Original Article

Association of Estrogen and Progesterone Receptors with Clinicopathological Prognostic Factors in Breast Cancer

Ali Abdul Hadi Abdul-Kareem, Qahtan A. Mahdi[1]

Departments of Surgery, Imamain Al-Kadhumain Medical City, [1]Collage of Medicine, Al-Nahrain University, Baghdad Iraq

Abstract

Background: The detection of the estrogen receptor (ER) and progesterone receptor (PgR) in women with breast cancer (BC) is considered a crucial step for prognostic evaluation and treatment choice in clinical practice. **Objectives:** This study aimed to evaluate the expression of the hormonal receptors (ER and PgR), their distribution, and their association with clinicopathologic prognostic parameters in a sample of Iraqi women with BC. **Materials and Methods:** The paraffin-embedded blocks from a total of 80 women diagnosed with primary invasive breast carcinomas with BC were examined by immunohistochemistry to assess the expression of ER and PgR status. Demographic and clinical data were collected from each patient in the preformed questionnaire. The association of steroid receptor expression with clinicopathologic parameters was assessed using binary logistic regression. **Results:** Among 80 BC women involved in the study, 54 (67.5%) and 39 (48.75%) had high expression of ER and PgR, respectively. High ER expression was significantly associated with older age (odds ratio [OR] = 4.8, 95% confidence interval [CI] = 1.16–19.81, $P = 0.03$), postmenopausal status (OR = 3.6, 95% CI = 1.25–10.33, $P = 0.015$), smaller tumor (OR = 0.27, 95% CI = 0.09–0.75, $P = 0.01$), and with noninvolvement of lymph node (OR = 0.11, 95% CI = 0.02–0.51, $P = 0.005$). High PgR expression, on the other hand, was significantly associated with older age (OR = 4.44, 95% CI = 1.02–19.39) and postmenopausal status (OR = 3.13, 95% CI = 1.24–7.88, $P = 0.016$). Concomitant overexpression of both receptors was significantly associated with postmenopausal status and noninvolvement of lymph nodes. **Conclusion:** High expression of ER and PgR seems to be a good prognostic indicator because it was associated with less aggressive tumors.

Keywords: Breast cancer, expression, hormonal receptors, prognosis

Introduction

Breast cancer (BC) is the most common cancer in women worldwide and one of the leading causes of cancer-related deaths in women. For the majority of women with BC, the tumors show biological expression of receptors for estrogen and progesterone, hormones that are known to promote growth and proliferation of the tumor cells.[1] In the past 50 years, drugs have been developed to modulate the binding of estrogen to its receptor and bring about significant improvement in survival for the vast majority of patients with estrogen receptor (ER)-positive BC. It was noted that the removal of the ovaries of women with BC led to improved survival in a considerable proportion of patients. However, the mechanism behind this improvement remained obscure, and it was thought to be due to the interruption of nerve connections between the ovaries and the breast.[2] The discovery of receptors for estrogen and progesterone in breast tissue in the 1960s provided the evidence for a classical ligand-receptor pathway in which breast epithelial cells respond to the hormonal influences of estrogen and progesterone.[3]

This study aimed to evaluate the expression of the hormonal receptors (ER and progesterone receptor [PgR]), their distribution, and their association with clinicopathologic prognostic parameters in a sample of Iraqi women with BC.

Materials and Methods

Study design and patients

The is a prospective study which included a total of 80 women diagnosed with primary invasive breast carcinomas at

Address for correspondence: Dr. Ali Abdul Hadi Abdul-Kareem, Imamain Al-Kadhumain Medical City, Baghdad Iraq.
E-mail: alibarood2019@gmail.com

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Al-Imamain Al-Kadhumain Medical City, Baghdad, Iraq, during the period from November 2018 to December 2019. The histolopathological diagnosis was performed on paraffin-embedded breast tissue blocks sampled from 23 (28.75%) fine-needle aspiration, 14 (17.5%) mastectomies, and 43 (53.75%) lumpectomies. On each sample, the histopathologic type and the Nottingham grade of the tumor were determined according to the criteria of Elston and Ellis.[4]

Eligible subjects were women older than 18 years having invasive BC in one or both breasts, pre- or postmenopausal.

