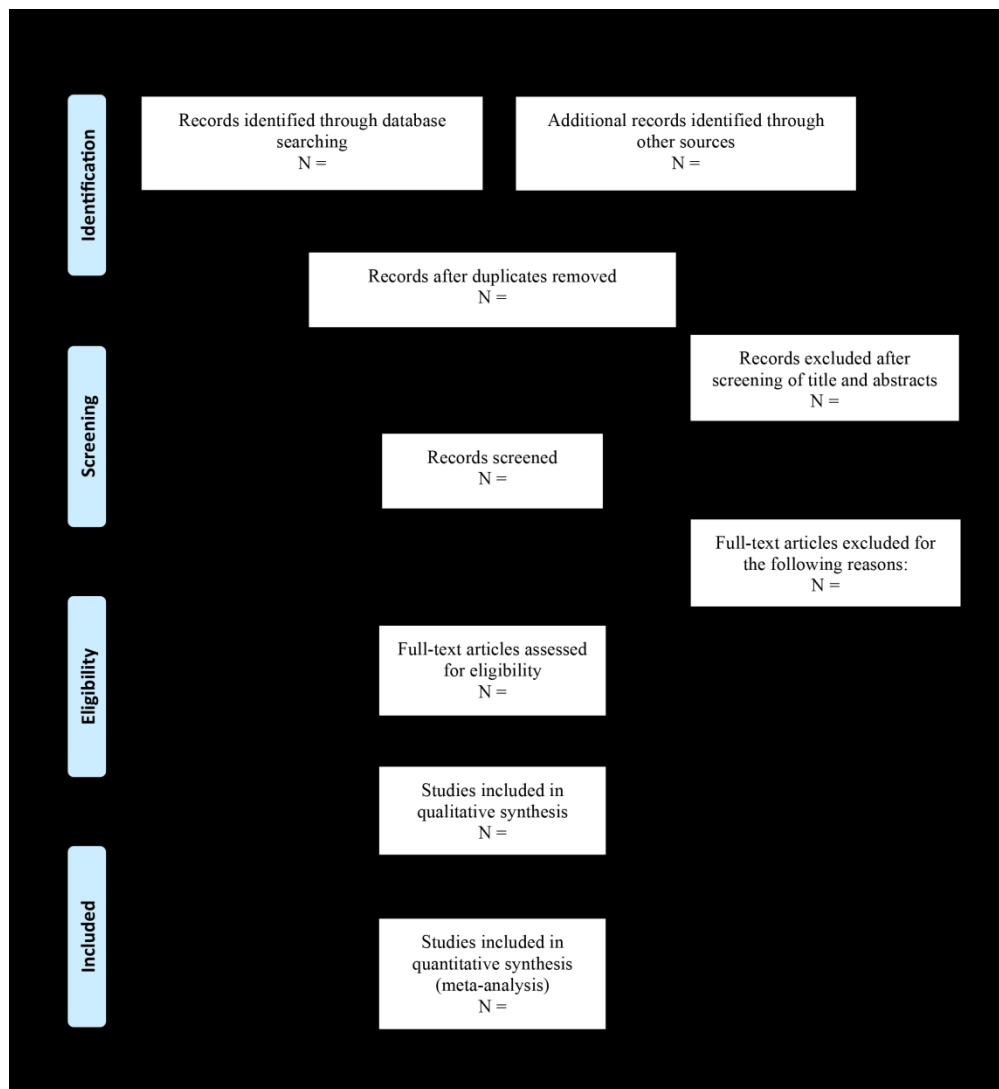


Figure 1 Flow diagram of study selection process.

