

ORIGINAL RESEARCH

Evaluating the association between some fertility hormones and breast cancer progression in postmenopausal women

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Abstract

Background: In postmenopausal women, this study aimed to evaluate serum levels of reproductive-related hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and progesterone (PRG)) in the progression of breast cancer (BC). **Methods:** The profile of these hormones was measured in 100 postmenopausal BC patients and 40 age-matched healthy women. **Results:** There was no significant difference ($p > 0.05$) in the serum level of PRG, PRL, LH and FSH hormones between patients and controls. There was no significant association between levels of PRL and PRG and BC advanced features. In contrast, results revealed that both FSH and LH serum levels ($\mu\text{IU/mL}$; expressed as median) were significantly ($p < 0.05$) associated with the BC progression and worse outcomes, including tumor late stages (25.3 vs. 13.1 for FSH; 12.4 vs. 8.2 for LH), lymph node invasion (23.4 vs. 13.2 for FSH; 11.5 vs. 6.4 for LH), high grades (24.9 vs. 13.7 for FSH; 11.5 vs. 6.9 for LH), large size (23.4 vs. 11.3 for FSH; 12.5 vs. 5.1 for LH), negative estrogen (28.4 vs. 14.9 for FSH; 12.5 vs. 9.4 for LH) and progesterone (18.7 vs. 18.9 for FSH; 10.2 vs. 10.0 for LH) receptor status. Moreover, both FSH and LH were significantly ($p < 0.05$) correlated with carcinoembryonic antigen (CEA) ($r = 0.508$, $r = 0.263$, respectively) and cancer antigen (CA) 15.3 ($r = 0.439$, $r = 0.271$, respectively). **Conclusions:** Elevated levels of serum FSH and LH seems to be implicated in BC aggressiveness behaviour. Although this needs more investigations, this finding may provide relevant information about the role of these gonadotrophins as therapeutic targets owing to their action in BC progression.

Keywords

Breast cancer; FSH; LH; Severity; Worse outcomes

1. Introduction

Breast cancer (BC) is a malignant growth that initiates in the lobules/ducts lining cells within the breast glandular tissue and its global prevalence continued an upward trend [1, 2]. In 2020, >2 million newly diagnosed BC patients and about 700,000 BC-related deaths occurred globally, contributing to both great psychological and economic costs and influencing the long-term quality of life [3]. BC is heterogeneous with specific traits that affect predictive and prognostic outcomes of cases after and before menopause [4]. The disparities in cancer features between old and young females may be associated with risk factors variations such as ethnicity or race, reproductive history and body size [4].

Although menopause does not cause BC, risk of developing BC elevates as a woman ages [5]. A female who experiences menopause after 55 years old has an elevated risk of uterine,

breast and ovarian tumors [5]. Longer estrogen exposure elevates a female's risk of BCs [6]. Thus, due to hormonal considerations, females who have experienced natural menopause are approximately twice as likely to develop BC [5]. In different age groups, cancer features and biological biomarkers play an important role in predicting outcomes [4]. Moreover, it is very important to evaluate factors significantly impact BC outcomes in postmenopausal BC patients [7].

About 80% of newly found cases in BC are hormone-dependent. It has been claimed that these hormones promote the formation and spread of tumors [8]. In contrast to the well-established relation between reproductive hormone levels and postmenopausal BC risk, it is unknown how a single circulating hormone detection can predict subsequent BC risk [9]. In this regard, early research suggests that luteinizing hormone (LH) may play a part in carcinogenesis. This hormone regulates cell migration and invasion in BC cells with func-

tioning LH receptors [10]. Prolactin (PRL) plays a major part in BC development and other hormonally sensitive tumours, including endometrial, ovarian, lung and pancreatic cancers, in addition to stimulating the growth of mammary glands [11]. Also, a meta-analysis's findings showed a favourable correlation between BC development and higher PRL levels [12]. Moreover, progesterone (PRG) also may have a function in BC etiology, and, to cure or prevent BC, there is interest in decreasing progesterone activity [13]. In the past, mechanistic studies implicate PRG in BC development, whereas limited data have not provided strong support for a risk association with blood levels [13]. Recently there is notable clinical and experimental evidence that PRG, at its physiological levels and alone, is incapable of develop BCs, thus its standing as a "carcinogenic" hormone is undeserved [14]. From another hand, PRG natural chemical structure is quite different from chemically synthetic progestins, which, at the cell level, causes different actions [15]. Compared to synthetic progestins, a meta-analysis including 86,881 postmenopausal females found that the use of natural PRG was related to a markedly lower BC risk [16]. Despite all of this, and regarding disease progression, it is suggested that PRG may promotes pre-neoplastic BC progression in the mature breast epithelium by stimulation of cyclical mammary stem cell proliferation or occult tumor initiating cells [13]. Moreover, it is suggested that BC progression is a result of PRG/progesterone receptor (PR) signaling and a switch from paracrine to autocrine proliferation regulation [13].

