

## Endogenous estradiol, estrogen and progesterone receptors increase benign and breast cancer risk among non-familial postmenopausal females

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### ABSTRACT

**Background:** Hormones and genetics play a critical role in breast cancer development, determining the association between plasma hormones and breast cancer risk among familial and non-familial females may provide insight into the etiology of breast cancer.

**Material and Methods:** 140 postmenopausal females during the period between June 2007 and May 2011 were enrolled in this study, 83 were breast cancer patients and 57 were benign patients. Plasma estradiol, progesterone and prolactin levels were estimated among familial and non-familial breast cancer females. Estrogen and progesterone receptor status was determined for all breast cancer and benign females.

**Results:** 20% of non-familial breast cancer and 16% of benign females have abnormal prolactin. 4% of non-familial breast cancer and 12% of benign females have abnormal progesterone. On the other hand, 57% of non-familial breast cancer females and 44% of non-familial benign females have abnormal serum estradiol. Plasma levels of estradiol were significantly associated with benign and breast cancer risk among both familial and non-familial females. While plasma levels of prolactin were significantly associated with breast cancer risk among non-familial females. Positive estrogen and progesterone receptors associated with increased benign or breast cancer risk among non-familial with high estradiol levels.

**Conclusion:** Abnormal plasma estradiol and positive estrogen and progesterone receptors associated with increased risk among postmenopausal both among non familial benign and breast cancer females. These findings suggest that estradiol, prolactin and estrogen and progesterone receptors evaluation might be useful to better identify females with non-familial hormone-dependent disease that should be considered in breast cancer pathogenesis as well as in the treatments.

**Key words:** Familial, estradiol, prolactin, estrogen receptor.

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## INTRODUCTION

**B**reast cancer is the most common cause of cancer death worldwide. Despite the numerous uncertainties surrounding the etiology of breast cancer, intensive genetic, epidemiological and clinical studies identified many risk factors associated with breast cancer.<sup>1</sup> Breast cancer risk factors include age, family history of breast cancer (5-10% of breast cancers are associated with defined gene mutation like BRCA mutations), early menarche and late parity and high circulating levels of steroid hormones.<sup>2-4</sup> Recently, chemo preventive trials showed that women who use anti-estrogen agents in the breast have reduced risk for breast cancer compared with those who do not use the drug.<sup>5</sup> Determining the association between circulating hormones and breast cancer risk may provide an insight into the etiology of this disease and may help identify women who are at high risk. This study aimed to determine circulating plasma hormones, estrogen and progesterone receptor status and correlate them with breast cancer risk among familial and non-familial females. Estrogens are synthesized from androgens in premenopausal ovary and in extra ovarian tissue including fat, muscle, liver and the breast by the

conversion of cholesterol which is made by the adrenal gland in post menopausal females. Estrogen contribute to tumor by promoting the proliferation of cells with existing mutation or perhaps by increasing the opportunity for mutations that regulate the growth and differentiation of mammary cells which may play an important role in the development of breast cancer.<sup>4-6</sup> Few studies demonstrate the association between breast cancer and circulating levels of estrogen has now been well confirmed among postmenopausal women.<sup>7-8</sup> In contrast a relatively few studies on circulating hormone levels and breast cancer have been conducted in premenopausal women. This is largely due to variation in sex steroid hormone levels, particularly estrogen over the menstrual cycle. Thus further assessments are needed to evaluate the association between estrogen level and breast cancer risk among females.

