Zagazig University Medical Journal
www.zumj.journals.ekb.eg

https://doi.org/10.21608/zumj.2025.354563.3807 Volume 31, Issue 5, May. 2025

Manuscript ID: ZUMJ-2501-3807
DOI:10.21608/zumj.2025.354563.3807

Original Article

Variation of serum complements and gonadotropins hormones in breast cancer

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Submit Date: 06-02-2025
Accept Date: 21-04-2025

ABSTRACT

Background: Breast cancer arises in a hormone-rich environment that influences its biological characteristics and ultimately impacts its clinical behavior. This study investigated the levels of serum complements, gonadotropin hormones, and steroid hormones in breast cancer patients to understand how these factors influenced the disease progression.
Methods: The study included 68 healthy women (mean age = 59. 03 ± 11. 4 years) as the control group and 89 women with clinically and pathologically confirmed breast cancer (mean age = 60 ± 12. 1 years). The analyzed biochemical markers included serum gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), steroid hormones (estrogen, progesterone, prolactin, testosterone), and complements (C3 and C4).
Results: The findings indicated significantly elevated levels of steroid hormone esestrogen, progesterone, prolactin, and testosterone as well as significantly higher levels of serum complements C3 and C4 in breast cancer patients compared to the control group. Additionally, breast cancer-affected women exhibited significantly higher serum LH and FSH concentrations relative to the control group.
Conclusions: Our study reveals that breast cancer cases present elevated serum levels of steroid hormones, gonadotropins, and complements,
Key words: Breast cancer;Complements; Hormones

INTRODUCTION

Breast cancer is among the most common cancers affecting women glob ally, with an increasing incidence each year [1, 2]. The last annual report of the Iraqi Cancer Registry released in 2018, that of the estimated population of 38 million, the total number of new cancer cases reached (31,502) cases. The total number of deaths due to cancer was (10,293) deaths [3]. The breast cancer incidence is gradually increasing, and the total number of cases is 6,094 or (34.06% of all cancer types), while the number of deaths has reached 1,166 cases or (23.02% of all cancers). The highest death rate was among women in the age group of 70 years and over. [4]. The condition is often diagnosed in middle-aged women at somewhat advanced stages [5], and aggressive variants are anticipated to be more common in these demographics. Research overthe past decade has underscored the importance of immune response in breast cancer development [6] and the potential use of immune indicators in breast cancer prognosis. Both the innate and adaptive immune systems include the complement system, comprising over 30 distinct proteins found in serum, tissue fluids, and on cell membrane surfaces, all regulated by a precise mechanism. The complement system plays a crucial role in activating the innate immune response through three pathways: classical, lectin, and

alternative [7]. Central to the complement system is Complement Component 3 (C3), which can be cleaved into C3a and C3b by proteases and activated either automatically at microbial surfaces or through proteases such as kallikrein and thrombin (known as alternative pathway activation) [8–10]. Activation of complement on tumor cells leads tothe production and covalent attachment of C3 activated fragments. Phagocytes and natural killer (NK) cells express the opsonin complement receptor, a typical C3 activated fragment, enhancing anticancer activity. Furthermore, complement activation produces C3a, a breakdown product of C3, which ultimately aids in forming a cytolytic membrane attack complex (MAC), thereby bolstering the body's ability to combat tumors [11]. However, as complement activation can harm healthy tissues, various soluble and membrane-bound proteins are crucial in regulating complement activity at different stages [12]. Aberrant complement activation may lead to various physiological and pathological issues, contributing to diseases such as inflammatory disorders and cancer [13]. C3 is vital for tumor development, progression, and immune defense, but an imbalanced complement system may significantly influence cancer occurrence and growth [14]. Previous studies have indicated that different concentrations of C3a can yield distinct effects in tumor cells, suggesting that complement C3 may be essential for tumor progression and may act in a concentration-dependent manner [15].

Breast cancer is the quintessential example of a hormone-dependent malignancy. Women, both premenopausal and postmenopausal, produce steroid hormones throughout their lives, albeit through different mechanisms governed mainl y by the ovaries in premenopausal women and the adrenal glands in postmenopausal women. Consequently, the hormonal environment in which breast cancer develops significantly influences its progression[16] Although the precise causes ofbreast cancer remain unknown, factors related to age and reproductive history are recognized as risk factors [16]. Among these risk factors, hormones such as progesterone (P) and estrogen (E) are critical in promoting the proliferation of breast cancer cells. Furthermore, prolonged exposure to hormones like E and P increases breast cancer risk [17–19]. The main serum estrogens are estrone (E1), estradiol (E2), and estriol (E3). Estradiol (E2) interacts with the estrogen receptor (ER) in breast tissue, influencing cell proliferation and apoptosis, thus affecting the onset and progression of breast cancer [20]. Additionally, a positive correlation has been identified between E2 levels and the incidence of postmenopausal breast cancer[21–23].