From another hand, follicle-stimulating hormone (FSH) and its receptor (FSHR) have an important function in several tumors, including ovarian [17], endometrial [18] and prostate [19] cancer. Via activating adenyl cyclase and subsequent elevated cyclic adenosine monophosphate levels, FSH-FSHR induces cancer cell proliferation, differentiation and metastasis [20]. Although BC tissues do not express FSHR, elevated FSH levels have been linked to a markedly worse prognosis in BC cases [21].

The aim of this study is to assess the role of FSH, LH, PRL and PRG hormones blood levels in BC development in postmenopausal Egyptian women. Also, this study aimed to determine whether these reproductive hormones impact BC aggressiveness features, including late tumor stages, high grades, large size, lymph node invasion, distant metastasis and the negative expression of progesterone receptor, estrogen receptor and human epidemic growth factor receptor-2 (HER2) protein.

2. Material and methods

2.1 Populations

This retrospective case-control study included a total of 140 Egyptian females (100 postmenopausal BC cases and 40 age-matched healthy females). This study included all postmenopausal patients diagnosed with breast cancer and admitted to the Mansoura University Oncology Centre, Egypt from July 2023 to August 2024. They were subjected to clinical, radiological and pathological BC diagnosis. The exclusion criteria were patients with any chronic diseases such as liver and kidney diseases, patients discharged from the

centre at their request and patients did not have a definitive BC histopathological diagnosis. None of the healthy individuals had a history of cancer. The international Tumor-Node-Metastasis (TNM) [22] classification system was used to register cancer characteristics. Clinicopathologic information and serum samples were obtained from each patient prior to the initiation of any particular therapies, following informed consent. The Ethics and Scientific Committees of Mansoura University in Egypt accepted this study, which complied with the 1975 Helsinki Declaration's ethical principles.

2.2 Biochemical tests

Blood samples were collected from each participant at room temperature following a 6–8 hour fast. They were centrifuged at 4000 rpm for 15 minutes. As a result, serum was isolated and kept until it was needed at -20°C . Using an automated analyser (XE-2100D, Sysmex, Kobe, Japan), another blood portion (treated with anticoagulant ethylenediaminetetraacetic acid) was employed for a full blood count. Fresh sera was evaluated for alanine and aspartate aminotransferases (ALT and AST), bilirubin, albumin, urea and creatinine using commercial kits supplied by the manufacturer in a fully automatic closed biochemistry analyser (BA200, Bio Systems, Barcelona, Spain). In accordance with the industrial protocol of commercial Enzyme-linked immunosorbent assay kits, CA 15.3 and CEA (MBS020144, MyBioSource, San Diego, CA, USA) were measured.

2.3 Reproductive hormones assessment

Circulating levels of FSH, LH, PRL and PRG were measured using a chemiluminescence assay (CLIA; Maglumi 800, Snibe, Shenzhen, China) in accordance with the manufacturer's instructions. Intra- and inter-assay variation was less than 3% for all hormones. As with all measurements, the laboratory technician who conducted the measurements was blinded to each participant condition (case/control). All samples were done in duplicate.

2.4 Statistical analyses

Absolute numbers were used to express qualitative variables. The median (interquartile range) and the mean $\pm$ standard deviation (SD) were used to represent non-normally and normally distributed data, respectively. Accordingly, the Kruskal-Wallis test and the Student *t* test were used to evaluate group differences. *p* value < 0.05 is significant. Both SPSS (version 21, IBM, Chicago, IL, USA) and GraphPad Prism (version 6, Dotmatics, San Diego, CA, USA) were used to conduct statistical analyses.

3. Results

3.1 Patient's characteristics

Due to age matching between patients and controls, there was no notable age difference ($p = 0.123$). Additionally, as shown in Table 1, the platelet count ($p = 0.429$), haemoglobin levels ($p = 0.154$), red ($p = 0.442$), and white ($p = 0.144$) blood cells, as well as liver and kidney function tests did not

TABLE 1. Clinical characteristics of postmenopausal patients and controls.

Variables	Breast cancer	Healthy	<i>p</i> value
Number	100	40	-
Mean age $\pm$ SD, yr	58.8 $\pm$ 8.3	56.5 $\pm$ 8.9	0.123
Hemoglobin (g/dL)	11.13 $\pm$ 1.50	12.25 $\pm$ 1.25	0.154
RBCs ($\times 10^{12}$ /L)	4.1 $\pm$ 0.61	4.3 $\pm$ 0.56	0.442
WBCs ($\times 10^9$ /L)	7.5 $\pm$ 2.70	6.9 $\pm$ 1.85	0.144
Platelet count ($\times 10^9$ /L)	249.4 $\pm$ 69.7	250.7 $\pm$ 51.7	0.429
ALT (U/L)	24.2 $\pm$ 8.1	24.6 $\pm$ 7.1	0.629
AST (U/L)	29.12 $\pm$ 7.16	28.12 $\pm$ 7.51	0.611
Total bilirubin (mg/dL)	0.71 $\pm$ 0.11	0.69 $\pm$ 0.13	0.513
Albumin (g/dL)	3.82 $\pm$ 0.31	4.06 $\pm$ 0.12	0.492
Creatinine (mg/dL)	1.09 $\pm$ 0.25	0.95 $\pm$ 0.29	0.324
Urea (mg/dL)	30.25 $\pm$ 6.34	29.45 $\pm$ 5.70	0.411
CEA (U/L)	3.0 (1.7–10.0)	-	-
CA 15.3 (U/L)	30.0 (17.2–43.5)	-	-
FSH (μ IU/mL)	18.9 (11.6–29)	14.9 (9.5–23)	0.486
LH (μ IU/mL)	10.1 (5.9–14.1)	6.5 (3.6–13.2)	0.806
Prolactin (ng/mL)	3.60 (2.4–6.1)	3.25 (2.5–8.3)	0.081
Progesterone (ng/mL)	1.12 (0.85–2.8)	1.20 (0.82–3.7)	0.474

