Breast Cancer Research and Treatment (2019) 178:497–504
https://doi.org/10.1007/s10549-019-05421-7

REVIEW

Prognostic value of receptor status conversion following neoadjuvant chemotherapy in breast cancer patients: a systematic review and meta-analysis

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Received: 10 April 2019 / Accepted: 24 August 2019 / Published online: 30 August 2019
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Abstract

Biomarkers of breast cancer such as hormone receptors (HR) and human epidermal growth factor 2 (HER2) can be altered after neoadjuvant chemotherapy (NAC). However, whether the conversion of these receptors affects the prognosis of patients remains to be determined. We sought to evaluate the prognostic value of HR and HER2 receptors before and after NAC and to analyze their clinical implications. Relevant studies were used to calculate the pooled hazard ratios, 95% confidence interval (95% CI). This meta-analysis included eight studies with 2847 patients. Compared to patients with HR+ → +, patients with HR+ → − have shorter disease free survival (DFS) (hazard ratio = 2.64, 95% CI 1.86–3.75) and overall survival (OS) (hazard ratio = 2.99, 95% CI 1.97–4.54). Furthermore, patients with HR− → + tend to achieve better DFS (hazard ratio = 0.83, 95% CI 0.60–1.17) compared to patients with HR− → −. Patients with HR− → + gain better OS (hazard ratio = 0.67, 95% CI 0.46–0.99) compared to patients exhibiting HR− → −. When comparing patients with HER2+ → − to patients with HER2+ → +, patients with HER2+ → − tended to achieve better DFS (hazard ratio = 1.65, 95% CI 1.08–2.53) though results for OS (hazard ratio = 1.16, 95% CI 0.54–2.49) were not statistically significant. Our data strongly support the need for redetection of HR and HER2 receptor status of surgical sample following neoadjuvant therapy. Changes in HR status induced by NAC can be used as a prognostic factor in breast cancer patients for predicting both OS and DFS. HER2 change may also be valuable for predicting prognosis. Further research should explore therapeutic strategies for those presenting receptor status conversion.

Keywords Breast cancer · Neoadjuvant chemotherapy · Receptor · Prognosis

Introduction

NAC is widely regarded as an important treatment option for early-stage breast cancer patients and is able to achieve similar long-term clinical outcomes as adjuvant treatment [1, 2]. Patients that achieve pathological complete response (pCR) may attain better clinical outcome [3, 4]. However, only a minority of patients achieve pCR following NAC therapy while the majority of the patients receiving NAC treatment still harbor residual disease [5]. Recent studies have reported HR and HER2 discordance levels before and after NAC treatment [6–8]. One particular review observed that discordance rates of estrogen receptor (ER), progesterone receptor (PR), and HER2 status were 2.5–17%, 5.9–51.7%, and 2.3–35%, respectively [9]. Another meta-analysis indicated instability of ER and PR status during NAC [10]. Finally, a large-scale retrospective study showed

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-019-05421-7) contains supplementary material, which is available to authorized users.

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that in approximately 21.4% of HER2-positive patients, the breast tumor converted to HER2-negative [11].

The results from several studies concerning the prognostic value of changes in these receptors levels following NAC remain controversial. Most of the studies concluded that patients with HR+ → − harbored poor prognosis in both OS and DFS [12]. However, Tacca et al. failed to observe a significant change in DFS and OS between patients with HR− → + and those with HR− → − [13]. Furthermore, Wang et al. found that HER2+ → − status was associated with a 2.64-fold (95% CI 1.10–6.31) increased risks for relapse comparing to patients with HER2+ → + [14]. Results are variable between different studies [15]. Due to the small sample sizes and contradictory findings of previous studies, in this investigation, we conducted a meta-analysis to clarify HR and HER2 discordance prognostic value and to explore their potential clinical value.

Methods

Search strategy

We performed a meta-analysis according to the guidelines of MOOSE [16]. Online databases including PubMed, EMBASE and the Cochrane library were searched to identify relevant literature published from 1950 to February 2018. For the literature search, the following key word combinations were incorporated: 'breast cancer,' 'neoadjuvant chemotherapy,' 'receptor,' and 'change,' 'discordance.' Abstracts from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and San Antonio Breast Cancer Symposium (SABCS) of the past 5 years were manually retrieved. Published studies were selected for analysis based on the following criteria: (1) English publications; (2) Studies focusing on breast cancer and NAC; (3) studies associated with HR or HER2 change and long-term outcome; (4) studies in human. Studies were excluded if they were either: (1) reviews or laboratory research on mechanisms and/or (2) studies that have overlapping data. For studies with insufficient data, we sent emails to the corresponding author for additional data or unpublished information needed for our meta-analysis study.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the studies by appraising the methodological value. This was judged by an eight-item instrument via three broad perspectives: the selection of studies; study comparability; and the ascertainment of the outcome of interest. After implementing a merit system of assigning points or "stars," we considered studies awarded with five points or higher as high-quality studies.

