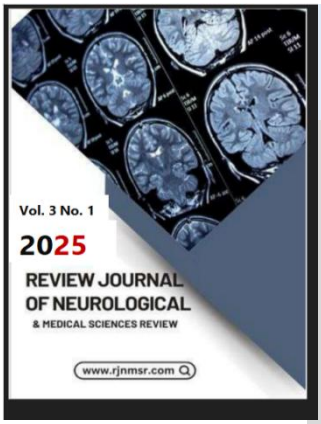

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A Narrative Review of Prevalence of Her$_2$ Positive Invasive and Non Invasive Breast Cancer

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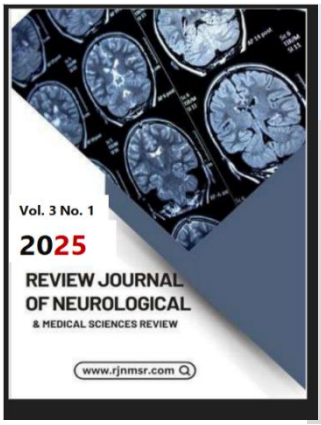
Abstract

Breast cancer is a prevalent malignancy in women globally, with the HER2-positive subtype exhibiting aggressive characteristics. This review examines the prevalence of HER2-positive breast cancer, focusing on both invasive and non-invasive forms. HER2, a transmembrane tyrosine kinase receptor, is overexpressed in a significant subset of breast cancers, influencing tumor behavior and prognosis. The review also explores the impact of HER2 status on disease progression and the effectiveness of current therapeutic strategies. Understanding the prevalence of HER2-positive breast cancer is crucial for tailoring effective treatments and improving patient outcomes.

Introduction

Breast cancer is the most commonly diagnosed malignancy in women worldwide and remains a major cause of cancer-related mortality. Among its various subtypes, Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer is



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particularly significant due to its aggressive nature and distinct therapeutic implications. HER2 is a transmembrane tyrosine kinase receptor encoded by the ERBB2 gene, and its overexpression or gene amplification is found in approximately 15-20% of breast cancer cases (Slamon et al., 1987).

HER2-positive breast cancer is associated with higher tumor aggressiveness, increased proliferation rates, and poorer prognosis compared to HER2-negative subtypes (Moasser, 2007). The advent of HER2-targeted therapies (e.g., trastuzumab, pertuzumab, and T-DM1) has revolutionized treatment, significantly improving survival rates (Piccart-Gebhart et al., 2005). Variability in HER2 prevalence across different populations highlights the need for regional and global studies to tailor treatment strategies and optimize healthcare resources. clinical impact of HER2 status, an in-depth understanding of its epidemiology, molecular mechanisms, and therapeutic advancements is essential for improving patient outcomes. This review aims to comprehensively analyze HER2 prevalence in breast cancer, regional variations, and advancements in targeted treatment. (Gonzalez-Angulo et al., 2007)

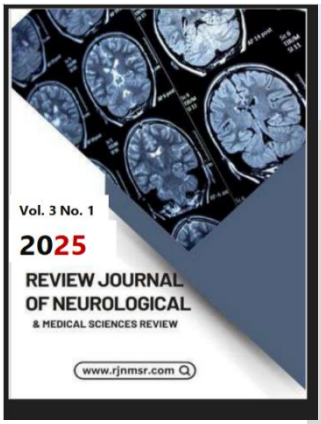
Furthermore, determining the right treatment decisions requires the early and precise diagnosis of HER2 status. When evaluating which patients are most likely to benefit from HER2-targeted treatments, standardized diagnostic methods like immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) are essential. However, differences in testing procedures and the availability of resources, particularly in low- and middle-income nations, may make it more difficult to diagnose and treat HER2-positive breast cancer in a timely manner. Globally, more equal cancer care and increased survival rates can be achieved by tackling these issues with enhanced diagnostic infrastructure and international cooperation. (Wolff et al., 2013)

Non-Invasive Breast Cancer (In Situ Carcinomas)

The term "non-invasive breast cancer" describes the existence of aberrant or malignant cells that have not migrated to the surrounding breast tissue and are still contained within the milk ducts or lobules. Non-invasive breast cancer is categorized as Stage 0, the earliest and most curable type of breast cancer, because the cells have not spread to nearby structures.

There are two main types of non invasive breast cancer:

Ductal Carcinoma In Situ (DCIS): Cancerous cells that reside inside the ductal system and have not yet spread to the surrounding breast tissue are the hallmark of ductal carcinoma in situ (DCIS), a non-invasive type of breast cancer. About 20% of newly discovered breast tumors are caused by it (Siegel et al., 2021). DCIS does not pose an immediate threat to life, but if treatment is not received, it can develop into invasive breast cancer. In order to lower the chance of recurrence, treatment options usually involve mastectomy or lumpectomy, frequently followed by radiation therapy. To further reduce the risk of recurrence, hormonal therapy, such as tamoxifen, may be suggested in cases where the DCIS is estrogen receptor (ER)-positive (Wapnir et al., 2011). Routine mammography screening has greatly improved the diagnosis of DCIS, enabling prompt management and superior long-term results. Risk



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stratification techniques are still being investigated in order to identify low-risk DCIS instances that can profit from less aggressive treatment.