Normally and non-normally distributed data were expressed as mean $\pm$ standard deviation (SD) and median (interquartile range), respectively. RBC: red blood cell; WBC: white blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CEA: carcinoembryonic antigen; CA 15.3: cancer antigen 15.3; FSH: follicle-stimulating hormone; LH: luteinizing hormone.

change significantly ($p > 0.05$). There was also no significant difference in the serum level of PRG ($p = 0.474$), PRL ($p = 0.081$), LH ($p = 0.806$) and FSH ($p = 0.486$) hormones (Table 1). Table 2 provided a summary of tumor-related data including tumor size, depth (stage), histological grade, lymph node invasion, and distant metastasis and the expression of progesterone and estrogen receptors and HER2 protein.

3.2 Reproductive hormones and BC severity

There was no significant association between levels of PRL and PRG and BC advanced features (Table 3). In contrast, both FSH and LH (Table 4) elevated circulating levels were significantly ($p < 0.05$) associated with the disease progression including tumor late stages, lymph node invasion, high grades, large size and negative estrogen receptor status. Although high FSH levels were not associated ($p > 0.05$) with negative progesterone receptor nor HER2 statuses, these elevated levels were associated ($p = 0.048$) with triple negative subtype. However, LH elevated levels were associated with patients with negative HER2 (Table 4). Moreover, both FSH (Fig. 1A,B) and LH (Fig. 1C,D) were significantly correlated with CEA and CA 15.3 in postmenopausal BC patients.

4. Discussion

BC is a heterogeneous disorder with varied response to therapy, behavior, molecular features and morphological appearances [23]. Recently, molecular targeted therapy, treatment

and individualized diagnosis for BC cases have become topics of intense research [24]. How to enhance BC patients' long-term prognosis and the overall survival rate has increasingly become the focus of clinicians [24]. It is, therefore, vital to evaluate risk factors associated with BC severity to improve or prevent the disease prognosis.

The prognostic importance of FSH, LH, PRL and PRG reproductive hormones in BC was investigated in this research. These hormones levels were evaluated in postmenopausal BC patients and healthy controls. Among BC patients, the association between circulating hormones levels with BC aggressiveness behavior was also assessed.

As the exclusion criteria in this study included all patients with chronic diseases, such as liver and kidney diseases, the platelet count, haemoglobin levels, red and white blood cells counts, as well as liver and kidney function tests did not change significantly ($p > 0.05$) between patients and controls. Although there was no significant ($p > 0.05$) difference in these hormones levels between BC cases and healthy controls, both FSH and LH blood levels were significantly related to BC progression including tumor late stages, lymph node invasion, high grades, large size and negative estrogen receptor status. LH elevated levels were also associated with negative HER2 expression. Elevated levels of FSH were associated ($p = 0.048$) with triple negative subtype. Moreover, both of them were significantly correlated with CEA and CA 15.3 in postmenopausal BC patients. Conversely, in each PRL and PRG there was no significant ($p > 0.05$) association with these tumor features.

Maintained levels of these hormones after menopause can

TABLE 2. Classification of postmenopausal breast cancer patients.

Clinicopathological features	No. (%)
Primary tumor stage	
Early stage (T1–T2)	44 (44%)
Late stage (T3–T4)	56 (56%)
Lymph node invasion	
Negative (N0)	33 (33%)
Positive (N1)	67 (67%)
Metastasis	
Negative (M0)	81 (81%)
Positive (M1)	19 (19%)
Histological grade	
Low grade (G1–G2)	45 (45%)
High grade (G3)	55 (55%)
Tumor size	
Small (≤ 2 cm)	32 (32%)
Large (> 2 cm)	68 (68%)
Estrogen receptor	
Negative	30 (30%)
Positive	70 (70%)
Progesterone receptor	
Negative	36 (36%)
Positive	64 (64%)
HER2	
Negative	41 (41%)
Positive	59 (59%)

HER2: human epidemic growth factor receptor-2.

