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Immunohistochemical Expression Profile of Cdk4 in Carcinoma Breast and Correlation to Clinicopathological Parameters- A Cross-Sectional Study

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ABSTRACT

Background

Breast carcinoma stands as the most commonly diagnosed cancer among women and is a leading contributor to cancer-related deaths in females. It is increasingly being identified at younger ages, with tumors that are often biologically aggressive and diagnosed at more advanced stages, thereby resulting in elevated mortality rates. In the context of personalized medicine, there is a pressing need to discover novel, effective prognostic and predictive biomarkers that are involved in the development and progression of breast cancer, as well as serve as potential therapeutic targets—particularly when considering the genetic variability among patients.

Among the many molecules and biomarkers implicated in the molecular pathogenesis of breast cancer, disruption of the cyclin D–cyclin-dependent kinase (CDK) regulatory axis may shift cells away from senescence and promote a more proliferative behavior. Cancer cells may exploit multiple pathways to enhance cyclin D-associated CDK activity. CDKs, through their interaction with cyclin D proteins, play a crucial role in advancing the cell cycle and are considered promising targets for cancer treatment, including in breast tumors.

Despite this, previous research has shown mixed findings regarding the role of CDK4 in breast cancer, and only a limited number of studies have been conducted in the Indian population. Therefore, the current study was designed to investigate the immunohistochemical (IHC) expression of CDK4 in breast carcinoma and examine its association with various clinicopathological parameters and molecular subtypes. The objective is to evaluate its potential prognostic and predictive significance, which could support better patient classification and contribute to more personalized treatment approaches.

Methods

Seventy cases of invasive breast carcinoma in which 66 cases w ere mastectomy specimens and four cases of lumpectomy specimens received in the Department of Pathology between January 2021 to December 2024 were included in our cross-sectional study (retrospective and prospective). Immunohistochemical staining was done on these cases using Cyclin-dependent kinase 4 (CDK 4). IHC expression profiles (with specific staining scoring system) were correlated with clinicopathological parameters like age, tumor size, histopathological grading, lymph node metastasis, lymphovascular invasion, perineural invasion and adjacent ductal carcinoma in situ, estrogen- receptor (ER), Progesterone-receptor (PR) and Human-epidermal growth factor receptor-2 (HER-2) expression and Ki-67 and molecular subtyping based on St. Gallen 2017 recommendation were done.

Results

CDK4 overexpression showed a statistically significant association with adverse prognostic parameters like patient group having lymph node metastasis (p=0.023) and perineural invasion (p=0.027). CDK4 overexpression also showed a

statistically

significant association with ER (p=0.047), PR (p=0.034), Her/2 neu (p<0.001) and also association with four molecular subtypes with p =0. 05. Based on intensity of staining parameters, significant association noted between perineural invasion and ER, PR and HER2neu receptor expression status with more strong association with Her- 2neu group compared to ER, PR group.

Conclusion

Significant association of CDK- 4 expression, which belongs to cyclin- dependent kinase family, regulating cell cycle, noted with lymph node metastasis, peri neural invasion and hormone receptor expression along with molecular sub typed breast carcinomas. These findings significantly correlate CDK-4 expression with higher risk of metastasis and hence associated with aggressive prognosis. Therefore CDK- 4 can be used as a potential anti- cancer drug target for better prognosis of the patients specially in hormone receptor sensitive patients.

Keyword: *: Breast cancer, lymph node metastasis, Cyclin Dependent Kinases (CDK-4). Lymphovasular invasion, perineural invasion, Molecular Classification*

