CORRELATION OF HER2 STATUS WITH HORMONE RECEPTORS ESTROGEN, PROGESTERONE RECEPTORS AND HISTOPATHOLOGIC FEATURES IN INVASIVE BREAST CARCINOMAS: A STUDY ON 117 CONSECUTIVE PATIENTS

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ABSTRACT

***Objective**: Nowadays, Estrogen Receptor (ER), Progesteron Receptor (PgR) and HER2 Receptor are commonly used markers in breast cancer (BC). Multifactorial features, chemical or molecular variety of conditions significant differences ethnic group or racial predilection.*

***Methods**: A total of 117 patients suffering from primary malignant invasive BCs was evaluated. ER, PgR and HER2 conditions are evaluated by the immunohistochemistry method as a routine for all cases of BC, where paraffin blocks of the cancer are exist.*

***Results**: Although the mean age at the time of diagnosis was 51years, ≥40 years of age comprised 96 (82.1%) of cases, 96 (82.1%) were observed invasive breast carcinoma no special type, mean diameter of tumor size 22.2 millimeters, the majority of breast carcinomas cases (47%) have a histologic grade 2, predominantly pathologic stage; pT1c: 43 (36.8%), most positive lymph node; pN1a: 22 (18.8%) identified. There was strong positive staining in ER, PgR and HER2 37.6%, 19.7%, and 21.4% of the cases, respectively. Triple negativity cases was found 25.67%. The presence of tumor size was associated with lymph-vascular invasion and lymph nodes status (P= 0.01, 0.044, P < 0.05).A significant relationship was found between positive ER staining and lymph-node status (P = 0.013). A significant relationship was found between positive HER2 staining and lymph-vascular invasion and tumor focality (P = 0.041, 0.044).*

***Conclusion**: These results show highly different disease, it varies amongst racial or ethnic predilatation. No statistically significant correlation was found between ER and PgR expression and HER2 staining. No association was found between the HER2 expression and histologic types, histologic grade, tumor size, lymph node status.*

***Keywords**: Breast, Cancer, Estrogen, HER2, Progesteron.*

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Introduction

Breast cancer is the most common incident site of women population all over the world. The estimated frequency of breast cancer rate from 25.2% of the total and higher incidence 43.3 per 100 000. Approximately 1.67 million new patients are described cancer worldwide and 521 thousand estimated deaths are because of breast cancer[1]. The difference between prognosis and several cultural or ethnic groups within a society and variable tumor expression HER2 status with hormone receptors. Several factors may occur to breast cancer.

The great majority subject age at menarche, late menapouse, breast density, first degree relative, diet, obesity, mutation and exposure of environmental or radiation[2]. Recently, Estrogen Receptors (ER) and Progesterone Receptors (PgR) showed 81% and 65% patients of breast carcinoma, through immunohistochemical staining respectively[3]. Approximately 26% cases of total breast carcinomas are positive in terms of HER2[4]. ER and PgR are partially slight prognostic variable, but either are powerful predictive factors for replying endocrine therapy. HER2 has been associated with the repetition of transtuzumab/similar chemothera-

py drugs, or lower response endocrine therapy and related prognostic variable for effect in lymph node negative and positive cases[5]. Prognostic and predictive factors of outcome of with or without metastasis lymph node are the breast cancers. In this study, our aim was comparing the invasive breast cancers histopathologic /demographic parameters and hormone receptors or HER2 status.

Materials and methods

In this study, the underwent specimens of cases with breast carcinoma which were taken cross-sectional and paraffin-embedded were examined. The materials were stained with hematoxylin-eosin and immunohistochemistry status for ER (Bio SB, mouse antibody), PgR (Biocare Medical, SP2, antibody clone is a rabbit monoclonal) (percentage of cells with nuclear positivity) and HER2 (ScyTek Laboratories, SP3, rabbit) (circumferential membrane staining). Statistical analysis was performed by using the SPSS software (version 21.0 for Windows). A P value less than 0.05 was considered statistically significant.

Results

Histopathologic Features and Related Factors

A total of 117 newly diagnosed cases were recorded with invasive breast cancer in the Department of Pathology, State Hospital from January 2011 to August 2017 in this study. The all cases with breast carcinoma were comprised of women. The mean age at the time of diagnosis was 51.0 (12.7) years (27 to 85 years).

