Prognostic significance of receptor expression discordance between primary and recurrent breast cancers: a meta-analysis

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Abstract

Purpose This meta-analysis aimed to investigate whether receptor (estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2]) discordances between primary and recurrent breast cancers affect patients’ survival.

Methods Search terms contained ER, PR, and HER2 status details in both primary and recurrent tumors (local recurrence or distant metastasis) in addition to survival outcome data (overall survival [OS] or post-recurrence survival [PRS]).

Results Loss of ER or PR in recurrent tumors was significantly associated with shorter OS as compared with receptor-positive concordance (hazard ratio [HR], 1.67; 95% confidence interval [% CI] 1.37–2.04; p < 0.00001 and HR, 1.45; 95% CI 1.21–1.75; p < 0.0001, respectively). Similar trends were observed in groups with only distant metastasis. Gain of ER was a significant predictor of longer PRS as compared with receptor-negative concordance (HR, 0.76; 95% CI 0.59–0.97; p = 0.03). Gain of PR was not a significant predictor of longer survival compared with receptor-negative concordance, but it could be related to better OS at distant metastasis. Both HER2 of loss and gain could be related to poor outcomes.

Conclusion This meta-analysis showed that receptor conversion in recurrent tumors may affect patient survival as compared with receptor concordance.

Keywords Breast cancer · Receptor discordance · Estrogen receptor · Progesterone receptor · Human epidermal growth factor receptor 2 · Prognosis

Abbreviations

ER Estrogen receptor
PR Progesterone receptor
HER2 Human epidermal growth factor receptor 2
BC Breast cancer
PRISMA-P Preferred reporting items for systematic review and meta-analysis protocols

PICO Participants, interventions, comparators, and outcomes
PROSPERO A prospective international register of systematic reviews
TNM Tumor–Node–Metastasis
IHC Immunohistochemical
Introduction

Hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 [HER2] status in primary breast cancers (BC) not only provides prognostic information but it is also crucial for deciding on an effective treatment plan. Previous studies have reported discordance in these three biological markers between primary and recurrent tumors [1–4].

Some meta-analyses have clarified the rates of receptor discordance in these biological markers between primary and recurrent tumors [5, 6]. In a recent meta-analysis, ER, PR, and HER2 receptor discordance rates were reported as 19.3% (95% CI 15.8–23.4), 30.9% (95% CI 26.6–35.6), and 10.3% (95% CI 7.8–13.6), respectively [5]. Current guidelines recommend that patients with BC metastasis undergo biopsy or excisional biopsy to evaluate the status of these receptors [7, 8].

Previous studies have reported that receptor discordance may affect patient survival [9–11]. By contrast, there is no survival difference between patients with receptor discordance and those with receptor concordance [2]. Thus, no clear consensus on whether discordances of these receptors affect patient survival has been reached. Moreover, it remains unknown whether adjuvant therapy can affect the survival of patients with receptor discordance [5, 10, 11]. The aim of this study is to investigate whether discordance of receptors (ER, PR, and HER2) between primary and recurrent tumors affect the survival of patients with BC compared with receptor concordance using a meta-analytic approach.

Methods

See Supplementary Text in the supplementary file for more information.
(1) receptor loss (positive to negative, +/−), status positivity with primary breast tumor converted to status negativity with recurrent breast tumor or

(2) receptor gain (negative to positive, −/+), status negativity with primary breast tumor converted to status positivity with recurrent breast tumor.

* The details are shown in Supplementary Fig. S1
Cases in which no change in status occurred between primary and recurrent tumors were considered to have “receptor concordance,” which was either positive-to-positive (+/+) receptor concordance or negative-to-negative (−/−) receptor concordance. We compared the differences in survival between receptor-discordant groups and receptor-concordant groups as follows: receptor-loss (+/−) group vs. receptor-concordant (+/+ group or receptor-gain (−/+ group vs. receptor-concordant (−/−) group.

**Statistical analysis**

Hazard ratio (HR) and 95% confidence interval (CI) were extracted from each study included in the final analysis. All results were calculated with a fixed-effects model. We also used a random-effects model to evaluate the difference in the heterogeneity between the two models. Statistical heterogeneity among studies was assessed using the I² test. We evaluated I² values according to the following definition: I² > 50%, high heterogeneity; I² 26–50%, moderate heterogeneity; and I² 0–25%, low heterogeneity.

