

Hormone receptor status of breast cancer in patients of different age groups, lymph node status histological type and tumor grade, an experience at King Fahad Medical City, Riyadh

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Abstract:

Aim: To see the relationship between receptor status and age of patients, tumor grade, histological type and lymph node involvement in breast cancer patients.

Methods: A retrospective review of histopathological reports of breast cancer cases that presented to KFMC over 5 years was made.

Results: Total of 345 patients were included. 63% of them were triple positive. 35% were ER/PR negative. 54% ER/PR positive and 11% were either ER or PR positive. Patients >45yrs were usually ER/PR positive 72.7% as compared to patients of age <45yrs who had more ER/PR negative tumors 39.4% ($p=0.044$). On comparison of ER/PR status with grade we found that ER/PR negative tumors were high grade and ER/PR positive were mostly low grade ($P=0.001$). We also found that HER2 negative tumors were mostly low grade 75% ($p=0.043$). On comparing histological type of tumors with receptor status we found that patients with invasive ductal cancer were mostly ER/PR Negative 91.3% as compared to ER/PR positive 87.8%. No correlation was found between receptor status and lymph node status ($p=0.961$).

Conclusion: Most of our breast cancer patients are triple positive. Young patients have more receptor negative tumors as compared to older patients. High grade tumors are mostly receptor status negative as compared to low grade ones.

Keywords: Hormone receptor of breast cancer, ER, PR, HER2

Introduction:

Breast carcinoma is the most common malignancy diagnosed among women worldwide, it accounts for 22% of all female cancers¹. A crucial development in the evaluation of breast carcinoma has been the realization that the presence of hormone (estrogen and progesterone) receptors in the tumor tissue correlates well with response to hormone therapy and chemotherapy.^{2,3}

The human epidermoid receptor (HER-2) proto-oncogene is amplified and as a result over expressed in 25% to 30% of human breast cancer and is usually associated with tumor aggressiveness and poor prognosis.⁴ In breast cancer, several studies identified the value of analyzing HER-2/neu as an approach to predict the response of

individual tumors to chemotherapy as well as in the use of recombinant humanized antibodies (trastuzumab).

Prognosis and management of breast cancer are influenced by the classic variables such as histologic type and grade, tumor size, lymph node status, status of hormone receptors estrogen receptors (ER) and progesterone receptors (PR) of the tumor and HER-2 status.^{5,6}

Previous studies have shown survival advantages among women with hormone receptor positive tumors relative to women with hormone receptor negative tumors.^{7,8} However, few studies have evaluated variations in the risks of breast cancer-specific mortality across ER/PR status by either demographic or clinical characteris-

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tics⁹. Therefore, we performed this retrospective review to elucidate the relationships between various prognostic indicators in breast cancer and provide knowledge regarding the prognostic utility of ER/PR status by demographic and clinical tumor characteristics.

Materials and methods:

This is a retrospective review, performed on 420 breast cancer patients. All breast cancer cases of any age that presented to the General surgery or oncology department of King Fahad Medical City Riyadh from January 2007 till January 2012 were included in the study. The histopathology reports of all these patients were reviewed and data including the age of the patients, histological type, grade of tumors, estrogen, progesterone and HER 2 receptor status and lymph node involvement was collected using a standard proforma.

All the slides were reviewed in the pathology laboratory of King Fahad medical city using the same method, thus eliminating inter laboratory error.

Estrogen and progesterone receptors were considered negative when concentration was below 10%. Her2 over expression was considered positive when complete and intense membrane was observed in 10% of tumoral cells by Hercep test. FISH was carried out on all tumors with Hercep test +2; tumors with a score of +3 by IHC or gene amplification by FISH were considered as HER2 positive. Those patients who had incomplete data were excluded from the study. The reason for having incomplete data was either missing files or because the patients had surgery done outside with no slides available or no surgery done at all, due to which we had no information on lymph node involvement. Statistical Analysis was done by Fisher's exact test or Chi-square test. P value of <0.05 was considered significant.

Patients were divided into two groups according to their age taking 45 the average age for menopause in Saudi Arabia.

Grade of the tumor was defined by the Modified Bloom Richardson grading, into Grade I well differentiated, Grade II moderately differentiated and Grade III poorly differentiated.

Our study was in accordance with the rules and regulations of the ethical committee of King Fahad Medical City (KFMC) and started after approval from the institutional review board.

