Chettinad Health City Medical Journal
Volume 13, Issue 4 - 2024, Pg. No. 121-127
Peer Reviewed & Open Access Journal

Research Article

Novel Stem Cell Markers of Prime Prognostic Importance in Carcinoma Breast

Thamilselvi Ramachandran[1], Anbu Lenin Kulandhaivel[2], Lalitha Rani N[3], Devi Venkatesan[4], Prakash H Muddegowda[5]

[1]Professor & Head, [4]Assistant Professor, Department of Pathology, VMKVMC, Vinayaka Missions University, Salem, India.
[2]Professor & Head, Department of Transfusion Medicine, VMKVMC, Vinayaka Missions University, Salem, India.
[3]Professor& Head, Department of Pathology, KAP Vishwanathan Government Medical College, Trichy, India.
[5]Associate Professor, Department of Pathology, Karwar Institute of Medical Sciences, Karwar, India.
DOI: https://doi.org/10.24321/2278.2044.202468

I N F O

Corresponding Author:
Prakash H Muddegowda, Department of Pathology, Karwar Institute of Medical Sciences, Karwar, India.
E-mail Id:
medicoprakash@gmail.com
Orcid Id:
https://orcid.org/0000-0003-4378-6552
How to cite this article:
Ramachandran T, Kulandhaivel A L, Rani N L, Venkatesan D, Muddegowda P H. Novel Stem Cell Markers of Prime Prognostic Importance in Carcinoma Breast. Chettinad Health City Med J. 2024;13(4):121-127.

Date of Submission: 2024-11-05
Date of Acceptance: 2024-12-03

A B S T R A C T

Introduction: The burden of breast cancer across the globe is rising and is anticipated to cross almost 2 million by 2030. Tumour markers estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)/neu along with cancer stem cells expression of CD24 and CD44 are crucial in predicting therapy resistance and prognosis.

Aim: This study was conducted to examine the expression of CD44/ CD24 and to compare and correlate the expression of ER, PR and HER2/neu with the expression of CD44/ 24, applied immunohistochemical markers on sectioned wax-embedded blocks of proven cases of carcinoma of the breast.

Materials and Method: The study spanned a duration of 3 years in a tertiary care centre and all histologically confirmed radical mastectomy cases were included. Immunohistochemical staining for ER, PR, HER2/ neu, CD44 and CD24 was performed in formalin-fixed, paraffin wax-embedded tissue sections.

Results: Seventy participants were enrolled in the study based on inclusion and exclusion criteria. All cases involved females, averaging an age of 56.2 years. Histologically majority of participants were of infiltrating ductal carcinoma. Most cases were of Triple Negative Breast Cancer (TNBC) type (40%) followed by Luminal A type (30.9%). Among Infiltrating Ductal carcinoma, 27 were of CD44+/ CD24+ type and 17 were of CD44-/ CD24+ type.

Conclusion: Our study results indicate a correlation between the CD44+/ CD24- phenotype and molecular subtypes, with the highest expression noted in the HER2 subtype. We hereby emphasise that early detection and better management of these cases through a multimodality approach of markers could help in improved survival.

Keywords: TNBC, CD24/ 44, Cancer Stem Cells, ER PR HER2/neu, Prognosis

Introduction

With an estimated 2.3 million new cases globally, breast cancer incidence in 2020 has surpassed lung cancer. By the year 2030, epidemiological studies indicate that breast cancer incidence globally will cross almost 2 million.[1–3]

In breast cancer, CD44 and CD24 are expressed and are linked to stem cells in both healthy & malignant breast tissues. Cancer stem cells are crucial as they are the origin of cells that can be resistant to chemotherapeutic agents, thereby contributing to complications like recurrence and spread of cancer. Additionally, tumour markers like Estrogen Receptor (ER), Human Epidermal growth factor receptor 2 (HER2), and Progesterone Receptor (PR) are prognostic tumour markers routinely used in breast cancer management.[4,5]

