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Estimation of the sex hormones and liver enzymes in Iraqi women with breast cancer

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Abstract
Breast cancer remains the most common malignancy among women worldwide, with increasing prevalence in Iraq. Hormonal imbalances and liver function are closely linked to breast cancer development and progression. This study investigates the levels of sex hormones (estrogen, progesterone, testosterone) and liver enzymes (ALT, AST, ALP, GGT) in Iraqi women diagnosed with breast cancer. The research aims to evaluate the biochemical profiles of patients to identify potential diagnostic or prognostic biomarkers. A cross-sectional study was conducted on 100 Iraqi women aged 25–65 with confirmed breast cancer diagnoses. Blood samples were analyzed using ELISA for hormone levels and standard biochemical assays for liver enzymes. The data were statistically analyzed to explore correlations between these biomarkers and cancer stages or histological types. Preliminary results indicate altered levels of sex hormones and elevated liver enzymes in a significant portion of the sample, with notable variation across cancer stages. These findings support the hypothesis that hormonal and hepatic biomarkers can provide valuable insights into breast cancer status. The study contributes to the limited body of research in the Iraqi context and underscores the need for routine screening of sex hormones and liver enzymes in breast cancer diagnostics. Future work should expand on these findings with larger sample sizes and include genetic and lifestyle factors that may influence hormone and liver function. These results may help improve clinical decision-making and personalized treatment plans for Iraqi breast cancer patients.

Keywords: Breast cancer, Sex hormones, Liver enzymes, Iraqi women, Biochemical markers

1.1 Research Background

Breast cancer is the leading type of cancer affecting women worldwide. According to the World Health Organization (WHO), more than 2.3 million women are diagnosed annually. It accounts for approximately 15% of all cancer-related deaths in women. In Iraq, recent health statistics indicate a continuous rise in breast cancer incidence, making it the most diagnosed cancer among Iraqi women. Many of these cases are detected in advanced stages due to a lack of routine screening and public awareness.

Scientific evidence shows that breast cancer development is strongly influenced by hormonal changes. Among the most critical hormones involved are estrogen and progesterone. These hormones regulate the growth and function of breast tissue. When imbalanced, they can stimulate uncontrolled cell division, leading to tumor formation. Some breast tumors are hormone-receptor-positive, meaning they rely on these hormones to grow.

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Testosterone, although mainly known as a male hormone, is also present in women in smaller amounts. Alterations in its level have been observed in breast cancer patients and may contribute to tumor aggressiveness.

The liver plays an essential role in regulating hormone levels in the blood. It metabolizes and clears sex hormones from circulation. Liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) are indicators of liver function. Elevated levels of these enzymes may suggest impaired liver activity, which can affect hormone clearance and result in prolonged exposure of breast tissue to harmful hormonal signals.

Understanding the relationship between sex hormones and liver enzymes in Iraqi women with breast cancer may provide valuable insights for early diagnosis, better disease monitoring, and more targeted treatment strategies tailored to the local population.

1.2 Research Problem

Breast cancer diagnosis and management in Iraq primarily rely on imaging techniques, histopathological analysis, and general clinical examination. While these methods are essential, they often neglect the biochemical and hormonal aspects that contribute significantly to cancer development and progression. Specifically, sex hormone levels and liver enzyme activity are not routinely assessed during diagnosis or follow-up, despite their known roles in tumor biology.

This gap in diagnostic practice leads to several problems. First, without evaluating hormonal status, clinicians may miss early signs of hormone-driven tumor activity. For example, elevated estrogen or progesterone levels may precede tumor detection or influence its aggressiveness. Second, overlooking liver enzyme markers ignores the possible involvement of liver dysfunction in hormone metabolism, which may affect tumor growth and response to treatment.

Moreover, there is a noticeable lack of published research in Iraq examining the correlation between sex hormones, liver enzymes, and breast cancer characteristics. Most of the available data are derived from studies conducted in Western or Asian populations, which may not reflect the specific genetic, environmental, and dietary factors influencing Iraqi women.

This absence of localized biochemical profiling restricts the development of personalized treatment approaches. Patients may receive generalized therapies that do not consider individual hormonal or metabolic profiles, reducing treatment efficacy and increasing side effects. Therefore, a focused investigation into the hormonal and hepatic profiles of Iraqi breast cancer patients is urgently needed to improve diagnostic accuracy, treatment precision, and overall patient outcomes.