Gonadotropin-releasing hormone analogs (GnRHa) substantially contribute to the adjuvant treatment of premenopausal patients with breast cancer. Several studies have shown that GnRHa can inhibit the progression of breast cancer and improve the survival of premenopausal patients with breast cancer (24). In addition, studies have shown that treatment with GnRHa appeared to protect against ovarian failure, reducing premature ovarian insufficiency (POI) incidence and the risk of early menopause and improving the rate of menses recovery and pregnancy after chemotherapy. therefore, European Society of Medical Oncology guidelines and European Society of Human Reproduction and Embryology guidelines have recommended GnRHa to protect ovarian function. However, there are still conflicting evidences about the effect of GnRHa in protecting ovarian function during tumor chemoradiotherapy; the evaluation criteria of ovarian function are also inconsistent, and the mechanism is not clear

Chemotherapy can induce ovarian damage and deplete the ovarian reserve through multiple mechanisms that directly affect the levels of endogenous sex hormones, including estradiol, progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) [24, 25]. Reproductive hormones are well-established as significant contributors to breast cancer development. Endogenous reproductive hormones have been associated with breast cancer risk and have been shown to promote tumor growth [27]. Previous research [28] and other studies [29, 30] have identified a correlation between hormone levels prior to treatment and prognosis in patients undergoing neoadjuvant chemotherapy (NAC). A recent study [31] linking chemotherapy-induced ovarian failure to improved prognosis emphasized the vital role of ovarian suppression following neoadjuvant/adjuvant chemotherapy in mitigating disease progression, regardless of hormone receptor status.

This study aims to evaluate the levels of complement components (C3 and C4), gonadotropins (LH, luteinizing hormone; FSH, follicle-stimulating hormone), and steroid hormones (estrogen, progesterone, prolactin, testosterone) in Iraqi women with breast cancer compared to a control group.

METHODS:

Subjects (premenopausal women)

The study included 89 women patients aged 29-70 years old suffering from breast tumors who attended Hiwa Hospital during a period from May/2023 to December/2024 for diagnostic or surgical operations without any prior history of receiving radiotherapy and chemotherapy and 68 healthy women with an age range from 22-66 years old were chosen as a control group from outside the hospital. After the respective hospital's ethical committee approved the study plan, participants supplied informed written agreement. The study received approval from the Ministry of Health of the Kurdistan region number 13/B/2078.

Collection of the blood

Before beginning any form of treatment, blood was drawn. Without applying a tourniquet, six milliliters of venous blood were drawn from each subject, collected in a polyethene tube, and left to stand at room temperature for 30 minutes. The material was then centrifuged for 10 minutes at 2000 x g. The collected serum was immediately transferred to a different test tube. These samples were either frozen at-20˚c for further analysis or directly evaluated for enzyme activity.

Determination of serum complement component and hormones

Serum levels of steroid hormones (estrogen, progesterone, prolactin, and testosterone), gonadotropins (luteinizing hormone and follicle-stimulating hormone), and complements (C3, and C4) were measured Using (ELISA) technique dependent on a kit made by the BioVision firm

STATISTICAL ANALYSIS

The data was analyzed by Microsoft Excel software and the Statistical Package for Social (SPSS version 20.0). For the quantitative variables—mean and standard deviation (SD)—we compared the two groups using unpaired Student's t-test. Quantitative variables were presented as frequency and percentage (%), and qualitative variables were analyzed with the Chi-square test or Fisher's exact test as needed. For statistically significant results, the P value was equal or less than 0.05,

RESULTS

Serum levels of complements C3 and C4

The results are shown in Figure (1), and they are based on the mean values of serum complements C3 and C4 levels.

As shown in Figure 2, there was a substantial rise (p =0.01) in the amount of estrogen hormones in breast cancer patients as compared to the healthy control group.

Serum levels of progesterone

Figure 2 shows the Mean SD values for progesterone in sera samples.

