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Risk factors of breast cancer and the role of progesterone and estrogen receptors as early diagnostic markers "in the Western region of Zawia"

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DECLARATION

I hereby declare that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged .

15 February 2026 **Marwa Fathi Mohammed Alqellali**

Dedication

To those who were the light along my path and the support in the most critical times.

My mother, my eternal source of encouragement,my father, the wellspring of wisdom my siblings, whose constant support lifted me.

The unseen hands and to everyone who believed in my abilities,my children, who endured the hardship of difficult times alongside me , I love you.

To the soul of my late husband, and to my esteemed supervisors who taught me how to walk the path of scientific research .

I dedicate this thesis to you,not as an end, but as a beginning of something better.

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To them, I dedicate this work.

ABSTRACT

Breast cancer remains a major public health concern globally and in Libya, with increasing incidence and mortality rates, particularly among older women. This study evaluated demographic, genetic, and non-genetic risk factors, including age, marital status, obesity, and family history, and assessed their association with breast cancer incidence. The findings revealed that age, obesity, and marital status were significantly associated with disease occurrence, while family history and smoking had a limited influence. Hematological and biochemical parameters showed notable alterations in breast cancer patients compared to controls. Platelet counts were significantly elevated ($P < 0.001$), while white blood cell counts were not significantly different ($P = 0.293$). Serum sodium levels were significantly decreased ($P<0.001$), whereas potassium levels showed no significant difference ($P=0.396$). Lactate dehydrogenase (LDH) was significantly elevated ($P < 0.001$), while other liver enzymes, uric acid, total protein and total bilirubin remained non-significant ($P = 0.618$, 0.851, 0.360, respectively). Lymphocyte counts and glucose levels were significantly lower in the patients ($P = 0.029$ and 0.013, respectively). The distribution of hormone receptors (ER and PR) and HER2 revealed that ER- and PR-positive tumors were more frequent, whereas HER2 positivity was less common. No significant association was found between estrogen receptor status and tumor grade ($P = 0.062$) or tumor side ($P = 0.726$), whereas progesterone receptor status was significantly correlated with tumor grade ($P = 0.002$) but not with tumor side ($P = 0.55$). HER2 expression appeared independent of tumor grade ($P = 0.465$) and laterality ($P = 0.461$), emphasizing the heterogeneity of breast cancer and the complexity of its molecular subtypes. Serum biomarkers CEA and CA 15-3 displayed variable patterns in relation to tumor grades. CEA levels showed no significant differences among grades ($P = 0.607$) or in relation to ER ($P = 0.423$), PR ($P = 0.565$), or HER2 ($P = 0.965$) status. CA 15-3 levels also did not differ significantly across tumor grades ($P = 0.548$) but were significantly associated with ER positivity ($P = 0.030$), while no significant correlation with PR or HER2. Overall, the study highlights the importance of early detection, comprehensive evaluation of hormone receptor and HER2 status, and awareness of modifiable risk factors such as obesity. The data suggests that CA 15-3 may provide limited prognostic value in ER-positive tumors, whereas CEA shows minimal utility in receptor-based stratification. Further large-scale studies incorporating molecular subtypes and additional biomarkers are recommended to refine prognostic assessments and improve clinical management of breast cancer.

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ABBREVIATIONS

ALK	Alkaline Phosphatase
AIs	Aromatase Inhibitors
ASCO/CAP	American Society of Clinical Oncology / College of American Pathologists
BC	Breast Cancer
BCL-2	B-cell lymphoma 2
BMI	Body Mass Index
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
CA 15-3	Cancer Antigen 15-3
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
cGy	Centigray (unit of radiation dose)
dsDNA	Double-Stranded DNA
ER	Estrogen Receptor
ERα	Estrogen Receptor alpha (a subtype of ER)
ESMO	European Society for Medical Oncology
EGFR	Epidermal Growth Factor Receptor
ET	Endocrine Therapies
FHS	Family History Score
GCO	Global Cancer Observatory
GCC	Gulf Cooperation Council

GOT	Glutamic-Oxaloacetic Transaminase
GPT	Glutamic-Pyruvic Transaminase
GWAS	Genome-Wide Association Studies
HBOC	Hereditary Breast and Ovarian Cancer syndrome
HCT	Hematocrit
HER2-neu	Human Epidermal Growth Factor Receptor 2
Hgb	Hemoglobin
IHC	Immunohistochemical
IL-6	Interleukin-6
ISLN	Ipsilateral Supraclavicular Lymph Node
Ki 67	Marker of cell proliferation
Lymph	Lymphocytes
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MRI	Magnetic Resonance Imaging
Neut	Neutrophils
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NLR	Neutrophil-to-Lymphocyte Ratio
PgR	Progesterone Receptor Gene
PR	Progesterone Receptor

PLT	Platelet Count
RBC	Red Blood Cell count
RR	Relative Risk
SERDs	Selective Estrogen Receptor Degraders
SERMs	Selective Estrogen Receptor Modulators
TN	Triple-Negative (Breast Cancer)
WHO	World Health Organization

CHAPTER I

1. Introduction

1.1 Background

Cancer is one of the main causes of mortality around the world. About 8 million deaths were recorded in 2008 as a result of malignant diseases, and this figure is estimated to reach 11 million by 2030 (Momenimovahed & Salehiniya 2019). Breast cancer (BC) is the second leading cause of death in the world, it is the most common cancer among women (Moghbeli 2019). BC is a public health dilemma all over the world, therefore awareness of the disease among the public is essential, which provides a positive impact on early detection of breast cancer (Akram *et al.*, 2017).

The World Health Organization has recorded that the number of deaths in 2020 reached 685,000 worldwide. Also, in the same year, 2.3 million cases of breast cancer were diagnosed, and this made it the most common cancer in the world. According to data from the Global Cancer Observatory (GCO) website and 2022 study approved by the World Health Organization, breast cancer ranks the first in terms of infection rates compared to other cancers. This makes it one of the most widespread and deadly cancers worldwide (Figure 1.1) (Arnold *et al*., 2022).

Breast Cancer is a complex and heterogeneous disease characterized by the abnormal proliferation of breast tissue, leading to tumor formation

This heterogeneity contributes to the cancer's ability to reprogram its gene expression and alter its behavior (Clusan *et al*., 2023).

Although the main causes of breast cancer in women are still unclear, nonhereditary causes and risk factors remain the predominant cause. These include early menarche, hormone intake, nutrition, alcohol consumption, smoking, and obesity, all of which are generally reported as risk factors (Løyland *et al*., 2024).

A **B**

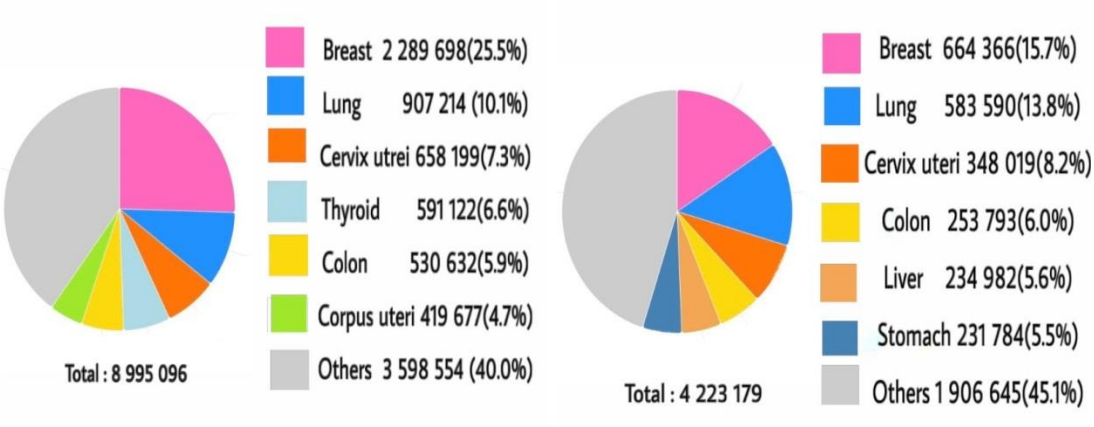


Figure (1.1) Estimates of incident cases and deaths of main cancer types worldwide in 2022. (A) Estimated number of new cancer cases. (B) Estimated number of cancer-related deaths in 2022 worldwide. Source: GLOBOCAN 2022.

Furthermore, only 5-10 % of breast cancer cases are hereditary, with germline mutations in BRCA1 or BRCA2 accounting for 30% of breast heritable cancer cases (Bray *et al*., 2018).

Several studies have identified that the risk factors of breast cancer are associated with various causes, late age of first full-term (if any) pregnancy, short periods of breastfeeding, dietary routine, quality and composition of meals, physiologic factors, lower age at menarche, and later menopause (Golubnitschaja *et al*., 2016).

Breast cancer is a multi-stage process, and its prevention is classified as one of the greatest challenges in the world. Early diagnosis is considered as one of the preferred methods of prevention, and this international percentage indicates that the five-year survival rate is higher than 80% due to early diagnosis (Sun *et al*., 2017).

Three predictive markers have independent prognostic value in breast cancer; estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (Her2-neu). Expression of ER appears in 80-90 % of patients with breast cancer, while PR expression appears in 70 80 % of cases. Overexpression of Her2-neu is present in 15-20 % of cases (Varma *et al*., 2024).