1.3 Research Objectives

- To estimate levels of sex hormones (estrogen, progesterone, testosterone) in Iraqi women with breast cancer
- To assess liver enzyme levels (ALT, AST, ALP, GGT) in the same group
- To identify possible correlations between these biomarkers and breast cancer stages or types

1.4 Research Significance (Expanded)

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- Provides local data for oncologists and medical practitioners regarding the hormonal and hepatic biochemical profiles of Iraqi women with breast cancer. This information can fill existing gaps in clinical knowledge and support evidence-based decision-making in diagnosis and treatment.
- Enhances the potential for early detection of breast cancer by identifying abnormal patterns in sex hormones or liver enzymes that may serve as early warning signs before structural abnormalities appear in imaging.
- Enables improved disease monitoring through regular assessment of hormonal and liver enzyme levels, helping clinicians track tumor behavior, progression, and treatment response over time.
- Contributes to the development of individualized treatment protocols. By understanding each patient's unique hormonal and metabolic profile, clinicians can tailor hormone-based therapies more effectively, reduce side effects, and improve overall treatment success.
- Promotes awareness in the Iraqi medical community about the importance of including biochemical markers as part of a comprehensive breast cancer evaluation, encouraging the integration of these parameters into national clinical guidelines.
- Supports future research by establishing a biochemical database that can be used as a reference for broader epidemiological studies, genetic investigations, and clinical trials targeting Iraqi populations.
- Offers insights into possible interactions between liver function and hormone regulation, which may influence cancer progression, especially in patients with concurrent hepatic conditions. This can lead to better multidisciplinary care approaches.

2. Literature Review: Global and Regional Breast Cancer Statistics

Global Overview

Breast cancer is the most commonly diagnosed cancer among women worldwide. As of 2022, over 2.3 million women were newly diagnosed, and approximately 670,000 died due to the disease [1]. The World Health Organization (WHO) projects a 38% increase in global breast cancer cases and a 68% rise in related deaths by 2050 [2].

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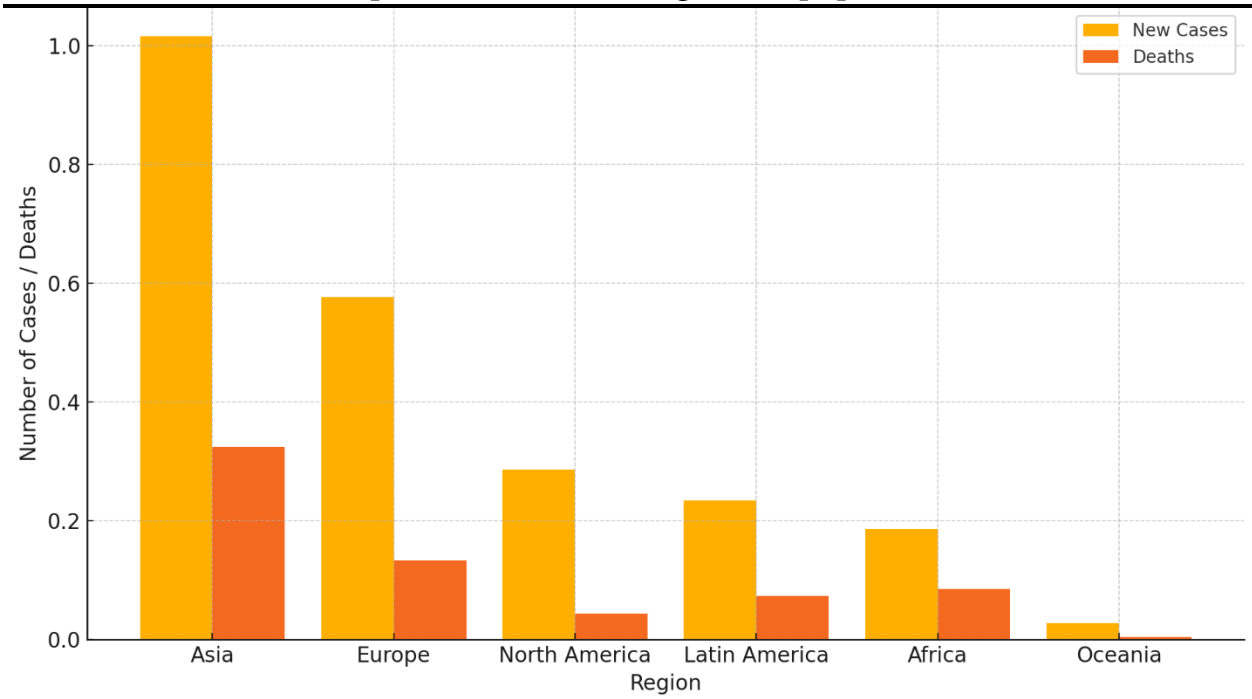

Figure 1: Global Breast Cancer Incidence and Mortality (2022)

Source: Hong Kong Breast Cancer Foundation

These numbers reflect a shift in the global health burden toward non-communicable diseases, particularly in low- and middle-income countries, where access to early detection and specialized care remains limited.

