DOI: 10.4274/gulhane.galenos.2025.37132
Gulhane Med J 2026;68(1):32-38

Association of epidermal growth factor receptor with hormone receptor and molecular subtypes in breast cancer patients from South India

Dhananjay B Alagundagi[1], Caren Dsouza[1], Kruthika Madappa[1], Sarath Kumar E[2], Vinay C Sangamesh[2], Prakash Patil[1], Praveenkumar Shetty[1]

[1]NITTE (Deemed to be University) KS Hegde Medical Academy, Mangaluru, Karnataka, India
[2]NITTE (Deemed to be University) Centre For Science Education And Research, Mangaluru, Karnataka, India

Cite this article as: Alagundagi DB, Dsouza D, Madappa K, Kumar E S, Sangamesh VC, Patil P, et al. Association of epidermal growth factor receptor with hormone receptor and molecular subtypes in breast cancer patients from South India. *Gulhane Med J.* 2026;68(1):32-38.

Date submitted:
04.07.2024
Date accepted:
07.10.2025
Publication Date:
18.03.2026

Corresponding Author:
Caren Dsouza, Prof., NITTE (Deemed to be University) KS Hegde Medical Academy, Mangaluru, Karnataka, India,
drcaren@nitte.edu.in

ORCID:
orcid.org/0000-0001-6790-8097

Keywords: Breast carcinoma, epidermal growth factor receptor, immunohistochemistry, triple negative breast cancer

ABSTRACT

Aims: Breast cancer (BC) remains a major global health challenge, characterized by molecular heterogeneity and a complex interplay of risk factors. Epidermal growth factor receptors (EGFRs) role in BC underscores the importance of targeted therapies and the need for personalized treatment approaches. This study aimed to examine EGFR expression in tumor samples from BC patients and assess its relationship with molecular subtypes and receptor status.

Methods: This cross-sectional study involved female BC patients with confirmed diagnoses. Core-cut biopsy specimens were formalin-fixed, paraffin-embedded, and assessed for EGFR expression using immunohistochemistry (IHC). A chi-square test was performed to assess its association. The patients' records were reviewed for demographic data, and receptor status was determined using IHC as part of routine clinical evaluation.

Results: A total of 62 BC patients were included in the study, with ages ranging from 25 to 70 years (mean ± standard deviation: 49.9±10.8 years). EGFR expression showed predominantly weak staining intensity (61.3%), followed by moderate staining (17.7%), no staining (17.7%), and strong staining (3.3%). Regarding receptor status, weak EGFR expression was prevalent in estrogen receptor (ER)-positive (57.9%) and progesterone receptor (PR)-negative (65.8%) patients, whereas strong EGFR expression was observed in the ER-negative, PR-negative, and human epidermal growth factor receptor 2 (HER2)/neu-negative subgroups (2 cases each). Assessment by molecular subtype showed a prevalence of weak and moderate EGFR staining in the Luminal B subtype, whereas strong EGFR expression was observed only in triple-negative BC patients (2 cases, 100%). However, there was no statistically significant association between EGFR expression and molecular subtypes or hormone receptor status.

Conclusions: EGFR expression was more common in aggressive subtypes, such as HER2-positive and Luminal B, highlighting its potential role in tumor progression. However, the lack of a significant association suggests that the relevance may be subtype-specific.

Introduction

Breast cancer (BC) remains one of the most prevalent and challenging health issues worldwide, affecting millions of women annually. It is the most common cancer and the leading cause of cancer-related deaths in women (1,2). Despite significant advancements in early detection and treatment, the incidence of BC continues to rise. Early detection methods have significantly contributed to earlier diagnoses and improved patient outcomes. However, the complex interplay of various risk factors, including genetics, age, lifestyle habits, and environmental influences, contributes to its increased prevalence (3). BC is a heterogeneous group of malignancies with distinct histological, molecular, and clinical characteristics. The molecular landscape of BC is highly diverse, with several key biomarkers and molecular targets playing crucial roles in its progression and treatment response (4). This heterogeneity requires a tailored treatment approach because subtypes of BC respond differently to therapeutic strategies. The primary treatment modalities for BC include surgery, chemotherapy, radiation therapy, hormone therapy, targeted therapy, and immunotherapy. Despite these advancements, challenges such as the development of treatment resistance, side effects, and disparities in access to care continue to impact patient outcomes (5,6).