Serum levels of testosterone

Testosterone levels in sera samples from healthy people and ovarian cancer patient groups were analyzed. Figure 2 displays the mean values of the testosterone concentration in sera samples. The findings demonstrated that, when compared to the control group, the serum concentration level in the ovarian cancer group increased significantly (P <0.01).

.**Serum levels of prolactin (PRL)**

Prolactin (PRL) concentrations in control and breast cancer patient sera were examined.

Figure 2 presents the mean SD values of PRL in sera samples. The finding shows that the serum PRL concentration is significantly higher (<0.001)**;** in the group of patients with breast cancer than it is in the control group.

Serum levels of Follicle-Stimulating Hormone (FSH)

Figure (3) shows the findings of comparing the FSH levels in the serum of Brest cancer patients with the control group. When breast cancer patients were compared to the healthy control group, serum levels of FSH were found to be significantly increased in breast cancer patients

Serum levels of Luteinizing hormone (LH)

Luteinizing hormone (LH) levels in control and breast cancer patient groups' sera were assessed. Figure (3) displays the mean and standard deviation of the serum LH levels

FIGURES

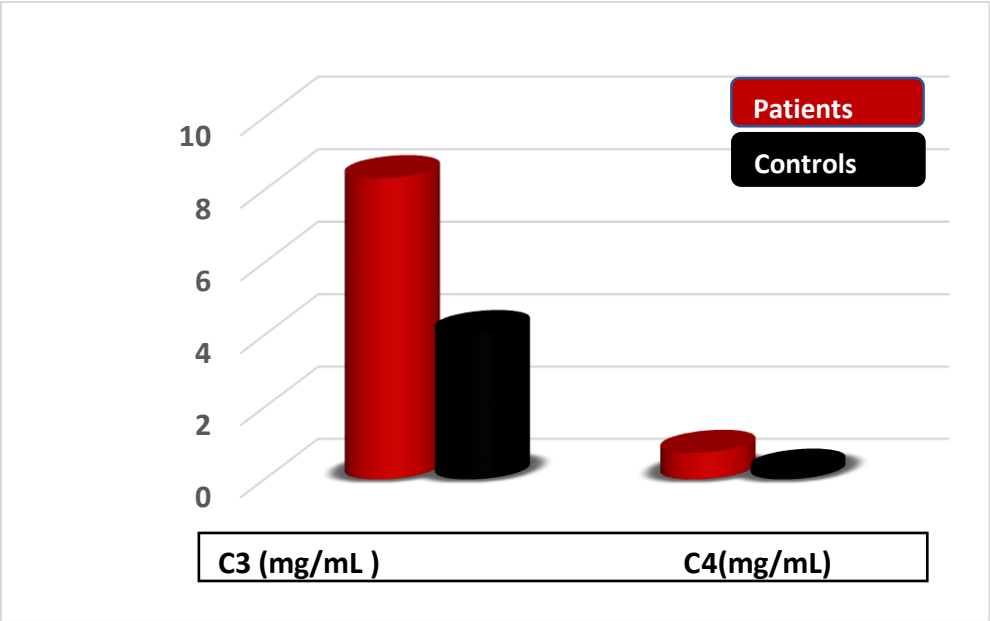

Figure (1) Mean value of C3 and C4 concentration in sera samples of control and patient groups