Estrogen receptor/progesterone receptor immunohistochemical analysis

The immunohistochemical analysis was performed on 3 μm thickness of breast tissue sections. Tissue sections were deparaffinized and heated in the drying oven BINDER ® (BINDER Company, Tuttlingen, Germany) for at least 12 h at 600°C to unmask the antigenic sites. The sections were stained using the Ventana BenchMark® GX in automatic mode (Ventana Medical Systems Inc., Tucson, AZ, USA) for the assessment of ER and PgR status. The antibody clones were monoclonal, developed in rats, consisted of SP1 for the ER and 1E2 for the PgR, and manufactured by Ventana Medical Systems, Inc.

Staining assessment of estrogen receptor/progesterone receptor

The visual analysis through the optic microscope allowed to evaluate the staining intensity (weak, moderate, and intense) and the percentage of tumor cells showing a nuclear immunostaining for ER and PgR (range: 0%–100%). According to the American Society of Clinical Oncology/College of American Pathologists guideline, tumors having 1% or more invasive BC cell staining were regarded as positive.[5] The immunostaining intensity and the percentages of stained cells for ER and PgR were reviewed independently by two pathologists. For the purpose of this study, the percentages of tumor cell nuclei positively stained for ER and PgR were considered. Demographic data (age and menopausal status), clinical data (histological type and tumor grade), and the status of ER and PgR were collected from each patient in the preformed questionnaire.

Statistical analysis

Data were collected in an Excel database from Windows 8 (Microsoft Corporation, Redmond, WA, USA) and analyzed with Statistical Package for the Social Sciences software version 25 (SPSS, IBM Company, Chicago, IL 60606, USA). A binary logistic regression test was used to analyze associations between classic clinicopathologic parameters (menopausal status, histological type, and tumor grade) with steroid receptor expression. Comparison between different ER/PgR combinations was performed using the Chi-square test. $P < 0.05$ was considered statistically significant.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. A written consent from each participant was obtained before data collection after explaining the aim of the study.

Results

Demographic and clinical characteristics of the patients

The mean age of the patients was 61.18 ± 11.4 years. Stratifying of the age into groups revealed that younger age (≤40 years) accounted only for 13.75%, while 50% of the included women were over 50 years old. Slightly more than half of the patients (57.5%) were premenopausal women. The vast majority of histopathological type was IDC accounting for 90% of cases, while ILC represented only 10% [Table 1].

Proportion of estrogen receptor expression

Out of 80 BC women involved in the study, histopathological examination revealed that 54 women (67.5%) had high expression of ER, while the other 36 (32.5%) showed low ER expression.

Proportion of progesterone receptor expression

High PgR expression was confirmed in 39 women (48.75%) versus 41 women (51.25%) had low PgR expression.

Association of estrogen receptor with demographic and clinical characteristics of the patients

Four factors were significantly associated with the high expression of ER [Table 2]. About 60% of women with high ER expression were over 50 years old compared with only 30.77% of those with low ER at this age (odds ratio [OR] = 4.8, 95% confidence interval [CI] = 1.16–19.81, $P = 0.03$).

Table 1: Demographic and clinical characteristics of the patients ($n = 80$)

Variables	Frequency (%)
Age (years)	
≤40	11 (13.75)
40-50	29 (36.25)
>50	40 (50)
Menopausal status	
Premenopausal	46 (57.5)
Postmenopausal	34 (42.5)
Pathological type	
IDC	72 (90)
ILC	8 (10)
Tumor size	
T1	58 (72.5)
T2	22 (27.5)
Lymph node status	
N0	44 (55)
N1	26 (32.5)
N2	10 (12.5)
Pathologic stage	
I	24 (30)
IIA	30 (37.5)
IIB	26 (32.5)

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma

Table 2: Association of estrogen receptor with demographic and clinical characteristics of the patients

Variables	High ER expression ($n=54$)	Low ER expression ($n=26$)	*P*	OR (95% CI)
Age (years)				
≤40	5 (9.26)	6 (23.08)	0.05	1.0
40-50	17 (31.48)	12 (46.15)	0.457	1.7 (0.42-6.88)
>50	32 (59.26)	8 (30.77)	0.03	4.8 (1.16-19.81)
Menopausal status				
Premenopausal	26 (48.15)	20 (76.92)	0.015	1.0
Postmenopausal	28 (51.85)	6 (23.08)		3.6 (1.25-10.33)
Pathological type				
IDC	49 (90.74)	23 (88.46)	0.75	1.0
ILC	5 (9.26)	3 (11.54)		0.78 (0.17-3.56)
Tumor size				
T1	44 (81.48)	14 (53.85)	0.01	1.0
T2	10 (18.52)	12 (46.15)		0.27 (0.09-0.75)
Lymph node status				
N0	35 (64.81)	9 (34.62)	0.015	1.0
N1	16 (29.63)	10 (38.46)	0.106	0.41 (0.14-1.21)
N2	3 (5.56)	7 (26.92)	0.005	0.11 (0.02-0.513)
Stage				
I	15 (27.78)	9 (34.61)	0.822	1.0
IIA	21 (38.89)	9 (34.61)	0.562	0.71 (0.23-2.23)
IIB	18 (33.33)	8 (30.8)	0.616	0.74 (0.23-2.39)