Epidermal growth factor receptor (EGFR), a member of the ErbB family of transmembrane receptor tyrosine kinases, has garnered significant attention as both a biomarker and a therapeutic target. It regulates cell proliferation, differentiation, and survival (7). The dysregulation of EGFR in BC leads to oncogenesis and tumor progression. The overexpression of EGFR in BC is associated with several adverse clinical outcomes, including larger tumor size, poor differentiation, and an increased risk of relapse (8,9). Studies have shown that the expressions of EGFR and human epidermal growth factor receptor 2 (HER2) (another member of the ErbB family) are often inversely correlated with estrogen receptor (ER) status. BC patients who are positive for EGFR and HER2 generally have a higher risk of relapse and a worse prognosis compared to those who are negative for these receptors (10,11). In ER-positive BC, EGFR overexpression has been linked to resistance to endocrine therapy, posing a significant challenge in treatment. Endocrine therapies, such as tamoxifen and aromatase inhibitors, effectively manage hormone receptor-positive BC. However, EGFR can interfere with these therapies, necessitating alternative or combination treatments to overcome resistance (12-14). This interplay between EGFR and hormone receptors underscores the complexity of BC treatment and the need for personalized therapeutic strategies. The present study aimed to investigate EGFR expression in a cohort of BC patients and to explore its association with molecular subtypes and receptor status.

Methods

Study design, patient selection, settings, and sample size

This cross-sectional study was conducted in the Department of General Surgery at a tertiary care hospital in Mangalore, India, from April 2021 to September 2022. The study included consenting female patients with a confirmed BC diagnosis; patients with recurrent BC and those who had received post-neoadjuvant therapy were excluded. Ethical approval was obtained from the institutional Ethics Committee of the KS Hegde Medical Academy (which has university status) and written informed consent was obtained from all patients (approval no.: EC/066/2021-22, date: 05.02.2021).

The sample size for this study was calculated using G*Power software (v. 3.1.9.4) with the following criteria: effect size =0.5, a 5% level of significance, 95% power, and degrees of freedom =2. The initial target sample size for the study, according to the sample size calculation, as per the sample size calculation, for the study was 100. However, due to the loss of some samples during standardization and challenges related to clinical relevance, the final sample consisted of 62 confirmed cases of BC patients.

Data collection

Clinical and demographic data were extracted from the patient's case records. The hormone receptor status and molecular subtypes were assessed by pathologists as part of routine diagnostic procedures. The hormone receptor expression was first determined using immunohistochemistry (IHC), as described below. Based on the presence or absence of ER, progesterone receptor (PR), and HER2 receptors, the samples were classified into molecular subtypes. The carcinomas were classified and graded according to the World Health Organization 2012 (15) and the Nottingham classification system (16).

Tissue preparation

The core cut biopsy specimens were fixed overnight in 10% buffered formalin, processed, and embedded in paraffin. These samples were then sectioned at 3-µm thickness using the rotary microtome (Leica RM2125 RTS, India) and mounted on positively charged slides. IHC was performed using the PolyExcel HRP/DAB Detection System (PEH002) Universal Kit (PathnSitu Biotechnologies, India). Firstly, the slides were heated on the hot plate at 90 ºC for 20 mins to remove the paraffin and were rehydrated through graded alcohols.

Antigen retrieval

The antigen was retrieved using a preheated sodium citrate buffer (pH 6) at 90 °C in a water bath. The slides were then cooled and washed with distilled water.