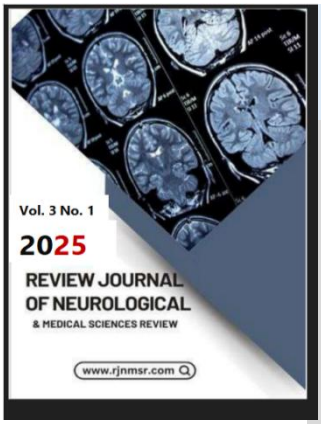
Lobular Carcinoma In Situ (LCIS): Abnormal cell growth within the breast's lobules, the glands that produce milk, is a defining feature of Lobular Carcinoma in Situ (LCIS). LCIS is a strong indicator of a higher chance of invasive breast cancer in either breast over time, even if it is not a real cancer in and of itself. Approximately 0.5 to 3.8% of cases have been documented to have it, making it less prevalent than Ductal Carcinoma in Situ (DCIS) and frequently found by chance during breast biopsies done for other purposes (King et al., 2015). LCIS is often not detectable by imaging alone since it does not develop a lump or exhibit obvious symptoms. Surgery is typically not required for the treatment of LCIS because it is non-invasive. Rather, care emphasizes routine monitoring using imaging, including MRI or mammography, and clinical breast exams (NCCN, 2023). Preventive measures for high-risk women can involve chemo-prevention, improved screening, and lifestyle changes. Tamoxifen and raloxifene are examples of selective estrogen receptor modulators (SERMs) that have demonstrated efficacy in lowering the risk of invasive breast cancer in women with LCIS, especially in cases where the estrogen receptor is positive (Cuzick et al., 2007). The existence of LCIS emphasizes the significance of individualized risk assessment, patient education, and attentive follow-up care, even though the danger of progression to invasive cancer is not urgent.

Invasive Breast Cancer

Invasive breast cancer results, when aberrant cells proliferate outside of the ducts or lobules and into the surrounding breast tissue. This type of cancer may spread to adjacent lymph nodes and, ultimately, to other organs, raising the possibility of more serious problems and influencing the prognosis as a whole.

Invasive Ductal Carcinoma (IDC): Invasive Ductal Carcinoma (IDC), the most prevalent kind of invasive breast cancer, starts in the milk ducts and spreads to the surrounding breast tissues (Rakha et al., 2008). IDC makes up 80–85% of all invasive breast cancers, and if it is not discovered early, it may spread to distant organs and lymph nodes. According to Jemal et al. (2011), early identification and therapy greatly enhance results and frequently stop cancer from spreading. Since IDC is known to be aggressive and to develop rapidly, improving survival rates requires early detection using screening techniques like mammography, ultrasound, or MRI. Sometimes a lump, changes in breast size or shape, or skin dimpling might lead to a diagnosis of IDC. Depending on the tumor's features, including hormone receptor status and HER2 expression, IDC is typically treated with a combination of surgery, chemotherapy, radiation therapy, and occasionally targeted medicines (Schmidt et al., 2018).

Invasive Lobular Carcinoma (ILC): The breast's milk-producing lobules give birth to Invasive Lobular Carcinoma (ILC), which spreads to neighboring tissues. Ten to fifteen percent of invasive breast cancers are caused by it (Howlader et al., 2014). In contrast to other forms of breast cancer, such Invasive Ductal Carcinoma (IDC), ILC tends to grow in a more diffuse or "linear" pattern, making it more difficult to



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detect on mammograms (Vineis et al., 2018). As a result, ILC frequently poses a challenge in early identification.

ILC may not develop into a noticeable lump because of its modest growth, making it more challenging to find during routine screenings, particularly in women with dense breast tissue. Other imaging methods, such as MRI or ultrasound, could be required in some circumstances in order to make an accurate diagnosis. Depending on the tumor's stage and molecular makeup, ILC is usually treated with surgery, followed by chemotherapy, hormone therapy (if the cancer is estrogen receptor-positive), and/or radiation therapy (Nassir et al., 2016). Early detection and therapy are essential for improving patient outcomes since, like IDC, ILC can spread to distant organs such the gastrointestinal system and bones.

