*Oncology Advances* **2024** vol. 2(4) | 174–183
DOI: 10.14218/OnA.2024.00027

## Systematic Review

# Receptor Discordance between Primary and Recurrent Breast Cancer: A Systematic Literature Review

Archana Haria[1], Jonathon Hill[1,2] and Kylie J. Mansfield[1*]

[1]*Graduate School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, NSW, Australia;* [2]*Oncology, Illawarra Shoalhaven Local Health District, Wollongong Hospital, Wollongong, NSW, Australia*

**Received:** August 27, 2024 | **Revised:** December 09, 2024 | **Accepted:** December 18, 2024 | **Published online:** December 25, 2024

## Abstract

**Background and objectives:** Breast cancer is the most common cancer among women, with hormone receptors playing a crucial role, not only in cancer cell growth but also as primary targets in breast cancer treatment. This systematic literature review aimed to summarize the current evidence on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) discordance rates between primary and recurrent breast cancer. Additionally, it seeks to identify how discordance affects prognosis, metastasis, and the potential evidence of primary tumor heterogeneity.

**Methods:** The databases Web of Science, Scopus, MEDLINE, and PubMed were searched for publications of original research in English from 2013 to 2023. Studies with paired histopathology from primary and recurrent breast cancer that employed immunohistochemistry and fluorescence *in situ* hybridization were included. Ten studies were deemed eligible for inclusion.

**Results:** Concordance between primary and recurrent breast cancer was high for ER (80%), PR (65%), and HER2 (85%). Average discordance rates were: ER 19%, PR 34%, and HER2 15%, with PR discordance consistently being the highest. Loss of ER and PR receptors was observed more frequently than gain, while the opposite trend was noted for HER2. Loss of ER and PR was associated with a worse prognosis. Discordance was also observed in cases of tumor metastasis.

**Conclusions:** Discordance in receptor expression between primary and recurrent breast cancer was common, highlighting the importance of re-biopsy in recurrent or metastatic breast cancer, if possible. Patients who lost hormone receptors experienced worse outcomes, suggesting the development of treatment-resistant tumor clones.

## Introduction

The World Health Organization reports that breast cancer is the most common cancer among women worldwide.[1] In 2022, it was estimated that there were 670,000 deaths from breast cancer globally,[1] and in 2024, it is estimated that 3,300 Australian women will succumb to the disease.[2] Fortunately, advances in prevention, early detection, and treatment have led to a decline in breast cancer deaths over the past three decades.[3] Key determinants of breast cancer treatment protocols include the presence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) on the primary tumor.[4,5] These hormone receptors are essential for cancer cell growth and serve as primary targets in breast cancer treatment.[5]

Hormone receptor (HR) status is predictive of response to treatment, influencing treatment choices, and is prognostic, with the hormonal profile affecting the risk of metastasis, recurrence rates, and survival.[6] Approximately 70% of patients diagnosed with breast cancer are hormone receptor-positive (i.e. ER and/or PR positive), which generally indicates a better prognosis.[6] HER2 amplification occurs in approximately 20% of breast cancers and is associated with a poorer prognosis.[5,6] The most aggressive form of breast cancer, with the poorest prognosis, is triple-negative (negative for ER, PR, and HER2), which occurs in about 15% of patients.[5,6]

Approximately 25–30% of patients will experience breast cancer recurrence during their lifetime.[7] Recurrent breast cancer is defined as cancer that reappears after initial treatment, either at the primary site or as a metastasis. Historically, it was assumed that re-

**Keywords:** Breast cancer; Estrogen receptor; Progesterone receptor; Human epidermal growth factor receptor 2; Discordance; Concordance; Tumor heterogeneity; Prognosis.

***Correspondence to:** Kylie J. Mansfield, Graduate School of Medicine, University of Wollongong, Northfields Ave, Wollongong, NSW 2522, Australia. ORCID: https://orcid.org/0000-0002-1472-4697. Tel: +61-2-4221-5851, E-mail: kylie@uow.edu.au

**How to cite this article:** Haria A, Hill J, Mansfield KJ. Receptor Discordance between Primary and Recurrent Breast Cancer: A Systematic Literature Review. *Oncol Adv* 2024;2(4):174–183. doi: 10.14218/OnA.2024.00027.

© 2024 The Author(s). This article has been published under the terms of Creative Commons Attribution-Noncommercial 4.0 International License (CC BY-NC 4.0), which permits noncommercial unrestricted use, distribution, and reproduction in any medium, provided that the following statement is provided. "This article has been published in *Oncology Advances* at https://doi.org/10.14218/OnA.2024.00027 and can also be viewed on the Journal's website at https://www.xiahepublishing.com/journal/oncoladv".

current breast cancer would retain the same receptor profile as the primary tumor. However, a review of the literature has demonstrated discordance rates for ER (19.3%, 95% confidence interval (CI) 15.8–23.4), PR (30.9%, 95% CI 26.6–35.6), and HER2 (10.3%, 95% CI 7.8–13.6) between primary and recurrent cancers,[8] indicating that such discordance may worsen survival outcomes.[9]

To identify receptor discordance, a re-biopsy of the recurrent cancer is needed to compare its hormone expression with that of the primary cancer. Some guidelines recommend re-biopsy for recurrent breast cancer;[10,11] however, this is not consistent across all guidelines, and the decision ultimately falls on the treating physician.[4,10,12–14] Biopsies may not be performed for various reasons, including the historical assumption that the receptor profiles remain the same, the risks and inconvenience of the procedure, and the potential impact on the patient's quality of life.[15,16] However, recent literature increasingly questions these assumptions.[9,15,17]

This systematic literature review (SLR) aimed to examine studies on receptor expression in primary and recurrent breast cancer published from 2013 to 2023 and synthesize the current understanding of receptor discordance, its impact on prognosis, and whether primary tumor heterogeneity plays a role in the discordance.

## Materials and methods

### *Inclusion/exclusion criteria*

Studies included in this SLR were original research papers, published in English between January 2013 and December 2023, comparing ER, PR, and HER2 receptor status in paired biopsies from primary and recurrent breast cancer. The main outcome measure was the discordance rate for each receptor, with the primary endpoint being the impact of discordance on prognosis. Studies were included if they measured receptor expression by immunohistochemistry (IHC) only (for ER and PR determination) or IHC combined with fluorescence *in situ* hybridization (FISH) for HER2.

### *Search strategy*

Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, Covidence (a software platform for SLRs) was used to ensure transparency and reproducibility in our review. A comprehensive search of four widely recognized databases—Web of Science, Scopus, MEDLINE, and PubMed—was conducted. The search terms used were ("Breast Cancer" OR "Breast Tumor" OR "Breast Neoplasms" OR "Mammary Carcinoma" OR "Breast Carcinoma") AND ("Recurrence" OR "Recurrent" OR "Relapse" OR "Secondary" OR "Metastatic") AND ("Discordance" OR "Discrepancy" OR "Change" OR "Conversion" OR "Switch") AND ("Primary" OR "Initial" OR "First Presentation") AND "Heterogen*".