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, ER: Estrogen receptor, OR: Odds ratio, CI: Confidence interval

Likewise, more than half of women with high ER expression were postmenopausal versus only 23.08% with low ER expression were in such menopausal status (OR = 3.6, 95% CI = 1.25–10.33, $P = 0.015$). Smaller tumor size also seemed to be significantly associated with high ER expression, as the tumor size in the majority of women with high ER expression (81.48%) was within the T1 stage compared to 53.85% of women with low ER expression who had such tumor size (OR = 0.27, 95% CI = 0.09–0.75, $P = 0.01$). Finally, 35 women (64.81%) of high ER expression had no lymph node involvement, while such a stage was only encountered in 9 women (34.62%) of low ER expression. On the other hand, each of pathological type and tumor stage appeared to have no significant association with ER expression.

Association of progesterone receptor with demographic and clinical characteristics of the patients

Two factors were found to be significantly associated with high expression PgR [Table 3]. Older age (over 50 years old) represented 64.1% of women with high PgR expression, and accounted for only 36.59% of women with low PgR expression (OR = 4.44, 95% CI = 1.02–19.39). Furthermore, postmenopausal women accounted for 56.41% and 29.27% of women with high and low PgR expressions, respectively (OR = 3.13, 95% CI = 1.24–7.88, $P = 0.016$).

Association of steroid hormone receptors with demographic and clinical characteristics of the patients

The proportion of high ER/high PgR, high ER/low PgR, low ER/low PgR, and lower/high PgR was 45%, 22.5%, 28.75%, and 3.75%, respectively. Regarding the expression level of the two receptors (ER and PgR), three factors have been found to have a significant association [Tables 3 and 4]. Nineteen premenopausal women (82.61%) showed low expression of both ER and PgR which was significantly higher than all other ER/PgR expression categories within the menopausal status. There was no involvement of lymph nodes in 72.22% of women with high expression of both receptors, while 100% of women with low ER/high PgR expression had N2 stage. Even though about 70% of women with high expression of both receptors lie with older age class and remarkably higher than other expression categories, the difference exceeded the acceptable level of significance. Furthermore, the tumor size in majority of women with high ER/PgR (83.33%) was within T1 stage which was greater than other groups although with no significant differences.

Discussion

The present study revealed that 67.5% and 48.5% of women with invasive BC had high expression of ER and PgR, respectively. Much lower percent was reported by the most recent Iraqi study in which the ER and PgR positivity among Iraqi women with invasive ductal carcinoma was 33.33% and 39.6%, respectively.[6] This variation may be related to the different techniques that were used in the detection of hormonal receptor expression. Globally, Effi *et al*.[7] recruited 302 women with primary invasive BC in the Ivory Coast, and reported that ER expression was superior to PgR expression accounting for 56% and 49% of cases, respectively. In a large Chinese study, Yao *et al*.[8] investigated the association of PgR expression with the clinical characteristics and prognosis in

Table 3: Association of progesterone receptor with demographic and clinical characteristics of the patients

Variables	High PgR expression (*n*=39)	Low PgR expression (*n*=41)	*P*	OR (95% CI)
Age (years)				
≤40	3 (7.69)	8 (19.51)	0.046	1.0
40-50	11 (28.21)	18 (43.9)	0.53	1.63 (0.36-7.48)
>50	25 (64.1)	15 (36.59)	0.047	4.44 (1.02-19.39)
Menopausal status				
Premenopausal	17 (43.59)	29 (70.73)	0.016	1.0
Postmenopausal	22 (56.41)	12 (29.27)		3.13 (1.24-7.88)
Pathological type				
IDC	35 (89.74)	37 (90.24)	0.941	1.0
ILC	4 (10.26)	4 (9.76)		1.06 (0.25-4.56)
Tumor size				
T1	32 (82.05)	26 (63.41)	0.062	1.0
T2	7 (17.95)	15 (36.59)		0.38 (0.14-1.07)
Lymph node status				
N0	26 (66.67)	18 (43.9)	0.118	1.0
N1	10 (25.46)	16 (39.02)	0.098	0.43 (0.16-1.169)
N2	3 (7.69)	7 (17.07)	0.108	0.3 (0.07-1.3)
Stage				
I	10 (25.64)	14 (34.15)	0.132	1.0
IIA	19 (48.72)	11 (26.83)	0.116	2.42 (0.81-7.26)
IIB	10 (25.64)	16 (39.02)	0.817	0.88 (0.28-2.72)