1. INTRODUCTION

According to the GLOBOCAN 2022 report by the International Agency for Research on Cancer (1), approximately 20 million new cancer cases were identified globally, with breast cancer being the second most commonly diagnosed type after lung cancer, comprising around 11.6% of all cases. Breast cancer also ranks as the most frequently diagnosed malignancy among both men and women (1). In India, it has emerged as the leading cancer type in terms of both incidence and mortality, contributing to 13.5% of all new cancer diagnoses and 10.6% of cancer-related deaths (2). Despite advances in therapeutic options, survival outcomes remain challenged by unequal access to healthcare facilities and late-stage diagnoses. Women diagnosed at stage I have a significantly higher survival rate of 93.3%, compared to a markedly lower survival rate of 24.5% for those diagnosed at stage IV, resulting in an overall survival rate of 73.8% (3). A population-based study from South India further revealed that women with lower levels of education tend to have poorer survival outcomes, often due to being diagnosed at more advanced stages of the disease (4). To improve patient outcomes, timely diagnosis, accurate prognostication, and tailored therapies are urgently needed. A promising area of research lies in understanding cell cycle regulation. The cell cycle is a highly conserved and meticulously controlled process within cancer genomics, ensuring proper genome replication and cell division through four distinct phases: G0/G1 (first gap), S (DNA synthesis), G2 (second gap), and M (mitosis), with built-in checkpoints that safeguard the integrity of DNA replication during the S phase and accurate chromosomal segregation during mitosis (5). Key checkpoints during the G1 and G2 phases are critical for determining whether a cell progresses through the cycle or pauses in the G0 phase. This progression is governed by cyclins and cyclin-dependent kinases (CDKs), a family of serine/threonine kinases. These enzymes form active complexes with cyclins that help regulate CDK stability, activation, and phosphorylation at specific cell cycle stages [6,7]. Cyclin/CDK complexes facilitate cell cycle progression by phosphorylating target genes, notably the tumor suppressor protein retinoblastoma (Rb). Their activation is stimulated by growth signals and suppressed by cell-cycle checkpoints that respond to DNA damage (8). Additionally, cyclin/CDK activity is downregulated by cyclin-dependent kinase inhibitors, highlighting their potential as therapeutic targets in cancer treatment.

Gaining insights into the molecular oncology of breast cancer is essential for identifying novel proteins and biomarkers that contribute to its development, progression, and clinical outcomes. Remarkable progress in gene expression technologies, particularly microarray analysis, has facilitated the simultaneous study of thousands of genes, allowing for more precise classification of breast carcinomas based on prognostic factors. Utilizing gene expression data, breast cancer can be classified into distinct molecular subtypes: Luminal A, Luminal B, HER2-enriched, and Triple-Negative or Basal-like types (9,10). CDK4 has been recognized as playing a vital role within these histological subtypes, particularly through its interactions with hormone receptors such as the estrogen receptor (ER), progesterone receptor (PR), HER2/neu, and the Ki-67 proliferation marker (11). Therapeutically, CDK4 inhibitors have demonstrated increased effectiveness in treating hormone receptor-positive breast cancers. However, their efficacy is limited in Triple-Negative Breast Cancer (TNBC), a subtype associated with poor prognosis. As a result, TNBC patients typically are not considered for high-dose chemotherapy, minimizing the risk of adverse treatment-related effects (12). Therefore, the current study was conducted in a tertiary care hospital in South India to evaluate the immunohistochemical (IHC) expression of CDK4, examining its role in the molecular pathogenesis of breast cancer and its correlation with various clinicopathological parameters and molecular subtypes

2. AIMS AND OBJECTIVES

1. Classification and grading invasive breast carcinoma according to the 2019 WHO classification, incorporating comprehensive clinical and pathological parameters.

2. To assess the immunohistochemical expression (IHC) of CDK 4 in all tissue samples from invasive breast carcinoma.

3. Correlate the expression profiles of CDK 4 with ER, PR, HER-2neu, and Ki-67 index in breast carcinoma

4. To evaluate potential prognostic and predictive significance of CDK4, which could support better patient classification and contribute to more personalized treatment approaches.

3. MATERIALS AND METHODS

We conducted a retrospective studies on total 70 cases including 66 mastectomy cases and 4 lobectomy cases of invasive breast cancer cases treated in our Pathology Department in between January 2019 and June 2024. Cases with post-chemotherapy status, trucut biopsies, and cases with insufficient material and blocks for immunohistochemical labeling were all excluded. Cases without access to mastectomy slides and blocks also were excluded. This study conducted was only after consent from the Institutional Ethical Committee. Before providing their informed consent, patients received patient information sheets and a comprehensive explanation of the trial.