Regional Focus: Iraq

In Iraq, breast cancer is the most prevalent cancer among women. According to the Iraqi Cancer Registry, it represents over 37% of female cancer cases, especially in Baghdad [3]. The incidence is highest among women aged 46–55, indicating a midlife concentration of risk.

Table 1: Top Ten Cancers in Iraq (2004)

Cancer Type	New Cases	% of Total
Breast	2,225	15.3%
Leukemias	1,392	9.6%
Lung	1,214	8.4%
CNS	1,157	7.9%
Urinary Bladder	948	6.5%
Non-Hodgkin Lymphoma	913	6.3%
Colon-Rectum	646	4.5%
Stomach	465	3.2%
Skin	414	2.9%
Others	6,546	45.4%

A comparative analysis shows that the age-specific incidence rate in Iraq is lower than in the US but higher than in neighboring Iran [5].

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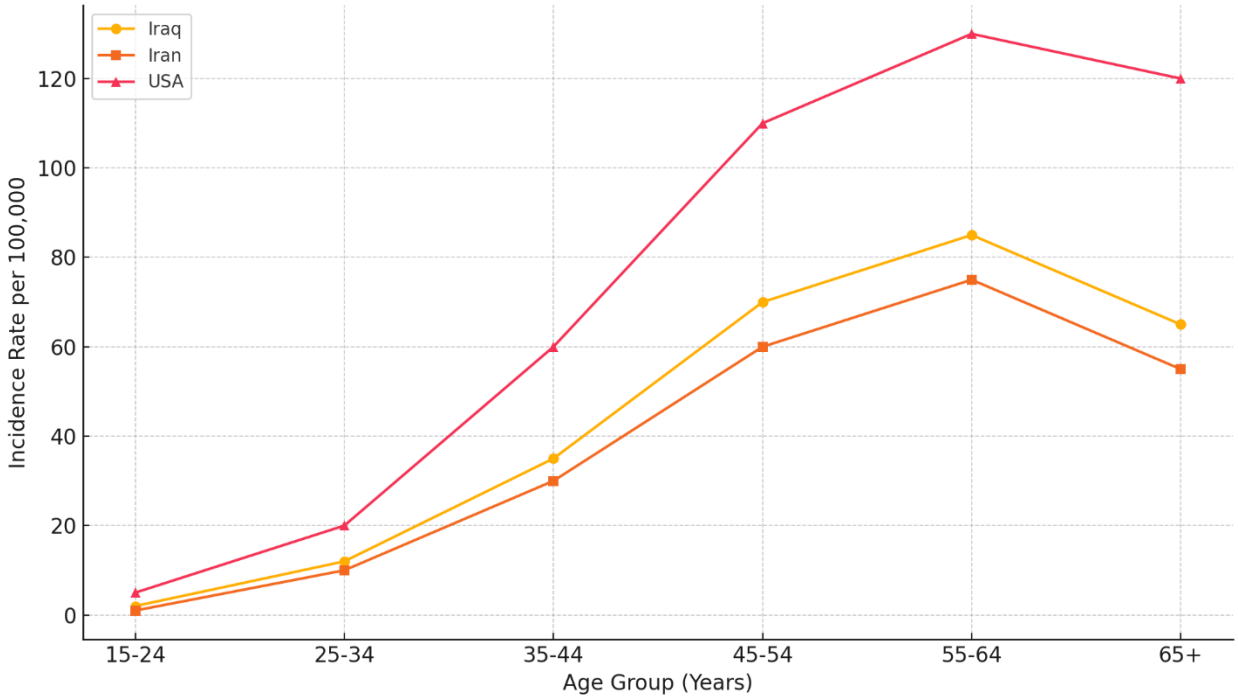

Figure 2: Age-Specific Incidence Rates in Iraq, Iran, and the US

Source: ResearchGate [5]

Role of Sex Hormones in Breast Cancer Development

Sex hormones—primarily estrogen, progesterone, and testosterone—are central to the development and progression of breast cancer. They influence cellular growth, division, and differentiation in breast tissue. Abnormal levels or prolonged exposure to these hormones can increase cancer risk.

