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REVIEW OPEN ACCESS

Prognostic Features and Clinical Outcomes Across Breast Cancer Subtypes Defined by Hormone Receptor and HER2 Status: A Literature Review

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Abstract

Introduction: Hormone-responsive breast cancer biologically varies from hormone-unresponsive breast cancer in treatment response. Hormone-responsive breast cancers are characterized by estrogen (ER) and progesterone (PR) receptors that, upon activation, alter gene expression and promote tumor growth. The presence of these receptors highlights ideal targets for treatments that block or lower hormone levels. In contrast, hormone-unresponsive breast cancers lack these receptors, exhibit insensitivity to endocrine therapy, and display poorer prognoses. Understanding the differences between hormone-responsive and unresponsive breast cancer presents crucial implications for developing effective treatment strategies, improving patient outcomes.

Methods: A literature review was conducted using PubMed to identify English-language, peer-reviewed studies published between 2014 and 2025 examining breast cancer subtypes based on ER, PR, and HER2 status. Clinical trials, population-based cohort studies, and subtype-specific analyses evaluating prognosis, metastatic potential, or treatment responsiveness were included. Fifteen studies met the inclusion criteria and were included in the qualitative synthesis.

Results: Hormone receptor-positive tumours expressing ER and PR demonstrated the most favourable outcomes, with slower metastasis and lower proliferative activity compared to receptor-negative tumours. Triple-negative breast cancer (TNBC) demonstrated the most aggressive biological course, characterized by increased metastatic potential and reduced responsiveness to endocrine therapy. Evidence from recent clinical trials indicates that in advanced TNBC, therapeutic benefit is primarily limited to immunotherapy-based combination strategies. While HER2 expression reflects a more aggressive biology, its presence enables targeted therapeutic intervention associated with improved patient outcomes.

Discussion: Differences in subtype biology, metastatic behaviour and treatment responsiveness highlight the importance of hormone receptor status and subtype classification in guiding the clinical management of breast cancer.

Conclusion: Hormone receptor status is a strong determinant of prognosis and treatment responsiveness across breast cancer subtypes, with HR-positive tumours demonstrating more favourable outcomes and TNBC exhibiting the most aggressive disease course. These findings emphasize the need to refine therapeutic strategies and guide the development of effective treatment options and molecular targets to improve outcomes across all breast cancer subtypes.

Keywords: estrogen receptor-positive breast cancer; Ki67; luminal breast cancer; metastasis; triple-negative breast cancer; progesterone receptor; HER2

Introduction

Breast cancer is the most common cancer affecting women worldwide, with new cases projected to increase by 38% globally by 2050 [1]. Breast cancer encompasses a broad spectrum of subtypes and underlying pathophysiological mechanisms, each associated with unique therapeutic approaches and clinical outcomes. Although multiple classification systems and criteria exist, breast cancer is most commonly categorized based on the expression of estrogen (ER), progesterone (PR), and human epidermal growth factor (HER2) receptors. Hormone receptor-positive (HR+) breast cancers differ biologically from hormone receptor-negative (HR-) breast cancers in both behaviour and treatment response. In comparison to HR+ breast cancer, HR- breast cancer presents with higher rates of metastasis, relapse, and poorer prognosis [2–4]. Accordingly, intrinsic molecular subtypes such as luminal A, luminal B, HER2 positive and basal-like have been established based on gene expression profiling [5].

Luminal A tumours are typically characterized by ER and PR positivity (ER+/PR+), lack of HER2 overexpression, and low proliferative activity, often reflected by low Ki-67 indices (typically defined as less than 20% in clinical practice) [5, 6]. Luminal B tumour subtypes are ER-positive and may also express PR. In general, PR expression is considered a favourable prognostic marker in breast cancer, with higher levels associated with improved clinical outcomes [4, 6]. Triple-

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negative breast cancers (TNBC) lack expression of ER, PR, and human epidermal growth factor (HER2) [7].