CLINICAL AND LABORATORY DATA COLLECTION

We collected clinical data including patient' s age, presenting complaints, menarche and obstetric history, familial presence of breast carcinomas as well as other cancers, consumption of birth control pills, and menopausal status, Estrogen receptor (ER), progesterone receptor (PR), Human epidermal growth factor (HER2), Ki-67 index, Nottingham histological grading (13), lymph node metastasis , lymphovascular and perineural invasion considered. The 8th - edition of AJCC staging of cancer criteria' was employed for staging purpose and 2017 St Gallen classification (14) were considered for molecular subtyping of breast carcinoma.

ER, PR, HER-2 NEU AND KI-67 INTERPRETATION

According to the All-red score, for ER, PR positivity noted in nucleus, the pro portion score (PS) (0 – 5) & % of positive cancerous cells are, in that order, 0 (0%), 1 (<1%), 2 (1 –10%), 3 (11–33%), 4 (34 – 66 %), and 5 (67–100 %). (13). Her-2neu was reported in compliance with the requirements (3): A score of 0 (negative) indicates that there is no immunoreactivity or that <10% of tumor cells exhibit immunoreactivity. 1 + (negative): While most cancer cells show weak, ineffective immunoreactivity, a small part of membrane positivity. 2 + (equivocal): mild to moderate overall positivity in > 10 % of cancerous, cells, or circumferentially strong staining in membranes of < 30% of cells, 3+ (positive): > thirty percent of the carcinoma cells must exhibit robust and uniform membrane staining along with a uniform pattern resembling chicken - wire(15). For Ki-67, 20% tumor cells staining positivity considered as baseline, <20% as low proliferation index and >20% as high proliferation index.

CDK 4 INTERPRETATION

For CDK4, according to Peurala E, et al, (16) cytoplasmic staining graded as 0 considered as negative, type I considered as weak positive, type 2 considered as moderately positive and type 3 as strongly positive staining. Also percentage of nuclei was assessed in each case and scored on the scale of 0 to 100%. It is categorized as <25%, 25 - 50% and >50% tumor cells stained.

STATISTICAL METHOD

Using SPSS software (24.0), data were statistically studied using Chi- square test. p- value of < 0.05 was taken as statistically significant.

4. RESULTS

Among 70 cases in our study, the entire population was of female gender (100 %). Age of our study patients ranged from 33- 77 years with a mean age of 56. 5 years. The maximum number of cases were noted above 50 years of age, n- 46 cases, (66%). The most common histological type was Invasive Carcinoma of Breast- NST (No Special type); n= 64 (91.4%), other types were Mucinous Carcinoma n= 2 (2.8%), Lobular Carcinoma n=1 (1.4%), Metaplastic Carcinoma n=1 (1.4%), Adenoid Cystic Carcinoma n=1 (1.4%), Papillary Carcinoma N=1 (1.4). The most common Nottingham histological grade was Grade II, n= 42 (60%), Grade I, n= 19 (27%), Grade 3, n= 9 (13%). Tumor size ranges between 1 -13 cm. Among the T-stage maximum patients are having T2 stage of tumor with 46 cases (65 %), T1 = 9 (13 %, T3 n = 9 (13%), T4, n= 6 (9%). Among the various lymph nodal stages, cases without nodal metastasis (N0) are of 31 cases (47%) and rest 35 patients (53 %) showed nodal metastasis with 17 cases (26%) and 10 cases (18 %) showed N1 and N2 stages respectively. 4 cases nodal metastasis could not been evaluated. Total 31 cases (44%) showed presence of lymphovascular invasion and only 9 cases (12%) showed perineural invasion. Half of the cases, 35 cases (50%) showed presence of ductal carcinoma-in-situ component along with adjacent invasive property. On the basis of immunohistochemical expression of markers, ER positivity noted in 44 cases (65%), E R negativity noted in 24 cases (35 %). 2 cases could not been retrieved for immunohistochemical staining. PR positivity noted in 42 cases (62%) and P R negativity noted in 26 cases (38 %). Her2 neu positivity noted in 21 cases (31%) and Ki - 67 high proliferation-index noted in 47 cases (70%). Surrogate molecular subtyping was done based on IHC expression profile, showing Luminal A 14 cases (21%), Luminal B 30 cases (43%) 10 cases (15%) HER - 2enriched and 14 cases (21 %) are of triple negative subtype. Hence, maximum cases encountered are