Forest plots were used to visualize heterogeneity among studies. Funnel plots were made to evaluate publication bias. A two-sided p-value of <0.05 was considered statistically significant in both models. In cases where I² values were much greater than 50% or significant, we performed sensitivity analysis or meta-regression analysis to evaluate reasons for the high heterogeneity. The risk of bias graph and bias summary were performed using Review Manager (RevMan) version 5.3. (The Cochrane Collaboration, Oxford, England) [19].

In cases where HR data or survival data were not explicitly stated in the literature, we extracted cumulative survival values using Engauge Digitizer software v12 from the relevant Kaplan–Meier survival curves. Moreover, we estimated the HR values from the extracted cumulative survival values using the Microsoft Excel spreadsheet reported previously [20]. We excluded groups with either fewer than ten total cases or fewer than five total events from our meta-analysis because we could not calculate data using our methods when the total number of cases of either the receptor-concordant or receptor-discordant group was too few.

**Results**

**Characteristics of eligible studies**

We identified 2,165 articles after excluding duplicated articles from the three electrical databases. After the first and second screenings, a total of 15 studies met all inclusion criteria. The discordance rate of selected articles between the two reviewers was 1.0% (21/2,165), and the κ value was 0.74, indicating a fair to good agreement. Some studies (4/15, 26.7%) included Stage IV BC at primary diagnosis [11, 21–23]. We excluded these four articles from our meta-analysis to minimize selection bias because survival data of patients with Stage IV BC are likely to skew meta-analysis results. Thus, 11 studies were finally selected (Table 1 and Supplementary Table S4) [24–34]. In these studies, diagnosis of a metastatic lesion was mainly performed by either core-needle biopsy or surgical excision. Some studies (4/11, 36.4%) included some cases that were diagnosed by fine-needle aspiration (FNA) of the metastatic lesion [25, 28, 30, 31]. We reasoned that these articles would not strongly affect survival data and therefore allowed their inclusion in our meta-analysis.

We evaluated these 11 remaining articles using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) (Supplementary Text, Supplementary Fig. S2A and S2B). In each domain group, κ-values for the agreement between two reviewers were either excellent or fair to good as shown in Supplementary Fig. S2C. Of the 11 studies included, the number of articles that had performed overall survival (OS) analysis or post-recurrence survival (PRS) analysis was summarized in Supplementary Table S5.

Centralized laboratory testing was performed in 8 articles (8/11: 72.7%). The details were as follows: 6 articles, testing for all samples; 1 article, testing for 45.6% of total cases (83/182 cases); and 1 article, testing for 84.3% of total cases (59/70). The median discordant rates for the receptor statuses were 19.7% (range, 10.7–32.5%) for ER, 32.5% (21.9–40.7%) for PR, and 10.3% (3.7–28.2%) for HER2. The threshold definition of both ER and PR was either ≥ 1% (4/11, 36.4%) [24, 27, 29, 34] or ≥ 10% (7/11, 63.6%) [24–26, 28, 30, 31, 33]. Of these, one study investigated a survival difference effect on OS of simultaneously ≥ 10% and ≥ 1% [24]. Another study did not clearly mention the definition of hormone receptor positivity [32]. The positive definition for HER2/CEP17 ratio was mainly decided as either ≥ 2.2 or ≥ 2.0.

In the selected articles, survival data were available in six studies (6/11, 54.5%) each for (1) local recurrences and distant metastases [25, 28, 30–32, 34] or (2) only distant metastases [24–27, 29, 33]. One study investigated the survival difference of both (1) and (2) [25].