Distant metastasis refers to the spread of primary tumor cells to distant organs or tissues, where they form subsequent metastases, and is the leading risk factor associated with higher mortality and morbidity rates [2]. Although metastasis can occur in all breast cancer subtypes and negatively impacts survival rates, the TNBC subtype is associated with increased rates of distant metastasis and cancer recurrence [7]. Furthermore, TNBC is clinically challenging to treat as it is less responsive to endocrine therapy, thus resulting in limited treatment options and poorer prognosis [7]. Given the diverse pathophysiology of breast cancer, the objective of this review is to build on existing literature and explore the treatment differences between hormone-responsive and unresponsive breast cancers.

Methods

A comprehensive search was conducted to synthesize current research on the differences in available therapeutic treatments and clinical outcomes between hormone-responsive and hormone-unresponsive breast cancer subtypes. Database searches were conducted using PubMed to identify English-language, peer-reviewed studies published from 2010 to 2025. The following keywords were used to search for appropriate breast cancer studies; estrogen receptor positive breast cancer; Ki67; luminal breast cancer; metastasis; triple-negative breast cancer; progesterone receptor. Studies were eligible for inclusion if they examined breast cancer subtypes addressing hormone receptor status, prognosis, metastatic behaviour or treatment implications. Likewise, studies were excluded if they did not address subtype-specific differences, were non-peer-reviewed sources, or contained incomplete or unclear outcome reporting. Both primary research articles and high-quality review articles were included if they directly informed subtype-specific prognosis, biological behaviour, or treatment responsiveness. In total, 15 studies met the inclusion criteria and were included in this literature review.

In this review, immunohistochemistry-based classifications (ER, PR, and HER2 status) are discussed separately from intrinsic molecular subtypes derived from gene expression profiling, acknowledging that these systems are correlated yet distinct.

Results

Hormone Receptor-Positive Subtypes

Luminal A

A key differentiator identified across the reviewed studies lies in a tumour's expression of estrogen and progesterone receptors, with ER-positive and PR-positive tumours demonstrating more favourable outcomes compared to other subgroups. Amongst the luminal subtypes, luminal A tumours, defined as ER-positive and/or PR-positive, represent the majority of luminal cancers. They are characterized by low proliferation rates, which contribute to their slower growth and improved prognosis [5–7]. These features account for their low histological grade, low Ki-67 expression levels (defined as less than 20%), and strong response to endocrine therapy [8]. Their responsiveness to hormone therapy, including tamoxifen or aromatase inhibitors, is associated with delayed recurrence and improved survival rates [7–9].

Although the other breast cancer subtypes demonstrate comparatively poorer prognoses, luminal A tumours are not exempt from metastatic progression. The development of metastasis remains a critical risk factor across all forms of breast cancer. Hormone-positive tumours are most commonly associated with bone-dominant metastatic patterns, in contrast to the liver, lung, and central nervous system (CNS) involvement more frequently observed in other subtypes [2, 10]. This preference for bone metastasis partially accounts for the favourable prognosis of luminal A breast cancer, as bone metastasis generally follows a more gradual progression and remains responsive to endocrine therapy. Parkes et al. and Jiang et al. report the greatest increase in median time from initial breast cancer diagnosis to bone metastatic presentation in HR+ (ER- and/or PR-positive) tumours, specifically HR+/HER2- patients, a group that overlaps substantially with luminal A tumours [2, 10]. This finding aligns with the highest overall survival probability observed in patients with HR+ tumours and reflects the slower biological course of these tumours [2, 3, 10].

Luminal B

Luminal B tumours express estrogen receptors and may be either progesterone receptor-positive or -negative. In comparison, the Luminal B cancers demonstrate higher proliferative activity, higher histological grade, and elevated Ki-67 levels [5–7]. Together, these characteristics manifest into earlier recurrence and a shorter time interval between initial breast cancer diagnosis and metastatic presentation [10]. Although luminal B tumours are also commonly associated with bone-dominant metastatic patterns, they have a greater capacity to metastasize to various visceral organs as well. Luminal B cancers showcase reduced sensitivity to endocrine therapy relative to luminal A subtypes [4, 6]. However, they are more responsive to neoadjuvant chemotherapy [6]. As such, luminal B subtype occupies an intermediate position within the HR+ cancers. This reinforces the observation that although they remain responsive to endocrine therapy, this subtype represents a faster recurring and a more clinically demanding form of breast cancer. Consequently, treatments tend to incorporate a combination of endocrine therapy and chemotherapy to slow their more rapid proliferative behaviour. Even with combined treatment modalities, luminal B cancers do not typically achieve the long-term favourable outcomes seen in luminal A cancers.

