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Clinicopathological relationship of Stanniocalcin-2 (STC2) expression in breast carcinomas

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Abstract

Aim: To assess Stanniocalcin-2 (STC-2) expression in breast cancer and explore its correlation with clinicopathological parameters and prognostic factors.

Materials and Methods: In this study, immunohistochemical STC2 staining was performed on 38 breast carcinoma patients who underwent modified radical mastectomy between March 2017 and November 2022. We examined its association with various prognostic factors, including age, histopathological subtype, histological grade, T stage, nodal metastasis, distant metastasis, lymphovascular invasion, tumor-infiltrating lymphocytes, hormonal status, HER2 status, Ki67 expression.

Results: The mean age was 63.4 ± 14.9 (min. 43–max. 98). High STC2 expression was found in 22 (57.9%) patients, while low STC2 expression was found in 16 (42.1%) patients. Age, histopathological subtype, histological grade, T stage, nodal metastasis, distant metastasis, lymphovascular invasion, tumor-infiltrating lymphocytes, hormonal status, HER2 status, and Ki67 expression were similar in the high and low STC2 expression groups. Overall survival (OS) was significantly higher in those with high STC2 expression ($p<0.05$). However, STC2 expression did not correlate with progression-free survival (PFS) ($p>0.05$). In univariate and multivariate Cox regression analysis for overall OS, STC2 expression, nodal metastasis, tumor-infiltrating lymphocytes (TIL), histological type, and PFS were identified as independent risk factors for poor OS. In univariate and multivariate Cox regression analysis for PFS, T stage, nodal metastasis, distant metastasis, TIL, histological type, and PFS were independent risk factors for poor PFS.

Conclusion: STC2 expression positively correlated with overall survival in breast carcinomas, suggesting that STC2 can be considered a favorable prognostic factor in this context.

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Introduction

Breast cancer represents one of the most prevalent malignancies affecting women, posing a significant global health challenge. Despite ongoing research, the molecular mechanisms underlying breast cancer remain incompletely understood. Recent investigations have, however, shed light on the impact of genetic and epigenetic changes in cancer development [1].

Stanniocalcin-2 (STC2) is a glycoprotein encoded by the STC 2 gene and regulates calcium and phosphate metabolism. [2]. The human STC is a 302-amino acid (aa) protein involved in estrogen receptor (ER) transport. Notably, STC2 exhibits high expression in normal tissues such as the breast, muscle, heart, testis, and pancreas [3].

STC2 overexpression has been associated with poor prognosis in various cancers, including nasopharyngeal carcinoma [4], pancreatic cancer [5], gastric and esophageal cancer [6], hepatocellular carcinoma [7], colorectal cancer [8], and endometrial cancer [9].

The majority of breast cancers are estrogen receptor-positive (ER+), with ER signaling activation leading to the hyperactivation of survival signaling pathways, promoting cell growth, and inhibiting apoptosis. Standard therapy for ER+ breast cancer includes anti-estrogen (ER) treatment [10]. STC2 demonstrates coexpression with ER in breast cancer cell lines. Clinically, both STC2 mRNA and protein levels exhibit a positive correlation with ER expression in human breast cancer samples [11,12].

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In our study, we conducted a comprehensive evaluation of STC-2 expression, clinical parameters, prognostic factors, and histopathological findings in breast carcinomas.

Materials and Methods

Patients data and tissue samples

Forty-five patients with invasive breast carcinoma, who underwent modified radical mastectomy between March 2017 and November 2022, were enrolled in this study. Seven patients with missing data were excluded; appropriate blocks were selected from the remaining 38 patients. All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the Helsinki Declaration. This study was approved by the Ethics Committee of Suleyman Demirel University Medical Faculty (date: 18.11.2022, no: 314).