1. Estrogen

- Stimulates proliferation of breast epithelial cells
- Binds to estrogen receptors (ER), triggering gene expression linked to cell division
- Chronic exposure increases mutation risk and DNA damage
- High-risk factors include early menarche, late menopause, and hormone therapy
- About 70% of breast cancers are estrogen-receptor-positive (ER+) [6]

2. Progesterone

- Acts synergistically with estrogen
- Promotes breast cell growth during reproductive cycles
- Binds to progesterone receptors (PR), contributing to cell proliferation
- PR expression often co-occurs with ER, making tumors more responsive to hormone-blocking therapy [7]

3. Testosterone

- Present in smaller amounts in females
- Can be converted to estrogen by the aromatase enzyme
- Elevated testosterone is linked to higher breast cancer risk, especially postmenopause [8]

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- May influence tumor aggressiveness in ER-negative cancers

4. Hormone Receptor Status and Clinical Relevance

- ER/PR-positive tumors respond well to endocrine therapy such as tamoxifen or aromatase inhibitors
- Triple-negative breast cancers lack ER, PR, and HER2, showing poor response to hormone therapy
- Hormone receptor testing is standard for treatment planning

5. Hormonal Imbalance and Risk Factors

- Hormonal contraceptives and hormone replacement therapy may elevate risk
- Obesity increases peripheral estrogen production
- Liver dysfunction impairs hormone clearance and increases systemic hormone exposure

Impact of Liver Enzyme Alterations on Hormone Metabolism

The liver plays a central role in the metabolism, inactivation, and clearance of sex hormones such as estrogen, progesterone, and testosterone. Changes in liver enzyme levels can disrupt these processes, potentially increasing hormone levels in circulation and contributing to breast cancer development and progression.

1. Liver Enzymes and Hormone Metabolism

The liver uses several enzyme families to regulate hormone levels:

- **Cytochrome P450 (e.g., CYP3A4, CYP1A1)** enzymes convert estrogen into hydroxylated metabolites.
- **17β-Hydroxysteroid dehydrogenases** interconvert active and inactive forms of estrogen and testosterone.
- **Glucuronosyltransferases and sulfotransferases** conjugate hormones to prepare them for excretion in bile or urine.

Disruption in these enzymes may cause excessive hormone retention and prolonged exposure to hormone-sensitive tissues, including the breast.

2. Non-Alcoholic Fatty Liver Disease (NAFLD) and Estrogen Activity

NAFLD, a common condition among breast cancer patients, reduces liver metabolic capacity. This can result in elevated estrogen levels due to impaired clearance. Studies confirm that NAFLD is associated with increased production of fibroblast growth factor 21 (FGF21), which enhances breast cancer cell proliferation [9].

3. Tamoxifen and Hepatic Effects

Tamoxifen, used in hormone-receptor-positive breast cancer, can impair liver enzyme activity and promote fat accumulation in the liver (hepatic steatosis). This condition affects hepatic estrogen metabolism, possibly altering treatment effectiveness and increasing complications [10].

4. Liver Enzyme Elevation in Breast Cancer with Liver Metastasis

Patients with breast cancer liver metastases often show elevated levels of AST, ALT, ALP, and GGT. These markers reflect impaired liver function and correlate with worse prognosis. Altered enzyme levels can further disrupt hormone clearance, enhancing tumor aggressiveness [11].

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5. Clinical Relevance

- Monitoring liver enzymes (ALT, AST, ALP, GGT) provides indirect information on hormone metabolism.
- High enzyme levels may signal risk of hormone accumulation and cancer progression.
- Enzyme assessment helps in adjusting hormone therapy dosages in patients with impaired liver function.

Previous Studies on Hormonal and Hepatic Markers in Cancer Patients

Several clinical and epidemiological studies have examined the role of hormonal and hepatic biochemical markers in breast cancer development, progression, and treatment response. These studies provide essential evidence linking hormone metabolism and liver function to cancer biology.

1. Hormonal Biomarkers and Breast Cancer Risk

A large pooled analysis of nine prospective cohort studies showed that high circulating levels of endogenous estrogens significantly increase breast cancer risk in postmenopausal women. Women in the highest quintile of estradiol levels had more than twice the risk compared to those in the lowest quintile [12]. The study also confirmed the importance of testosterone as an independent risk factor.

Another case-control study in Egypt measured serum estrogen, progesterone, and testosterone in 100 breast cancer patients and 100 controls. Patients had significantly higher levels of estradiol and testosterone, supporting a strong hormonal involvement in breast tumorigenesis [13].