**Influence of receptor discordance on OS**

The ER-loss (+/−) and PR-loss (+/−) groups were significantly associated with shorter OS compared with the ER-concordant (+/+ and PR-concordant (+/+ groups, respectively ([Fixed-effects model] ER groups: HR, 1.67; 95% CI 1.37–2.04; p < 0.00001; PR groups: HR, 1.45; 95% CI 1.21–1.75; p < 0.0001. [Random-effects model] ER groups:
| Authors       | Published year | Total cases with recurrence (n) | Total cases with details of statuses in both primary and recurrent tumors (n) | Country       | Study design | Patient selection’s term (years) | Age at primary diagnosis: median (range) | Centralized laboratory testing | Review by pathologists | Receptor positive definition |
|---------------|----------------|---------------------------------|-------------------------------------------------------------------------|---------------|--------------|---------------------------------|------------------------------------------|-------------------------------|---------------------------|--------------------------------|
| Curtit E, et al | 2013           | 489                             | 235 235 219                                                           | France        | Retrospective | 1998–2010                        | 53 (26–89)                                | NA (single institution)       | No                        | > 10% 3+, 2+ (HER2 gene amplification by FISH) |
| Duchnowska R, et al | 2012           | 120                             | 120 119 119                                                           | Poland        | Retrospective | 1996–2011                        | 49a (26–80)                               | Yes                           | Yes                       | AS 3–8 or ≥ 1% ≥ 10% 3+, 2+ (HER2 gene amplification by FISH) |
| Lindström LS, et al | 2012           | 1010                            | 459 430 104                                                           | Sweden        | Retrospective | 1997–2007                        | NA                                       | No (testing at some laboratories) | No                        | ≥ 10% 3+, 2+ (HER2 gene amplification by FISH) |
| Hoefnagel LD, et al | 2012           | 233                             | 233 233 233                                                           | The Netherlands | Retrospective | 1985–2009                        | 53.9a (25–93)                            | Yes                           | Yes                       | ≥ 1% or ≥ 10% 3+, 2+ (HER2 gene amplification by SISH) |

SISH: HER2 copies/tumor cell nucleus ≥ 6
| Authors                  | Published year | Total cases with recurrence (n) | Total cases with details of statuses in both primary and recurrent tumors (n) | Country | Study design | Patient selection’s term (years) | Age at primary diagnosis: median (range) | Centralized laboratory testing | Review by pathologists | Receptor positive definition |
|-------------------------|----------------|--------------------------------|--------------------------------------------------------------------------------|---------|--------------|---------------------------------|------------------------------------------|-------------------------------|--------------------------|-------------------------------|
| Niikura N, et al        | 2012           | 947                            | NA NA 182 USA                                                                  |          | Retrospective | 1997–2008                      | 48.2 (24–85)                             | Yes: 83 cases, No: 99 cases (46: review of slides stained by the other institution, 53 cases: slides were not available. Stained results were obtained by patients’ referral documents or communications) | Yes: 129 cases, No: 53 cases slides were not available. (Stained results were obtained by patients’ referral documents or communications) | ER, PR ≥ 10% 3+ and/or HER2 gene amplification by FISH | HER2/CEP17 ratio was ≥ 2.0 |
| Meng X, et al           | 2016           | 627                            | 627 627 503 China                                                              |          | Retrospective | 2002–2016                      | 44 (22–79)                                | Yes (single institution)                    | Yes                                     | ≥ 1%                      | 3+, 2+ (HER2 gene amplification by FISH) | HER2/CEP17 ratio > 2.2 |
| Fujii K, et al          | 2017           | 70                             | 70 69 70 Japan                                                                |          | Retrospective | 1990–2012                      | 54.5° (NA)                                | Yes: all recurrent lesions and 59 primary lesions, No: 11 primary lesions | Yes                                      | AS ≥ 3 and moderate-to-intense nuclear staining of ≥ 10% | 3+, 2+ (HER2 gene amplification by FISH) | HER2/CEP17 ratio > 2    |
Table 1 (continued)

