TACC3 as a Prognostic Marker in Breast Carcinoma, an Immunohistochemical study in Qena University Hospitals

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Abstract

Background: Transforming acidic coiled-coil 3 (TACC3) protein is linked to several forms of human cancer. Yet, its precise role in breast cancer (BC) remains unclear.

Objectives: This study aims to evaluate the immunohistochemical (IHC) expression of TACC3 in BC and its correlation with clinicopathological features and hormonal receptors expression.

Patients and methods: TACC3 was immunohistochemically examined in 60 cases of primary BC from the pathology lab at Qena University Hospital (during the period from April 2021 to April 2023). Alongside this analysis, the patients were also assessed for estrogen receptor, progesterone receptor, HER2/neu, and ki67 index.

Results: A statistically significant association between TACC3 with age, lymph node metastasis, tumor necrosis, ER, and PR expression (p values = 0.049, 0.020, 0.006, 0.042 and 0.006, respectively) was detected. There was no statistically significant difference between TACC3 and tumor stage, lymphovascular emboli, perineural invasion, histological type, HER-2 status and Ki67 (p value > 0.05).

Conclusion: These results suggest that TACC3 may be of valuable prognostic value BC. Furthermore, TACC3 might be a potential candidate for targeted therapy.

Keywords: TACC3; Breast cancer; Estrogen receptor; Progesterone receptor.
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Introduction

Breast cancer (BC) is a leading cause of cancer in women worldwide. While advancements in diagnosis and treatment have been made, the incidence of invasive breast cancer (IBC) has been on the rise in many low- and middle-income countries in recent years **(Francies et al., 2020)**. Conversely, high-income nations like the United States, Canada, the United Kingdom, and Australia experienced a decline in BC incidence rates in the early 2000s. This decrease was attributed, in part, to a reduced use of postmenopausal hormone therapy following the publication of the Women's Health Initiative trial. The trial established a link between postmenopausal hormone use and increased breast cancer risk **(Lukong et al., 2017)**.

While the incidence of breast cancer (BC) varies between industrialized and developing countries, it remains the most common type of cancer among women in Egypt **(Azim et al., 2023)** reported an age-specific incidence rate of 48.8 per 100,000 women in Egypt. Furthermore, the Egyptian National Cancer Institute (NCI) indicates that BC constitutes a significant 18.9% of all cancer cases in women **(Seif Abd Elalem et al., 2023)**.

Breast cancer (BC) is a complex disease with diverse molecular profiles, leading to variations in tumor behavior and patient prognosis. This heterogeneity at the molecular level has spurred extensive research efforts to identify and classify BC subtypes based on their gene expression patterns. This knowledge is crucial for tailoring treatment strategies and improving patient outcomes **(Harish et al., 2020)**.

While the analysis of global gene expression patterns, particularly those related to cell growth and behavior, has been instrumental in identifying intrinsic molecular subtypes of breast cancer with clinical significance, the vast majority of healthcare systems rely primarily on immunohistochemical examination of biomarkers (ER, PR, HER2, and Ki-67) for surrogate molecular classification due to time and cost constraints **(Gion et al., 2021)**. However, the examination of global gene expression patterns has led to the identification of gene signatures that predict patient outcomes and treatment response **(Armingol et al., 2021)**.

Gene expression studies have significantly advanced our understanding of the complex nature of breast cancer (BC). In 2000, a groundbreaking molecular classification identified four distinct BC subtypes: **1) ER+/luminal:** These tumors express estrogen receptors and have a favorable prognosis. **2) HER2+ (HER2-enriched):** These tumors overexpress the HER2 gene, leading to aggressive growth. **3) Basal-like:** Characterized by the absence of ER, PR, and HER2 receptors, these tumors are often associated with poor prognosis. **4) Normal-like:** These tumors exhibit a gene expression profile similar to normal breast tissue, often with a favorable prognosis. These subtypes differ in their clinicopathological characteristics, prognosis, and response to therapies. This molecular classification has significant clinical utility, guiding treatment strategies and improving patient outcomes, and is now widely incorporated into international treatment guidelines **(Tsang and Tse, 2020)**.