All cases were histopathologically confirmed based on the criteria outlined in the 5th edition of the World Health Organization classification of breast tumors [13]. The examination followed Protocol 2023 of the College of American Pathologists for the Examination of Specimens from Patients with Invasive Breast Cancer. Parameters such as histopathological subtype, histological grade, T stage, nodal metastasis, distant metastasis, lymphovascular invasion, tumor-infiltrating lymphocytes, Estrogen (ER) and Progesterone Receptor (PR) status, HER2 status, and Ki67 status were determined. Tumor stage was retrospectively determined for all patients in accordance with the American Joint Committee on Cancer's TNM Classification System [14].

Age, gender, presence of metastasis, and information on progression-free survival (PFS) and overall survival (OS), were retrieved from the hospital database.

Immunohistochemistry

STC2 antibodies (clone ab63057, 1/50 diluted, polyclonal rabbit antibody; Abcam, USA) were applied to tumor-representative blocks. All slides were prepared with primary antibodies on the Dako-Omnis fully automated staining device using Agilent secondary kits.

Tissue samples, including spleen tissue samples serving as an antibody-positive control and a negative control, were processed using an automated immunohistochemistry device.

Immunohistochemical analysis of STC2

Cytoplasmic staining of STC2 was evaluated by three blinded pathologists. The staining intensity was classified using the following scale: 0 for no staining, 1 for weak staining, 2 for moderate staining, and 3 for strong staining (Figure 1). The percentage of tumor cells stained was categorized as follows: 0 for staining less than 5% (considered negative), 1 for staining between 5% and less than 25%, 2 for staining between 25% and less than 50%, 3 for staining between 50% and less than 75%, and 4 for staining 75% or more. The STC2 immunostaining score was determined by multiplying the percentage positivity score by the staining intensity score, resulting in a total score ranging from 0 to 12 [15]. STC2 expression levels below 5 were considered low, while levels above 5 were classified as high.

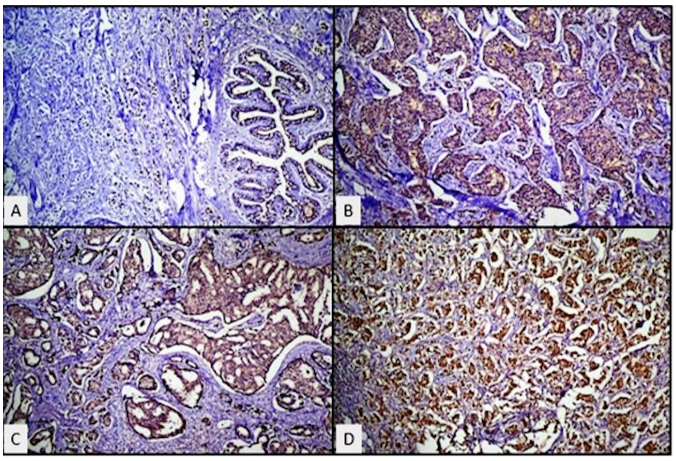

Figure 1. A: Cytoplasmic expression of STC-2 (low staining), B: Low staining of STC-2 in ductal carcinoma in situ, C and D: Cytoplasmic high staining of STC-2 in invasive carcinoma (DAB STC2x100).

Statistical analysis

Statistical evaluation was performed using the Statistical Package for Social Sciences (SPSS) for Windows 27 (IBM SPSS Inc., Chicago, IL). The suitability of the variables for normal distribution was examined using both visual and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were presented as numbers, percentages, means, and standard deviations. The Mann-Whitney U test, Pearson Chi-square test, and Fisher's exact test were used to evaluate the relationship between clinicopathological data of tumor cases and STC2 expressions. Overall survival and progression-free survival times were estimated using the Kaplan-Meier method and examined by the log-rank test. The association of variables with survival was further analyzed using univariate and multivariable Cox regression models. In statistical analysis, $p<0.05$ was considered significant.