Hormone Receptor-Negative Breast Cancer (TNBC)

Across all datasets examined in this review, hormone receptor-negative (HR-) tumours displayed a markedly more aggressive clinical course and poorer prognosis across all breast cancer subtypes reflecting their reduced benefit from endocrine therapy. Triple-negative breast cancers (TNBC), which frequently, but not exclusively, align with the basal-like molecular subgroup, are estrogen receptor-negative, progesterone receptor-negative, and HER2-negative. For this reason, the name "triple negative" was designated to this cancer subtype. TNBC accounts for a smaller proportion of breast cancer diagnoses, affecting approximately 15-20% of individuals. Triple-negative breast cancers are associated with aggressive biological behaviour and increased metastatic potential [7]. Conner et al. reports an increased tendency for TNBCs to metastasize to the lung, liver, and brain [11]. TNBC is unresponsive to endocrine therapy or medications targeting HER2. As a result, chemotherapy remains the primary treatment option for TNBCs.

Upon in vivo investigation of various invasive TNBC cell lines, the highest metastatic and tumorigenic lines were found to be MDA-MB-231, MDA-MB-468, and BT549 [2]. Conner et al. reported that cell morphology, which reflects differences in cellular shape and invasive behaviour, was a strong predictor of metastatic potential compared to cell line identity alone [11]. These morphological differences are characteristic of TNBC, which lacks hormone receptor and HER2 expression and as a result, cannot be stratified using receptor-based classification frameworks applied to HR+ or HER2+ breast cancer. Despite the variability that exists at the cellular level, this heterogeneity may underlie TNBC's more aggressive clinical course and poorer survival relative to other breast cancer subtypes [3, 6].

HER2-Positive Subtype

HER2-positive tumours demonstrate a more aggressive biological and clinical profile when compared to HR+, HER2-negative tumours [4]. Although HER2-positive cancers exhibit less aggressive metastatic progression than triple-negative breast cancer, they do not demonstrate the prolonged interval between diagnosis and metastatic progression observed in HR-positive tumours, particularly in cases of bone-dominant metastasis [2]. Overall, the metastatic behaviour of HER2-amplified tumours follows an intermediate biological course, with a generally poorer prognosis when compared to hormone-responsive breast cancers, but improved long-term outcomes in comparison to the TNBC subtype.

Discussion

Collectively, a consistent pattern emerged across the studies reviewed, revealing that the underlying biological differences between hormone receptor-positive and hormone receptor-negative breast cancer subtypes fundamentally shape both the therapeutic strategy and clinical prognosis. Tumours defined by estrogen and progesterone receptor expression are eligible for and often respond favorably to endocrine therapy, partly due to their low proliferation and slower growth rates [7–9]. Among the studies included in this review, IHC-defined HR+ tumours, particularly those co-expressing estrogen and progesterone receptors, conferred the highest survival probability, relative to other IHC-based subgroups, irrespective of the interval to metastatic progression, including cases with distant spread [2, 3, 6]. These findings reinforce the need for accurate receptor evaluation in guiding treatment selection, as misclassification of receptor status may lead to suboptimal therapeutic decisions. While immunohistochemistry and molecular profiling are central to subtype determination, there are limitations to both approaches relating to technical variability and tumor heterogeneity, highlighting the importance of comprehensive receptor assessment.