Immunostaining procedure

After antigen retrieval, the slides were treated with a peroxidase quencher, "Peroxidase Block," to inhibit endogenous peroxidase activity, followed by a 1% bovine serum albumin (BSA) blocking solution to prevent nonspecific binding. Then, the primary antibody (sc-374607, mouse monoclonal, lot no. A1514, Santa Cruz Biotechnology, TX, USA, diluted 1:100 in 1% BSA) against the target antigen, EGFR, was applied to the sections and incubated overnight at 4 °C. Similarly, for hormone receptors, their respective primary antibodies were used (ER: PR042; PR: PR068; and HER2: PR047), all of which are rabbit monoclonal. The next day, slides were washed with Tris-NaCl wash buffer (pH 7), incubated with the poly-HRP-conjugated secondary antibody "Target Binder" for 30 mins at 37 °C in the dark, and washed again with the wash buffer.

Staining and counterstaining

The slides were incubated with horseradish peroxidase, "Poly HRP," for 20 min and washed before adding the chromogen diaminobenzidine (DAB) to visualize immunostaining. The unstained DAB was removed using a wash buffer, and the haematoxylin counterstain was applied to the sections for 5 seconds. Finally, the slides were rinsed in tap water, dehydrated with graded alcohols, cleared with xylene, and mounted on the coverslip with distrene, plasticizer, xylene mountant. Appropriate positive and negative control slides were included in each batch to ensure the reliability of the results. The expression of EGFR in the patient cohort was categorized based on staining intensity as follows: 0 (no staining), 1+ (weak staining intensity), 2+ (moderate staining intensity), and 3+ (strong staining intensity) (17).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). A chi-square test was used to assess the association between EGFR expression and molecular subtypes and receptor status in BC. A p-value <0.05 was considered statistically significant. The results were presented as frequencies for tumor grade, ER/PR status, and HER2 expression.

Results

Patient demographic characteristics

The patients' ages ranged from 25 to 70 years, with a mean ± standard deviation of 49.9±10.8 years. The age distribution indicated that most patients (53.2%) were aged between 46 and 60 years, while 17.7% were older than 60 years. Tumor size classification revealed T2 tumors as the most prevalent (33.9%), and the lymph node involvement assessment showed N1 status in 45.2% of patients. Regarding hormone receptor status, 56.5% of patients were ER-positive, 33.9% were PR-positive, and 61.3% were HER2/neu-positive. The distribution of BC subtypes identified Luminal B as the most common (50.0%), followed by triple-negative BC (TNBC) (30.6%) (Table 1).

Intensity of EGFR staining among the patients

The EGFR expression with weak, moderate, and strong staining intensities was observed in 55 patients (82.2%) of the cohort. The weak staining intensity was the most common observation, occurring in 38 patients (61.3%), suggesting lower levels of EGFR expression (Figure 1). Moderate or no staining intensity was observed in 11 patients (17.7%). Only two patients (3.2%) exhibited strong staining intensity, indicating higher levels of EGFR expression.

Table 1. Characteristics of breast cancer patients (n=62)

Variables	Value
Age (in years)	
30-45	18 (29.0)
46-60	33 (53.2)
>60	11 (17.7)
Mean age (years) mean ± SD	49.9±10.8
Tumor grade	
T1	8 (12.9)
T2	21 (33.9)
T3	16 (25.8)
T4	17 (27.4)
Lymph node status, n (%)	
N0	19 (30.6)
N1	28 (45.2)
N2	7 (9.7)
N3	8 (11.3)
Molecular subtypes, n (%)	
Luminal A	4 (6.5)
Luminal B	31 (50.0)
HER2	8 (12.9)
TNBC	19 (30.6)
Hormone receptor status, n (%)	
ER positive	35 (56.5)
ER negative	27 (43.5)
PR positive	21 (33.9)
PR negative	41 (66.1)
Her2Neu positive	20 (32.3)
Her2Neu negative	38 (61.3)
Her2Neu Equivocal	4 (6.4)

*: Lymph node status refers to the presence or absence of cancer in the lymph nodes. N0: No cancer found in nearby lymph nodes; N1: Cancer has metastasised to 1-3 lymph nodes; N2: Cancer found in 4-6 lymph nodes; N3: Cancer has metastasised to 10 or more lymph nodes, or to lymph nodes near the collarbone or internal mammary nodes.
SD: Standard deviation, TNBC: Triple-negative breast cancer, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2.

