

# Association between the expression of hormone receptors, Her-2/neu overexpression and tumor characteristics in women with primary breast cancer

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## Abstract

Her-2/neu overexpression has been correlated with poor prognostic tumors. The association between breast tumor characteristics and expression of ER, PR, Her-2/neu overexpression, patient's age, tumor size, type and grade were retrospectively evaluated in 226 primary breast cancer referred to Armin pathobiology laboratory in 2005. We found that 21.7% of cases had HER-2/neu overexpression. HER-2/neu overexpression in ER negative cases (28.4%) was higher than ER positive cases (18.4%) and HER-2/neu overexpression in PR negative cases (28.4%) was higher than PR positive cases (18.0%). The frequency of HER-2/neu overexpression decreased from ER-PR- to ER+PR+ (30.7% to 18.8%). The frequency of HER-2/neu overexpression decreased significantly ( $P < 0.05$ ) from ER-PR- to ER+PR+ (45.5% to 20.5%) in low grade tumors and HER-2/neu overexpression decreased from ER-PR- to ER+PR+ (18.8% to 15.4%) in high grade tumors but this difference was not significant ( $P = 0.790$ ). Our results revealed higher proportion of ER- and PR- tumors associated with HER-2/neu overexpression, also younger patients have higher rate of HER-2/neu overexpression.

## INTRODUCTION

The HER-2/neu (c-erbB-2) is an oncogene that encodes a transmembrane glycoprotein with tyrosin kinase activity known as p185, which belongs to the family of epidermal growth factor receptor [12]. Cells transfected with HER-2/neu acquire a more malignant phenotype, with stimulation of cell proliferation, invasion and metastasis. This has been confirmed in the clinic: women with Her-2/neu positive breast cancer have a worse prognosis than those with Her-2/neu negative cancer [134]. although Her-2/neu overexpression has been correlated with poor prognostic tumor characteristics such as higher histological grade, S phase fraction, increased tumor size, increased number of involved lymph nodes, absence of lobular histology and negative or lower Estrogen receptor (ER) expression [15] but its role as an independent prognostic factor is not significant in multivariate analysis [16].

Semiquantitative measurement using immunohistochemistry (IHC) for the Her-2/neu membrane receptor protein can accurately predict gene amplification [7].

Estrogen receptor (ER) correlates inversely with the presence of epidermal growth factor receptor [1] also it has been suggested that there is an inverse relation between the expression of the progesterone receptor (PR) and Her-2/neu in women with ER<sup>+</sup> breast cancer [58].

The aim of this study was to determine the relation between Her-2/neu overexpression and other clinicopathological factors in women with operable breast cancer.

## MATERIALS AND METHODS

The association between breast tumor characteristics and expression of ER, PR, Her-2/neu overexpression, patient's age, largest tumor size, tumor type and tumor grade were retrospectively evaluated in 226 women with primary breast cancer referred to Armin pathobiology laboratory in 1384. The evaluation of histopathologic characteristics was carried out on paraffin-embedded tissue blocks which were stained with Hematoxylin & Eosin. The Immunohistochemistry staining for ER, PR and Her-2/neu were done on paraffin-embedded tissue blocks according to the envision method using primary monoclonal antibodies (Dako Kits).

The DAKO scoring system for Her-2/neu was defined as negative for scores 0 & 1+ and positive for score 2+ & 3+ and overexpression for score 3+ (Table1)[1].

Using the H score for ER and PR, a negative result was defined as a score of  $\leq 50$ , weakly positive as 51-100, moderately positive as 101-200 and strongly positive as  $>200$ . Tumor grading was performed according to Richardson & Bloom grading system [1].

In a univariate analysis the association between ER, PR and Her-2/neu was evaluated and the chi square test was used to examine the categorical variables and the association between ER, PR expression and other clinicopathologic variables.

The results were considered statistically significant if the P value was  $< 0.05$ . All analysis were performed with SPSS version 11.0 for windows.

## RESULTS

Table 2 summarizes the clinicopathological features of all 226 women with primary operable breast cancer. HER-2/neu was expressed as defined by a DAKO score 3+ and a DAKO score 2+ or 3+ in 21.7% and 36.3% of all patients, respectively.