TABLE 3. Impact of PRL and PRG levels on BC progression in postmenopausal patients. Data were expressed as median (inter quartile range).

Categories	Prolactin (ng/mL)	<i>p</i> value	Progesterone (ng/mL)	<i>p</i> value
Primary tumor stage				
Early stage (T1–T2)	4.1 (2.4–7.2)	0.2649	1.2 (0.9–2.4)	0.9250
Late stage (T3–T4)	3.2 (2.3–4.2)		1.1 (0.85–3.2)	
Lymph node invasion				
Negative (N0)	3.8 (2.2–7.2)	0.8961	1.1 (0.84–2.6)	0.9143
Present (N1)	3.4 (2.4–5.7)		1.2 (0.9–3.2)	
Metastasis				
Negative (M0)	3.6 (2.4–7.2)	0.3181	1.1 (0.9–2.5)	0.2566
Present (M1)	3.4 (2.2–3.9)		2.2 (0.9–3.4)	
Tumor histological grade				
Low grade (G1–G2)	2.9 (2.0–5.2)	0.0789	1.5 (0.9–2.6)	0.5007
High grade (G3)	3.7 (2.8–7.9)		1.1 (0.84–3.6)	
Tumor size				
Small (≤ 2 cm)	3.5 (2.3–6.9)	0.6614	1.3 (0.9–2.5)	0.6669
Large (> 2 cm)	3.6 (2.4–5.4)		1.0 (0.84–3.6)	

TABLE 3. Continued.

Categories	Prolactin (ng/mL)	<i>p</i> value	Progesterone (ng/mL)	<i>p</i> value
Progesterone receptor				
Negative	3.4 (2.2–4.5)	0.3714	1.1 (0.8–2.5)	0.4847
Positive	3.8 (2.4–7.2)		1.1 (0.9–3.6)	
Estrogen receptor				
Negative	3.7 (2.2–4.4)	0.7910	0.9 (0.7–1.6)	0.0201
Positive	3.3 (2.4–6.9)		1.3 (0.9–3.6)	
HER2				
Negative	3.2 (2.2–7.0)	0.5672	1.1 (0.84–2.5)	0.8144
Positive	3.7 (2.5–6.1)		1.2 (0.9–3.4)	
Triple negative	3.0 (2.2–4.1)	0.1370	1.5 (0.7–2.5)	0.7590
Other subtypes	3.6 (2.4–7.2)		1.1 (0.9–3.2)	

HER2: human epidemic growth factor receptor-2.

TABLE 4. Impact of FSH and LH levels on BC progression in postmenopausal patients. Data were expressed as median (inter quartile range).

Categories	FSH (μIU/mL)	<i>p</i> value	LH (μIU/mL)	<i>p</i> value
Primary tumor stage				
Early stage (T1–T2)	13.1 (6.2–22.6)	0.0010	8.2 (4.1–11.0)	0.0019
Late stage (T3–T4)	25.3 (16.1–33.7)		12.4 (8.9–19.9)	
Lymph node invasion				
Negative (N0)	13.2 (6.1–21.9)	0.0069	6.4 (3.9–10.6)	0.0021
Present (N1)	23.4 (12.9–30.7)		11.5 (9.0–17.4)	
Metastasis				
Negative (M0)	20.1 (12.2–29.8)	0.2763	10.3 (5.6–15.1)	0.7303
Present (M1)	23.0 (10.3–28.8)		9.4 (5.7–12.3)	
Tumor histological grade				
Low grade (G1–G2)	13.7 (10.3–26.4)	0.0218	6.9 (4.2–11.1)	0.0050
High grade (G3)	24.9 (13.8–32.5)		11.5 (9.3–17.4)	
Tumor size				
Small (≤2 cm)	11.3 (5.3–18.9)	0.0025	5.1 (2.9–8.4)	0.0001
Large (>2 cm)	23.4 (13.7–30.3)		12.5 (9.4–19.9)	
Progesterone receptor				
Negative	18.7 (11.0–31.4)	0.7073	10.2 (7.1–17.1)	0.3635
Positive	18.9 (11.8–27.5)		10.0 (4.2–13.3)	
Estrogen receptor				
Negative	28.4 (17.1–36.2)	0.0169	12.5 (9.2–20.8)	0.0115
Positive	14.9 (10.9–27.0)		9.4 (4.5–12.6)	
HER2				
Negative	18.9 (11.9–30.5)	0.4544	11.4 (8.14–19.0)	0.0461
Positive	18.2 (10.9–27.5)		8.2 (4.2–12.5)	
Triple negative	29.3 (19.6–36.1)	0.0480	11.4 (7.5–15.8)	0.4180
Other subtypes	17.2 (11.3–27.5)		10.0 (5.2–13.6)	

FSH: follicle-stimulating hormone; LH: luteinizing hormone; HER2: human epidemic growth factor receptor-2.