Sources:**Total N =**

PubMed N =

Cochrane Library N =

EMBASE N =

OVID N =

Web of Science N =

Other sources N =

N records after duplications removed**N records after screening of titles and abstracts****N records after further evaluation** (N records were excluded for the following reasons: Non-clinical studies; Patients with metastatic or advanced BC; No detection of HRD, wrong evaluation methods of HRD score, or other cutoff values; and Non-human studies)**N records included in qualitative synthesis****N records included in quantitative synthesis (meta-analysis)**



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Line 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Line 7
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Line 102
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Line 114
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Line 144
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Line 124
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Line 124
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Line 132
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Line 175
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Line 182
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Line 182
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Line 191
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Line 206
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Line 206
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Line 206
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Line 206
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Line 206
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Line 215
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Line 220
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	NA
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	NA
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	NA
	23b	Discuss any limitations of the evidence included in the review.	NA
	23c	Discuss any limitations of the review processes used.	NA
	23d	Discuss implications of the results for practice, policy, and future research.	NA
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Line 50
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Line 243
Competing interests	26	Declare any competing interests of review authors.	Line 244
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA



PRISMA 2020 Checklist

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BMJ Open

Impact of homologous recombination deficiency biomarkers on outcomes in patients with early breast cancer: a systematic review protocol

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Primary Subject Heading:	Oncology
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Keywords:	Breast tumours < ONCOLOGY, Adult oncology < ONCOLOGY, Cancer genetics < GENETICS

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4 1 **Impact of homologous recombination deficiency biomarkers**
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12 5 **Hao Liao,^{1†} Wendi Pei,^{2†} Jianxin Zhong,¹ Huiping Li^{1*}**
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17 9 Hospital and Institute, Beijing, China,
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19 2 Center for Reproductive Medicine, Department of Obstetrics and Gynecology,
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26 27
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30 16

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26 **ABSTRACT**

27 **Introduction** Breast cancer patients with homologous recombination deficiency (HRD)
28 such as germline BRCA1/2 mutations would respond to DNA-damaging drugs. Several
29 clinical studies have revealed that HRD biomarkers were associated with the outcomes
30 of patients with early breast cancer (EBC). However, no systematic review has
31 determined the prognostic role of HRD biomarkers in EBC patients. Therefore, this
32 study will systematically combine and analyze the results of previous studies, to
33 facilitate the clinical use of HRD detection in EBC.

34 **Methods and analysis** We will search five databases including PubMed, Cochrane
35 Library, EMBASE, OVID, and Web of Science through December 2021, with no
36 language restriction. Two reviewers will independently screen all records based on pre-
37 established inclusion and exclusion criteria. The main outcomes include pathological
38 Complete Response, Disease-free Survival, and Overall Survival. In addition, all
39 studies included must contain the detection of HRD score, HRD status, or HRD-related
40 gene mutational status and protein expression. Data extraction will be carried out by
41 two reviewers independently according to a self-designed template. The Newcastle-
42 Ottawa Quality Assessment Scale and Jadad scale will be used for quality assessment
43 for cohort studies and randomized clinical trials, respectively. Review Manager version
44 5.3.5 will be utilized to perform meta-analysis. Both the Q test and I^2 statistic will be
45 used to assess heterogeneity. Subgroup and sensitivity analysis will be conducted if
46 significant heterogeneity appears and cannot be reduced by using a random-effect
47 model.

48 **Ethics and dissemination** Ethical approval is not required for a systematic review. The
49 results will be disseminated through international and national conferences or peer-
50 reviewed publications.

51 **PROSPERO registration number** CRD42021286522.

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55 **Strengths and limitations of this study**

56 This systematic review will follow the Preferred Reporting Items for Systematic
57 Reviews and Meta-Analyses guidelines.

58 Stringent inclusion and exclusion criteria will be used to select clinical studies assessing
59 the impact of homologous recombination deficiency (HRD) biomarkers (HRD score,
60 HRD status, and HRD-related gene mutational status and protein expression) on
61 outcomes of patients with early breast cancer.

62 Internationally recognized scales will be used for the quality assessment, to exclude
63 low-quality studies and enhance the credibility of pooled results.

64 Differences in patient cohort, sample size, treatment regimen, and measure of
65 homologous recombination deficiency biomarkers may yield significant heterogeneity.