Association of EGFR with hormone receptors

The analysis of EGFR staining intensity concerning hormone receptor status and HER2/neu receptor status in BC patients revealed distinct patterns within the studied cohort (Table 2). Among the 62 patients, the distribution of EGFR staining varied notably between ER-positive and ER-negative cases (Table 3). Weak EGFR staining was seen in 22 cases (57.9%) of ER-positive patients and in 16 cases (42.1%) of ER-negative patients. Moderate staining was more frequent in ER-positive patients (7 cases, 63%) than in ER-negative ones (4 cases, 36.4%).

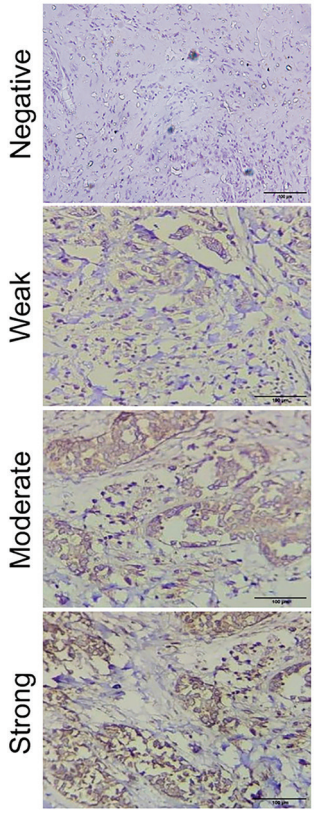

Figure 1. Representation of epidermal growth factor receptor staining intensity

No EGFR staining was observed in 6 ER-positive patients (54.5%) and in 4 ER-negative patients (45.5%). However, strong EGFR staining was exclusive to the ER-negative subgroup (2 cases, 100%).

Regarding PR status, weak EGFR staining was notably more frequent in PR-negative patients (25 cases, 65.8%) compared with PR-positive patients (13 cases, 34.2%). Moderate and no staining intensities were each observed in 7 PR-negative patients (63.6%), compared with 4 PR-positive patients (36.4%). Strong EGFR staining was observed exclusively in PR-negative cases (2 cases, 100%).

In contrast to the ER and PR findings, EGFR staining intensity differed markedly among HER2/neu groups. Weak EGFR staining was observed in 23 HER2/neu-negative cases (62.2%), 12 HER2/neu-positive cases (32.4%), and 2 equivocal cases (5.3%). EGFR staining intensity was absent in HER2/neu-negative patients (7 cases, 63.6%), HER2/neu-positive patients (3 cases, 27.3%), and equivocal patients (1 case, 9.1%). Moderate EGFR intensity was noted in 6 HER2/neu-negative patients (50%), 5 HER2/neu-positive patients (41.7%), and 1 equivocal patient (8.3%). As in ER and PR subgroups, strong EGFR staining was found exclusively in HER2/neu-negative cases (2 cases, 100%).

Association of EGFR with molecular subtypes

EGFR staining intensity and the molecular subtypes of BC showed no significant association in the current cohort (Table 3). The distribution of molecular subtypes among patients with weak EGFR staining was as follows: Luminal B (52.6%), TNBC (28.9%), HER2 (13.2%), and Luminal A (5.3%); for patients with no staining, the distribution was Luminal B (45.5%), TNBC (36.4%), Luminal A (9.1%), and HER2 (9.1%). Moderate EGFR staining was prevalent in the Luminal B group (54.5%), followed by HER2-enriched (18.2%), TNBC (18.2%), and Luminal A (9.1%). Furthermore, strong EGFR staining was exhibited only in the TNBC group (100% of patients).