Clinicopathological factors linked to final results, most often overall survival [OS], are known as prognostic markers, and they are used to assess the

risk of death in BC following surgery **(Wang et al., 2020)**. Tumor size, nodal status, and histological grade are the attributes that have been proven in clinical practice. The Nottingham Prognostic Index, which divides patients into excellent, moderate, and poor prognostic groups, is based on these three factors and was obtained by a retrospective, multivariate regression analysis **(Mahitha, 2021)**.

One of the TACC family proteins, transforming acidic coiled-coil-containing protein 3 (TACC3), has a gene on chromosome 4's short arm **(Akbulut, 2021)**. The Aurora A kinase has TACC3 as a physiological target **(Zheng et al., 2023)**. It is necessary for the formation and stability of microtubules during mitotic division. The centrosome is where it localizes. This mechanism is necessary for the development of the mitotic spindle, which is in charge of the last phase of chromosomal segregation. Anomalous centrosomes and microtubules would result in defective mitotic spindle formation, which would be linked to tumor growth and carcinogenesis **(Meraldi, 2016)**. This elucidates the purported involvement of TACC3 in many cancers. The expression of TACC3 was found to be associated with the progression of malignancies in the lungs **(Chen et al., 2022)**, ovaries **(Saatci and Sahin, 2023)**, esophagus **(Huang et al., 2015)**, CNS **(Matsuda et al., 2022)**, and sarcomas as well **(Matsuda et al., 2017)**.

Because blocking TACC3 may stop the tumor from developing and spreading, it may be a promising candidate for targeted therapy **(Tong et al., 2020)**.

Therefore, the purpose of this study is to investigate TACC3 expression and its correlation with other clinical and histological prognostic variables in BC patients.

Patients and methods

Cases Collection

A total of sixty full-face tumor tissue slices, preserved in formalin and embedded in paraffin, were taken from specimens obtained from conservative breast surgery and modified radical mastectomy patients with axillary dissection who had BC. Between April 2021 and April 2023, the cases were gathered from the pathology department of the Qena University Hospital. The Research Ethical Committee, Faculty of Medicine, South Valley University provided ethical approval (ethical approval # SVU-MED-PAT005-2-21-4-188) for this work to be conducted.

Age, laterality, kind of operation, tumour size, histological type, lympho-vascular invasion, perineural invasion, lymph node status, carcinoma in situ, type and grade of the cancer, and lymphocyte infiltration (immune responses) were among the clinicopathological criteria gathered and examined.

Among the exclusion criteria were:

1) Cases with missing data.
2) Patients undergoing a straightforward mastectomy or lumpectomy without axillary sampling.
3) IHC cases having a HER2 score of 2+, but no SISH or DISH report is provided.
4) Cases received neo-adjuvant chemotherapy (NACTH).

Histopathological analysis

For pathological analysis, the paraffin blocks of the tumour sections were serially sectioned at a thickness of 4 μm and stained with standard Hematoxylin and Eosin stains. The

tumours were histologically classified in compliance with the most recent WHO guidelines **(Cserni, 2020)**. The Nottingham Grading System was used to grade the histology of the tumours **(Pandya and Shah, 2012)**.

According to **(Kuhn et al., 2023)**, the term "lympho-vascular invasion" refers to the presence of tumor cells within an endothelial-lined area (a blood vessel or lymphatic channel) outside the tumor's boundary.

Stromal tumor infiltrating lymphocytes (TILs) were classified as high TILs (≥30%) or low TILs (<30%) **(SHIBEL et al., 2019)**.

Staging and molecular Classification: The TNM staging approach was utilized for tumour staging in accordance with the most recent version of the AJCC staging manual **(Luo et al., 2020)**.

