Assessing the Association between PR and Different Clinico-Pathologic Breast Cancer Features

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Abstract

Background: Breast cancer is the most common malignancy in females and characterized by high morbidity and mortality. A plethora of data supporting the role of hormone receptors in breast cancer, exist. The majority of these data has focused on the roles of estrogen receptor (ER) and epidermal growth factor receptor (Her2). Data regarding the role of progestin receptor are not as prevalent as ER receptor. This study aims at assessing the association between PR and different clinico-pathologic breast cancer features.

Methods: Clinicopathologic and demographic data from a cohort of 298 patients who referred to King Hussein Medical City (KHMC) between 2007 and 2014 were retrieved and analyzed.

Results: The average age of the cohort under investigation was 51.2 years with most of the patients having intraductal tumors. Two hundred and three patients had PR positive tumors (68%). Patients with PR negative tumors were more likely to have lymphovascular invasion ($\chi2=4.6$, $p=0.03$). Additionally, patients with PR positive tumors were more likely to have ER positive tumors ($\chi2=102.7$, $p<0.0001$) and Her2 negative tumors ($\chi2=11.5$, $p=0.001$). Interestingly patients with PR positive and negative tumors did not differ in age, tumor size or number of lymph nodes involved.

Conclusion: Progesterone receptor status affects different clinico-pathologic breast cancer features. The exact role of PR and its impact on breast cancer progression should be assessed in a larger study.

Key words: Breast cancer, progesterone receptor, lymphovascular invasion

Introduction

Breast cancer is the most common type of cancer among females (1). Every year, about 246,660 females will be diagnosed with breast cancer (1). Breast cancer is considered the second leading cause of cancer related mortality in the United states accounting for about 40,450 deaths in 2016 (1).

Hormone receptor and Her2 status are well established prognostic factors in breast cancer patients (2-4). Additionally, they have an essential role in selecting treatment modality (2). The majority of data on the association between hormone receptor expression treatment modality and prognosis are derived from studies with a main focus on estrogen receptor (ER) (2-4). Data on the possible interaction between progesterone receptor and outcome is still limited. Nishimukai suggested a role of PR in prognosis in postmenopausal breast cancer patients (5). The role of PR as a possible prognostic factor and its interaction with different clinicopathologic data outside this age group is still unknown. Accordingly, we are aiming at assessing the association between PR and different clinico-pathologic breast cancer features.

Methods

Patients with an established diagnosis of invasive breast cancer who underwent surgery in the King Hussein Medical City (KHMC), Royal Medical Services, Jordan between the years 2007 and 2014 were recruited in this study. The diagnosis of invasive breast cancer was performed using tumor samples from the resected tumors in the pathology department in the KHMC. Tumor characteristics for breast cancer patients were extracted from relevant pathology reports issued by Pathology Department at RMS at time of diagnosis of disease. Reports included details of the clinico-pathologic characteristics including tumor histologic type and size, ipsilateral axillary lymph node status, lymphovascular invasion, histologic grade, and detailed receptor status. Expression status of estrogen receptor (ER) and progesterone receptor (PR) was determined using immunohistochemical methods. Activity greater than 1% was considered positive for each hormone receptor. Evaluation of Human Epidermal Growth Factor Receptor 2 (HER2) was assessed by immunohistochemical analysis in which scores of 0 or +1 were considered negative while a score of +3 was considered positive for HER2 receptor overexpression. For unclear results of immunohistochemical analysis (+2), fluorescence in situ hybridization (FISH) analysis positive for gene amplification was considered to be positive for HER2 expression. The study was approved by the ethics committee in the Royal Medical Services (approval number: 2/2018/ (37)).