Results:

We reviewed a total of 420 files out of which 75(17.8%) patients were excluded due to incomplete data. 35% (n=127) of our patients had ER/PR negative tumors. 54% (n=198) had ER/PR positive disease and 11%(n=40) had either ER or PR positive tumors respectively. 53.5% (191) of the included patients were HER2 positive. So a total of 63 % (218) of our patients were triple positive (Luminal B), while 37 % (127) had triple negative tumors respectively. Figure 1.

Of the total 345 patients included 120(34.7%) were <45 yrs and 225 (53.5%) were >45 years old. Younger patients >45yrs were usually ER/PR positive 72.7 % (n=144) as compared to patients of age <45yrs who had more ER/PR negative tumors (n=50) 39.4 % (p=0.044). However on comparing age with Her2 status no significant difference was found in the two groups (p=0.075). Table 1.

Most of the tumors were of grade II i.e. 53.9 % (n=186) followed by grade III i.e. 40.6 % (n=140). On comparison of ER/PR status with grade of tumor we found that more ER/PR negative tumors were high grade i.e. grade III 62.1

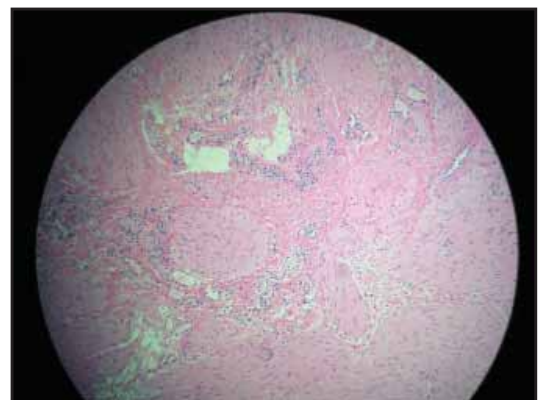


Figure 1: Frequency of various hormone receptors

Table 1: Comparison of Receptor Status with Age of Patient

Receptor status	Age <45	Age > 45
ER & PR NEG	50(39.4%)	77(66.7%)
ER OR PR POS	16(40.0%)	24(60%)
ER& PR POS	54(27.3%)	144(72.7%)
HER 2 POS	56%	53%
HER 2NEG	44%	47%

%(n=77). While low grade tumors were mostly ER/PR positive ($P=0.001$). We also found that HER2 positive tumors are mostly Grade III 57.8 %(n=85) while those with HER2 negative are mostly low grade 75 %(n=12) ($p=0.043$). Figure 2.

Of all the patients included 93% (n=321) had invasive ductal cancer, 6.7 % (n=23) had invasive lobular cancer and 5.5% (n= 19) had other histological types i.e. ductal carcinoma in situ etc. On comparison of the histological type of tumors with receptor status we found that patients with invasive ductal cancer were mostly ER/PR Negative 91.3 % (n=116) as compared to ER/PR positive 87.8 % (n=173). While patients with invasive lobular carcinoma had ER/PR positive tumors mostly (n= 16) i.e. 8.1% as compared to negative (n=2) 1.6%, ($p=0.003$).

Among the 420 files reviewed only 251 (59.8%) had information about the lymph node status of the tumor and no significant correlation was found between receptor status and lymph node status ($p=0.961$). As shown in the table 1.

Discussion:

Breast cancer is a heterogeneous group of tumors and is the most common malignant tumor among female malignancies.⁹⁻¹¹ Ovarian steroid hormones are necessary for the normal development of the female breast and an imbalance precipitates neoplastic process.^{9,12} Previous studies have shown survival advantages among women with hormone receptor-positive tumors relative to women with hormone receptor-negative tumors^{9,13-15}. It has been shown that PR status is associated independently with disease-free and overall survival, in that ER+/PR+ patients have a better prognosis than ER+/PR- patients.¹⁴ It has been established that increased expression

