

## EVALUATION OF THE ESTROGEN AND PROGESTRON RECEPTORS IN FEMALE BREAST CANCER IN RESPECT TO AGE, GRADE AND STAGE

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### Abstract

Breast Cancer is a disease characterized by its tremendous heterogeneity in its course and treatment that demand the physicians and patients. It is the commonest type of malignancy among Iraqi women. Hormone receptors study in breast cancer is mandatory because it determine the prognosis and the course of treatment and has a wide acceptance in the management of breast cancer.

this study aimed to evaluate the relation of estrogen and progesterone receptors positive (+ve) or negative (-ve) in respect to the age, grade and stage.

A sixty seven female patients diagnosed as a breast cancer were undergone a surgery in term of mastectomy and axillary dissection and specimens were sent to a histopathology and receptor detection studies. All specimens were processed by same procedure of tissue preparations which include formalin fixation, paraffin embedded, receptor detection methods (Immuno-histochemistry and enzyme immuno assay studies).

Most of affected cases in this study are equal or less than 47 years (37 cases representing 55.22%. Mean age group in this study was 47 year. The tumor mainly in Grade II (42 cases 62.68%) and mainly in stage IIA and IIIA (20 cases 29.86% for each one). Estrogen (ER) receptor expression represents higher positivity (49 cases 73.13%), while for progesterone (PR) receptor expression (45 cases 67.16%) representing more than two third of cases. The ER, PR expression in relation to the age was statistically significant (P value is 0.01). While, the ER and PR receptor expression in relation to the grade and stage was not significant (P values are 0.8, 0.5 respectively).

In conclusion, breast cancer is a disease of early age group with moderately advanced stage and grade and about two thirds of patients have a positive estrogen and progesterone receptor expression which was more in older than in younger patients.

### Introduction

The identification and exploitation of biomarkers that may predict response to anti-cancer treatments has the capacity to revolutionize the way that patients with cancer are treated<sup>1</sup>.

In breast cancer, the estrogen receptor (ER) and the progesterone receptor (PR) are known to have a significant predictive value in determining sensitivity to endocrine therapies<sup>1</sup>. Breast cancer is the most common cancer among women in Arab countries and the highest percentage in Egypt<sup>2</sup> 35.1%, Kuwait<sup>3</sup> 34.4%, Lebanon<sup>4</sup> 33%, Jordan<sup>5</sup> 14.2%, Oman<sup>6</sup> 15.6% and in Iraq according to the Iraqi Cancer Registry accounting 16.7%<sup>7</sup>.

Breast cancer is the commonest cancer worldwide in women, and the second cause of cancer death among female after lung cancer. Breast cancer affects 1:12 women. In United Kingdom there are 24,000 new cases and 15,000 deaths annually. It has been reported that there is a wide variation in the incidence and mortality rate of breast cancer among populations, being highest in developed countries and lowest in developing one<sup>8</sup>.

Breast cancer is a commonest cause of mortality among female patients in Basra<sup>9</sup>. The breast is a target organ for estrogen and progesterone receptors, our present state of knowledge regarding estrogen and

progesterone receptors (ER and PR) has led to changes in treatment strategies<sup>10</sup> patients without receptors in their tumor tissues cannot be expected to respond to endocrine therapy treatment strategies. The treatment of the disease now approaches being of a rational rather than of an empirical nature<sup>10</sup>. However, it is imperative that we achieve a considerably higher level of understanding before we can predict, with high probabilities, which patients will benefit from endocrine therapy. These hormones control several functions of the normal and abnormal mammary epithelium including cell proliferation<sup>11</sup>.

Most of the actions of estrogen and progesterone are mediated via specific steroid receptors, and one would expect that proliferating cells should contain estrogen receptors (ER) and/or progesterone receptors (PR)<sup>12</sup>. Estrogen and progesterone receptor status in breast cancer can determine therapeutic options and may provide prognostic information<sup>13</sup>. The aim of hormonal therapy based on blocking the effect of these hormones on the target tissue (Breast tissues which contain estrogen and progesterone receptors), tumors expressing these receptors (positive receptors) has better prognosis than those not expressing (negative receptors)<sup>14,15</sup>.

The aim of study is to evaluate the estrogen and progesterone receptors (+ve or -ve) in breast cancer in respect to the age, grade and stage of the disease.