| Authors          | Published year | Total cases with recurrence (n) | Total cases with details of statuses in both primary and recurrent tumors (n) | Country   | Study design | Patient selection’s term (years) | Age at primary diagnosis: median (range) | Centralized laboratory testing | Review by pathologists | Receptor positive definition |
|------------------|----------------|--------------------------------|--------------------------------------------------------------------------------|-----------|--------------|---------------------------------|------------------------------------------|-------------------------------|--------------------------|--------------------------|
| Karlsson E, et al | 2014           | 177                            | 127 101 73                                                                     | Sweden    | Retrospective | 2000–2011                       | NA                                       | Yes                           | No                       | ≥ 10%                    |
|                  |                |                                |                                                                                  |           |              |                                 |                                          |                               |                          | 3+, 2+ (HER2 gene amplification by FISH) |
|                  |                |                                |                                                                                  |           |              |                                 |                                          |                               |                          | HER2/CEP17 ratio ≥ 2.0 or ≥ 4.0 |
|                  |                |                                |                                                                                  |           |              |                                 |                                          |                               |                          | HER2 gene copy number/tumor cell |
| Stueber TN, et al| 2019           | 196                            | 196 196 196                                                                     | Germany   | Retrospective | 2000–2013                       | 56.6 a (NA)                             | Yes                           | No                       | (≥ 1%)                  |
|                  |                |                                |                                                                                  |           |              |                                 |                                          |                               |                          | NA                       |
| Shin HC, et al   | 2016           | 188                            | 144 144 107                                                                     | Korea     | Retrospective | 2000–2010                       | 46 (24–71)                              | Yes                           | No                       | ≥ 10%                    |
|                  |                |                                |                                                                                  |           |              |                                 |                                          |                               |                          | 3+, 2+ (HER2 gene amplification by FISH) |
| Ju G, et al      | 2018           | 151                            | 151 151 85                                                                      | China c   | Retrospective | 2006–2016                       | 56.6 (32–82)                           | NA (two institutions)         | Yes                      | ≥ 1%                    |
|                  |                |                                |                                                                                  |           |              |                                 |                                          |                               |                          | 3+, 2+ (HER2 gene amplification by FISH) |
|                  |                |                                |                                                                                  |           |              |                                 |                                          |                               |                          | HER2/CEP17 ratio ≥ 2.0 or HER2/CEP17 ratio < 2.0 and average HER2 copies/cells ratio ≥ 6.0 |

| Authors       | ER | PR | HER2 | FISH ratio |
|---------------|----|----|------|------------|
| Curtit E, et al | 195 (83.0) | 40 (17.0) | 29 (12.3) | 11 (4.7) |
| Duchnowska R, et al | 85 (70.8) | 35 (29.2) | 22 (18.3) | 13 (10.9) |
| Lindström LS, et al | 310 (67.6) | 149 (32.4) | 113 (24.6) | 36 (7.8) |
| Hoefnagel LD, et al | 198 (85.0) | 35 (15.0) | 23 (9.9) | 12 (5.2) |
| Niikura N, et al | NA | NA | NA | NA |
| Meng X, et al   | 462 (73.7) | 165 (26.3) | 106 (16.9) | 59 (9.4) |
| Fujii K, et al  | 55 (78.6) | 15 (21.4) | 9 (12.8) | 6 (8.6) |
| Karlsson E, et al | 109 (85.8) | 18 (14.2) | 15 (11.8) | 3 (2.4) |

Curtit E, et al 195 (83.0) 40 (17.0) 29 (12.3) 11 (4.7) 166 (70.6) 69 (29.4) 52 (22.1) 17 (7.3) 211 (96.3) 8 (3.7) 6 (2.6) 6 (2.6)
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Lindström LS, et al 310 (67.6) 149 (32.4) 113 (24.6) 36 (7.8) 255 (59.3) 175 (40.7) 142 (33.0) 33 (7.7) 89 (85.6) 15 (14.4) 9 (8.6) 6 (5.8)
Hoefnagel LD, et al 198 (85.0) 35 (15.0) 23 (9.9) 12 (5.2) 157 (67.4) 76 (32.6) 49 (21.0) 27 (11.6) 221 (94.8) 12 (5.2) 6 (2.6) 6 (2.6)
Niikura N, et al NA NA NA NA
Meng X, et al 462 (73.7) 165 (26.3) 106 (16.9) 59 (9.4) 414 (66.0) 213 (34.0) 158 (25.2) 55 (8.8) 448 (89.1) 55 (10.9) 22 (4.4) 33 (6.5)
Fujii K, et al 55 (78.6) 15 (21.4) 9 (12.8) 6 (8.6) 44 (63.8) 25 (36.2) 15 (21.7) 10 (14.5) 63 (90.0) 7 (10.0) 0 (0) 7 (10.0)
Karlsson E, et al 109 (85.8) 18 (14.2) 15 (11.8) 3 (2.4) 61 (60.4) 40 (39.6) 30 (29.7) 10 (9.9) 66 (90.4) 7 (9.6) 4 (5.5) 3 (4.1)
HR, 1.70; 95% CI 1.34–2.15; \( p < 0.0001 \); PR groups: HR, 1.49; 95% CI 1.20–1.86; \( p = 0.0003 \) (Fig. 2A, C).

