RESEARCH COMMUNICATION

Breast Cancer Subtypes Identified by the ER, PR and HER-2 Status in Thai Women

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Abstract

Expression of estrogen-receptor (ER), progesterone-receptor (PR) and HER-2 has recently been linked with various breast cancer subtypes identified by gene microarray. This study aimed to document breast cancer subtypes based on ER, PR and HER-2 status in Thai women, where expression of these subtypes may not be similar to those evident in Western women. During 2009 to 2010, histological findings from 324 invasive ductal carcinomas (IDC) at Siriraj Hospital were studied. Various subtypes of IDC were identified according to expression of ER, PR and HER-2: luminal-A (ER+;PR+/-;HER-2–), luminal-B (ER+;PR+/-;HER-2 +), HER-2 (ER-;PR-;HER-2+) and basal-like (ER-;PR-;HER-2–). As well, associations of tumor size, tumor grade, nodal status, angiolymphatic invasion (ALI), multicentricity and multifocality with different breast cancer subtypes were studied. Of 324 IDCs, 143 (44.1%), 147 (45.4%), 15 (4.6%) and 12 (3.7%) were T1, T2, T3 and T4, respectively. Most tumors were grade 2 (54.9%) and had no nodal involvement (53.4%). According to ER, PR and HER-2 status, 192 (59.3%), 40 (12.3%), 43 (13.3%) and 49 (15.1%) tumors were luminal-A, luminal-B, HER-2 and basal-like subtypes. HER-2 subtype presented with large tumor (p=0.04, ANOVA). Luminal-A IDC was associated with single foci (p<0.01, χ2). HER-2 and basal-like subtypes were likely to have high tumor grade (p<0.01, χ2). In addition, HER-2 subtype had higher number of nodal involvement (p=0.048, χ2). In conclusion, the luminal-A subtype accounted for the majority of IDCs in Thai women. Percentages of HER-2 and basal-like IDCs were high, compared with a recent study from the USA. The HER-2 subtype was related with high nodal invasion. The findings may highlight biological differences between IDCs occurring in Asian and Western women.

Keywords: Breast cancer subtype - ER - PR - HER 2 - Thai cases

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Introduction

Breast cancer is the most common cancer in women worldwide. Etiology of breast cancer is unclear, but is linked with various genetic abnormalities. Data from research studying on gene microarrays suggested that each breast cancer may have different genetic profiles. Based on genetic profiles, invasive ductal carcinoma (IDC) is classified into different 5 molecular subtypes: luminal-A, luminal-B, HER-2, basal and normal-breast like subtypes (Sorlie et al., 2001;Sorlie et al., 2003). Different subtypes may have different presenting features, different locoregional relapse, and different prognosis (Ihemelandu et al., 2008;Nguyen et al., 2008;Voduc et al., 2010;Wiechmann et al., 2009). Basal-like and HER-2 subtypes were associated with aggressive clinical behaviors and poor survival outcome. While, patient with luminal A subtype had the best survival outcome (Carey et al., 2006;Kyndi et al., 2008).

Gene expression profiling by DNA microarray is expensive and may not be feasible in clinical practice. The technology requires a special platform and expertise. In general clinical practice, expression of estrogen receptor (ER), progesterone receptor (PR) and HER-2 are used to identify aggressiveness of breast cancer, and thus tailoring the treatment. Although, ER, PR and HER-2 status may not accurately classify the subtypes, the three markers has been used as surrogate markers to identify various breast cancer subtypes (Nguyen et al., 2008;Wiechmann et al., 2009). Moreover, the technique of immunohistochemistry in identifying expression of ER, PR and HER-2 is much easier and cheaper than gene microarray, but provides significant information to discriminate good and poor prognosis breast cancer.

Therefore, this study aimed primarily to document subtypes of breast cancer, identified by ER, PR and HER-2 status in Thai women. In addition, attention was focused on relationships between the various breast cancer subtypes and a number of important clinico-pathological features.

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Materials and Methods

A total of 321 patients with 324 primary invasive ductal carcinoma (including 3 patients with bilateral breast cancer) diagnosed and had clinical and pathological information available at Department of Surgery, Faculty of Medicine Siriraj Hospital during November 2009 to June 2010 were included in the study. Bilateral breast cancers were regarded individually on the basis of the characteristics of each cancer. The study was ethically approved by the Institutional Board Review.

Tumors were classified into subtypes as follows: luminal-A (ER+, PR+/-, HER-2-), luminal-B (ER+, PR+/-, HER-2+), HER-2 (ER-, PR-, HER-2+), and basal-like (ER-, PR-, HER-2-) (Wiechmann et al., 2009). Positivity for ER or PR was documented when any nuclear staining was evidenced, according to the St Gallen consensus 2009 (Goldhirsch et al., 2009). HER-2 was determined as positive if the immunohistochemistry (IHC) result showed 3+ or in case of 2+ with confirmation by any of FISH or CISH tests. Nodal positivity included macrometastases and micrometastases, but not isolated tumor cells. Multicentricity and multifocality were defined when the presence of tumor in multiple quadrants or the discontinuous growth of tumor in the same quadrant.