In breast tumours, a small, distinct group of cancer stem cells may be responsible for initiating tumour formation, driving tumour progression and contributing to chemotherapy and radiation resistance, ultimately playing a key role in treatment failure and disease relapse. Analysing CD44/ 24 expression to identify and track breast cancer stem cells could be crucial for predicting therapy resistance and prognosis, thereby, providing a novel target to cure breast cancer.[6]

This study aimed to evaluate the expression of CD44/ CD24 & to compare and correlate the expression of ER, PR and HER2/neu with the expression of CD44/ 24, applied immunohistochemical (IHC) markers on sectioned wax-embedded blocks of confirmed breast carcinoma cases.

Aim & Objectives

- To study the CD44/ CD24 expression in histopathologically proven cases of carcinoma breast
- To compare and correlate ER, PR and HER2/neu expression with the expression of CD44/ CD24

Materials & Method

This study was conducted between August 2019 and September 2022 (3 years) in a tertiary care centre located in South India and all surgical specimens of suspected/ confirmed malignant tumours were included in the study. This was both a retrospective and a prospective study. Study included 55 cases of histologically proven carcinoma of breast and informed consent was obtained from all the participants.

Histologically confirmed cases of carcinoma breast were selected and tumour sections from these cases were selected, sectioned and stained using monoclonal antibodies for ER. These were correlated with tumour size and grade.

Inclusion Criteria: All mastectomy cases with histologically proven carcinoma breast and markers study

Exclusion Criteria: Trucut biopsies and lumpectomy specimens, or mastectomy cases without markers study

The institutional ethical committee approved the study.

Data collected during the study included age, sex, tumour size, tumour site, histological type, histological grade (using Modified Bloom Richardson System), number of lymph nodes, and lymph node size.

For the immunohistochemistry study (IHC), five sections, each of 3-micron thickness from each block were cut and mounted on positively charged slides. Routine haematoxylin and eosin staining was performed. Antigen retrieval was performed by Pressure Technique–Multi Epitope Retrieval System (MERS). Tris–EDTA at pH 9.0 was used. IHC was performed using the visualisation system PolyExcel (Micropolymer detection kit) of ER, PR, HER2/neu, CD44 (PATHINSITU, USA) and CD24 (Abclonal, USA). IHC staining for ER, PR, HER2/neu, CD44 and CD24 was conducted on tissue sections preserved in formalin, and embedded in paraffin wax. The staining procedure was followed as per the guidelines of the manufacturer.

All the IHC markers were classified as either positive or negative. Negative cases were defined as those with no staining or staining in fewer than 10% of tumour cells, while positive cases were those with staining in more than 10% of tumour cells. When at least 10% of tumour cells were evaluated on a scale of 0–3+, positivity was considered if ER and PR showed strong nuclear staining (3+). Similarly, in HER2/neu immunostaining, positivity was considered when strong membranous staining (3+) was noted in a minimum of 10% of tumour cells. Markers were considered negative when staining intensity scores were 0–1+.

Results

The study included a total of seventy patients who had a modified radical mastectomy for breast carcinoma in our institution during the study period of three years (August 2019 – September 2022). Based on inclusion criteria, the study included 55 cases, and amongst them, 50 were invasive ductal carcinoma, 2 medullary carcinomas, 2 mucinous carcinomas & one lobular carcinoma.

The average age of patients was 56.2 years (range: 30–80 years). All were females without any breast cancer family history.

The average age at the time of breast carcinoma diagnosis was 56.2 years. The majority of them (70.9%) were 50 years of age or older (Tables 1 & 2). 1.8% of the cases belonged to the age group of less than 35 years, whereas 5.45% of the cases belonged to the age group of less than 40 years.