Statistical analysis

The HRs for the outcomes and their 95% CI were extracted via multivariable analyses. Otherwise, we used the Excel spreadsheet that was provided by Tierney et al. for extraction and the Engauge Digitizer software version 10.6 to reproduce data using the survival curves [17]. The heterogeneity test for pooled hazard ratios was verified using the Higgins-I^2 statistics. A random-effects model was applied when significant heterogeneity was observed ($I^2 > 50\%$). Otherwise, the fixed-effects model was utilized. Publication bias was estimated by using Begg's test and Egger's test with a funnel plot. All P values were calculated using a two-sided test, and a P value < 0.05 was considered statistically significant. All statistical analyses in our study were conducted with STATA12 (Stata Corp LP, College Station, TX, USA), Engauge Digitizer (V.10.6) and Microsoft Excel (V.2013, Microsoft Corporation, Redmond, Washington, USA).

Search result

As shown in Fig. 1, relevant articles ($n = 1987$) were retrieved. Through a preliminary screening, 1730 articles were excluded by title and abstract, language, reviews ,and duplication. Afterwards, 228 articles were excluded due to irrelevancy to survival. With regards to the remaining 29 articles, 21 full-text articles were excluded because

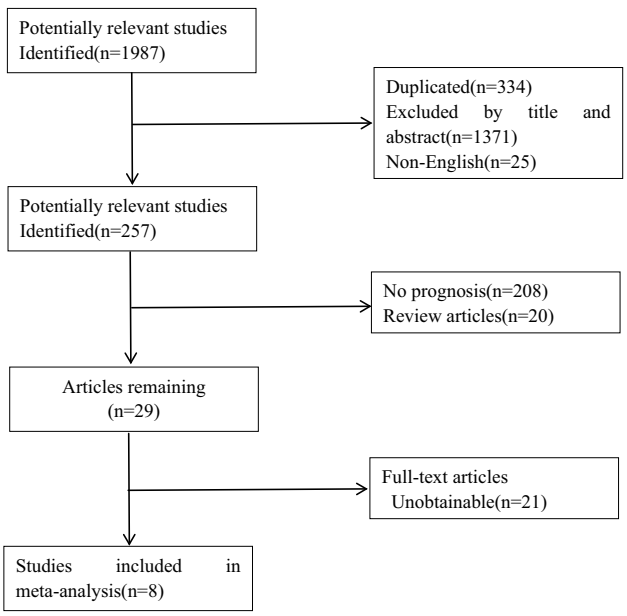

Fig. 1 Flow diagram of the systematic search and selection process of articles

relevant information could not be obtained from the corresponding authors. Only eight articles were included in this meta-analysis.

Study characteristics

The general characteristics of patients from all the included studies are shown in Table 1. 2847 patients were included in eight studies. The reported mean or median follow-up ranged from 3.0 to 7.2 years. All patients HR status of pre-NAC and surgical specimens were identified by using immunohistochemistry (IHC) analysis. HER2 overexpression was defined as an IHC score of 3 + in three studies. For patient with a score of 2 + IHC, fluorescence in situ hybridization (FISH) was tested except for one study [18]. In addition, we discovered that in three studies [12, 18, 19] patients were administered endocrine therapy if HR was positive at any point in time. This was helpful to conduct subgroup analysis and to investigate the effect of endocrine therapy in patients with HR conversion. Table 1 summarizes other relevant information.

Meta-analysis

NAC induced change rate was 17.88%, 22.83%, and 19.29% for ER, PR, and HR, respectively. The incidence of ER, PR, HR, and HER2 gain and loss is shown in Table 2. The ratio of PR conversion is higher than that of ER, which aligned with the observations in the previous study [9]. HER2 change rate (11.76%) was higher than the previous largest study (7.38%) [20]. A plausible explanation may be that the administered proportion of anti-HER2 therapy was different in two cohorts [9].