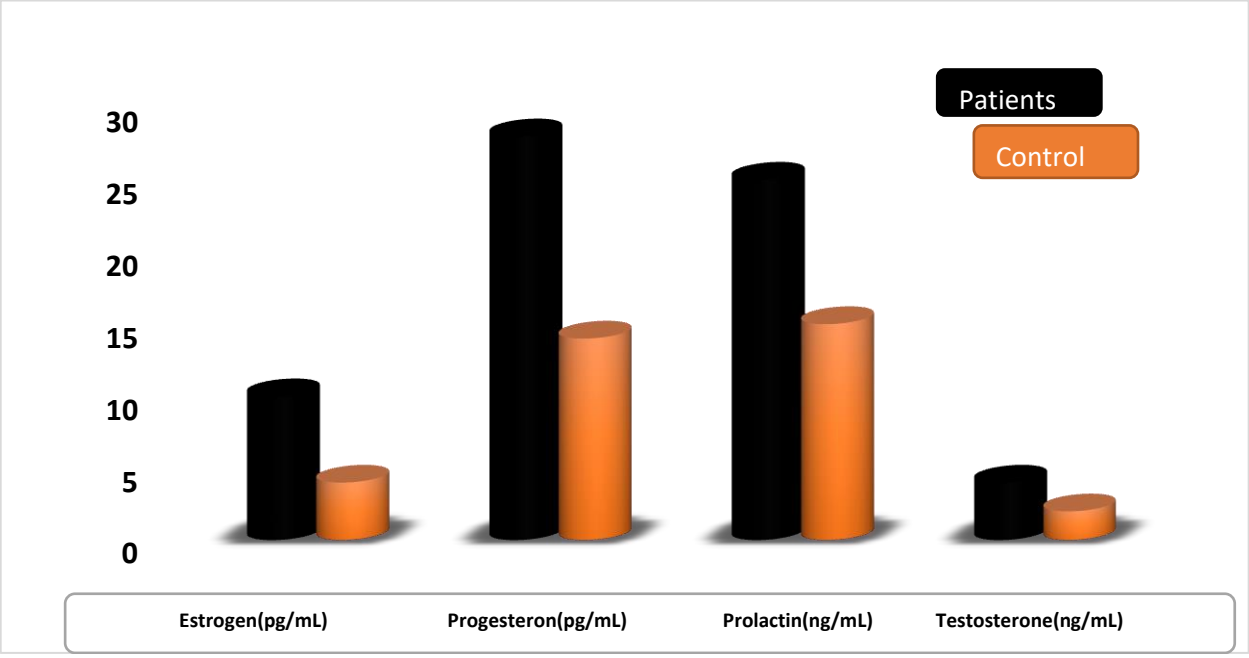

Figure 2: Mean values of serum Estrogen & progesteron Testosterone &prolactin levels in control and Breast cancer patients

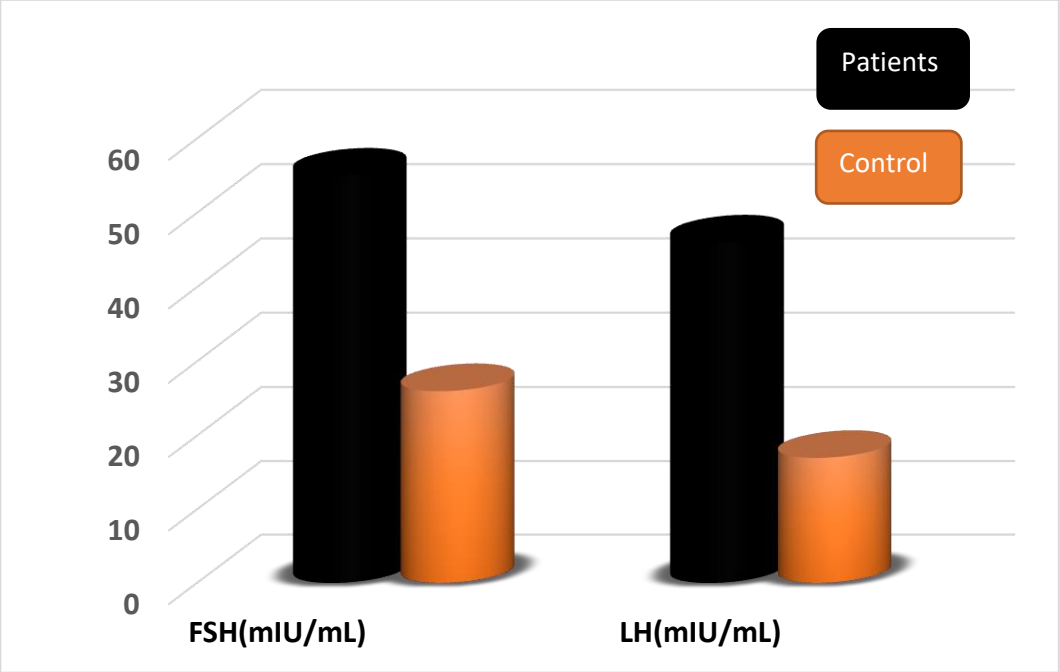

Figure 3: Mean values of serum gonadotropin hormones (LH & FSH,) levels in control and Breast cancer patients

DISCUSSION

According to the findings in Figure 2, breast cancer patients had significantly higher levels of the hormones estrogen and progesterone than the healthy control group (p =0.01). The findings were consistent with earlier studies that indicate progesterone may play a role in the development of breast cancer [60].