The ER-gain (−/+ ) and PR-gain (−/+ ) groups were not significantly associated with OS when compared with the ER-concordant (−/−) and PR-concordant (−/−) groups ([Fixed-effects model] ER groups: HR, 0.90; 95% CI 0.68–1.19; \( p = 0.45 \); PR groups: HR, 0.77; 95% CI 0.59–1.01; \( p = 0.06 \), [Random-effects model] ER groups: HR, 0.98; 95% CI 0.59–1.63; \( p = 0.94 \); PR groups: HR, 0.81; 95% CI 0.54–1.23; \( p = 0.32 \) (Fig. 2B and D).

Data regarding HER2-loss analysis were available in only 2/11 studies [27, 32]. However, these data were insufficient to perform a meta-analysis according to our methods. Likewise, data regarding HER2-gain analysis were also available in 2/11 studies [27, 32]. We were able to extract HR data from only one study according to our methods (HR, 2.17; 95% CI 0.82–5.74; \( p = 0.12 \)) [27].

Influence of receptor discordance on PRS

The ER-loss (+/−) and PR-loss (+/−) groups were significantly associated with shorter PRS compared with the ER-concordant (+/+) and PR-concordant (+/+) groups, respectively ([Fixed-effects model] ER groups: HR, 1.72; 95% CI 1.40–2.11; \( p < 0.00001 \); PR groups: HR, 1.54; 95% CI 1.27–1.87; \( p < 0.00001 \), [Random-effects model] ER groups: HR, 1.76; 95% CI 1.39–2.22; \( p < 0.00001 \); PR groups: HR, 1.56; 95% CI 1.26–1.93; \( p < 0.0001 \) (Fig. 3A and C).

The ER-gain (−/+ ) group was significantly associated with longer PRS compared with the ER-concordant (−/−) group ([Fixed-effects model] HR, 0.76; 95% CI 0.59–0.97; \( p = 0.03 \), [Random-effects model] HR, 0.76; 95% CI 0.59–0.97; \( p = 0.03 \) (Fig. 3B). There was no significant difference in PRS between the PR-gain (−/+ ) and PR-concordant (−/−) groups ([Fixed-effects model] HR, 1.10; 95% CI 0.85–1.43; \( p = 0.47 \), [Random-effects model] HR, 1.12; 95% CI 0.84–1.49; \( p = 0.45 \) (Fig. 3D).

HER2-loss data were available in 3/11 studies [26, 28, 33]. Only one study was eligible for comparison between these two groups (HR, 2.78; 95% CI 1.61–4.76; \( p = 0.0002 \)) [28]. HER2-gain data were available in two studies [26, 33], but the data were insufficient for meta-analysis.

Influence on survival in patients with distant metastasis

In the subgroup with only distant metastasis not including local recurrences, the OS of both ER-loss (+/−) and PR-loss (+/−) groups was significantly shorter than those of ER-concordant (+/+) and PR-concordant (+/+) groups, respectively ([Fixed-effects model] ER groups: HR, 1.70; 95% CI 1.35–2.14; \( p < 0.0001 \); PR groups: HR, 1.28; 95% CI 1.02–1.60; \( p = 0.03 \), [Random-effects model] ER groups:
Fig. 2 Forest plots comparing overall survival between receptor-loss/gain groups and receptor-concordant groups. A Comparison of OS between ER-loss (+/−) group and ER-concordant (+/+) group. B Comparison of OS between ER-gain (−/+ ) group and ER-concordant (−/−) group. C Comparison of OS between PR-loss (+/−) group and PR-concordant (+/+) group. D Comparison of OS between PR-gain (−/+ ) group and PR-concordant (−/−) group. ER estrogen receptor, OS overall survival, PR progesterone receptor

Fig. 3 Forest plots comparing post-recurrence survival between receptor-loss/gain group and receptor-concordant group. A Comparison of PRS between ER-loss (+/−) group and ER-concordant (+/+) group. B Comparison of PRS between ER-gain (−/+ ) group and ER-concordant (−/−) group. C Comparison of PRS between PR-loss (+/−) group and PR-concordant (+/+) group. D Comparison of PRS between PR-gain (−/+ ) group and PR-concordant (−/−) group. ER estrogen receptor, PR progesterone receptor, PRS post-recurrence survival
HR, 1.70; 95% CI 1.35–2.14; p < 0.00001; PR groups: HR, 1.28; 95% CI 1.02–1.60; p = 0.03) (Fig. 4A and C).

