RESEARCH ARTICLE

Immunohistochemistry Subtypes (ER/PR/HER) of Breast Cancer: Where Do We Stand in the West of Saudi Arabia?

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Abstract

In Saudi Arabia, cancer of breast is ranked the most frequent neoplasm and second source of cancer death in the female population. Breast cancer (BC) fast diagnosis, prognosis and medication management necessitate, these days, immunohistochemistry (IHC) assessment of hormone receptors and HER2 expression profile. The present report defines the IHC profile of ER, PR and HER2 in Saudi female breast neoplasms of ductal and lobular types and associations ER, PR and HER2 expression patterns with various clinicopathological factors (age, type of tumor, size, laterality, histological grade, and involvement of axillaries lymph nodes). Ninety nine cases of breast tumors were recruited from the pathology department archive of King Abdulaziz University Hospital, Kingdom of Saudi Arabia. ER, PR and HER2 expression was assessed using IHC staining. Ductal carcinomas with a variety of histological grades constituted 88 (88.8%) of total cases. Seventy four (77.8%), 59 (62.1%), and 35 (36.8%) of ductal carcinomas showed positive staining for ER, PR and HER2, in that order. Remaining breast cancer cases were four (4%) lobular carcinomas and two (2%) mixed form of ductal and lobular types, which were ER+, PR+, and HER2-. Breast cancer expression pattern of ER, PR and HER2 in Saudi female is different from that of Tunisian and Jordanian female populations and closer to the expression pattern of Egyptian, Lebanese, Iraqi and western country females. Furthermore, the present study found two IHC patterns of breast cancer ER+/PR-/HER2+ (5%) and ER+/PR-/HER2- (11.1%), which had not been reported in other Arabic studies. Thus the rates of IHC expression patterns in breast cancer show some variation among Arabic female populations.

Keywords: Breast cancer - ER - HER2 - PR - immunohistochemistry - Saudi Arabia females

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Introduction

Cancer of breast is universally ranked first widespread malignancy in female population. In Saudi Arabia, it is placed in similar position among cancers in female population and it accounted for 25.1% of all newly diagnosed female malignant tumors in 2009 (Al-Eid and Garcia, 2012). The crude incidence rate for female breast carcinoma in Saudi Arabia was (22.7) per 100,000 female population. Morphological distribution of female breast cancer showed that invasive or infiltrating ductal carcinoma (IDC) was 78.2%, invasive or infiltrating lobular carcinoma (ILC) was 6.3%, invasive ductal carcinoma mixed with other types was 2.2%, and 0.9% were mixed type of invasive ductal and lobular carcinomas. The remaining were other types of morphology (Al-Eid and Garcia, 2012).

Breast tumors are well known as a highly heterogeneous tumors with diverse biological, pathological, clinical characteristics and response to treatment which has been attributed partially to various risk factors including reproductive, genetic and environmental (Di Cosimo and Baselga, 2010; Ban and Godellas, 2014). Many recent reports have restated its heterogeneity based on molecular and genetic profile and classification (Prat and Perou, 2011; Tamimi et al., 2012). Many classic variables influence breast cancer prognosis and management such as histopathology type of tumor, grade, size, involvement of lymph nodes, immunohistochemistry profile of hormone receptors and, in recent years, status of HER2 (Horita et al., 2001; Kaptain et al., 2001).

ER, PR and HER2 are essential in the estimation process of breast cancer prognosis and play central role in its management and treatment choice worldwide (Lund et al., 2010; Ge et al., 2012; Khokher et al., 2013). Estrogen enacts a crucial function in cell proliferation and breast cancer progression (Lazennec et al., 2001), as it is described the major mitogenic steroid in neoplastic transformation for the cells of luminal epithelium and may play important role in prognosis (Anderson et al., 1998; Izadi et al., 2012). Salmon and his colleagues reported the connection between the amplification of HER2 gene and bad prognosis in 1987 (Slamon et al., 1987). Furthermore, disease-free survival was strongly associated with HER2

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amplification (Slamon et al., 1987; Najafi et al., 2013). Status of HER2 is also important for treatment choice especially for patients with metastatic tumors, who respond better for additional medication such as Herceptin (Cobleigh et al., 1999; Shak, 1999; Khokher et al., 2013). The use of hormonal therapy, HER2-targeted therapy, as well as chemotherapy depend on hormone receptors and HER2 expression profile, especially the presence of ER which is believed to be of great value in forecasting about 50% to 75% hormonal therapy response rate (Osborne et al., 1980; Wittliff, 1984).