Patients <40 years of age comprised 21 (17.9%) of cases, while ≥40 years of age comprised 96 (82.1%) of cases. First diagnostic methods and procedure of specimens; 13 (11.1%) cases were ultrasound-guided tru-cut core/needle biopsy, 37 (31.6%) cases of complete excision (less than total mastectomy) and 67 (57.3%) cases of mastectomy (total, with axillary contents) were diagnosis. Between breast cancers, 96 (82.1%) were observed invasive breast carcinoma with any special type (NST, also known ductal carcinoma) (see Figure 1a) and metaplastic carcinoma, invasive cribriform carcinoma, carcinoma with neuroendocrine differentiation, mixed type carcinoma, mucinous carcinoma, apocrine carcinoma each one case (0.9%) (see Table 1).

	Number (%)
Age groups	
<40 years	21 (17.9%)
≥40 years	96 (82.1%)
Procedure of specimens	
Mastectomy with axillary diss.	67 (57.3%
Excision	37 (31.6%)
Tru-cut core/needle biopsy	13 (11.1%)
Histologic cancer types	
Invasive carcinoma (NST)	96 (82.1%)
Invasive lobular carcinoma	10 (8.5%)
Invasive papillary carcinoma	3 (2.6%)
Carcinoma with medullary f.	2 (1.7%)
Others cancers types (total)	6 (5.4%)
Histologic grade (Nottingham)	
Grade 1 (scores 3,4,5)	42 (35.9%)
Grade 2 (scores 6,7)	55 (47%)
Grade 3 (scores 8,9)	20 (17.1%)
Tumor focality	
Single focus	106 (90.6%)
Multiple focus	11 (9.4%)
Ductal Carcinoma In Situ (DCIS)	
No DCIS is present	59 (50.4%)
DCIS is present	58 (49.6%)
Architectural Patterns	
Comedo	4 (3.4%)
Solid	17 (14.5%)
Papillary	3 (2.6%)
Cribriform	6 (5.1%)
Mixed	22 (18.9%)
LCIS	6 (5.1%)
Lymph-Vascular Invasion	
Not identified	98 (83.8%)
Present	19 (16.2%)

Table 1: Relation between cancer type, age groups and rates in cases of histopathologic features.

Tumor size (size of largest invasive carcinoma); mean diameter of all types of cancers 22.2 milimeters (mm) (1.15 to 72 mm). The majority of breast carcinomas cases (47%) have a histologic grade (Nottingham histologic score); 2 (scores of 6, 7) 55 (47%), in situ carcinoma solid or mixed type and pathologic stage; pT1c: Tumor >10 mm but ≤20 mm in greatest dimension 43 (36.8%), positive

lymph node; pN1a: Metastases in 1 to 3 axillary lymph nodes, at least 1 metastasis greater than 2.0 mm, 22 (18.8%) identified. On mean % 62.7 (42 of 67) cases with breast tumor observed with axillary lymph node metastasis and 37% (25 cases) were lymph node negative. The presence of tumor size was associated with lymph-vascular invasion and lymph nodes status (P= .01, .044, P < .05). ER and PgR testing; negative <1% immunoreactive cancer cells, positive immunoreactive tumor cells present (≥1%). Average intensity of staining; Weak, moderate, strong. Sixty-seven (57.3%) cases of breast carcinoma were positive ER (see Table 2).

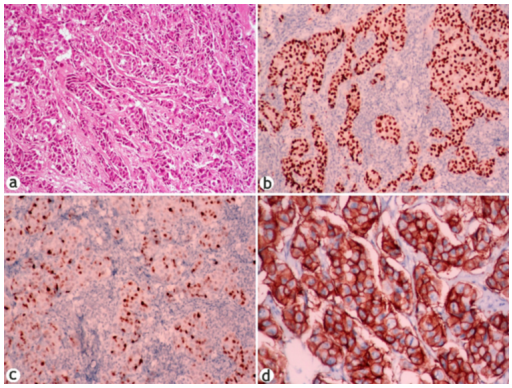

Figure 1: İnvasive breast carcinoma, NST. (**A**) The cancergrow as trabeculae, diffuse sheets, and a mixture of these patterns in addition to less showing gland/tubule formation, staining with hematoxylin-eosin (H&E, 20x objective). Immunohistochemical stains (**B**) Estrogen receptor, diffuse strong nuclear staining. (**C**) Progesteron Receptor, positive, moderate nuclear staining. (**D**) HER2 protein strong complete membranous staining.