Currently, estrogen and progesterone receptor expressions are the most important and valuable predictive factors. Testing for steroid receptors such as ER and PR by immunohistochemistry is the well-known standard of care with, almost 70–80% of the tumors in breast cancer being ER and/or PR positive. The level of ER and PR positivity increases with age, reaching its highest levels in postmenopausal women (Allerd *et al*., 2009). Breast cancer whose malignancy is deficient in ER and PR do not benefit from hormonal treatment (Masood 2000). Moreover, HER2/neu oncogene expression is also important in breast cancer tumorigenesis. The HER2/neu receptor is a member of the epidermal growth factor receptor family of receptor tyrosine kinases, which are important mediators of of proliferation and differentiation of cells (Roskoski 2004). Positive HER2/neu has been considered to be a negative predictor of response to hormonal therapy, adjuvant radiotherapy, and adjuvant chemotherapy (Ivkovic-Kapicl *et al*., 2007). The molecular heterogeneity of breast cancers, revealed through the differential expression of key genes, and classified into four main subtypes:

1. Luminal A: Characterized by ERα expression, these tumors are less aggressive, with low proliferation rates. They may express PR but do not express HER2.

2. Luminal B: Also ERα-positive, these tumors are more aggressive than Luminal A due to higher expression of genes involved in proliferation and the cell cycle. Luminal B cancers may express PR and typically also express HER2.

3. HER2-Positive: Defined by overexpression of HER2, these cancers are aggressive and often lack ER and PR expression.

4. Basal-Like (Triple-Negative): Lacking ER, PR, and HER2, these tumors are highly aggressive and associated with a poorer prognosis. (Clusan *et al*., 2023) (Figure 1.2).

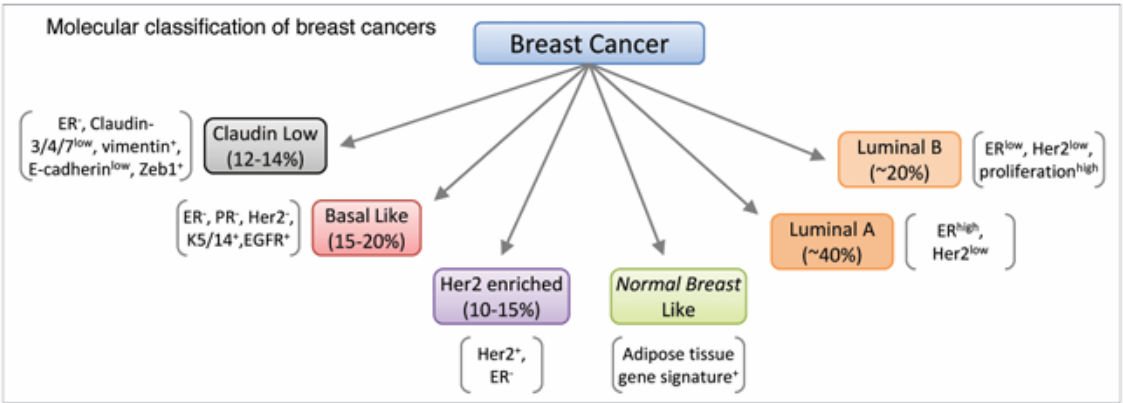


Figure (1.2) Molecular classification of breast cancer (Malhotra *et al* ., 2010).

1.2 Significance of the study

Over the last decades, an association between sex steroids and premenopausal breast cancer risk has been proven. High levels of circulating estrogen are strongly associated with an increased risk of breast cancer in premenopausal women. Because of these consistent associations, the research was directed towards to find out if circulating hormone levels could be used clinically to help determine a postmenopausal woman's individual risk of breast cancer and could help direct the frequency of mammographic screening or use of chemo preventive agents.

1.3 Aims and objectives

The overall aim of this study was to explore potential biomarkers for use in breast cancer diagnosis. The specific aims are as follows:

1. Determine the incidence rates of breast cancer among women in the Western region of Libya among patients who are regularly attending the National Cancer Institute at Sabratha.
2. Investigate the risk factors that may be associated with and contribute to the development of the disease.
3. Analyze data from patients such as (CBC, CEA , CA 15-3), liver function, and kidney function, as biomarkers for breast cancer patients.
4. Investigate the role of steroid hormones (progesterone and estrogens) as biomarkers and Find out the human epidermal growth factor receptor2 (HER2) as a predictive biomarker in breast cancer.

CHAPTER II

2. Literature Review

2.1 Basic antomy of female breast

The female breasts are specialized exocrine glands located on the front chest wall, between the sternum and midaxillary line, overlying superficial chest muscles. The breast skin, covering the entire external surface, including the nipple and areola, consists of an outer epidermis and an inner dermis rich in collagen (types I and II) and elastin, giving it mechanical strength. Firmly connected to the underlying fibro-adipose tissue, the skin contributes to structural support (McGhee& Steele 2023). The breast is influenced by the female sex hormone estrogen. The levels of estrogen decline as menopause approaches, which also decreases the glandular tissues (Rivard *et al*., 2025).

Female breasts vary considerably in size and shape .Some females have a large amount of breast tissue and have larger breasts, while others have smaller of tissue and little breast fat. In fact, it depends upon genetic, racial, and dietary factors, and the age, parity and menopausal status of the individual. The breasts may be hemispherical or conical in form with a base measuring 10–12 cm and a thickness of 5–7 cm (Figure 2.1). The main bulk of the breast tissue is localized to its upper outer quadrant. This part is more implicated in breast cancer (Bistoni & Farhadi 2015).

The nipple–areola complex plays an important role in breastfeeding ; it is situated between the fourth and fifth ribs in nulliparous women. The complex typically measures 3–4 cm in diameter and is ideally located in the centre of the breast mound. The nipple contains 15–20 lactiferous ducts. The nipple–areola complex consists of keratinizing stratified squamous epithelium with a thick basal melanin deposition. Melanocytes give them a darker colour than the rest of the breast (Bistoni & Farhadi 2015).

The underlying breast is made of epithelial components that consist of lobules, where milk is produced, which connect to ducts that lead out to the nipple. These lobules and

ducts are located and spread throughout the fibrous tissue and adipose tissue that form the main part of the breast (Bistoni & Farhadi 2015).

The breast skin obtains its blood supply from the subdermal plexus; these tiny blood vessels, connect with deep underlying arterioles and supply the breast parenchyma (Rivard *et al*., 2025).

Moreover, the breast also has widespread lymphatic drainage that runs both superficially (areolar and subareolar plexus) and deep within the breast.The superficial lymphatics continue posteriorly and medially and reach the axillary lymph nodes (Rivard *et al*., 2025).

Sensory innervation to the breast is come from branches of the intercostal nerves T3-T5. Other nerves that supply sensory innervation include the lower cervical plexus. The lateral cutaneous branch of T4 provides sensation to the nipple (Rivard *et al*., 2025).

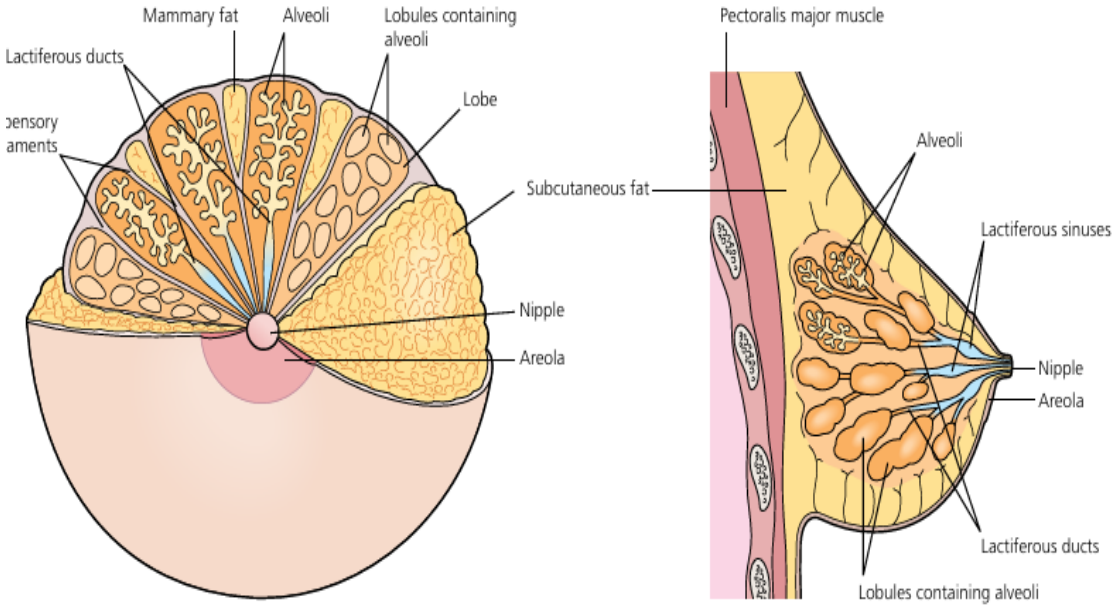
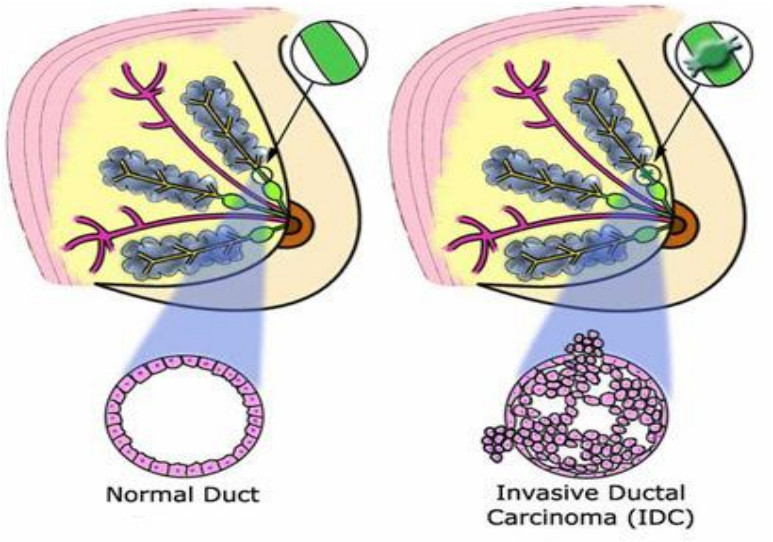