The current basis of ER, PR and HER2 evaluation in mammary gland neoplasms is immunohistochemistry staining which has become wide spread in health institutions (Allred et al., 1998; Barnes and Hanby, 2001; Allred et al., 2009; Hammond et al., 2010; Chuthapisith et al., 2012; Kadivar et al., 2012). Results of this assessment impact directly on treatment options, as well as predict likely response to hormonal therapy (Payne et al., 2008; Barlett et al., 2011). ER and PR are nuclear proteins and the expression is assessed in nuclei of tumor cells (Hammond et al., 2010). It is known that well-differentiated tumors are usually hormone receptor positive in contrast to poorly differentiated ones that are more often hormone receptor negative (Stanford et al., 1986). In latest years, several studies have recognized dissimilar subtypes of breast cancer, which are morphologically similar, with a variety of therapeutic response and prognosis by the use of immunohistochemistry staining profile of ER, PR and HER2, which recently become part of the routine pathology reports (Bauer et al., 2007; Cheang et al., 2009).

Our study aims to find out the rate of IHC ER+, PR+ and HER2+ in breast cancer of Saudi females, and to weigh them against those of other populations which stated in the literature. Furthermore, link the IHC profile of ER, PR and HER2 with various clinicopathological aspects (age, size of tumor, histopathological type and grade and involvements of lymph node).

Materials and Methods

Ninety nine patient's files with breast cancer, from the period between January 2011 and December 2013, were recruited from pathology department archive at King Abdulaziz University Hospital. Patient's reports were revised for age of patient, tumor histopathological classification and grade, on top of ER, PR and HER2 manifestation. Archive materials of breast cancer cases were obtained initially as paraffin-embedded blocks or surgical specimens, which were formalin fixed, and then were processed, sectioned and hematoxylin and eosin stained.

Classification and grading of breast cancer were consistent with WHO categorization of breast tumors (Tavassoli and Devilee, 2003) and modified Nottingham Grading System respectively.

Hormone receptors and HER2 expression were evaluated using routine immunohistochemistry staining (IHC). Semi quantitatively measurement were employed for positive ER and PR stained nuclei and HER2 stained membranes. The immunohistochemistry staining patterns were ranked in terms of intensity of stain as following: +3 strong, +2 moderate, and 0 or +1 no staining or weak. The estimated grade of staining intensity reflected positive stained tumor cells that count more than 10%.

Results

Ninety nine cases of breast cancer were revised; ductal carcinoma constitutes the majority of cases accounting for 88.8%; IDC was 83.8% and ductal carcinoma in situ (DCIS) was 5%. ILC accounted for 3% and lobular carcinoma in situ (LCIS) represented only 1%. Mixed invasive ductal and lobular carcinoma was 2%. Other histologic patterns of breast cancer were recorded such as mucinous carcinoma, glycogen-rich clear cell carcinoma, adenosquamous carcinoma, and medullary carcinoma which accounted for 2%, 1%, 1%, and 1% respectively (Table 1). Twenty one tumors was of grade I, 47 of grade II, 21 of grade III and 10 cases were not reported. IDC revealed different grades I, II, and III accounting for 16 (16.1%), 46 (46.4%), and 21 (21.2%) cases respectively.

The median age of breast cancer cases was 53.7 ranging from 28 to 80 years. Sizes of tumors differed from 0.3 to 12cm, with 3.53cm median size. Fifty four breast carcinomas were left sided and forty five were right sided. At the time of surgical removal of breast tumors, 53 patients (53.5%) displayed positive lymph nodes. Seventy five tumors (75.7%) were ER+, 59 (59.5%) were PR+ and 32 (32.3%) were HER2+ (Table 1). Almost two third (61.3%) of ER+ cases were older than 50 years. Out of 20 ER- cases, seven (35%) were younger than 50 years.