Table 3 shows data of HER-2/neu overexpression scoring in primary operable breast cancers based on DAKO scoring system.(univariate analysis). There was no correlation between HER-2/neu overexpression and ER state, PR state, tumor grade, tumor size and patient age.

Table 4 shows the frequency of HER-2/neu overexpression in the different ER/PR phenotypes ( $ER^-PR^-$ ,  $ER^-PR^+$ ,  $ER^+PR^-$  and  $ER^+PR^+$ ) of breast cancer. The frequency of HER-2/neu overexpression decreased from  $ER^-PR^-$  to  $ER^+PR^+$  (30.7% to 18.8%) but this difference was not significant ( $p=0.057$ ).

Table 5 shows the frequency of HER-2/neu overexpression in the different joint ER/PR phenotypes ( $ER^-PR^-$ ,  $ER^-PR^+$ ,  $ER^+PR^-$  and  $ER^+PR^+$ ) in low and high grade tumors.

The frequency of HER-2/neu overexpression decreased significantly ( $P<0.05$ ) from  $ER^-PR^-$  to  $ER^+PR^+$  (45.5% to 20.5%) in patients with low grade tumor, also the frequency of HER-2/neu overexpression decreased from  $ER^-PR^-$  to  $ER^+PR^+$  (18.8% to 15.4%) in patients with high grade tumor but this difference was not significant.

**Figure 1**

Table 1: scoring system for Her-2/neu

Staining pattern	score	Her-2/neu protein overexpression assessment
No staining is observed or membrane staining is observed in less than 10% of the tumor cells	0	negative
A faint/barely perceptible membrane staining is detected in more than 10% the tumor cells . the cells are only stained in part of their membrane	1+	negative
A weak to moderate complete membrane staining is observed in more than 10% of the tumor cells	2+	weakly positive
A strong complete membrane staining is observed in more than 10% of the tumor cells	3+	strongly positive

**Figure 2**

Table 2: summarises the clinicopathological features of all 226 women with primary operable breast cancer

Clinicopathological feature	N	%
Her-2/neu state		
Negative(score 0,1)	144	63.7
Positive(score 2,3)	82	36.3
Her-2/neu state		
Negative(score 0,1,2)	177	78.3
Positive(score 3)	49	21.7
ER expression		
Negative	81	35.8
Positive	141	62.4
Missing	4	1.8
PR expression		
Negative	81	35.8
Positive	139	61.5
Missing	6	2.7
Tumor grade		
1-2	133	58.8
3	32	14.2
Missing	61	27
Tumor size		
≤20 mm	134	59.3
>20 mm	71	31.4
Missing	21	9.3
Age		
≤50 years	122	54.0
>50 years	97	42.9
Missing	7	3.1
Type		
Ductal carcinoma	191	84.5
Lobular carcinoma	21	9.3
Other	8	3.5
Missing	6	2.7
<b>Total</b>	<b>226</b>	<b>100</b>

**Figure 3**

Table 3: Association between Her-2/neu overexpression and tumor characteristics in 226 women with primary breast cancer

	HER-2/neu overexpression		P-value
	Negative	positive	
ER expression			0.085
Negative	58(71.6%)	23(28.4%)	
Positive	115(81.6%)	26(18.4%)	
PR expression			0.071
Negative	58(71.6%)	23(28.4%)	
Positive	114(82.0%)	25(18.0%)	
Tumor grade			0.235
1-2	99(74.4%)	34(25.6%)	
3	27(84.4%)	5(15.6%)	
Tumor size			0.497
≤20 mm	102(76.1%)	32(23.9%)	
>20 mm	57(80.3%)	14(19.7%)	
Age			0.073
≤50 years	91(74.6%)	31(25.4%)	
>50 years	82(84.5%)	15(15.5%)	

**Figure 4**

Table 4: Frequency of HER-2/neu overexpression by joint ER/PR status

	HER-2/neu overexpression		Total
	Negative	positive	
ER-PR-	52(69.3%)	23(30.7%)	75
ER-PR+	6(100%)	0(0.0%)	6
ER+PR-	6(100%)	0(0.0%)	6
ER+PR+	108(81.2%)	25(18.8%)	133
<b>Total</b>	<b>172(78.2%)</b>	<b>48(21.8%)</b>	<b>220</b>
<b>P-value= 0.057</b>			