Figure. (2.1) Section of the breast: (left) inner structure of the mammary gland; (right) section of the breast showing milk flow (Bistoni & Farhadi 2015)

2.2 Pathology of breast cancer

Cancer cells are very similar to normal cells, but they are not identical. Cancer occurs in breast tissues, usually in the inner lining of the milk ducts or lobules , and develops into benign tumors or even metastatic carcinomas after continuous stimulation by various carcinogenic factors (Figure 2.2). (Sharma *et al*., 2010). Tumor microenvironments include the stromal influences or macrophages, which plays vital roles in breast cancer initiation and development (Sun *et al*., 2017). It has been suggested that the mammary gland of rats could be provoked to neoplasms when only the stroma was exposed to carcinogens, not the extracellular matrix or the epithelium (Sun *et al*., 2017). Macrophages can cause a mutagenic inflammatory microenvironment, which can induce angiogenesis and enable cancer cells to escape immune rejection (Sun *et al*., 2017). There are two major types of breast cancer. *In situ* carcinomas and invasive (infiltrating) carcinomas, the *in situ* carcinomas may arise in either ductal or lobular epithelium and confined there, with no invasion of the underlying basement membrane that would constitute an extension beyond epithelial boundaries. However, when there is a spread of the ductal or lobular malignancy beyond the basement membrane that constitutes the epithelial border, and then the malignancy is known as invasive (or infiltrating) ductal or lobular carcinoma, and in this case, cancer becomes life-threatening to the patient with death(Richie & Swanson 2003).



Figure(2.2) Normal and invasive duct of breast (Sharma *et al*., 2010).

2.3 Pathological diagnosis and prognostic markers in breast cancer

Accurate pathological diagnosis is vital for determining the appropriate treatment and predicting the prognosis of breast cancer. Prognostic and therapeutic markers of breast cancer are categorized into three main groups:

1. Classical Parameters: These include histologic type and grade, tumor size, lymph node status, tumor necrosis, and skin invasion.

2. Immunohistochemical (IHC) Markers: These consist of estrogen receptor (ER), progesterone receptor (PR), and, more recently, HER2/neu.

3. Molecular Markers: Emerging markers provide deeper insights into breast cancer biology.

Breast carcinoma classification based on IHC markers has significant therapeutic and prognostic implications and can be performed using routine paraffin blocks. Breast cancer is a complex disease with distinct biological subtypes, each with its own natural history, clinical presentation, and molecular features. These subtypes provide more detailed prognostic and therapeutic information than viewing breast cancer as a single disease entity.

Understanding prognostic factors, especially hormone receptor status, is essential for identifying high-risk patients with a likelihood of recurrence. This enables targeted management using neoadjuvant chemotherapy and close follow-up (Santosh *et al*., 2021).

2.4 Risk factors of breast cancer

The cause of breast cancer is multifactorial, and several risk factors contribute to the possibility of developing breast cancer. These factors include both non-modifiable factors and modifiable factors. Non-modifiable risk factors include female sex, age, gender, genetic mutation, and density of breast tissue, while modifiable risk factors are obesity, menstrual and reproductive factors, radiation exposure, hormone replacement therapy, alcohol, and high-fat diet (Nindrea *et al*., 2017).

2.4.1 Non-modifiable factors

- **Female sex**

Breast cancer is overwhelmingly diagnosed in women, with men accounting for less than 1% of all cases. However, over the past 30 years, breast cancer in men has been gradually increasing, possibly due to factors like obesity and longer male life expectancy (Kamińska *et al*., 2015).

The increased risk of breast cancer among women is primarily because of the enhanced hormonal stimulation. While men who present insignificant estrogen levels, breast cells in women are very vulnerable to estrogen and progesterone hormones, as well as any disruptions in their balance. Estrogens and androgens circulation are positively associated with an increased risk of breast cancer (Key *et al*., 2013).

The fluctuations within the physiological levels of the endogenous levels of sex hormones lead to a higher risk of breast cancer in the case of premenopausal and postmenopausal women (Folkerd and Dowsett 2013).

Histopathological studies show that over 80% of male breast cancers are ER and PR positive, often linked with high bcl-2 expression. Yet, response to tamoxifen is often weaker in men, and ER positivity doesn't guarantee a better outcome. Overexpression of HER2 is rare in male cases and has little prognostic value (Kamińska *et al*., 2015).

- **Age:**

Age is one of the main factors that predict the incidence of cancer. Studies have confirmed the existence of a close relationship between breast cancer and age, as the greater the age, the greater the chances of contracting the disease. Approximately 99.3% and 71.2% of all breast cancer-associated deaths in America were reported in women over the age of 40 and 60, respectively (Sun *et al*., 2017).

A study conducted at the Oncology Institute in Sabratha -Libya, showed that the advanced age has a higher chances of infection, as the most affected age for women at the age of 48-49 whereas, for men at the age of 54 years. (Kamoka & Alawaini 2022).

BC is most common in women around menopause and is much less frequent in women under 45. In the Polish population, incidence increases steadily between ages 40–59, then levels off and slightly decreases after age 70. There's also a clear link between age and estrogen receptor (ER) status: ER-positive tumors become more common with age, especially after menopause, while ER-negative tumors are more common in younger women up to age 50 and then stabilize. This helps explain why postmenopausal women are more likely to have ER-positive breast cancers (Kamińska *et al*., 2015).

- **Family history**

A family history of breast cancer is a major factor associated with an increased risk of developing breast cancer. Almost 13–19% of patients diagnosed with breast cancer report a first-degree relative affected by the BC (Łukasiewicz *et al*., 2021). BC occurs more frequently in close relatives, with a first-degree relative (mother, sister, daughter) (Sharma *et al*., 2010).

Brewer *et al*., (2017) analyzed the impact of family history on breast cancer risk in the UK, involving over 113,000 women. The results showed a significant increase in breast cancer risk with the largest family history score (FHS), with women with multiple relatives having a 2.5-fold higher risk.

The incidence rate of breast cancer is significantly higher in all of the patients with a family history regardless of age. This association is due to epigenetic alteration and the environmental factors acting as possible triggers (Wu *et al*., 2018). A family history of ovarian cancer, which is characterized by *BRCA1* and *BRCA2* mutations—might also induce a higher risk of breast cancer (Elik *et al*., 2015).

- **Genetic mutation**

The genetic mutation, as the genes associated with breast cancer occur with many mutations and abnormal amplification, as well as oncogenes and anti-tumor genes, which play major roles in the process of tumor initiation, including BRCA1 / BRCA2. The deficiency or defect in their work leads to a defect in the cells and their work, and this defect forms an abnormal growth of cells, eventually causing the formation of tumor, (Sun *et al*., 2017).

BRCA1 is the first major gene associated with hereditary breast cancer, which is located on chromosome 17. This gene was identified in 1990 using linkage analysis in families with suggestive pedigrees. In 1994, *BRCA2* was mapped to chromosome 13 (Shiovitz and Korde 2015).

BRCA1 and *BRCA2* mutations are inherited in an autosomal dominant fashion, but act on the cellular level as tumor suppressor genes involved in double-stranded DNA (dsDNA) break repair. It has been found that female carriers of mutations in *BRCA1* or *BRCA2* have a 50-85% risk of breast cancer (King *et al*., 2003).

Rearrangements and deletions in *BRCA1* or *BRCA2* can also change the function of BRCA, resulting in an identical clinical syndrome to that seen in carriers of mutations in these genes. This clinical syndrome is referred to as the Hereditary Breast/Ovarian Cancer (HBOC) syndrome, despite the fact that there are patients with this same clinical picture who are found to be negative for mutations in both *BRCA1* and *BRCA2* (Rakha *et al*., 2008)., Additionally, there is an increased risk of ovarian cancer, of 10–40% for *BRCA1* carriers and 10%–20% for *BRCA2* carriers (King *et al*., 2003).

Tumors result to mutations in *BRCA1* tend to be of the basal-like phenotype, with a high histologic grade, and do not express the estrogen receptor (ER), progesterone receptor (PR), or Her2/*neu*, which called triple-negative tumor (Rakha *et al*., 2008). Therefore, it is critical to identify individuals with a hereditary cancer syndrome, as this significantly affects their clinical management. According to European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) women with mutations in *BRCA1*, *BRCA2*, should be counseled concerning breast awareness and breast self-exam starting at age 18, Clinical breast exam, and imaging with a combination of mammography and magnetic resonance imaging (MRI) is strongly recommended annually (Lowry *et al*., 2012).