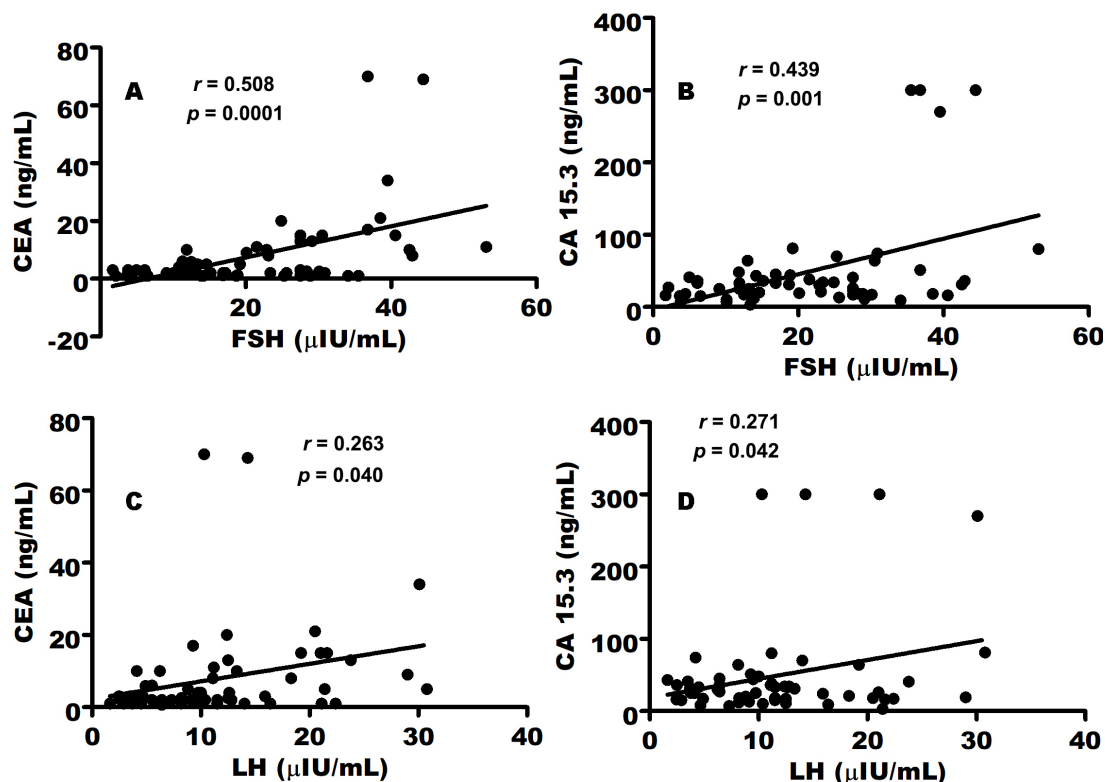


FIGURE 1. Correlation between FSH and both (A) CEA ($r = 0.508$) and (B) CA 15.3 ($r = 0.439$) serum levels revealed a significant ($p < 0.001$) association in postmenopausal breast cancer patients. Similarly, LH was significantly correlated with (C) CEA and (D) CA 15.3 ($r = 0.263$ and 0.271 , respectively). CEA: carcinoembryonic antigen; CA 15.3: cancer antigen 15.3; FSH: follicle-stimulating hormone; LH: luteinizing hormone.

be explained in the light of some evidence that have been previously confirmed in previous studies. Ovarian aging earliest hormonal evidence is the selective FSH increase owing to decreasing inhibin B (granulosa cell number marker) levels [25]. With the ovulatory cycles loss and the decrease in ovarian function, gonadotropin-releasing hormone (GnRH) pulses occur more commonly [26] while decreasing estradiol concentrations permit elevates in both GnRH [27] and in its related gonadotropin responses [28]. After menopause in the medial basal hypothalamus, some autopsy studies suggest an elevate in GnRH expression [29]. This effect is mediated by a decrease in the inhibitory neuropeptide, dynorphin, and an increase in the stimulatory neuropeptides, kisspeptin and neurokinin B [30]. Moreover, in postmenopausal women, FSH and LH disappearance half-life is prolonged as a consequence of changes in these 2 glycoprotein hormones isoform composition with the estradiol loss [31, 32].

Several reproductive factors are related to BC risk, potentially through a hormonal pathway [33]. In Shi study, they evaluated whether or not high blood FSH causes great severity of BC of both pre- and post-menopausal patients [34]. Compared to benign breast tissue vessel, they found that FSH receptor was highly expressed on endothelium of BC vessel [34]. Also, it was reported that FSH promoted the angiogenesis on human umbilical vein endothelial cells (HUVEC) as it elevated matrix metalloproteinase expression, activated phosphorylation of a wide range of kinases and calcium influx and stimulated HUVEC invasion, migration and proliferation

[34]. Their clinical investigation revealed a linear positive association between microvessel density of BC and FSH level [34].