Prognostic value of HR status conversion for patients with HR+ → – and patients with HR+ → +

A total of three studies [12, 18, 19] for DFS analysis and three studies [12, 18, 19] for OS analysis. The results of our meta-analysis show that patients with HR+ → – were associated with less DFS and OS than patients with HR+ → +, for pooled hazard ratio = 2.64, 95% CI 1.86–3.75 and hazard ratio = 2.99, 95% CI 1.97–4.54, respectively (Figs. 2, 3). A subgroup analysis was conducted in three studies [12, 18, 19] in which all patients were administrated endocrine therapy at any time when HR appeared positive. For this subgroup, patients with HR+ → – showed significantly shorter DFS and OS than patients with HR+ → +, for pooled hazard ratio = 2.79(95% CI 1.84–4.22) and hazard ratio = 3.14(95% CI 1.95–5.03), respectively.

Prognostic value of HR status conversion for patients with HR– → + and patients with HR– → –

DFS and OS analysis were conducted in four studies [12, 13, 18, 19]. Heterogeneity was not found. Compared to

Table 1 A summary of the different investigations and their characteristics used in this study

Author, year	Country	Design	No. of patient	Pre-NAC testing	Detect method	Outcome (shown)	Median or mean follow-up (years)	NAC regimen
Tacca, 2007 [13]	France	P	420	FNA or CNB	IHC	OS/DFS (SC)	NR	AVCF/NAM/TNCF/FAC
Mittendorf, 2009 [21]	USA	R	142	CB	FISH	DFS (SC)	3.1	T → FAC, H
Guarneri, 2013 [15]	Italy	P	107	CB	IHC/FISH	DFS (RE)	NR	T → FAC, H/L/H + L
Tan, 2014 [18]	China	R	296	CNB	IHC	OS/DFS (RE)	3.5	FAC/AC → T/AT/TAC
Jin, 2015 [12]	China	P	423	NR	IHC/FISH	OS/DFS (RE)	3.7 (0.2–12.4)	TCb/CAF/NA/TA.
Lim, 2016 [19]	Korea	R	322	CB	IHC/FISH	OS/DFS (RE)	5.3 (0.4–9.2)	AC/AC → T/TG, H/L
Wang, 2017 [14]	China	R	549	FNA	IHC	OS (RE)	3.0	TCr/TCrH
Yoshida, 2017 [22]	Japan	R	588	FNA or CNB	IHC/FISH	DFS (RE)	6.2	A/T, H

The key to the abbreviations as follows: *CB* core biopsy, *CNB* core needle biopsy, *FISH* fluorescence in situ hybridization, *FNA* fine needle aspiration, *IHC* immunohistochemistry, *NR* not reported, *P* prospective study(in study design column), *R* retrospective study, *RE* reported, *SC* survival curve. The key to the abbreviations in the NAC regimen as follows: *A* anthracycline, *C* cyclophosphamide, *Cb* carboplatin, *F* fluorouracil, *H* trastuzumab, *L* lapatinib, *M* methotrexate, *N* vinorelbine, *P* cisplatin (in NAC regimen column), *T* taxanes. Only HER2+ patients received trastuzumab treatment

Table 2 Change in ER, PR,HR, and HER2 status of the primary tumor after neoadjuvant therapy

Primary tumor	*n*	Residual tumor	*n*	Ratio %
ER status		ER status		
Positive	277	Positive	229	82.67
		Negative	48	17.33
Negative	288	Positive	53	18.40
		Negative	235	81.60
PR status		PR status		
Positive	267	Positive	191	71.54
		Negative	76	28.46
Negative	298	Positive	53	17.79
		Negative	245	82.21
HR status		HER2 status		
Positive	907	Positive	764	84.23
		Negative	143	15.77
Negative	493	Positive	127	25.76
		Negative	366	74.24
HER2 status		HER2 status		
Positive	556	Positive	439	78.96
		Negative	117	21.04
Negative	549	Positive	13	2.37
		Negative	536	97.63

The key to the abbreviations as follows: *ER* estrogen receptor, *PR* progesterone receptor, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2