Of the total 55 cases, 81.8% were more than 5 cm in size and lymph node involvement was found to be positive

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202468

for 69.1% of cases. The majority of the cases i.e. 47.3% were of histological grade II followed by 45.5% cases of histological grade I. The majority of the cases (92.7%) were of histological type invasive ductal carcinoma (Tables 1 & 2).

Table 1.Descriptive Statistics of Characteristics of Tumour with ER, PR, HER2/neu

Characteristics		All Cases N = 55	Luminal A HR+/ HER2- n = 17 (30.9%)	Luminal B HR+/ HER2+ n = 5 (9%)	HER2 +ve HR-/ HER2+ n = 11 (20%)	TNBC HR-/ HER2- n = 22 (40%)	p Value
Age characteristics							
Mean age years (SD)		56.2 (10.3)	61 (10.7)	57.4 (8.96)	55 (7.01)	52.8 (10.6)	0.090
Age groups (years)	≥ 50	39 (70.9)	13 (23.6)	4 (7.3)	9 (16.4)	13 (23.6)	0.461
	< 50	16 (29.1)	4 (7.3)	1 (1.8)	2 (3.6)	9 (16.4)	
Tumour histopathology							
Tumour size (cm)	> 5	10 (18.2)	1 (1.8)	0 (0.0)	4 (7.3)	5 (9.1)	0.133
	≤ 5	45 (81.8)	16 (29.1)	5 (9.1)	7 (12.7)	17 (30.9)	
Lymph node involvement	Positive	38 (69.1)	13 (23.6)	5 (9.1)	8 (14.5)	12 (21.8)	0.178
	Negative	17 (30.9)	4 (7.3)	0 (0.0)	3 (5.5)	10 (18.2)	
Histological grade	Grade 1	25 (45.5)	10 (18.2)	1 (1.8)	5 (9.1)	9 (16.4)	0.093
	Grade 2	26 (47.3)	6 (10.9)	2 (3.6)	6 (10.9)	12 (21.8)	
	Grade 3	4 (7.3)	1 (1.8)	2 (3.6)	0 (0.0)	1 (1.8)	
Histological types							
Intra Ductal CA		51 (92.7)	17 (30.9)	5 (9.1)	10 (18.2)	19 (34.5)	0.836
Lobular CA		1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	
Medullary CA		1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	
Mucinous CA		2 (3.6)	0 (0.0)	0 (0.0)	1 (1.8)	1 (1.8)	

ER – Estrogen receptor, PR – Progesterone receptor, Her2/neu – Human epidermal growth factor receptor 2/neu, HR – hormone receptor, CA – carcinoma, TNBC – Triple negative breast cancer

Table 2.Descriptive Statistics of Characteristics of Tumour with CD44/ 24 Expression

Characteristics		All Cases N = 55	CD44+/ CD24+ n = 29 (52.7%)	CD44+/ CD24- n = 4 (7.3%)	CD44-/ CD24+ n = 17 (31%)	CD44-/ CD24- n = 5 (9%)	p Value
Age characteristics							
Mean age years (SD)		56.2 (10.3)	55.8 (11.4)	56.5 (6.56)	56 (10.3)	58.6 (6.91)	0.959
Age groups (years)	≥ 50	39 (70.9)	19 (34.5)	3 (5.5)	12 (21.8)	5 (9.1%)	0.477
	< 50	16 (29.1)	10 (18.2)	1 (1.8)	5 (9.1)	0 (0.0)	
Tumour histopathology							
Tumour size (cm)	> 5	10 (18.2)	5 (9.1)	1 (1.8)	4 (7.3)	0 (0.0)	0.664
	≤ 5	45 (81.8)	24 (43.6)	3 (5.5)	13 (23.6)	5 (9.1)	