of Luminal-B subtype CDK 4 showed statistically significant association with lymph node involvement status(p= 0.0233), perineural invasion(p value= 0.0277), and among the hormone- receptor expression status with ER (p value=0.047), PR (p value=0.0344), but very strongly with HER-2 neu (p value=<0.001),and also with Molecular Sub-Typing of breast carcinoma (p value=0.056) noted, but, other parameters showed no significant correlation with CDK 4 expression with Molecular Sub-Typing of breast carcinoma (p value=0.056) noted, but, other parameters showed no significant correlation with CDK 4 expression.

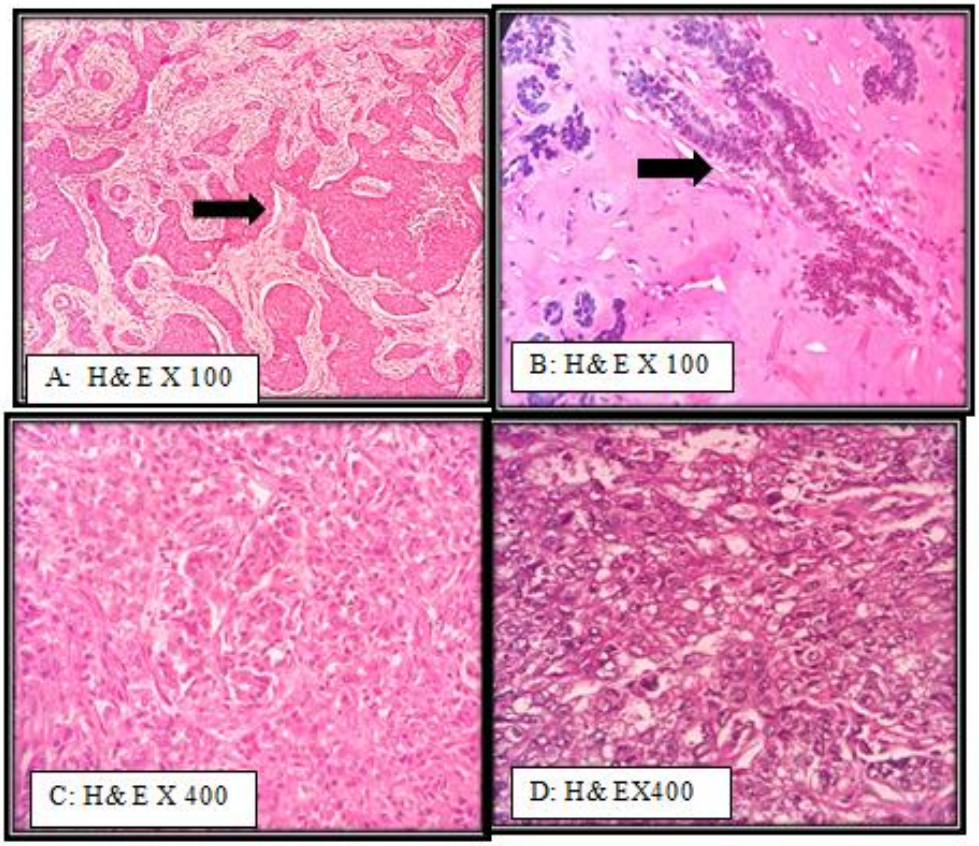

Figure 1: A- A Case of Invasive Breast Carcinoma- No Special Type (NST) With Nests Of Tumor Cells Infiltrating Into Breast Parenchyma (Arrow) (H& E, 100X)

B- Invasive Breast Carcinoma With Tumor Cells of Grade I Nuclear Pleomorphism In Desmoplastic Stroma (H& E, 100X)