On serum complement levels in patients with malignancies, little information is available. Our findings showed that breast cancer patients had greater serum C3, C4 concentrations than the healthy individuals in the control groups. The prolonged presence of a tumor mass, which serves as an antigenic stimulus for ongoing antibody production, may be the cause of the elevated complement concentrations in cancer disease. The complement system was required by the antigen-antibody complexes, which led to increased creation to maintain normal levels. It's possible that this enhanced production has a rebound effect that promotes high complement concentrations; the current data provide strong support for this notion.

The complement system is sufficiently specialized to prevent damage to host cells and can rapidly identify and eliminate microbial infiltration [33]. It is often believed to inhibit tumor growth. However, the effectiveness of antibody immunotherapy is frequently limited by specific circumstances [34].

The complement pathway can promote tumor growth through increased chronic inflammation, immunosuppression, and angiogenesis, while it also suppresses carcinogenesis by enhancing acute inflammation and tumor cell lysis [35]. Various earlier studies suggest that Complement 3 (C3) may influence both the initiation and progression of cancer. For example, an increase in plasma C3 levels in lung cancer patients has been linked to a decrease in survival time [36].

Estimates indicate that metastases account for approximately 90% of cancer-related deaths [37]. Furthermore, the ability of malignant cells to activate the complement C3 protein may contribute to cancer dissemination [38]. To determine whether the therapeutic effect on tumor prognosis is directly related to blood C3 levels, several studies have been conducted. In cell tests or animal models, individuals with various

cancers, including breast, lung, ovarian, colon, and liver cancer, may exhibit significant improvements in their C3/C3a levels [39]. Research indicates that Complement C3 has the potential to serve as an early diagnostic biomarker for several types of cancer [40]. Within the immune system's defense mechanisms, the complement system plays a crucial mediating role.

Complement has traditionally been considered a component of the anti-tumor immune system, serving as a vital mediator in host defense. Numerous studies have demonstrated that this system is actively involved both systemically and locally within the tumor microenvironment (TME). Many tumor tissues contain complement components; for instance, oropharyngeal squamous cell carcinomas, follicular and mucosal-associated lymphoid tissue lymphomas, as well as C4d, a fragment derived from C4, have all been found to possess complement components [41]

Complement 4 (C4) is one of the inflammatory mediators that aids in the formation of immune complexes and the regulation of immune aggregation binding. Furthermore, the thyroid gland has been observed to express C4 at higher levels compared to the heart, pancreas, and thymus. Several studies have identified a correlation between certain malign ancies and aberrant C4A expression. Tikhonov et al. reported a link between serum C4A and the onset of colorectal cancer [42]. Zhang et al. found that the chemosensitive group for epithelial ovarian cancer exhibited significantly higher blood C4A levels than the chemoresistant group [43]. Additionally, Broek et al. and Lu et al. discovered that patients with papillary thyroid carcinoma (PTC) had elevated serum C4A/B levels compared to benign thyroid nodules and healthy individuals [44, 45].

Higher blood estrogen levels have been shown to elevate the likelihood of distant metastases in postmenopausal breast cancer patients with ER-negative tumors. In a nested case-control cohort from a randomized food intervention trial (Women's Health Eating and Living research), Rock et al. [56] similarly established a significant relationship between serum estrogen levels and patient survival. Given that estradiol is considered a key factor in the carcinogenesis of ER-positive tumors, our discovery that serum estradiol levels independently influence the prognosis of individuals with ER-negative tumors is noteworthy. Recent experimental studies, which suggest that estradiol regulates the development of ER-negative breast cancer cell lines, align with our findings. For example, Gupta et al. [57] reported that estrogen stimulates host angiogenesis and the recruitment of stromal cells from the bone marrow, thereby fostering the development, stromalization, and angiogenesis of an ER-negative breast cancer cell line. Additionally, Banka et al. [58] demonstrated that the incidence of lung metastasis significantly increased in ovariectomized mice injected with an ER-negative mouse mammary cancer cell line following estradiol treatment. These studies indicate a distinct mechani sm involving the host microenvironment through which estradiol may act as a potent promoter of metastasis in ER-negative cancers. Furthermore, it is plausible that more aggressive ER-negative breast tumors are associated with elevated estrogen levels due to a shared origin, potentially generating a significant inflammatory response that raises estrogen levels.

According to the findings in Figure 2, breast cancer patients had significantly higher levels of the hormones estrogen and progesterone than the healthy control group ($p = 0.01$). The findings were consistent with earlier studies that indicate progesterone may play a role in the development of ovarian cancer [60].