66 **INTRODUCTION**

67 Cancer refers to a disease in which cells divide uncontrollably and invade normal
68 tissues[1]. In the pathogenesis of most cancers, normal cells need to undergo certain
69 genetic changes to become cancerous such as activation of proto-oncogenes and
70 inactivation of tumor suppressor genes[2]. For example, the occurrence of
71 retinoblastoma is often accompanied by the mutation of the tumor suppressor gene
72 RB1[3]. Endogenous (replication stress, oxygen radicals, and cell metabolism) and
73 exogenous (radiation, viral infection, and chemotherapy) damaging factors continually
74 act on the genome of cells and caused different degrees of DNA lesions[4]. And what
75 protects organisms from cancer is that cells have inherent repair mechanisms to
76 eliminate these damaging events. DNA damages that occur on a single strand are to be
77 dealt with by a number of simple repair pathways including base-excision repair (BER),
78 nucleotide-excision repair (NER), direct repair (DR), and mismatch repair (MMR). On
79 the contrary, DNA double-strand break (DSB), which is the most severe DNA lesion
80 and the main driver of cancer, requires sophisticated repair pathways such as NHEJ
81 (non-homologous end joining) and HR (homologous recombination)[5]. The HR
82 system utilizes a homologous sister chromatid (available in the S and G2 phases of cell
83 cycle) as a template to copy and replace damaged DNA in a relatively error-free

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4 84 manner compared with NHEJ[6]. A number of key genes including BRCA1/2, RAD51,
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6 85 and PALB2 will encode functional proteins and get involved in the process of repair[7].
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8 86 If these genes are mutated, the HR system will fail to perform the repair function, which
9
10 87 is so-called HR deficiency (HRD), leading to the accumulation of somatic mutations,
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12 88 chromosomal aberrations, and genomic scars (heritable genomic changes resulted from
13
14 89 DNA repair defeat), as well as the development of cancer, especially breast cancer
15
16 90 (BC)[8, 9].

17
18 91 BC is a highly heterogeneous disease and treated mainly based on the receptor
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20 92 expression status. In recent years, with the development of sequencing technology and
21
22 93 our further understanding of genetic variation of cancer, numerous genes are being used
23
24 94 to screen for available therapeutic targets[10]. For example, DNA-damaging drugs such
25
26 95 as PARP inhibitors and platinums have been shown to significantly improve
27
28 96 Progression-free Survival in patients with advanced triple-negative BC (TNBC) with
29
30 97 germline BRCA1/2 mutations[11, 12]. Moreover, based on the latest data from phase
31
32 98 III OlympiA trial, adjuvant olaparib was shown to significantly improve the primary
33
34 99 endpoint of invasive Disease-free Survival (DFS) vs. placebo in patients with germline
35
36 100 BRCA1/2-mutated high-risk EBC (3-year invasive DFS rate: 85.9% vs. 77.1%; hazard
37
38 101 ratio 0.58, 95% confidence interval 0.41-0.82, $P<0.001$)[13]. Therefore, as key genes
39
40 102 in the process of HR, BRCA1/2 are generally detected to determine the HRD status of
41
42 103 BC patients. However, only 4% and 22% HRD can be attributed to germline BRCA1/2
43
44 104 mutations in BC and TNBC, respectively[14-16]. On this condition, biomarkers with
45
46 105 wider coverage are needed to identify more BC patients with HRD. The HRD score is
47
48 106 an algorithmic assessment of three measures of loss of heterozygosity (LOH), large-
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50 107 scale transition (LST), and telomeric allelic imbalance (TAI)[17]. This kind of
51
52 108 assessment along with BRCA mutation detection is now widely used to define the HRD
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54 109 status.

55
56 110 Several studies have investigated the prognostic role of HRD score in early BC
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58 111 (EBC)[18-21]. Telli et al assessed the HRD score in three neoadjuvant TNBC trials and
59
60 112 found that a HRD score ≥ 42 or the presence of BRCA1/2 mutations were correlated