Immunohistochemistry

On positively charged slides, paraffin slices were cut at a thickness of 4 μm. sections stained with the Ventana BenchMark GX autostainer for ER, PR, HER2, and Ki67. Hematoxylin was utilized as a counterstain, along with a Ventana Ultraview DAB detection system. In situations where HER2 class 2+ was present, a SISH / DISH report was acquired. The immunostaining data were given a semiquantitative score. Positive nuclear staining (i.e., greater than 1%) was considered ER and PR positive **(Zhang and Tang, 2017)**. HER2 received the following scores: zero for no staining or faint incomplete membranous staining in less than 10% of cells; 1+, for faint incomplete membranous staining in more than 10% of cells; 2+, for weak to moderate complete staining in more than 10% of cells; and 3+, for strong complete staining in more than 10% of cells. Only a score of three was deemed favourable **(Zhang et al., 2020)**.

Ki-67 staining and scoring interpretation

The Ki-67 score, which is the proportion of positively stained cells to all malignant cells assessed, should only include nuclear staining (as well as mitotic figures stained with Ki-67) **(Feng et al., 2020)**. Ki-67 scoring was carried out at the hot areas or tumor edge. Because the invasive edge is generally regarded as the most biologically active area and is most likely to influence the course of the disease, three fields were scored at the tumor periphery for the former. Hot spots are regions with high concentrations of Ki-67 staining **(Saha et al., 2017)**. At least three randomly chosen, high-power (×40 objective) fields were counted when staining is uniform **(Ibrahim et al., 2022)**. Cases with > 15% positive nuclei were classified as high Ki-67 expression, and those with < 15% were classified as low Ki-67 expression **(Soliman and Yussif, 2016).**

Assessment of IHC staining for TACC3

Dako autostainer was used to immunostain the sections. The detecting system EnVision FLEX was employed. We used the immunohistochemistry study of TACC3 expression approach that was outlined and employed by **(Elmahdy et al., 2023)**. The staining intensity and extent were taken into account while evaluating the expression. A score of 0 indicated negative staining, 1 indicated faint staining, 2 indicated moderate staining, and 3 indicated strong staining. The percentage of positive cells (0–100) was used to score the staining extent. **Elmahdy et al., 2023** stated that the final score is product of intensity score multiplied by the extent score.

Cytoplasmic and /or nuclear staining is considered positive **(Lauffart et al., 2007)**.

Screening and imaging of slides

In order to screen each slide, a BX41 microscope was used. A high-definition digital microscope camera that was attached to the same microscope was used to capture the images.

Statistical analysis

The information was gathered, coded, edited, and imported into IBM SPSS, version 27 of the Statistical Package for Social Science. For the categorical variables, the data were shown as numbers and percentages; for the numerical variables and ranges were displayed. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to determine whether the data were normally distributed. The Mann Whitney U test and Kruskal Wallis test were employed for comparing groups.

Results

Included in this study were sixty female patients with breast cancer, ranging in age from twenty-five to seventy-two years, with a mean age of 50.87± 12.454 years. Thirty-four women (56.7%) had a left breast lesion, and twenty-six (43.3%) had a right breast lesion. Just 3.3% of patients have conservative breast surgery (CBS) with axillary dissection, compared to the majority of patients (96.7%) who have modified radical mastectomy (MRM).***Pathological features of tumors***

Ninety percent of the cases were of the invasive ductal carcinoma histological type. Grade II tumors outnumbered grade III tumors by 96.7% to 3.3%. T2 was more common than T3 in terms of tumor size (56.7% versus 36.7%). 33.3% of the patients had N1, 23.3% had N2, and 10% had N3 in terms of lymph node metastases. Four patients (6.7%) experienced perineural invasion, while forty patients (66.7%) developed lymphovascular emboli. Forty patients (66.7%) exhibited tumor necrosis, while twenty patients (33.3%) had carcinoma in situ. Regarding the extent of stromal TILs, 56 cases (93.33%) showed low TILs and 4 cases showed high TILs (6.67%).

Results of immunohistochemical staining

Positive TACC3 expression was detected in about 93.3% of BC specimens **(Fig.1).** In 76.7% and 86.7% of the specimens, respectively, the immunohistochemical staining revealed positive ER and PR. HER2 was found to be positive in just 6.7% of the samples. In 63.3% of the cases, Ki-67 was elevated.

