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Expression of Stanniocalcin-1 as a Predictor of Recurrence in Breast Cancer Patients

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Abstract

BACKGROUND: About 40% of breast cancer patients will experience a recurrence and the life expectancy will decrease from 95% to 40%. Stanniocalcin-1 (STC1) is a biomarker that is thought to have potential as a risk factor for recurrence.

AIM: The objective of the study is to determine the role of STC1 expression as a risk factor for recurrence in breast cancer patients.

METHODS: Cross-sectional observational study on breast cancer patients, assessed the clinicopathological character and seen whether the patient's condition had a recurrence. Immunohistochemical staining with STC1 antibody was performed on the patient's paraffin block. Reading of immunohistochemical preparations using the Allred score method by looking at five fields of view. Data analysis regarding the relationship between STC1 and recurrence was carried out using the Chi-square test or Fisher's Exact test, then Logistic regression analysis was performed to determine the significant relationship between risk factors for recurrence.

RESULTS: Expression of STC1 was significantly different in patients who had recurrence and who did not experience recurrence (P = 0.000). There was a significant relationship between STC1 expression with age, tumor size, lymph node status, type of cancer, estrogen receptor status, and stage at diagnosis (P < 0.005).

CONCLUSION: It can be concluded that STC1 has a strong relationship with recurrence, so it has the potential to be used as a predictor of recurrence in breast cancer.

Introduction

Breast cancer is one of the most common types of cancer in women in the world. In 2018 there were around 2.89 million women diagnosed with breast cancer with a mortality rate of 627,000 people [1]. In Indonesia, in 2018 there were 59,256 women diagnosed with breast cancer, with the mortality rate reaches 12.75% [1], [2]. Breast cancer treatment is a multidisciplinary treatment that includes systemic therapy, local therapy, and supportive therapy. However, all of these efforts still have a risk of recurrence in the future, especially in patients with advanced stages [3], [4]. Approximately 40% of patients who have undergone a series of breast cancer therapy will experience a recurrence.

Recurrence of breast cancer will reduce the patient's life expectancy by up to 40% whereas patients who do not experience recurrence have a life expectancy of 95% [5], [6]. The risk of recurrence in breast cancer should be known early because in addition to affecting life expectancy, recurrence will also affect the patient's quality of life and increase hospital costs. Several factors that influence the recurrence of breast cancer include young age, tumor size, biomarker status of Human Epidermal Growth Factor Receptor 2 (HER-2), Estrogen Receptor (ER), negative Progesterone Receptor (PR), presence of lymph node involvement, high grade in anatomical pathology [6], [7], [8], [9].

One of the biomarkers that are thought to be a predictor of recurrence in breast cancer is Stanniocalcin-1 (STC1) [10], [11]. STC1 which is a protein excreted by several organs including the thyroid, ovaries, liver, prostate, and kidneys. STC1 is strongly expressed in breast cancer tissue and is not expressed in normal breasts [12]. STC1 has been investigated to play a role in cancer signaling in the PI3K/Akt pathway which will affect the invasiveness of cancer cells [13]. Several studies have also shown that therapy with STC1 antibody can inhibit the aggressiveness of cancer cells in cases of triple-negative breast cancer (TNBC) *in vitro*.

Based on this, it is suspected that STC1 has the potential as a predictor of cancer. However, until now there has been no further research on this matter.

Therefore, research is needed on the expression of STC1 as a risk factor for recurrence in breast cancer patients and to determine the relationship between STC1 expression on the incidence of recurrence in breast cancer patients.

Methods

This research is an observational study with a cross-sectional study method. The research sample was paraffin block from breast cancer patients who underwent surgery at Kariadi Hospital from January 2016 to December 2016. Anatomical pathology and immunohistochemistry examinations were carried out at the Anatomical Pathology Department of Faculty of Medicine Diponegoro University/Kariadi Hospital Semarang. Demographic data, staging, and biomarker status (Estrogen Receptor, Progesterone Receptor, and Human Epidermoid Receptor-2) were taken from the patient's medical records. Further confirmation of the patient's current condition through medical records and telephone.

The population of this study was invasive breast cancer patient in women with Stage I, II, and III who came and were treated at Kariadi Hospital Semarang Indonesia.