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4 113 with the objective response rate to platinum-based therapy[18]. SWOG S9313 is a
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6 114 phase III randomized study, comparing the efficacy of simultaneous anthracycline (A)
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8 115 and cyclophosphamide (C) and sequential A→C in more than 3000 stage I/II BC
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10 116 patients. Sharma et al investigated the prognostic role of HRD status in a subset of
11
12 117 patients from SWOG S9313. The results indicated that HRD positive status was
13
14 118 associated with better DFS (hazard ratio 0.72, 95% confidence interval 0.51–1.00,
15
16 119 $P=0.049$)[19]. Significant associations between HRD positive status and higher
17
18 120 pathological Complete Response (pCR) rates of EBC patients were also revealed in two
19
20 121 studies by Loibl et al and Telli et al, respectively[20, 21]. Despite all the above efforts,
21
22 122 the detection of HRD biomarkers has not been incorporated into the clinical practice of
23
24 123 BC. In addition, no systematic review has explored the relationship between HRD
25
26 124 biomarkers and the prognosis of EBC patients. Therefore, we will firstly systematically
27
28 125 combine and analyze the results of previous studies in this study, to facilitate the clinical
29
30 126 use of HRD detection in EBC.

31 127 **METHODS AND ANALYSIS**

32
33 128 This systematic review is expected to begin on December 1, 2021 and end on June 30,
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35 129 2022 and will be conducted and reported according to the Preferred Reporting Items
36
37 130 for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[22]. This
38
39 131 review's protocol has been registered in the International Prospective Register of
40
41 132 Systematic Reviews.

42 43 133 **Search strategy**

44
45 134 Five databases including PubMed, Cochrane Library, EMBASE, OVID, and Web of
46
47 135 Science will be searched from December 1, 2021 to March 31, 2022, with no language
48
49 136 restriction. Medical Subject Headings and free text will be combined to search for
50
51 137 concepts such as 'Breast Neoplasms' and 'Early' and 'Recombinational DNA Repair'
52
53 138 and 'Biomarkers'. The detailed example of the search strategy applied in PubMed is
54
55 139 available in online **Supplemental File 1**. In addition, we will search the reference lists
56
57 140 of recognized studies to identify additional papers.
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141 **Study selection**

142 All records identified through database searching will be imported into EndNote
143 version 9.1 software. Firstly, duplicates will be removed using the built-in recognition
144 function of the software by the lead author. Then, all records will be screened by two
145 reviewers independently according to the title and abstracts. After that, the potentially
146 relevant full-text articles will be reviewed by the same two reviewers independently
147 based on pre-established inclusion and exclusion criteria. Finally, the remaining full-
148 text articles will be assessed for eligibility by the team. Disagreements between the two
149 reviewers will be settled by discussion. The particular reason for exclusion of each
150 reviewed article will be recorded and presented in the final manuscript. In addition, the
151 reference lists of recognized studies will be searched to make sure that no potentially
152 eligible article is missed.

153 **Inclusion criteria**

154 **Types of studies**

155 Clinical studies investigating the impact of HRD biomarkers (HRD score, HRD status,
156 and HRD-related gene mutational status and protein expression) on outcomes in
157 patients with EBC will be included. Concretely, the HRD-related genes/proteins mainly
158 include ATM, ATR, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, MRE11A,
159 NBN, PALB2, RAD51C, RAD51D, RBBP8, SLX4, and XRCC2[23]. This review will
160 include articles published in any language, with no restriction of date. Non-English
161 articles potentially eligible for inclusion will be translated to obtain enough data. The
162 rationality of treatment regimens in all included studies will be confirmed by the lead
163 author based on the recommendations of NCCN clinical practice guidelines[24]. For
164 studies involving grouping, the treatment regimen received by patients in each group
165 should be comparable.

166 **Types of participants**

167 Patients with histologically confirmed EBC.

168 **Interventions/exposures**

169 High HRD score, positive HRD status, positive gene mutational status, and positive

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4 170 protein expression. Specifically, the assessment of HRD score should include three
5 171 measures of tumor genomic instability (LOH, LST, and TAI), with a cutoff of 42[18].

172 **Comparators/control**

173 Low HRD score, negative HRD status, negative gene mutational status, and loss of
174 protein expression.

175 **Main outcomes**

176 Each study should contain at least one of the following outcomes:

- 177 1. pCR: no invasive carcinoma in primary site and negative regional lymph node
178 (ypT0/ypTis ypN0) after neoadjuvant therapy[25];
- 179 2. DFS: the time from randomization to disease recurrence or death due to disease
180 progression;
- 181 3. Overall Survival (OS): the time from randomization to death from any cause.