Relation between TACC3 expression and clinicopathological parameters and molecular subtyping

TACC3 expression was statistically significant higher in younger age, right sides breast cancer, tumors with lymph node metastasis, and tumor necrosis (p values = 0.049, 0.005, 0.020, and 0.006, respectively) (**Table.1**).

Table 1. Relation between TACC3 expression and clinicopathological parameters and molecular subtyping (N=60).

Parameters		Total	TACC 3 expression (H score)		P value	
	No (%)		Median (IQR)			
Age (years)	12 (20%)		25-39 (12)		110 (10-120)	0.049*
	14 (23.3%)		40-50 (14)		60 (30-180)	

	34 (56.7%)	> 50 (34)	40 (20-57.50)	
Laterality	26 (43.3)	Right (26)	60 (40-135)	**0.005***
	34 (56.7%)	Left (34)	30 (10-60)	
Histological type	54 (90%)	IDC (54)	50 (20-110)	**0.017***
	4 (6.7%)	ILC (4)	25 (10-40)	
	2 (3.3%)	Mixed (2)	0 (0-0)	
Pathological tumor staging	4 (6.7%)	T1 (4)	35 (20-50)	**0.602**
	34 (56.7%)	T2 (34)	40 (25-132.50)	
	22 (36.7%)	T3 (22)	40 (20-110)	
Lymph node metastasis	20 (33.3%)	N0 (20)	40 (20-100)	**0.020***
	20 (33.3%)	N1 (20)	25 (10-40)	
	14 (23.3%)	N2 (14)	60 (40-120)	
	6 (10%)	N3 (6)	110 (40-180)	
Lympho-vascular emboli	40 (66.7%)	Positive (40)	40 (12.50-110)	**0.825**
	20 (33.3%)	Negative (20)	40 (20-100)	
Perineural invasion	4 (6.7%)	Positive (4)	40 (12.50-110)	**0.825**
	56 (93.3%)	Negative (56)	40 (20-100)	
Tumor necrosis	20 (33.3%)	Absent (20)	20 (10-40)	**0.006***
	40 (66.7%)	Present (40)	60 (32.50-110)	
Carcinoma in situ	40 (66.7%)	Absent (40)	40 (12.50-117.50)	**0.975**
	20 (33.3%)	Present (20)	45 (20-60)	
Tumor-infiltrating lymphocytes (TILs)	56 (93.3%)	High	65 (20-110)	**0.905**
	4 (6.7%)	Low	40 (20-107.50)	

"*" Significant (mann whiteny test and Kruskal Wallis test, P<0.05)