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202468

Lymph node involvement	Positive	38 (69.1)	18 (32.7)	2 (3.6)	15 (27.3)	3 (5.5)	0.216
	Negative	17 (30.9)	11 (20.0)	2 (3.6)	2 (3.6)	2 (3.6)	
Histological grade	Grade 1	25 (45.5)	10 (18.2)	2 (3.6)	12 (21.8)	1 (1.8)	0.198
	Grade 2	26 (47.3)	16 (29.1)	2 (3.6)	5 (9.1)	3 (5.5)	
	Grade 3	4 (7.3)	3 (5.5)	0 (0.0)	0 (0.0)	1 (1.8)	
Histological types							
Intra ductal CA		51 (92.7)	27 (49.1)	3 (5.5)	17 (30.9)	4 (7.3)	0.031
Lobular CA		1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	
Medullary CA		1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	
Mucinous CA		2 (3.6)	1 (1.8)	0 (0.0)	0 (0.0)	1 (1.8)	

CD – cluster of differentiation, CA - carcioma

Table 3.Statistical Analysis of Biomarker Expression in Correlation with Types of Tumours

Biomarker	CD44+/ CD24+ (n = 29)	CD44+/ CD24- (n = 4)	CD44-/ CD24+ (n = 17)	CD44-/ CD24- (n = 5)
Luminal A (n = 17)				
Positive	10	0	7	0
Negative	19	4	10	5
Sensitivity (%)	58.8	0.0	41.2	0.0
Specificity (%)	50.0	89.5	73.7	86.8
Kappa value	0.0738	-0.133	-0.149	-0.133
Agreement	Slight	Nil	Nil	Nil
Luminal B (n = 5)				
Positive	3	0	1	1
Negative	26	4	16	4
Sensitivity (%)	60	48	20	20
Specificity (%)	0	92	68	92
Kappa value	0.0253	-0.088	-0.0577	0.120
Agreement	Slight	Nil	Nil	Slight
HER2 +ve (n = 11)				
Positive	2	0	6	3
Negative	27	4	11	2
Sensitivity (%)	18.2	0.0	54.5	27.3
Specificity (%)	38.6	90.9	75.0	95.5
Kappa value	-0.268	-0.020	0.245	0.286
Agreement	Nil	Nil	Fair	Fair
TNBC (n = 22)				
Positive	14	4	3	1
Negative	15	0	14	4
Sensitivity (%)	63.6	18.2	13.6	4.5
Specificity (%)	54.5	100.0	57.6	87.9
Kappa value	0.173	0.211	-0.299	-0.0870
Agreement	Slight	Fair	Nil	Nil

CD – cluster of differentiation, Her2/neu – Human epidermal growth factor receptor 2/neu, TNBC – Triple negative breast cancer

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202468

Molecular subtyping of breast cancer showed that most histopathologically confirmed cases were of Triple Negative Breast Cancer (TNBC) type (40%) followed by Luminal A type (30.9%). Lymph node involvement was found to be positive for 13 of the Luminal A molecular subtype followed by 12 cases belonging to the TNBC molecular subtype of breast carcinoma. The histological grading revealed 12 cases of TNBC histological grade II, which was the major subcategory. Among the cases of histological type invasive ductal carcinoma, 19 were of TNBC molecular subtype and 17 were of Luminal A molecular subtype (Table 1).

CD44, CD24 expression analysis in breast cancer tissues revealed that the majority of histopathologically confirmed cases were of CD44+/ CD24+type (52.7%) followed by CD44-/ CD24+ type (31%). Lymph node involvement was found to be positive for 18 of the CD44+/ CD24+ type followed by 15 cases belonging to the CD44-/ CD24+ type. The histological grading revealed 16 cases of CD44-/ CD24+ type and histological grade II, which is the major subcategory. Among the cases of histological type infiltrating ductal carcinoma, 27 were of CD44+/ CD24+ type and 17 were of CD44-/ CD24+ type (Table 2).

