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Relationship between plasma progesterone, estradiol and prolactin concentrations and breast cancer in pre and postmenopausal women

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Hormones such as estrogen, progesterone and prolactin are implicated in a number of ways as possible causes of breast cancer. Throughout women life cycle, breast development and function depend on complex critical interplay of these hormones. The acknowledged gaps in our understanding concerning progesterone, estrogen and prolactin hormones involvement in human breast cancer has exposed the need to conduct this study for better understanding of the role played by these hormones in breast cancer during pre and post menopause status in order to influence prevention and treatment of breast cancer. Ninety women were enrolled, (80%) of them were breast cancer patients and the other (20%) were breast benign lesion patients. At attending King Hussein Medical Center, blood samples were collected and analyzed for plasma estradiol, prolactin and progesterone. Of the 72 breast cancer patients (66.6% and 33.4%), and of the 18 breast benign patients (27.8% and 72.2%) were in menopause and premenopausal, respectively. Of the breast cancer and benign patients groups, 55.6% of each had an association with either high plasma estradiol, prolactin or progesterone concentrations. Of the breast cancer patients that had association with high plasma hormonal concentrations, 47.5% had high plasma estradiol concentrations (155.0±36 pg/ml) and 89.5% of these were in menopause. Of the breast benign patients, 60% had high plasma prolactin concentrations (55.2±10.6 ng/ml). Menopausal breast cancer is associated with high plasma estradiol concentrations, while premenopausal breast benign were associated high plasma prolactin concentrations which indicate that high plasma estradiol in menopause is a risk factor for breast cancer development while high prolactin in premenopausal is a risk factor for breast benign. Therefore, breast cancer and benign are highly hormonal dependent.

Key words: breast cancer, premenopausal and postmenopausal, plasma hormones

Breast cancer is the second most common cancer among women after skin cancer and is the second most common cause of death among women after lung cancer. The causes of breast cancer are very complicated. Although about 7% of breast cancers are of genetical background, the rest are due to environmental causes [1]. Hormones such as estrogen, progesterone and prolactin are implicated in a number of ways as possible causes of breast cancer. Throughout women life cycle, breast development and function depend on complex critical interplay of these hormones [2]. Many breast cancers are hormone dependent, meaning hormones turn on breast cancer cell growth.

Estradiol is considered the most significant breast cancer risk factor because of its direct role in stimulation breast cell division or via its effects on other hormones and due its support of the growth of estrogen-responsive tumors [2]. Although, no study has clearly demonstrated a relationship between breast cancer and estrogen levels in premenopausal women [3]. Women with high estrogen levels were more likely to go on to develop breast cancer [4]. Postmenopausal women with high plasma estrogen levels have twice the risk of developing breast cancer as women with low levels [5].

Prolactin hormone is essential for breast development and lactation [6–8]. High plasma prolactin levels were associated with a modestly increased risk of postmenopausal breast cancer [7, 8]. About 95% of breast cancers expressed receptors for prolactin, meaning that they would be responsive to the stimulatory effect of prolactin [9–11]. However, in a study by Tworoger et al [12], a non significant positive relationship between prolactin levels and postmenopausal breast cancer was observed. Progesterone stimulates breast development during pregnancy [13]. About 65% of estrogen positive breast

Table 1: Reference values for plasma estradiol, progesterone, and prolactin hormones during follicular, ovulation, luteal and menopause status

Stage	follicular	ovulation	luteal	menopause
Estradiol (pg/ml)	30-100	130-350	50-180	< 60
Progesterone (ng/ml)	0.15-0.7	-	2-25	0.06-1.6
Prolactin (ng/ml)	-	-	23.5	10.2 (3.8-25.8)

cancers are also progesterone receptors positive, which means that progesterone may turn on breast cancer cell growth [14]. However, progesterone proliferative effects on mammary gland development and tumor genesis are not well recognized [15–17].

Therefore, the acknowledged gaps in our understanding concerning progesterone, estrogen and prolactin hormones involvement in human breast cancer has exposed the need to conduct this study to better understanding the role played by these hormones in breast cancer during pre and post menopause status in order to influence prevention and treatment of breast cancer.

Patients and methods

A total of ninety women were enrolled in this study. Of these (72), 25-90 years of age (53.5±1.5 years) were histopathologically diagnosed with breast cancer and (18) diagnosed as benign patients aged from 17 to 70 years (40.3±3.4 years). All patients were attending King Hussein Medical Center (Amman, Jordan) during the period between June 2007 and May 2008. All participants had signed a consent form and were interviewed personally by one of the researchers to fill a questionnaire form including information about; age, age at menopause, martial status, medical history, parity, cancer type, family history of breast cancer, type of therapy and medication, timing of blood draw in regards to menstrual cycle status, birth control way and reproductive history. All forms were completed before blood samples collection.