Results

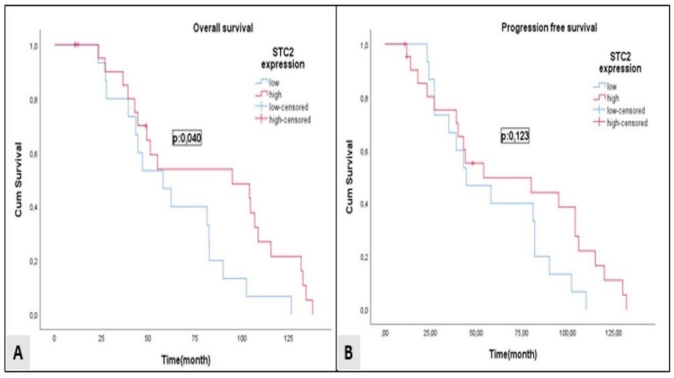

Figure 2. A,B) Overall survival and Progression-free survival based on STC2 expression.

Table 1. Relationship between STC2 expression and clinicopathological features.

	STC2 expression		p value
	low	high	
Age	60.9±3.2	65.1±3.5	0.397
Histological type			
NOS	15(44.1%)	19(55.9%)	0.124
Lobular	1(33.3%)	2(66.7%)	
Mucinous	0(0%)	1(100%)	
Histologic grade			
G1	4(50%)	4(50%)	0.560
G2	8(42.1%)	11(57.9%)	
G3	4(36.4%)	7(63.6%)	
T stage			
T1-2	11(39.3%)	17(60.7%)	0.411
T3-4	5(50%)	5(50%)	
Nodal metastasis			
No	9(36%)	16(64%)	0.238
Yes	7(53.8%)	6(46.2%)	
Distant metastasis			
No	10(35.7%)	18(64.3%)	0.168
Yes	6(60%)	4(40%)	
Lymphovascular invasion			
No	8(38.1%)	13(61.9%)	0.41
Yes	8(47.1%)	9(52.9%)	
Tumor-infiltrating lymphocytes			
No	8(34.8%)	15(65.2%)	0.213
Yes	8(53.3%)	7(46.7%)	
Estrogen receptor			
Positive	14(43.8%)	18(51.2%)	0.498
Negative	2(33.3%)	4(66.7%)	
Progesterone receptor			
Positive	14(48.3%)	15(51.7%)	0.168
Negative	2(22.2%)	7(77.8%)	
Her2			
Negative	14(42.4%)	19(57.6%)	0.654
Positive	2(40%)	3(60%)	
Ki67			
≤ 20	4(40%)	6(60%)	0.822
20-50	11(42.3%)	15(57.7%)	
>50	1(50%)	1(50%)	

Forty-five patients were initially screened, and thirty-eight were ultimately included in the study. The mean age was 63.7±14.9 (min. 43-max. 98). Among the patients, 34 (89.5%) had nonspecific invasive breast carcinoma, 3 (7.9%) had invasive lobular carcinoma, and 1 (2.6%) had mucinous carcinoma. The most common histological grade was Nottingham grade 2 (57.9%), while grade 1 was the least common (21.1%). Tumor-infiltrating lymphocytes were present in 15 patients. Estrogen receptor (ER) positivity was observed in 32 patients (84.2%), progesterone receptor (PR) positivity in 29 patients (76.3%), HER2 positivity in 5 patients (13.1%), and Ki67 expression (>20%) was high in 28 patients (73.7%). The T stage was categorized into two groups: 28 (73.7%) were classified as T1-2, and 10 (26.3%) were classified as T3-4. Thirteen patients exhibited lymph node metastasis, and 10 had distant or-

Table 2. In univariate and multivariate Cox regression analyses for Overall survival.