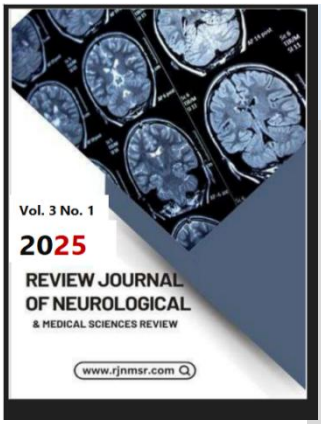
Other Rare Invasive Types:

Triple-Negative Breast Cancer (TNBC), The aggressive subtype of breast cancer known as triple-negative breast cancer (TNBC) is distinguished by the lack of expression of the human epidermal growth factor receptor 2 (HER2), progesterone receptors, and estrogen receptors. Because of this, TNBC responds less well to targeted therapy like HER2 inhibitors and traditional hormonal therapies, which work well for other subtypes of breast cancer. TNBC is more frequently diagnosed in younger women and those with a BRCA1 gene mutation, and it makes up about 10–20% of all instances of breast cancer (Dent et al., 2009). TNBC has a higher chance of recurrence because of its aggressive character, which causes it to develop and spread more quickly, especially in the first few years after diagnosis (Zhao et al., 2016). Chemotherapy is usually used to treat TNBC, however research is being done to find more potent immunotherapies and targeted medicines for this difficult subtype. Chemotherapy is usually used to treat TNBC, however research is being done to find more potent immunotherapies and targeted medicines for this difficult subtype (Lehmann et al., 2011).

Inflammatory Breast Cancer (IBC), A rare and aggressive kind of breast cancer, inflammatory breast cancer (IBC) is distinguished by its quick onset and unique clinical characteristics, such as breast redness, swelling, and warmth, frequently without the presence of a noticeable lump. IBC is caused by cancer cells that obstruct lymphatic veins in the breast's surface, which results in the typical inflammatory symptoms (Feng et al., 2019). Early detection and timely treatment are essential for this form of breast cancer since it usually develops and spreads quickly. IBC makes up 1% to 5% of all cases of breast cancer, however because of its aggressive character, it is linked to a worse prognosis (Ibrahim et al., 2018). Adjuvant chemotherapy or hormonal therapy, assuming the tumor is hormone receptor-positive, is typically administered after neoadjuvant chemotherapy, surgery, and radiation therapy (Cheng et al., 2017). IBC is more likely to spread to distant organs such the liver, lungs, and bones even with vigorous treatment.

Background on HER2 in Invasive and Non-Invasive Breast Cancer

The Human Epidermal Growth Factor Receptor 2 (HER2), encoded by the ERBB2 gene located on chromosome 17q12, is a transmembrane tyrosine kinase receptor belonging to the epidermal growth factor receptor (EGFR) family. HER2 plays a vital



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role in cell proliferation, differentiation, and survival. In breast cancer, HER2 overexpression or gene amplification occurs in approximately 15-20% of cases, leading to aggressive tumor behavior and poor prognosis (Zhao et al., 2025)

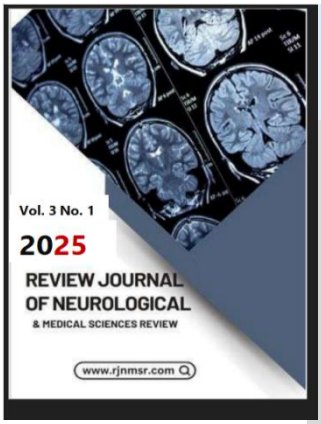
HER2 in Non-Invasive Breast Cancer: HER2 can be over-expressed in non-invasive (in situ) breast cancer, particularly in Ductal Carcinoma In Situ (DCIS), but its role differs from invasive types. HER2 over-expression is found in 50–60% of DCIS cases, which is higher than in invasive breast cancer (Allred et al., 2008). Studies suggest that HER2-positive DCIS is associated with higher nuclear grade, increased proliferation, and a higher risk of progression to invasive breast cancer (Bianchi et al., 2020).HER2-targeted therapy is not routinely used for DCIS but is being investigated for preventing invasive transformation. Unlike DCIS, HER2 over-expression is rare in LCIS, suggesting a different molecular pathway for progression (Riva et al., 2022).LCIS is more often associated with hormone receptor-positive (HR+) tumors rather than HER2-driven carcinogenesis.

HER2 in Invasive Breast Cancer: In invasive breast cancer, HER2 overexpression leads to aggressive tumor behavior, high proliferation rates, and increased metastatic potential.HER2 in Invasive Ductal Carcinoma (IDC)HER2-positive IDC accounts for 15-20% of invasive breast cancers (Moasser, 2007).HER2 signaling promotes angiogenesis, cell survival, and resistance to apoptosis, making tumors more aggressive and likely to metastasize (Gonzalez-Angulo et al., 2007).Before targeted therapies, HER2-positive IDC was associated with worse survival outcomes than HER2-negative cases. However, the introduction of trastuzumab (Herceptin) and other HER2 inhibitors has significantly improved prognosis (Piccart-Gebhart et al., 2005).

HER2 positivity is rare in ILC, observed in less than 5% of cases (Howlader et al., 2014).ILC is more often hormone receptor-positive and HER2-negative, making it less responsive to HER2-targeted treatments.

