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Study of HER2 in Breast Cancer Disease

[*]Baraa R. Mhmood [a]. Thikra A. Allwsh[b]*

[a]*Biochemistry laboratory, Ibn Al Atheer Children's Hospital, Mosul, Iraq*
[b]*Department of chemistry, College of Science, University of Mosul, Mosul, Iraq*

Abstract

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase growth receptor protein, Positive HER2 status has been linked with aggressive tumor behavior and resistance to cytotoxic and endocrine therapies. Breast cancer is a complex disease and the major cause of mortality in women worldwide. There are several subtypes of breast cancer and many options for treatment. This study aimed to know the hormonal changes associated with HER2+ve breast cancer in pre and postmenopausal Iraqi women. This study included 80 healthy women and 78 newly diagnosed breast cancer patients, 35 postmenopausal and 43 premenopausal. Depending on the HER2 test the patients were divided into two groups, positive and negative. The group of patients with positive (HER2) test was adopted and the negative group was excluded. Our result shows that there are a significant decrease in progesterone and a non-significant increase in Estradiol, FSH, and LH in premenopausal HER2+ve breast cancer patients but there is a significant increase in estradiol, FSH, and LH in postmenopausal HER2 +ve breast cancer patients. There is a significant decrease in TSH within the normal range in both pre and postmenopausal patients compared with a control group. There is a significant negative relationship between progesterone, and FSH, a negative relationship between progesterone and LH in premenopausal patients with HER2 positive test. Also, there is a significant negative relationship between progesterone and TSH, a negative relationship between progesterone, estradiol, and FSH. And a positive relationship between progesterone and LH in postmenopausal patients with HER2 positive test.

Keywords: HER2, progesterone, estradiol, TSH

1. Introduction

HER2 is a transmembrane protein having tyrosine kinase activity that initiates different signaling pathways such as regulating cell growth, survival, and differentiation and participates in cellular proliferation and differentiation [1]. The overexpression of human epidermal growth factor receptor 2 (HER2) is a gained genetic alteration that is firmly established as an indicator of poor prognosis in breast cancer [2], and it is the most aggressive of all the breast cancers, is unresponsive to treatment, highly angiogenic, proliferative and has the lowest survival rate [2,3]. Over 5%–6% of breast cancer patients have been linked to gene mutations that went through the ages of the family [4].

Breast cancer is the most common cancer in women and a leading cause of cancer death worldwide [5]. In most cases, it's a pattern of hormone-dependent cancer [6]. According to the International Agency for Research on Cancer, there is about 2.3 million new cases of breast cancer were recorded in the world during 2020 [7]. Obesity, getting older, some hormone replacement therapy (including estrogen and progesterone) taking during menopause all of that can increase the risk factor of breast cancer [8].

There are 4 major kinds of breast cancers based on factors involved in tumor growth: endocrine receptor (estrogen or progesterone receptor) positive, human epidermal growth factor receptor 2 (HER2) positive, triple positive (estrogen, progesterone, and HER2 receptor-positive), and triple-negative (absence of estrogen, progesterone, and HER2 receptors) [9, 10].

Thyroid hormone can increase the expression level of cyclin D1 (a cell cycle regulating protein), leading to several tumor types, including breast cancer [11]. Sundry studies have reported a positive association between hyperthyroidism and breast cancer risk, whereas other studies have reported no association between hypothyroidism or hyperthyroidism and the risk of breast cancer [12, 13]. Thyroid hormones seem to promote breast cancer cell proliferation and increase the effect of estradiol and therefore may play a role in breast cancer development and progression [11, 13].

*Corresponding author e-mail; baraa.raad.mahmood@gmail.com .
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Women secrete steroid hormones thorough out their lives, even with a different pattern, which is regulated mainly by the ovary in the premenopausal, and the adrenal gland in the postmenopausal [6]. Endogenous estrogen may enhance the growth, stromalization, and angiogenesis of an estrogen receptor-negative breast cancer cell line [12, 14, 1+5].

Gonadotropins can directly or indirectly foster cell proliferation in breast cancer. Luteinizing hormone engages in the tumor progression of breast cancer using luteinizing hormone choriogonadotropin receptor [13, 16, 17].

Aim of the study

The study aims to investigate human epidermal growth factor receptor 2 (HER2) and hormonal changes in pre and postmenopausal breast cancer patients in Iraqi women and the relationship between them.

Material and methods

78 newly diagnosed breast cancer patients from Oncology and Nuclear Medicine Hospital in Mosul, Iraq, and 80 healthy women have participated in this study. Their ages ranged between (30 - 60) years. The group of patients and control was classified into two groups; the first one is postmenopausal; includes 35 breast cancer patients and 40 control. The second is premenopausal; includes 43 breast cancer patients and 40 control.