At blood sample collection, stage of menstruation, time of last menstruation and age of menopause were recorded in order to decide whether the plasma hormonal concentrations were within the reference values or above. Venous blood specimens were collected in (EDTA) tubes, and centrifuged immediately to separate plasma, which kept frozen at (-20°C) until analysis. Plasma estradiol, progesterone, and prolactin concentrations were assayed by enzyme immunoassay test (ELISA, BioCheck, Inc, USA) using universal micro plate reader (ELx800, USA). The minimum detectable concentrations of progesterone, estradiol, and prolactin were (0.3 ng/ml), (5 pg/ml), and (20 ng/ml); respectively. Coefficient variation for progesterone, estradiol and prolactin were (6%,4.2%); (3.2%,5.4%), and (5.5%,3.6%); respectively. Reference values for plasma estradiol [18], progesterone [19], and prolactin [20] concentrations during follicular, ovulation, luteal and menopause are shown in (Table 1.).

Statistical analysis of the data was performed using the statistical package for the Social sciences SPSS 11.5 (SPSS Inc Chicago, IL) statistical program. Results were expressed as mean ± SE, 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

As shown in Table 2, highly significant differences were observed between number of breast cancer and benign patients. At blood collection, 80% (72/90) of the patients were diagnosed with breast cancer and ranged in age from 25-90 years (53.5±1.5 years) and 20% (18/90) diagnosed as benign patients ranged in age from 17-70 years (40.3±3.4 years). Also, a significant difference was noticed between the two groups in percentage of premenopausal or menopausal women. Forty eight of the 72 (66.6%) diagnosed breast cancer patients were in menopausal statues and 33.3% (24/72) were premenopausal, while 5 of the 18 (27.8%) benign patients were menopausal and 13/18 (72.2%) were premenopausal (Table 2.).

Forty of seventy two (55.6%) breast cancer patients had high association with either high plasma estradiol, progesterone or prolactin concentrations. The rest 32/72 (44.4%) had plasma estradiol, progesterone, and prolactin concentrations within reference values. And eighty percent (32/40) of breast cancer patients that had high association with high hormonal concentrations were in menopause status (Table 3.). Of the nineteen breast cancer patients that had high plasma estradiol concen-

Table 2: Percentages of breast cancer and benign patients in premenopausal and menopause

			Premenopausal		Menopausal	
	n	%	n	%	n	%
Breast cancer	72	80	24	33.3	48	66.6
Benign	18	20	13	72.2	5	27.8
Total	90		37	41.0	53	59.0

Table 3: Percentages of breast cancer and benign premenopausal and menopause patients having high plasma hormone concentrations

						Premenopausal		Menopausal	
	n	%	High plasma hormone	n	%	n	%	n	%
Breast cancer n=72	40	55.6	Prolactin (ng/ml)	9	22.5	4	44.4	5	55.6
			Progesterone (ng/ml)	12	30.0	2	16.7	10	83.3
			Estradiol (pg/ml)	19	47.5	2	10.5	17	89.5
				40		8	20.0	32	80.0
Benign n=18	10	55.6	Prolactin (ng/ml)	6	60.0	4	66.7	2	33.3
			Progesterone (ng/ml)	2	20.0	-	-	2	100.0
			Estradiol (pg/ml)	2	20.0	-	-	2	100.0
				10		4	40.0	6	60.0

trations, 17 patients (89.5%) were in menopause, from the 12 patients that had high progesterone concentrations, 10 (83.3%) were in menopause, however, only five of nine (55.6%) breast cancer patients that had high prolactin plasma concentrations were in menopause. On the other hand, 10 of the 18 (55.6%) benign patients had high association with either high plasma estradiol, progesterone or prolactin concentrations. The rest 8/18 (44.4%) had plasma estradiol, progesterone, and prolactin concentrations within reference values. Also (60%) of the benign patients that had high association with high hormonal concentrations were in menopause status (Table 3.).

As shown in Table 4, high positive association was observed between high plasma estradiol concentrations and breast cancer incidence and low positive association was noticed between either high prolactin or progesterone concentrations. However, 19 of the 40 (47.5%) breast cancer patients had high plasma estradiol concentration (155.0±36.0 pg/ml), 12 of 40 (30.0%) had high plasma progesterone concentration (10.5±2.5 ng/ml) and 9 (22.5%) had high plasma prolactin concentration (62.0±11.5 ng/ml). Six of the 10 benign patients (60.0%) had high plasma prolactin concentration (55.20±10.6 ng/ml), while 2/10 (20.0%) had high plasma estradiol concentration (218.0±47.0 pg/ml) and the other 20.0% had high plasma progesterone concentration (3.0±0.4 ng/ml).

In addition, data in this study revealed that plasma prolactin, progesterone and estradiol concentrations in breast cancer patients during premenopausal period were significantly ($p<0.05$) higher than that observed in menopause status. However, in benign patients plasma prolactin concentration was significantly ($p<0.05$) higher in menopause (67±27.5 ng/ml) as compared to that in benign premenopausal women (49.3±11.1 ng/ml) (Table 5.).