Table 2. Association of EGFR expression with hormonal receptor status in breast cancer patients (n=62)

Hormone receptor	Status	EGFR expression						
		No, n (%)	Weak, n (%)	Moderate, n (%)	Strong, n (%)	χ2 value	df	p-value
ER	Negative	5 (45.5)	16 (42.1)	4 (36.4)	2 (100.0)	2.87	3	0.412
	Positive	6 (54.5)	22 (57.9)	7 (63.6)	0 (0.0)			
PR	Negative	7 (63.6)	25 (65.8)	7 (63.6)	2 (100.0)	1.09	3	0.780
	Positive	4 (36.4)	11 (34.2)	4 (36.4)	0 (0.0)			
HER2	Negative	7 (63.6)	23 (62.2)	6 (50.0)	2 (100.0)	4.81	9	0.851
	Positive	3 (27.3)	12 (32.4)	5 (41.7)	0 (0.0)			
	Equivocal	1 (9.1)	2 (5.4)	1 (8.3)	0 (0.0)			

EGFR: Epidermal growth factor receptor, ER: Estrogen receptor, df: Degrees of freedom, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2.

Table 3. Association of EGFR expression with molecular subtypes of breast cancer

Molecular subtypes	EGFR expression				χ^2 value	df	p-value
	No	Weak	Moderate	Strong			
HER2, n (%)	1 (9.1)	5 (13.2)	2 (18.2)	0 (0.0)	6.06	9	0.733
Luminal A, n (%)	1 (9.1)	2 (5.3)	1 (9.1)	0 (0.0)			
Luminal B, n (%)	5 (45.5)	20 (52.6)	6 (54.5)	0 (0.0)			
TNBC, n (%)	4 (36.4)	11 (28.9)	2 (18.2)	2 (100.0)			

EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer, df: Degrees of freedom

Discussion

EGFR expression exhibited predominantly weak staining intensity (61.3%). Regarding receptor status, weak EGFR expression was prevalent in ER-positive patients (57.9%) and PR-negative patients (65.8%), whereas strong EGFR expression was observed in ER/PR/HER2/neu-negative subgroups. Assessment of molecular subtype showed a prevalence of weak and moderate EGFR staining in the Luminal B subtype, while strong EGFR expression was observed only in TNBC patients. However, there was no statistically significant association between EGFR expression and either molecular subtypes or hormone receptor status.

EGFR expression is a well-studied biomarker in BC, with positivity rates ranging from 14% to 91% across various studies (18). The present study found EGFR expression in 82.2% of the patient cohort. A study by Choccalingam et al. (19), observed high EGFR expression in HER2-positive patients. However, differences in Luminal B and TNBC subtypes between studies highlight variability in EGFR expression across populations and in study methodologies. For instance, Hashmi et al. (20) reported significantly lower EGFR expression (18.7%) in TNBC patients compared to our findings (78.9%). Such variations may be due to differences in patient demographics, sample sizes, and detection methodologies.

Regarding hormonal receptors, EGFR expression was observed in 46.7% of ER-positive cases, 54.8% of PR-negative cases, and 50% of HER2-negative cases. These findings did not show a significant association between EGFR expression and hormone receptor status, corroborating Choccalingam et al. (19), except for ER-positive cases with an inverse correlation. The lack of a strong association between EGFR and hormone receptor status suggests that EGFR expression might be independent of hormone receptor pathways. This is crucial for understanding the pathways that influence BC progression and treatment resistance.

HER2 expression is a critical biomarker in BC, impacting its prognosis and treatment strategies. In ductal carcinoma *in situ* (DCIS), HER2 positivity is prevalent in up to 50% of cases, particularly in high-grade lesions, and is associated with aggressive disease features, such as larger tumor size, high nuclear grade, and elevated proliferation indices (21). HER2-positive DCIS has an increased risk of recurrence compared to HER2-negative DCIS (22). Targeted therapies like trastuzumab can improve outcomes for HER2-positive patients, emphasizing the importance of accurate HER2 status assessment for personalized treatment (22). However, the role of HER2 in the progression from DCIS to invasive BC remains complex. Despite its association with aggressive features and higher recurrence rates, HER2-positive DCIS may not be the primary driver of progression to invasive disease (23). HER2 overexpression is more common in DCIS than in invasive BC, suggesting it may be more crucial in the initiation rather than the progression of DCIS (21). Invasive cancers may arise from HER2-negative precursor lesions or HER2-negative subclones within DCIS (21). Further research is needed to clarify the intricate relationship between HER2 expression, disease progression, and treatment response (21-23).