In contrast, 50 (42.7%) cases were negative. There was strong positive staining in 37.6% of the cases (44 cases) (see Figure 1b). No association was found between the ER expression and histologic types, histologic grade, tumor size, lymph-vascular invasion (P = .917, .195, .194, .561, P > .05). A significant relationship was found between positive ER staining and lymph-node status (P = 0.013, P < 0.05). The expression of PgR in all patients was as follows; 23 cases (19.7%) had strong staining (see Figure 1c) and 70 patients (59.8%) had no staining or negative (see Table 2). No association was found between the PgR expression and histologic types, tumor size, lymph node status, lypmh-vascular invasion (P= .083, .703, .255, .066, P > .05). Negative (Score 0 or 1+); no staining showed or incomplete, faint present membrane staining in ≤10% or >10% of invasive cancer cells, equivocal (Score 2+); incomplete weak to moderate circumferential membrane staining in >10% or complete, intense, circumferential membrane staining in ≤10% of invasive cancer cells, positive (Score 3+); (complete, intense, circumferential membrane, >10% of invasive cancer cells) (see Figure 1d). The expression of HER2 in all cases was as follows; 25 cases (21.4%) had positive staining score 3+ and 54 cases (46.2%) had no staining score 0+ or 1+ (see Table 2).

Estrogen Receptor (ER)	Number (%)
Negative	50 (42.7%)
Weak	13 (11.1%)
Moderate (Intermediate)	10 (8.5%)
Strong	44 (37.6%
Total	117 (100%)
Progesteron Receptor (PgR)	
Negative	70 (59.8%)
Weak	6 (5.1%)
Moderate (Intermediate)	17 (14.5%)
Strong	23 (19.7%)
N/A	1 (0.9%)
Total	117 (100%)
HER2 Status	
Negative (Score 0+)	54 (46.2%)
Negative (Score 1+)	23 (19.7%)
Equivocal (Score 2+)	11 (9.4%)
Positive (Score 3+)	25 (21.4%)
N/A	4 (3.4%)
Total	117 (100%)

Table 2: Expression for ER, PgR and HER2.

No association was found between the HER2 expression and histologic types, histologic grade, tumor size, lymph node status, (P= .411, .090, .710, .665, P > .05). A significant relationship was found between positive HER2 staining and lymph-vascular invasion and tumor focality (P = .041, .044, P < .05). A significant relationship was found between positive ER staining and PgR staining (P = .042, P < .05). No statistically significant correlation was found between ER and PgR expression and HER2 staining (P = .128, .906, P > .05). In our study, we didn't observe any staining ER, PgR, HER2 in 29 (25.67%) cases with invasive breast carcinoma.

Discussion

Different race/ethnic structures and socio cultural economic conditions may influence receptor status and tumor type[6]. In our study, invasive breast carcinoma of no special type (NST) (ductal, not otherwise specified) type is prevalent in other breast carcinoma types. Another study showed that the immune staining 43.9% of ER and 26.6% PgR was reactive in breast tumor cases in India. Hormone receptors were observed in predominantly negative (56.1% and 63.4% cases)[7]. Recently researcher have demonstrated a high rate of hormone receptor negative patients (46.5%).8 We observed no or negative staining in 50 cases with ER (42.7%) while 70 patients with PgR (59.8%), indicating that the majority of hormone receptor for breast cancer patients had no reactivity. There is also consistent result in the documented English literature. It has recently been documented that ER status is a significant prognosis associated with breast carcinoma. Allegre et al reported ER positivity was related with a favorable long-term clinical course[8,9].

Chariyalertsak et al documented the findings of the study different population ER and PgR lower rates in 36.1% and 45.8% respectively[10]. The same authors reported low grade cancer and related ER positive during ER negative status was found associated to high histologic grade or poorly differentiation. However, current literature recognized that, ER status have little prognostic significance and the ER positive disease course can be relatively indolent, but have revealed no significant the long-term prognosis[8].