- **Density of breast tissue**

Individuals with denser breast tissue e are at higher risk of breast cancer. Those individuals have more milk ducts, glands, and connective tissue. Compared to women with little or no dense breast tissue. The density of thr breast can only be detected by a mammogram, but dense breasts also make the image more difficult to interpret.

Dense tissue on a mammogram appears white, like tumors, while fatty tissue appears dark, covering a tumor (Terry and Colditz 2023; Obeagu& Obeagu 2024).

Numerous genome-wide association studies (GWAS) stated that some genetic variants associated with breast cancer are also associated with mammographic breast density (Terry and Colditz 2023).

2.4.2. Modifiable risk factors

- **Obesity**

Acoording to the World Health Organisation (WHO) and many national authorities, obesity is defined as (a state of excess body fatness). The current rate of obesity, body mass index (BMI >30 kg/m^2) is estimated as 26% in British women, and it may increase up to 43% by 2030 (James *et al*., 2015).

Obesity is one of the factors related to the risk of breast cancer, and several study have found a relationship between obesity and the risk of breast cancer. Obesity is an independent risk factor for breast cancer in postmenopausal women, especially in women with positive estrogen receptor (ER) and positive progesterone receptor (PR) subtypes. However, positive relations between obesity and the development of breast cancer have also been demonstrated for triple-negative (TN) breast cancer (Gravena *et al*., 2018).

Furthermore, ER-positive breast cancer after menopause occurs due to higher estrogen levels. Obese postmenopausal women tend to have high estradiol, estrone, and testosterone, and lower sex hormone-binding globulin, which elevates free estrogen in the circulation. Women in the highest hormone level group have about double the risk of breast cancer compared to those in the lowest group. Estrogen levels are also higher in breast tissue, especially in tumors. BMI affects these tissue hormone levels. Additionally, obesity-related inflammation elevates the production of IL-6, which increases aromatase activity and further boosts local estrogen levels in breast tissue (Picon-Ruiz *et al*., 2017).

- **Reproductive factors**

Reproductive factors such as early menarche, late menopause, late age at first pregnancy, and low parity can increase the risk of breast cancer risk. The risk increases each 1-year delay in menopause by 3%. The risk decrese each 1-year delay in menarche or each additional birth by 5% or 10%, respectively (Sun *et al*., 2017). Studies showed that early menarche (before age 12) increases breast cancer risk, likely due to longer lifetime exposure to estrogen. However, more recent research suggests that age at menarche may not significantly affect risk across different breast cancer subtypes in women aged 20 to 44 years (Rojas and Stuckey 2016).

- **Smoking**

Evidence suggests that smoking before menopause increases breast cancer risk, especially for women who began smoking before their first pregnancy or smoked heavily over time(Winters *et al*., 2017).

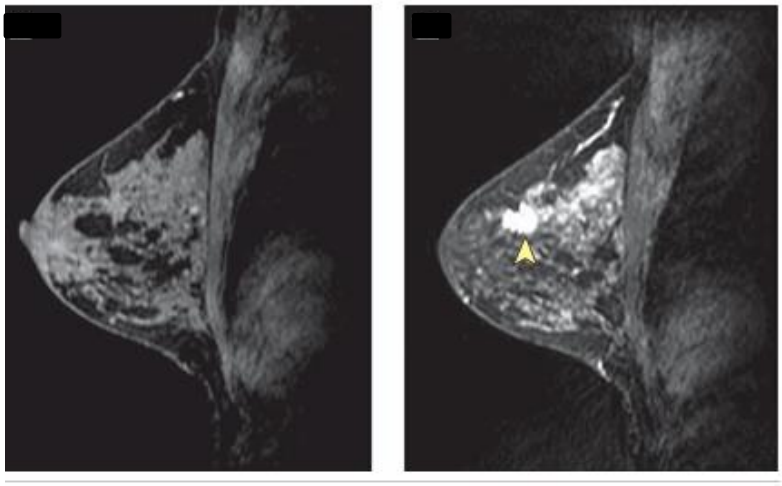
Passive smoking may be a higher risk factor for BC compared to active smoking. It has been suggested that active smoking is associated with tobacco's anti-estrogen effects, which can reduce the impact of estrogen in the body and may reduce the exposure to smoking-related carcinogens. Passive smoking does not "benefit" from the anti-oestrogenic effect but results in sustained exposure to carcinogenic compounds such as N-nitrosamines, benzenes, carbon monoxide and carbon dioxide, which persist in side stream smoke, leading to increased risk of breast oncogenesis (Winters *et al*., 2017; Daly *et al.*, 2021).

2.5 Screening of breast cancer

Diagnosis is a very important stage, as breast cancer is usually diagnosed by a biopsy obtained from the ducts or nodes, by a mammogram, or by palpation based on the presence of a mass in the breast or the armpit. Mammography is an effective screening tool that uses low-energy X-rays to take high-resolution images of the breast (Sharma *et al*., 2010; Sun *et al*., 2017). After the diagnosis, the stage of breast cancer and its progress are determined, and this helps to determine the appropriate type of treatment for the patient (Sharma *et al*., 2010). Inheritance of both BRCA1 and BRCA2 genes significantly increases the risk of breast cancer. These genes are

identified through screening tests to identify mutation carriers and families at risk of breast cancer, and this is considered a type of early diagnosis (Fllippini &Vega 2013).

Another screening tool for breast cancer is MRI (Figure 2.3). It is more sensitive than mammography in women at high risk, especially in detecting invasive ductal carcinoma. Moreover, MRI is not affected by breast density and has benefits in detecting occult primary breast cancer, axillary nodal metastasis, residual tumors after neoadjuvant chemotherapy, or other small tumors (Greenwood *et al*., 2013). MRI can measure tissues as small as 0.5 mm^3, but its specificity is less than that of mammography, with detection rates ranging from 37% to 100% (Enriquez & Listinsky 2009).



(Figure .2.3) Magnetic resonance imaging examination of the breast (Elmore *et al*., 2005).

2.6 The relationship between female steroids and breast cancer

In 1882, Thomas William Nunn first reported a case of a woman who had spontaneous breast cancer regression 6 months after menopause, thus suggesting a link between ovarian function and breast cancer (D'Abreo & Hindenburg 2013).

Estrogens, also known as oestrogens are one of the key hormones responsible for the progression and regulation of female reproductive system and have an important role in the non-reproductive system. Furthermore, estrogens are pleiotropic steroids that play a regulatory role in a myriad of physiological processes from reproduction to lipid metabolism (Al-Shami *et al*., 2023).

Estrogen and progesterone hormones are essential regulators in the development and function of normal breasts, as well as critical in breast cancer. Development of the breast occurs postnatally, during puberty, and at the onset of pregnancy (Russo& Russo 2004). Both estrogen and progesterone are critically involved in these normal evolving processes, having highly coordinated functions in the development of the ductal structures and enlargement of lobules of the normal epithelium. Thus, these behaviors become undermined in the onset of breast cancer, connecting the two steroids in the enhancement and progression of cancer (Hilton *et al*., 2018). An animal studies also supports that estrogens stimulate mammary tumors, and decreased exposure to estrogens has an opposite effect. Thus, disorders of the estrogens hormone are great risk factors for human breast cancer (Tian *et al*., 2018).

Progesterone, a 21-carbon steroid hormone, plays a critical role in the female menstrual cycle, pregnancy, and embryogenesis by binding to progesterone receptors (PR). Research in breast mouse models, normal human breast cultures, and clinical studies indicates that estrogen and progesterone are the primary steroid hormones driving mammary gland development.

Estradiol and epithelial ERα signaling are essential for ductal elongation during early puberty, while progesterone/PR is not required at this stage. However, PR signaling becomes critical in the epithelial compartment for ductal elongation and side branching when estrogen levels increase. During early pregnancy, PR signaling facilitates the substantial expansion of the epithelial compartment, while in mid-to-late pregnancy, progesterone is necessary for alveolar differentiation. Near term, progesterone switches to inhibit terminal differentiation, and its removal is essential for lactation to occur (Li *et al*., 2022).

The estrogen receptors are essential for facilitating estrogen actions and functions; a dimeric nuclear protein binds to DNA and has a role in controlling gene expression. Estrogen moves in passively into the cell and binds to it, then activates the ER (Al-Shami *et al*., 2023).

The role of PR and ER in the normal breast during the menstrual cycle is that estrogen receptor (ER) and progesterone receptor (PR) levels exhibit distinct peaks in the normal mammary gland. ER peaks are observed during the proliferative phase (days

3–8) and again in the luteal phase (days 25–26). PR expression peaks first around ovulation (days 13–14) and again in the luteal phase (days 21–23). This cycling of ER and PR is characteristic of the normal mammary gland but is often absent in certain breast carcinomas.

Studies on the role of ER and PR in breast biology rely heavily on mouse models, which provide valuable insights into human breast development. ER is essential at earlier stages for ductal elongation, while PR signaling becomes critical at later stages for branching and differentiation. These findings highlight the complex interplay of these receptors in regulating normal mammary gland development (Li *et al*., 2022).

Breast cancer is a hormone-dependent disease, and approximately 70–80% of breast cancers express progesterone receptors and/or estrogen receptors that are related to cancer cell growth and spread. (Lin *et al*., 2004; Al-Shami *et al*., 2023).

Moreover, ER-positive tumors overexpress the ER, whereas tumors that contain a small number of receptors and sometimes lack the receptors are called ER-negative (Al-Shami *et al*., 2023). It has been shown that patients with ER-negative have lower survival rates in the first few years, and their tumors are more aggressive (Hähnel *et al*., 2004).