There was no significant difference in the OS between the ER-loss (+/−) and ER-concordant (+/+) group regardless of the definition of hormone receptor positivity and type of model (Supplementary Fig. S3A and S3C).

In subgroup analysis for the 1% or 10% thresholds of hormone receptor positivity

The ER-loss (+/−) and PR-loss (+/−) groups were significantly associated with shorter OS compared with the ER-concordant (+/+) and PR-concordant (+/+) group regardless of the definition of hormone receptor positivity and type of model (Supplementary Fig. S3A and S3C).

In subgroup analysis for the 1% or 10% thresholds, the ER-gain (+/−) group was not associated with OS compared with the ER-concordant (+/+) group in both of the models, respectively (Supplementary Fig. S3B). Meanwhile, in the subgroup analysis of 1% threshold, the OS of PR-gain (+/+) group was significantly longer than those of the PR-concordant (+/+) group in the fixed-effects model (HR, 0.66; 95% CI 0.47–0.90; p = 0.01) but not significant in the random-effects model (HR, 0.68; 95% CI 0.45–1.03; p = 0.07) (Supplementary Fig. S3D).

There was no significant difference between the high- and low-risk-of-bias groups in the analysis of the OS in both models (Supplementary Fig. S4).

In the subgroup analysis of the low-risk-of-bias group, both the ER-loss (+/−) and PR-loss (+/−) groups had a significantly shorter OS than those of the ER-concordant (+/+) group.

Subgroup analysis according to the assessment of risk of bias

There was not a significant difference between the high- and low-risk-of-bias groups in the analysis of the OS in both models (Supplementary Fig. S4).

In the subgroup analysis of the low-risk-of-bias group, both the ER-loss (+/−) and PR-loss (+/−) groups had a significantly shorter OS than those of the ER-concordant (+/+) group.
survival [25, 27, 29]. Thus, a meta-analysis was conducted in cases excluding the discrepant study, an analysis defined as “ER-gain’ (+/+) group vs. ER-concordant’ (−/−) group” (Supplementary Table S6). Statistical heterogeneity was not observed ($I^2 = 0\%$; $p = 0.91$), and the OS of the ER-gain’ (+/+) group was marginally associated with better OS than that of the ER-concordant’ (−/−) group (HR, 0.74; 95% CI 0.54–1.01; $p = 0.06$).

Meanwhile, in the PR-gain analysis on OS, statistical heterogeneity was marginally high (Fig. 2D). We performed meta-regression analysis to investigate whether the HR of PR-gain (−/+) could influence the rates of the other variables in the primary tumors for each article. The rate of HER2-positivity in the primary tumor was significantly correlated with the HR of PR-gain (−/+) on the OS analysis ($p = 0.034$) (Supplementary Table S7 and Supplementary Fig. S6).

We were unable to evaluate the risks of publication bias with Egger’s test because each analysis contained fewer than ten studies. Funnel plots on each analysis are summarized in Supplementary Fig. S7.

**Discussion**

In the current meta-analysis study, we showed that loss of either ER or PR in recurrent tumors was significantly associated with poor prognosis in terms of OS and PRS. Gain of ER tends to be associated with better outcome in terms of longer PRS but not OS compared with receptor-negative primary and recurrent tumors. HER2 loss and gain could be related to poor outcome as compared with receptor-positive and receptor-negative concordance, respectively. As Li et al. reported a meta-analysis on the prognostic impact of receptor discordance after neoadjuvant chemotherapy, it did not investigate patient survival in cases of recurrent tumors [35]. To our knowledge, this is the first report to investigate whether receptor discordance affects the survival of patients with recurrent tumors using the meta-analytic method.

In the analysis of distant metastasis (Fig. 4), trends for each result were similar to the total analysis of OS (Fig. 2). Furthermore, statistical heterogeneity tended to be lower compared with those analyses. It is estimated that there are survival differences between local and distant in some previous reports [36, 37]. However, the reason for this could not be clarified herein because survival differences of patients that had only local recurrence not having distant metastases between receptor discordance and receptor concordance were unavailable.