The results were imported into Covidence, and duplicate articles were automatically identified and removed. Two independent reviewers conducted a rigorous screening process (Fig. 1). In the initial screening phase, we reviewed the titles and abstracts, excluding studies (n = 374) that did not align with our research goals, lacked a full title or abstract, were gray literature (e.g., abstracts from conference meetings, non-peer-reviewed literature), were review articles, case reports, or were not in English.

The secondary screening phase involved a full-text review, excluding articles (n = 63) that did not address the research question, did not employ paired immunohistochemistry biopsy testing, or lacked data suitable for further analysis. Inclusion and exclusion decisions were independently assessed by two authors (AH and KJM), with disagreements resolved through discussion until a consensus was reached. A total of 10 articles met the study criteria (Fig. 1).

## Results

### *Study characteristics*

A total of 10 studies comparing receptor expression in primary and recurrent breast cancer were included in this SLR. The majority of these articles were published in the last three years (n = 7, since 2020),[18–24] with the remaining three published in 2018,[25] 2017,[26] and 2014.[27] These studies represent a wide geographical distribution, including Germany,[21,25] the USA,[23,24] China,[18,20,22] Australia,[27] the Netherlands,[24,26] and India (Table 1).[19] Most studies were retrospective cohort studies (n = 8), with only two being prospectively planned (Table 1).[21,22] The included studies had significant duration, ranging from four years to 50 years.[19,27] Sample sizes varied significantly, ranging from 20 (for a study of six years' duration) to 1,173 patients (for a study of nine years' duration), indicating a broad spectrum of study scales (Table 1). While most studies included data from more than 100 patients (n = 6),[18,20–24] some studies (n = 4) provided results from a smaller number of patients (20 to 55),[19,25–27] limiting the generalizability of findings to the broader breast cancer patient population.

The study participants were generally representative of women diagnosed with breast cancer, with ages ranging from 21 to 82 years. The mean/median age reported in seven studies was approximately 50 years,[18–20,22,24,25,27] aligning with typical diagnosis ages for breast cancer in women.[3] However, it is important to note that these women had experienced recurrences following initial treatment, underscoring age as an independent risk factor for breast cancer recurrence.[28,29] The receptor expression of the primary breast cancer at diagnosis was provided in all included studies and was comparable to the reported literature.[5,6] Hormone receptor expression varied from 28% PR-positive to 92% ER-positive.[26,30] Overall, approximately 60% of the primary breast cancers were HR-positive at initial diagnosis, comparable to published reports of approximately 70% of patients having HR-positive cancer at diagnosis.[6] HER2 expression averaged at just over 20%, with a range between 4% and 44%,[24,26] aligning with expected rates of HER2 amplification in breast cancers at diagnosis.[5,6]

The most common sites for metastasis (Table 1) were bone,[18,19,21,22,26,27] liver,[18–20,22,23,26,27] lungs,[18–20,22,23,26,27] and brain,[19,22–24,26,27] consistent with literature reports on breast cancer metastasis.[30,31]

### *Methods used for determining receptor status*

It has been postulated that receptor discordance may stem from a genuine biological manifestation of tumor heterogeneity or technical challenges, such as the inconsistent reproducibility of IHC, techniques.[32–34] Therefore, the first consideration in evaluating the literature was the methods used to determine receptor expression. To ensure consistency and comparability, this study included literature that utilized IHC only (for ER and PR determination) or IHC with FISH in the case of HER2 (Table 2).[18–27] The Royal College of Pathologists in Australia recommends including FISH for equivocal IHC findings for HER2.[35]

IHC is widely used by pathologists to detect the presence of specific antigens or receptors in tissue samples, aiding in cancer identification and differentiation. In terms of breast tissue, there is

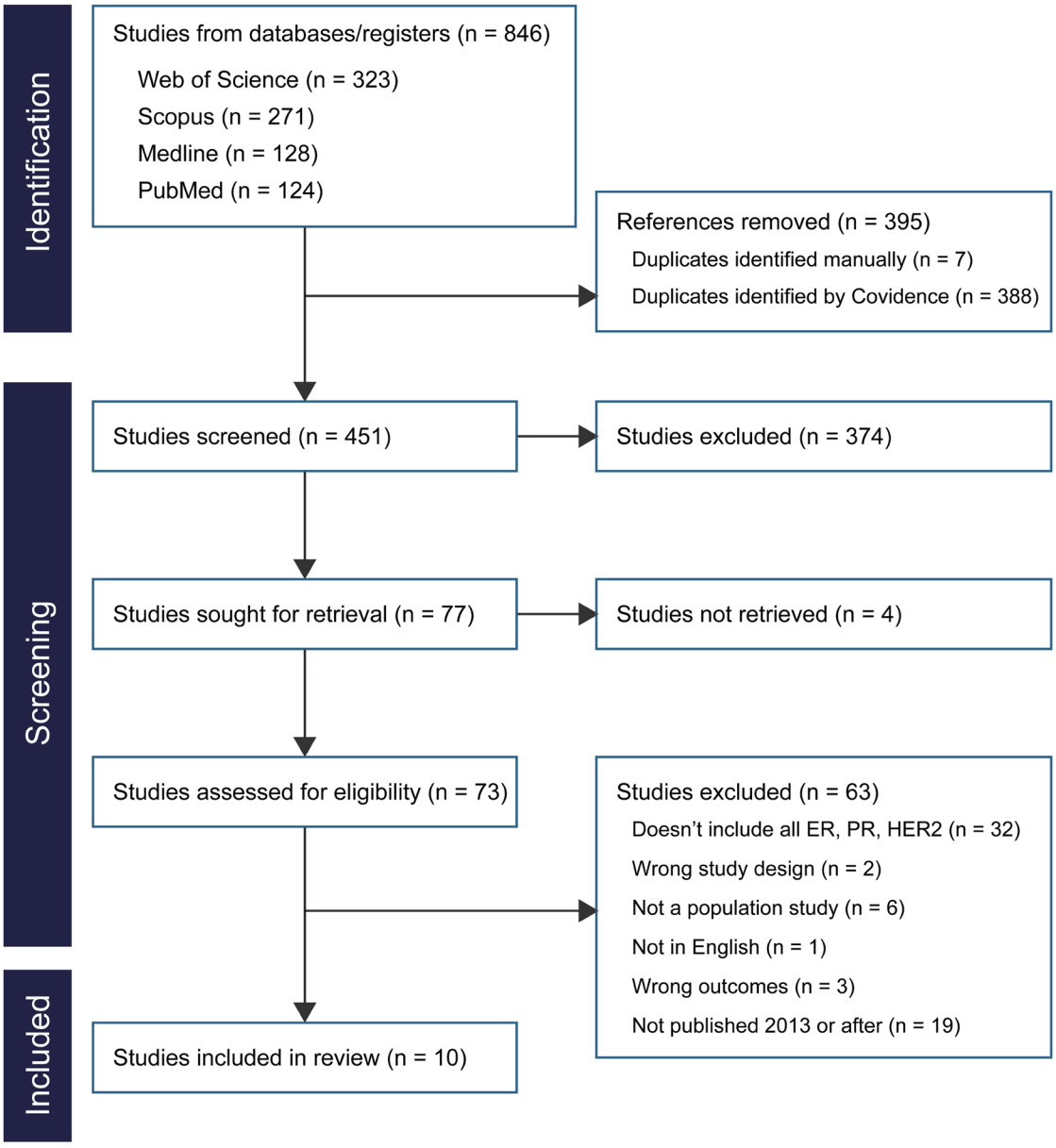


**Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram illustrating the identification, screening, and selection of articles included in this systematic literature review.** Eligible studies were original research papers that compared estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) receptor status in primary and recurrent breast cancer, published between 2013 and 2023, and written in English.