Discussion

In this study, we found that most of the breast cancer patients (66%) were in the menopause status and most of breast benign patients (72.2%) were premenopausal. A high percent of breast cancer patients had high association with either high plasma estradiol, progesterone or prolactin concentrations indicating that these hormones may be implicated in a number of ways in breast cancer development. Of the forty breast cancer patients that had association with high hormonal concentrations, 47.5 % had high plasma estradiol levels and 89.4% of these women were in menopause. In this study we found also that percentages of breast cancer patients having high plasma progesterone (30%) or prolactin (22.5%), concentrations were significantly lower than that of estradiol (47.5%). The low percentage of women that had high plasma progesterone levels mean that there is no positive association with breast cancer. This finding contrasts with the held opinion augmented by progesterone hypothesis that progesterone contributes to the development of breast cancer [21]. The high plasma estradiol concentrations observed in menopause of breast cancer patients might be a risk factor for development of breast cancer, these findings are in agreement with that cited by Dorgan [5]

Table 4: Mean plasma prolactin, progesterone, and estradiol concentrations in breast cancer and benign patients that had high levels of these hormones.

Hormones	Benign n=10			Cancer n=40		
	n	%	Mean±SE	n	%	Mean± SE
Prolactin (ng/ml)	6	60.0	55.2±10.6	9	22.5	62.0±11.5*
Progesterone (ng/ml)	2	20.0	3.0±0.4	12	30.0	10.50±2.5*
Estradiol (pg/ml)	2	20.0	218.0±47.0	19	47.5	155.0±36.0*

n=number of patients with high level of plasma hormones
* differ significantly ($p\leq0.05$)

Table 5: Mean plasma prolactin, progesterone, and estradiol concentrations in breast cancer and benign patients at premenopausal and menopausal status that had high levels of these hormones

	Benign n=10				Cancer n=40			
	Premenopausal		Menopausal		Premenopausal		Menopausal	
	n	Mean±SE	n	Mean± SE	n	Mean±SE	n	Mean±SE
Prolactin (ng/ml)	4	49.3±11.1	2	67±27.5*	4	75.8±24.2*	5	50.7±7.9
Progesterone (ng/ml)	-		2	3.0±0.40	2	23.2±4.8*	10	8±2.1
Estradiol (pg/ml)	-		2	218.0±47.0	2	438.2±31.6*	17	121.6±16.4

n= total number of patients with high level of plasma hormones.
* differ significantly ($p \leq 0.05$)

who indicated that postmenopausal women with high plasma estrogen concentration have twice the risk of developing breast cancer as women with low levels, and high plasma estrogen is considered the most significant breast cancer risk factor because of its important role in stimulating breast caner cell proliferation.

As breast cancer is considered to be a hormonal dependent cancer, and it is critically important to avoid factors that would promote too much estradiol [22], especially after menopause, in which estrogen is made primarily in tissues such as fat, muscle, liver and breast. Factors that increase plasma estradiol levels after menopause are associated with an increase risk of breast cancer. These include taking hormone replacement therapy [1, 22, 23], being obese (as estradiol increased in obesity) and excessive alcohol intake [1, 24].

Data presented in this study showed that plasma prolactin levels were not positively associated with breast cancer in pre or post menopausal patients, these findings are consistent with those reported by Tworoger et al [12] who did not find an association between prolactin and breast cancer in premenopausal women. In addition, Lee et al [25] observed no significant association between plasma prolactin in relation to breast cancer risk. In another study [26], it has not been shown that prolactin increases risk of breast cancer. On the contrast, Tworoger et al [8] in another study reported that prolactin was modestly associated with an increased breast cancer risk which might be implicated in breast cancer etiology.

In this study, the positive relationship observed between high plasma prolactin and incidence of breast benign was generally similar in magnitude to that found for high plasma estradiol and breast cancer. As 55.6% of the benign patients had high association with high hormonal concentrations, 60.0% of them had high plasma prolactin concentrations. Therefore, high plasma prolactin concentrations may be implicated in breast benign development. Although prolactin is secreted primarily from anterior pituitary, expression in both normal and malignant breast tissue has been reported [9, 27, 28]. Prolactin removal from nonmalignant breast tissue inhibits the growth of epithelial cells [29, 30].

Also data presented in this study showed that most of benign patients were in premenopausal status (72.2%) which indicates that breast benign is highly associated with premenopausal. High plasma prolactin concentration were associated with a modestly increased risk of postmenopausal breast cancer [8, 31, 32] but in this study, patients with post menopausal breast cancer had no association with high plasma prolactin concentrations and this is in consistent with [12, 33, 34] who observed a non significant positive relationship between plasma prolactin concentrations and increased risk of postmenopausal breast cancer.

In conclusion, breast cancer and breast benign lesions were highly associated with endocrine changes during pre and post menopausal status. Therefore, this should be taken in consideration in planning for prevention and treatment of both breast cancer and benign.

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