

Significance of HER2-related factor in HER2-low breast cancer

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INTRODUCTION & AIM

- Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is present in approximately 20% of breast cancer patients. HER2-targeted therapies are widely used to treat of HER2-positive breast cancer.
- HER2 expression is evaluated by HER2 protein using immunohistochemistry (IHC), and ERBB2 gene amplification by fluorescence in situ hybridization (FISH) is performed in routine clinical practice for breast cancer. Some studies have suggested that increased ERBB2 mRNA expression is involved in the HER2-dependent progression of breast cancer.
- Various binding proteins for HER2 and HER2-dependent signaling are promoted by their interactions.

In this study, we aimed to investigate the relationship between HER2 expression in IHC, ERBB2 expression, and HER2-binding proteins and to clarify the characteristics of cases with different levels of HER2 expression.

METHOD

Breast cancer tissues were obtained from 58 patients (2008-2011) undergoing breast cancer surgeries at Tohoku University Hospital.

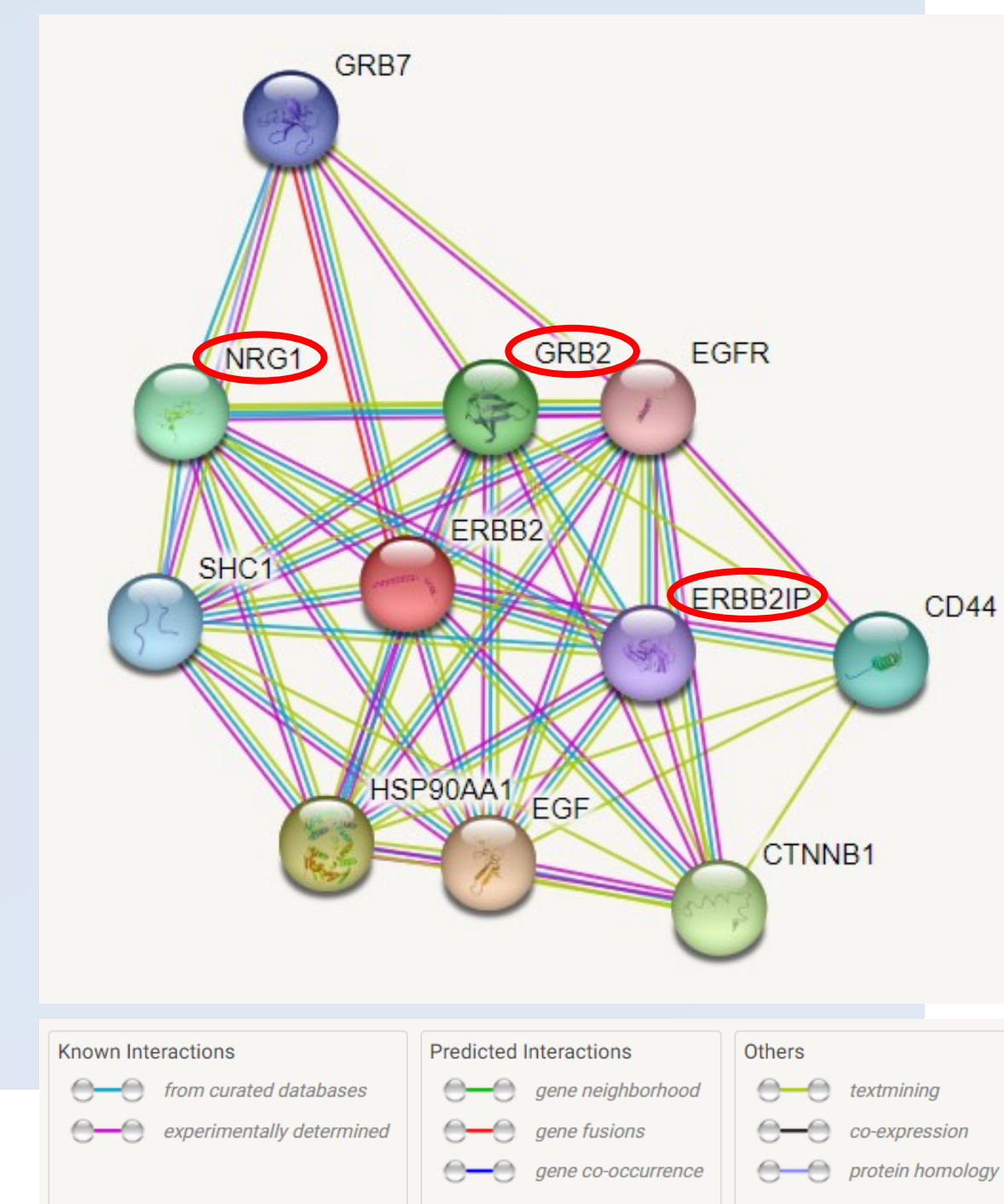
(HerceptTest, score 0: N = 20, score 1: N = 12, score 2: N = 13, score 3: N = 13)

The study was approved by the ethics committee at Tohoku University.