a large range of markers that could be used to identify cancer, to differentiate benign lesions from carcinoma, or to differentiate between carcinoma *in situ* and invasive carcinoma.[36] For this review, HR expression discordance was chosen as HR status is predictive of treatment and is a good prognostic indicator, influencing metastasis risk, recurrence rates, and survival.[6] In contrast to IHC, FISH examines DNA expression related to a specific receptor, such as HER2 in breast cancer. In cases where the IHC result for HER2 is equivocal, FISH can identify patients with HER2-positive tumors who could benefit from HER2-targeted therapy.[37] Identification of HER2 amplification is crucial as it is associated with a poor prognosis and a more aggressive form of breast cancer.[6,37] IHC with FISH was used for HER2 status determination in 8 of the included studies.[18,19,22–27] Two studies did not indicate the HER2 threshold used.[20,21]

Another important consideration was the threshold used to confirm receptor expression, commonly defined as the percentage of positive cells. The use of a threshold for scoring IHC results by counting the percentage of positive cells is common and was the first scoring system used by pathologists.[38,39] A threshold of at least 1% positive cells indicates eligibility for hormonal therapy.[36] The 2021 St. Gallen International Consensus Guidelines categorize breast cancer based on the percentage of positive cells: responsive (10%), response uncertain (1–9%), and nonresponsive

**Table 1. Main characteristics of studies included in the systematic literature review**

| Author | Study design | Duration | No. of patients | Age (range) | % Receptor positive at diagnosis | Sites of metastatic biopsy | Setting |
|---|---|---|---|---|---|---|---|
| Hu *et al*., 2023[18] | Single centre Retrospective analysis | 6 years (2014–2019) | 130 | Median 55 (24,86) | ER: 63%; PR: 60%; HER2: 32% | Liver, lung, bone, other | China |
| Shanthala *et al*., 2023[19] | Prospectively planned retrospective single-centre cohort study | 4 years | 51 | Median 46 (24, 68) | ER: 92%; PR: 82%; HER2: 10% | Lung, liver, bone, ovaries, adrenal, cervix, brain, pleura | India |
| Lv *et al*., 2022[20] | Single centre Retrospective analysis | 9 years (2010–2018) | 1,173 | Median 46 (27–82) | ER: 57%; PR: 53%; HER2: 30% | Liver, lymph nodes, chest wall, lungs, breast, bone, stomach, colon, other | China |
| Kolberg-Liedtke *et al*., 2021[21] | Prospectively planned retrospective multi-centre cohort study | 30 year (1980–2010) | 592 | Unspecified | ER: 66%; PR: 60%; HER2: 16% | Visceral, bone, lymph node/ soft tissues | Germany |
| Zhao *et al*., 2021[22] | Retrospective single institutional cohort | 12 years | 426 | Mean 45.9 | ER: 59%; PR: 50%; HER2: 21% | Bone, lung, liver, CNS, lymph nodes, soft tissue | China |
| Chen *et al*., 2020[23] | Retrospective single institution cohort | 21 years (1998–2019) | 390 | Unspecified | ER: 76% ER; PR: 55% PR; HER2: 22% | Bone, liver, lung, brain | USA |
| Hulsbergen *et al*., 2020[24] | Retrospective muti-institutional cohort | 17 years (2001–2018) | 219 | Mean 51.85 (SD 10.61) | ER: 53%; PR: 36%; HER2: 44% | Brain | USA, Netherlands |
| Thangarajah *et al*., 2018[25] | Retrospective cohort | 6 years (2013–2018) | 20 | Mean 56 (21,70) | HR: 50%; HER2: 25% | Supraclavicular | Germany |
| Szekely *et al*., 2017[26] | Autopsy study | 13 years (2001–2014) | 25 | Unspecified | ER: 64%; PR: 28%; HER2: 4% | Lung, bone, liver, adrenal, CNS, Gynae organs, other | Netherlands |
| Cummings *et al*., 2014[27] | Retrospective longitudinal single centre cohort study of autopsies | 50 years (1957–2007) | 55 | Median 52 | ER: 49%; PR: 58%; HER2: 23% | Lung, bone, liver, adrenal, CNS, Gynae organs, other | Australia |

CNS, central nervous system; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SD, standard deviation.

(0%).[12] Four studies used a 1% threshold for positive ER or PR receptor expression,[18,19,23,26] while three studies used a 10% threshold.[22,24,25] The remaining three studies did not report the threshold used.[20,21,27]

The final distinction was whether the researchers determined their own receptor expression results or used pathology department reports. Most of the included studies (n = 6) examined pathology database slides or biopsy samples independently,[18,19,22,23,26,27] minimizing inter-observer variability and strengthening the findings. Four studies based their analysis on pathology reports produced at the time of clinical diagnosis.[20,21,24,25]

### *Results relating to receptor discordance*

The primary purpose of this SLR was to examine ER, PR, and HER2 receptor expression in primary and recurrent breast cancer tissue. Table 3 provides an overview of receptor concordance, discordance, gain, and loss across the 10 included studies published between January 2013 and December 2023.[18–27] Receptor concordance refers to unchanged receptor status between primary and recurrent breast cancer. Receptor discordance indicates a change in receptor status between primary and recurrent breast cancer. Receptor gain occurs when a receptor that was not present in the primary tumor is detected in the recurrent tumor, while receptor loss refers to when a receptor that was present in the primary tumor is no longer detected in the recurrent tumor.