Role of HER2 in Cancer Development and Progression

A member of the ErbB family of receptor tyrosine kinases, which are essential for controlling cell growth, survival, adhesion, migration, and differentiation, is the human epidermal growth factor receptor 2 (HER2), also referred to as ErbB2. Instead of being activated by direct ligand binding, HER2 enhances signal transmission by acting as a preferred dimerization partner for other ligand-bound ErbB receptors. The development and progression of a number of aggressive malignancies, including breast cancer, gastric, ovarian, endometrial, lung, and bladder cancers, have been linked to overexpression or amplification of the HER2 gene.The PI3K/AKT/mTOR and RAS/RAF/MEK/ERK cascades are two examples of downstream signaling pathways that are constitutively activated in the context of cancer due to HER2 overexpression or gene amplification. According to Warden and Sliwkowski (2001), these pathways encourage unchecked cell proliferation, suppression of apoptosis, angiogenesis, and metastasis—all of which are important characteristics of cancer. Since HER2 gene amplification is present in 15–20% of breast cancer tumors, the carcinogenic potential of HER2 is well established. In comparison to HER2-negative tumors, these HER2-positive tumors are typically



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more aggressive, linked to greater recurrence rates, and have a worse prognosis (Slamon et al., 1987; Ross et al., 2003).

Crucially, the development of targeted medicines as a result of the identification of HER2's function in carcinogenesis has completely changed the way that HER2-positive tumors are treated. The first approved targeted therapy was trastuzumab (Herceptin), a monoclonal antibody against HER2, which has greatly improved outcomes for patients with HER2-positive breast cancer (Vogel et al., 2002). Other HER2-targeted agents, such as pertuzumab, lapatinib, neratinib, and trastuzumab emtansine (T-DM1), have since been developed, offering additional therapeutic options and improving survival rates further. Resistance, both acquired and inherent, continues to be a therapeutic problem in spite of the effectiveness of HER2-targeted treatments. According to Nahta et al. (2006), resistance mechanisms include changes in the HER2 receptor, the activation of compensatory signaling pathways, and the loss of downstream tumor suppressors such PTEN. Strategies such as combination therapy and next-generation HER2 inhibitors are being investigated as part of the ongoing research to comprehend and overcome these resistance mechanisms.

In conclusion, HER2 is essential for the initiation and spread of cancer, mostly because of its overexpression and amplification, which cause abnormal cell signaling pathway activation. HER2 is one of the most researched oncogenes in the field of cancer biology due to its importance as a therapeutic target and prognostic marker.

Methods for Determining HER2 Status in Breast Cancer

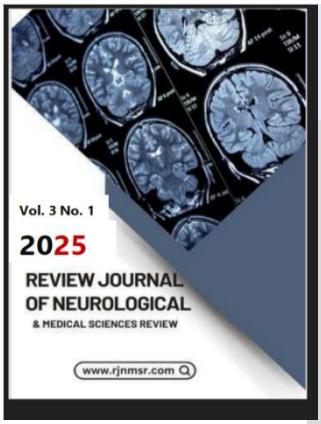
In breast cancer, HER2 status is essential for precise diagnosis, prognosis, and therapy planning, especially since HER2-targeted treatments such as trastuzumab only work in patients whose tumors overexpress HER2 or exhibit HER2 gene amplification. To assess HER2 status, a number of well-established techniques are employed, each with specific benefits and drawbacks. The most often utilized methods are fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and, more recently, next-generation sequencing (NGS) and chromogenic in situ hybridization (CISH).

These techniques are recommended by organizations such as the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) to ensure accurate classification and treatment selection (Wolff et al., 2018).

Immunohistochemistry (IHC)

IHC detects HER2 protein overexpression on the cell membrane using antibodies that bind to HER2. The reaction is visualized using chromogenic dyes, producing a brown stain that is examined under a microscope. IHC is cost-effective, widely available, and the first-line test for HER2 status.

The HER2 expression level is graded on a 0 to 3+ scale based on staining intensity and completeness (Wolff et al., 2018). The ASCO/CAP recommendations state that a score of 0 or 1+ indicates HER2-negative status, a score of 3+ indicates HER2-positive status, and a score of 2+ indicates equivocal status (requiring more testing) (Wolff et al., 2018). Although IHC is widely accessible, reasonably priced, and simple, it is semi-quantitative and susceptible to interobserver variability.



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Fluorescence In Situ Hybridization (FISH)

The most reliable method for verifying HER2 gene amplification is FISH, particularly when IHC results are unclear (2+). To measure the HER2/CEP17 ratio, fluorescently labeled DNA probes that bind to the HER2 gene and a control probe—typically CEP17—are used. HER2-positive is defined as having an average HER2 copy number of ≥6 signals per cell or a ratio of ≥2.0. Compared to IHC, FISH offers a more objective and quantitative evaluation that is less impacted by tissue fixation artifacts (Press et al., 2002). But it costs more, needs specific tools, and in borderline situations, the interpretation might still be difficult.

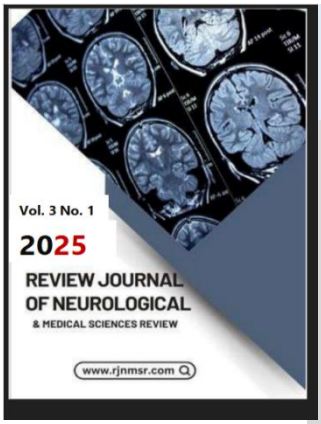
Comparison of IHC and FISh

Because HER2-targeted medications like trastuzumab and pertuzumab only work in patients with HER2-positive tumors, determining the HER2 status in breast cancer is crucial for choosing the right therapy. The two main methods for determining HER2 status are fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). Despite being widely used and advised by recommendations, their approaches, interpretations, and therapeutic applications are different.