After the data is collected, then tabulation and coding are carried out. Statistical analysis was performed using SPSS version 25 software (SPSS, IBM). Analysis of the data regarding the relationship of STC1 with recurrence using the Chi-square test or Fisher's Exact test, then Logistic regression analysis was carried out to determine the relationship between significant risk factors for recurrence.

Results

This study involved fifty-two breast cancer patients who met the requirements for completeness of medical records and paraffin blocks were still available in the Anatomical Pathology Department of the Kariadi Hospital (Figure 1), fifty-two breast cancer patients were divided into two groups, namely the group with recurrence of thirty-two patients and the group without recurrence as many as twenty patients. Most of the patients who experienced recurrence were patients aged more than 46-years-old, the most character in tumor size was T3, lymph node status was N2 and N3, mostly stage III, most subtype was triple-negative, the most histopathological grade was intermediate and most STC1 scoring was >6.7 (Table 1). There was a significant relationship between ER, PR, and STC1
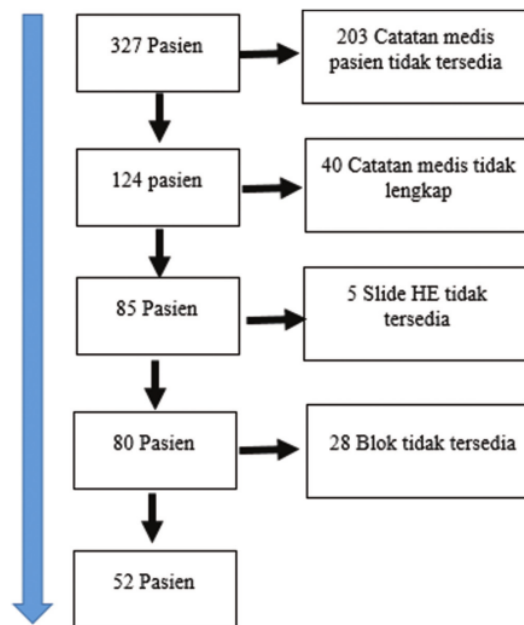

Figure 1: Flow of getting research sample

expression on recurrence and there was no significant relationship between HER-2 expression and recurrence in breast cancer patients (Table 2). There was a significant relationship between STC1 expression and cancer subtype (TNBC) and the patient's lymph node status (N3) (Table 3).

Table 1 shows that several risk factors for recurrence in breast cancer include age, tumor size, lymph node involvement, stage, tumor type (Luminal, HER-2, and TNBC), and STC1 expression. The results of statistical tests with Chi-Square found several risk factors that were significantly associated with recurrence, i.e., age more than 45-years-old, tumor size > T2, with lymph node involvement, TNBC subtype, and strong STC1 expression.

Several significant risk factors in the Chi-Square test will then be tested with logistic regression, previously several risk factors were categorized into 2 categories such as stage, tumor size, nodule, and age. From the results of the logistic regression test, it was found that Crude OR was greater than Adjusted OR for STC1 expression > 6.7, stage > 2, age > 45 and TNBC cancer type, while tumor size < T2, KGB N0 status, and ER status (+) has a smaller Crude OR than the Adjusted OR. This shows that recurrence is influenced by STC1 expression > 6.7, stage > 2, age > 45 and type of TNBC cancer, while tumor size <2, N0 lymph node status and ER (+) status are protective factors against recurrence (Table 4).

In IHC examination, STC1 is expressed on the cell membrane and cytoplasm which will appear brownish in color, as in Figure 2a according to Allred