In our experience, axillary lymph node positivity correlated with ER positivity. In this study, 42% cases of metastatic lymph node were observed ER over expression. ER+ cases are potential treated as tamoxifen or aromatase inhibitors[11]. More recently, only PR positive expression is not associated with prognosis for ER positive invasive breast tumor[12] and PR no independent prognostic significance[13].

In a different study, which was observed by Keshgegian et al, was found for ER-/PgR+ and ER-/PgR- cases no significant relationship long-term disease-free survival and no metastatic course[14]. In similar, another study reported that the reactivity of ER and PgR was not associated with age of the cases, largest tumor dimension or number of positive lymph nodes[10].

In our study, ≥40 year old women and <40 year old women are compared and >40 year old women showed a higher PR positivity. This finding subject matter investigation agree with those descriptions in the literature[15]. Nordenskjöld et al reported at least %10 positivity of PgR related low recurrence risk after endocrine therapy (tamoxifen) for cases with ER+ cancers[16]. We found, the mean size of tumors immune reactivity ER+ was 23 mm versus 21 mm for those PgR+ reactivity. On the other hand, cancers with positivity score 3+ HER2 immune reactivity mean size of tumors were 23.8 mm.

In our study, the results weren't correlated with literature study[17]. Mudduwa detected HER2 expression in 19.1% (26/136) of invasive breast cancer, in this study more frequent cases HER2 status were negative[18]. HER2 positivity in our study was found 21.4% (score 3+) and researcher showed results are relationship with our study. HER-2 was expressed (immune staining scores of 2+ or 3+) in 30.8% of breast cancers (36/113)[19]. Patients from HER2 score 3+ reactivity suitable for transtuzumab treatment and cases form score 2+ considered fluorescence in situ hybridization (FISH) analysis[20].

Vasudha et al reported ER, PgR and HER2 negative stained of breast cancer 51.73%, 62.4% and 72.72%, respectively[21]. Dent et al reported 180 of 1.601 cases (11.2%) triple negative breast cancer (TNBC)[21]. Carey et al identified TNBC (basal-like breast cancer subtype) low to high incidence ratio different ethnical groups. In this study, African American women and non-African American women have been observed. High rate African American women 39% while non-African American and African American women and rate low incidence of 16%, 14% respectively[22]. The rate of TNBC results were consistent with the literature. The rates of hormone receptor and HER2 negative in various researcher are consistent with findings in the literature. TNBC may be detected in 10-17% of all invasive breast carcinoma. TNBC related worst prognosis, high recurrence rate and causes of death in this disease has occasionally been reported[23].

In this study, we describe any TNBC relation with the lymph node metastasis, lympho-vascular metastasis or pathologic tumor staging. Dent el al reported similar result, in the study count of lymph node positive group mild higher in the TNBC cases compared with the any positive markers group[21]. On the other hand, previously investigation have reported no association between hormone receptor

status and axillary lymph node metastasis in invasive breast tumor[24]. Although some investigators have regarded relationship HER2 status and histologic grade. The authors a recent series of female breast cancer was found HER2 over expression ratio of of 3.9%, 20.4%, and 38.9% in cancers of histologic grade 1, 2, and 3[25].

In our study lymph-vascular invasion (LVI) present cases predominantly HER2 negative or equival (63.2%) and only 7 cases was score 3+. In our study lymph-vascular invasion (LVI) present and lymph node positive (LN) cases, large size tumors was also significantly higher compared LVI not identified and LN negative patients. We found that LVI present and LN positive cases mean diameter size of largest invasive carcinoma 31.7 mm, 28 mm while later cases mean diameter 20 mm and 18.9 mm observed. HER2 overexpression which we have found, was not related with histological tumor grade and TNBC wasn't related with lymph node metastasis, lympho-vascular metastasis or pathologic tumor staging.

In brief,In our study, reactivity of ER and PgR was not associated with age of the cases, largest tumor dimension or number of positive lymph nodes. These results show highly different disease, it varies amongst racial or ethnic predilatation.

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