182 **Exclusion criteria**

183 Articles that meet the following criteria will be excluded:

- 184 1. Non-clinical studies including reviews, conference abstracts, case reports and series,
185 and comments;
- 186 2. Patients with metastatic or advanced BC;
- 187 3. No detection of HRD, wrong evaluation methods of HRD score, or other cutoff
188 values;
- 189 4. Non-human experiments.

190 **Data extraction**

191 Two reviewers will independently extract data from the included studies into a self-
192 designed data extraction template. If some important data are not available in the
193 articles, we will make contact with the first or corresponding authors for potential
194 support. Differences in opinion between the two reviewers will be settled by discussion.
195 The study selection process is shown in **Figure 1**. The following study characteristics
196 will be collected:

197 **Study details**

198 First author, year of publication, country/region, study design, and setting (neoadjuvant

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4 199 and adjuvant);

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6 200 **Patients characteristics**

7 201 Patient subtype (hormone receptor-positive, human epidermal growth factor receptor
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9 202 2-positive, and TNBC), number of patients, and treatment regimen;

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11 203 **Evaluation indicators**

12
13 204 Main outcomes (pCR, DFS, and OS), HRD biomarkers (HRD score, HRD status, and
14
15 205 HRD-related gene mutational status and protein expression), and score of quality
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17 206 assessment.

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19 207 **Quality assessment**

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21 208 Two reviewers will independently conduct quality assessment using the Newcastle-
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23 209 Ottawa Quality Assessment Scale (NOS) for cohort studies and Jadad scale for
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25 210 randomized clinical trials, respectively[26, 27]. The NOS consists of three key items:

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27 211 1. Selection; 2. Comparability; and 3. Outcome. One point will be added when there is
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29 212 enough support information for an item. One study that obtains at least 6 points will be
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31 213 considered as high quality, with a full score of 9 points[26]. The Jadad scale includes
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33 214 four key items: 1. Randomization; 2. Double blinding; 3. Concealment of allocation;
34
35 215 and 4. Withdrawals and dropouts. If the description of one item is described and
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37 216 appropriate, two points will be added to this item. On the contrary, if the description is
38
39 217 not described or inappropriate, the score for this item will be zero. If the rating falls
40
41 218 between the two situations, one point will be added. Specially, for the item of
42
43 219 withdrawals and dropouts, only 1 and 0 point can be chosen. The full score of Jadad
44
45 220 scale is 7 points, and a score of more than 3 points means high quality[27].

46
47 221 **Statistical analysis**

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49 222 **Data synthesis**

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51 223 All data will be synthesized narratively and quantitatively. If there are more than two
52
53 224 studies for one outcome, meta-analysis will be further conducted[28]. Otherwise, we
54
55 225 will only carry out systematic review with descriptive analysis. Review Manager
56
57 226 version 5.3.5 (Cochrane Collaboration, Oxford, UK) will be used to pool the results.
58
59 227 Odds ratios and hazard ratios along with 95% confidence intervals will be calculated

228 using the Mantel–Haenszel method and inverse variance method, respectively. Forest
229 plots will be used to present the pooled results. For all statistical tests, a two-tailed *P*-
230 value of <0.05 will be considered statistically significant.

231 **Heterogeneity assessment**

232 Before pooling the results, both the *Q* test and *I*² statistic will be used to assess
233 heterogeneity. A *P*-value of <0.1 and an *I*² value of >50% indicate significant
234 heterogeneity across studies. A fixed-effect model will be used unless considerable
235 heterogeneity arises. Alternatively, a random-effect model will be used.

236 **Subgroup and sensitivity analysis**

237 If significant heterogeneity appears and cannot be reduced by using a random-effect
238 model, subgroup analysis or sensitivity analysis will be conducted to find possible
239 source of heterogeneity. The grouping methods of subgroup analysis will be based on
240 the study characteristics, patient subtypes, chemotherapy regimens, or HRD detection
241 methods, while the sensitivity analysis will be conducted by omitting the data of
242 individual studies. The potential source of heterogeneity can be identified if the
243 heterogeneity decreases significantly when carrying out subgroup analysis based on one
244 factor or discarding data from one study.