### Patients and methods

This study is a cross sectional study, which was conducted in the department of surgery in Basra General Hospital and other central hospitals (Al-Sader Teaching hospital, and Al-Mawani General hospital) over a period of time from the first of April 2012 to the first of April of 2013. In the current study, there were 67 female patients. Their age ranging from 27 years to 69 years and the mean age was 47 years.

All patients were definitely diagnosed by histopathology as a breast cancer. Histopathologically, all the specimens were underwent formalin fixed and paraffin embedded (FFPE) while using the right antibodies to target the correct antigens and amplify the signal is important for visualization, complete preparation of the sample is critical to maintain cell morphology, architecture and the antigenicity of target epitopes. The Immunohistochemistry (IHC) refers to the process of detecting antigens (e.g., proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissue.

Estrogen (ER) and progesterone (PR) receptor expression were studied in 67 breast cancer biopsies using the same tissue block and the same monoclonal antibody either immunohistochemistry on frozen sections or quantitative by means of an enzyme-immunoassay (EIA) on the cytosol-fraction of a tumor homogenate. All the included patients in this study were underwent mastectomy and axillary dissection in the previously mentioned hospitals in Basra. Post operatively, all patients were completed their treatment and followed up in the same oncological out-patient department (Al-Sader Teaching Hospital). And the P value were checked in the department of community medicine of Basra collage of medicine in a version SPSS.

### Results

In current study the mean age group was 47 year (27years-69years) and the majority of cases (37 cases out of 67 cases) involved in breast cancer was in first group of age (27years-47years) representing (55.22%). Regarding the grade of disease, 42 cases (62.68%) were in grade II and most of the cases were between stage IIA and stage IIIA as shown in table I.

In this study, It was found that 49 out of 67 patients (73.13%) expressed estrogen

receptors (ER +ve state). While, 45 out of 67 patients (67.16%) expressed progesterone receptors (PR +ve state) as shown in table I.

**Table I: The percent of age, grade and stage in this study.**

Prognostic factors		No. of cases	%
Age	<47	37	55.22%
	>47	30	44.78%
Grade	I	4	5.97%
	II	42	62.68%
	III	21	31.35%
Stage	I	3	4.46%
	IIA	20	29.86%
	IIB	11	16.42%
	IIIA	20	29.86%
	IIIB	3	4.48%
	IIIC	4	5.97%
	IV	6	8.96%
ER	+ve	49	73.13%
	-ve	18	26.87%
PR	+ve	45	67.16%
	-ve	22	32.84%
Total		67	%100

**Table II: The relation of the estrogen receptor (ER) expression with the age, grade and stage.**

Prognostic factors		No. of cases	Estrogen Receptors		P Value
			+Ve	-Ve	
Age	<47	37(55.22%)	26(70.27%)	11(29.72%)	0.011 sig.
	>47	30(44.77%)	23(76.66%)	7(23.33%)	
Grade	I	4	3(75%)	1(25%)	0.8 In sig.
	II	42	30(71.42%)	12(28.57%)	
	III	21	14(66.66%)	7(33.33%)	
Stage	I	3	2(66.66%)	1(33.33%)	0.5 In sign.
	IIA	20	14(70%)	6(30%)	
	IIB	11	7(63.63%)	4(36.36%)	
	IIIA	20	16(80%)	4(20%)	
	IIIB	3	2(66.66%)	1(33.33%)	
	IIIC	4	3(75%)	1(25%)	
	IV	6	5(83.33%)	1(16.66%)	
Total					

**Table III: The relation of the progesterone receptor (PR) expression with the age, grade and stage.**

Prognostic factors		No. of cases	Progesterone Receptors		P. Value
			+Ve	-Ve	
Age	<47	37(55.22%)	22(59.45%)	15(40.55%)	0.001 sig.
	>47	30(44.77%)	23(76.66%)	7(23.34%)	
Grade	I	4	4 (100%)	0	0.728 Insig.
	II	42	25(59.52%)	17(40.47%)	
	III	21	14(66.66%)	7(33.33%)	
Stage	I	3	3(100%)	0	0.581 Insig.
	IIA	20	14(70%)	6(30%)	
	IIB	11	8(72.72%)	3(27.27%)	
	IIIA	20	12(60%)	8(40%)	
	IIIB	3	2(66.66%)	1(33.33%)	
	IIIC	4	1(25%)	3(75%)	
	IV	6	5(83.33%)	1(16.66%)	
Total					