The data further revealed a clear divergence between ER+/PR+ tumours and those with mixed receptor expression, such as the ER+/PR- subtype [4, 6]. Progesterone receptor expression generally serves as a favourable prognostic marker, with higher expression correlating with improved survival outcomes [6]. Consequently, the ER+/PR- phenotype shows a lower overall survival rate and reduced sensitivity to endocrine therapy but exhibits a stronger response to chemotherapy [6]. These findings highlight the biologically relevant heterogeneity within the HR+ status, indicating that patients with the ER+/PR+ phenotype may benefit from earlier adoption of endocrine therapy and chemotherapy [4].

Worse prognoses emerge for triple-negative breast cancers, marked by high proliferative activity and early metastatic spread due to the limited availability of therapeutic targets [3, 6]. The classification of six TNBC cancer xenografts conducted by Conner et al. revealed heterogeneity in TNBC cell lines and wide variability in tumour growth and metastasis [2, 12]. These findings, however, have yet to be translated into established TNBC treatment subgroups, despite their cell-line-specific differences. Triple-negative breast cancer's unique molecular portrait means that the standard treatment course most commonly includes chemotherapy to address its aggressive nature; however, phase III date from Cortes et al. indicate that the addition of pembrolizumab improved overall survival in selected patients [5, 7, 13]. One of the primary hindrances to chemotherapy is developing resistance to anticancer drugs, which further limits therapeutic options for TNBCs. The development of drugs tailored to specific breast cancer subtypes and different cell lines, such as highly metastatic lines within TNBCs, may be a promising research avenue for future actionable therapeutic targets.

Advances in targeted therapy, such as in the case of HER2-positive breast cancers, has transformed the clinical trajectory of breast cancer subtypes. HER2 overexpression

represents an early molecular event in breast cancer progression and prior to HER2-targeted approaches, metastatic or recurrent breast cancer detection rates were significantly lower [5]. Once HER2-targeted therapy was established, and drugs such as trastuzumab, pertuzumab and tyrosine kinase inhibitors were introduced, long-term outcomes became more favourable [14, 15]. While these breakthroughs in research are transformative, an important note is to be made relating to availability and access to such treatments. There are differences in survival probability present between high Human Development Index (HDI) countries and medium- and low-HDI regions. While survival probability is projected to increase in high HDI countries, medium and low-HDI regions are expected to observe a decrease [1]. Differences in HER2-targeted therapeutic treatments and various other factors contribute to such healthcare disparities, and underscores an important reality, that therapeutic treatments must also be paired with equitable access in order to contribute to a more favourable outcome.

Collectively, the extent to which a tumour relies on hormonal signalling constitutes one of the single largest predictors of clinical course and prognosis among breast cancer subtypes. Intrinsically, hormone responsive breast cancers have more treatment opportunities available to them. This is predominantly due to their benefit from endocrine therapy which is generally well tolerated and displays less off-target toxicity than chemotherapy [7]. Certain limitations remain within hormone receptor-negative tumours, particularly within the TNBC subtype, as a more aggressive treatment course of action is typically required, which poses additional risks to the patient.

As breast cancer research advances, a more sophisticated understanding of subtype biology is central to the development of increasingly precise molecular targets. These will then guide therapeutic strategies to depend on more detailed molecular features than by its placement within a broader subtype grouping. Pairing scientific insight with equitable implementation has potential to meaningfully move breast cancer prognosis in a more positive direction within reach for all patients across all breast cancer subtypes.

Conclusions

This review evaluated the shared and distinct characteristics between hormone response and hormone unresponsive breast cancer. Overall breast cancer prognosis varies depending on ER, PR and HER2 receptor expression, as well as health disparities across low-, medium- and high-HDI regions. These findings highlight the importance of addressing tumour subtype-specific features and reducing disparities to improve survival probability and patient outcomes. Future studies should further investigate the development of targeted strategies for hormone-unresponsive breast cancer to overcome current therapeutic limitations.

List of Abbreviations

CNS: central nervous system
ER: estrogen receptor
HDI: human development index
HER2: human epidermal growth factor receptor 2
IHC: immunohistochemistry
PR: progesterone receptor
TNBC: triple-negative breast cancer

Conflicts of Interest

No competing interests are declared.