In our meta-analysis, we found that significant heterogeneity between the 1% and 10% thresholds was found during PR analysis. The reason for statistical heterogeneity has not been clarified; however, previous studies have suggested that the rate of PR positivity is a more continuous variable as a prognostic factor [15, 38]. In particular, some studies have reported that cases with 1–10% PR expression behaved the same as those with receptor-negative disease [39–41]. Thus,
the prognosis would be different according to the threshold definition.

Some studies have reported that adjuvant therapy could influence the receptor discordance in our selected articles. However, because our meta-analysis did not focus it as a primary endpoint, the relation between receptor discordance and adjuvant treatment requires further investigation. Meanwhile, some studies have reported a treatment strategy that was altered in reference to receptor changes in recurrent BC [1, 2, 42–44]. Moreover, discordant cases could lead to inappropriate hormone therapy treatments after the recurrence [2, 10] and treatment alteration based on receptor discordance could affect patient survival [29]. Those findings and our results highly recommended performing a biopsy of recurrent tumors to provide information for altering treatment strategies. However, performing a biopsy of all recurrent sites is invasive, costly, and cannot describe all recurrent sites. Liquid biopsy may be beneficial to detect tumor heterogeneity in circulating tumor cells [45, 46].

Discordance in those receptors has been reported due to analytical error, intratumoral heterogeneity [47], and cellular clonal evolution [48, 49]. The mechanisms of receptor discordance have been gradually elucidated [50]. Unfortunately, the molecular mechanisms for receptor discordance cannot be explained by the results of our study.

Some limitations of our study are as follows: (1) We could not perform a meta-analysis for HER2 discordance. The total number of HER2-discordant cases was too small in each study. A large number of studies will be required to verify these findings, especially for the HER2-gain group. Additionally, all studies were mainly based on 2007 or 2013 ASCO/CAP guidelines [17, 18] but not on the updated guidelines [51]. (2) In cases that we were not able to get HR and 95% CI data even if we inquired each corresponding author to get the data about HR and 95% CI on each article, we extracted those data using specialized software. This technique is commonly used to perform meta-analyses, but the calculated data are not the same as the original data, especially in cases of including more censored cases as most studies include censored data. Additionally, one article suggested no significant differences, but our calculations showed a significant association with poor survival [24]. (3) Each cohort contained different clinicopathological characteristics and different treatment options (adjuvant therapies or systemic therapies after recurrence), particularly between hormone receptor-positive and negative patients. Multivariate analytic results to adjust the confounding factors were mentioned in some original articles but not all articles. Thus, our conclusion regarding the effect of receptor discordance may not be robust as clinicopathological characteristics and treatment options are different among each cohort and our analysis could not fully adjust the confounding factors. In cases wherein clinicopathological characteristics are different among studies, a random-effects model results could be more appropriate than a fixed-effects model. Lim et al. have reported that the clinicopathological staging and survival outcomes are different between Asian and European groups [52]. Therefore, a random-effects model results would be more recommended in the subgroup analysis according to the study area. (4) Our meta-analysis included many studies performed over several decades, which could introduce bias because treatment strategies could vary with time.

In conclusion, in this meta-analysis, we have shown that receptor discordance between primary tumors and recurrent tumors could be associated with patient OS and PRS compared with receptor concordance. Analyzing receptor status to confirm the diagnosis of recurrent BC would provide information for altering treatment strategies based on either receptor-loss or receptor-gain status of recurrent tumors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-021-06390-6.

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Author contributions SS, GB, and EAR conceptualized and designed the study. SS, BMS, and SK collected articles and evaluated those data. SS and GB performed the statistical analysis and interpreted the data. SS, GB, ARG, HT, ST, AS, and EAR wrote, reviewed, and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Declarations

Conflict of interest SK has received honoraria from Daiichi Sankyo co. Ltd, Taiho Pharmaceutical Co. Ltd, Eli Lilly and Company, MSD K.K., AstraZeneca K.K., and Novartis Japan. HT received research grant (Taiho Pharmaceutical Co. Ltd., GORYO Chemical, Inc., and Roche Diagnostics K.K.) and scholarship donation (Chugai Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., and Eli Lilly and Company). The other authors declare no conflict of interest.

Ethics approval and consent to participate This study used only previously published data and does not include original participants’ data.

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