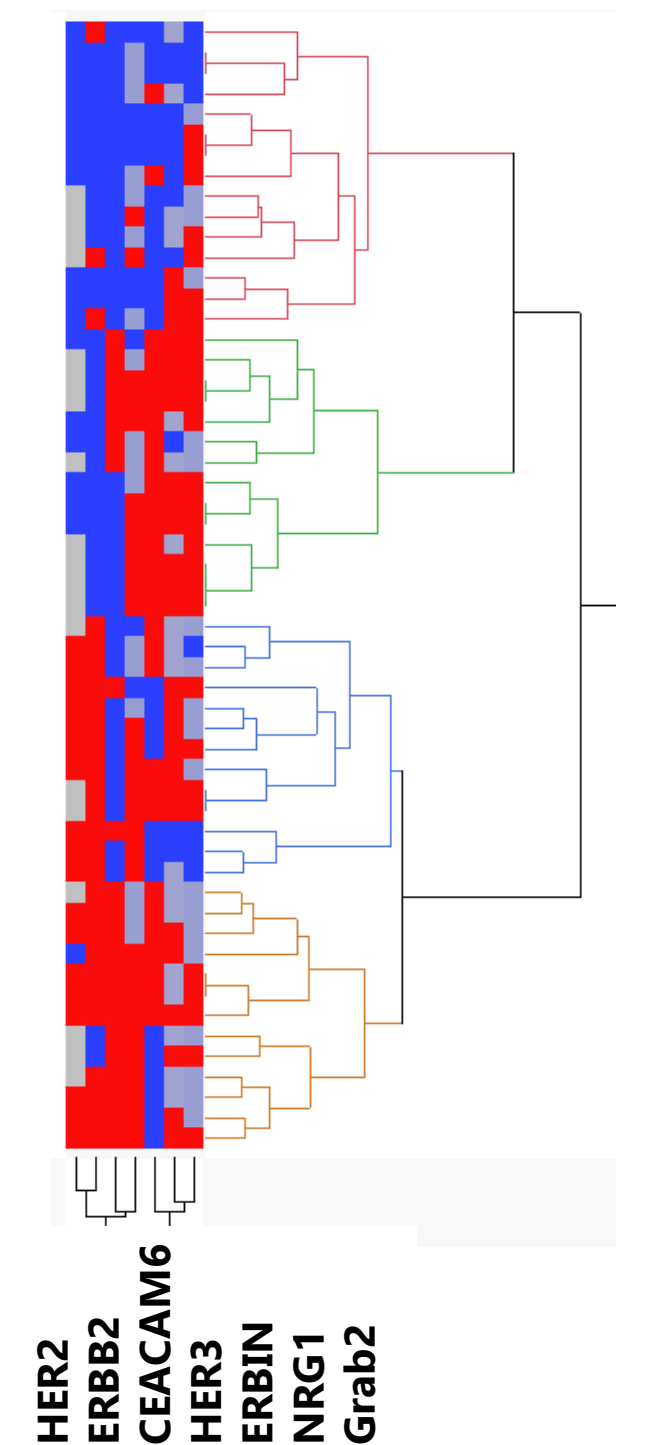
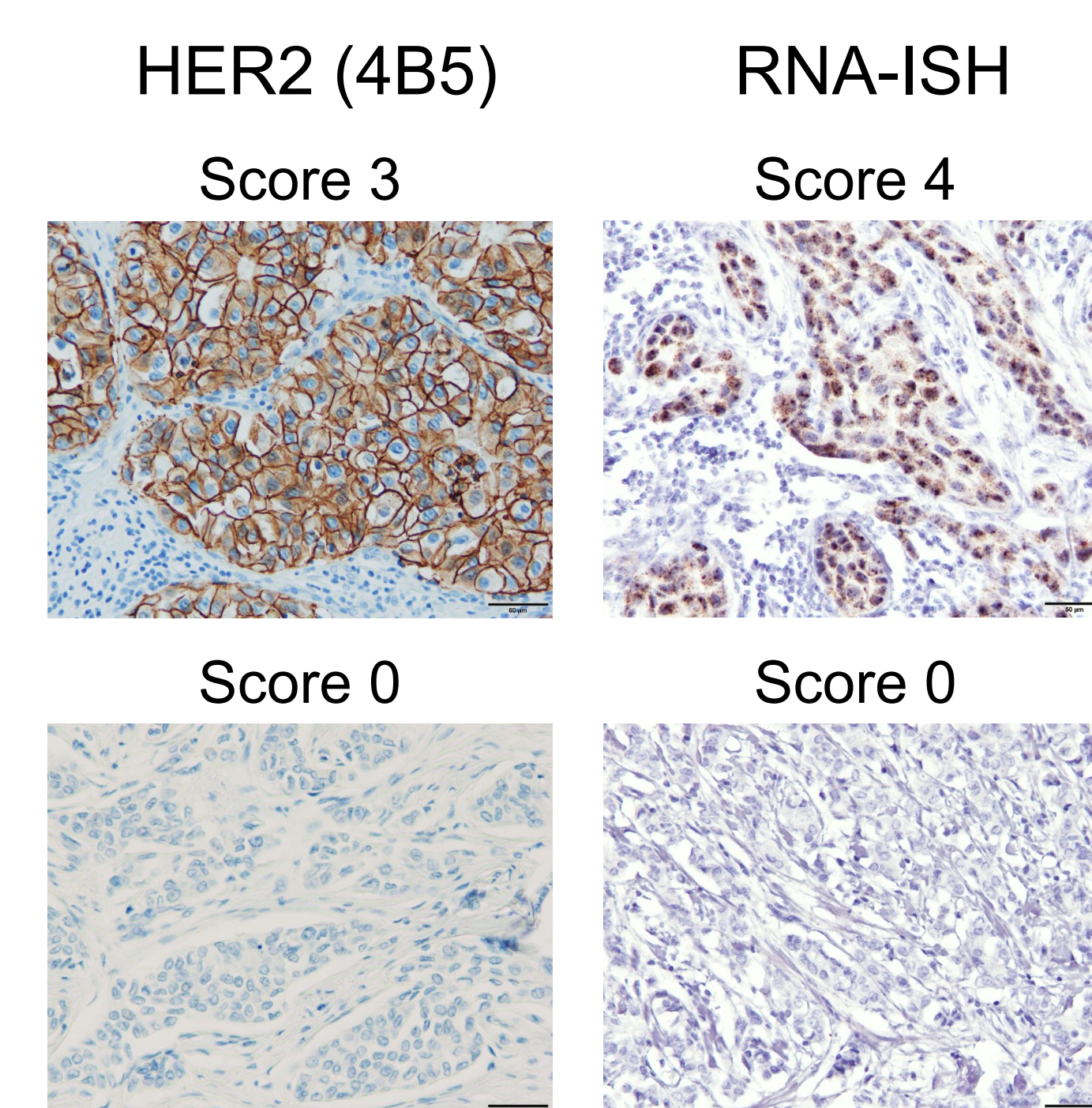