C- Invasive Breast Carcinoma With Tumor Cells Grade II Nuclear Pleomorphism (H& E, 400X)

D- Invasive Breast Carcinoma With Tumor Cells Grade III Nuclear Pleomorphism (H& E,400X)

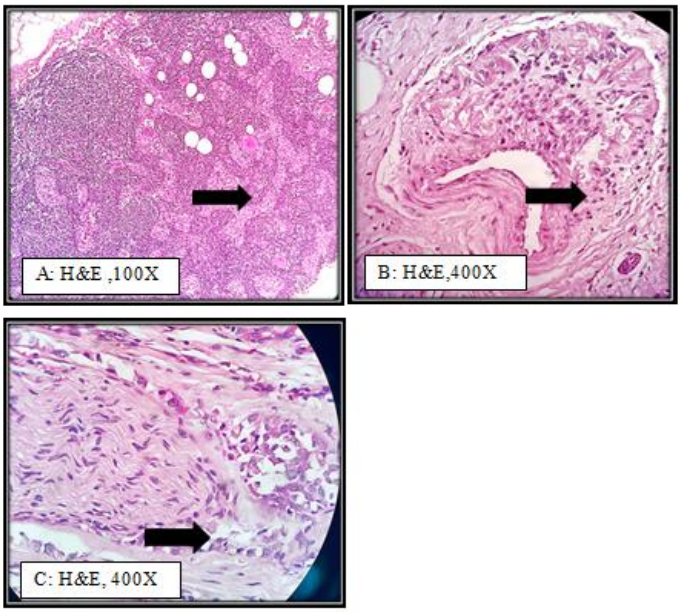

Figure 2:

A- Lymph Node Showing Metastatic Tumor Deposits (H&E ,100X)

B-Frequency Of Lymphovascular Invasion In Our Study (H&E,400X)

C-Perineural Invasion In Invasive Breast Carcinoma (H&E, 400X)

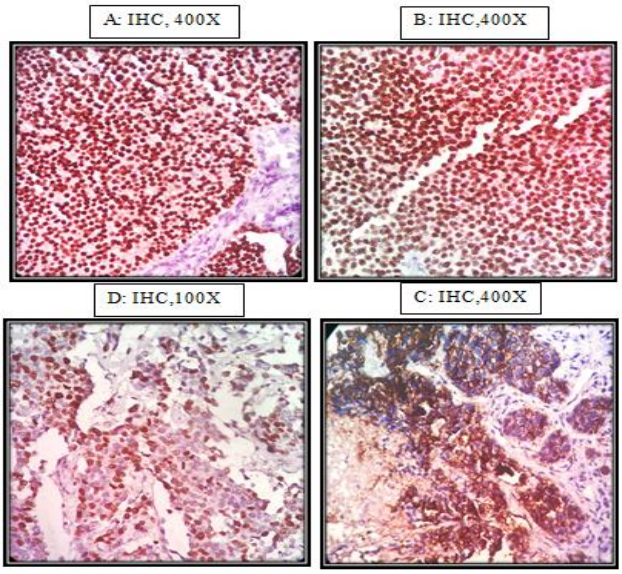

Figure 3:

A-Tumor Cells Showing Estrogen Positivity (IHC, 400X)

B- Tumor Cells Showing Progesterone Positivity (IHC,400X)

C- Tumor Caells Showing Her-2neu Positivity (IHC,400X)

D- Tumor Cells Showing Moderate Ki-67 Index (IHC,100X)