The present study assessed EGFR expression in 62 patients and found that most exhibited low EGFR expression. However, higher EGFR expression was observed in the Luminal B and TNBC subtypes. These findings suggest that EGFR may play a critical role in the pathogenesis and progression of these subtypes. EGFR overexpression has been associated with larger tumor size, higher proliferation rates, genomic instability, and a higher likelihood of HER2 overexpression and lower hormone receptor levels (23,24). Furthermore, preclinical studies have demonstrated that EGFR overexpression leads to malignant transformation, increased proliferation, and resistance to apoptosis in BC models (24). EGFR has also been implicated in resistance to hormone therapy through crosstalk with ER (25-27). The activated form of EGFR, phosphorylated EGFR (pEGFR), has been associated with an antiapoptotic effect through the PI3K pathway and is correlated with poor prognosis in lung cancer (28,29). In BC, simultaneous expression of EGFR and pEGFR has emerged as a more promising prognostic marker in invasive carcinomas (30).

Invasive micropapillary carcinoma (IMPC) is a rare and distinct histological subtype of BC, comprising approximately 0.9-2% of all BC cases (31). It is characterized by an aggressive clinical course, a high likelihood of lymph node involvement, and a unique histopathological architecture (31). Despite its

aggressive features, survival rates for IMPC are comparable to those of other BC subtypes (32). Accurate recognition of IMPC is essential for guiding clinical management, particularly concerning axillary assessment and surgical planning (32). A case report by Verras et al. (33), highlights the challenges in managing IMPC due to its unique histological characteristics. It underscores the need for clinical awareness to optimize treatment strategies. The report details the case of a woman diagnosed with IMPC who underwent tumor and lymph node marking, primary systemic therapy, and oncoplastic surgery with sentinel lymph node biopsy. Despite the imaging suggesting a complete radiological response to neoadjuvant chemotherapy, pathology revealed multiple areas of high-grade micropapillary DCIS. One of the five sentinel lymph nodes removed showed micro-metastatic infiltration with extranodal extension (33).

Our study also highlights the predictive value of EGFR expression. The correlation between EGFR and poor prognosis and aggressive tumor characteristics, such as higher proliferation rates and genomic instability, emphasizes its role as a marker of disease progression. However, the inconsistency in its prognostic significance across studies, potentially due to small sample sizes and varying methodologies, calls for more standardized and large-scale studies to validate these associations.

Overall, the high rate of EGFR expression observed in the present study, particularly in HER2-positive and TNBC subtypes, highlights the potential clinical significance of this biomarker in BC. EGFR may serve as a therapeutic target and a prognostic marker, especially in aggressive BC subtypes. However, further research is needed to establish the clinical utility of EGFR assessment in routine practice and to develop targeted therapies that effectively inhibit EGFR signaling in BC.

Study Limitations

Though our study provides insights into EGFR in BC, it has certain limitations. The main limitation of our study is the relatively small sample size and single-institution recruitment, which may limit the generalizability of our findings. Larger, multi-center studies are necessary to confirm the patterns of EGFR expression and its clinical implications across diverse populations. Further research should focus on molecular mechanisms underlying EGFR-mediated resistance pathways and on developing combination therapies targeting EGFR and other pathways involved in BC progression.