Table 1: Patient characteristics and recurrence

Characteristics	Recurrency			No recurrencies	p	Current condition		p
	Locoregional	Distant	Mixed			Dead	Alive	
Age								
<45	1 (5.9)	3 (17.6)	1 (5.9)	12 (70.6)	0.003*	5 (29.4)	12 (70.6)	0.014*
46-59	3 (10)	18 (60)	3 (10)	6 (20)		22 (73.3)	8 (26.7)	
≥60	1 (20)	2 (40)	0 (0)	2 (40)		3 (60)	2 (40)	
Tumor Size								
T1	0 (0)	0 (0)	0 (0)	1 (100)	0.004*	0 (0)	1 (100%)	0.000*
T2	2 (12.5)	2 (12.5)	0 (0)	12 (75)		3 (18.8)	13 (81.3)	
T3	1 (5)	11 (55)	1 (5)	7 (35)		12 (60)	8 (40)	
T4	2 (13.3)	10 (10)	3 (20)	0 (100)		15 (100)	0 (0)	
Node Status								
N0	1 (3.6)	7 (25)	2 (7.1)	18 (64.3)	0.001*	10 (35.7)	18 (64.3)	0.006*
N1	2 (25)	9 (69.2)	0 (0)	2 (15.4)		10 (76.9)	3 (23.1)	
N2	2 (25)	5 (62.5)	1 (12.5)	0 (0)		7 (87.5)	1 (12.5)	
N3	0 (0)	2 (66.7)	1 (33.3)	0 (0)		3 (100)	0 (0)	
Stage								
I	0 (0)	(0)	(0)	1 (100)	0.001*	0 (0)	1 (100)	0.000*
II	1 (4.5)	4 (18.2)	1 (4.5)	16 (72.7)		6 (27.3)	16 (72.7)	
III	4 (13.8)	19 (65.5)	3 (10.3)	3 (10.3)		24 (82.8)	5 (17.2)	
Subtype								
Luminal	10 (28.6)	4 (11.4)	2 (5.7)	19 (54.3)	0.015*	14 (40)	21 (60)	0.001*
HER-2	0 (0)	4 (80)	0 (0)	1 (20)		4 (80)	1 (20)	
TNBC	1 (8.3)	9 (75)	2 (16.7)	0 (0)		12 (100)	0 (0)	
Histopatological grade								
Grade II	4 (9.5)	18 (42.9)	3 (7.1)	17 (40.5)	0.938*	23 (54.8)	19 (45.2)	0.305**
Grade III	1 (10)	5 (50)	1 (10)	3 (30)		7 (70)	3 (30)	
STC-1								
Allred score>6.7	3 (14.8)	19 (70.4)	1 (3.7)	4 (14.8)	0.001**	23 (85.2)	4 (14.8)	0.001**
Allred score≤6.7	1 (4)	4 (16)	3 (12)	18 (72)		7 (28)	18 (22)	

HER-2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer, STC-1: Stanniocalcin-1, *P value <0.05

Table 2: Relationship between STC1, ER, PR, and HER-2 expression with recurrence

Immunology profile	Recurrence n (%)	No recurrence n (%)	p
ER			
ER (+)	16 (44.4)	20 (55.6)	0.001**
ER (−)	16 (100)	0 (0)	
PR			
PR (+)	16 (44.4)	20 (55.6)	0.001**
PR (−)	16 (100)	0 (0)	
HER 2			
HER 2 (+)	5 (71.4)	2 (28.6)	0.402**
HER 2 (−)	26 (57.8)	19 (42.2)	
STC-1			
Allred score>6.7	23 (85.2)	4 (14.8)	0.001**
Allred score≤6.7	7 (28)	18 (10)	

*Statistical test using Spearman's correlation. Significant value if <0.05. **Statistical test using Fisher's Exact Test. Significant value if P<0.05. STC-1: Stanniocalcin-1, ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor 2.

Score > 6.7 while in Figure 2b and c with Allred Score ≤ 6.7.

Table 3: Relationship of STC-1 expression and patient characteristics

Characteristics	STC-1		
	Allred score>6.7 n (%)	Allred score≤6.7 n (%)	p
Age			
<45	5 (29.4)	12 (70.6)	
46–59	18 (60)	12 (40)	0.055*
≥60	4 (80)	1 (20)	
Tumor Size			
T1	0 (0)	1 (100)	
T2	6 (37.5)	10 (62.5)	0.284*
T3	11 (55)	9 (45)	
T4	10 (66.7)	5 (33.3)	
Node Status			
N0	10 (35.7)	18 (64.3)	
N1	9 (69.2)	4 (30.8)	0.030*
N2	7 (87.5)	1 (12.5)	
N3	1 (33.3)	2 (66.7)	
Stage			
I	0 (0)	1 (100)	
II	8 (36.4)	14 (63.6)	0.069*
III	19 (65.5)	10 (34.5)	
Subtypes			
Luminal	14 (40)	21 (60)	
HER-2	4 (80)	1 (20)	0.047*
TNBC	9 (75)	3 (25)	
Histopathologic grades			
Grade II	21 (50)	21 (50)	0.729
Grade III	6 (60)	10 (40)	

*Statistics test using Chi-square. The value is significant if P<0.05. **Statistical test using Fisher's Exact Test. Significant value if P<0.05. STC-1: Stanniocalcin-1, HER-2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer.