The expression of biomarkers in correlation with the types of tumours was statistically determined by the level of agreement. The agreement between the TNBC molecular subtype and CD44+/ CD24- expression in the breast cancer tissues was found to be fair with Cohen's kappa value of 0.211. Also, the highest specificity of 100% was observed for CD44+/ CD24- expression in the TNBC molecular subtype. The agreement between HER2 +ve molecular subtype and CD44-/ CD24+ and CD44-/ CD24- expressions were also found to be fair with Cohen's kappa value of 0.245 and 0.286, respectively (Table 3).

Discussion

The prognostic factors for breast carcinoma clinically considered are age, morphological features i.e. tumour size, histologic grade, lymph node status, tumour stage, lymphovascular invasion and ER, PR, and HER2/neu receptor expression status. The novel cluster of differentiation (CD) markers like CD44/ CD24 are also found to have prognostic implications towards patient survival.[6–8]

The average patient age in the current study was 56.2 years which coincides with the age group of carcinoma breast incidences among Indian women.[2] In a systematic review of TNBC cases over a decade, the average age was 46.2 years, while another meta-analysis reported an average age of 50 years.[8,9]

Grade 3 was the most common histologic grade (Modified Bloom Richardson) in the Korean study,[9] and similar data was also found in other Indian studies. However, in our study, Grade 2 was the most common histologic grade. T2N1aM0 (Stage IIA) was the most common disease stage in our study population.[8,9]

Most studies show the prevalence of luminal A as the most common type, while in our study TNBC or basal-like breast cancer was comparatively more common.[10] In our study prevalence of TNBC was 40%, while in other Indian studies, it varied between 27–35% with an average of 31%. In the Western world, the prevalence of TNBC is usually between 12-17%. This high prevalence of TNBC is probably contributing to the high fatality rate in patients due to breast cancer in our country.[8,9]

In our study, 25.4% of cases were positive for ER PR and 32.7% of cases showed HER2 positivity. The hormone positivity of our population is less than that of other similar study in south India (25.4% vs 41.5%)[11] but we have observed a similar rate of higher HER2 positivity (32.7% vs 35.4%). HER2/neu + have complicated management, high recurrent rates and poor prognosis.[12]

In our study, a tumour size of more than 5 cm was noted in 18% of cases. In Indian studies, it varies between 3–65% with an average of 24%, which is within the standard range. In 69% of the cases, lymph nodes showed the presence of tumour cells, while it varied between 39% and 90% with an average of 57% in other studies.[7]

Hormone receptor-positive cancers generally grow at slower rates, when compared with hormone receptor-negative cancers. Molecular subtyping of breast cancer, in our study, revealed the majority of histopathologically confirmed cases were of Triple Negative Breast Cancer (TNBC) type (40%) followed by Luminal A type (30.9%). Finding each specific type/ hormone receptor sensitivity has a distinct response to cancer therapy including drug resistance.[8,9,13,14]

In the present study, 32.4% of the patients had HER2+ which is present in other studies.[7,15]

Ahmed et al. and Mylona et al., in their study, reported that CD44-/ CD24+ was associated with shorter metastasis-free survival time and poor prognosis in the group of grade 2 tumours.[16,17] In our study, CD44-/ CD24+ expression was observed mainly in grade 1 tumours.

In a study by Horiguchi et al., higher CD44+ expression was related to smaller tumour size, negative axillary LN and lower stage.[18] In our study, higher expression of CD44+ was observed in 60% (35) of cases, with a majority in the 5th decade [66.7% (22)], and tumour size less than 5 cm with lymph node positivity. Higher CD44 expression is related to poor prognosis and metastatic involvement of lymph nodes.[18,19]

In a study by Baumann et al., higher CD24+ expression was related to increased tumour cell metastasis *in vivo,* proliferation, spreading and invasion.[20] In a study reported

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202468

by Athanassiadou et al. higher CD24 expression correlated with increased stage, tumour grade 3, and positive lymph node.[21] In our study, higher expression of CD24+ was observed in 46 cases, with a majority in the 5th decade with tumour size less than 2.5 cm and lymph node positivity.