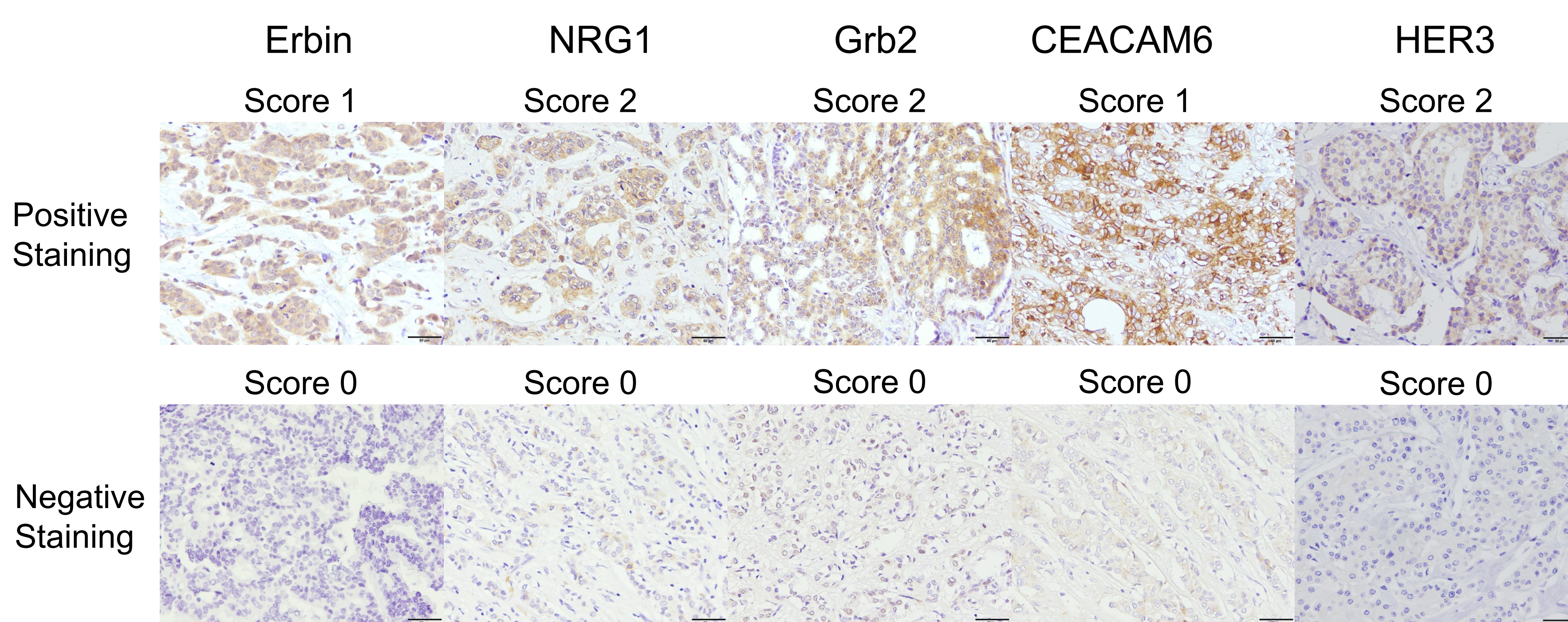
Immunohistochemistry (IHC):