All grade I breast carcinomas (21 cases) of different types were ER+ and PR+, except 5 cases were PR-, and

Table 1. Status of IHC Markers in Different Breast Cancer Types

Tumor classification		Total cases (99)	ER+	ER-	PR+	PR-	HER2+	HER2-	Not documented
Ductal carcinoma	Ductal carcinoma in-situ	5 (5%)	5 (5%)	0	5 (5%)	0	3 (3%)	2 (2%)	
	Invasive ductal caecinoma	83	63	19	48	34	28	54	1
	(88.8%)	(83.8%)	(63.6%)	(19.1%)	(48.4%)	(34.3%)	(28.2%)	(54.5%)	
Lobular carcinoma (4%)	Lobular carcinoma	1 (1%)							1
	83 (83.8%) in-situ								
	Invasive lobular carcinoma	3 (3%)	2 (2%)	0	2 (2%)	0	0	2 (2%)	1
Mixed invasive ductal & lobular carcinoma			2 (2%)	2 (2%)	0	2 (2%)	0	0	2 (2%)
Mucinous carcinoma		2 (2%)	2 (2%)	0	2 (2%)	0	0	2 (2%)	
Glycogen-rich clear cell carcinoma			1 (1%)	1 (1%)	0	0	1 (1%)	1 (1%)	0
Adenosquamous carcinoma			1 (1%)	0	1 (1%)	0	1 (1%)	0	1 (1%)
Medullary carcinoma		1 (1%)							1
Total		99	75	20	59	36	32	63	4
			(75.7%)	(20.2%)	(59.5%)	(36.3%)	(32.3%)	(64.6%)	

Table 2. IHC Profile of Breast Carcinoma Types

Breast cancer types		Total number	Triple positive	Triple negative	ER+/PR+/ HER2-	ER+/PR-/ HER2+	ER+/PR-/ HER2-	ER-/PR-/ HER2+	Not documented
		99	16 (16.1%)	9 (9%)	43 (43.4%)	5 (5%)	11 (11.1%)	11 (11.1%)	4
Invasive ductal carcinoma	I	16	3 (3%)		9 (9%)	1 (1%)	3 (3%)		
	II	46	9 (9%)	4 (4%)	20 (20.2%)	3 (3%)	7 (7%)	2 (2%)	1
	III	21	1 (1%)	4 (4%)	6 (6%)		1 (1%)	9 (9%)	
Ductal carcinoma in-situ		5	3 (3%)		2 (2%)				
Lobular carcinoma in-situ		1							1
Invasive lobular carcinoma		3			2 (2%)				1
Mixed ductal & lobular carcinoma		2			2 (2%)				
Mucinous carcinoma		2			2 (2%)				
Glycogen-rich clear cell carcinoma		1				1 (1%)			
Adenosquamous carcinoma		1		1 (1%)					
Medullary carcinoma		1							1

Table 3. IHC Profile of Breast Carcinoma in Literature

	"Iraq (Runnak et al., 2012)	Tunisia (Kallel et al., 2012)	Lebanon (Esaghir et al., 2014)	UAE (Dawood et al., 2011)	Egypt (Aiad et al., 2014)	Jordan (Sughayer et al., 2006)	SA (Rudat et al., 2014)	SA (current study)
ER+	78.30%	61.20%	74.40%	ND	73%	50.80%	69%	75.50%
PR+	64.20%	51%	69%	ND	63%	57.50%	61.50%	59%
HER2+	20.40%	29.60%	23.80%	ND	37%	17.50%	25.10%	32%
ER+/PR+/HER2-	54.70%	ND	ND	65.80%	55%	ND	57.30%	43.40%
ER+/PR+/HER2+	5.70%	ND	ND	14.30%	23%	ND	15.10%	16.10%
ER-/PR-/HER2+	10.90%	ND	ND	4.90%	14%	ND	10%	11.10%
ER-/PR-/HER2-	12.40%	17.30%	12.30%	10.40%	8%	ND	17.70%	9%
ER+/ PR-/HER2+	ND	ND	ND	ND	ND	ND	ND	5%
ER+/ PR-/HER2-	ND	ND	ND	ND	ND	ND	ND	11.10%

*ND: Not documented

only five cases were HER2+. All forty seven grade II tumors were whichever ER+ or PR+, except two cases were negative for both, while the majority of cases (68%) were HER2-. On the other hand, only 8 (38%) cases of grade III tumors were positive whichever ER or PR, and 10 (47.6%) cases were positive for HER2.