ER concordance was reported in eight out of the 10 studies (Table 3).[18–20,22–25,27] In one study,[21] ER and PR were reported together as hormone receptors. On average, across the eight studies, ER concordance was reported to be 80.69% (discordance 19.31%). This is consistent with previously reported ER discordance rates.[8] ER concordance ranged from 44.44% to 86.90%.[18,20] Hu *et al*.[18] reported a concordance of 44.44%, meaning that 44.44% of patients (or n = 58) of the 130 included patients had similar levels of ER expression in their primary and recurrent breast cancer. ER gain was reported in six out of 10 studies,[18–20,22–24] with an average ER gain of 7.19%, ranging from 1.85% to 29.17%.[18,24] ER loss

**Table 2. Methods used to determine receptor expression in the included studies**

| Author | Cancer receptor determination method | Threshold for HR +ve | Threshold for HER2 | Method of determination |
|---|---|---|---|---|
| Hu *et al*., 2023[18] | Information of pathology records and patients' record followed by paired slides review - statuses were determined using IHC +/− FISH | >1% IHC | IHC±FISH# | Independent analysis |
| Shanthala *et al*., 2023[19] | Pathology database of specimens and patients' medical records followed by paired slides review using IHC +/− FISH according to ASCO/CAP 2013/2018 guidelines | >1% IHC | IHC±FISH# | Independent analysis |
| Lv *et al*., 2022[20] | Pathology reports of patients - methodology unspecified | Unspecified | Unspecified | Patient pathology report |
| Kolberg-Liedtke *et al*., 2021[21] | Information of pathology records and patients' record - statuses were determined using IHC | Unspecified | Unspecified | Patient pathology report |
| Zhao *et al*., 2021[22] | Information of pathology records and patients' record followed by paired slides review - statuses were determined using IHC +/− FISH | >10% IHC | IHC±FISH# | Independent analysis |
| Chen *et al*., 2020[23] | Pathology database of specimens followed by paired slides review using IHC +/− FISH according to ASCO/CAP 2013/2018 guidelines | >1% IHC | IHC±FISH# | Independent analysis |
| Hulsbergen *et al*., 2020[24] | Information of pathology records and patients' record - statuses determine using IHC +/− FISH | >10% IHC | IHC±FISH# | Patient pathology report |
| Thangarajah *et al*., 2018[25] | Information of pathology records and patients' record - statuses were determined using IHC +/− FISH | >10% IHC | IHC±FISH# | Patient pathology report |
| Szekely *et al*., 2017[26] | Pathology database of specimens and patients' medical records followed by available specimen slides and autopsy extraction of tissue samples using IHC +/− FISH according to ASCO/CAP 2013 guidelines | >1% IHC | IHC±FISH# | Independent analysis |
| Cummings *et al*., 2014[27] | Review of pathology and autopsy database of specimens using IHC +/− FISH | Any level of IHC | IHC±FISH# | Independent analysis |

#For human epidermal growth factor receptor 2 (HER2) determination, immunohistochemistry (IHC) was performed first, with a HER2 score of 0-1+ indicating negative (-ve), 2+ as equivocal, and 3+ as positive (+ve). Fluorescence *in situ* hybridization (FISH) was used for confirmation when HER2 IHC results were equivocal. ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; HR, hormone receptor;

was reported in seven out of 10 studies,[18–20,22,24,26] with an average ER loss of 14.2%, ranging from 10.6% to 62.5%.[20,26] These findings indicate dynamic changes in ER status over time in primary and recurrent breast cancer.

Similarly, PR concordance was reported in 8 out of the 10 studies (Table 3).[19,20,22–27] On average, PR concordance was 65.51%, with discordance of 34.39%, aligning with previously reported rates.[8] PR concordance ranged from 31.37% to 74.76%.[18,24] This was again similar to the PR discordance of 30.9% reported previously.[8] PR gain was reported in six out of 10 studies,[18–20,22–24] with an average PR gain of 9.54%, ranging from 2.86% to 33.33%.[18,24] PR loss was reported in seven out of 10 studies,[18–20,22–24,26] with an average PR loss of 25.61%, ranging from 22.1% to 90.91%.[20,26] These findings also indicate dynamic changes in PR status over time in primary and recurrent breast cancer.

Compared to ER and PR, HER2 concordance shows the least variation between primary and recurrent breast cancer (Table 3). A previous meta-analysis reported a discordance rate of 10.3% for HER2 between primary and recurrent breast cancer.[8] HER2 concordance was recorded in nine out of the 10 included studies.[18–25,27] On average, HER2 concordance was 84.97% (discordance 15.04), although HER2 concordance ranged from 70% to 96.4%.[25,27] HER2 gain was reported in seven out of 10 studies,[18–24] with an average HER2 gain of 9.59%, ranging from 1.96% to 14.9%.[19,21] HER2 loss was reported in eight out of 10 studies,[18–24] with an average HER2 loss of 5.97%, ranging from 2.49% to 50.0%.[24,26] These findings indicate some dynamic changes in HER2 status over time. Due to the lack of data, no correlations between HR loss and HER2 receptor gain could be determined, but this remains an important area for future research.

### *Impact of hormone receptor loss on prognosis or metastasis*

A measure of prognosis was reported in seven of the 10 included studies, although it was measured in various ways (Table 4).[18,19,21–24,26,27] Three studies utilized Disease-Free Survival as a measure of prognosis,[18,22,23] which is the time between initial diagnosis and recurrence. Three studies utilized Post-Recurrence Survival, or survival time from recurrence to death,[21,22,24] and three studies utilized Overall Survival, which accounts for the time from initial diagnosis to death.[22,23,27]

All seven included studies that reported on prognosis observed a poorer prognosis associated with receptor loss.[18,19,21–24,27] Two studies also noted that patients with receptor gain had a better prognosis with treatment.[22,24] The impact of receptor loss in recurrent breast cancer on prognosis is important, as the included studies showed a higher degree of HR (ER and PR) loss compared to receptor gain (see the average scores at the bottom of Table 3; ER 14% loss, 7% gain; PR 26% loss, 9% gain).[20–23] Two studies suggested that adjuvant endocrine treatment for primary cancer was likely associated with the loss of PR and ER in recurrent breast cancer.[20,22] Similar to antimicrobial resistance, receptor discordance may be due to tumor heterogeneity in primary cancer, where some cells are successfully treated while others are resistant and seed recurrences.