Honeth et al. have identified that HER2-positive tumours had high expression of CD24.[22] Jang et al. identified that expression of CD44 was significantly correlated with HER2 negative status. They also showed that the expression of CD24 was significantly correlated with HER2-positive status.[4] In our study also, HER2-positive tumours showed higher expression of CD24, while HER2 negative status was associated with expression of CD44. Wu et al. have identified that the CD44+/ CD24- phenotype was significantly associated with TNBC. CD24+/ CD44- phenotype was more associated with the HER2-positive subtypes.[23] Similar data was also found in our study regarding the association of TNBC with CD44+/ CD24- and all four cases in our study showing CD24+/ CD44- showed HER2 positive status.

Limitations

The participants were not followed up because of the pandemic situation, so disease-free survival could not be assessed which was one of the objectives. The sample size was small due to logistic support.

Conclusion

Triple-negative breast cancer cases were more in our study. They are considered a bad prognosis as it is recognised to be less favourable to treatment. Our results showed a correlation between the CD44+/ CD24- phenotype and molecular subtypes, with the maximum expression occurring in the HER2 subtype.

The stem cells causing cancer may contribute to treatment resistance due to their capacity to endure chemotherapy and radiotherapy. Identifying these cells using cancer stem-cell markers could potentially lead to new treatment strategies for breast cancer. We hereby emphasise that early detection and better management of these cases through a multimodality approach of markers could help in improved survival.

Source of Funding: Vinayaka Missions University

Conflict of Interest: None

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 May;71(3):209-49. [PubMed] [Google Scholar]
2. Mehrotra R, Yadav K. Breast cancer in India: present scenario and the challenges ahead. World J Clin Oncol. 2022 Mar 24;13(3):209-18. [PubMed] [Google Scholar]
3. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. CA Cancer J Clin. 2011;61(6):409-18. [PubMed] [Google Scholar]
4. Jang MH, Kang HJ, Jang KS, Paik SS, Kim WS. Clinicopathological analysis of CD44 and CD24 expression in invasive breast cancer. Oncol Lett. 2016 Oct;12(4):2728-33. [PubMed] [Google Scholar]
5. Lindström LS, Karlsson E, Wilking UM, Johansson U, Hartman J, Lidbrink EK, Hatschek T, Skoog L, Bergh J. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol. 2012 Jul 20;30(21):2601-8. [PubMed] [Google Scholar]
6. Marzagalli M, Fontana F, Raimondi M, Limonta P. Cancer stem cells-key players in tumor relapse. Cancers (Basel). 2021 Jan 20;13(3):376. [PubMed] [Google Scholar]
7. Christiana JS, Balakrishnan K, Hemalatha G, Maheshwari KU. Clinical and histomorphological profile of breast neoplasms. Int J Sci Stud. 2016;4(4):170-5.
8. Sandhu GS, Erqou S, Patterson H, Mathew A. Prevalence of triple-negative breast cancer in India: systematic review and meta-analysis. J Glob Oncol. 2016 Jun 29;2(6):412-21. [PubMed] [Google Scholar]
9. Sarkar S, Akhtar M. Triple negative breast cancer prevalence in Indian patients over a decade: a systematic review. Int J Clin Biostat Biom. 2022;8:045. [Google Scholar]
10. Pandit P, Patil R, Palwe V, Gandhe S, Patil R, Nagarkar R. Prevalence of molecular subtypes of breast cancer: a single institutional experience of 2062 patients. Eur J Breast Health. 2019 Nov 20;16(1):39-43. [PubMed] [Google Scholar]
11. Sanmathi BS, Narayanan GS, Amogh PS, Kumar KB. Breast cancer in young women: analysis of incidence, clinicopathological profile and biological behaviour in a tertiary care institute from South India. Asian Pac J Cancer Biol [Internet]. 2024 [cited 2024 Dec 12];9(3):295-300. Available from: http://waocp.com/journal/index.php/apjcb/article/view/1446 [Google Scholar]
12. Stat bite: lifetime probability among females of dying of cancer. J Natl Cancer Inst. 2004 Jun 2;96(11):818. [PubMed]
13. Qing T, Karn T, Rozenblit M, Foldi J, Marczyk M, Shan NL, Blenman K, Holtrich U, Kalinsky K, Meric-Bernstam F, Pusztai L. Molecular differences between younger versus older ER-positive and HER2-negative breast cancers. NPJ Breast Cancer. 2022;8(1):119. [PubMed] [Google Scholar]
14. Siadati S, Sharbatdaran M, Nikbakhsh N, Ghaemian N. Correlation of ER, PR and HER-2/Neu with other prognostic factors in infiltrating ductal carcinoma