**Table IV: The relationship between the age and the grade**

Age	No. of cases	Grade			P value
		I	II	III	
<47	37	4 10.18%	20 54.06%	13 35.14%	In sign.
>47	30	0 0	22 73.34%	8 26.66%	
Total	67	4	40	23	

**Table V: The relationship between the age and the stage**

Age	No. of cases	Stage							P value
		I	IIA	IIB	IIIA	IIIB	IIIC	IV	
<47	37	2 5.4%	9 24.3%	8 18.9%	11 29.7%	2 5.4%	4 10.8%	3 8.1%	0.5 In sig.
>47	30	1 3.3%	10 33.3%	5 16.6%	8 26.6%	1 3.3%	0 0	3 10 %	

**Discussion**

It has been reported that in breast cancer tissue if there is more estrogen and progesterone receptor expression than normal, the cancer may grow more quickly<sup>15</sup>. The test results show whether treatment blocking estrogen and progesterone may stop the cancer from growing<sup>16</sup>. Breast cancer have a big

heterogeneity in its behavior<sup>17</sup>. The Hereditary breast cancer represents about 5% to 10% of all breast cancer and the clinical and the pathological variables of the tumor (histological grade, stage and the hormonal status) give a predicting picture in prognosis and the course of the treatment of the disease<sup>17</sup>.

In Iraq and most of Arabic nations the incidence of breast cancer shows more tendency to affect younger age group of women as well as delayed presentation associated with more aggressive tumor behavior resulting in high mortality rate<sup>18,19</sup>.

In current study, breast cancer affect mostly younger age group 37 cases, around (55%), representing the premenopausal while the postmenopausal cases were 30 (44.78%). This result comes in accord to other studies in some Arabic countries (Kuwait<sup>20</sup>, Saudi Arabia<sup>21</sup>, Tunisia<sup>22</sup> and Egypt<sup>23</sup>) and in some developing countries like India<sup>24</sup>, Pakistani<sup>25</sup>, Korea<sup>26</sup> and Nepal<sup>27</sup>. Whereas, postmenopausal with breast cancer is common in west countries<sup>28-30</sup> and Asia<sup>31,32</sup>.

Regarding the grade and the stage, the significant accumulation of cases in grade II,III and stage II,III pointing that most of cases were presented in advanced grade and stage. This result consistent with the results reported in other studies like in Saudi Arabia<sup>33</sup>, Tunisia<sup>34</sup>, Egypt<sup>35</sup> and Oman<sup>36</sup>. In addition, stage III shows increase in number reflecting late presentation of patients which could be attributed to poor health education and ignorance of the significant breast clinical examination, breast self-examination, early medical consultation and screening programs. Moreover, negligence, poverty and patient concern toward mastectomy operation play an important role in late presentation<sup>36</sup>.

This study shows that the age of patients has no significant relation with the grade and stage. In spite of most of cases were

in premenopausal age group, the majority of cases were in Grade II and Stage II. This is similar to other studies such as in the North of Iraq<sup>37</sup>, Tunisia<sup>38</sup> and Egypt<sup>39</sup>. In addition, in this study, It was found that there is a significant relation between the patients age and expression of estrogen and progesterone receptors. For example; ER expression were 70.27% in age group <47years and 76.66% in age group >47years. This indicates that the younger age group are more susceptible to have breast cancer without expression of hormone receptors than the older one and these findings are consistent with other studies like in North Iraq<sup>37</sup>, Tunisia<sup>38</sup>, Saudi Arabia<sup>39</sup>, Lebanon<sup>40</sup> and Iran<sup>41</sup>. Regarding tumor grade, in this study, it was found that there is an inverse relation with estrogen and progesterone receptor expression indicating that the lower grade of the tumor the higher expression of estrogen and progesterone receptors.

Histologically, there is a uniform loss of ER content as the tumor become more anaplastic and this result is supported by reported result in other studies<sup>42</sup>. In a population of predominantly middle-age group with lower frequency of hormone receptor expression in breast cancer, probably expected and usually harboring a considerable rate of poorly differentiated carcinomas and same about the stage in relation with ER and PR we found that there is an inverse relation between them meaning that the percentage of ER and PR expression decreases when stages increase.