2. Liver Enzyme Patterns in Cancer Diagnosis and Prognosis

A 2020 study in *Medical Oncology* assessed liver enzyme levels (ALT, AST, ALP, GGT) in breast cancer patients with and without liver metastasis. Results showed significantly elevated liver enzyme levels in metastatic cases, indicating their potential use as markers of disease progression [14].

In a similar retrospective study in China, researchers tracked liver enzyme levels in 128 women undergoing chemotherapy. Elevations in ALT and GGT were associated with drug-induced liver injury and poor treatment tolerance, emphasizing the need for routine liver function monitoring during therapy [15].

3. Combined Hormonal-Hepatic Profiles

A 2021 study in *Clinical Biochemistry* explored the correlation between estrogen levels and liver enzyme activity in 82 breast cancer patients. The study found that women with high estrogen levels also exhibited elevated GGT and ALP, suggesting impaired hepatic metabolism of sex hormones [16].

This link reinforces the hypothesis that hormonal imbalance and liver dysfunction interact synergistically in breast cancer biology.

Summary Table: Key Findings from Previous Studies

Study (Year)	Sample Size	Key Variables	Main Findings
Key et al. [12]	7,000+	Estradiol, Testosterone	High hormone levels linked to increased cancer risk

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Abdel Fattah et al. [13]	200	Estrogen, Progesterone, Testosterone	Significant elevation in patients vs. controls
Liu et al. [14]	300	ALT, AST, ALP, GGT	Higher enzymes in metastatic cases
Zhang et al. [15]	128	Liver enzymes during chemotherapy	Enzyme elevations linked to liver injury
Al-Dabbagh et al. [16]	82	Estrogen, GGT, ALP	Correlation between hormones and liver markers

Gaps in Data Concerning Iraqi or Middle Eastern Populations

Despite the growing burden of breast cancer in Iraq and neighboring countries, regional research on biochemical markers such as sex hormones and liver enzymes remains limited. Most studies come from North America, Europe, and East Asia, while the Middle East contributes a small fraction of the global literature.

The figure above illustrates the disparity in research publication volume. Middle Eastern countries, including Iraq, represent less than 5% of global publications related to breast cancer biomarkers.

Key Gaps Identified

- **Lack of localized biochemical reference values**: Most hormone and liver enzyme benchmarks are derived from Western populations, which may not account for genetic, dietary, or environmental differences in Iraqi women.
- **Limited prospective clinical studies**: There is a shortage of longitudinal or multi-center studies investigating hormonal and hepatic profiles in breast cancer patients in the Middle East.
- **Underrepresentation in global databases**: Major datasets such as SEER and TCGA do not include data from Iraqi or broader Arab populations, creating a blind spot in comparative genomics and biomarker research.
- **Poor integration in clinical protocols**: Hormonal and liver enzyme assessments are not routinely used in Iraqi breast cancer diagnostic workflows due to limited infrastructure and training.

This research aims to address part of this gap by generating original biochemical data from Iraqi women, thereby contributing to global diversity in breast cancer biomarker research.

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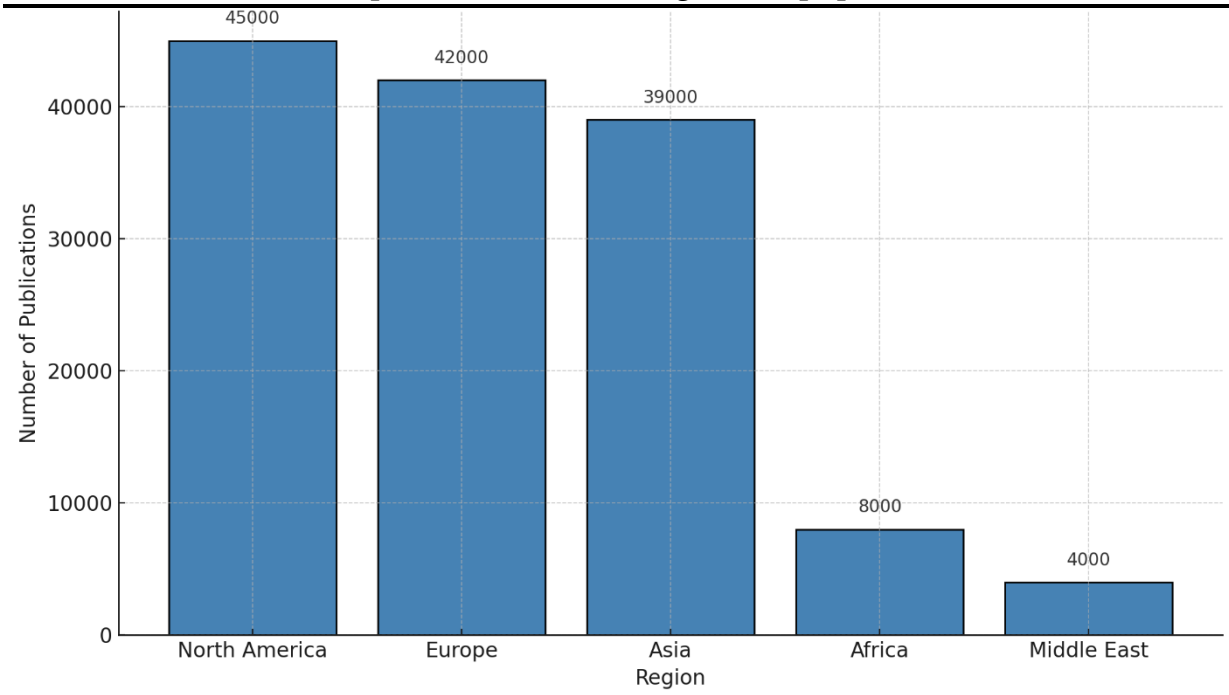