	OS Univariate					OS Multivariate			
	HR (95% CI for HR)			p value		HR (95% CI for HR)			p value
Age	1.011	1.036	0.399	0.986	Age	1.005	0.953	1.061	0.845
STC 2 expression	2.159	1.021	4.565	**0.044**	STC 2 expression	5.326	1.635	17.351	**0.006**
Histologic grade	1.030	0.666	1.595	0.893	Histologic grade	2.282	0.773	6.736	0.135
T stage	1.916	0.835	4.398	0.125	T stage	0.636	0.130	3.119	0.577
Nodal metastasis	2.717	1.256	5.877	**0.011**	Nodal metastasis	2.850	0.505	16.100	0.236
Distant metastasis	1.913	0.837	4.375	0.124	Distant metastasis	0.253	0.028	2.254	0.218
ER	0.874	0.354	2.159	0.771	ER	5.148	0.488	54.322	0.173
PR	0.826	0.363	1.881	0.649	PR	0.349	0.036	3.431	0.367
HER2	0.449	0.156	1.291	0.137	HER2	0.380	0.060	2.392	0.303
Ki67	1.023	0.569	1.840	0.939	Ki67	0.352	0.069	1.784	0.207
LVI	1.578	0.785	3.172	0.200	LVI	2.897	0.741	11.324	0.126
TIL	2.922	1.412	6.049	**0.004**	TIL	1.268	0.373	4.316	0.704
Histological type	1.010	0.600	1.700	0.971	Histological type	2.437	1.153	5.151	**0.020**
PFS	0.970	0.982	0.958	**0.000**	PFS	0.953	0.932	0.974	**0.000**

HR:Hazard Ratio, OS:Overall survival, STC 2: Stanniocalcin 2, ER: Estrogen Receptor, PR: Progesterone Receptor, HER2: Human epidermal growth factor receptor 2, LVI: Lymphovascular Invasion, TIL: Tumor Infiltrating Lymphocytes, PFS:Progression-free survival.

Table 3. In univariate and multivariate Cox regression analyses for Progression-free survival.

	PFS Univariate					PFS Multivariate			
	HR (95% CI for HR)			p value		HR (95% CI for HR)			p value
Age	1.010	0.986	1.034	0.432	Age	1.006	0.966	1.047	0.779
STC 2 expression	1.763	0.842	3.691	0.132	STC 2 expression	1.452	0.560	3.763	0.443
Histologic grade	0.989	0.608	1.608	0.963	Histologic grade	0.844	0.384	1.855	0.673
T stage	2.547	1.063	6.102	**0.036**	T stage	2.038	0.632	6.569	0.233
Nodal metastasis	3.280	1.440	7.470	**0.005**	Nodal metastasis	2.216	0.422	11.649	0.347
Distant metastasis	2.389	1.013	5.633	**0.047**	Distant metastasis	0.954	0.174	5.224	0.957
ER	0.720	0.291	1.778	0.476	ER	2.320	0.277	19.407	0.437
PR	0.726	0.321	1.644	0.443	PR	0.256	0.029	2.266	0.221
HER2	0.564	0.214	1.481	0.245	HER2	0.727	0.126	4.194	0.721
Ki67	0.998	0.516	1.931	0.996	Ki67	0.731	0.214	2.497	0.617
LVI	1.285	0.635	2.598	0.485	LVI	0.719	0.237	2.185	0.561
TIL	2.186	1.054	4.533	0.036	TIL	1.009	0.351	2.898	0.987
Histological type	1.016	0.628	1.643	0.949	Histological type	1.237	0.575	2.660	0.586
PFS	0.927	0.898	0.957	**0.000**	PFS	0.931	0.900	0.962	**0.000**

HR:Hazard Ratio, OS:Overall survival, STC 2: Stanniocalcin 2, ER: Estrogen Receptor, PR: Progesterone Receptor, HER2: Human epidermal growth factor receptor 2, LVI: Lymphovascular Invasion, TIL: Tumor Infiltrating Lymphocytes, PFS:Progression-free survival.

gan metastasis. Of the thirty-eight patients with STC2, 22 (57.9%) demonstrated high expression, while 16 (42.1%) exhibited low expression. No significant correlation was observed between STC2 expression and the clinical data ($p>0.05$). Table 1 presents the clinicopathological characteristics of the patients based on STC2 expression.

