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Serum Follicular stimulating hormone, Luteinizing hormone, and Prolactin levels in Benign and Malignant Disorders of Breast in Libyan women

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ABSTRACT: Cancer is a leading and emerging public health concern in most countries. Among different types of benign and malignant breast diseases, female breast cancer is the most frequent cancer and a major etiology of mortality worldwide. The present study is aimed to compare the serum levels of gonadotropins, and prolactin in benign and malignant disorders of the breast in Libyan Women. A total of 76 cases of breast carcinoma patients (age: 30 – 55 years); 22 cases of fibrocystic cases (age: 18 to 50 years) were selected from department of surgery, 7th October Hospital, Benghazi, Libya. Age matched controls (n=52) clinically free from both malignant and benign disorders of breast were included in this study. Venous blood samples were collected from all the patients and controls. Levels of serum gonadotropins and prolactin were estimated inall groups. Statistical analysis was done using SPSS software using Mann-Whitney and Wilcoxon tests. Results showed a significantly elevated circulating level of serum gonadotropins in patients with breast carcinoma with in increase in age and body-mass index, in comparison with controls. Whereas prolactin level did not correlate positively in breast cancer cases. A non-significant decrease in serum gonadotropins and prolactin levels in benign fibrocystic cases in comparison with control group. The correlation between pituitary hormones and breast cancer risk is shown by a significant rise in gonadotrpins level. Further follow-ups and advance researches are warranted to unravel the molecular mechanism.

1. INTRODUCTION

Cancer is a leading and emerging public health concern in most countries. Among different types of benign and malignant breast diseases, female breast cancer is the most frequent cancer and a major etiology of mortality worldwide (1). The breast cancer incidence varies across the globe, with the lowest in Asia and Africa whereas it is higher in North America and north and west Europe(2). The occurrence of carcinoma breast was noticed as 1 in 18 women globally. Breast cancer is the second major factor for female mortality in Africa and Southeast Asia whereas cervical cancer being the first cause(1). From 2007 to 2017, there was a raise in the number of carcinoma breast cases by 35% with several contributing factors such as 15% of the aging population, a population growth of 13%, and 4.1% of age-specific cases(3). The incidencein breast cancer increases with age, doubling about every 10 years until menopause, when the rate of increase dramatically slows. By the ages 75 to 80, the curve actually decreases(4). Though the population in the Arab country has a lower

incidence, the rates are gradually increasing in comparison with Europe and the USA. This raise in incidence can be attributed to various contributing factors such as lifestyle modifications, lack of physical activity, obesity, use of oral contraceptives, late marriage, etc., and partly due to enhanced detection and diagnosis(5).

Libya, North African, and Arab Maghreb countries with more than six million population according to 2019 data by World bank(6). The incidence of breast cancer was 18.8/100,000 females in Libya(7). In Western Libya, female breast cancer is the most frequent cancer stated by a study in 2020(5). The Benghazi Cancer Registry showed breast cancer in female attributes to 15% of all cancer-related mortality in cases diagnosed during 2003 - 2005 in Eastern Libya(8). Delay in the diagnosis of breast cancer is a serious issue in Libya and with a concomitant intricate interaction between various factors and with progressive advanced stages(9) underpins the mortality rate. Diagnosis of breast cancer at an early stage and wider treatment modalities improves the survival rates and quality of life (10).

The benign breast diseases (BBD) in women are varied groups of pathologies mostly associated with benign fibrocystic alterations in the breast (11). The most frequent BBD in women includes mastalgia, benign tumors, mammary duct ectasia, mastitis, and fibrocystic changes (12). BBD poses a higher risk to develop breast cancer in a later stage(13). These benign diseases include a wide spectrum of histologic features which are subdivided into proliferative and non-proliferative lesions. The proliferative lesions are further classified as hyperplastic atypia with a greater risk of emerging as breast cancer and atypia without hyperplasia(14). The non-proliferative lesions have a lesser risk of developing later breast cancer, without- or weak family history of breast cancer(14, 15).

The most common classification of malignant breast pathologies is either invasive or non-invasive. The non-invasive breast cancer is with the potential to progress to invasive form, whereas invasive forms are more concerning due to their metastatic ability to various remote viscera(11). The non-invasive breast carcinoma is further classified as (a). Ductal carcinoma *in situ* with the proliferation of cancer cells in the duct-lobular system of the mammary gland and (b). Lobular carcinoma *in situ,* characterized by the proliferation of cancer cells in the multiple lobules of the mammary gland. The ductal or lobular origin of epithelial tumors are usual forms of invasive breast cancers, with other types being carcinoma with medullary features, mucinous, and tubular carcinoma, etc(16).