Prolactin is a paradoxical hormone known as the pituitary hormone of lactation, which has more than 300 actions correlated to quasi-ubiquitous distribution of its receptors, lactation and reproduction.<sup>9</sup> It may increase breast cancer proliferation and inhibit apoptosis.<sup>10</sup> Prolactin levels and risk of breast cancer among premenopausal

women has been studied, and a significant positive association has been observed among both pre and postmenopausal breast cancer females.<sup>11-12</sup>

Progesterone has been hypothesized to both decrease and increase breast cancer risk.<sup>13-14</sup> Progesterone levels appear to be a modest risk factor for both pre and postmenopausal breast cancer with significant inverse association among progesterone levels and breast tumors risk.<sup>15-16</sup>

Women with family history of breast cancer are at increased risk of this disease, but no study shows the relation between plasma hormones levels and familial breast cancer. Multiple lines of evidence support the role of hormones in the etiology of breast cancer.<sup>4</sup> The aim of this study is to determine the level and evaluate the role of estradiol, progesterone and prolactin as risk factors among familial and non familial breast cancer. At the same time, correlate these levels with estrogen and progesterone receptor status.

## Material and Method

140 benign and malignant breast cancer females attending King Hussein Medical Center and Al-Basheer hospital (Amman, Jordan) during the period between June

2007 and May 2011 were enrolled in this study. Participants had signed a consent form and were interviewed to complete a questionnaire form including information about age, family history of breast cancer and therapy and medication. Malignant breast cancer and benign patients were categorized into familial breast cancer according to breast cancer history (family have at least one first degree or second-degree relatives diagnosed with breast cancer). Venous blood specimens were collected in EDTA tubes, centrifuged immediately for plasma separation then kept frozen at -20°C until analysis. Plasma estradiol, progesterone, and prolactin levels were assayed<sup>17-19</sup> by enzyme immunoassay test (ELISA, BioCheck, Inc, USA) using universal micro plate reader (ELx800, USA). Progesterone and Estrogen receptors were assayed by DakoCytomation CA (USA).

Statistical analysis of the data was performed using the statistical package for the social science SPSS 11.5 (SPSS Inc Chicago, IL) statistical program. Results were expressed as mean  $\pm$  ES, t-test was used to compare the significance of the mean differences between two groups. The differences were considered significant if the

obtained P value was less than or equal to (0.05).

## Results

One hundred and forty cancerous and benign females were in this study. Eighty three females were breast cancer and fifty seven were benign patients.

No statistical differences were found between the mean age of onset of familial benign ( $41.8 \pm 5.77$ ) compared to familial breast cancer ( $53.65 \pm 2.9$ ) (table 1). Also no statistical differences were found between the mean menopause age of familial benign females ( $55.00 \pm 3.32$ ) compared to the familial breast cancer ( $49.39 \pm 1.73$ ).

About fifty seven percent of non-familial breast cancer females have abnormal estradiol and about twenty percent have abnormal prolactin. On the hand, about eight and ten percent of familial breast cancer have abnormal estradiol and prolactin. The same trend appears on benign in cancer; plasma levels of estradiol, progesterone among non-familial females were forty four percent and twelve percent, respectively. On the other hand about sixteen percent of benign cancers have abnormal prolactin (table 2).

Estrogen and progesterone positive receptors were statistically significant

among benign, breast familial and non-familial cancers with high estradiol ( $p=.039$ ).

## Discussion

Breast cancer is the most common cancer overall as well as the most common malignancy afflicting women in Jordan. According to the latest statistics from the Jordan National Cancer Registry, breast cancer ranked first among cancer in females, accounting for 36.7% of all female cancers, and is the leading cause of cancer deaths among Jordanian women.<sup>20</sup>

Our study showed that familial breast cancer occurs at earlier age compared to non-familial (table 2), but, there is no statistical differences between mean ages of cancer onset among postmenopausal familial and non-familial breast cancer and benign females. Typically, young women present with more benign pathologies, especially in those harboring familial predisposition for breast cancer and this risk declined among older females.<sup>21</sup>

There is marked and consistent association between late age of menopause and breast cancer risk.<sup>22</sup> For women with menopause below 40 years, the risk of developing breast cancer was about 50% that of women with menopause over age 50.<sup>23</sup> In Jordan,

Jordanian women are afflicted with breast cancer (median age is 51) at a much younger age than women in Western countries (median age is 65), when they are still raising children.<sup>20</sup>