of breast. Iran J Pathol. 2015 Summer;10(3):221-6. [PubMed] [Google Scholar]
15. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29. [PubMed] [Google Scholar]
16. Ahmed MA, Aleskandarany MA, Rakha EA, Moustafa RZ, Benhasouna A, Nolan C, Green AR, Ilyas M, Ellis IO. A $CD44^{-}/CD24^{+}$ phenotype is a poor prognostic marker in early invasive breast cancer. Breast Cancer Res Treat. 2012;133(3):979-95. [PubMed] [Google Scholar]
17. Mylona E, Giannopoulou I, Fasomytakis E, Nomikos A, Magkou C, Bakarakos P, Nakopoulou L. The clinicopathologic and prognostic significance of $CD44^{+}/CD24^{-/low}$ and $CD44^{-}/CD24^{+}$ tumor cells in invasive breast carcinomas. Hum Pathol. 2008;39(7):1096-102. [PubMed] [Google Scholar]
18. Horiguchi K, Toi M, Horiguchi SI, Sugimoto M, Naito Y, Hayashi Y, Ueno T, Ohno S, Funata N, Kuroi K, Tomita M, Eishi Y. Predictive value of CD24 and CD44 for neoadjuvant chemotherapy response and prognosis in primary breast cancer patients. J Med Dent Sci. 2010;57(2):165-75. [PubMed] [Google Scholar]
19. Bànkfalvi A, Terpe HJ, Breukelmann D, Bier B, Rempe D, Pschadka G, Krech R, Böcker W. Gains and losses of CD44 expression during breast carcinogenesis and tumour progression. Histopathology. 1998;33(2):107-16. [PubMed] [Google Scholar]
20. Baumann P, Cremers N, Kroese F, Orend G, Chiquet-Ehrismann R, Uede T, Yagita H, Sleeman JP. CD24 expression causes the acquisition of multiple cellular properties associated with tumor growth and metastasis. Cancer Res. 2005;65(23):10783-93. [PubMed] [Google Scholar]
21. Athanassiadou P, Grapsa D, Gonidi M, Athanassiadou AM, Tsipis A, Patsouris E. CD24 expression has a prognostic impact in breast carcinoma. Pathol Res Pract. 2009;205(8):524-33. [PubMed] [Google Scholar]
22. Honeth G, Bendahl PO, Ringnér M, Saal LH, Gruvberger-Saal SK, Lövgren K, Grabau D, Fernö M, Borg A, Hegardt C. The $CD44^{+}/CD24^{-}$ phenotype is enriched in basal-like breast tumors. Breast Cancer Res. 2008;10(3):R53. [PubMed] [Google Scholar]
23. Wu Y, Sarkissyan M, Elshimali Y, Vadgama JV. Triple negative breast tumors in African-American and Hispanic/Latina women are high in $CD44^{+}$, low in $CD24^{+}$, and have loss of PTEN. PLoS One. 2013 Oct 22;8(10):e78259. [PubMed] [Google Scholar]

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202468