Conclusion

In conclusion, while most patients exhibited low EGFR expression, no significant association was found between EGFR expression and BC subtypes or hormone receptor status, suggesting that EGFR alone may have limited value as a marker for BC classification. This underscores the importance of comprehensive molecular profiling for more accurate prognosis and tailored treatment strategies.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the institutional Ethics Committee of the KS Hegde Medical Academy (which has university status) (approval no.: EC/066/2021-22, date: 05.02.2021).

Informed Consent: Written informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.B.A., C.D., K.M., Concept: C.D., K.M., P.P., P.S., Design: C.D., K.M., P.S., Data Collection or Processing: C.D., K.M., Analysis or Interpretation: D.B.A., K.M., S.K.E., V.C.S., Literature Search: D.B.A., S.K.E., V.C.S., P.P., Writing: D.B.A., C.D., K.M., P.P.

Conflict of Interest: The authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, et al. Current and future burden of breast cancer: global statistics for 2020 and 2040. *Breast.* 2022;66:15-23.
2. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast canser statistics, 2022. *CA Cancer J Clin.* 2022;72(6):524-541.
3. Mehrotra R, Yadav K. Breast cancer in India: present scenario and the challenges ahead. *World J Clin Oncol.* 2022;13(3):209-218.
4. Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. *Mol Oncol.* 2011;5(1):5-23.
5. Burguin A, Diorio C, Durocher F. Breast cancer treatments: updates and new challenges. *J Pers Med.* 2021;11(8):808.
6. Barrios CH. Global challenges in breast cancer detection and treatment. *Breast.* 2022;62 Suppl 1(Suppl 1):S3-S6.
7. Wykosky J, Fenton T, Furnari F, Cavenee WK. Therapeutic targeting of epidermal growth factor receptor in human cancer: successes and limitations. *Chin J Cancer.* 2011;30(1):5-12.
8. Gonzalez-Conchas GA, Rodriguez-Romo L, Hernandez-Barajas D, Gonzalez-Guerrero JF, Rodriguez-Fernandez IA, Verdines-Perez A, et al. Epidermal growth factor receptor overexpression and outcomes in early breast cancer: A systematic review and a meta-analysis. *Cancer Treat Rev.* 2018;62:1-8.
9. Ali R, Wendt MK. The paradoxical functions of EGFR during breast cancer progression. *Signal Transduct Target Ther.* 2017;2:16042-.

10. Alqaisi A, Chen L, Romond E, Chambers M, Stevens M, Pasley G, et al. Impact of estrogen receptor (ER) and human epidermal growth factor receptor-2 (HER2) co-expression on breast cancer disease characteristics: implications for tumor biology and research. *Breast Cancer Res Treat.* 2014;148(2):437-444.

11. Fei Y, Yu H, Huang S, Chen P, Pan L. Expression and prognostic analyses of early growth response proteins (EGRs) in human breast carcinoma based on database analysis. *PeerJ.* 2019;7:e8183.

12. Hanker AB, Sudhan DR, Arteaga CL. Overcoming endocrine resistance in breast cancer. *Cancer Cell*. 2020;37(4):496-513.

13. Miller TW, Balko JM, Fox EM, Ghazoui Z, Dunbier A, Anderson H, et al. ERα-dependent E2F transcription can mediate resistance to estrogen deprivation in human breast cancer. *Cancer Discov.* 2011;1(4):338-351.

14. Ma CX, Reinert T, Chmielewska I, Ellis MJ. Mechanisms of aromatase inhibitor resistance. *Nat Rev Cancer.* 2015;15(5):261-275.

15. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology.* 2020;76(2):182-188.

16. Rakha EA, El-Sayed ME, Lee AH, Elston CW, Grainge MJ, Hodi Z, et al. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. *J Clin Oncol.* 2008;26(19):3153-3158.

17. Hashmi AA, Naz S, Hashmi SK, Irfan M, Hussain ZF, Khan EY, et al. Epidermal growth factor receptor (EGFR) overexpression in triple-negative breast cancer: association with clinicopathologic features and prognostic parameters. *Surg Exp Pathol*. 2019;2(1):1-7.