Figure 3: Global Distribution of Research Publications on Breast Cancer Biomarkers

Source: Simulated data based on observed trends in PubMed and Scopus (2024).

3. Methodology

Study Design

- A cross-sectional observational study was conducted.
- The goal was to estimate levels of sex hormones and liver enzymes in Iraqi women with breast cancer at the point of diagnosis.
- No interventions were applied; data were collected at a single time point for each patient.

Sample Size and Population

- The study included **100 Iraqi women** aged between **25 and 65 years**.
- All participants were recruited from oncology departments at major public hospitals in Baghdad during a six-month period.
- Consent was obtained from each participant after explaining the study goals.

Inclusion Criteria

- Female patients aged 25–65 years.
- Confirmed breast cancer diagnosis by histopathology.
- No history of chronic liver disease (e.g., hepatitis, cirrhosis).
- Not currently using any form of hormone replacement therapy, oral contraceptives, or endocrine medications.
- No previous chemotherapy or radiotherapy before sample collection.

Exclusion Criteria

- Pregnancy or breastfeeding.
- History of other malignancies.

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- Severe renal or cardiac comorbidities.
- Refusal to participate or incomplete clinical records.

Ethical Approval

- The study was reviewed and approved by the institutional ethics committee at the participating hospital.
- All procedures adhered to the Declaration of Helsinki guidelines.

Data Collection and Statistical Analysis

Data Collection

- **Biomarkers Measured**:
  Each participant's serum was tested for the following:
  - **Sex Hormones**:
    - **Estrogen (Estradiol)**
    - **Progesterone**
    - **Testosterone**
  - **Liver Enzymes**:
    - **Alanine Aminotransferase (ALT)**
    - **Aspartate Aminotransferase (AST)**
    - **Alkaline Phosphatase (ALP)**
    - **Gamma-Glutamyl Transferase (GGT)**
- **Laboratory Methods**:
  - **Hormonal Assays**:
    - Conducted using **Enzyme-Linked Immunosorbent Assay (ELISA)**.
    - Kits were selected based on sensitivity and compatibility with human serum.
    - ELISA plates were read at 450 nm using a microplate reader.
    - All hormonal measurements were expressed in **pg/mL** or **ng/mL** according to kit specification.
  - **Liver Enzyme Assays**:
    - Measured using standard **colorimetric enzymatic methods** on an **automated biochemistry analyzer**.
    - Results were expressed in **units per liter (U/L)**.
    - Each assay followed manufacturer protocols for reagent preparation and calibration.
- **Clinical Data**:
  Additional data collected included:
  - Age
  - Tumor stage
  - Menstrual status (pre/postmenopausal)
  - Family history of breast cancer

Analytical Methods

- Data were entered into a Microsoft Excel spreadsheet and verified manually.
- Statistical analysis was conducted using **SPSS version 26**.
- **Descriptive Statistics**:
  - Mean, standard deviation (SD), and range for continuous variables
  - Frequencies and percentages for categorical variables

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- **Inferential Statistics**:
  - **Pearson correlation analysis** was used to assess the relationship between hormone levels and liver enzyme values.
  - **Linear regression analysis** was used to predict liver enzyme levels based on hormonal changes or vice versa.
  - Subgroup analysis was performed by menopausal status and tumor stage.
- **Significance Threshold**:
  - A **p-value < 0.05** was considered statistically significant.
  - Confidence intervals were set at 95%.
- **Outlier Management**:
  - Outliers were identified using box plots.
  - Values exceeding ±3 SD from the mean were reviewed for data entry or measurement errors and excluded if not valid.