IHC is a protein-based test that looks for the expression of the HER2 protein on tumor cell membranes using certain antibodies. Semi-quantitative scores of 0, 1+, 2+, or 3+ are assigned to the results according to the pattern and intensity of the membrane staining. Amplification of the HER2 gene is determined by further FISH testing; scores of 0 and 1+ are regarded as HER2-negative, 3+ as positive, and 2+ as inconclusive. IHC's accessibility, quick response time, and affordable price make it a popular first-line screening technique. It is a subjective approach, though, and variables like tissue fixation and variations in antibody performance may have an impact on its precision (Wolff et al., 2018).

In contrast, FISH is a molecular cytogenetic method that uses fluorescently labeled probes that bind to the HER2 gene and a chromosome 17 centromere control (CEP17) to identify HER2 gene amplification at the DNA level. Next, the HER2/CEP17 ratio is computed. HER2 positive is indicated by a ratio of ≥2.0 or an average of ≥6 signals per cell for the HER2 gene copy number. FISH is very helpful in resolving equivocal IHC situations and is thought to be more objective and quantitative than IHC. However, it necessitates specialist fluorescence microscopy and is more costly and technically demanding. Furthermore, long-term analysis may be limited due to the degradation of the fluorescent signals over time (Press et al., 2002).

FISH is regarded as the gold standard for diagnostic accuracy, particularly when it comes to verifying HER2 gene amplification in instances that are unclear. Nevertheless, when IHC results are obviously negative (0/1+) or positive (3+), both approaches have a high concordance rate (around 85–90%). The prevalence of discordance is highest in instances with an IHC score of 2+, highlighting the significance of reflex testing using FISH to guarantee precise classification (Perez et al., 2006). FISH measures gene copy number, which can offer more conclusive evidence in cases that are unclear, whereas IHC analyzes HER2 at the protein level and represents true receptor expression.



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In conclusion, FISH and IHC work well together, with FISH providing quantitative, confirmatory evaluation in ambiguous circumstances and IHC acting as an affordable initial test. The most precise assessment of HER2 status is ensured by using both techniques in accordance with accepted clinical criteria, which is crucial for directing targeted therapy in breast cancer.

Global Prevalence of HER2-Positive Non-Invasive Breast Cancer

Non-invasive breast cancers, such as ductal carcinoma in situ (DCIS), are confined within the ducts of the breast tissue and have not invaded surrounding tissues. The prevalence of HER2 positivity in DCIS varies widely across studies, with reported rates ranging from 14% to 50%. This variation can be attributed to differences in study populations, detection methods, and criteria for HER2 positivity. Notably, HER2-positive DCIS has been associated with a higher risk of progression to invasive breast cancer, underscoring the importance of accurate HER2 assessment in non-invas lesions.

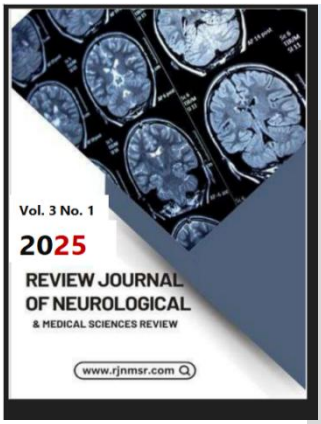
Over the past decades, the prevalence of HER2-positive breast cancer has exhibited notable trends, influenced by advancements in diagnostic techniques, screening programs, and therapeutic interventions. Several studies have reported a decrease in the proportion of HER2-positive breast cancer cases over time. For instance, a Finnish population-based study observed a decline from 21.6% between 1982 and 1986 to 13.6% between 2004 and 2005.

The implementation of breast cancer screening programs has impacted the detection rates of different breast cancer subtypes. Research indicates that HER2-positive tumors are less frequently detected in screening programs compared to non-screen-detected cases. Specifically, the prevalence of HER2-positive breast carcinomas was found to be 8.8% and 6.4% in two series of screen-detected tumors, compared with 16.4% and 13% in non-screen-detected carcinomas.

A study analyzing data from the Scottish Cancer Registry between 1997 and 2016 reported distinct temporal trends in breast cancer incidence by molecular subtypes. While the study did not specify the exact trends for HER2-positive subtypes, it highlighted the importance of understanding subtype-specific incidence to inform public health strategies.

The introduction and widespread use of targeted therapies, such as trastuzumab, have significantly improved outcomes for patients with HER2-positive breast cancer. These therapeutic advancements may influence the observed prevalence rates over time. Diagnostic Improvements: Enhanced accuracy in determining HER2 status through methods like immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) has led to more precise classification of breast cancer subtypes, potentially affecting reported prevalence rates.