Statistical Analysis:
All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 22.00 (SPSS Inc., Chicago, IL). Chi square test was used to assess significance between dichotomous data. Statistical difference between continuous variables was detected using either student t-test or ANOVA as appropriate. A p value of less than 0.05 was considered significant

Results

Patients' demographics:
In this study we recruited 298 patients with invasive breast cancer. The average age of the cohort under investigation was 51.2 years (51.2±12.97). About half of the patients (163 patients) were 45-65 years of age at the time of presentation. Patients younger than 45 years of age accounted for about 34.4% (99 patients) of the study population. Almost half of the sample presented with intermediate grade tumors. Progesterone receptor was detected in 203 (68.1%) of the patients. On the other hand, estrogen receptor was detected in 215 (72.1%) patients. Table 1 (next page) provides full demographic data of the patients.

Progesterone receptor presence was not related to the age at presentation, tumor size or number of lymph nodes involved:
Patients with different progesterone receptor status at the time of presentation were similar with regard to the age on presentation (Figure 1 A). The average age at presentation in patients with progesterone receptor positive tumors was about 50 years of age which was similar to what is observed in patients with progesterone receptor negative tumors. Similarly, the size of the tumor (3.9 vs. 4.2) as well as the number of involved lymph nodes (4 vs. 5) were similar between patients with progesterone receptor positive tumors and progesterone receptor negative tumors (Figure 1 B and C; respectively).

Patients with PR negative tumors were more likely to have lymphovascular invasion
At the time of presentation, about 45% of the patients who had lymphovascular invasion had a PR negative tumor. In contrast patients who had PR positive tumors constituted more than 70% of the patients ($\chi2=4.6$, $p=0.03$) (Figure 2A).

PR negative tumors are more common in high grade tumors
The majority of patients (80%) who presented with either low or intermediate grade tumors had PR positive tumors (Figure 2 B). This percentage is dramatically reduced in patients with high grade tumors. About 50% of patients who had high grade tumor did not have PR expression ($\chi2=80.6.7$, $p<0.0001$).

PR negative tumors were more likely in patients with ER negative tumors
The expression of PR was more common (90%) in patients with ER positive tumors (Figure 3 A). At the same time, about 80% of patients who had ER negative tumors had a concomitant lack of PR ($\chi2=102.7$, $p<0.0001$).

PR negative tumors were more likely with Her2 negative tumors
About half of the patients who had Her2 positive tumors had PR positive tumors (Figure 3 B). In contrast, the majority of patients (70%) who had her2 negative tumors did not have detectable concomitant PR expression ($\chi2=11.5$, $p=0.001$).

Table 1: Population Characteristics

Characteristic		n (%)
Age (years)		
	≤45	99 (34.49)
	45-65	163 (47.39)
	≥65	25 (18.12)
LVI		
	Yes	158 (53)
	No	140 (47)
PNI		
	Yes	73 (24.5%)
	No	224 (75.5%)
Histologic grade		
	High	116 (41.6)
	Intermediate	137 (49.1)
	Low	23 (8.2)
Number of involved lymph nodes		
	0	48 (28.2)
	1-3	107 (35.9)
	≥4	143 (64.9)
Estrogen Receptor		
	Yes	215 (72.1)
	No	83 (27.9)
Progesterone Receptor		
	Yes	203 (68.1)
	No	95 (31.9)
Her2		
	Yes	65 (21.8)
	No	233 (78.2)

Figure 1: The association between different clinical parameters and progesterone receptor expression status. Patients with different PR expression status had similar age at presentation (A), tumor size (B) and number of involved lymph nodes (C). data represent mean±SEM.