Sample collection

Ten milliliters of venous blood were aseptically obtained (for premenopausal patients, blood samples were collected between days three to five of their menstrual cycle). All samples were allowed to coagulate and were centrifuged at 3500 rpm for seven minutes. The serum obtained was aspirated into a clean vial and stored at -20◦C until analyses were done [18].

Hormonal assay

HER2 status test was provided using immunohistochemistry test to positive or negative [19] Serum progesterone, estradiol (E2), Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH) were determined using Enzyme-Linked Fluorescent Assay (ELFA) on miniVIDAS system Analyzer (Biomerieux Corporation, France) using Biomerieux kits.

Statistical analysis

Mean ± SD of studied hormone levels were calculated using Microsoft Excel 2007. The obtained data were subjected to analysis of variance (ANOVA) test followed by multiple comparisons analysis through Least Significant Difference (LSD) test using SPSS 20.0 version.

RESULT AND DISCUSSION

Hormones play important role in breast cancer development and treatment. The hormonal disorder in both pre and postmenopausal breast cancer patients reduces the opportunities for survival.

The result demonstrated that the (HER2) test in the group of breast cancer patients showed that some of them had a positive test while others were negative. The group of patients with positive (HER2) test was adopted and the negative group was excluded.

These results were in agreement with [20], [2], and [21], these HER2 positive in breast cancer patients might be due to it is more aggressive, less responsive to treatment, and decrease overall survival.

Breast cancer in postmenopausal women is widely known to be less aggressive than cancer in younger women [22].

The serum levels of hormones and HER2 status of the control and both pre and postmenopausal breast cancer patients are shown in table (1). The result also elucidated that breast cancer patients have a significant decrease in progesterone levels in premenopausal patients compared with a control group. A low level of progesterone increases the risk of breast cancer due to reduce anti-apoptotic protein expression [23]. These results were in agreement with [20], [2], and [21].

There is a non-significant increase in serum levels of estradiol in premenopausal patients compared with a control group. But there is a significant increase in estradiol levels in postmenopausal patients compared with the control group as shown in Table (1). A high level of estradiol increases the risk of breast cancer for it is a role in enhancement the mitogenic activity of breast epithelial cells [24). High estradiol levels may act as an effective metastases-promoter in HER2 positive breast cancer by a novel mechanism involving

the host microenvironment [14]. In postmenopausal patients, high estradiol levels and low progesterone levels were associated with an increased risk of breast cancer [25]. There is a significant increase in serum levels of FSH and LH in patients compared with a control group as shown in Table (1). FSH and LH are reproductive hormones synthesized by the pituitary gland in response to gonadotrophin-releasing hormone (GnRH) from the hypothalamus. The high level of FSH and LH in both pre and postmenopausal patients compared with a control group is associated with overexpression of HER2 and that considered a worse prognosis in breast cancer [2]. FSH promotes cancer cell proliferation, differentiation, and metastasis by activating adenylyl cyclase [26]. LH engages in the tumor progression of breast cancer using the luteinizing hormone choriogonadotropin receptor (LHCGR) [27].

Table 1: The HER2 and hormones in the serum of newly diagnosed pre and postmenopausal breast cancer patients and control

Parameter	**Premenopausal Control Mean ±SD**	**Premenopausal Patient Mean ±SD**	**P-value**	**Postmenopausal Control Mean ±SD**	**Postmenopausal Patient Mean ±SD**	**p-value**
HER2	Negative	Positive		Negative	Positive	
Progesterone ng/ml	11.174 ± 4.44	0.95 ± 0.77	0.00*	0.55 ± 0.01	0.44 ± 0.10	0.06
Estradiol pg/ml	70.46 ± 35.1	113.32 ± 76.6	0.072	5.50 ± 3.07	15.37 ± 7.68	0.00*
FSH ml U/ml	10.10 ± 5.43	32.42 ± 11.54	0.763	30.95 ± 14.6	79.35 ± 31.7	0.00*
LH ml U/ml	8.79 ± 4.88	37.74 ± 12.21	0.380	16.11 ± 12.2	30.70 ± 12.9	0.00*
TSH µIU/ml	1.96 ± 2.03	0.23 ± 0.79	0.03*	2.19 ± 1.18	0.18 ± 0.48	0.00*

*Significant difference at $P \leq 0.05$

HER2: Human epidermal growth factor receptor 2; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone

There is a significant decrease in TSH levels in both pre and postmenopausal patients compared with a control group as shown in Table (1). The alteration in thyroid hormone levels within the normal range may be concomitant with the proliferative activity of breast tumors in newly diagnosed euthyroid breast cancer patients [17]. The overexpression of the HER2 receptor can cause activation of growth kinase signaling like extracellular signal-regulated kinases (ERK) which expressed protein kinase intracellular signaling molecules that are involved in the regulation of meiosis, mitosis, and differentiated cells [28]. This study demonstrated that low TSH levels within the euthyroid range increase the risk of breast cancer. Table (2) show the relationship between the hormones in premenopausal patients. There is a significant negative relationship between progesterone and FSH, a negative relationship between progesterone and LH, a positive relationship between progesterone, estradiol, and TSH, and this agrees with Ajaya et al. [13]. A significant negative relationship between FSH and LH. Estradiol related to FSH and LH by negative relationship. And FSH related to LH by a significant positive relationship.