Jordanian breast cancer median age is close to menopausal age which is ranging between  $46.21 \pm 4.32$  non-familial and  $55.00 \pm 3.32$  familial benign and  $48.95 \pm 0.72$  non-familial and  $49.39 \pm 1.73$  familial breast cancer (table 1). Although early onset breast cancer represents inherited effects on immature mammary epithelium, while late-onset breast cancer likely follow extended exposures to promoting stimuli like plasma hormones of susceptible epithelium that has failed to age normally.<sup>24</sup> Our data showed no statistical difference between menopausal age among familial and non-familial benign females.

The key finding of the present study is that non-familial benign and breast cancer seems to be a hormonal dependent, females with abnormal hormones are (41/57=71.9%) (67/83=88.7%) for benign and breast cancer, respectively as shown in table (2). Most non-familial breast cancer patients had either high plasma levels of estradiol, or prolactin, while benign breast cancers had increased plasma levels of estradiol, progesterone or prolactin indicating that

these hormones may be implicated in a number of ways in breast cancer development. These results support the lines of evidence which suggests the role of these hormones in breast cancer.<sup>25-29</sup>

Estrogen and progesterone may be mediated through steroid hormone receptor expression, or through cell cycle proteins: p21, p27 and cyclin D1. However, prolactin may be mediated through modulation of membrane receptors.<sup>30</sup>

Cancer that is hormone-sensitive is slightly slower growing and has a better chance of responding to hormone-suppression treatment, than cancer that is hormone receptor negative. Gene expression profiling studies have shown that estrogen receptor positive and estrogen negative breast cancers are distinct diseases at the transcriptomic level, that additional molecular subtypes might exist within these groups, and that the prognosis of patients with estrogen positive disease is largely determined by the expression of proliferation-related genes. Our data shows that most non familial benign and breast cancers have abnormal estradiol, prolactin and are estrogen and progesterone receptor positive.

Our data shows that hormonal factors have low roles in the development that

familial breast cancer. This may be due to the fact that about fifty percent of familial breast cancer caused by either highly penetrant genes like BRCA1 and BRCA2, or by low penetrant genes like PALB2, BRIP1, ATM, NBS1, RAD50, CHEK2, P53 and PTEN<sup>2</sup>. The other 50% may be caused by unidentified genes.

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## ANNEX

**Table 1. Comparison between the mean age of onset, menopausal age between familial and non familial benign and breast cancer females**

	n	Age (years) mean±ES	Age of menopause (years) mean±ES	p-value
Benign	41	non-familial 44.59± 2.85	Non-familial 46.21± 4.32	0.48
	16	familial 41.8 ± 5.77	familial 55.00± 3.32	
Breast cancer	67	non-familial 57.81± 1.6	non-familial 48.95± 0.72	0.67
	16	familial 53.65± 2.9	familial 49.39±1.73	
p-value		0.67	0.58	
		0.43	0.72	

**Table 2. Percentage of familial and non familial benign and breast cancer females with abnormal hormone levels and estrogen and progesterone receptor positives**

Type	Hormone receptor	Familial (%)	Non-familial (%)	P-value
Breast cancer	Prolactin	8(9.6)	17(20.4)	0.03
	Er+/Pr+	1	9	0.87
	Progesterone	1(1.2)	3(3.6)	0.76
	Er+/Pr+	0	3	0.75
	Estradiol	7(8.4)	47(56.6)	0.045
	Er+/Pr+	2	31	0.05
Total		16	67	83
Benign cancer	Prolactin	4(7.0)	9(15.8)	0.44
	Er+/Pr+	1	6	0.43
	Progesterone	6(10.5)	7(12.3)	0.5
	Er+/Pr+	0	4	-
	Estradiol	6(10.5)	25(43.8)	0.032
	Er+/Pr+	2	19	0.039
Total		16	41	57