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, PgR: Progesterone receptor, OR: Odds ratio, CI: Confidence interval

Table 4: Association of steroid hormone receptors with demographic and clinical characteristics of the patients

Variables	High ER/High PgR (*n*=36)	High ER/Low PgR (*n*=18)	Low ER/Low PgR (*n*=23)	Low ER/High PgR (*n*=3)	*P*
Age, years					
≤ 40	2 (55.56%)	3 (16.67%)	5 (21.74%)	1 (33.33%)	0.058
40-50	9 (25%)	8 (44.44%)	10 (43.48%)	2 (66.67%)	
>50	25 (69.44%)	7 (37.79%)	8 (34.78%)	0 (0%)	
Menopausal status					
Premenopausal	16 (44.44%)	10 (55.56%)	19 (82.61%)	1 (33.33%)	0.027
Postmenopausal	20 (55.56%)	8 (44.44%)	4 (17.39%)	2 (66.67%)	
Pathological type					
IDC	33 (91.67%)	16 (88.89%)	21 (91.3%)	2 (66.67%)	0.574
ILC	3 (8.33%)	2 (11.11%)	2 (8.7%)	1 (33.33%)	
Tumor size					
T1	30 (83.33%)	14 (77.78%)	12 (52.27%)	2 (66.67%)	0.066
T2	6 (16.67%)	4 (22.22%)	11 (47.83%)	1 (33.33%)	
Lymph node status					
N0	26 (72.22%)	9 (50%)	9 (39.13%)	0 (0%)	<0.001
N1	10 (27.78%)	6 (33.33%)	10 (43.48%)	0 (0%)	
N2	0 (0%)	3 (16.67%)	4 (17.39%)	3 (100%)	
Stage					
I	9 (25%)	5 (27.78%)	10 (43.48%)	0 (0%)	0.248
IIA	17 (47.22%)	4 (22.22%)	7 (30.43%)	2 (66.67%)	
IIB	10((27.78%)	9 (50%)	6 (26.09%)	1 (33.33%)	

3030 women primary invasive BC. The proportion of high and low PgR expression was found to be 35.74% and 64.26%, respectively. Almost similar findings were reported by several previous studies.[9,10]

In general, it was estimated that 70%–80% of BC in women express high ER.[11] In healthy women, ER expression is largely heterogeneous within different areas of breast tissue. Only a small fraction of epithelial cells in ducts and lobules are ER-positive. In this regard, the ER levels in the mammary gland are affected by the menstrual cycle, with more ER-positive cells in the follicular stage of the cycle.[12] However, in BC, this expression is undergone a dramatic change. Yang *et al*.[13] analyzed 270 BC cases included in a population-based BC case–control study conducted in Poland. ER and PgR levels were significantly higher

in BC cells than in normal adjacent tissue which was, in turn, showed higher expression of these receptors than remote tissues. It was proposed that several genetic and epigenetic changes may occur with the cancerous breast tissues with an eventual alteration in the expression profile of ER and/or PgR.[14]

In the present study, four factors were significantly associated with the high expression of ER. Such expression was significantly associated with older ages (OR = 4.8, 95% CI = 1.16–19.81, P = 0.03). This implies that women with >50 years old have 4.8-fold probability to express high ER than women ≤40 years old. In accordance with the present results are many previous studies from Iraq showed that the positive expression of ER and PR was increasing with age.[15-17] Furthermore, this result agrees with this result of an Indian study including 132 newly diagnosed cases of invasive BC.[18] The authors found that the older age group had a higher frequency of ER/PgR expression (28/40) than the younger age group (18/30).

The other factor which was significantly associated with ER expression in the current study was menopausal status (OR = 3.6, 95% CI = 1.25–10.33, P = 0.015). This entails that postmenopausal women with BC have 3.6-time more likely to have high ER expression than their premenopausal counterparts. This result is in a complete agreement with the most previous studies in this regard. In Pakistan, Faheem *et al*.,[19] assessed the ER expression in 1226 women with invasive BC and reported a very strong association between high expression of this receptor and postmenopausal status. However, Effi *et al*.[7] did not found such an association among women in Ivory Coast. This variation in the results may factor such as ethnic and race variation between different studies, fault in taking the menopausal history, and technical issues.