Table (3) show the relationship between the hormones in postmenopausal patients. There is a significant negative relationship between progesterone and TSH, a negative relationship between progesterone, estradiol, and FSH. And a positive relationship between progesterone and LH.

Estrogen and progesterone have a couple of sites of negative feedback on gonadotropin secretion: the pituitary and the hypothalamus. The presence of more than one site of negative feedback has the potential advantage of allowing for more precise and differential control of FSH and LH levels [29]. The aging diminishes pituitary responsiveness to GnRH.

Estrogen stimulates thyroid growth. Also stimulates the thyroid to make the thyroid hormone

precursor, thyroglobulin. increases the protein that carries thyroid hormones in the blood.

Progesterone and thyroid hormones have a reciprocal relationship. progesterone can increase thyroid hormone levels in the blood. Progesterone also decreases the amount of protein that carries thyroid in the blood so that more thyroid hormones can be free and get into the cells. Thyroid hormone affects the female reproductive axis [13, 14]. Disorders of the thyroid gland are responsible for dysregulation of the hypothalamus, pituitary, gonadal axis, and hypothyroidism is associated with oligomenorrhea [30].

Hypothyroidism causes an increase in the levels of thyroid releasing hormone (TRH) which in turn stimulates the secretion of thyroid-stimulating hormone (TSH) and prolactin (PRL) and PRL inhibits the synthesis and secretion of gonadotrophins.

estrogen levels within a physiological range have a direct negative feedback effect at the pituitary in women and also stimulates the thyroid to make the thyroid hormone precursor, thyroglobulin. HER2 responsible for initiating many cellular signaling pathways, principally the mitogen-activated protein kinase (MAPK), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and protein kinase C (PKC), all of that contributed to increase hormonal imbalance and then increase breast cancer risk in HER2 positive patients[7].

Table 2: the correlation between the hormones in HER2 positive premenopausal breast cancer patients

Parameter		Progesterone	Estradiol	FSH	LH	TSH
Progesterone	Pearson correlation	1	0.108	-0.424*	-0.324	0.279
	Sig (2-tailed)		0.609	0.034	0.114	0.177
Estradiol	Pearson correlation	0.108	1	-0.086	-0.230	0.027
	Sig (2-tailed)	0.609		0.684	0.269	0.898
FSH	Pearson correlation	-0.424*	-0.086	1	0.447*	-0.178
	Sig (2-tailed)	0.034	0.684		0.025	0.396
LH	Pearson correlation	-0.324	-0.230	0.447*	1	-0.009
	Sig (2-tailed)	0.114	0.269	0.025		0.966
TSH	Pearson correlation	0.279	0.027	-0.178	-0.009	1
	Sig (2-tailed)	0.177	0.898	0.396	0.966	

*correlation is significant at the 0.05 level (2-tailed)

Table 3: the correlation between the hormones in HER2 positive postmenopausal breast cancer patients

Parameter		progesterone	Estradiol	FSH	LH	TSH
Progesterone	Pearson correlation	1	-0.015	-0.167	0.030	-0.507**
	Sig (2-tailed)		0.943	0.424	0.885	0.010
Estradiol	Pearson correlation	-0.015	1	-0.392	0.260	0.100
	Sig (2-tailed)	0.943		0.053	0.210	0.636
FSH	Pearson correlation	-0.167	-0.392	1	0.136	0.059
	Sig (2-tailed)	0.424	0.053		0.516	0.778
LH	Pearson correlation	0.030	0.260	0.136	1	-0.111
	Sig (2-tailed)	0.885	0.210	0.516		0.596
TSH	Pearson correlation	-0.507**	0.100	0.059	-0.111	1
	Sig (2-tailed)	0.010	0.636	0.778	0.778	

**Correlation is significant at the 0.01 level (2-tailed)

Conclusion

The research had shown that HER2- positive breast cancer is associated with hormonal changes in pre and postmenopausal Iraqi women. Also, this study inferred that the low progesterone level in HER2-positive premenopausal breast cancer patients increases the risk of breast cancer. Also, the high level of estradiol, FSH, and LH increase the risk of breast cancer in HER2 positive postmenopausal breast cancer patient

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