In clinical practice, these subtypes are primarily identified using immunohistochemical (IHC) markers, such as ERα, PR, and HER2, which serve as substitutes for transcriptomic data. These biomarkers are crucial for prognostic assessment and determining appropriate therapeutic strategies.

2.7 Estrogen and progesterone receptors in breast cancer

Estrogen and progestrone receptors are proteins expressed on the cells that bind to both estrogen and progestron. These receptors play a vital role in sexual development and reproduction. However, they are also involved in the growth of breast cancer. The majority of breast cancers show overexpression of estrogen receptors (ERs) and progesterone receptors (PRs) (Yip & Rhodes 2014).

Oestrogen and progesterone receptors are useful and very powerful predictors. Because the presence of oestrogen and progesterone receptors is associated with response to hormonal treatment (Badowska-Kozakiewicz *et al*., 2015).

Steroid hormones (estrogen and progestrone) are lipid contents diffuse a cross the breast epithelial membrane, entre the cells, and binds to their receptor in the nucleus. This cause a conformational change resulting in activation of estrogen-responsive genes that allows the receptors to bind to a specific DNA sequence called hormone response elements (HREs) . This binding regulates the transcription of the target gene and affects cellular processes (Ikeda *et al*., 2015).

There are two forms of the estrogen receptor (ER), including α and β, coded for by two different genes. The ER-α form is of clinical significance while, the functions of ERβ are complex and varied. In triple-negative breast cancer, ERβ inhibits tumor progression through interaction with androgen receptors (Liu *et al*., 2020).

The ERα form is a nuclear transcription factor activated by estrogen and plays a key role in breast cancer. Around 60–70% of breast cancers express ER, and its presence is both a prognostic marker and predictive of response to endocrine therapies like SERMs and aromatase inhibitors, which improve survival. Accurate ER testing is therefore essential in breast cancer treatment planning (Selli *et al*., 2016).

According to hormone receptor status, breast cancer can be separated into four distinct subgroups, ER+PR+, ER+PR-, ER-PR+ and ER-PR-. ER-negative (ER-) are more likely in younger patients compared with older patients. Epidemiology and End Results (SEER) cancer registries in the USA found that the ER-positive (ER+) rates increased with age, but at a slower pace after ages 50–54 years, whereas the ER- age-specific breast cancer rates did not increase after ages 50–54 years. Interestingly, the proportion of ER+ breast cancers being higher in the developed Western countries and lower in the developing countries (Yip & Rhodes 2014). Estrogen receptor α (ERα) and progesterone receptor (PR) are important biomarkers in breast cancer that are used for prognosis and predicting response to endocrine therapies (ET), such as Selective Estrogen Receptor Modulators (SERMs), Aromatase Inhibitors (AIs), and Selective Estrogen Receptor Degraders (SERDs). ERα plays a key role in these therapies, and BCs co-expressing PgR generally respond better to treatment. The Progesterone Receptor Gene (PGR) expression depends on ERα, and a negative PgR status may indicate disrupted ERα signaling, which can impair the response to ET. While the prognostic value of PgR expression has been debated (Figure 2.4) it remains a component of genomic tests like the 21-gene recurrence score (Oncotype

DX) and 50-gene PAM-50, which help classify BC into molecular subtypes. Joint evaluation of ERα, PgR, HER2, and Ki67 via immunohistochemistry (IHC) has proven useful for further subclassifying BC into luminal A-like and luminal B-like phenotypes, with PgR expression at 20% of tumor cells being a key discriminating factor. According to ASCO/CAP guidelines, BC is considered PgR-negative if less than 1% of tumor cells show immunoreactivity(Kunc *et al*., 2021).

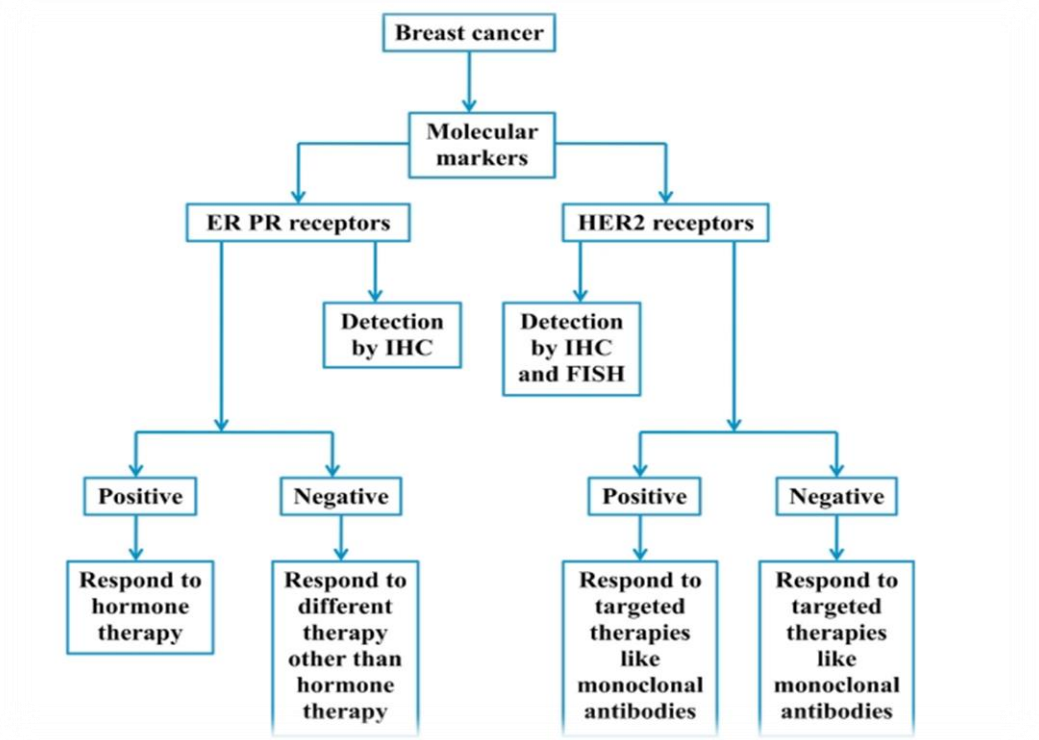


Figure (2.4) U**se of molecular markers in therapeutic decision (Mohanty *et al*., 2022)**

In breast cancer, cells with these receptors use hormonal signals for growth similar to normal cells. However, due to DNA damage, cancerous cells grow rapidly and uncontrollably. Endocrine steroid hormones activate ERs and PRs, promoting proliferation, survival, and metastatic spread of neoplastic cells.

Breast cancers with ER and PR expression tend to grow more slowly and predictably compared to cancers driven by other receptors, such as HER2. This slower progression is associated with a better prognosis (Mohanty *et al*., 2022). HER2 is a transmembrane tyrosine kinase receptor involved in cell signaling, typically activated through heterodimerization with other related receptors (EGFR, HER3, HER4).

Around 15% of invasive breast cancers exhibit HER2 gene amplification and overexpression. Identifying HER2-positive tumors is essential for guiding the use of targeted therapies like trastuzumab, which is both highly effective and well-tolerated. Newer HER2-targeted treatments, such as pertuzumab and lapatinib, also show effectiveness, either alone or in combination (Calhoun & Collins 2015).

2.8 Immune response in breast cancer

Immune cells have a major role in identifying tumors according to the type of response. T cells protect against the development of the disease, as some groups of evidence indicate that the involvement of the tumor in the infiltration of leukocytes causes the development of malignancy (DeNardo & Cousseus 2007). Regulatory T cells are activated, and tumor immune cells infiltrate into lymphocytes, and this is a predictor of breast cancer (Gatti-mays *et al*., 2019). Where peripheral blood is used as a biomarker, for example, the percentage of lymphocytes (NLR), carcinoembryonic antigen (CEA), carbohydrates, and antigen CA15-3, where their levels are studied before and after treatment, and it has been proven that NLR and CA15-3 are among the indicator and diagnostic elements (Yu *et al*., 2022).

3. CHAPTER III

Subjects and Methods

3.1 Ethical approval

The interview began after explaining the study objectives to the participants. Participants were given assurances regarding the confidentiality of the collected data. The Institutional Ethics Review Committee and the Research Ethics Committee at the National Cancer Institute in Sabratha approved the study procedures under reference number (3/475).

3.2 Study population

This study was carried out in the National Cancer Institute Sabratha (NCI), which is one of the leading comprehensive cancer centers in Libya. It is well-attended by patients who are referred from all over the country especially the Western region. A total of 124 BC cases (124 females) ; (mean age, 49.7 ± 9.0 years) diagnosed between November 2024 to March 2025, and registered with NCI were enrolled. Besides, 50 healthy individuals (50 females; mean age, 64.2 years) as controls were enrolled. Study participants were collected from patient files to obtain information on demographic characteristics. Other details were collected for each patient from medical records.

3.3 Study Design

Patients with confirmed breast cancer who attended the National Cancer Institute in Sabratha and underwent mammography, MRI, and histological examination were recruited for this study.

3.4 Blood sampling

The blood analysis was performed by retrieving the most recent laboratory test results available in the patients' clinical and treatment follow-up files. The extracted data included complete blood count (CBC), hemoglobin (HGB) levels, red blood cell (RBC) count, hematocrit (HCT), white blood cell count, and lymphocyte percentages. Additionally, liver and kidney function tests, steroid hormone levels, and tumor

marker analyses were collected. These data were subsequently used as the foundation for the current study.