**Table 3. Rates of reported receptor concordance, discordance, or change in the included studies**

| Study | Estrogen receptor | | | | Progesterone receptors | | | | HER2 receptors | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Concordance | Discordance | ER gain | ER loss | Concordance | Discordance | PR gain | PR loss | Concordance | Discordance | HER2 gain | HER2 loss |
| Hu *et al.*, 2023[18] | 44.44% | 55.56% | 29.17% | 26.39% | 47.23% | 52.77% | 33.33% | 19.44% | 74.62% | 25.38% | 8.96% | 16.42% |
| Shanthala *et al.*, 2023[19] | 52.94% | 47.06% | 23.53% | 23.53% | 31.37% | 68.63% | 23.53% | 45.10% | 94% | 6.00% | 1.96% | 3.92% |
| Lv *et al.*, 2022[20] | 86.90% | 13.10% | 6.90% | 10.60% | 68.70% | 31.30% | 9.10% | 22.10% | 86.20% | 13.80% | 10.10% | 3.80% |
| Kolberg-Liedtke *et al.*, 2021[21] | 81.3%# | – | 5.5%# | 13.2%# | see ER# | see ER# | see ER# | see ER# | 78.40% | 21.60% | 14.90% | 6.70% |
| Zhao *et al.*, 2021[22] | 78.90% | 21.10% | 6.30% | 14.80% | 66.80% | 33.20% | 5.50% | 27.70% | 88.40% | 11.60% | 6.10% | 5.50% |
| Chen *et al.*, 2020[23] | 81.66% | 18.34% | 2.58% | 15.76% | 59.71% | 40.29% | 9.28% | 31.01% | 86.29% | 13.71% | 5.92% | 7.79% |
| Hulsbergen *et al.*, 2020[24] | 83.34% | 16.66% | 1.85% | 14.81% | 74.76% | 25.24% | 2.86% | 22.38% | 89.55% | 10.45% | 7.96% | 2.49% |
| Thangarajah *et al.*, 2018[25] | 80.00% | 20.00% | – | – | 63.20% | 36.80% | – | – | 70.0% | 30.0% | – | – |
| Szekely *et al.*, 2017[26] | – | | – | 62.50% | – | – | – | 90.91% | – | – | – | 50.0% |
| Cummings *et al.*, 2014[27] | 56.40% | 43.60% | – | – | 67.30% | 32.70% | – | – | 96.40% | 3.60% | – | – |
| Average* | 80.69% | 19.31% | 7.19% | 14.22% | 65.51% | 34.49% | 9.54% | 25.61% | 84.96% | 15.04% | 9.59% | 5.97% |

#Findings reported by Kolberg-Liedtke *et al.*[37] included both estrogen receptor (ER) and hormone receptor (HR) combined. *Average weighted according to sample size. HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

The literature suggests that ER and PR expression is not only discordant during breast cancer recurrence (following diagnosis and subsequent treatment) but also unstable during the metastatic process.[40–43] Shanthala and associates observed that PR loss may indicate a shift toward a more aggressive phenotype.[19] Zhao *et al*.[22] reported higher ER discordance in distant metastasis compared to local metastasis. Receptor discordance has also been noted in axillary lymph node metastases, identified during primary tumor biopsies and when assessing patients with multiple primary breast tumors.[40,44–46] Chen *et al*.[19] also observed discordance within the same organ and reported discordance between two different metastatic sites. Szekely found greater discordance of primary and recurrent tumors than between two separate recurrent tumor sites.[26] The hypothesis is that HR receptor loss leads to a shift toward a more aggressive phenotype, which is more likely to metastasize, is associated with tumor recurrence, and is less responsive to treatment, leading to poorer prognosis (Fig. 2).[32]

## Discussion

This systematic review of the literature provides evidence for receptor discordance between primary and recurrent breast cancer. This review adds to the existing evidence refuting the assumption that primary and recurrent breast cancer cells have uniform receptor profiles.[16,47–49] The current study identified discordance rates comparable to those in a previous meta-analysis,[8] for ER (19.3% vs 19.3%) and PR (34.9% vs 30.9%), but higher HER2 discordance (15.04% vs 10.3%). The precise cause of receptor discrepancy between primary and recurrent breast cancer remains unclear. Possible mechanisms include tumor heterogeneity, bio-evolution of the tumor, drug resistance, and differences in sampling/assay techniques.[11,50–54] Very little has been explored in the literature to date on tumor heterogeneity as the mechanism of receptor discordance. Tumor heterogeneity, the concept that not all cells in a tumor are identical, may be the cause of the observed variability in the expression of ER, PR, and HER2.[16,55,56]

At its crudest level, the treatment of breast cancer assumes uniformity within the tumor. However, tumor heterogeneity has been observed both between different tumor lesions in the same patient (inter-tumoral heterogeneity) and within a single lesion (intra-tumoral heterogeneity).[18,20,27,56] Tumor heterogeneity could lead to reduced treatment response, potentially affecting patient management and prognosis.[57] While it adds complexity to treatment decisions, recognizing tumor heterogeneity is essential for personalizing treatment strategies. Two studies in the current review noted that primary cancer adjuvant endocrine treatment was associated with a loss of PR and ER in recurrent breast cancer.[20,22] This may result from inherent heterogeneity within the primary tumor itself. This heterogeneity could manifest in two ways: adaptive evolution, where tumor cells develop resistance to treatments and evolve over time, resulting in receptor status changes; and selective replication, where a subpopulation of cells lacking certain receptors, such as ER and PR, survive treatment and continue to replicate, contributing to overall heterogeneity and receptor discordance in recurrent tumors.

Understanding tumor heterogeneity is crucial for comprehending disease progression and treatment outcomes, and it necessitates further research. Biopsies of recurrent cancer can offer insights into disease behavior, treatment resistance, and tumor cell evolution, potentially leading to improved targeting of treatments and better patient outcomes. However, whether metastatic tumors should be biopsied remains debated, despite numerous publica-

**Table 4. Impact of receptor discordance on prognosis and metastasis**

| Author | Disease free survival | Overall survival | Post recurrence survival | Other | HR influences on prognosis | HER2 influence on prognosis | Reported discordance in metastasis |
|---|---|---|---|---|---|---|---|
| Hu *et al*., 2023[18] | X | | | Ki67 marker | +ve receptor status had better prognosis than those with -ve receptor status | Trend (not significant) for HER2 expression or HER2 gain → prolonged survival | |
| Shanthala *et al*., 2023[19] | | | | Correlation with staging of cancer | ER loss more frequently associated with worse prognosis | No comment | Yes |
| Kolberg-Liedtke *et al*., 2021[21] | | | X | | +ve receptor status had better prognosis than those with -ve receptor status | HER2 loss was associated with poorer post recurrence survival compared to concordant HER2 | |
| Zhao *et al*., 2021[22] | X | X | X | | +ve receptor status had better prognosis than those with -ve receptor status | Prognosis related to treatment not HER2 expression | Yes |
| Chen *et al*., 2020[23] | X | X | | | +ve receptor status → better prognosis than those with -ve receptor status | Trend (not significant) for HER2 gain → prolonged survival | Yes |
| Hulsbergen *et al*., 2020[24] | | | X | | ER loss was identified with worse prognosis | No comment | |
| Szekely *et al*., 2017[26] | | | | | | | Yes |
| Cummings *et al*., 2014[27] | | X | | | +ve receptor status had better prognosis than those with -ve receptor status | No comment | |

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

tions and some updated guidelines recommending it.[4,10–14] All of the studies included in this SLR recommended re-biopsy of metastatic lesions if possible.[18–27]

The available research on the clinical significance of primary and recurrent tumor profiles is variable, with limited prospective data to guide clinical practice. Understanding the impact of ER, PR, and HER2 conversion on treatment schedules and breast cancer patient survival remains incomplete. The available data are limited, as is the optimal time for retesting tumor biology. In this context, clinical judgment remains crucial for guiding a reassessment of tissue biology. The decision to re-biopsy is multifactorial, involving considerations of patient impact (e.g., safe biopsy locations, acceptance of repeat biopsies, pain/discomfort, and treatment planning) versus the benefits of confirming receptor expression and making appropriate treatment choices. In the future, non-invasive diagnostics (liquid biopsies) could identify tumor cell markers, enhance clinical decision-making, and increase confidence in treatment choices for tumor recurrences, as well as being valuable aids for future research in this field.[58]