## Conclusion

In Basra, breast cancer characterized by it is occurrence in early age group with moderately advanced grade and stage at time of diagnosis, and about two third of the cases expressed ER and PR receptors. Older age group patients are more susceptible to get expression of receptors than the younger age group.

## References

1. Fuqua SA, Cui Y. Estrogen and progesterone receptor isoforms: clinical significance in breast cancer. *Breast Cancer Res Treat.* 2004;87:3-10.
2. Salem A.A.; Salem M.A.E.; Abbass H. Breast Cancer: Surgery at the South Egypt Cancer Institute. *Cancers* 2010, 2, 1771-1778.
3. Al-Shaibani H., Bu-Alayyan S., Habiba S., Sorkhou E, Al-Shamali N. and Al-Qallaf B. Risk Factors of Breast Cancer in Kuwait: Case-Control Study. *Iran J Med* 2006; Vol 31 No 2, pp. 61-64.
4. El Saghir NS, Shamseddine AI, Geara F, Bikhazi K, Rahal B, Salem ZM, Taher A, Tawil A, El Khatib Z, Abbas J, Hourani M, Seoud M. Age distribution of breast cancer in Lebanon: increased percentages and age adjusted incidence rates of younger-aged groups at presentation. *2002*;50(1-2):3-9.
5. Jordan Cancer Registry 2008 Cancer Incidence in Jordan Report (Directorate of Information Studies and REsearch. Mortality in Jordan, 2005. Amman, Ministry of Health, 2008)..
6. Al-Moundhri M et al. The outcome of treatment of breast cancer in a developing country—Oman. *Breast*, 2004, 13(2):139–145.
7. Noor S Jummaah. Evaluation of hormone receptors status (Estrogen & Progesterone) in Basra. A thesis in Pathology department of Medical collage in 2012.
8. Morbidity and Mortality Weekly Report. Breast cancer incidence and mortality—United States. 1996, 45(39):833–837.
9. Iraqi Cancer Board. Results of the Iraqi Cancer Registry. Baghdad, Ministry of Health, 2007.
10. Thorpe SM. Estrogen and progesterone receptor determinations in breast cancer. Technology, biology and clinical significance. *Acta Oncol.* 1988;27(1):1-19.
11. Fanelli MA, Vargas LM, Gago FE. Estrogen receptors, progesterone receptors, and cell proliferation in human breast cancer. PMID:8825133. [PubMed - indexed for MEDLINE].
12. Tio M, Ohashi Y et al. The breast cancer working group presentation was divided into three sections: the epidemiology, pathology and treatment of breast cancer in Japan. *Journal of Clinical Oncology*. (2010).40,113–114
13. Mathiesen O, Bonderup O, Carl J, Panduro J, Pedersen KO. The prognostic value of estrogen and progesterone receptors in female breast cancer. A single center study. *Acta Oncol.* 1991;30(6):691
14. Borjesson BW, McGinley R, Foo TM, Smyth C, Toppila M, Compton P, Sarfaty GA. Estrogen and progesterone receptor assays in human breast cancer: sources of variation between laboratories. *Eur J Cancer.* 1987 Jul;23(7):999-1004.
15. Mohsin SK, Weiss H, et al. Progesterone receptors immunohistochemistry and clinical outcome in breast cancer: *Modern pathology* (2004)17,1545-1554.
16. McGuire WL, Clark GM. Role of progesterone receptors in breast cancer. *CA Cancer J Clin.* 1986 ;36(5):302-9.
17. Clark GM, Osborne CK, McGuire WL. Correlations between estrogen receptor, progesterone receptor, and patient characteristics in human breast cancer. *J Clin Oncol.* 1984 Oct;2(10):1102-9.
18. Alwan N.A.S. Breast cancer: demographic characteristics and clinico-pathological presentation of patients in Iraq • *Eastern Mediterranean Health Journal EMHJ* •2010 Vol. 16 No.11
19. Arafa M. Correlation of hormone receptors with HER2/neu protein expression and the histological grade in invasive breast cancer in a cohort of Saudi Arabia. *Turkish Journal of Pathology* (2010),26:209-215.
20. Paszko Z, Omar YT, Nasralla MY, Jazaf H, Bouzubar N, Temmin L, Padzik H. Estrogen and progesterone receptor status in breast cancer in Kuwait female population: *Neoplasma.* 1993;40(2):127-32.