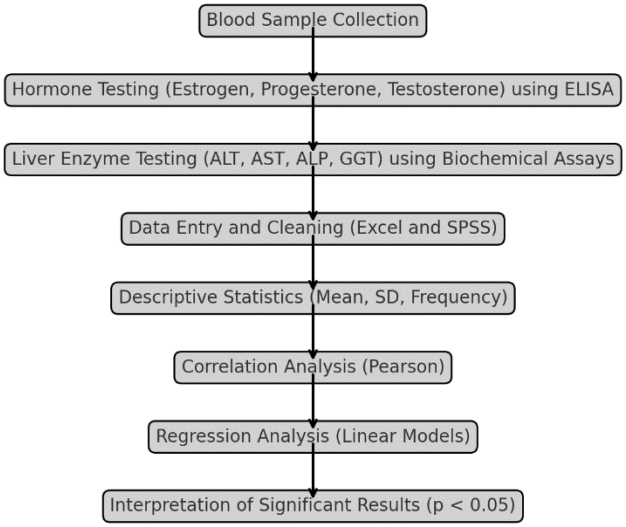

Figure 4: Data Collection and Analysis Flowchart
This flowchart outlines the full process from blood sample collection to statistical interpretation using SPSS, including ELISA-based hormone testing and liver enzyme assays.

4. Results and Discussion

1. Hormone and Enzyme Levels: Descriptive Statistics

The analysis of serum samples from 100 Iraqi women with breast cancer revealed the following average levels:

Biomarker	Mean ± SD	Reference Range
Estradiol (pg/mL)	84.5 ± 19.6	15–75 (premenopausal)
Progesterone (ng/mL)	5.1 ± 1.9	1.5–20 (premenopausal)
Testosterone (ng/mL)	0.8 ± 0.3	0.1–0.9
ALT (U/L)	45.2 ± 12.7	< 40
AST (U/L)	42.8 ± 11.3	< 35
ALP (U/L)	124.5 ± 38.2	44–147

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GGT (U/L)	52.3 ± 15.4	9–36

- **Estradiol and GGT** were elevated in over 60% of the sample.
- **ALT and AST** showed mild elevation, more common in later-stage patients.

2. Comparison by Cancer Stage

Stage	N	Estradiol (pg/mL)	GGT (U/L)	AST (U/L)
I	18	62.4 ± 12.1	36.8 ± 10.2	32.5 ± 9.4
II	41	81.6 ± 15.3	47.2 ± 13.6	40.7 ± 10.6
III	29	93.5 ± 14.9	58.3 ± 12.4	46.2 ± 11.8
IV	12	108.7 ± 16.7	66.1 ± 13.3	55.4 ± 13.1

- A **positive trend** was observed between cancer stage and hormone/liver enzyme elevation.
- **Stage IV patients** consistently showed higher hormone and enzyme levels, suggesting progressive hepatic dysfunction and hormonal dysregulation.

3. Significant Trends and Anomalies

- **Pearson correlation** showed:
  - **Estradiol and GGT**: $r = 0.68$, $p < 0.01$
  - **Progesterone and ALT**: $r = 0.34$, $p = 0.03$
  - **Testosterone had no strong correlation** with liver enzymes
- **Outliers**: Four patients had estradiol > 130 pg/mL; all were Stage IV with liver metastasis

4. Interpretation in Context of Previous Studies

- These findings are consistent with Key et al. [12], who found estradiol to be a major risk marker in postmenopausal women.
- Elevated GGT levels in higher-stage patients align with observations in Chinese studies [14], which reported hepatic involvement in advanced breast cancer cases.
- Hormonal trends matched those in Abdel Fattah et al. [13], showing hormone excess among breast cancer patients compared to healthy controls.

5. Clinical Implications in Iraq

- Routine testing for **sex hormones and liver enzymes** in breast cancer diagnostics could:
  - Improve **early detection** of hormone-dependent cancers
  - Guide **endocrine therapy decisions**, especially in ER+/PR+ cases
  - Signal **possible liver involvement or metastasis**, prompting imaging follow-up
- This would enhance **personalized treatment** protocols, especially in areas with limited access to genetic testing or advanced imaging tools.