The prevalence of HER2-positive breast cancer is influenced by various factors, notably ethnicity and geographical location. Studies have demonstrated that the incidence of HER2-positive breast cancer varies among different ethnic groups Non-Hispanic White Women exhibits the highest incidence of hormone receptor-positive (HR+)/HER2-negative (HER2–) breast cancer. Non-Hispanic Black Women women have the highest rates of hormone receptor-negative (HR–)/HER2– breast cancer.



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Non-Hispanic Asian/Pacific Islander and Hispanic Women show varying incidence rates across different breast cancer subtypes, with specific patterns differing by group. These disparities suggest that genetic, environmental, and socioeconomic factors may play roles in the development of specific breast cancer subtypes among different ethnicities. Geographical location also impacts the prevalence of HER2-positive breast cancer: In United States the incidence of HER2-positive breast cancer subtypes varies across different regions, influenced by factors such as access to healthcare, socioeconomic status, and screening practices.

A systematic review and meta-analysis revealed a higher prevalence of HER2-positive breast cancer in Indian women compared to Western countries. This variation may be attributed to genetic differences, lifestyle factors, and disparities in healthcare infrastructure. These geographical disparities underscore the importance of considering regional factors when developing breast cancer screening and treatment strategies

Advancements in testing methods and the standardization of protocols for assessing Human Epidermal Growth Factor Receptor 2 (HER2) status have significantly impacted the reported prevalence rates of HER2-positive breast cancer.

Impact of Improved Testing Methods Enhanced diagnostic techniques, such as immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH), have improved the accuracy of HER2 status determination. These methods have reduced false-positive and false-negative results, leading to more precise prevalence estimates.

A study highlighted that inter laboratory variation in HER2 testing poses challenges for targeted therapy, emphasizing the need for accurate and standardized testing to ensure optimal disease management. The implementation of standardized testing protocols has minimized variability in HER2 assessment across different laboratories.

An international proficiency-testing ring study demonstrated that standardization efforts led to more consistent and reliable HER2 testing results, thereby influencing reported prevalence rates.

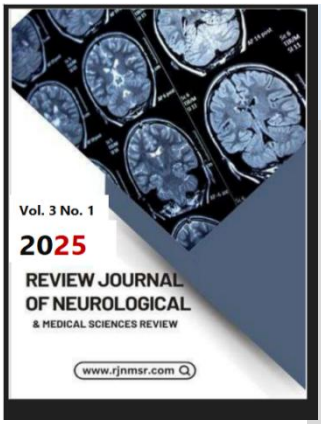
The combination of improved testing methods and standardization has led to more accurate identification of HER2-positive cases. This accuracy ensures that prevalence rates reflect the true distribution of HER2-positive breast cancer, which is crucial for guiding appropriate treatment decision-source allocation.

HER2 and HR

The interplay between Human Epidermal Growth Factor Receptor 2 (HER2) status and hormone receptor (HR) status is fundamental in classifying breast cancer subtypes, which in turn influences treatment strategies and prognostic outcomes.

Breast Cancer Subtypes Based on HER2 and Hormone Receptor Status Breast cancers are categorized based on the presence or absence of hormone receptors—estrogen receptor (ER) and progesterone receptor (PR)—and HER2 protein overexpression. The primary subtypes include:

HR-Positive/HER2-Negative (HR+/HER2−): Tumors express ER and/or PR but do not over-express HER2. This is the most prevalent subtype, accounting for approximately 70% of breast cancer cases.



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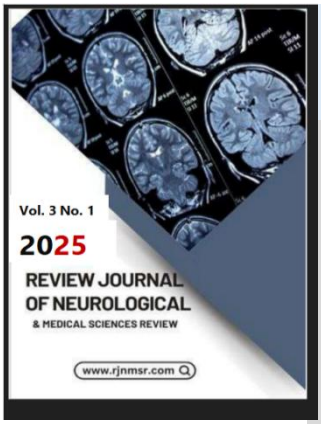
HR-positive/HER2-positive (HR+/HER2+): Tumors express ER and/or PR and over-express HER2.
HR-negative/HER2-positive (HR−/HER2+): Tumors do not express ER or PR but over-express HER2.
Triple-negative (HR−/HER2−): Tumors lack expression of ER, PR, and HER2.
Different biological traits, clinical consequences, and therapeutic responses are displayed by each subtype. The biology and treatment strategy of HER2-positive cancers are greatly impacted by their co-expression, which can arise in both HR-positive and HR-negative settings. HR+/HER2+ tumors, also known as "luminal B-like (HER2+)" tumors, are a physiologically diverse population that responds well to both endocrine therapy and HER2-targeted therapy. However, resistance to one or both treatments may result from interactions between the HER2 and ER signaling pathways. The effectiveness of endocrine medications like tamoxifen or aromatase inhibitors may be diminished by HER2 activation, which has been demonstrated to downregulate ER expression and enhance ligand-independent activation of ER signaling (Richer et al., 1998; Arpino et al., 2008).
On the other hand, HR-negative HER2-positive tumors are more likely to be aggressive, proliferate more quickly, and have a worse prognosis than their HR-positive counterparts. Since endocrine therapy is ineffective for these cancers, which are largely driven by HER2 signaling, HER2-targeted medications—such as trastuzumab, pertuzumab, and lapatinib—are the cornerstone of treatment. Interestingly, compared to HR-positive tumors, HR-negative/HER2-positive cancers may relapse more quickly, but they frequently have a stronger initial response to HER2-targeted therapy and chemotherapy (Duffy et al., 2008).
The possible resistance mechanisms resulting from pathway cross-talk can make the clinical management of patients with dual-positive (HR+/HER2+) malignancies difficult. Studies indicate that utilizing drugs like trastuzumab in conjunction with tamoxifen or aromatase inhibitors to disrupt both the HER2 and hormone pathways may enhance results. Targeting downstream cell cycle regulators impacted by both ER and HER2 signaling, recent trials have also investigated the use of CDK4/6 inhibitors in this subgroup (Johnston et al., 2020).The relationship between HER2 and hormone receptors in breast cancer is intricate and important from a therapeutic standpoint. These indicators' co-expression influences prognosis and calls for a multimodal therapy strategy that, where suitable, combines endocrine and HER2-targeted treatments.