Discussion

STC1 is a protein that is an oncogene if the amount is excessive in the human body. Under normal conditions, STC1 will be expressed in several tissues such as the thyroid, ovary, liver, prostate, and kidney [14]. Expression of STC1 is associated with recurrence in breast cancer because of the nature of STC1 that can affect cancer cell growth, angiogenesis, and metastasis [11], [13], [15].

Table 4: Relationship of recurrence with breast cancer characteristics and expression of STC-1

Risk factors	Recurrence		Crude OR	Adjusted OR	95% CI
	Yes	No			
STC1 score>6.7	23	4	14.79	31.03	2.115–455.511
Tumor size<T2	25	9	7.22	0.49	0.19–12.559
Stage	24	5	13.6	164.7	1.426–19037.7
ER Status (+)	14	2	8.75	0.93	0.003–3.017
Nodal Status N0	20	4	9.00	0.42	0.030–6.072
Age>45	25	11	0.2	0.40	0.032–4.797
TNBC	11	1	12.15	294.1	1.840–47003.5

STC-1: Stanniocalcin-1, ER: Estrogen receptor, TNBC: Triple-negative breast cancer.

In this study, the majority of breast cancer patients were luminal types (67.3%) this is in accordance with the data that most breast cancers in Indonesia are luminal types, which is around 41.3% both luminal A and luminal B.20 In this study as many as 30.8% of patients with luminal type A had a recurrence in the first 2 years after the patient finished treatment, this exceeded the estimated recurrence in patients with luminal type, which was about 20%. In this study, it was found that the type of TNBC cancer was the type that experienced the most recurrences compared to the others. in this study it was found that the type of TNBC cancer will express STC1 strongly, this is in accordance with research conducted by Brantley which states STC1 as a predictor of recurrence in TNBC subtype, as previously known that TNBC subtype is a cancer with worst prognosis amongst all types of breast cancer [10], [16], [17], [18].
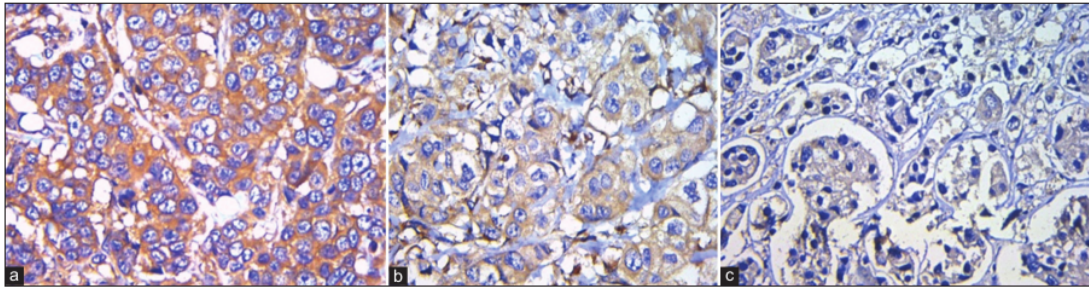
Figure 2: Microscopic expression of Stanniocalcin-1

In a previous study, it was found that patients with STC1 (+) will mostly experience locoregional recurrence at 3 years after completion of treatment, but in this study, most of them experienced distant recurrence, this is possible because the patients in the previous study were mostly diagnosed in stage I and II while the patients in this study were mostly diagnosed at stage II and III.

Conclusion

Recurrence in breast cancer can be detected with the expression of STC1, besides that patient characteristics are also closely related to recurrence, in this study patients with a strong expression of STC1, stage > 2, age > 45 years and the type of TNBC cancer are patients who are susceptible to recurrence. This study can be used as the basis for further research using STC1 as a therapeutic target to prevent breast cancer recurrence.

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