In accordance with our results, Sanchez *et al.* [35] found in T-47D BC cells that both FSH and LH alter the expression of genes implicated in invasion, motility and adhesion via their receptors activation. They reported that LH affected the expression of varied genes involved in tumor biology of these BC cells [35]. In *in vivo* rat model of BC progression, they found a direct association between these gonadotrophins and the tumor growth extent and, thus, they highlighted that these hormones could potentially associate with BC progression, particularly in post-menopausal cases who typically have high gonadotrophin levels [35]. From another hand, Sheng *et al.* [18] findings suggested that FSH stimulates endometrial cancer metastasis and proliferation.

At the cellular level, BC development is impacted by the cytokines and hormones secreted by the ovary and the placenta (reproductive factors) [36]. The majority of BCs (about 80% of new cases) depend on hormones [8, 36]. In this setting, these hormones are known to promote cancer development and progression [10]. By controlling many kinases that activate actin cytoskeletal proteins, LH hormone can regulate cell invasion and migration in BC cells that express its functional receptors (LHR) [10]. Via rapid extra-gonadal LHR signaling to the Rous sarcoma virus oncoprotein (Src)/Focal Adhesion Kinase/paxillin pathway, Mondaca *et al.* [10] showed that LH induces paxillin phosphorylation and this process results

in the phosphorylation/activation of the nucleation promoter factors cortactin and N-Wiskott-Aldrich syndrome protein (N-WASP). As a consequence, Arp2/3 complexes induce actin polymerization, required to promote cell invasion, migration and adhesion, so stimulating tumor cells metastatic spread [10]. Similarly, some studies have reported the impact of FSH receptors (FSHRs) on various BC cell lines, such as T-47D, MCF-7, MDA-MB-231 and SK-BR-3. These cancerous cells proliferation and survival may be enhanced by FSH [37]. Moreover, FSH, as an estrogen main regulator, may related to estrogen dysregulation, further influencing the BC pathogenesis. In postmenopausal patients, interactions between estrogen and FSH may explain BC treatment complexity [37].

Preoperatively elevated serum levels of CEA and CA 15.3 have suggested by previous studies to be significantly related to BC severity in the multivariate analysis including advanced stage, axillary node metastasis and large tumor size. Also, compared to those with normal levels, BC cases with elevated CEA and CA 15.3 levels exhibited a worse BC prognosis, even in stage-matched analysis [38, 39]. In this study, both FSH ($r = 0.508$ ($p = 0.0001$); $r = 0.439$ ($p = 0.001$), respectively) and LH ($r = 0.263$ ($p = 0.040$); $r = 0.271$ ($p = 0.042$), respectively) elevated levels were significantly correlated with CEA and CA 15.3 in postmenopausal BC patients.

Traditionally, BC is assorted in the light of the presence of some receptors (progesterone (PR), estrogen (ER), human epidemic growth factor receptor-2 (HER2)) [40]. Molecular classification based on immunohistochemistry reveals a close association of these receptors with BC prognosis. In BC patient, this step is considered as a standard regimen for selecting the most useful approaches [41]. The initial BC predictive molecular biomarkers are PR and ER as cases with positive receptors generally possess high hormone therapy sensitivity [41]. Also, another oncogene related to BC progression is the gene coding HER2, and an abnormality in HER2 expression has close relation with BC development, onset, metastasis and invasion [41]. Another important preliminary result of this study that needs further evaluation and future studies is that elevated FSH and LH levels were associated with negative estrogen receptor and HER2 expression.

Despite our important result, some limitations including retrospective nature and single-center cohort may exist. Also, this study, owing to limited resources, lack adjustment for some potential confounding variables that may influence fertility hormones including menopause timing, age, adiposity and behavioral factors. Thus, further multicenter studies including additional cohort are required to validate these observations.

5. Conclusions

Our findings endorse that FSH and LH elevated levels may have extragonadal effects on BC progression and poor outcomes. Therefore, we encourage initiatives to integrate the measurement and management of such hormones into the follow-up of BC patients. Especially in post-menopausal females with high gonadotrophins circulating levels, it may provide new perspectives for therapeutic drugs.

AVAILABILITY OF DATA AND MATERIALS

Data supporting the reported results are available from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

MAA—conceptualized the study. MAA, SSM, MAEAE, AA—investigation and experimental work. NHA, MMES—supervision and validation of the study. AA—samples providing and collection. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