245 **Publication bias**

246 Stata version 12.0 (Stata Corporation, College Station, TX, USA) will be used to
247 evaluate potential publication bias using Egger's and Begg's test. A *P*-value of <0.05
248 will be considered a significant publication bias.

249 **Patient and public involvement**

250 Patients and/or the public are not involved in the design, conduct, reporting or
251 dissemination plans of this research.

252 **ETHICS AND DISSEMINATION**

253 Ethical approval is not required in this study because no data are related to an individual
254 patient. The results will be disseminated through international and national conferences
255 or peer-reviewed publications.

256 **Author contributions** HaL, WP, and JZ were responsible for the conception of the

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3
4 257 study plan, and preparation of the manuscript. HuL reviewed the study plan and
5
6 258 manuscript and offered comments and edits.

7
8 259 **Funding** None.

9
10 260 **Competing interests** None declared.

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12 261 **Patient consent for publication** Not required.

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14 262 **Data sharing** No additional data available.

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24 267 appropriate credit is given, any changes made indicated, and the use is non-commercial.
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26 268 See: <http://creativecommons.org/licenses/by-nc/4.0/>.

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4 **355 Figure legend**

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6 **356 Figure 1** Flow diagram of study selection process.
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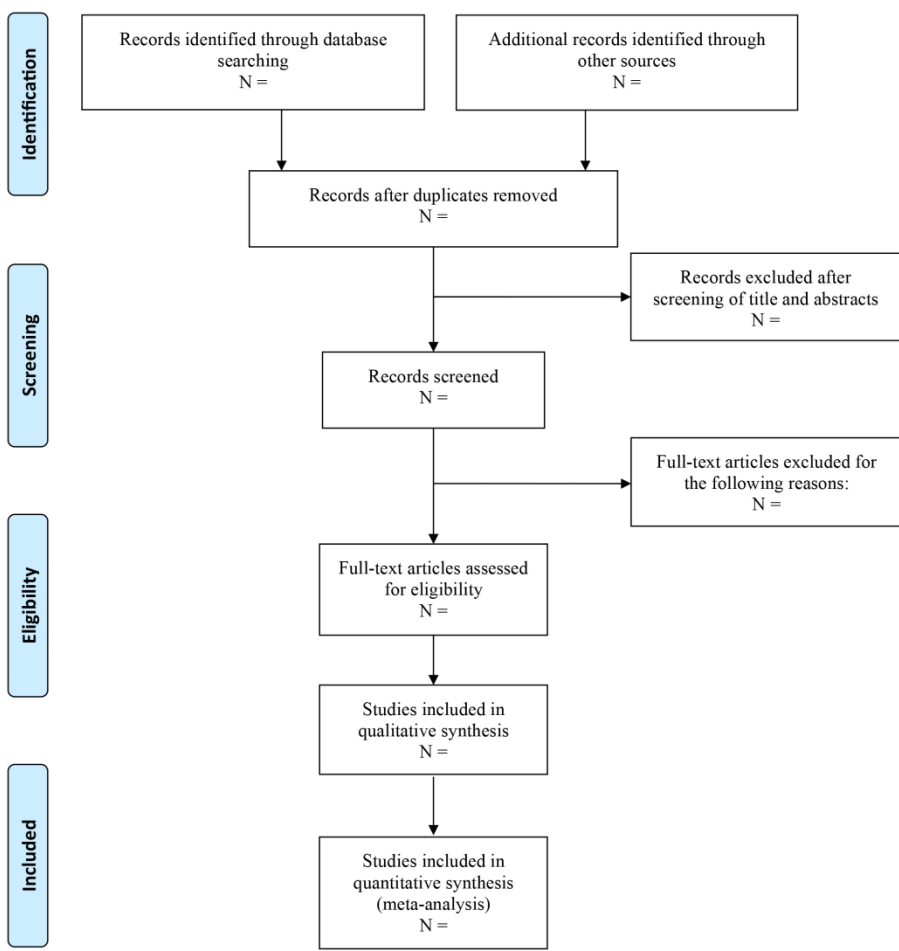


Figure 1 Flow diagram of study selection process.