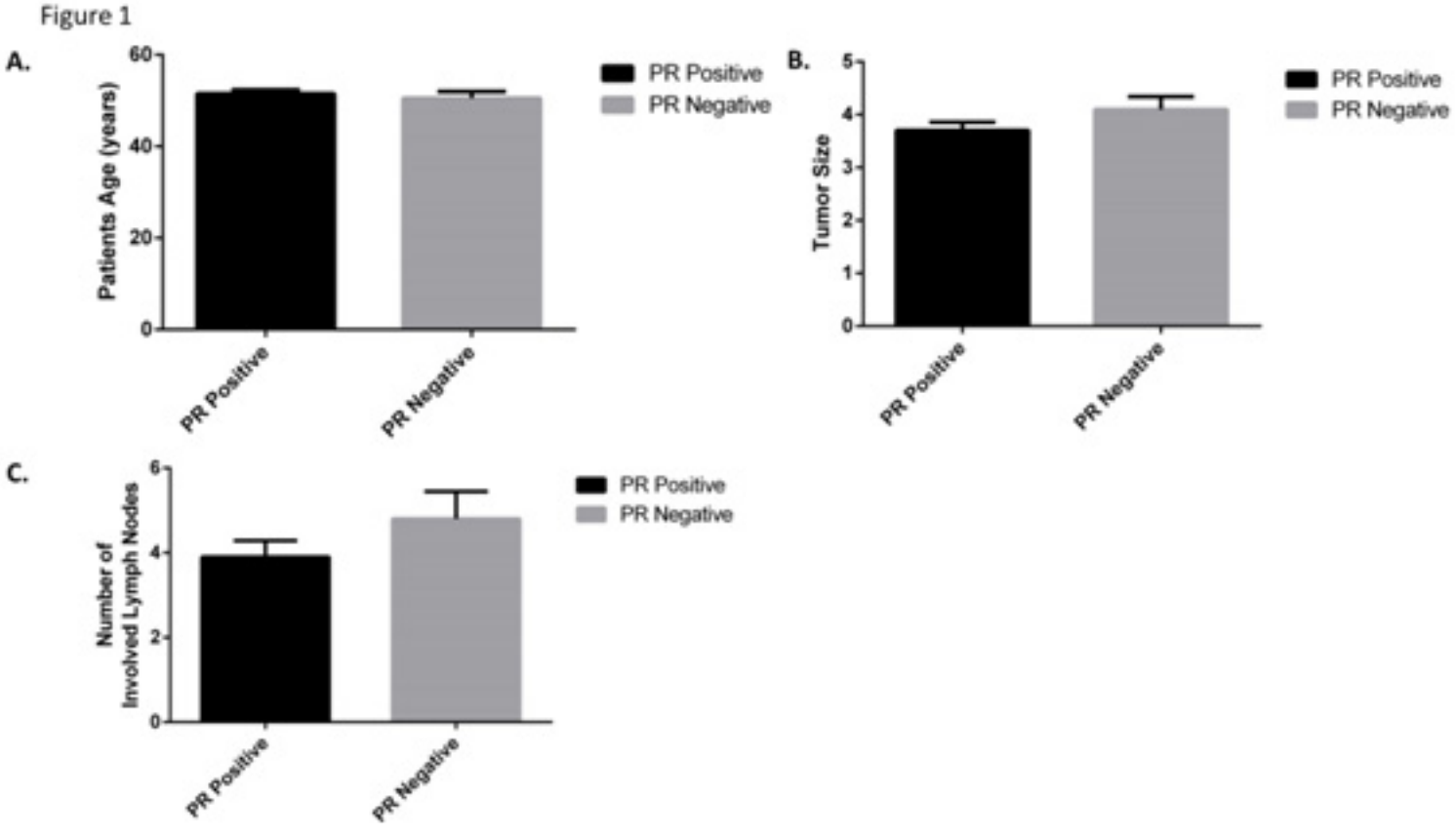


Figure 2: The association of PR expression and pathologic parameters. Patients with PR negative tumors were more likely to have lymphovascular invasion (A) and to present with high grade tumor (B). Data represent the percentage of the patients in each class.