- NRG1 (Neuregulin 1)
- ERBIN (ErbB2 interacting protein)
- Grb2 (Growth factor receptor-binding protein 2)
- CEACAM6 (Carcinoembryonic antigen-related cell adhesion molecule 6)
- HER2 (4B5)
- HER3

RNAscope in situ hybridization (RNA-ISH): ERBB2



RESULTS & DISCUSSION



	Erbin		P-value	NRG1			P-value	Grb2			P-value	CEACAM6		P-value	HER3			P-value
	0	1		0	1	2		0	1	2		0	1		0	1	2	
Herceptest																		
HER2-negative	9	11	0.9726	7	5	8	0.1989	4	5	11	0.0557	16	4	0.0496	7	7	6	0.0383
HER2-low	8	10		2	7	9		0	7	11		9	9		1	6	11	
HER2-positive	11	9	0.5158	3	7	10	0.9283	5	8	7	0.0204	9	11	0.7579	1	5	14	0.8409
4B5																		
HER2-negative	9	9	0.4188	7	3	8	0.0695	4	4	10	0.0382	14	4	0.1932	7	7	4	0.0056
HER2-low	7	12		2	8	9		0	7	12		11	8		1	5	13	
HER2-positive	10	8	0.2523	2	7	9	0.9804	4	8	6	0.0221	8	10	0.4126	1	5	12	0.9935

	RNA-ISH					P-value
	0 (N=19)	1 (N=9)	2 (N=11)	3 (N=7)	4 (N=12)	
Herceptest						
0 (N=20)	9	6	5	0	0	
1 (N=12)	6	2	3	1	0	
2 (N=13)	4	1	1	3	4	<0.0001
3 (N=13)	0	0	2	3	8	
HER2-negative (N=20)	9	6	5	0	0	
HER2-low (N=18)	10	3	4	1	0	<0.0001
HER2-positive (N=20)	0	0	2	6	12	
4B5						
0 (N=18)	10	5	3	0	0	
1 (N=17)	8	4	5	0	0	
2 (N=8)	1	0	2	4	1	<0.0001
3 (N=15)	0	0	1	3	11	
HER2-negative (N=18)	10	5	3	0	0	
HER2-low (N=19)	9	4	6	0	0	<0.0001
HER2-positive (N=18)	0	0	1	5	12	

Grb2 expression was significantly higher in HER2-low than in HER2-negative and was significantly higher in HER2-low than in HER2-positive breast cancers. In Herceptest, CEACAM6 positivity was significantly more frequent in HER2-low than in HER2-negative breast cancers. In "4B5", NRG1 scores tended to be higher in HER2-low than in HER2-negative breast cancers. HER3 expression was significantly higher in HER2-low breast cancers than in HER2-negative breast cancers. ERBB2 expression showed a positive correlation with HER2 expression.

Cluster analysis showed that HER2-negative breast cancers classified into the same cluster as HER2-low breast cancers exhibited high HER2 binding protein expression. Clusters containing breast cancers with positive, low, and negative HER2 expression were characterized by high ERBB2 scores and high expression of HER2 binding protein, suggesting the possibility that breast cancer may be promoted in a HER2-dependent manner through interaction with HER2 binding protein.

CONCLUSIONS

HER2-low and HER2-negative breast cancers include cases with similar characteristics to HER2-positive breast cancers, suggesting potential applicability of therapies targeting HER3 and other HER2 binding proteins.

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