**Figure 5**

Table 5: Frequency of HER-2/neu overexpression for low grade and high grade tumor by joint ER/PR status

	Grade1-2		Total	Grade3		Total
	HER-2/neu overexpression			HER-2/neu overexpression		
	Negative	positive		Negative	positive	
ER-PR-	18(54.5%)	15(45.5%)	33	13(81.3%)	3(18.8%)	16
ER-PR+	5(100%)	0(0.0%)	5	0	0	0
ER*PR-	4(100%)	0(0.0%)	4	2(100%)	0(0.0%)	2
ER*PR+	70(79.5%)	18(20.5%)	88	11(84.6%)	2(15.4%)	13
Total	97(74.6%)	33(25.4%)	130	26(83.9%)	5(16.1%)	31
P-value Grade1-2= 0.011						
P-value Grade3= 0.790						

## DISCUSSION

In our study, we found that 36.3% of cases were HER-2/neu positive (score 2-3) and 21.7% of cases showed HER-2/neu overexpression (score 3). HER-2/neu overexpression is found in 20% to 30% of cases with invasive carcinoma [19101112].

Presence of estrogen receptor was significantly associated

with high nuclear and low histologic grades and older patients' age groups [1].

We found that 62.4% and 61.5% of cases were ER positive and PR positive, respectively. The percentage of ER positive cases reported in literatures is 60% to 70% [1213] or 70% to 90% [14] and PR positive cases are reported 60% to 70% [14].

Our results show 86.6% of breast cancers were low grade (grade 1-2) and 19.4% were high grade (grade 3). (Missing cases, not included).

In our study 80.8% of cases were Ductal carcinoma, 9.5% Lobular carcinoma and 3.6% were other histologic types including Medullary, Colloid, tubular, mucinous carcinoma and adenocarcinoma. (Missing cases, not included).

We compared HER-2/neu overexpression in hormone receptor positives and hormone receptor negatives in relation to other clinicopathologic characteristics in primary operable breast cancer. HER-2/neu overexpression in ER negative cases (28.4%) was higher than ER positive cases (18.4%) and HER-2/neu overexpression in PR negative cases (28.4%) was higher than PR positive cases (18.0%), although these differences were not significant. According to most of the studies, presence of estrogen receptor (ER) and progesteron receptor (PR) correlates inversely with HER-2/neu overexpression [1911141516171819].

Patients 50 years of age or younger were more likely to have HER-2/neu overexpression than patients older than 50 years (25.4% versus 15.5%). It should be pointed out that higher rates of HER-2/neu overexpression in young patients have been documented in previous studies [8910172021], but in other studies, no correlation were found between age of patient and HER-2/neu overexpression [11162223].

We did not find any correlation between size of the tumor with HER-2/neu overexpression, which is similar to some previous studies [162224] and disagree with other studies [91518].

We also found no correlation between grade of the tumor and HER-2/neu overexpression, which is similar to some studies [20222325] and disagree with other studies [111215161819].

The frequency of HER-2/neu overexpression decreased from ER<sup>+</sup>PR<sup>-</sup> to ER<sup>+</sup>PR<sup>+</sup> (30.7% to 18.8%) but this difference was not significant (p=0.057). In another study, this decrease was significant [15].

The frequency of HER-2/neu overexpression decreased

significantly (P<0.05) from ER<sup>+</sup>PR<sup>-</sup> to ER<sup>+</sup>PR<sup>+</sup> (45.5% to 20.5%) in patients with low grade tumor, also the frequency of HER-2/neu overexpression decreased from ER<sup>+</sup>PR<sup>-</sup> to ER<sup>+</sup>PR<sup>+</sup> (18.8% to 15.4%) in patients with high grade tumor but this difference was not significant (P=0.790). In two other studies, these decreases in low and high grade tumors were significant [1415].

Our results show higher proportion of ER<sup>-</sup> and PR<sup>-</sup> tumors associated with HER-/neu overexpression, also younger patients have higher rate of HER-2/neu overexpression.

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