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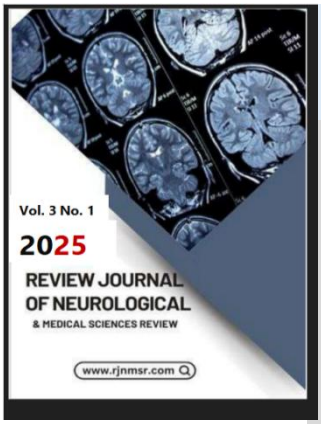
Clinical Implications of Combined Receptor Status

Subtype	HR Status	HER2 Status	Biological Features	Prognosis	Treatment Approach
HR+/HER2−	Positive	Negative	Luminal A-like; low proliferation	Best prognosis	Endocrine therapy (e.g., tamoxifen, AIs); ± CDK4/6 inhibitors
HR+/HER2+	Positive	Positive	Luminal B-like; pathway cross-talk; intermediate proliferation	Intermediate prognosis	Endocrine therapy + HER2-targeted therapy ± chemotherapy
HR−/HER2+	Negative	Positive	Non-luminal; highly proliferative; aggressive	Poorer prognosis	HER2-targeted therapy + chemotherapy
Triple-Negative (TNBC)	Negative	Negative	Basal-like; lacks targetable receptors	Poorest prognosis	Chemotherapy; emerging immunotherapy options

Prognostic Outcomes by Subtype Survival rates vary among the different subtypes:

Subtype	HR Status	HER2 Status	5-Year Disease-Free Survival (DFS)	5-Year Overall Survival (OS)	Prognostic Notes
HR+/HER2−	Positive	Negative	~85–90%	~90–95%	Best prognosis; low grade tumors; respond well to endocrine therapy
HR+/HER2+	Positive	Positive	~75–85%	~85–90%	Intermediate prognosis; benefit from dual HER2 and hormone blockade



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HR−/HER2+	Negative	Positive	~65–75%	~75–85%	Aggressive subtype; responds well to HER2-targeted therapy + chemo
Triple-Negative (TNBC)	Negative	Negative	~60–70%	~65–75%	Poorest prognosis; high recurrence rate; limited targeted therapies

While significant advancements have been made in understanding and treating HER2-positive breast cancer, several areas still require further research:

Mechanisms of Endocrine Therapy: Resistance to endocrine therapy poses a significant challenge in managing hormone receptor-positive (HR+) breast cancer. Understanding the mechanisms behind this resistance is crucial for developing effective treatments. Potential factors contributing to resistance include:

ESR1 Mutations: Mutations in the ESR1 gene, which encodes the estrogen receptor, can lead to estrogen-independent tumor growth, diminishing the efficacy of therapies like aromatase inhibitors. miRNA Regulation: Alterations in microRNAs may activate alternative growth pathways or inhibit estrogen receptor expression, contributing to therapy resistance The G-protein-coupled estrogen receptor (GPER) has been implicated in tamoxifen resistance and increased metastatic potential. Further research is needed to elucidate these mechanisms and develop strategies to overcome endocrine resistance.

Influence of HER2 Overexpression on Endocrine Resistance

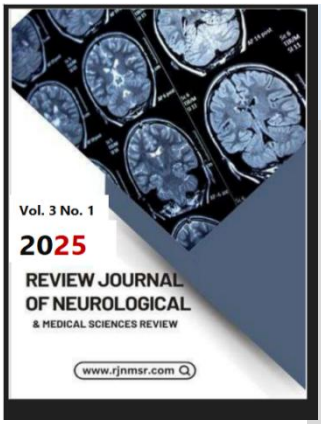
HER2 overexpression is associated with a poorer prognosis and has been linked to endocrine therapy resistance. The crosstalk between HER2 and estrogen receptor signaling pathways suggests that HER2 overexpression may enhance estrogen agonist activity, leading to reduced therapy effectiveness. Investigating this relationship could inform the development of combination therapies to improve patient outcomes.