18. Suo Z, Risberg B, Kalsson MG, Willman K, Tierens A, Skovlund E, et al. EGFR family expression in breast carcinomas. C-erbB-2 and c-erbB-4 receptors have different effects on survival. *J Pathol*. 2002;196(1):17-25.

19. Choccalingam C, Rao L, Rao S. Clinico-pathological characteristics of triple negative and non triple negative high grade breast carcinomas with and without basal marker (CK5/6 and EGFR) expression at a Rural Tertiary hospital in India. *Breast Cancer (Auckl).* 2012;6:21-9.

20. Hashmi AA, Edhi MM, Naqvi H, Faridi N, Khurshid A, Khan M. Clinicopathologic features of triple negative breast cancers: an experience from Pakistan. *Diagn Pathol.* 2014;9:43.

21. Akrida I, Mulita F. The clinical significance of HER2 expression in DCIS. *Med Oncol.* 2022;40(1):16.

22. Borgquist S, Zhou W, Jirström K, Amini RM, Sollie T, Sørlie T, et al. The prognostic role of HER2 expression in ductal breast carcinoma in situ (DCIS); a population-based cohort study. *BMC Cancer.* 2015;15:468.

23. Thorat MA, Levey PM, Jones JL, Pinder SE, Bundred NJ, Fentiman IS, et al. Prognostic and predictive value of HER2 expression in ductal carcinoma in situ: results from the UK/ANZ DCIS randomized trial. *Clin Cancer Res.* 2021;27(19):5317-5324.

24. Rimawi MF, Weiss HL, Bhatia P, Chamness G, Elledge RM. EGFR expression in breast cancer: Association with biologic phenotype, prognosis, and resistance to adjuvant therapy. *J Clin Oncol.* 2006;24(18_suppl):513.

25. Massarweh S, Osborne CK, Jiang S, Wakeling AE, Rimawi M, Mohsin SK, et al. Mechanisms of tumor regression and resistance to estrogen deprivation and fulvestrant in a model of estrogen receptor-positive, HER-2/neu-positive breast cancer. *Cancer Res.* 2006;66(16):8266-8273.s

26. Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. *Annu Rev Med.* 2011;62:233-247.

27. Xie Y, Han X, Yu J, Yuan M, Yan Y, Qin J, et al. EGR3 and estrone are involved in the tamoxifen resistance and progression of breast cancer. *J Cancer Res Clin Oncol.* 2023;149(20):18103-18117.

28. Sonnweber B, Dlaska M, Skvortsov S, Dirnhofer S, Schmid T, Hilbe W. High predictive value of epidermal growth factor receptor phosphorylation but not of EGFRvIII mutation in resected stage I non-small cell lung cancer (NSCLC). *J Clin Pathol.* 2006;59(3):255-259.

29. Kanematsu T, Yano S, Uehara H, Bando Y, Sone S. Phosphorylation, but not overexpression, of epidermal growth factor receptor is associated with poor prognosis of non-small cell lung cancer patients. *Oncol Res.* 2003;13(5):289-298.

30. Magkou C, Nakopoulou L, Zoubouli C, Karali K, Theohari I, Bakarakos P, et al. Expression of the epidermal growth factor receptor (EGFR) and the phosphorylated EGFR in invasive breast carcinomas. *Breast Cancer Res.* 2008;10(3):R49.

31. Verras GI, Tchabashvili L, Mulita F, Grypari IM, Sourouni S, Panagodimou E, et al. Micropapillary breast carcinoma: from molecular pathogenesis to prognosis. *Breast Cancer (Dove Med Press).* 2022;14:41-61.

32. Yang YL, Liu BB, Zhang X, Fu L. Invasive micropapillary carcinoma of the breast: an update. *Arch Pathol Lab Med.* 2016;140(8):799-805.

33. Verras GI, Mulita F, Tchabashvili L, Grypari IM, Sourouni S, Panagodimou E, et al. A rare case of invasive micropapillary carcinoma of the breast. *Prz Menopauzalny.* 2022;21(1):73-80.