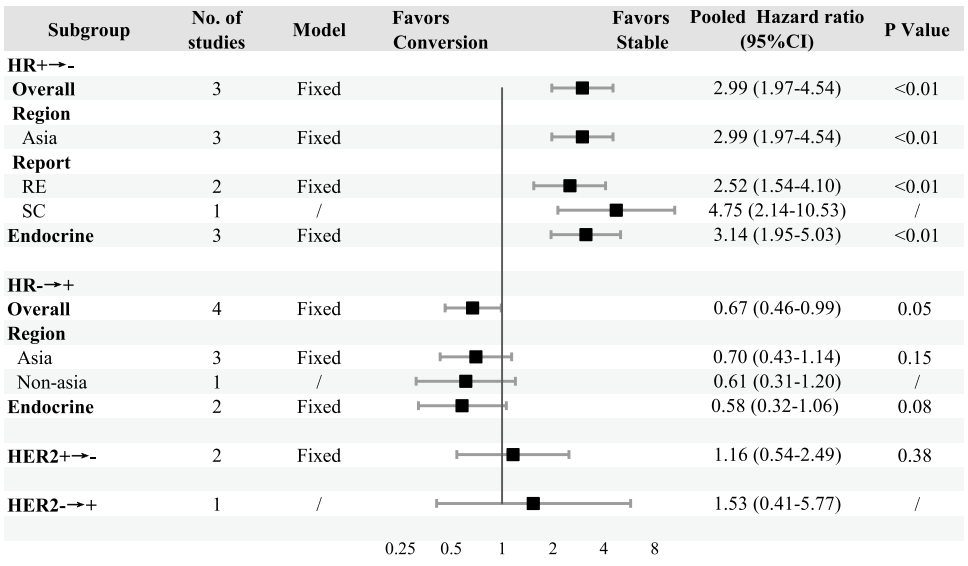

Fig. 2 A summary of OS of patients with receptor conversion. *NA* not applicable, *RE* reported, *SC* survival curve. Endocrine is subgroup with adjuvant endocrine therapy that if HR was detected to be positive at any time-point. We take for significant difference when $P < 0.05$

patients with HR− → −, patients with HR− → + achieve better OS (hazard ratio = 0.67, 95% CI 0.46–0.99). Patients with HR− → + tend to achieve better DFS (hazard ratio = 0.83, 95% CI 0.60–1.17) compared to patients exhibiting HR− → −. A subgroup analysis was conducted in two studies [18, 19] in which patients were administrated adjuvant endocrine therapy at any time when HR appeared positive. For patients with HR− → −, patients with HR− → + may achieve longer OS (hazard ratio = 0.58, 95% CI 0.32–1.06). No statistical significance was found for these

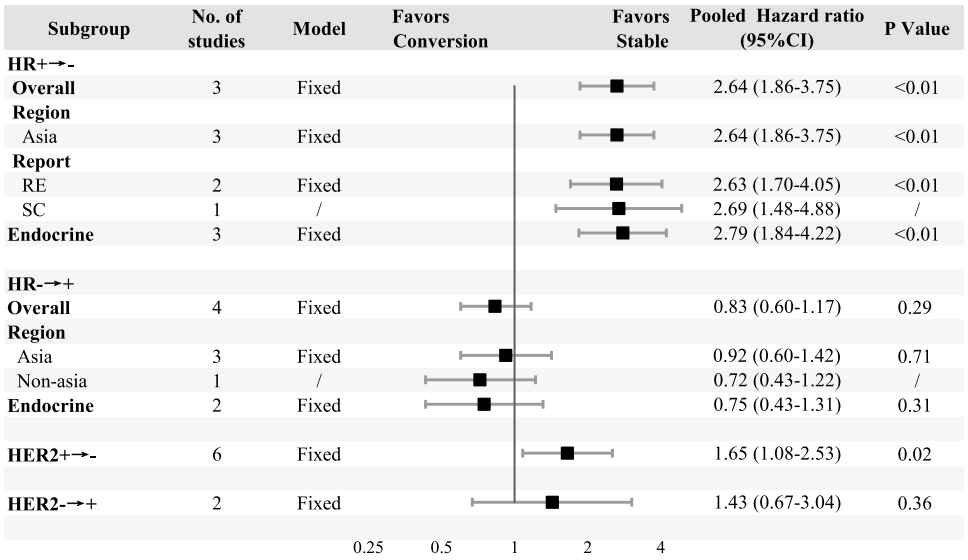

Fig. 3 A summary of DFS of patients with receptor conversion. *NA* not applicable, *RE* reported, *SC* survival curve. Endocrine is subgroup with adjuvant endocrine therapy that if HR was detected to be positive at any time-point. We take for significant difference when $P < 0.05$

two groups in the DFS analysis (hazard ratio = 0.75, 95% CI 0.43–1.31) (Figs. 2 and 3).