Optimal public health improvement can be attained with a better prognosis of breast cancer achieved by early detection and diagnosis. A sizeable number of evidence about the breast cancer circulating potential biomarkers are documented. However, the information, regarding the levels of hormones such as prolactin (PRL) and gonadotropins i.e follicular stimulating hormone (FSH), and luteinizing hormone (LH) in circulation, are scanty, especially in a female breast cancer patient in Libya. Thus the present study is aimed to compare the serum levels of gonadotropins, and PRL in benign and malignant disorders of the breast.

2. MATERIALS AND METHODS

Subjects

A total of 150 Libyan women were included in this study. This study was conducted during the period from 2013 to 2014. Three groups of subjects were included in this study distributed as follows: Group I- 76 patients with a histologically confirmed diagnosis of breast cancer aged between (30–70) years; 22 patients with benign breast (fibrocystic) disorders aged between (18-50) years were collected from the department of surgery, 7th October Hospital as well as from Benghazi Medical Center. The results obtained from breast cancer and fibrocystic cases were compared with 52 cases of clinically age-matched normal females considered as controls.

In this study, all participants were asked to fill in a lifestyle questionnaire and interview, included information containing questions regarding reproductive history, on ages at menarche, menopause, first birth, parity; and family history of breast cancer.

The patients were selected by systematic randomization sampling. Demographic, clinical, pathological, and therapeutic data were collected from patients' hospital records. Anthropometric measurements (e.g. height, weight) were recorded. The height and weight were measured and obesity was defined as body mass index (BMI) of $\geq$ 30 kg/ m^2, where BMI was calculated by dividing the weight in kilograms on height in meters squared. PRL was taken during rest or early morning before mastectomy and before taking chemotherapy or/and radiotherapy for breast cancer patients.

Sample Collection

Blood samples (5 ml) were collected by venous arm puncture from each patient then transferred immediately to a clean dry plain tube. After removing the needle, the blood was allowed to clot for at least (10-15) min at room temperature then serum was separated by centrifugation at 3000 rpm for 15 minutes, carefully transferred to plastic tubes, and stored at 2-8 ºC for 24 hours prior to assay. Serum samples were either analyzed immediately or stored at -20 ºC until they were analyzed for further use.

Then serum levels of gonadotropins and PRL were measured, in all participants of the study, by Cobas E 411 analyzer using electroluminescent immunoassay (ECLIA) method by using ROCHE ready equipment in the department of biochemistry and hormones at Al-Gomhorryia Hospital, Benghazi, Libya.

Estimation of serum levels of FSH, LH and PRL:

The FSH, LH and PRL assay methods were adopted from Tietz NW (1995), and Fahie-Wilson et al., (2013) (17, 18).

FSH assay: It employs two different monoclonal antibodies specifically directed against human FSH. The test was done by incubating twice with a biotinylated monoclonal FSH-specific antibody, and a monoclonal FSH-specific antibody labeled with a ruthenium complex form a sandwich complex and streptavidin-coated microparticles. This complex is bound to the solid phase via the interaction of biotin and streptavidin. The reaction mixture was aspirated into the measuring cell where the microparticles are magnetically captured onto

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the surface of the electrode. The chemiluminescent emission, induced by the application of voltage to the electrode then induces, was measured by a photomultiplier.

LH assay: It employs two monoclonal antibodies specifically directed against human LH. The two specific antibodies are used to recognize particular conformations, with the biotinylated antibodies detecting an epitope constructed from both subunits whereas the antibody with the ruthenium complex label detects an epitope from the β-subunit. As a result, the Elecsys LH assay shows negligible cross-reactivity with FSH, TSH, hCG, hGH, and hPL

Prolactin assay: Elecsys Prolactin II assay uses two monoclonal antibodies specifically directed against human prolactin. The test was done by incubating twice with a biotinylated monoclonal Prolactin-specific antibody, and a monoclonal Prolactin-specific antibody labeled with a ruthenium complex form a sandwich complex and streptavidin-coated microparticles. This complex is bound to the solid phase via the interaction of biotin and streptavidin (18).

Statistical analysis: The statistical analysis was done using SPSS 16.0 software. A Mann-Whitney U test and Wilcoxon tests were used to analyze the data. A 'p' value less than 0.05 is considered as statistically significant.

3. RESULTS

Age and BMI are summarized in table.1, in which the age of participants in breast cancer cases varied from 30 -70 years, in fibrocystic cases age varied from 18-50 years having the mean age ±SD (47.8±11.2years), and (31.6±11.6 years) respectively, and the control group (41.4±9.6 years) has the age varied from 18–56 years.