Ethics Approval and/or Participant Consent

This review did not require prior ethics approval or participant consent as it did not involve human participants, animal subjects or original experimental data.

Authors' Contributions

JN: formulated and designed the review, conducted the literature search and analysis, drafted and revised the manuscript, approved the final version to be published, and agrees to be accountable for all aspects of the work.

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References

[1] Kim J, Harper A, McCormack V, Sung H, Houssami N, Morgan E, et al. Global patterns and trends in breast cancer incidence and mortality across 185 countries. Nature Medicine [Internet]. 2025 Feb 24;31(4). https://doi.org/10.1038/s41591-025-03502-3
[2] Parkes A, Clifton K, Al-Awadhi A, Oke O, Warneke CL, Litton JK, et al. Characterization of bone only metastasis patients with respect to tumor subtypes. npj Breast Cancer. 2018;4(1). https://doi.org/10.1038/s41523-018-0054-x
[3] Howlader N, Cronin KA, Kurian AW, Andridge R. Differences in breast cancer survival by molecular subtypes in the United States. Journal of the National Cancer Institute. 2018 Jan 1;110(1):65–72. https://doi.org/10.1093/jnci/djx099
[4] Blows FM, Driver KE, Schmidt MK, Broeks A, van Leeuwen FE, Wesseling J, et al. Subtype-specific outcomes in breast cancer: evidence for prognostic value of progesterone receptor expression within luminal A and B classes. Journal of the National Cancer Institute. 2015 May 1;107(5):djv108. https://doi.org/10.1093/jnci/djv108

[5] The Use of Immunotherapy for Treatment of Gynecologic Malignancies [Internet]. Exon Publications. [cited 2025 Feb 24]. https://exonpublications.com/index.php/exon/article/view/487

[6] Feeley LP, Mulligan AM, Pinnaduwage D, Bull SB, Andrulis IL. Distinguishing luminal breast cancer subtypes by Ki-67, progesterone receptor or TP53 status provides prognostic information. Modern Pathology. 2014 Apr;27(4):554–561. https://doi.org/10.1038/modpathol.2013.153

[7] Yersal O, Barutca S. Biological Subtypes of Breast Cancer: Prognostic and Therapeutic Implications. World Journal of Clinical Oncology. 2014 Jun 10;5(3):412. https://doi.org/10.5306/wjco.v5.i3.412

[8] Smith I, Robertson JFR, Kilburn LS, Wilcox M, Evans A, Holcombe C, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. Lancet Oncology. 2020 Nov;21(11):1443–1454. https://doi.org/10.1016/S1470-2045(20)30458-7

[9] Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. New England Journal of Medicine. 2016 Nov 17;375(20):1925–1936. https://doi.org/10.1056/NEJMoa1607303

[10] Jiang X, Chen G, Sun L, Liu C, Zhang Yukai, Liu M, et al. Characteristics and survival in bone metastatic breast cancer patients with different hormone receptor status: a population-based cohort study. Frontiers in Oncology. 2022 Aug 18;12:977226. https://doi.org/10.3389/fonc.2022.977226

[11] Conner SJ, Guarin JR, Le TT, Fatherree JP, Kelley C, Payne SL, et al. Cell morphology best predicts tumorigenicity and metastasis in vivo across multiple TNBC cell lines of different metastatic potential. Breast Cancer Research. 2024 Mar 11;26(1). https://doi.org/10.1186/s13058-024-01796-8

[12] Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. Journal of Clinical Investigation. 2011 Jul;121(7):2750–2767. https://doi.org/10.1172/JCI45014

[13] Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. The New England Journal of Medicine. 2022;387(3):217–226. https://doi.org/10.1056/NEJMoa2202809

[14] von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. New England Journal of Medicine. 2017 Jul 13;377(2):122–131. https://doi.org/10.1056/NEJMoa1703643

[15] Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. New England Journal of Medicine. 2015 Feb 19;372(8):724–734. https://doi.org/10.1056/NEJMoa1413513

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