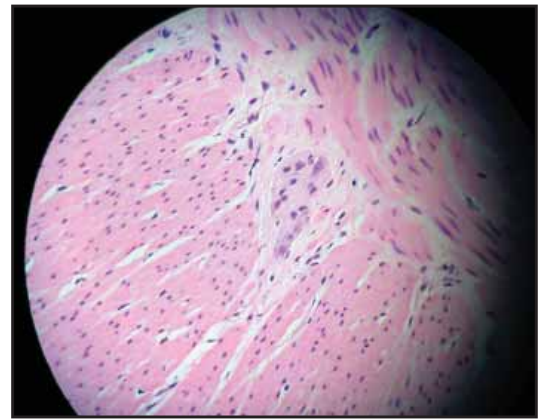


Figure 2: Comparison of ER/PR status with tumor grade ($p=0.001$)

of HER2 oncoprotein or its corresponding gene amplification have been associated with an aggressive phenotype of breast cancer in terms of disease-free and overall survival.^{14,16-17} HER-2/neu is analyzed as an approach to predict the response of individual tumours to chemotherapy as well as in the use of recombinant humanized antibodies (trastuzumab) to the HER-2/neu protein in the active management of patients with metastatic breast disease.⁴

35% (n=127) of our patients had ER/PR negative tumors and 54% (n=198) had ER/PR positive disease. Similar rates were shown by Barnes et al (50 %ER/PR +).¹⁸ In contrast Suvarchala et al in 2011 reported ER+/PR+ to be 32.81% and ER-/PR- 42.19% in Indian women respectively.¹⁵ Similarly, Desai et al (48%) and Dutta et al (66%) obtained a high incidence of steroid receptor non reactivity in breast cancer^{19,20}. There appears to be variation in steroid receptor positivity in the Asian population. Differences in ER and PR status by race, particularly between black and white are known. Chariyalerstak et al reported similar observations with lower rates of ER and PR reactivity in breast cases in Thailand²¹. So Saudi women have higher incidence of ER/PR positive tumors, this observation was also reported in a study on 852 breast cancer women by Satti et al in 2011.²²

Triple negative disease, which in most studies shows frequency between 10% and

24%^{23, 24} were found in 37% of our patients.

However, this finding is in line with previous observations by Al-Tamimi et al²⁵ in whose series the triple-negative group comprised 39%, suggesting that the distribution of molecular subgroups of breast cancer is different in middle-eastern as opposed to western populations.

Many studies from Europe and America have been reported showing that young age at diagnosis is as an independent predictor of poor survival²⁶. Many studies have shown that young women had a tendency to have larger tumor sizes, more positive lymph nodes, more negative hormone receptors, higher tumor grades than older women.^{3, 14, 17, 27} Similarly our study showed that younger women had more receptor negative tumors as compared to older women ($p=0.044$). Suvarchala et al¹⁵ and Pourzand et al²⁷ also reported same findings. Kwan et al²⁸ also found a higher frequency of younger women with the triple negative subtype. Satti et al²² failed to show any difference in hormone receptor sensitivity among old and young subgroups.

Our study showed that the reactivity for steroid receptors was observed to decrease with increasing grade. Grade III tumors were more receptor status negative as compared to grade I and II tumors. ($p=0.001$). This correlates well with other studies done by Madhuri et al²⁹ in 2010, Suvarchala et al¹⁵ in 2011, Pathak et al⁹ in 2011 who also showed the same inverse relationship between receptor status and increasing tumor grade.

A direct relationship was found between ER/PR positivity and ductal carcinoma type. Majority of ductal and lobular carcinoma were ER/PR positive, whereas other histological types were ER/PR-. This has been the experience reported previously by Satti and Nadji et al^{22, 30}. In contrast, the reverse was observed for HER2 positivity when considering IDC type and histological grade, with 75% of grade I and 42% grade III were HER2 negative. From above findings it is obvious that the higher the grade, the more likely that ductal carcinoma will be HER2 positive and ER/PR.

No strong correlation could be established between receptor status and lymph node involvement may be because of the sample size being small. Pourzand et al²⁷ in 2011 and Azizun-Nisa et al in 2008¹¹ also failed to establish any correlation between lymph node status and receptor status.

Conclusion:

In conclusion, this study from a large oncology referral centre of Saudi Arabia demonstrated clearly that most of our patients were ER/PR positive and triple positive (luminal type B). Young patients tend to have more receptor negative tumors as compared to older patients, suggesting aggressiveness of disease. A clear correlation between receptor status and grade of tumour (being high grade tumors are mostly receptor status negative), but failed to identify a definitive relationship between receptor status and lymph node involvement. This study illustrates the changing trends of immunohistochemical profile of breast cancer in the region and will serve as one of the baseline studies for future work and breast cancer management strategies.

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