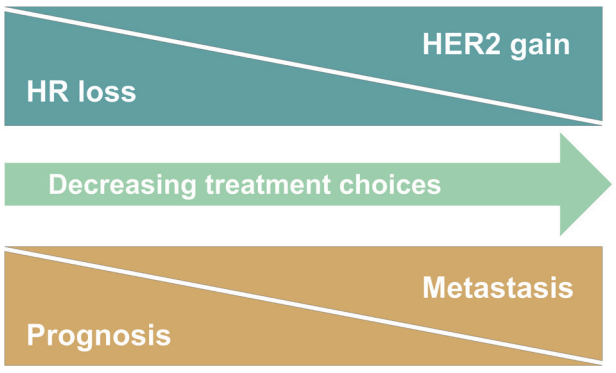


**Fig. 2. Breast cancer receptor status and its impact on therapy, metastasis, and prognosis.** HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

Agreement on study design or techniques is vital for ensuring the reliability and validity of results, allowing the field to progress. Collection of consistent demographic data, including treatments undertaken, age at diagnosis of primary and recurrent breast cancer, and patient menopausal status, would facilitate comparisons between studies. The retrospective nature of many of the included studies likely limited data availability, preventing comparisons between receptor discordance and treatments undertaken. Unravelling the complexity of tumor heterogeneity will likely involve a mix of methodologies, such as longitudinal studies, randomized controlled trials, and molecular profiling techniques. More retro-

spective studies could help identify patients most likely to benefit from certain treatments or at higher risk of recurrence. Focusing on these considerations would enhance our understanding of breast cancer, improve clinical practices, and revolutionize breast cancer research and clinical trial design, leading to more effective, personalized treatment strategies.

## Conclusions

Our study aimed to enhance the understanding of receptor discordance, its prognostic implications, and the evidence suggesting tumor heterogeneity in breast cancer. The discordance rates observed between primary tumors and metastatic sites were consistent with the loss of hormone receptor expression, suggesting the emergence of resistant tumor clones. Authors of the included studies found that patients with a loss of ER and PR had a worse prognosis, while those with receptor gain responded well to treatment changes, leading to a better prognosis. Our study highlights the need for further research to fully comprehend the implications of tumor heterogeneity and receptor discordance. A deeper understanding of these factors could significantly impact the treatment and prognosis of breast cancer patients.

## Acknowledgments

The authors wish to acknowledge the contribution of Prof. Phil Clingan in the original study design and Prof. Paul de Souza for advice relating to the final manuscript.

## Funding

This study received no external grant support or other financial assistance.

## Conflict of interest

The authors declare no conflicts of interest.

## Author contributions

Study concept and design (AH, KJM, JH), acquisition of data (AH, KJM), analysis and interpretation of data (AH, KJM), drafting of the manuscript (AH, KJM), critical revision of the manuscript for important intellectual content (JH, KJM), and study supervision (KJM). All authors have made significant contributions to this study and have approved the final manuscript.

## Data sharing statement

The compiled data from the systematic review of the literature used to support the findings of this study are included within the article.

## References

[1] World Health Organization. Breast Cancer Fact Sheet. Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer. Accessed 26 August 26, 2024.

[2] Australian Institute of Health and Welfare. Cancer Data in Australia. Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia. Accessed August 26, 2024.

[3] Cancer Australia. Breast Cancer in Australia Statistics 2023. Available from: https://www.canceraustralia.gov.au/cancer-types/breast-cancer/statistics. Accessed August 26, 2024.

[4] Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, *et al*. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32(12):1475–1495. doi:10.1016/j.annonc.2021.09.019, PMID:34678411.

[5] Clusan L, Ferrière F, Flouriot G, Pakdel F. A Basic Review on Estrogen Receptor Signaling Pathways in Breast Cancer. Int J Mol Sci 2023;24(7):6834. doi:10.3390/ijms24076834, PMID:37047814.

[6] Waks AG, Winer EP. Breast Cancer Treatment: A Review. JAMA 2019;321(3):288–300. doi:10.1001/jama.2018.19323, PMID:30667505.

[7] Courtney D, Davey MG, Moloney BM, Barry MK, Sweeney K, McLaughlin RP, *et al*. Breast cancer recurrence: factors impacting occurrence and survival. Ir J Med Sci 2022;191(6):2501–2510. doi:10.1007/s11845-022-02926-x, PMID:35076871.

[8] Schrijver WAME, Suijkerbuijk KPM, van Gils CH, van der Wall E, Moelans CB, van Diest PJ. Receptor Conversion in Distant Breast Cancer Metastases: A Systematic Review and Meta-analysis. J Natl Cancer Inst 2018;110(6):568–580. doi:10.1093/jnci/djx273, PMID:29315431.

[9] Shiino S, Ball G, Syed BM, Kurozumi S, Green AR, Tsuda H, *et al*. Prognostic significance of receptor expression discordance between primary and recurrent breast cancers: a meta-analysis. Breast Cancer Res Treat 2022;191(1):1–14. doi:10.1007/s10549-021-06390-6, PMID:34613502.

[10] Cardoso F, Paluch-Shimon S, Schumacher-Wulf E, Matos L, Gelmon K, Aapro MS, *et al*. 6th and 7th International consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). Breast 2024;76:103756. doi:10.1016/j.breast.2024.103756, PMID:38896983.

[11] Henry NL, Somerfield MR, Dayao Z, Elias A, Kalinsky K, McShane LM, *et al*. Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 2022;40(27):3205–3221. doi:10.1200/JCO.22.01063, PMID:35759724.

[12] Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, *et al*. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol 2021;32(10):1216–1235. doi:10.1016/j.annonc.2021.06.023, PMID:34242744.

[13] Loibl S, André F, Bachelot T, Barrios CH, Bergh J, Burstein HJ, *et al*. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2024;35(2):159–182. doi:10.1016/j.annonc.2023.11.016, PMID:38101773.

[14] Raghu Subramanian C, Talluri S, Mullangi S, Lekkala MR, Moftakhar B. Review of Bone Modifying Agents in Metastatic Breast Cancer. Cureus 2021;13(2):e13332. doi:10.7759/cureus.13332, PMID:33738175.

[15] Dowling GP, Keelan S, Cosgrove NS, Daly GR, Giblin K, Toomey S, *et al*. Receptor Discordance in Metastatic Breast Cancer; a review of clinical and genetic subtype alterations from primary to metastatic disease. Breast Cancer Res Treat 2024;207(3):471–476. doi:10.1007/s10549-024-07431-6, PMID:39090418.