Percentage was used in calculation of most demographic and some clinical data. When comparing the clinico-patholocial characteristics amongst different subtypes, Chi-square (X^2) test was used for binary variables and analysis of variance (ANOVA) was used for continuous variables . Multivariate logistic regression was used to determine whether subtype was independently predictive of nodal involvement and/or multicentric/multifocal disease after controlling for age, tumor size, and tumor grade (high vs. intermediate/low). Luminal-A was the reference group. Patients with missing data were excluded from multivariate analysis. All statistical tests were two sided. P-value of ≤ 0.05 was considered statistical significant. All statistical analyses were performed by SPSS version 12 (SPSS,Chicago,IL).

Results

The average age of 321 women in the study was 52 (25-94) years. Most tumors were T1 and T2 disease at presentation. Tumor were T1, T2, T3 and T4 in 143 (44.1%), 147 (45.4%), 15 (4.6%) and 12 (3.7%), respectively. Most tumors were grade 2 (54.9%) and had no nodal involvement (53.6%). Angiolymphatic invasion (ALI) was evidenced in 82/269. Multicentricity and/or multifocality were present in 12.9%. All relevant clinical and pathological variables were summarized in Table 1. ER, PR and HER-2 positivity were identified in 232 /324 (71.6%), 209/324 (64.5%) and 83/324 (25.6%). According to ER, PR and HER-2 status (as described in materials and methods); 192 (59.3%), 40 (12.3%), 43 (13.3%) and 49 (15.1%) tumors were luminal-A, luminal-B, HER-2 and basal-like subtypes.

Tumor subtypes and associated clinico-pathological features were shown in Table 2, with univariate analysis. HER-2 subtype tended to present with a larger tumor size (p=0.04, ANOVA), higher number of N2 and 3 diseases (nodal involvement ≥ 4) (p=0.048, χ2) and higher percentage of multicentricity and or multifocality (p<0.01, χ 2). Luminal-A tumors were associated with single foci (p<0.01, χ2). However, the HER-2 and basal-like subtypes were more likely to be grade 3 tumors (p<0.01, χ2).

On multivariate analysis, subtypes were not predictive

Table 1. Clinical and Pathological Variables of 324 IDCs Included in the Study

Characteristics	N (%)
Average age (range)	52 (25 – 94)
Tumor size	
T1	143 (44.1)
T2	147 (45.4)
T3	15 (4.6)
T4	12 (3.7)
N/A	7 (2.1)
Nodal status	
N0	173 (53.4)
N1	77 (23.8)
N2	39 (12.0)
N3	34 (10.5)
N/A	1 (0.03)
Tumor grade	
Grade 1	36 (11.1)
Grade 2	178 (54.9)
Grade 3	104 (32.1)
N/A	6 (1.8)
Multicentric/foci	
Yes	42 (12.9)
No	278 (85.8)
N/A	4 (1.2)
Angiolymphatic invasion	
Yes	82 (25.3)
No	187 (57.7)
N/A	55 (17.0)
Estrogen receptor (ER)	
Positive	232 (71.6)
Negative	92 (28.4)
Progesterone receptor (PR)	
Positive	209 (64.5)
Negative	115 (35.5)
HER-2	
Positive	83 (25.6)
Negative	241 (74.3)

Table 2. Univariate Analysis to Demonstrate Association Between Tumor and Clinico-pathological Variables By Subtype

Clinico-pathologic variables	A[1]	B[2]	HER-2	Basal-like	p value*
Age (N=321)	53	52	53	53	0.98
Tumor size (N=317)	2.3	2.7	3	2.8	0.04
Nodal involvement (N=323)					
Node positive (%)	45.8	42.5	52.4	46.9	0.39
N2 and N3 (%)	17.7	25	35.7	28.6	0.04
Tumor grade (N=318)					
Grade 3 (%)	18.6	32.5	64.3	60.4	<0.01
Multicentric/multifoci (N=320) (%)	8.4	12.5	28.6	18.8	<0.01
ALI (n=269) (%)	28.4	24.3	47.2	29.3	0.12

* X^2 test for binary variables, ANOVA for continuous variablesUnion for International Cancer Control, [1]Luminal-A, [2]Luminal-B

Table 3. Multivariate Logistic Regression Demonstrated Factors Related with Multicentric/foci and Nodal Status