3.5 Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 27). Descriptive statistics, including means and standard deviations, were computed to summarize the continuous variables, while frequencies and percentages were calculated for categorical variables. Independent sample t-tests were conducted to compare the mean values of hematological and biochemical parameters between the experimental (breast cancer patients) and control groups. One-way analysis of variance (ANOVA) was used to evaluate differences in tumor marker levels across different cancer stages. Chi-square tests were performed to assess associations between categorical variables, such as hormone receptor status (ER, PR, HER2) and tumor laterality or co-expression. The level of statistical significance was set at $P < 0.05$ for all analyses.

4. CHAPTER IV

RESULTS

4.1 Distribution of subjects by socio-demographic factors

Over a period of up to six months, 124 breast cancer patients were enrolled in this study. Data were collected using anonymized data to protect patient privacy and included a variety of demographic and health information.

4.1.1 Age group, marital status, family history, locatation, smoking, grade and body-mass index

Table (4.1) Distribution of age group among patients with BC (N=124)

Variable	Categories	Count	%	Chi square	P value
Age group	25-35	6	4.8	47.290	< 0.001
	35-45	31	25.0		
	45-55	41	33.1		
	55-65	39	31.5		
	65-75	7	5.6		

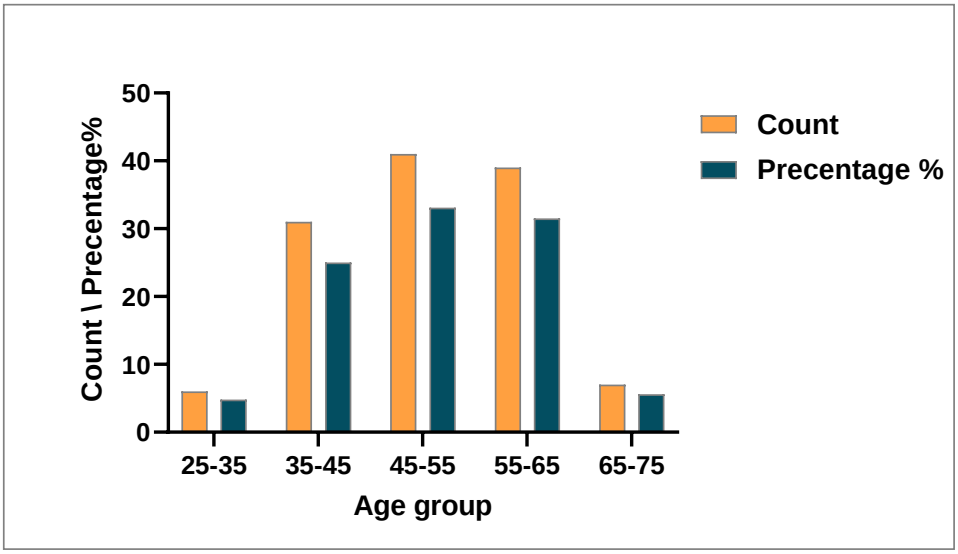


Figure (4.1) Prevalence of breast cancer in different age groups.

This study comprised 124 female participants with a mean age of 51 years ranging from 27 to 75 years. There was a statistically significant difference between age

groups (p< 0.001). The most affected age groups were 45–55 years (33.1%) and 55–65 years (31.5%), aligning with global trends that show increasing breast cancer risk with advancing age. A very small percentage were between 25-35 and 65-75 years old (4.8%) (Table and Figure 4.1).

Table (4.2). Distribution of marital status among patients with BC (N=124)

Variable	Categories	Count	%	Chi square	P value
Marital status	Single	22	17.74	160.710	< 0.001
	Married	91	73.39		
	Divorced	5	4.03		
	Widow	6	4.84		

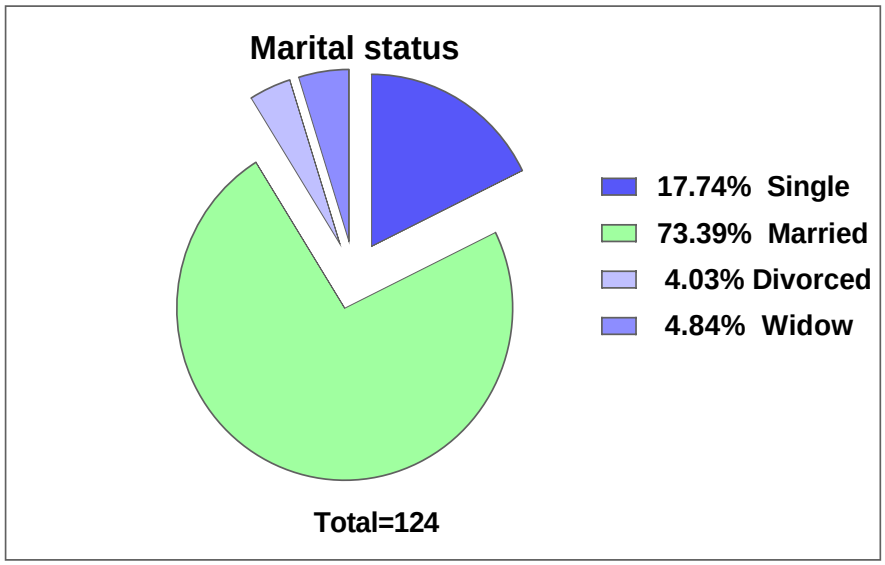


Figure (4.2) Marital status distribution of breast cancer cases

Table 4.2 present the marital status of the participants with breast cancer. Significant differences were observed across different marital statuses ($P < 0.001$). The majority of participants were married 73.39%, while only 17.74% were single, and a smaller portion were divorced or widowed, 4.03% and 4.84%, respectively(Figure 4.2).

Table (4.3) Distribution of family history among patients with BC (N=124)

Variable	Categories	Count	%	Chi square	P value
Familyhistory	First degree	26	20.9	58.081	< 0.001
	Second degree	17	13.7		
	No relationship	81	65.3		

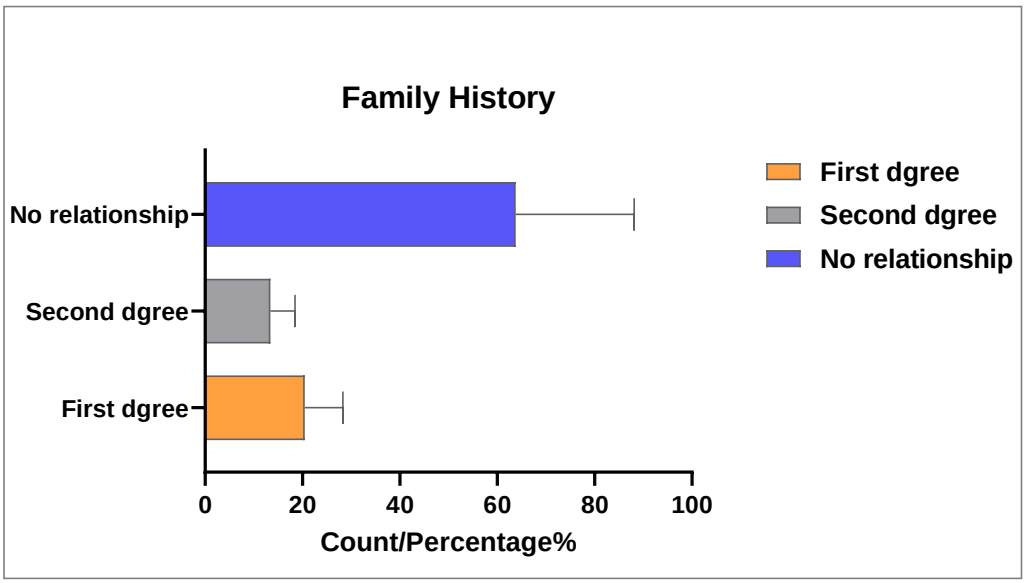


Figure (4.3). Distribution of first- and second-degree relatives in breast cancer patients with a positive family history.

Regarding family history of cancer, 20.9% of patients reported a first-degree relative and 13.7% a second-degree relative, while 65.3% had no known familial relationship, suggesting a notable proportion may have sporadic or non-hereditary breast cancer (Table and Figure 4.3).