[16] Grinda T, Joyon N, Lusque A, Lefèvre S, Arnould L, Penault-Llorca F, *et al*. Phenotypic discordance between primary and metastatic breast cancer in the large-scale real-life multicenter French ESME cohort. NPJ Breast Cancer 2021;7(1):41. doi:10.1038/s41523-021-00252-6, PMID:33863896.

[17] Criscitiello C, André F, Thompson AM, De Laurentiis M, Esposito A, Gelao L, *et al*. Biopsy confirmation of metastatic sites in breast cancer patients: clinical impact and future perspectives. Breast Cancer Res 2014;16(2):205. doi:10.1186/bcr3630, PMID:25032257.

[18] Hu X, Chen W, Li F, Ren P, Wu H, Zhang C, *et al*. Expression changes of ER, PR, HER2, and Ki-67 in primary and metastatic breast cancer and its clinical significance. Front Oncol 2023;13:1053125. doi:10.3389/fonc.2023.1053125, PMID:37188174.

[19] Shanthala S, Amirtham U, Gopal C, N SM, Jacob L, Babu G. Study of Biomarker Discordance between Primary and Recurrent Sites and its Clinical Implications in Metastatic Breast Cancer : A Single Institution-

al Study from India. South Asian J Cancer 2024;13(2):90–98. doi:10.1055/s-0043-1775807, PMID:38919661.
[20] Lv H, Niu L, Zhang M, Zeng H, Zhao S, Yan M. Diagnostic diversity and heterogeneity of tumors: a real-world study of metastasis re-biopsy in advanced breast cancer. Chin Med J (Engl) 2022;135(17):2076–2082. doi:10.1097/CM9.0000000000001969, PMID:35916549.
[21] Kolberg-Liedtke C, Wuerstlein R, Gluz O, Heitz F, Freudenberger M, Bensmann E, *et al*. Phenotype Discordance between Primary Tumor and Metastasis Impacts Metastasis Site and Outcome: Results of WSG-DETECT-PriMet. Breast Care (Basel) 2021;16(5):475–483. doi:10.1159/000512416, PMID:34720807.
[22] Zhao W, Sun L, Dong G, Wang X, Jia Y, Tong Z. Receptor conversion impacts outcomes of different molecular subtypes of primary breast cancer. Ther Adv Med Oncol 2021;13:17588359211012982. doi:10.1177/17588359211012982, PMID:33995598.
[23] Chen R, Qarmali M, Siegal GP, Wei S. Receptor conversion in metastatic breast cancer: analysis of 390 cases from a single institution. Mod Pathol 2020;33(12):2499–2506. doi:10.1038/s41379-020-0615-z, PMID:32620918.
[24] Hulsbergen AFC, Claes A, Kavouridis VK, Ansaripour A, Nogarede C, Hughes ME, *et al*. Subtype switching in breast cancer brain metastases: a multicenter analysis. Neuro Oncol 2020;22(8):1173–1181. doi:10.1093/neuonc/noaa013, PMID:31970416.
[25] Thangarajah F, Vogel C, Pahmeyer C, Eichler C, Holtschmidt J, Ratiu D, *et al*. Profile and Outcome of Supraclavicular Metastases in Patients with Metastatic Breast Cancer: Discordance of Receptor Status Between Primary and Metastatic Site. Anticancer Res 2018;38(10):6023–6026. doi:10.21873/anticanres.12952, PMID:30275235.
[26] Szekely B, Nagy ZI, Farago Z, Kiss O, Lotz G, Kovacs KA, *et al*. Comparison of immunophenotypes of primary breast carcinomas and multiple corresponding distant metastases: an autopsy study of 25 patients. Clin Exp Metastasis 2017;34(1):103–113. doi:10.1007/s10585-016-9830-x, PMID:27885435.
[27] Cummings MC, Simpson PT, Reid LE, Jayanthan J, Skerman J, Song S, *et al*. Metastatic progression of breast cancer: insights from 50 years of autopsies. J Pathol 2014;232(1):23–31. doi:10.1002/path.4288, PMID:24122263.
[28] Ono Y, Yoshimura M, Hirata K, Yamauchi C, Toi M, Suzuki E, *et al*. The impact of age on the risk of ipsilateral breast tumor recurrence after breast-conserving therapy in breast cancer patients with a > 5 mm margin treated without boost irradiation. Radiat Oncol 2019;14(1):121. doi:10.1186/s13014-019-1327-8, PMID:31291997.
[29] He XM, Zou DH. The association of young age with local recurrence in women with early-stage breast cancer after breast-conserving therapy: a meta-analysis. Sci Rep 2017;7(1):11058. doi:10.1038/s41598-017-10729-9, PMID:28894168.
[30] Riggio AI, Varley KE, Welm AL. The lingering mysteries of metastatic recurrence in breast cancer. Br J Cancer 2021;124(1):13–26. doi:10.1038/s41416-020-01161-4, PMID:33239679.
[31] Liu K, Huang AL, Chen XQ, Wu SG. Patterns of distant metastasis and survival outcomes in de novo metastatic breast cancer according to age groups. Front Endocrinol (Lausanne) 2024;15:1385756. doi:10.3389/fendo.2024.1385756, PMID:38752173.
[32] Kao JY, Tsai JH, Wu TY, Wang CK, Kuo YL. Receptor discordance and phenotype change in metastatic breast cancer. Asian J Surg 2021;44(1):192–198. doi:10.1016/j.asjsur.2020.05.032, PMID:32622530.
[33] Gerlinger M, Rowan AJ, Horswell S, Math M, Larkin J, Endesfelder D, *et al*. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012;366(10):883–892. doi:10.1056/NEJMoa1113205, PMID:22397650.
[34] Pusztai L, Viale G, Kelly CM, Hudis CA. Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. Oncologist 2010;15(11):1164–1168. doi:10.1634/theoncologist.2010-0059, PMID:21041379.
[35] Royal College of Pathologists of Australasia. Guideline: ASCO CAP 2018 HER2 Testing for Breast Cancer Guidelines - Recommendations for Practice in Australasia. Available from: https://www.rcpa.edu.au/getattachment/fecd094c-aaf4-416b-9ed5-4a61f5ac1a93/ASCO-CAP-2018-HER2-Testing-for-Breast-Cancer-Guide.aspx. Accessed August 26, 2024.
[36] Zaha DC. Significance of immunohistochemistry in breast cancer. World J Clin Oncol 2014;5(3):382–392. doi:10.5306/wjco.v5.i3.382, PMID:25114853.
[37] Petroni S, Caldarola L, Scamarcio R, Giotta F, Latorre A, Mangia A, *et al*. FISH testing of HER2 immunohistochemistry 1+ invasive breast cancer with unfavorable characteristics. Oncol Lett 2016;12(5):3115–3122. doi:10.3892/ol.2016.5125, PMID:27899970.
[38] Barnes DM, Harris WH, Smith P, Millis RR, Rubens RD. Immunohistochemical determination of oestrogen receptor: comparison of different methods of assessment of staining and correlation with clinical outcome of breast cancer patients. Br J Cancer 1996;74(9):1445–1451. doi:10.1038/bjc.1996.563, PMID:8912543.
[39] Fisher ER, Anderson S, Dean S, Dabbs D, Fisher B, Siderits R, *et al*. Solving the dilemma of the immunohistochemical and other methods used for scoring estrogen receptor and progesterone receptor in patients with invasive breast carcinoma. Cancer 2005;103(1):164–173. doi:10.1002/cncr.20761, PMID:15565575.
[40] Georgescu R, Boros M, Moncea D, Bauer O, Coros MF, Oprea A, *et al*. Discordance Rate in Estrogen Receptor, Progesterone Receptor, HER2 Status, and Ki67 Index Between Primary Unifocal and Multiple Homogenous Breast Carcinomas and Synchronous Axillary Lymph Node Metastases Have an Impact on Therapeutic Decision. Appl Immunohistochem Mol Morphol 2018;26(8):533–538. doi:10.1097/PAI.0000000000000483, PMID:28099174.
[41] Aitken SJ, Thomas JS, Langdon SP, Harrison DJ, Faratian D. Quantitative analysis of changes in ER, PR and HER2 expression in primary breast cancer and paired nodal metastases. Ann Oncol 2010;21(6):1254–1261. doi:10.1093/annonc/mdp427, PMID:19858088.
[42] Ataseven B, Gologan D, Gunesch A, Kehl V, Hoegel B, Beer M, *et al*. HER2/neu, Topoisomerase 2a, Estrogen and Progesterone Receptors: Discordance between Primary Breast Cancer and Metastatic Axillary Lymph Node in Expression and Amplification Characteristics. Breast Care (Basel) 2012;7(6):465–470. doi:10.1159/000345467, PMID:24715828.
[43] Jensen JD, Knoop A, Ewertz M, Laenkholm AV. ER, HER2, and TOP2A expression in primary tumor, synchronous axillary nodes, and asynchronous metastases in breast cancer. Breast Cancer Res Treat 2012;132(2):511–521. doi:10.1007/s10549-011-1610-3, PMID:21667123.
[44] Kuncman W, Orzechowska M, Kuncman Ł, Kordek R, Taran K. Intertumoral Heterogeneity of Primary Breast Tumors and Synchronous Axillary Lymph Node Metastases Reflected in IHC-Assessed Expression of Routine and Nonstandard Biomarkers. Front Oncol 2021;11:660318. doi:10.3389/fonc.2021.660318, PMID:34804912.
[45] Zhao S, Xu L, Liu W, Lv C, Zhang K, Gao H, *et al*. Comparison of the expression of prognostic biomarkers between primary tumor and axillary lymph node metastases in breast cancer. Int J Clin Exp Pathol 2015;8(5):5744–5748. PMID:26191291.
[46] Onisâi M, Dumitru A, Iordan I, Aliuș C, Teodor O, Alexandru A, *et al*. Synchronous Multiple Breast Cancers-Do We Need to Reshape Staging? Medicina (Kaunas) 2020;56(5):230. doi:10.3390/medicina56050230, PMID:32403360.
[47] Aurilio G, Disalvatore D, Pruneri G, Bagnardi V, Viale G, Curigliano G, *et al*. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. Eur J Cancer 2014;50(2):277–289. doi:10.1016/j.ejca.2013.10.004, PMID:24269135.
[48] Nishimura R, Osako T, Okumura Y, Tashima R, Toyozumi Y, Arima N. Changes in the ER, PgR, HER2, p53 and Ki-67 biological markers between primary and recurrent breast cancer: discordance rates and prognosis. World J Surg Oncol 2011;9:131. doi:10.1186/1477-7819-9-131, PMID:22004841.
[49] Ongaro E, Gerratana L, Cinausero M, Pelizzari G, Poletto E, Giangreco M, *et al*. Comparison of primary breast cancer and paired metastases: biomarkers discordance influence on outcome and therapy. Future Oncol 2018;14(9):849–859. doi:10.2217/fon-2017-0384, PMID:29527957.
[50] Almstedt K, Krauthauser L, Kappenberg F, Wagner DC, Heimes AS, Battista MJ, *et al*. Discordance of HER2-Low between Primary Tumors and Matched Distant Metastases in Breast Cancer. Cancers (Basel) 2023;15(5):1413. doi:10.3390/cancers15051413, PMID:36900203.