Figure 2 presents the Mean values for progesterone in serum samples. The results depicted in Figure 2 indicate that breast cancer patients exhibited significantly elevated levels of estrogen and progesterone compared to the healthy control group ($p < 0.01$). These findings align with previous studies suggesting a po tential role of progesterone in the development of ovarian cancer [60]. Epidemiologic studies have consistently linked breast cancer risk in postmenopausal women to serum estrogen concentrations [61]. Additionally, substantial indirect evidence implies that endogenous progesterone may contribute to breast cancer development [62], with the presence of the progesterone

receptor indicating hormone-responsive cancer. Nevertheless, a direct correlation between risk and serum progesterone levels has not been established [63]. The cyclical variation of these hormones in serum, particularly estradiol, complicates the evaluation of the association between sex steroid levels and risk in premenopausal breast cancer [64]. The European Prospective Investigation into Cancer and Nutrition, the largest prospective cohort study involving premenopausal women to date [65], has recently reported no association for estrogens, despite comprehensive efforts to account for temporal fluctuations and marked risk increases for women exhibiting higher serum levels of testosterone and adrenal androgens [66]. It is possible that serum hormone levels may not correlate as strongly with cancer risk as those in breast tissue, which are also likely to be more temporally stable. However, quantifying tissue hormone concentrations in population studies poses challenges due to the heterogeneity of breast tissue and the invasive nature of necessary sampling methods.

The precise mechanisms by which progesterone exerts its beneficial effects remain unclear. Progesterone is known to counteract estrogen by activating P-hydroxysteroid Dehydrogenase, an enzyme that metabolizes estrogen. Unopposed estrogen induces protease production in breast cancer cells across various pH levels, both intracellularly and extracellularly. During the follicular phase of menstruation, tumor manipulation may facilitate the dissemination of cells capable of establishing distant metastases. This protease activity ceases promptly after the unopposed estrogen environment is disrupted by rising progesterone levels, due to the short half-life of the proteases. Furthermore, increased production of growth factors, coupled with reduced natural killer (NK) cell activity under estrogen influence, may create a conducive environment for micrometastasis development. A study of autopsies indicated higher mitotic counts in breast epithelium during the luteal phase, suggesting that progesterone does not inhibit breast tissue proliferation**.**

Progesterone, a steroid hormone, plays a significant role in a number of physiological-pathophysiological processes, including bone development and cancer development. It is crucial to comprehend the ways through which progesterone hormones function, particularly in terms of figuring out their receptors [70].

Strong prognostic indicators for contralateral breast cancer, distant metastasis, and local relapse include elevated baseline serum testosterone levels. Evidence suggesting that high urinary testosterone levels are associated with a poor prognosis in breast cancer patients supports the three-decade-old hypothesis that androgens significantly contribute to the onset and progression of breast cancer. Insulin stimulates the ovaries' production of androgens. Numerous studies have demonstrated that obese patients, who often present with hyperinsulinemic insulin resistance and elevated sex hormone levels, experience reduced survival rates.

High blood testosterone concentrations may indicate the presence of breast cancer. The biological function of androgens is dependent on how they interact with their unique receptors (androgen receptors), a subclass of receptors known as nuclear receptors. Nuclear receptors function as a protein that regulates the rate at which genetic information is transcribed from DNA to messenger RNA by binding to a specific DNA sequence. Androgen receptors play a role in tumorigenesis processes, either on their own or in conjunction with other transcription coregulators and growth factor, androgen receptors and estrogen (ER) receptors are expressed in ovarian surface epithelial cells, which is the normal ovary cell. The presence of androgen receptors is linked to several kintypes of malignant tumors, like those found in the prostate, breast, and bladder [72]. Functional ovarian tissue is associated with high amounts of androgens and a rise in the rate at which testosterone is generated in ovarian thecal cells, identifying the high circulating levels of androgens in ovarian cancer. Numerous investigations classified the cancer cells by their grade and clinical stage and found a correlation between circulating androgen concentrations and the increased vulnerability of ovarian carcinoma patients [73]. Endometriosis has a high concentration of androgen receptor mRNA, which raises the rate at which endometrioid and clear-cell carcinomas proceed, raising the possibility that both androgen receptors and androgens themselves may be implicated in the development and spread of these carcinomas.