Results showed highly significant changes in the age among the groups (P<0.000). A high significance (P<0.001) was observed in breast cancer cases when compared with control. Age in fibrocystic group was significant (P<0.01) when compared with the control. It was also highly significant (P<0.000) when compared between breast cancer and fibrocystic cases. The BMI was non-significant among the groups (P< 0.081) The observed values of the BMI measurements (mean ± S.D) in breast cancer cases were 33.3±20.4 Kg/m^2, in the fibrocystic group were 27.1±5.6 Kg/m^2 and the control group was 27.7±8.1 Kg/m^2. There was a non-significant BMI in the fibrocystic group (P<0.881) and breast cancer cases (P< 0.048) when compared to control.

Table.1 Mean and standard deviation values of Age and BMI

Parameter	Breast cancer cases N=76 (mean ± S.D)	Fibrocystic cases N=21 (mean ± S.D)	Controls N=52 (mean ± S.D)	p-Value
Age	47.8±11.2	31.6±11.6	41.4±9.6	p< 0.001 p<0.01
BMI (Kg/m2)	33.3±20.4	27.1±5.6	27.7±8.1	NS

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Table 1: Mean value of age and BMI in control group, fibrocystic and breast cancer cases. (p< 0.001- Control vs breast cancer cases; p<0.0- Control vs fibrocystic cases), (NS)-Non-significant.

The level of serum FSH in breast cancer cases, fibrocystic, and control groups are presented in table 2. FSH levels showed a significant increase (P< 0.000) in breast cancer cases 78.1±119.6 mIU/ml, when compared to controls 19.6±24.5 mIU/ml. Very highly significant (P< 0.000) FSH serum level was observed among the groups. The level of FSH was significantly (P<0.004) increased in patients suffering from breast cancer when compared with fibrocystic group.Whereas, the level of FSH was not significantly altered (P<0.893) in fibrocystic group when compared to control group.

The level of serum LH in the breast cancer patients, fibrocystic and control is presented in table 2. LH (mean ± S.D) levels showed a significant increase in breast cancer cases (23.1±21.0 mIU/ml) when compared to control group (15.4±14.7 mIU/ml). A significant alterations in the level of serum LH (P< 0.022) was observed among the groups. The level of LH was significantly high (P< 0.020) in patients suffering from breast cancer group when compared to control group. Whereas, the level of LH was not significantly altered (P<0.33) in breast cancer cases when compared with fibrocystic group. Similarly the LH level was not significantly changed (p< 0.674) in fibrocystic group when compared to controls.

The level of PRL in the breast cancer patients, fibrocystic and control is presented in table 2. Present study indicate a non-significant decrease in PRL (uIU/ml) levels in both breast cancer (285.6±250 uIU/ml) and fibrocystic (350.4±277 uIU/ml) group as compared to control (399.8±608.8 uIU/ml). But this decrease in the PRL level was not significant (P< 0.527) in breast cancer group when compared with fibrocystic group. Similarly, in comparison with control we observed a non-significant decrease (P<0.646) of PRL level in fibrocystic group and breast cancer group (P<0.128).

Table 2. Mean and standard deviation values of FSH,LH and Prolactin.

Parameter	Breast cancer cases, N=76 (mean ± S.D)	Fibrocystic cases, N=21 (mean ± S.D)	Control, N=52 (mean ± S.D)	p-Value
FSH (mIU/ml)	78.1±119.6	16.7±29.3	19.6±24.5	p<0.000 p=0.004
LH (mIU/ml)	23.1±21.0	13.5±12.6	15.4±14.7	0.020
Prolactin (uIU/ml)	285.6±250	350.4±277.6	399.8±608.8	0.308

TABLE 2: Mean circulating levels of FSH, LH and PRL in control group, fibrocystic and breast cancer cases. (p<0.000- Control vs Breast cancer groups; p=0.004 Breast cancer vs fibrocystic cases; p=0.020- Control vs Breast cancer groups)

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4. DISCUSSION

In the present study, we analyzed the levels of PRL, FSH, and LH hormones in the serum of the patients with benign and malignant breast diseases as well as in controls.

Age is a one of the major risk factors for breast cancer development. We observed the age of the breast cancer patients in this study were ranged from (30–70) years, with a mean age of (47.8±11.2) years. In addition, majority of the patients presented in hospital with advanced stages of the disease. The mean age of the breast cancer cases in this study was slightly higher than that reported study done focused on the age of women with breast cancer in Libya(7). The age pattern is identical with age of breast cancer patients in Africa or Middle and North Africa (MENA) region(19, 20).These observations suggest that Libyan and other African breast cancer patients are dominantly of premenopausal type.

In this study, we found breast cancer patients having higher BMI than the controls, but the difference was not statistically significant. Excess body weight has been linked to an increased risk of postmenopausal breast cancer and growing evidence suggests that obesity is associated with poor prognosis in women diagnosed with early-stage breast cancer (21-23). A study by Jee et al. found that higher BMI could increase risk of breast cancer in Korean population (24). Conversely, a study by Palmer et al. demonstrated that lower BMI was associated with breast cancer risk(25).