Prognostic value of HER2 status conversion for patients with HER2+ → – and patients with HER2+ → +

DFS and OS analysis were conducted in six studies [12, 14, 15, 19, 21, 22] and two studies [12, 19], respectively. DFS of patients with HER2+ → – was significantly worse than DFS of patients with HER2+ → + (hazard ratio = 1.65, 95% CI 1.08–2.53). No statistical significance was found for OS analysis (hazard ratio = 1.16, 95% CI 0.54–2.49) (Figs. 2 and 3).

Prognostic value of HER2 status conversion for patients with HER2– → + and patients with HER2– → –

There were only two studies [12, 22] reporting outcomes of patients with HER2– → + and patients with HER2– → –. No statistical significance was found both in DFS (hazard ratio = 1.43, 95% CI 0.67–3.04) and OS analysis (hazard ratio = 1.53, 95% CI 0.41–1.77) respectively (Figs. 2, 3).

Sensitivity analysis

To confirm the outcome of our analyses, we conducted a sensitivity analysis by sequentially eliminating one study at a time. No single study could influence the pooled HRs and 95% CIs of the meta-analysis.

Risk of publication bias in studies

Due to limited studies ($n = 4$) in HR status conversion, the publication bias was not conducted. In HER2 status conversion, no significant publication bias was found (Fig. 4).

Discussion

Similar to the findings of previous studies [9, 10], our meta-analysis showed that HR and HER2 were lost or gained in a considerable proportion of patients after receiving NAC.

It is noteworthy that 13.8% and 2.6% of patients gained ER or HER2, respectively, following NAC. If test of HR and HER2 status in residual tumor had not been conducted, these patients may have lost the opportunity to receive adjuvant hormonal therapy or adjuvant anti-HER2 therapy. The ASCO/CAP recommends that patients with metastatic disease receive a HER2 test performed at a metastatic site [23]. However, in a neoadjuvant setting, the ASCO/CAP do not prescribe a similar recommendation. Based on the high proportion of patients with HR or HER2 status change and the prognostic value of these receptors conversion, we propose redetection of HR and HER2 status of surgical sample following neoadjuvant therapy. To our knowledge, our study is the first systematic review and meta-analysis regarding long-term outcome of receptor conversion before and after NAC. Patients with receptor discordance may benefit from changing therapy.

In our meta-analysis, patients with HR+ → – presented both worse DFS and OS compared to patients with HR+ → +. Shorter DFS and OS in patient with HR+ → – may mean HR loss is a more aggressive phenotype. In sub-group analysis involving three studies in which patients were