Figure 2 presents the mean values of PRL in sera samples. The finding shows that the serum PRL concentration is significantly higher (p=0.0001)**;** in the group of patients with breast cancer than it is in the control group. These findings closely matched those of study [74], in which significant-high serum PRL levels were seen in cancer patients. In addition to being characterized by an increase in the major concentrations of prolactin, the high levels of prolactin reported in a notable proportion of patients with breast cancer may signal a more serious malfunction in the hypothalamic dopamine system.
There is substantial evidence indicating that the locally produced hormone prolactin plays a significant role in several malignancies, including prostate, breast, and colon cancers. Elevated circulating prolactin levels have been observed in breast cancer patients, suggesting its possible involvement in the disease's development. Women diagnosed with breast cancer exhibit notably higher blood prolactin levels, making it a potential indicator of breast cancer [75]. Several studies contest the notion that increased serum prolactin is merely a consequence of heightened anterior pituitary hormone production due to stress associated with a cancer diagnosis. Reports indicate that various cancer types exhibit different levels of elevated serum prolactin. Research involving healthy individuals has shown that while mild emotional stress can lead to increases in serum prolactin, such reactions are relatively uncommon..
the results revealed a statistically significant increase ($p < 0.05$) in the level of the FSH hormone. The findings were consistent with earlier studies that indicate FSH may play a role in the development of ovarian cancer [76].

The high circulating quantity of prolactin should be sufficient to activate prolactin signaling in malignancy, despite the fact that prolactin alone was not expressed abnormally or excessively in breast carcinoma. These increased serum prolactin levels must originate from the anterior pituitary or an external source, such as white blood cells. The prolactin signaling in breast carcinoma may have been enhanced as a result of a remarkable increase in the response to a prolactin-specific stimulation, leading to a high proliferation of cancer cells and cell survival rate. Prolactin may also aid in the development of tumors by promoting the growth of cancerous tissue and complicating phosphorylation pathways involved in cellular adhesion.

Figure (3) illustrates the comparison of serum FSH levels between breast cancer patients and a control group. The analysis showed a statistically significant increase ($p < 0.05$) in FSH hormone levels among breast cancer patients compared to the healthy control group. These results align with earlier studies suggesting that FSH may contribute to cancer development [76].
FSH promotes the formation and development of ovarian follicles and supports the testes in producing mature spermatozoa. It plays a significant role in various cancers, including prostate, endometrial, and ovarian cancers [77]. FSH activates adenylyl cyclase, resulting in increased cAMP levels, which in turn encourages the growth, differentiation, and metastasis of cancer cells [78]. The overexpression of Her-2 in ovarian cancer may be associated with elevated levels of FSHR [79]. Although FSHR expression has not been observed in primary breast cancer tissues, high FSH levels are correlated with poor prognosis in premenopausal breast cancer patients [80]. Additionally, FSH has been linked to the proliferation of breast cancer cells and an increased risk of breast cancer in women undergoing infertility treatments [81].

FSH and LH belong to the same family of glycoprotein hormones as thyroid-stimulating hormone (TSH) and placental hCG. They serve as the primary regulators of reproductive function within the endocrine system, also overseeing steroidogenesis and gametogenesis in both the ovary and testis. FSH acts through FSHR to enhance follicular cell activity, with FSHR being expressed exclusively in the sterol cells of the testis and the granulosa cells of the ovary. Additionally, FSHR expression has been identified in cancer cells. However, the specific role of gonadotropins in cancer growth and development, along with its molecular mechanisms, remains largely unclear. FSH and LH receptors are part of the G protein-coupled receptor superfamily; notably, their extensive ectodomains contain a leucine-rich repeat vital for ligand binding. While FSHR expression is seldom observed in breast cancer tissues or cell

lines, it has been detected in various cancer cells. The human genome contains numerous leucine-rich GPCRs (LGRs), and other LGR subgroups, in addition to FSHR, are capable of transmitting gonadotropin signals. Given the widespread distribution of FSH within the cytoplasm of breast cancer epithelial cells and the observation that both benign mammary tumors and breast cancer possess higher levels of FSH compared to normal cells, further investigation into the expression of leucine-rich GPCRs in this context is warranted. Additionally, further resea rch is required to determine whether FSH enhances Her-2 expression and cell proliferation via the LGR subgroup, as FSH may exert its effects through a distinct receptor in the malignant transformation of breast cancer, rather than through conventional FSHR.

Luteinizing hormone (LH) levels in the sera of control and ovarian cancer patient groups were evaluated. Figure 3 presents the mean and standard deviation of the serum LH levels. The results indicate a statistically significant increase in blood LH levels in the breast cancer group ($P = 0.0001$) compared to the control group. These findings align with those of [84], which found that cancer patients exhibited serum LH levels higher than typical physiological values.