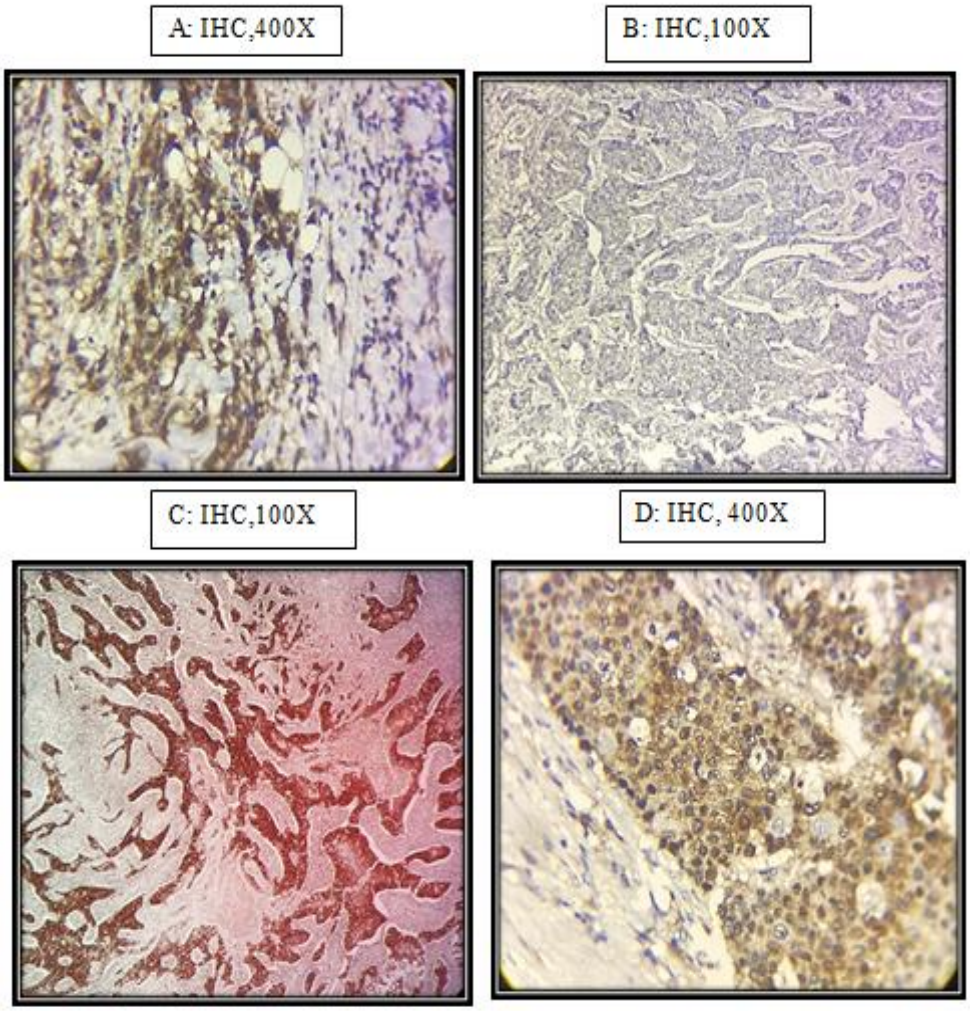

Figure 4:

A- Control (Ihc,400x),

B- Negative (Ihc,100x),

C- High Percentage of Cells Staining (Ihc,100x),

D- High Intensity of Cells Staining (Ihc, 400x)