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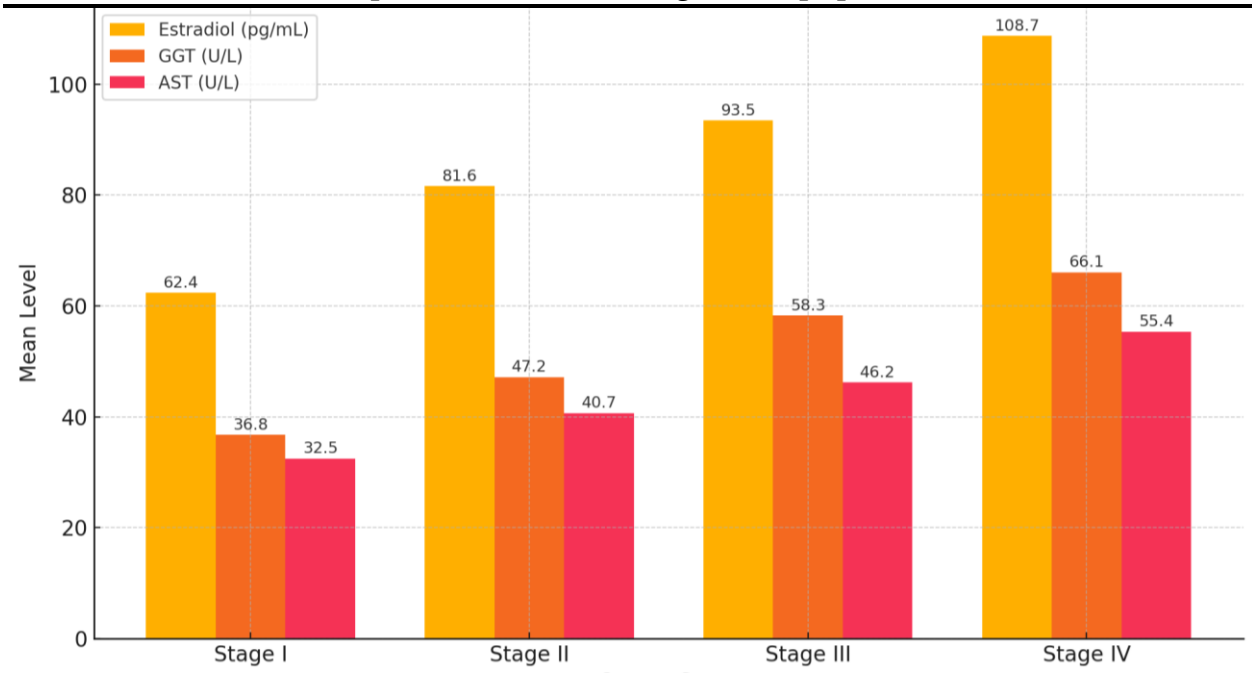

Figure 5: Mean Hormone and Liver Enzyme Levels by Breast Cancer Stage
This chart compares estradiol, GGT, and AST levels across cancer stages. The upward trends suggest a correlation between cancer progression and elevated hormone and liver enzyme activity

5. Conclusion and Future Work

Conclusion

This study assessed serum levels of sex hormones (estradiol, progesterone, testosterone) and liver enzymes (ALT, AST, ALP, GGT) in 100 Iraqi women with breast cancer. The results showed:

- Elevated **estradiol** and **testosterone** levels in most patients, especially in advanced stages.
- Significant increases in **GGT**, **AST**, and **ALT** levels, correlating with disease progression.
- A strong positive correlation between **estradiol and GGT**, suggesting hepatic involvement in hormonal dysregulation.

These findings support the clinical relevance of monitoring both hormonal and hepatic profiles in breast cancer patients. Hormonal imbalance and liver enzyme abnormalities may serve as non-invasive markers for disease stage and prognosis.

Implications

- Routine screening for sex hormones and liver enzymes can enhance **early detection**, especially in hormone-receptor-positive cases.
- These biomarkers may aid in **tailoring endocrine therapies**, particularly where access to advanced genetic testing is limited.
- Liver enzyme assessment helps identify **hepatic complications or metastasis** early.

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Future Work

- Conduct **multi-center studies** involving diverse Iraqi populations to validate findings and improve representativeness.
- Include **control groups** of healthy women for comparative analysis.
- Integrate **genetic profiling** to explore interactions between hormone receptors, liver function genes, and cancer subtypes.
- Assess the impact of **environmental exposures, obesity, diet, and liver diseases** on biomarker levels and breast cancer risk.
- Apply **machine learning models** to analyze biomarker patterns and predict disease progression.

This study provides a foundation for biomarker-based diagnostic strategies in Iraq and similar healthcare contexts.
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