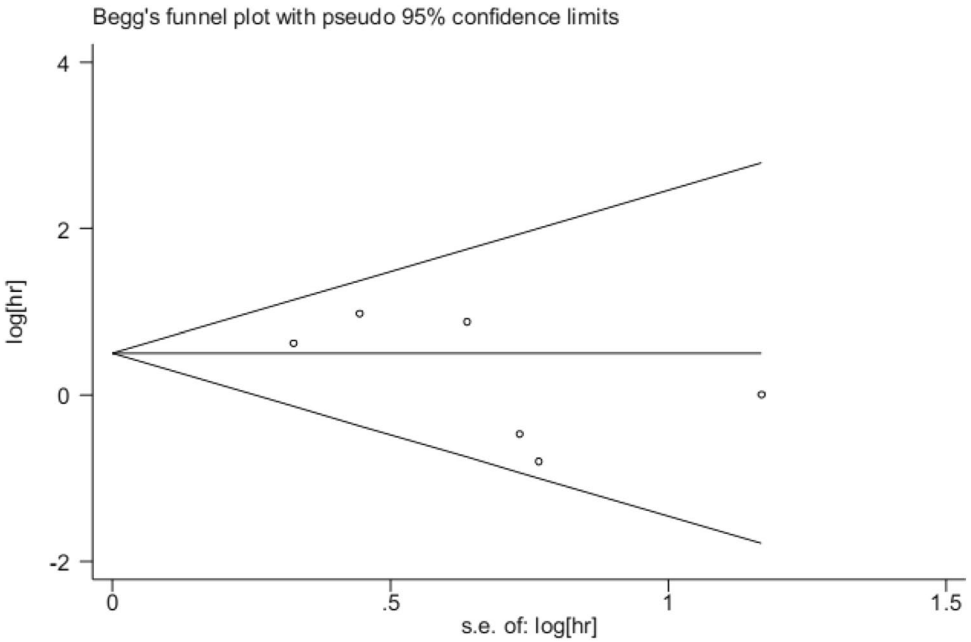

Fig. 4 Publication bias for studies involving HER2 conversion

administrated adjuvant endocrine therapy at any time when HR appeared positive, patients with HR+ → − also had shorter DFS and OS. These results may indicate that patients with HR+ → − gain limited benefit from adjuvant endocrine therapy. Currently, no general agreement exists in whether adjuvant endocrine treatment should be administered to patients with HR changes following NAC treatment. Adjuvant endocrine therapy is likely administrated if HR is detected to be positive at any point in time. There was only one retrospective trial [24] designed to research the value of adjuvant endocrine therapy in patients with HR+ → − (57 patients administered endocrine therapy and 40 patients were not administered endocrine therapy). The DFS of adjuvant endocrine therapy group was significantly higher than that of the group without adjuvant endocrine therapy. However, the 5-year OS was not statistically significance. Therefore understanding the role of adjuvant endocrine therapy in patients with HR+ → − requires further trials and future investigation.

Patients with HR− → + may attain additional therapy options. Our meta-analysis indicates that patients with HR− → + tend to have better DFS and OS in contrast with patients with HR− → −. Since not all patients with HR− → + received adjuvant endocrine treatment, the value of adjuvant endocrine treatment in patients with HR− → + has not been clearly evaluated.

Patients with HER2+ → − exhibited poor DFS. However, we did not find a statistically significant difference in OS for patients with HER2+ → −. HER2 instability is seen in primary tumors [14, 15] and in metastatic settings [11, 25]. A retrospective analysis [11] involved 182 advanced breast cancer patients with HER2+ → − at the metastatic site. There were statistically significant differences in OS between patients with HER2+ → − and patients with HER2+ → +, whether or not patients were given trastuzumab. However, in the HER2+ → − subgroup, OS did not differ between those who did and did not receive trastuzumab. These results suggest that patients with loss of HER2 status may be less sensitive to trastuzumab.

Previous research suggested that receptor changes were indicators of poor prognosis for both residual [18, 19] and metastatic sites [11, 25, 26]. Our meta-analysis showed that the prognosis of the majority of patients with HR conversion or HER2 conversion were poor. The hypothesized mechanisms of receptors changes is as follows: (1) Receptor change might be associated with genetic instability. Heterogeneity widely exists in breast tumor [27]. Receptors status change leads to less differentiation and higher aggressiveness [28]. This change may further exacerbate tumor recurrence and metastasis. (2) Primary tumor biological characters may be changed by NAC. These changes in receptors are indicators of a survival mechanism of tumor cells in order to resist the effects of chemotherapy.

Limitations

We recognize that our study harbors limitations. First, we chose English-based articles which may have led to missing important data published in other languages. There may also be clinical heterogeneity among studies, such as age, race, NAC regime as well as the tested methodology. Furthermore, tumor heterogeneity may have previously existed, and sampling by core needle biopsy before NAC

may not have been entirely representative of the character of the tumor [29]. The role of anti-HER2 can also have a significant impact on HER2 expression [9, 11]. However, due to limited information from previous studies, we could not investigate the effect of anti-HER2 treatment on HER2 status in NAC. In addition, referring to the previous work of Juo et al. [30], we subjectively defined DFS by including the data from recurrence-free survival (RFS). This aim was to include the maximal number of relevant clinical studies. Last but not the least, since pathological assay methods and receptor cut-off values were different in enrolled studies, results, and conclusions of our meta-analysis should be used cautiously.

Conclusion

Our data strongly support the need for redetection of HR and HER2 status of surgical sample following neoadjuvant therapy. Changes in HR status induced by NAC can be used as a prognostic factor in patients for both OS and DFS. Further, HER2 change may also be valuable for predicting prognosis. Further research is necessary to explore therapeutic strategies for patients in the status conversion subgroup.

Acknowledgements This study was supported by grants from the National Key R&D Program of China No. 2016YFC0904900, National Natural Science Foundation (No. 81673509 and No. 81573504) of PR China, Beijing Municipal Natural Science Foundation (No. 7171012) and National Science and Technology Major Projects for "Major New Drugs Innovation and Development" (No. 2017ZX09304028 and No. 2017ZX09101001).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable- this article does not contain any studies with human participants performed by any of authors.

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