Table (4.4) Distribution of Location

Variable	Categories	Count	%	Chi square	P value
Location	Triploi	17	13.71	86.339	< 0.001
	Zawia	37	29.84		
	Surman	9	7.26		
	Sabratha	13	10.48		
	West Sabratha	30	24.19		
	Aljabl Alghrbi	5	4.03		
	South	6	4.84		
	Tarhona	2	1.61		
	Janzour	5	4.03		

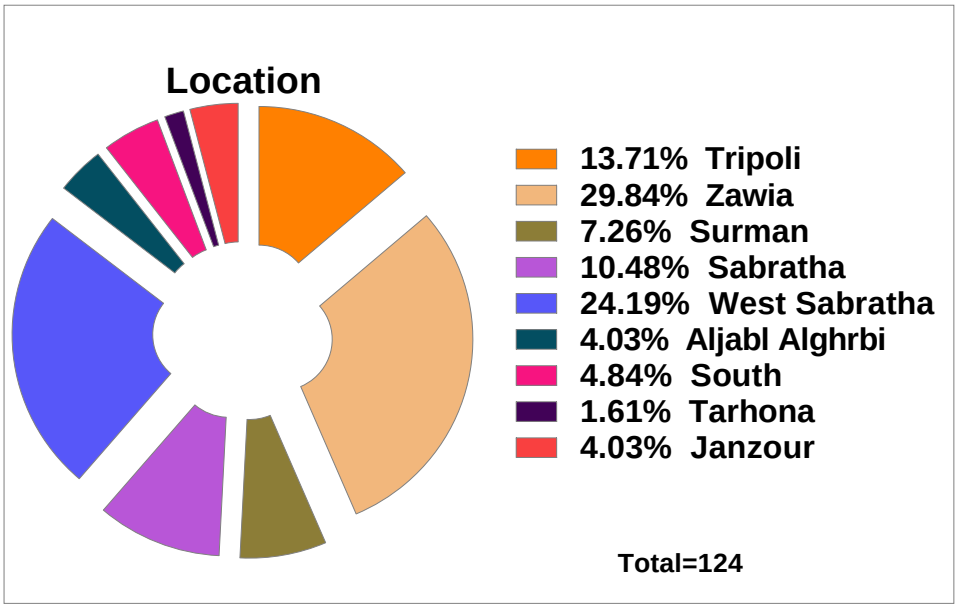


Figure (4.4). Distribution of BC according to area of residence

Geographical distribution shows that the largest proportions of participants were from Zawia (29.84%) and West Sabratha (24.19%), followed by other areas such as Tripoli (13.71%), Sabratha (10.84%). This may reflect both population distribution and access to diagnostic services (Table and Figure 4.4).

Table (4.5) Distribution of Smoking status

Variable	Categories	Count	%	Chi square	P value
Smoking	Never smoke	123	99.2	120.032	< 0.001
	Current	1	0.8		

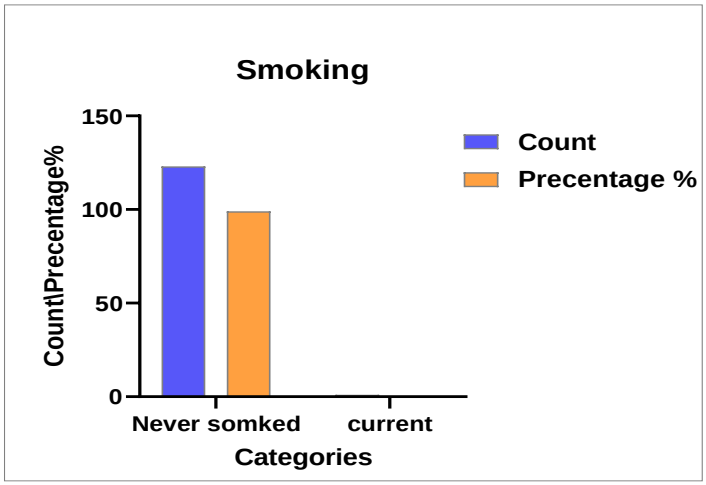


Figure (4.5) Smoking Status of Patients with Breast Cancer

With regard to smoking status, an overwhelming majority (99.2%) had never smoked, it is obvious that all participants were female (Table and Figure 4.5).

Table (4.6). Distribution of Body Mass Index (BMI) in Patients (n=65)

Variable	Categories	Count	%	Chi square	P value
BMI	Normal weight	13	20.0	14.431	< 0.001
	Overweight	16	24.6		
	Obesity	36	55.4		

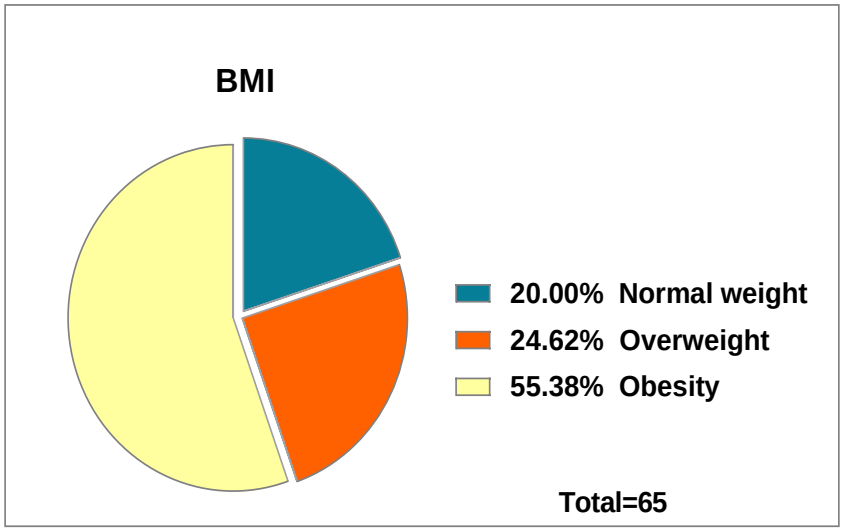


Figure (4.6) Prevalence of BC stratified by BMI categories

In terms of BMI, a high percentage of patients were classified as obese (55.4%), followed by overweight (24.6%) and normal weight (20.0%), highlighting obesity as a significant potential risk factor (Table and Figure 4.6).

Table (4.7). Distribution of breast cancer tumor grades (N=112)

Variable	Categories	Count	%	Chi square	P value
grade	I	10	8.93	30.496	< 0.001
	II	51	45.54		
	III	51	45.54		

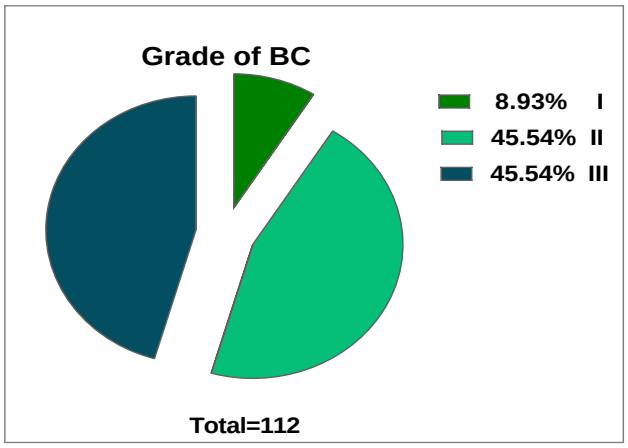


Figure (4.7). Distribution of breast cancer grades in the study population

Clinically, the most common cancer grades were grade II,III (45.54 %) while only (8.8%) of patients were diagnosed at grade I.(Table and Figure 4.7).

4.2 Hematological biomarkers between BC patients and healthy controls

Hematological parameters between breast cancer patients and healthy controls (Table 4.8) were also investigated in this study. No significant differences between patients with breast cancer and the control group in terms of MCH and MCHC (P= 0.728 , P= 0.155), respectively.While a significant decreased were observed in BC patients in terms of RBC HGB, HCT, MCV , MCHC (P< 0.001) and lymphocytes (P=0.293). On the other hand, platelet count (PLT) was significantly higher in the BC patient groups than in controls (P < 0.001). WBC and nuetrophil, show non-significant value, P= 0.293 and P=0.62) respectively (Table and Figure 4.8).

Table (4.8). Hematological parameters of BC patients (N=124) and controls (N=50)

Parameters	Groups	N	Mean	Std	T value	P value
WBC ($10^3/\mu L$)	**BC Patients**	105	6.74	3.905	-1.054	0.293
	Control	50	7.37	2.294		
RBC ($10^6/\mu L$)	**BC Patients**	104	4.00	0.729	-3.259	<0.001
	Control	50	4.40	0.675		
Hgb (g/dl)	**BC Patients**	105	11.53	1.685	-4.755	< 0.001
	Control	50	12.60	1.075		
HCT(%)	**BC Patients**	105	33.61	4.328	-9.519	< 0.001
	Control	50	39.30	2.982		
MCV(fL)	**BC Patients**	104	83.42	7.217	-4.120	< 0.001
	Control	50	88.07	4.936		
MCH (Pg)	**BC Patients**	104	28.44	4.185	0.348	0.728
	Control	50	28.27	1.999		
MCHC(g/dL)	**BC Paients**	104	37.55	2.285	9.18	<0.0001
	Control	50	30.83	4.928		
PLT ($10^3/\mu L$)	**BC Patients**	103	306.12	133.918	3.717	< 0.001
	Control	50	247.55	60.879		
Lymphocyte (%)	**BC patients**	94	31.32	11.144	2.2026	0.0294
	Control	50	34.96	8.396		
Neutrophil (%)	**BC patients**	91	58.83	14.161	0.497	0.62
	Control	48	57.89	8.141		

Blood values in BC patients and control were analyzed with independent Student's t-test; P<0.005 was considered significantly higher . Data were expressed as mean and Std. WBC: white blood cell count; PLT=Platelet; Neut = Neutrophils; Lymph = Lymphoycyte.