Table: 1 – Association of Cdk4 with Clinicopathological Variables

CLINICOPATHOLOGICAL VARIABLES	CDK 4 EXPRESSION				
	1+	2+	3+	TOTAL	P VALUE
AGE					
<50 YEARS	5 (21%)	10 (42%)	9 (38%)	24 (100%)	0.617
>50 YEARS	14 (30%)	19 (41%)	13 (28%)	46 (100%)	
NOTTINGHAM GRADING					
GRADE I	5 (26%)	8 (42%)	6 (32%)	19 (100%)	
GRADE II	11 (26%)	17 (40%)	14 (33%)	42 (100%)	0.977
GRADE III	3 (33%)	4 (44%)	2 (22%)	9 (100%)	
T STAGE					
T1	2 (40%)	2 (40%)	1 (20%)	9 (100%)	
T 2	13 (24%)	22 (41%)	19 (35%)	46 (100%)	
T 3	4 (36%)	5 (45%)	2 (18%)	9 (100%)	0.754
T 4	3 (50%)	2 (33%)	1 (17%)	6 (100%)	
NODAL STAGE (N- STAGE)					
N 0	14 (45%)	11 (35%)	6 (19%)	31 (100%)	
N I	8 (47%)	5 (29%)	4 (24%)	17 (100%)	**0.0233**
N II	0	4 (40%)	6 (60%)	10 (100%)	
N III	0	5 (63%)	3 (38%)	8 (100%)	
LYMPHOVASCULAR INVASION (LVI)					
PRESENT	7 (23%)	14 (45%)	10 (32%)	31 (100%)	0.731
ABSENT	12 (31%)	15 (38%)	12 (31%)	39 (100%)	
PERINEURAL INVASION (PNI)					
PRESENT	2 (29%)	0	5 (71%)	7 (100%)	**0.0277**
ABSENT	17 (27%)	29 (46%)	17 (27%)	63 (100%)	
ER RECEPTOR EXPRESSION					
POSITIVE	9 (20%)	22 (50%)	13 (30%)	44 (100%)	**0.047**
NEGATIVE	10 (41%)	5 (21%)	9 (38%)	24 (100%)	
PR RECEPTOR EXPRESSION					
POSITIVE	8 (19%)	22 (52%)	12 (29%)	42 (100%)	**0.0344**
NEGATIVE	12 (46%)	5 (19%)	9 (35%)	26 (100%)	
HER-2neu RECEPTOR EXPRESSION					
POSITIVE	12 (57%)	4 (19%)	5 (24%)	21 (100%)	**<0.001**
NEGATIVE	7 (15%)	23 (49%)	17 (36%)	47 (100%)	
KI-67 INDEX					
LOW	6 (30%)	5 (25%)	9 (45%)	20 (100%)	0.584
HIGH	15 (32%)	19 (40%)	13 (28%)	47 (100%)	
MOLECULAR SUBTYPES					
LIMINAL A	1 (7%)	4 (29%)	9 (64%)	14 (100%)	
LUMINAL B	10 (33%)	14 (47%)	6 (20%)	30 (100%)	**0.056**
HER-2 ENRICHED	5 (50%)	3 (30%)	2 (20%)	10 (100%)	
TRIPLE NEGATIVE	3 (21%)	6 (43%)	5 (36%)	14 (100%)	

5. DISCUSSION

CDK4, being one of the most commonly amplified genes across human cancers, is known to play a significant role in the

proliferation of primitive stem cells and the development of mammary progenitor cells. This highlights its potential involvement in breast cancer stem cell (BCSC) maintenance, tumor recurrence, and resistance to therapy. Despite its apparent importance, there is a lack of comprehensive studies examining the association between CDK4 gene expression and different molecular subtypes of breast cancer, as well as its influence on patient prognosis and clinical outcomes.

A study conducted in 2016 reported that CDK4 was markedly overexpressed in breast cancer tissue compared to adjacent normal breast parenchyma (17). The most pronounced CDK4 expression was identified in the triple-negative or basal-like subtype, which is known for its aggressive clinical behavior. In contrast, Luminal A breast cancers, typically associated with better prognosis, exhibited significantly lower CDK4 levels (18). Among all breast cancer subtypes, triple-negative breast cancer (TNBC) shows the lowest five-year survival rates, and this subtype demonstrated notably elevated CDK4 gene expression. A strong correlation was particularly evident between CDK4 expression and tumors that were negative for estrogen and progesterone receptors, whereas no significant relationship was observed in HER2-positive cases (19). Given these observations, our study also aimed to assess CDK4 as a potential anti-cancer target, potentially offering new strategies for treatment and improved prognostication. The prognostic relevance of high-grade tumors often depends on the level of cellular proliferation and differentiation. Grade 3 tumors, which are poorly differentiated and exhibit rapid growth, contrast with grade 1 and 2 tumors that display more structured and slower proliferating characteristics. This supports the hypothesis that CDK4 may play a role in the expansion of breast cancer stem cells, particularly since high-grade tumors are often enriched with such early stem-like cells. Furthermore, the heightened CDK4 expression observed in the aggressive basal-like TNBC subtype correlates with the poor clinical outcomes typically seen in these cases, including high tumor grade and ER/PR negativity. Studies have shown that CDK4 inhibition not only suppresses its gene expression but also triggers a phenotypic transformation in TNBC, steering it toward a more epithelial and luminal-like profile. This shift has been associated with better clinical responses, highlighting CDK4 inhibition as a promising therapeutic strategy for TNBC management. Collectively, these findings emphasize the potential of CDK4 as a negative prognostic marker in TNBC patients (20).