During the median follow-up of 67.7 months, 10.5% (4) of the patients died. The median progression-free survival (PFS) was 54 (95% CI; 12.5-95.5) months, and overall survival (OS) was 62 (95% CI: 20-104.5) months.

Patients with high STC2 expression exhibited a longer life expectancy, and a statistically significant difference was observed (p: 0.040). Although progression-free survival was extended in those with high STC2 expression, no statistically significant relationship was observed (p: 0.123) (Figure 2).

In univariate and multivariate Cox regression analyses for OS, STC2 expression, nodal metastasis, tumor-infiltrating lymphocytes (TIL), histological type, and PFS were identified as independent risk factors for poor OS (Table 2).

Similarly, in univariate and multivariate Cox regression analyses for PFS, T stage, nodal metastasis, distant metastasis, TIL, histological type, and PFS were independent risk factors for poor OS (Table 3).

Discussion

Breast cancer stands as the second leading cause of mortality among women, representing 26% of all cancers diagnosed in women [17]. Key receptors such as Estrogen

Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor 2 (HER2) play pivotal roles in guiding treatment decisions and predicting prognosis for these tumors. The activation of estrogen receptor signaling induces hyperactivation of survival pathways, fostering cell growth and suppressing apoptosis. Consequently, anti-estrogen therapy has become the standard approach for ER-positive breast cancer patients. Approximately 15–20% of breast cancer cases exhibit cerbB2 amplification and/or overexpression, correlating with an unfavorable prognosis [18,19].

A notable correlation has been identified between STC2 overexpression and adverse clinical outcomes in various cancer types [4-9]. However, conflicting evidence has also suggested that STC2 may play a potential tumor suppressor role in breast cancer [10,21].

In our current study, consistent with the literature, STC2 is co-expressed with ER in breast cancer cells, and clinical evidence demonstrates positive correlations between STC2 mRNA and protein levels and ER expression in breast cancer samples [10].

Yamamura et al. reported improved disease-free survival rates in breast cancer cases with high STC2 expression in their study [20]. Similarly, our study observed longer survival rates in cases with high STC2 expression.

Esseghir et al. conducted a study evaluating STC2 expressions, establishing a significant relationship with overall disease-free survival [21]. In our study involving 38 invasive breast cancer cases, a similarly significant association with extended disease-free survival was identified.

A study conducted by Brantley et al. involving 841 breast cancer cases demonstrated that STC2 is not prognostic for determining recurrence and survival in late-stage breast cancer [22]. However, our study revealed that patients with high STC2 expression exhibited longer survival, and this finding held significance in terms of prognosis.

Di and colleagues demonstrated that the regulation of STC2 mRNA stability significantly influences cell proliferation and metastasis in 54 breast cancer cases [23]. This study highlights the importance of changes in STC2 levels in breast cancer, revealing their impact on prognosis. Contrary to these findings, our study found that high STC2 expression is associated with longer survival. This discrepancy may be attributed to the fact that our study was based on immunohistochemical analysis and involved a smaller sample size. The variation between reports suggests that the role of STC2 in carcinoma development may depend on the specific type of cancer.

Limitations

Several limitations are noteworthy in our study. First and foremost, it adopts a retrospective design, inherently subject to the constraints associated with retrospective analyses. Additionally, the study suffers from a small sample size, limiting the generalizability of our findings. Furthermore, the distribution of cases lacks homogeneity, introducing a potential source of bias.

Conclusion

Our investigation identified STC2 expression, tumor-infiltrating lymphocytes, nodal metastasis, and histological type as independent risk factors. This finding holds potential implications for prognosis assessment. Notably, STC2 expression demonstrated an association with overall survival in our study. However, the retrospective nature, small sample size, and non-homogeneous case distribution in our study warrant cautious interpretation. To establish STC2 as a reliable prognostic marker in breast cancer, further studies involving larger cohorts are necessary for broader clinical applicability.

Ethical approval

This study was approved by the Ethics Committee of Suleyman Demirel University Medical Faculty (date: 18.11.2022, no: 314).

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