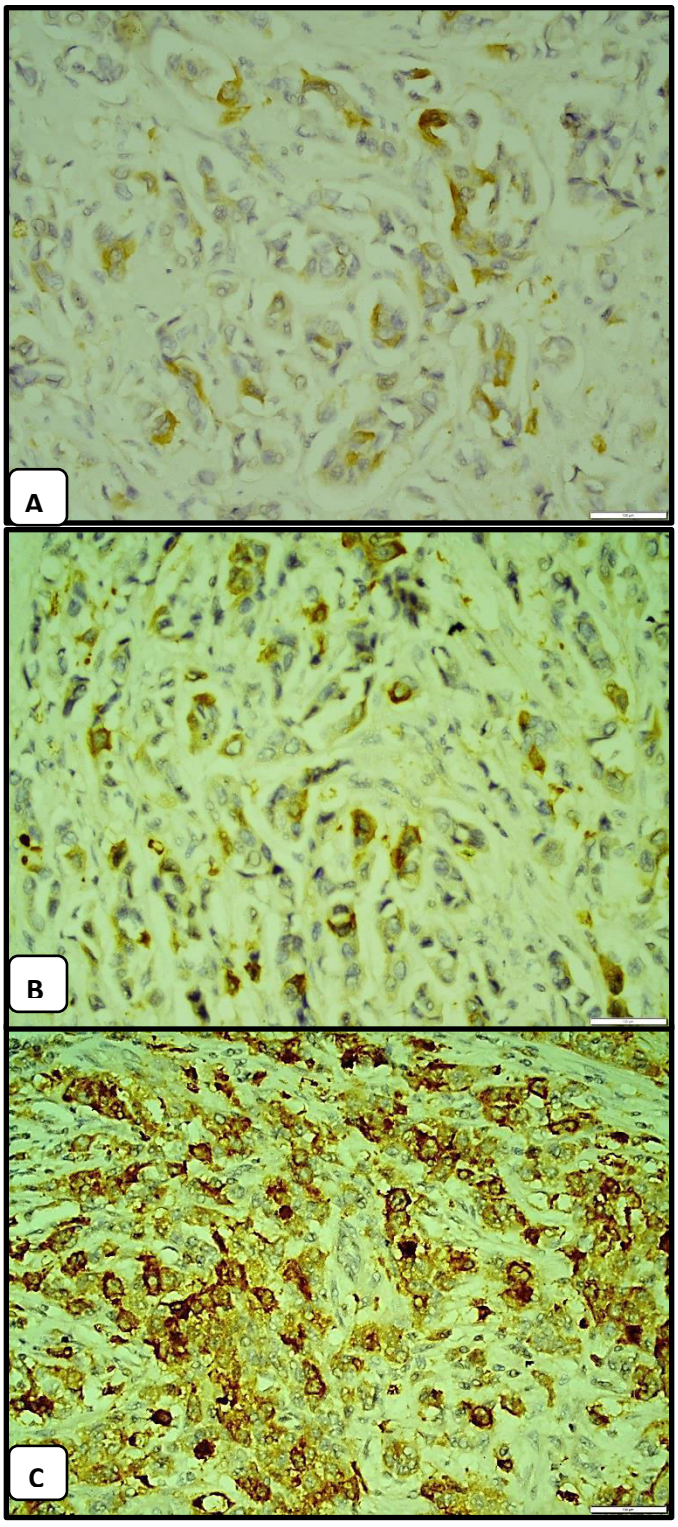

Fig.1.TACC3 expression in BC. A) Weak TACC3 expression (x400). B) Moderate TACC3 expression (x400). C) Strong TACC3 expression (x400).

Correlation between TACC3 expression and Ki67, ER, PR, and HER2

There was a significant difference between the TACC3 H score with ER & PR status, with the median TACC3 H score being considerably higher in tumors with absent ER and PR expression compared to those expressing ER and PR (p-value = 0.042 & 0.006 respectively). The expression of the TACC3 H score and the status of HER2 and Ki-67 was not statistically significant (**Table.2**).

Table 2. Association between TACC3 expression and ER, PR, HER2 and Ki67 IHC

Parameters				TACC3 expression (H score)	P value
		Frequency	Percentage (%)	Median (IQR)	
ER status	**Positive**	**46**	76.7%	**40 (40)**	**0.042***
	Negative	**14**	23.3%	**110 (80)**	
PR status	**Positive**	**52**	86.7%	**40 (40)**	**0.006***
	Negative	**8**	13.3%	**120 (105)**	
HER2 status	**Positive**	**4**	6.7%	**70 (60)**	**0.512**
	Negative	**56**	93.3%	**40 (90)**	
Ki-67 status	**High**	**38**	63.3%	**40 (90)**	
	Low	**22**	36.7%	**30 (50)**	**0.165**
TACC 3 H score	**Mean ± SD**	**67.50 ± 66.368**			
	Median (range)	40 (0-240)			
	Positive	56	93.3%		
	Negative	4	6.7%		

"*" Significant (mann whiteny test, P<0.05)

Discussion

According to **Testa et al., 2020**, breast cancer exhibits heterogeneity in terms of molecular changes, cellular makeup, and clinical results. While data related to many elements of breast cancer treatment has advanced significantly over the past three decades, metastatic breast cancer patients continue to have poor outcomes, with a median overall survival time of 24 to 36 months **(Waks and Winer, 2019)**. According to **Torre et al., 2017,** this illness is currently the most frequent cancer in women, accounting for 25% of cancer diagnoses and 15% of cancer-related deaths in women.