In our study, CDK4 expression was found to be highest among patients aged over 50 years. When evaluating tumor histological grades, Emmi P. et al. (16) reported no statistically significant correlation between CDK4 expression and tumor grade. However, their study did observe an increasing trend in CDK4 positivity with higher-grade tumors. This observation is consistent with our findings and reinforces the established notion that CDK4 contributes to enhanced cellular proliferation. Additionally, Han-Xiang An et al. (17) concluded that CDK4 gene amplification or expression was not significantly correlated with tumor size or lymph node involvement. Similarly, our study did not find a significant association between CDK4 expression and tumor size. However, unlike their findings, we observed a statistically significant relationship between CDK4 expression and lymph node metastasis, with a p-value of <0.0233. Furthermore, our analysis did not reveal any significant association between CDK4 expression and lymphovascular invasion (LVI) or perineural invasion (PNI).

Richard S. Finn et al. (18), in their review article, emphasized a strong link between CDK4 and hormone receptor-positive breast cancers, particularly those that are estrogen receptor (ER) positive. Their findings also highlighted that elevated estrogen levels are associated with increased cellular proliferation, which underpins the rationale for using CDK4 inhibitors as a central therapeutic approach in managing breast cancers undergoing endocrine therapy. Similarly, Murad G. et al. (19) reported that high progesterone receptor (PR) expression correlates with better responsiveness to CDK4 inhibitors, suggesting a close relationship between CDK4 activity and progesterone signaling. In alignment with these findings, our study demonstrated a statistically significant association between CDK4 expression and the presence of ER, PR, and HER2 markers. C.G. Murphy et al. (21) further elaborated that estrogen receptor activity can directly enhance Cyclin D1 expression, which binds to and activates CDK4, thereby promoting tumor cell proliferation.

Additionally, Pavlovic et al. (22) established a strong correlation between CDK4 and specific molecular subtypes of breast cancer—particularly Luminal A and Luminal B—due to their frequent association with ER and PR positivity. However, they also noted a lack of substantial evidence linking CDK4 expression to triple-negative breast cancers (TNBC). Contrary to this, Ye Hu et al. (23) reported that TNBCs may exhibit heightened sensitivity to CDK4 inhibition. In our study, CDK4 expression demonstrated a statistically significant relationship with breast cancer molecular subtypes ($p = 0.056$), further supporting its potential role in subtype-specific prognostic evaluation and targeted therapy.

6. CONCLUSION

This study evaluated the Immunohistochemical (IHC) expression patterns of key proteins involved in the molecular pathogenesis of breast carcinoma, with a specific focus on cell cycle regulatory proteins, particularly cyclin-dependent kinase 4 (CDK 4).

CDK4 inhibitors have demonstrated anti-cancer properties, especially in hormone receptor-positive breast cancer cases. In our analysis, CDK4—a member of the cyclin-dependent kinase family—showed a statistically significant correlation with adverse pathological features, notably lymph node metastasis and perineural invasion. Furthermore, multivariate analysis revealed a significant association between CDK4 expression and the molecular subtypes of breast carcinoma. These

findings highlight the critical involvement of CDK4 in breast cancer progression through its role in regulating the cell cycle. Given its association with negative prognostic indicators, CDK4 may serve as a valuable prognostic marker in breast cancer. Additionally, beyond its established relevance in ER-positive tumors, CDK4 may also have potential therapeutic implications in HER2-positive cases.

To strengthen and validate these results, further research is warranted using a larger patient cohort. Future studies should incorporate functional assays—both in vivo and in vitro—to quantify protein expression levels, assess gene expression, and evaluate long-term survival outcomes for a more comprehensive prognostic assessment

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