Treatment Strategies for Less Common Breast Cancer Subtypes While significant progress has been made in treating common breast cancer subtypes, less prevalent forms, such as triple-negative breast cancer, lack effective therapies. This disparity highlights the need for research focused on developing targeted treatments for these challenging subtypes.

Individualized Therapy Based on Genetic Factors Advancements in genetic profiling have opened avenues for personalized breast cancer treatments. Research into how genetic variations influence disease progression and treatment response could lead to more effective, individualized therapies.

Optimal Sequencing of Endocrine Therapy Combinations

Determining the most effective sequence of endocrine therapy combinations for HR+/HER2− advanced breast cancer remains an area requiring further investigation.



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Research into first-line and second-line therapy combinations could enhance treatment efficacy and patient outcomes.

Addressing these research gaps is essential for improving the management and outcomes of HER2-positive breast cancer patients. Advancements in the treatment of HER2-positive breast cancer are being propelled by ongoing clinical trials and the development of emerging therapies. Below is an overview of notable developments:

Camizestrant AstraZeneca's investigational drug, Camizestrant, has shown promising results in a late-stage clinical trial. The trial demonstrated a statistically significant improvement in progression-free survival compared to standard treatments. When combined with a cyclin-dependent kinase inhibitor, Camizestrant also exhibited trends toward delaying disease progression. The safety profile was consistent with previous findings, with no new safety concerns identified.

Trastuzumab Deruxtecan (Enhertu) Trastuzumab deruxtecan, marketed as Enhertu, has been evaluated in clinical trials for patients with metastatic HER2-low breast cancer. The studies indicated that Enhertu extended survival longer than standard chemotherapy in this patient population, offering a new therapeutic option for those with lower levels of HER2 expression.

BPX-603 CAR-T Cell Therapy A Phase 1/2 open-label study is investigating BPX-603, a HER2-specific dual-switch chimeric antigen receptor T-cell (CAR-T) therapy. This therapy is being tested in patients with previously treated, locally advanced or metastatic solid tumors that are HER2-amplified or overexpressed. The study aims to assess the safety, tolerability, and clinical activity of BPX-603.

Tucatinib in Combination Therapies Clinical trials are exploring the efficacy of combining tucatinib with other therapies for advanced HER2-positive breast cancer. One such study involves patients with advanced HER2-positive breast cancer who have stable extracranial disease but have experienced intracranial disease progression. Participants receive local therapy followed by standard treatments combined with tucatinib to evaluate its effectiveness in preventing further disease progression.

Emerging Targeted Therapies Research continues to focus on developing new targeted therapies for HER2-positive breast cancer, especially for patients who develop resistance to existing treatments like trastuzumab. These emerging therapies aim to improve outcomes and provide additional options for patients with this aggressive subtype of breast cancer.

These ongoing clinical trials and emerging therapies represent significant strides in the management of HER2-positive breast cancer, offering hope for improved patient outcomes through innovative treatment strategies.

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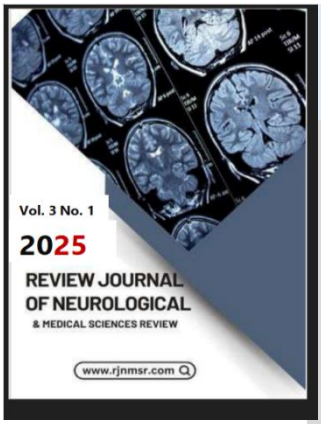

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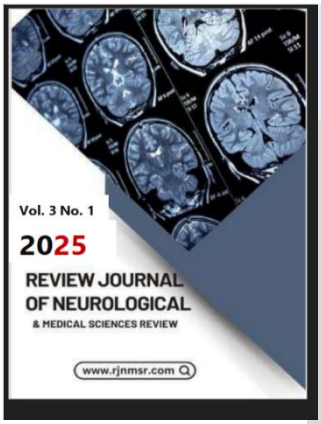

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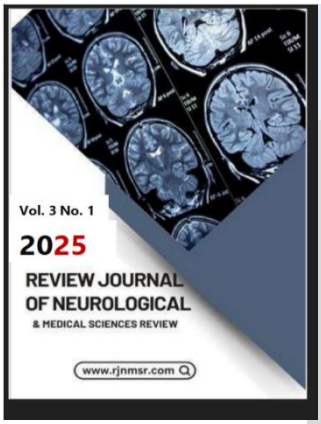

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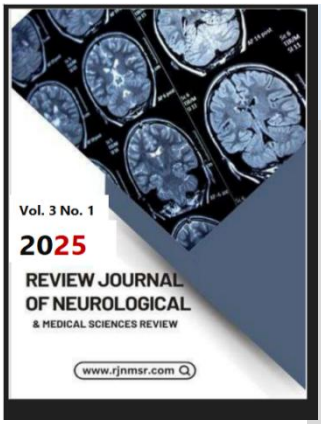

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