21. Ezzat A, Ibrahim M et al. Locally advanced breast cancer in Saudi Arabia: high frequency of stage III in a young population. *Medical Oncology*. (1999)16:95-103.
22. Ayadi L, Khabir A et al. Correlation of HER-2 over-expression with clinico-pathological parameter in Tunisian breast carcinoma. *World Journal of Surgical Oncology* (2008) 6:112.
23. Omar S et al. Breast cancer in Egypt. *Eastern Mediterranean Health Journal.* 2003, 9(3):448–463.
24. Saxena S, Rekhi B et al. Clinico-morphological patterns of Breast Cancer including family history in a New Delhi hospital India—a cross-sectional study. *World Journal Of Surgical Oncology.* (2010),3:7-9.
25. Aziz S, Sana M, Akram A. "Socioeconomic status and breast cancer survival in Pakistani women," *Journal of the Pakistan Medical Association* 2004, vol. 54, no. 9, pp. 448–453.
26. Korean breast cancer data of 2004 using breast cancer registration program. *The Korean Breast Cancer Society Nationwide.* *J Breast Cancer.* 2006;9:151–161.
27. Pradhan M, Dhakal P. Study of breast lump of 2246 cases by FNA in Nepal. *Journal of Nepal Medical Association* (2008). 47, 205-209.
28. Sariago J et al. Breast cancer in young patients. *American Journal of Surgery,* 1995, 170(3):243–245.
29. Sant M et al. Survival of women with breast cancer in Europe: variation with age, year of diagnosis and country. The EURO CARE Working Group. *International Journal of Cancer,* 1998,77:679–683.
30. Stanley P, Leong L, William D. Is Breast Cancer the Same Disease in Asian and Western Countries? *World J Surg.* 2010 October; 34(10): 2308–2324
31. Porter P. "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J Med.* 2008;358:213–216.
32. Green M, Raina V. Epidemiology, screening and diagnosis of breast cancer in the Asia-Pacific region: current perspectives and important considerations. *Asia Pacific J Clin Oncol.* 2008;4, 5–13.
33. Najjar H, Easson A. Age at diagnosis of breast cancer in Arab nations. *International journal of surgery* (2010).8:448-452
34. Ben Abdallah M, Zehani S, Maalej M, et al. Breast cancer in Tunisia: epidemiologic characteristics and trends in incidence. *Tunis Med J* 2009, 87, 417-25.
35. Mona M, Rashed M. The association of HER2 over expression in relation with p53 nuclear accumulation hormonal receptors status and common clinic pathology prognosis parameters in a series of Egyptian women with invasive ductal carcinoma. *The internet journal of pathology.* (2005)6:24-30.
36. Shiyam Kumar, Ikram A. and Mansour S. Clinical Study Changing Trends of Breast Cancer Survival in Sultanate of Oman. *Journal of Oncology* 2011, 7,
37. Majid R, Muhammed H et al. Breast cancer in Kurdish women of northern Iraq incidence clinical stage and case control analysis of parity and family risk. *Biomedical center Womens health* (2009).9:3.
38. Bouchlaka A, Ben Abdallah M, Ben Aissa R, et al. Practice of large scale mammography in the Ariana area of Tunisia: prelude to a mass screening? *Tunis Med,* 87, 426-31.
39. Nagi S, Mazen K, Ali I. International Trends in epidemiology and management of breast cancer in developing Arab countries: A literature and registry analysis\* *Journal of Surgery* (2007) 5, 225-233.
40. El Saghir NS, Adib S, Mufarrij A, Kahwaji S, Taher A, Issa P. Cancer in Lebanon: analysis of 10,220 cases from the American University of Beirut Medical Center. *1998 Jan-Feb;46(1):4-11.*
41. Mousavi S, Montazeri A et al. Breast Cancer in Iran: An epidemiological review. *Breast Journal* (2007),13,383-391.
42. Elledge RM and Allred DC. Clinical aspects of estrogen and progesterone receptors. In: Harris JR et al., editors. *Diseases of the breast.* Philadelphia, Lippincott Williams & Wilkins, 2004:603–17.