Variables	Multi/foci	Node positive	N2 and N3
	OR[1] (95% CI)	OR[1] (95% CI)	OR[1] (95% CI)
Subtype			
Luminal-A	1	1	1
Luminal-B	1.7 (0.5–5.6)	0.7 (0.2–1.8)	1.7 (0.5–5.5)
HER-2	2.6 (0.8–8.0)	0.4 (0.1–1.4)	0.8 (0.2–2.7)
Basal-like	2.4 (0.7–7.5)	0.7 (0.3–2.0)	2.2 (0.7–6.8)
Tumor size (N=317)			
	0.9 (0.7–1.2)	1.5 (1.1–1.9)[2]	1.7 (1.2–2.3)[2]
Tumor grade (N=318)			
Grade 1, 2	1	1	1 0.8
Grade 3	1.0 (0.4–2.7)	2.3 (1.1–4.8)[3]	1.0 (0.4–2.5)
ALI (N=269)			
No	1	1	1
Yes	3.8 (1.6–9.1)[2]	12.8 (6.2–26.3)[2]	13.4 (5.8–30.6)[2]
Age (N=321)			
	0.9 (0.9–1.0)	0.9 (0.9–1.0)	1.0 (0.9–1.0)

[1]Adjusted OR; [2]<0.01; [3]<0.02

of multicentricity, multifocality, nodal metastases and high-volume nodal involvement. However, tumor size, tumor grade and angiolymphatic invasion were factors related with enhancing risk of nodal involvement with the OR of 1.5 (95% CI = 1.1-1.9, 2.3 (95% CI = 1.1-4.8) and 2.8 (95% CI = 6.2-26.3), respectively. In addition, tumor size (OR 1.7; 95% CI, 1.2-2.3) and ALI (OR 13.4; 95% CI, 5.8-30.6) were predictive factors for high-volume nodal involvement (Table 3).

Discussion

Advance in basic breast cancer research, in particular DNA microarray technology, has resulted in a new classification of breast cancer subtypes. The breast cancer subtypes related to various clinical outcomes, including overall survival (Ihemelandu et al., 2008; Sorlie et al., 2001). Luminal subtypes demonstrated better clinical outcomes than basal like and HER-2 subtypes (Sorlie et al., 2001; Sotiriou et al., 2003).

Evidence suggested that subtypes of breast cancer identified by DNA microarray may approximately relate to expression of commonly used markers in breast cancers: ER, PR and HER-2 status (Nguyen et al., 2008; Wiechmann et al., 2009), and use of three markers is easier and more cost-effectiveness in clinic, comparing with DNA microarray. In a recent consensus at St. Gallen in 2011, additional immunohistochemical staining of Ki-67 was supported for defining tumor subtypes, mainly in the distinction between luminal A and luminal B subtypes (Goldhirsch et al., 2011).

In this study, expression of ER PR and HER-2 are used to classify breast cancer into various subtypes. The findings from the study demonstrated different information, in the Asian population, where expression of markers may be different from information reported from the Western population. More frequent HER-2 subtype was observed in Thai women. In a study from the USA, HER-2 subtype comprised 6% of all invasive ductal cancer (Wiechmann et al., 2009), whereas the figure was 13% in this study in Thai women. HER-2 subtype possibly resulted in a poor outcome with a high locoregional relapse after breast conserving surgery and mastectomy (Kyndi et al., 2008; Nguyen et al., 2008). Therefore, this might highlight the difference in breast cancer between Asian and Western women, in term of tumor aggressiveness. However, in this study, not all patients who had HER-2^{2+} on immunohistochemistry were confirmed with standard FISH or CISH techniques.

Moreover, findings in the study have confirmed the aggressiveness of HER-2 subtype breast cancer, as previously evidenced (Sorlie et al., 2001;Sotiriou et al., 2003). Patients with HER-2 subtypes in this study were likely to have multicentricity/multifocality, as well as large tumors. In addition, on multivariated analysis, high number of N2 and N3 diseases (nodal involvement ≥ 4) and high percentage of grade 3 were documented in HER-2 subtype tumor.

Triple negative (ER, PR and HER-2 negative) breast cancer is linked with a poor clinical outcome (Hudis and Gianni, 2011), and is approximately comparable to basal-like subtype on gene microarray. In our study from Thai women, basal-like subtype breast cancer or triple negative comprised 15%, which was equivalent to the study in a study from the USA (Wiechmann et al., 2009). Based on findings in our study, 28% of breast cancer women were either basal-like or HER-2 subtype, comparing with 20% in the Western women. This, again, may explain more aggressiveness and poorer clinical outcome of breast cancer in the Thai women and possibly other Asian women.

However, this study had some limitations which were addressed here. Firstly, expression of ER, PR and HER-2 was used in order to determine subtype. In fact, although it is more feasible, it may not be accurately comparable to subtypes identified by gene microarray. The use of additional markers, such as Ki-67, is suggested in the further study. Secondly, identification of HER-2 positivity was mainly based on immunohistochemistry. Only 5 of 55 with HER-2 2+ were tested with FISH or CISH (all were negative). These may conceivably lead to potential misclassification of a subset of luminal-B tumors into the luminal-A subtype and a subset of HER-2 tumors into the basal-like subtype.

In conclusion, most invasive ductal carcinomas in Thai women were luminal-A subtype. Percentages of HER-2 and hasal-like tumors were higher, as compared with a recent study from the USA. HER-2 subtype seemed to relate with poor pathological features. Tumor size, tumor grade and ALI were related with nodal involvement. Tumor size and ALI were related with high volume nodal involvement.

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