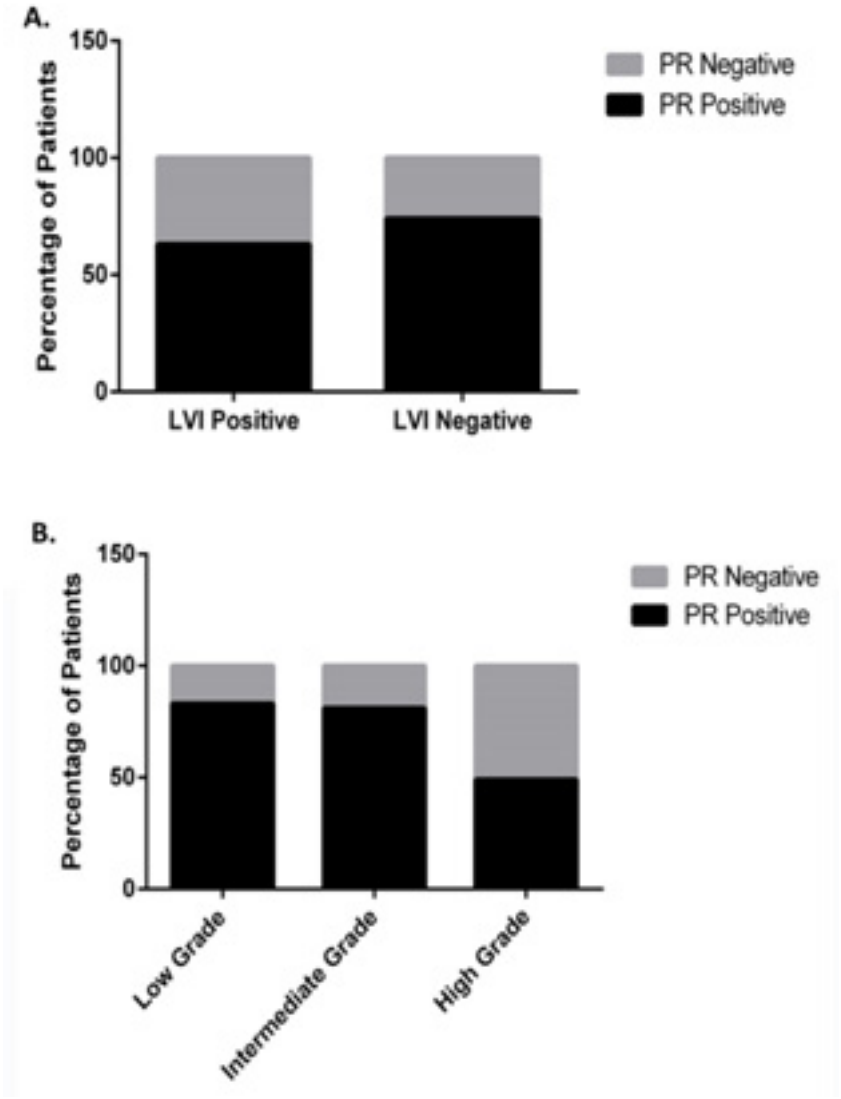
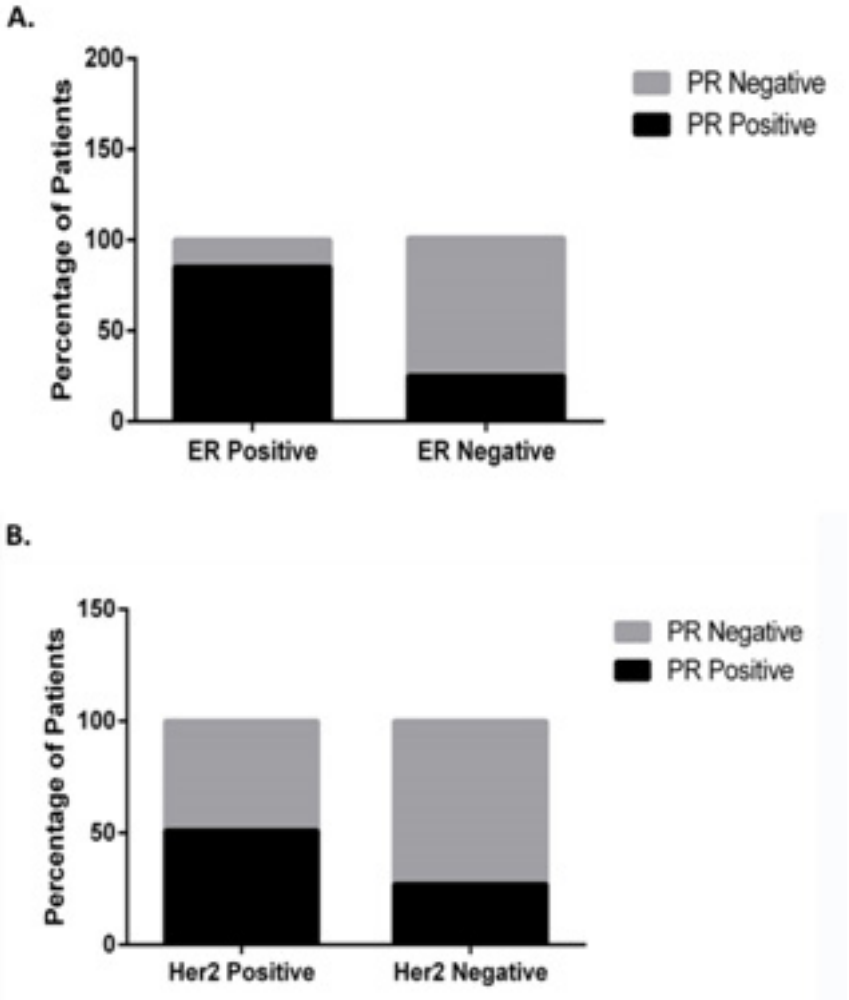