Marker expression status was sorted in six groups. First, sixteen cases (16.1%) of breast carcinoma were ER+/PR+/HER2+ (triple positive), 13 (13.1%) of which were IDC of various grades (I: 3%, II: 9%, III: 1%) and the rest (3%) were of DCIS. Second, 9 (9%) cases were ER-/PR-/HER2- (triple negative), 8 (8%) of which were IDC of grades II and III with equal percentage of 4% for both, the ninth case was adenosquamous carcinoma. Third, Forty three cases (43.4%) were ER+/PR+/HER2-, 35 (35.3%) of which were IDC of different grades (I: 9%, II: 20%, III: 6%) and the rest were 2% for each of DCIS, ILC, mixed invasive ductal & lobular carcinoma, and mucinous carcinoma. Fourth, 5 cases (5%) were ER+/PR-/HER2+ consisted of IDC grade I (1%), and grade II (3%), as well as 1% Glycogen-rich clear cell carcinoma. Fifth, 11 cases (11.1%) were ER+/PR-/HER2-, all of which were IDC of different grades (I: 3%, II: 7%, III: 1%). Sixth, 11 cases (11.1%) were ER-/PR-/HER2+, comprised of grades II and III of IDC (Table 2).

Discussion

Ninety nine cases of breast cancer were contained within the current study with a median age of 53.7 years which is similar to that reported in Arabic countries (Kallel et al., 2012; Aiad et al., 2014). In comparison with females of Western countries, the median age of Saudi females is lower with almost ten years difference (Stead et al., 2009; Sandhu et al., 2010). The results of the present study revealed that remarkable number of patients (53.5%) have lymph nodal metastasis which is consistent with other Asian and Arabic studies (Aryandono et al., 2006; Ambroise et al., 2011; Kallel et al., 2012; Aiad et al., 2014). Whereas the majority of patients, in developed countries, have a negative lymph node status (Taucher et al., 2003; Huang et al., 2005; Stead et al., 2009).

The average size of tumors in the current study was 3.5cm ranged from 0.3-12cm; the size of tumor in sixty three (63.6%) cases was larger than 2cm, which is similar to other Arabic and Asian studies (Aryandono et al., 2006; Azizun-Nisa et al., 2008; Vaidyanathan et al., 2010; Ambroise et al., 2011; Kallel et al., 2012; Aiad et al., 2014). On the other hands, the majority of breast tumors in the western countries are smaller than 2cm, which could be as a result of the frequent early detection and screening programs (Taucher et al., 2003; Duffy et al., 2006).

Status of hormone receptors and tumor responsiveness to hormone therapy are essential factors in the managing of breast malignant tumor and survival of patient. The majority of the studies that assessed the profile of ER, PR and HER2 were conducted in the developed countries. Many studies recorded changes in the histological expression of hormone receptor in different races and ethnic among females residing the United States. Furthermore, racial background and geographical location play important roles in the survival of patients (Pegoraro et al., 1986; Ruder et al., 1989; Gapstur et al., 1996; Joslyn, 2002).

Racial groups who reside United States of America such as native Americans, African Americans, Mexicans, Filipinos, Koreans, Vietnamese, Chinese, Indians had elevated risk up to 3.1 folds of having breast cancer

with ER- and PR- in comparison with non-Hispanic whites (Li et al., 2002). Chu and colleagues documented that breast cancer showed difference in the profile of hormone receptors which were ER+/PR+ (63.9%), ER-/PR- (19.8%), ER+/PR- (12.8%), and ER-/PR+ (3.6%) with white American females (Chu et al., 2001). On the other hand, 48.3% of breast cancers among black American females were ER+/PR+, furthermore, 34.8%, 11.8%, and 5% were ER-/PR-, ER+/PR- and ER-/PR+ respectively (Chu et al., 2001). In Europe, 80.6% of breast cancers of Austrian females were ER+ and 61.3% were PR+ (Stierer et al., 1993). In China, ER was positive in 53%, and 61.6% of breast cancers of premenopausal and postmenopausal females respectively, whereas, positive stain of PR was 51.5% and 46.2%, respectively (Chow and Ho, 2000). Breast cancer of Thai females showed almost similar percentage of hormone receptors expression status to Chinese females (Lertsanguansinchai et al., 2002). Twenty four percent and almost 14% of breast cancers among Nigerian females were ER+ and PR+ respectively (Ikpatt & Ndoma-Egba, 2003).