The FSH and LH are the gonadotropins secreted by anterior pituitary gland basophilic chromophil cells known as gonadotrophs. These gonadotropins are glycoprotein hormones containing heterodimers subunits, alpha, and beta. The beta subunits are encoded by distinct genes which provides target cell specificity(26). These gonadotropins control steroidogenesis and gametogenesis through their receptors FSHR and LHR on gonads. In the present study, we found there was a statistically significant increase in the levels of FSH & LH in breast cancer cases and a non-significant decrease in FSH & LH levels in fibrocystic group in comparison to controls. Similar to our findings, an elevated FSH concentration was observed in a post-menopausal breast cancer patient with Her-2 positive. Also in breast cancer, higher Ki67 levels with elevated serum gonadotropins levels documented by Zhou et.al.(27). Significantly elevated levels of gonadotrpins in breast cancer patients in comparison to normal control a study by Selviet. al. (28). In contrary with our study findings, a study by Kuijper et al. that showed low level of luteinizing hormone/choriogonadotropin receptor (LH/CGR) expression or even undetectable in breast cancer indicating a low level of LH(29). In advanced breast cancer, the FSH concentration was low and LH level remains unaltered whereas low FSH and LH concentration in early breast cancer as reported by Wang et al(30). A study by Sundaram et.al. demonstrated that serum of patients with clinically diagnosed mammary dysplasia, a benign breast disease, showed elevated LH level, with a normal level of FSH and a non-significant change in prolactin level(31). Recent experimental studies revealed, by mediating the cytoskeletal rearrangement, these gonadotropins influence the group of genes involved in disease progression as well as regulate the spread and intrusion of the breast cancer cells, thus FSH and LH may have a potential for breast cancer progression (32, 33).

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Prolactin is a lactogenic polypeptide hormone produced by the acidophilic chromophil cells known as lactotrophs of the anterior pituitary gland. The PRL has an essential role in facilitating the breast epithelial cell multiplication, and the alveolar maturation of the mammary gland(34). Several factors that stimulate the circulating PRL level include pregnancy, lactation, mental stress, strenuous physical exercise, etc, whereas it is inhibited by dopamine (35). Human plasma has various distinct forms of circulating PRL with several functions, however, there is no evidence suggesting the role of these differential forms in influencing the risk of breast cancer (36). The data in the present study showed that plasma prolactin levels were not positively associated with breast cancer patients, these findings are consistent with those reported by Tworoger and Hankinson who did not find an association between prolactin and breast cancer in premenopausal women (35). In addition, Lee et al. observed no significant association between plasma prolactin in relation to breast cancer risk (37). In disagreement with our results, a report by Eliassen et.al. showed that pre-menopausal women with breast cancer displayed an elevated level of serum prolactin (38). A study by Ali et al. showed significantly elevated levels of serum PRL in breast cancer of women in the age group 40-50 years, in Iraq (39). Numerous case reports have shown the development of breast cancer may be highly associated with marked increase of prolactin in prolactinoma(36, 40,41). A nested case-control prospective study has shown a strong positive correlation with plasma PRL level and breast carcinoma risk in premenopausal females (42). However, few studies documented a non-significant positive correlation between prolactin level and postmenopausal breast cancer risk (43, 44). Evidence from rodent and *in-vitro* experiments focused on the underlying mechanism of the PRL's role in breast carcinogenesis. High levels of PRL receptors are expressed in breast cancer cells, whereas their expression is low in normal breast tissue (42). PRL initiates tumor formation, accelerates growth rates of the tumor by triggering the cell proliferation rate, and modulate angiogenesis (45-47). Exogenous administration of PRL markedly increased the tendency of mammary tumor formation and the opposite effect is noted in the suppression of PRL (48).

5. CONCLUSION

The levels of gonadotropins are positively associated, whereas negatively associated PRL level in breast cancer cases. In fibrocystic cases the gonadotropin and PRL levels are negatively associated. Further follow-up as well as advance researches are warranted to unravel the molecular mechanism. This study has demonstrated that serum levels of hormones of FSH and LH may play important roles in the development of breast cancer and benign breast disorders. Although, PRL hormone in our study is not high enough to be used as a tumor marker. Therefore, hormones should be routinely estimated in breast cancer patients for better treatment approaches as well as monitoring of disease progression in both breast cancer and benign disorders it is preferable that the measurement of the serum levels of hormones is supported by the measurement of the receptors so that the finding will be more reliable.

Declaration of interest

The authors declare that there is no conflict of interest

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