Main search algorithm:

(((("Breast Neoplasms"[Mesh]) OR (((((((((((((((((((((((((((((((((((((((Breast Neoplasm)
 OR (Neoplasm, Breast)) OR (Breast Tumors)) OR (Breast Tumor)) OR (Tumor, Breast))
 OR (Tumors, Breast)) OR (Neoplasms, Breast)) OR (Breast Cancer)) OR (Cancer,
 Breast)) OR (Mammary Cancer)) OR (Cancer, Mammary)) OR (Cancers, Mammary))
 OR (Mammary Cancers)) OR (Malignant Neoplasm of Breast)) OR (Breast Malignant
 Neoplasm)) OR (Breast Malignant Neoplasms)) OR (Malignant Tumor of Breast)) OR
 (Breast Malignant Tumor)) OR (Breast Malignant Tumors)) OR (Cancer of Breast)) OR
 (Cancer of the Breast)) OR (Mammary Carcinoma, Human)) OR (Carcinoma, Human
 Mammary)) OR (Carcinomas, Human Mammary)) OR (Human Mammary
 Carcinomas)) OR (Mammary Carcinomas, Human)) OR (Human Mammary
 Carcinoma)) OR (Mammary Neoplasms, Human)) OR (Human Mammary Neoplasm))
 OR (Human Mammary Neoplasms)) OR (Neoplasm, Human Mammary)) OR
 (Neoplasms, Human Mammary)) OR (Mammary Neoplasm, Human)) OR (Breast
 Carcinoma)) OR (Breast Carcinomas)) OR (Carcinoma, Breast)) OR (Carcinomas,
 Breast))) AND ((((((Primary) OR (Early)) OR (Operable)) OR (Resectable)) OR
 (Curable)) OR (Non-metastatic)) OR (Non-advanced))) AND (("Recombinational
 DNA Repair"[Mesh]) OR (((((((((((((((((((((((((((((((((((((((Recombinational DNA Repair) OR (DNA
 Repair, Recombinational)) OR (Repair, Recombinational DNA)) OR (Recombinational
 Repair of DNA)) OR (DNA Recombinational Repair)) OR (Homologous
 Recombinational Repair)) OR (Homologous Recombinational Repairs)) OR
 (Recombinational Repair, Homologous)) OR (Repair, Homologous Recombinational))
 OR (Homologous Recombination Repair)) OR (Recombination Repair, Homologous))
 OR (Homologous Recombination Repair of DNA)) OR (Homologous Recombination
 DNA Repair)) OR (Recombination Repair)) OR (Repair, Recombination)) OR
 (Homologous Recombination Double-Stranded Break DNA Repair)) OR (Homologous
 Recombination Double Stranded Break DNA Repair)) OR (Homology-Directed
 dsDNA Break Repair)) OR (Homology Directed dsDNA Break Repair)))) AND
 (((biomarkers) OR (biomarker)) OR (gene)) OR (protein))

Sources:**Total N =**

PubMed N =

Cochrane Library N =

EMBASE N =

OVID N =

Web of Science N =

Other sources N =

N records after duplications removed**N records after screening of titles and abstracts****N records after further evaluation** (N records were excluded for the following reasons: Non-clinical studies; Patients with metastatic or advanced BC; No detection of HRD, wrong evaluation methods of HRD score, or other cutoff values; and Non-human studies)**N records included in qualitative synthesis****N records included in quantitative synthesis (meta-analysis)**

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location where item is reported
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Line 51
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Line 5-19
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Line 256-258
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Line 259
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Line 67-120
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Line 121-126, line 166-181
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Line 154-181
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Line 134-135
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Line 136-140

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Line 142-143
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Line 143-152
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Line 191-195
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Line 198-206
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Line 176-181
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Line 208-220
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Line 223-225
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	Line 225-230
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Line 237-244
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Line 224-225
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Line 246-248
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Not applicable

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.