In the Arabic countries, the frequency of IHC positive hormone receptor and HER2 in addition to IHC subtypes of breast cancer showed great variation (Table 3). Runnak and colleagues in 2012 investigated 514 cases of breast cancer among Iraqi females of different origin Arabic and Kurdish. They found that 73.2% of tumors were ER+ and 64.2% were PR+, while only 20.4% of breast cancer cases were HER2+. Frequency of IHC subtypes of breast cancer were 54.7%. 5.7%, 10.9%, and 12.4% for ER+/PR+/HER2-, ER+/PR+/HER+, ER-/PR-/HER2+, ER-/PR-/HER- respectively (Runnak et al., 2012). In a study investigated Tunisian female breast cancer, ER+, PR+ and HER2+ were present in 61.2%, 51%, and 29.6% of tumors cases in that order, furthermore, triple negative subtype was present in 17.3% of cases (Kallel et al., 2012). Recently a similar study in Lebanon documented frequency rate of 74.4% for positive estrogen and 69% for PR+ while HER2+ was 23.8% and triple negative subtype (ER-/PR-/HER2-) was (12.3%) (Esaghir et al., 2014). In United Arab Emirates (UAE), Dawood and his associates reported the incidence rate of 65.8, 14.3, 4.9, and 10.4 percent for subtypes of female breast cancer ER+/PR+/HER2-, ER+/PR+/HER+, ER-/PR-/HER2+, ER-/PR-/HER- respectively (Dawood et al., 2011). Aiad and colleagues in Egypt reported 73%, 63%, and 37% respectively for ER+, PR+, and HER2+. Moreover, they discovered IHC expression pattern of breast cancer as following 55% for ER+/PR+/HER2-, 23% for ER+/PR+/HER2+, 14% for ER-/PR-/HER2+, and 8% for ER-/PR-/HER2- (Aiad et al., 2014). In Jordan, it was found that 50.8% of tumors were ER+ and 57.5% were PR+, while only 17.5% of breast cancer cases were HER2+ (Sughayer et al., 2006). Recently in Al Khobar in Saudi Arabia (SA), the rates of positive hormone receptors and HER2 in breast cancer using IHC were 69.2, 61.5, and 25.1 percent for ER, PR, and HER in the same order. The research team found also IHC subtypes of breast cancer to be ER+/PR+/HER2- (57.3%), ER+/PR+/HER2+ (15.1%), ER-/PR-/HER2+ (10%), and ER-/PR-/HER2- (17.7%) (Rudat et al., 2014).

Despite the small panel of cases in the present study, the rates of positive IHC staining of ER, PR and HER2 in Saudi female mammary tumors are in harmony and fall in the same range of other female populations such as Austria, Egypt, Iraq, Lebanon, and USA (Stierer et al., 1993; Jatoi et al., 2007; Runnak et al., 2012; Esaghie et al., 2014; Aiad et al., 2014). On the other hand, female's breast cancer in China, Thai, Nigeria, Tunisia, and Jordan showed lower rates of IHC positive stain of hormone receptor and HER2 than the results of the current study (Chow & Ho, 2000; Lertsanguansinchai et al., 2002; Ikpatt & Ndoma-Egba, 2003; Sughayer et al., 2006; Kallel et al., 2012), this might be somewhat elucidated by the age at diagnosis; for example 63.6% of Saudi females contrasted to only thirty nine percent of Jordanian females (Tarawneh et al., 2010) are older than 50 years at breast cancer diagnosis. Furthermore, 69.5% of the ER- Jordanian females were younger than 50 years (Sughayer et al., 2006). Alternative contributing factors to these findings could be biological and lifestyle aspects.

The present study found two IHC patterns of breast cancer ER+/PR-/HER2+ (5%) and ER+/PR-/HER2- (11.1%), which had not been reported in other Arabic studies. The other IHC patterns of breast cancer in our study showed different weight from other Arabic studies (Table 3). The most common IHC pattern in the present study is ER+/PR+/HER2- (43.4%) is lower than other studies by at least (11%). Triple positive IHC pattern of breast cancer in Saudi females is higher than other Arabic female populations except Egyptian females. The rate of ER-/PR-/HER2+ pattern was almost similar in all Arabic studies including ours except the UAE females who have the lowest prevalence (4.9%). On the other hand, triple negative IHC pattern in our study was the lowest in comparison with other Arabic studies (Sughayer et al., 2006; Dawood et al., 2011; Runnak et al., 2012; Kallel et al., 2012; Esaghir et al., 2014; Aiad et al., 2014; Rudat et al., 2014). These differences in IHC pattern rates among Arabic female's populations could be due to racial background deviation or unexpected heterogeneity of breast cancer which might explain the variation in prognosis.

A wide-ranging study of ER, PR, HER2 and additional main clinicopathological parameters as tumor grade and stage, and DNA microarray for the possible involved genes is recommended so as to understand the causes of such differences. This may offer broaden understanding into the etiology of breast cancer in diverse ethnic populations.

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