Figure 3: The association between PR expression status and ER and Her2 expression.
Patients who had PR negative tumors were more likely to have ER (A) and Her2 negative tumors (B). Data represent the percentage of the patients in each class.



Discussion

The aim of this study was assessing the association between PR and different clinico-pathologic breast cancer features in patients with invasive breast cancer. The expression of PR did not differ among patients with comparable tumor size, number of lymph nodes involved and age at presentation. In contrast patients who had PR negative tumors, were more likely to have lymphovascular invasion, tumors with higher grades, ER negative tumors, and Her2 negative tumors.

Our data did not detect a relationship between tumor size, number of involved lymph nodes, and the age at the time of presentation with the expression of PR. Similarly, Arpino et al. did not detect a relationship between tumor size and lymph node involvement in both patients with sporadic and familial breast cancer (6). In contrast, Nishimukai et al. reported that patients with PR negative tumors were more likely to have larger tumor sizes (5). This discrepancy might be related to the differences in the populations addressed in these two studies. The population assessed by Nishimukai et al., was postmenopausal breast cancer patients (5). In our study, we included patients without regard to their menopausal status and a good proportion of patients in our study were younger than the age of menopause.

The association between lymphovascular invasion and outcomes in patients with breast cancer is well established (2-4, 7-9). Patients who had lymphovascular invasion at the time of presentation are expected to have poor outcome as compared to patients without lymphovascular invasion (2-4, 7, 9). In this study, our results suggest an association between lymphovascular invasion and the lack of PR expression. Similarly, Marinho et al. reported a negative association between ER, PR status and LVI (10). On the other hand, Ugras et al. reported that lack of hormone receptors as well as Her2 receptors were associated with lower incidence of lymphovascular invasion (4). In their study, their focus was on patients with triple negative tumors, which constitutes a totally different type of breast cancer.

Data from our study suggest that patients with PR negative tumors are more likely to present with high grade tumors. In postmenopausal women, lack of PR expression was shown to be associated with poor outcome in terms of disease free survival (5). This association was not detected in premenopausal women with breast cancer. In this study we demonstrated that PR expression status may predict a more aggressive tumor type at the time of presentation.

Our results suggest a co-regulation of ER, HER2 and PR expression. Patients with PR negative tumors were more likely to be ER negative. Similarly, Nishimukai et al. reported that patients with low PR expression had lower ER expression (5). Moreover, Howlader et al. reported similar findings on the relationship between the expression of PR, ER and Her2 in data derived from a US based database (11).

In conclusion, our data suggest an association between PR expression and different breast cancer clinicopathologic data. Additionally, lack of PR expression was associated with predictors of poor prognosis and outcome. More studies are required to establish the favorable effect of progesterone receptor expression on prognosis and outcome among breast cancer patients.

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