[51] Anand AS, Velayudhan ST. Discordance of Estrogen & Progesterone Receptors After Neoadjuvant Chemotherapy in Breast Cancer- an Indian Study. Indian J Surg Oncol 2016;7(3):316–319. doi:10.1007/s13193-016-0515-3, PMID:27651692.

[52] Sighoko D, Liu J, Hou N, Gustafson P, Huo D. Discordance in hormone receptor status among primary, metastatic, and second primary breast cancers: biological difference or misclassification? Oncologist 2014;19(6):592–601. doi:10.1634/theoncologist.2013-0427, PMID: 24807915.

[53] Rüdiger T, Höfler H, Kreipe HH, Nizze H, Pfeifer U, Stein H, *et al*. Quality assurance in immunohistochemistry: results of an interlaboratory trial involving 172 pathologists. Am J Surg Pathol 2002;26(7):873–882. doi:10.1097/00000478-200207000-00005, PMID:12131154.

[54] Amir E, Ooi WS, Simmons C, Kahn H, Christakis M, Popovic S, *et al*. Discordance between receptor status in primary and metastatic breast cancer: an exploratory study of bone and bone marrow biopsies. Clin Oncol (R Coll Radiol) 2008;20(10):763–768. doi:10.1016/j.clon.2008.08.005, PMID:18824337.

[55] Pertschuk LP, Axiotis CA, Feldman JG, Kim YD, Karavattayhayyil SJ, Braithwaite L. Marked Intratumoral Heterogeneity of the Proto-Oncogene Her-2/neu Determined by Three Different Detection Systems. Breast J 1999;5(6):369–374. doi:10.1046/j.1524-4741.1999.97088.x, PMID:11348316.

[56] Davis BW, Zava DT, Locher GW, Goldhirsch A, Hartmann WH. Receptor heterogeneity of human breast cancer as measured by multiple intratumoral assays of estrogen and progesterone receptor. Eur J Cancer Clin Oncol 1984;20(3):375–382. doi:10.1016/0277-5379(84)90084-1, PMID:6323188.

[57] Kalinowski L, Saunus JM, McCart Reed AE, Lakhani SR. Breast Cancer Heterogeneity in Primary and Metastatic Disease. Adv Exp Med Biol 2019;1152:75–104. doi:10.1007/978-3-030-20301-6_6, PMID:31456181.

[58] Adhit KK, Wanjari A, Menon S, Siddhaarth S. Liquid Biopsy: An Evolving Paradigm for Non-invasive Disease Diagnosis and Monitoring in Medicine. Cureus 2023;15(12):e50176. doi:10.7759/cureus.50176, PMID:38192931.