Smaller tumor size also seemed to be significantly associated with high ER expression in the present study (OR = 0.27, 95% CI = 0.09–0.75, P = 0.01) which implies that BC women with T2 stage are 3.7-time less likely to have high ER expression compared with women with T1 stage. In accordance with this result is the study of Badowska Kozakiewicz *et al*.[11] among Polish women. Analysis of ER and PgR expression showed that the greater expression of ER was in the T1 stage (51%), while only 1%–2% of T3 and T4 stages, respectively, expressed ER. Almost similar result was also obtained by Faheem *et al*.[19] among Pakistani women. In contrast, Gupta *et al*.[20] have failed to find such an association between tumor size and ER expression among Indian women, may be attributed to the relatively small sample size (50 women).

It is nonreasonable to assume a direct negative relationship between ER expression and tumor size, However, there are several explanations for this association. One explanation hypothesizes that in the absence of ER, estrogen can enhance the tumor growth through many alternative pathways such as increase infiltration of tumor-associated macrophage into the tumor tissue.[21] The other explanation assumes the activation of a number of human kinases such as PIK3CB in ER-negative BC. These kinases are key regulators of signaling pathways that control many cellular functions including proliferation, migration, and survival with an eventual growing and surviving of tumor cells.[22]

The last factor which was inversely associated with high ER expression in the present study was lymph node involvement (OR = 0.11, 95% CI = 0.02–0.513, P = 0.005). That means women with the N2 stage are about 10-time less likely to have high ER expression compared to those having no lymph node involvement, which is in agreement with most of the other series.[23,24]

Only two factors were found to be significantly associated with high expression PgR. The first one was older age (OR = 4.44, 95% CI = 1.02–19.39) which implies that BC women older than 50 years have 4.4-time more likely to have highly express ER. The other factor was that postmenopausal status was significantly associated with high PgR expression (OR = 3.13, 95% CI = 1.24–7.88, P = 0.016). Comparing with other studies, most available works indicated no clear correlation between PgR expression and age.[25,26] On the other hand, Yao *et al*.[8] reported an inverse correlation between these two variables.

Like in age factor, previous studies indicated positive association[20] or no or inverse association between PgR and postmenopause.[8,27] This discrepancy between the different studies is largely attributed to the variation in sample size ethnicity and race, the criteria used for evaluation of receptor expression, and the stage at which the biopsies are collected.[21]

In the present study, the proportion of high ER/high PgR, high ER/low PgR, low ER/low PgR, and lower/high PgR was 45%, 22.5%, 28.75%, and 3.75%, respectively. These proportions vary widely among different studies. In Effi *et al*.[7] study, they were 43.38%, 12.58%, 38.41%, and 5.63%, respectively. In another study, these proportions were 60.4%, 5.9%, 30.7%, and 2.9%, respectively.[20] Interestingly, Hefi *et al*.[28] have demonstrated that the last category does not represent a distinct biological subtype or clinically important cancer. Rather, it is an artifact result from an inappropriate fixation during slide processing that leads to loss of epitopes of paraffin-embedded breast tissue.

As regard for the expression level of the two receptors (ER and PgR), two factors have been found to have a significant association. The first factor was the significant association of high expression of both receptors with postmenopausal status. This result is consistence with that obtained by Bao *et al*.[29] among Chinese women. However, Elwood and Godolphin[30] demonstrated that the ER/PgR status has no significant association with the menopausal status.

The other factor is the involvement of lymph node which was inversely associated with high expression of both receptors. This result corroborates with almost all studies in this regard. Sofi *et al*.[18] found that patients with no involvement of lymph node and lower tumor grade were more likely have high

expression of ER/PgR compared to patients with multiple lymph node involvement and advance stage. Almost similar results were obtained by Badowska-Kozakiewicz *et al*.,[11] suggesting the inverse relationship between the high expression of steroid hormonal receptor and the aggressiveness of BC.

Collectively, these data indicated that high expression of ER is associated with older age, postmenopausal status, small tumor size, and no involvement of lymph nodes. The presence of high expression of ER and PgR is a good prognostic indicator because it is an indicator of less aggressive tumors. The expression of steroid hormone receptor should be routinely evaluated. According to the result of this evaluation, endocrine hormonal therapy should be adapted for patients with high expression of both receptors or ER receptor. Otherwise, chemotherapy/radiotherapy will be the best treatment choice.

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Conflicts of interest

There are no conflicts of interest.

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