According to the 1975 Helsinki Declaration's ethical principles, the study protocol was accepted by the Ethics and Scientific Committees of Mansoura University (R.21.o7.1376). Clinicopathologic information and serum samples were obtained from each patient prior to the initiation of any particular therapies, following informed consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] Giaquinto AN, Sung H, Newman LA, Freedman RA, Smith RA, Star J, *et al.* Breast cancer statistics 2024. CA: A Cancer Journal for Clinicians. 2024; 74: 477–495.
- [2] Aslam A, Mustafa AG, Hussnain A, Saeed H, Nazar F, Amjad M, *et al.* Assessing awareness, attitude, and practices of breast cancer screening and prevention among general public and physicians in Pakistan: a nation with the highest breast cancer incidence in Asia. International Journal of Breast Cancer. 2024; 2024: 2128388.
- [3] Wang F, Skiba MB, Follis S, Liu N, Bidulescu A, Mitra AK, *et al.* Allostatic load and risk of invasive breast cancer among postmenopausal women in the U.S. Preventive Medicine. 2024; 178: 107817.
- [4] Bosompem K, Yorke J, Buckman TA, Brenu SG, Nyantakyi M, Aitpillah FS, *et al.* Comparative analysis of breast cancer characteristics in young premenopausal and postmenopausal women in Ghana. Scientific Reports. 2024; 14: 2704.
- [5] Støer NC, Vangen S, Singh D, Fortner RT, Hofvind S, Ursin G, *et al.* Menopausal hormone therapy and breast cancer risk: a population-based cohort study of 1.3 million women in Norway. British Journal of Cancer. 2024; 131: 126–137.
- [6] Al-Shami K, Awadi S, Khamees A, Alsheikh AM, Al-Sharif S, Ala' Bereshy R, *et al.* Estrogens and the risk of breast cancer: a narrative review of literature. Heliyon. 2023; 9: e20224.