LH initiates the early phase of steroidogenesis , though its association with breast cancer has been minimally explored. LH is secreted by the pars distalis of the pituitary gland in response to the hypothalamus's pulsatile release of LH-releasing hormone (LHRH) [85]. LH shares the alpha subunit with human chorionic gonadotropin and thyrotropin. Although there is evidence that blood LH levels fluctuate hourly, daily, and in relation to the menstrual cycle, tissue LH concentrations likely vary less frequently, especially when LH is bound to its receptor. Gunasegaram et al. conducted the only other study measuring LH and other hormones in breast tissue [86]. They found elevated levels of LH and prolactin in breast cancer tissue, irrespective of disease stage, while follicle-stimulating hormone and human chorionic gonadotropin levels were increased in samples from women with stage II disease. Limitations of the study include a small sample size (27 breast cancer patients versus 8 control autopsy cases), a large tissue requirement for tests (2 g), and the lengthy hormone extraction process. Additionally, there was a notable age difference between the groups, with 71% of the cancer patients being postmenopausal, whereas all control patients were under the age of 37. We were unaware of this report before concluding our research.

Luteinizing hormone, a hormone that is released by the pituitary gland and is a member of the gonadotropin family, is thought to control the synthesis of ovarian steroids.

Breast cancer gonadotropin hormone indicates that the disease's development is associated with elevated circulating gonadotropins (FSH and LH). The involvement of luteinizing hormone in breast cancer progression has been documented in several studies. Previous research has shown that luteinizing hormone inhibits Fas-induced apoptosis in ovarian cancer cells. Reports suggest that luteinizing hormone may enhance the growth and dissemination of breast cancer via the PI3K/AKT signaling pathway. Numerous studies indicate that gonadotropin-producing hormones facilitate the migration and proliferation of breast cancer OV207 cells by phosphorylating ERK1/2 signaling in a calcium-dependent manner. However, the mechanisms by which luteinizing hormone influences cancer cell proliferation remain largely unclear. The current study reveals elevated levels of luteinizing hormone of unknown origin. Previous reviews have associated amenorrhe a with increased luteinizing hormone and decreased estradiol levels, contributing to elevated serum luteinizing hormone. Several hypotheses have been proposed in earlier studies.

The gonadotropin profile prompted a review of atypical etiologies of amenorrhea characterized by high LH, normal FSH, and low estradiol. Based on a literature survey, several hypotheses have been proposed. Immunostaining has shown that the production of luteinizing hormone by ovarian cancer was halted. Some studies suggest that cancer cells in the ovarian granulosa secrete luteinizing hormone, potentially increasing its secretion from the pituitary glands.

One possible contributing factor is a gonadotropin-releasing hormone-like molecule found in the

healthy cells of the ovarian granulosa. In patients with ovarian carcinoma, the Ovarian Granulosa Cell Cancer may influence the synthesis of gonadotropin-releasing hormone. Additionally, a mutation in the luteinizing hormone receptor, a rare cause of amenorrhea associated with elevated luteinizing hormone levels, may also explain the increased levels observed in ovarian granulosa cancer cells. It is conceivable that cancer cells may inadvertently secrete a substance that elevates luteinizing hormone levels in the bloodstream.

CONCLUSIONS

The findings of the current investigation indicate that elevated serum levels of steroid hormones, gonadotropins, and complements are noteworthy as potential disease markers in breast cancer. This study supports the need for further rese arch involving larger patient populations, as it suggests that hormonal changes resulting from certain diets may enhance breast cancer prognosis. Incorporating serum hormone measurements into the standard diagnostic process for breast cancer patients is recommended, and consideration should be given to dietary or medical interventions aimed at reducing testosterone levels, should their predictive significance be validated in larger studies. Additionally, the alter ation of serum complement levels shows a significant association with breast cancer, suggesting that these biochemical markers may serve as effective prognostic indicators for affected individu als.

Conflict of Interest:

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

Financial Disclosures:

None declared

Acknowledgements

The authors wish to thank Salahaddin University and Hiwa Hospital Staffs for their support in conducting the study.

Funding Support

None declared

Consent for publication Not applicable.

Competing interests The authors declare no conflict of interest.

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Citation

Ismail, P., Ali, L., Fattah, C. Variation of serum complements and gonadotropins hormones in breast cancer. *Zagazig University Medical Journal*, 2025; (2005-2018): -. doi: 10.21608/zumj.2025.354563.3807