The Aurora A kinase target TACC3 was first discovered by **Still et al., 1999** as a member of the TACC family that was situated on human chromosome 4p16, adjacent to FGFR in breast cancer **(Santolla and Maggiolini, 2020)**. TACC3 is an essential protein in the process of cellular division from a physiological standpoint since it aids mitotic spindle's formation **(Shi et al., 2023)**. TACC3 expression was examined pathologically in a range of cancers and was discovered to represent a separate bad prognostic factor **(Du et al., 2016)**.

The purpose of this study was to evaluate TACC3's

immunohistochemistry expression as a predictive factor in BC by contrasting its expression with clinicopathologic characteristics. In the current investigation, patients with younger age, LN metastases, tumor necrosis, negative ER, and PR expression had a median TACC3 H score in BC specimens that was considerably higher. Conversely, no statistically significant correlation is observed with the remaining histological and clinical characteristics.

TACC3 expression in breast cancer has not been extensively studied before**. Huo et al., 2021** found a substantial correlation between TACC3 mRNA expression and younger age, as well as negative expression of ER and PR, which is in line with the current data results. Additionally, in keeping with the current investigation, **Song et al., 2018** found that TACC3 was considerably greater in breast cancer patients who had lymphoid nodal metastases than in those who did not. Furthermore, a number of research on various malignancies have shown a link between TACC3 expression and unfavorable prognostic markers including lymph node metastasis. According to **Huang et al., 2015**, esophageal squamous cell carcinoma patients with lymphoid nodal metastases express TACC3 at a much higher level than those without the metastasis. According to the research of **Jiang et al., 2016**, tissues from metastatic lymph nodes also exhibit increased TACC3 expression. These findings suggest that changes in TACC3 protein levels could play a role in the initiation and spread of tumors.

The association between higher TACC3 expression and lymph node metastasis may be attributed to its role in stimulating the PI3K/Akt and ERK signaling pathways, which results in an epithelial-mesenchymal transition and promotes tumor development, invasiveness and discohesiveness **(Akanda et al., 2021).**

To our knowledge, no previous study described correlation between laterality and TACC3 immunohistochemical expression in breast cancer. There is previous study suggested that left-side BC laterality was significant ($p < 0.00001$) in the women populations compared to the right side based on the pooled size with possible high-risk factors, including handedness, older women, body mass index, people with black skin, invasive type carcinoma, and estrogen receptor-negative BC. These findings suggest that there may be a complex interplay of genetic, environmental, and lifestyle factors that contribute to left-side BC laterality **(Zheng et al., 2024**). So, we can suggest the higher TACC3 expression in right sided BC may be attributed to genetic, environmental or lifestyle factors and require further investigations.

Klauber-DeMore et al. (2006), reported that breast cancers that develop in younger individuals have more aggressive biological characteristics than those in older individuals and are more likely to be ER negative. Thus, we can suggest that higher TACC3 expression in younger individulas could be related to hormonal differences, genetic predispositions and require further molecular studies age.

In the current study, high TACC3 was correlated with tumor necrosis. TACC3 is a protein involved in various cellular processes, including cell division and microtubule organization resulting in rapid growth. **Lin et al. (2018)** discovered that the overexpression of TACC3 was

positively connected with tumor aggressiveness in patients with bladder cancer.Cancer cells can undergo necrosis as a result of rapid growth, nutrient deprivation **(Parker Kerrigan, 2014).** While the direct role of TACC3 in necrosis hasn't been extensively studied. Thus, further studies are recommended to clarify the interactions between TACC3 and other proteins or signaling pathways involved in necrosis.

Targeting TACC3 results in cell death in mitosis and interphase in cancer cells with centrosome amplification because it also has spatiotemporal functions across the cell cycle **(Saatci and Sahin, 2023)**. There are several restrictions on our investigation. Initially, there were comparatively few patients and histological kinds. As a result, the forthcoming trials ought to take this into account. Second, IHC was the only method used to assess TACC3 expression; further research on genetic abnormalities and transcriptional systems may have revealed different biological functions.

Conclusion

TACC3 may be a useful biomarker for breast cancer prognosis. To evaluate the therapeutic role of TACC3 in connection to patient survival and its therapeutic role in BC, more research is still advised.

Conflict of interest: The authors of this study have no conflict of interest related to this publication.

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