- [17] Nahmias-Blank D, Maimon O, Meirovitz A, Sheva K, Peretz-Yablonski T, Elkin M. Excess body weight and postmenopausal breast cancer: emerging molecular mechanisms and perspectives. *Seminars in Cancer Biology*. 2023; 96: 26–35.
- [18] Tavčar Kunštič T, Debeljak N, Fon Tacer K. Heterogeneity in hormone-dependent breast cancer and therapy: steroid hormones, HER2, melanoma antigens, and cannabinoid receptors. *Advances in Cancer Biology*. 2023; 7: 100086.
- [19] Zhang X, Tworoger SS, Eliassen AH, Hankinson SE. Postmenopausal plasma sex hormone levels and breast cancer risk over 20 years of follow-up. *Breast Cancer Research and Treatment*. 2013; 137: 883–892.
- [10] Mondaca JM, Uzair ID, Castro Guijarro AC, Flamini MI, Sanchez AM. Molecular basis of LH action on breast cancer cell migration and invasion via kinase and scaffold proteins. *Frontiers in Cell and Developmental Biology*. 2020; 8: 630147.
- [11] Hathaway CA, Rice MS, Collins LC, Chen D, Frank DA, Walker S, *et al.* Prolactin levels and breast cancer risk by tumor expression of prolactin-related markers. *Breast Cancer Research*. 2023; 25: 24.
- [12] Aranha AF, Dos Anjos LG, Turri JAO, Simões RS, Maciel GAR, Baracat EC, *et al.* Impact of the prolactin levels in breast cancer: a systematic review and meta-analysis. *Gynecological Endocrinology*. 2022; 38: 385–390.
- [13] Trabert B, Sherman ME, Kannan N, Stanczyk FZ. Progesterone and breast cancer. *Endocrine Reviews*. 2020; 41: 320–344.
- [14] Horwitz KB, Sartorius CA. 90 years of progesterone: progesterone and progesterone receptors in breast cancer: past, present, future. *Journal of Molecular Endocrinology*. 2020; 65: T49–T63.
- [15] García-Sáenz M, Ibarra-Salce R, Pozos-Varela FJ, Mena-Ureta TS, Flores-Villagómez S, Santana-Mata M, *et al.* Understanding progestins: from basics to clinical applicability. *Journal of Clinical Medicine*. 2023; 12: 3388.
- [16] Asi N, Mohammed K, Haydour Q, Gionfriddo MR, Vargas OL, Prokop LJ, *et al.* Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. *Systematic Reviews*. 2016; 5: 121.
- [17] Feng F, Liu T, Hou X, Lin X, Zhou S, Tian Y, *et al.* Targeting the FSH/FSHR axis in ovarian cancer: advanced treatment using nanotechnology and immunotherapy. *Frontiers in Endocrinology*. 2024; 15: 1489767.
- [18] Sheng S, Liu W, Xue Y, Pan Z, Zhao L, Wang F, *et al.* Follicle-stimulating hormone promotes the development of endometrial cancer *in vitro* and *in vivo*. *International Journal of Environmental Research and Public Health*. 2022; 19: 15344.
- [19] Kourbanhousen K, Joncas F, Wallis CJD, Hovington H, Dagenais F, Fradet Y, *et al.* Follicle-stimulating hormone (FSH) levels prior to prostatectomy are not related to long-term oncologic or cardiovascular outcomes for men with prostate cancer. *Asian Journal of Andrology*. 2022; 24: 21–25.
- [20] Kilanowska A, Ziółkowska A, Stasiak P, Gibas-Dorna M. cAMP-dependent signaling and ovarian cancer. *Cells*. 2022; 11: 3835.
- [21] Zhou J, Chen Y, Huang Y, Long J, Wan F, Zhang S. Serum follicle-stimulating hormone level is associated with human epidermal growth factor receptor type 2 and Ki67 expression in post-menopausal females with breast cancer. *Oncology Letters*. 2013; 6: 1128–1132.
- [22] Greene FL. The current staging and classification systems of breast cancer and their pitfalls: is it possible to integrate the complexity of this neoplasm into a unified staging system? *Critical Reviews in Oncology/Hematology*. 2022; 178: 103781.
- [23] Xiong X, Zheng L, Ding Y, Chen Y, Cai Y, Wang L, *et al.* Breast cancer: pathogenesis and treatments. *Signal Transduction and Targeted Therapy*. 2025; 10: 49.
- [24] Zhang Y, Shu C, Maimaiti Y, Wang S, Lu C, Zhou J. A review of the advancements in targeted therapies for breast cancer. *Cureus*. 2023; 15: e47847.
- [25] Wang Y, Wang N, Zhang X, Fu Z, Pang C, Zhang Y, *et al.* Adult-type granulosa cell tumor associated with elevated luteinizing hormone: two rare case reports. *Medicine*. 2024; 103: e37069.
- [26] Gill S, Lavoie HB, Bo-Abbas Y, Hall JE. Negative feedback effects of gonadal steroids are preserved with aging in postmenopausal women. *The Journal of Clinical Endocrinology and Metabolism*. 2002; 87: 2297–2302.
- [27] Gill S, Sharpless JL, Rado K, Hall JE. Evidence that GnRH decreases with gonadal steroid feedback but increases with age in postmenopausal women. *The Journal of Clinical Endocrinology and Metabolism*. 2002; 87: 2290–2296.
- [28] Shaw ND, Histed SN, Srouji SS, Yang J, Lee H, Hall JE. Estrogen negative feedback on gonadotropin secretion: evidence for a direct pituitary effect in women. *The Journal of Clinical Endocrinology and Metabolism*. 2010; 95: 1955–1961.
- [29] Rance NE, Uswandi SV. Gonadotropin-releasing hormone gene expression is increased in the medial basal hypothalamus of postmenopausal women. *The Journal of Clinical Endocrinology and Metabolism*. 1996; 81: 3540–3546.
- [30] Rance NE, Krajewski SJ, Smith MA, Cholanian M, Dacks PA. Neurokinin B and the hypothalamic regulation of reproduction. *Brain Research*. 2010; 1364: 116–128.
- [31] Wide L, Eriksson K, Sluss PM, Hall JE. Serum half-life of pituitary gonadotropins is decreased by sulfonation and increased by sialylation in women. *The Journal of Clinical Endocrinology and Metabolism*. 2009; 94: 958–964.
- [32] Sharpless JL, Supko JG, Martin KA, Hall JE. Disappearance of endogenous luteinizing hormone is prolonged in postmenopausal women. *The Journal of Clinical Endocrinology and Metabolism*. 1999; 84: 688–694.
- [33] Satpathi S, Gaurkar SS, Potdukhe A, Wanjari MB. Unveiling the role of hormonal imbalance in breast cancer development: a comprehensive review. *Cureus*. 2023; 15: e41737.
- [34] Shi S. High follicle-stimulating hormone (FSH) promotes tumor angiogenesis of breast carcinoma of menopausal women. *Fertility and Sterility*. 2016; 106: e81–e82.
- [35] Sanchez AM, Flamini MI, Zullino S, Russo E, Giannini A, Mannella P, *et al.* Regulatory actions of LH and follicle-stimulating hormone on breast cancer cells and mammary tumors in rats. *Frontiers in Endocrinology*. 2018; 9: 239.
- [36] Sarda AK, Jogdand SD. Predisposing and overall effects of reproductive hormones on breast cancer: a review. *Cureus*. 2023; 15: e45956.
- [37] Li C, Ling Y, Kuang H. Research progress on FSH-FSHR signaling in the pathogenesis of non-reproductive diseases. *Frontiers in Cell and Developmental Biology*. 2024; 12: 1506450.
- [38] Park BW, Oh JW, Kim JH, Park SH, Kim KS, Kim JH, *et al.* Preoperative CA 15-3 and CEA serum levels as predictor for breast cancer outcomes. *Annals of Oncology*. 2008; 19: 675–681.
- [39] Ryu JM, Kang D, Cho J, Lee JE, Kim SW, Nam SJ, *et al.* Prognostic impact of elevation of cancer antigen 15-3 (CA15-3) in patients with early breast cancer with normal serum CA15-3 level. *Journal of Breast Cancer*. 2023; 26: 126–135.
- [40] Iqbal MS, AlAbayah HNA, Tabassum A, Arbaeen AF, Sannan NS, Qadi HHH, *et al.* Expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 in breast cancer: a two-year retrospective study. *Al-Azhar International Medical Journal*. 2023; 4: 29.
- [41] Zhao X, Yang X, Fu L, Yu K. Associations of estrogen receptor, progesterone receptor, human epidemic growth factor receptor-2 and Ki-67 with ultrasound signs and prognosis of breast cancer patients. *Cancer Management and Research*. 2021; 13: 4579–4586.

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