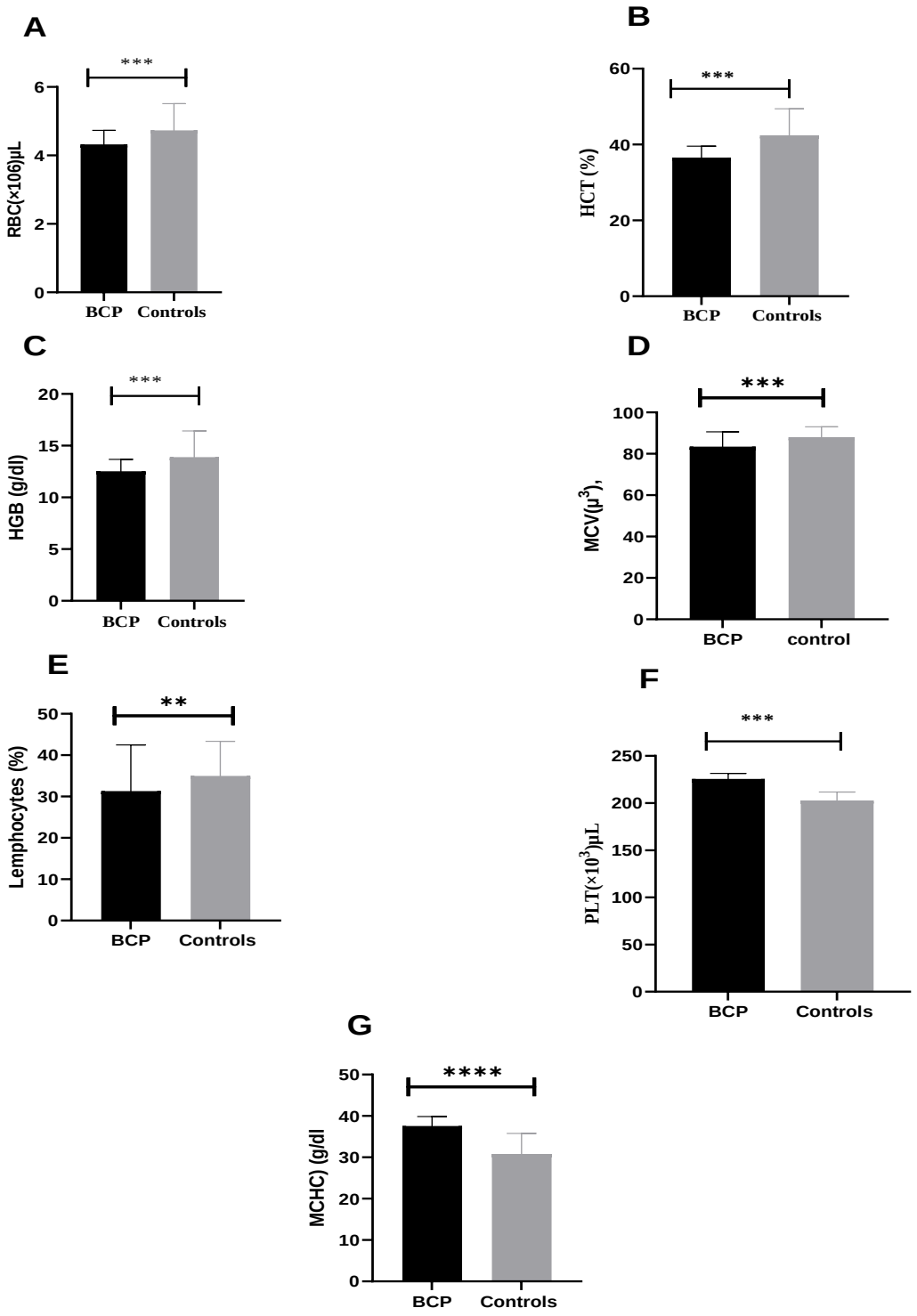


Figure (4.8) The bar charts illustrate the differences in the mean ±SE of CBC parameters between healthy controls and BCP patients. (A), RBC (B), HCT(C), HGB (D), MCV (E), neutrophils (F), PLT (E), MCHC. **P,0.05, ***P < 0.001 and ****P>0.0001.

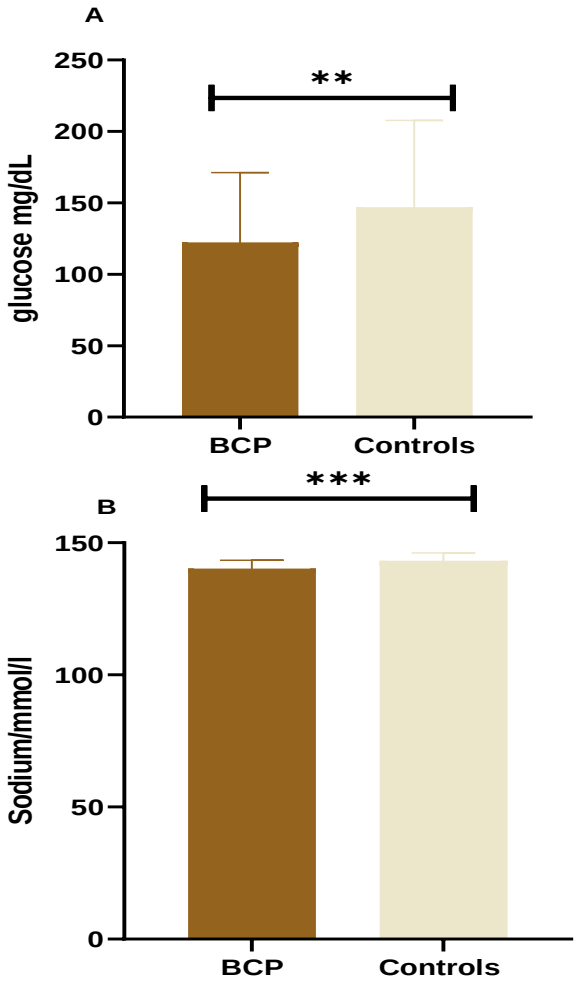
4.3 Evaluation of biochemical parameters in BC patients and control groups.

Table 4.9 displays a comparison of various biochemical parameters between breast cancer patients and control groups. Several parameters show marked deviations, raising important physiological and clinical considerations. The results showed no statistically significant difference between the BC patients and control regarding urea (*P*=0.868); creatinine (*P*=0.831); and chloride (*P*=0.913) . Sodium showed a significantly higher among BC patients *(P=< 0.001*). Glucose levels were significantly lower in the BC patients (*P*= 0.013)(Figure 4.9).

Table (4.9). Evaluation of biochemical parameters in BC patients (N=124) and Control Groups (N=50)

Parameters	Group	N	Mean	Std	T value	P value
Glucose(mg/dL)	**BC patients**	77	122.36	48.838	-2.509	0.013
	Control	49	147.01	60.754		
Urea(mg/dL)	**BC patients**	105	35.09	100.399	-0.167	0.868
	Control	50	37.49	24.394		
Creatinine(mg/dL)	**BC patients**	106	0.94	2.231	0.214	0.831
	Control	50	0.87	0.890		
Sodium(mmol/L)	**BC patients**	96	140.25	3.121	-5.511	< 0.001
	Control	46	143.20	2.918		
Potassium(mmol/L)	**BC patients**	96	5.63	14.339	0.853	0.396
	Control	47	4.38	0.430		
Chloride(mmol/L)	**BC patients**	91	103.85	15.908	-0.110	0.913
	Control	47	104.10	2.172		

Biochemical parameters in patients and control were analyzed with independent Student's t-test; P<0.005 was considered a significant. Data were expressed as mean and Std.



Figure(4.9) Evaluation of biochemical parameters in BC patients and control groups

The bar charts illustrate the differences in the mean ±SE of glucose and potassium between healthy controls and BCP patients. (A), glucose level and (B) sodium level. Bars indicate mean ± SEM. ** P< 0.05 and ***P <0.001

4.4 Analysis of liver and protein biochemical parameters in BC patients and control groups.

Liver functions were also investigated in order to find out the proteins levels changes over time, and it may be used as an indicator in patients with breast cancer (Table 4.10). No significant differences were found between the BC patients and control groups for most liver function tests including GOT (P = 0.261), GPT (P = 0.129; ALK (P = 0.829); uric acid (P= 0.618); total protein (P = 0.851), and total bilirubin (P

= 0.360). However, lactate dehydrogenase (LDH) levels were significantly higher in the BC patients ($p < 0.001$), indicating a notable difference in this parameter (Figure 4.10).

Table (4.10). Evaluation of biochemical parameters in BC patients (N=124) and Control Groups (50)

Parameters	Group	N	Mean	Std	T value	P value
GOT(U/L)	**BC patients**	100	29.81	64.427	1.128	0.261
	Control	45	18.92	9.185		
GPT(U/L)	**BC patients**	99	22.52	23.577	1.529	0.129
	Control	46	16.88	12.205		
ALK(U/L)	**BC patients**	84	109.33	119.094	0.216	0.829
	Control	46	104.88	99.198		
U.acid(mg/dL)	**BC patients**	54	6.11	10.552	0.500	0.618
	Control	48	5.34	1.487		
T.protein(g/dL)	**BC patients**	53	7.09	0.585	-0.189	0.851
	Control	45	7.55	16.119		
T.Bili(mg/dL)	**BC patients**	89	0.62	1.400	-0.925	0.360
	Control	46	2.54	14.089		
LDH(U/L)	**BC patients**	36	225.53	221.100	4.760	< 0.001
	Control	49	49.96	11.390		

Liver function and protein parameters in patients and control were analyzed with independent Student's t-test; P<0.005 was considred significantly higher . Data were expressed as mean and Std. GOT= Glutamic-Oxalocetic Transaminase ; GPT= Glutamic Pyruvic Transaminase; ALK= Alkaline Phosphatase ;U.acid = Uric Acid; T.protein= Total protein**;**T.Bili= Total Bilirubin; LDH= Lactate dehydrogenese

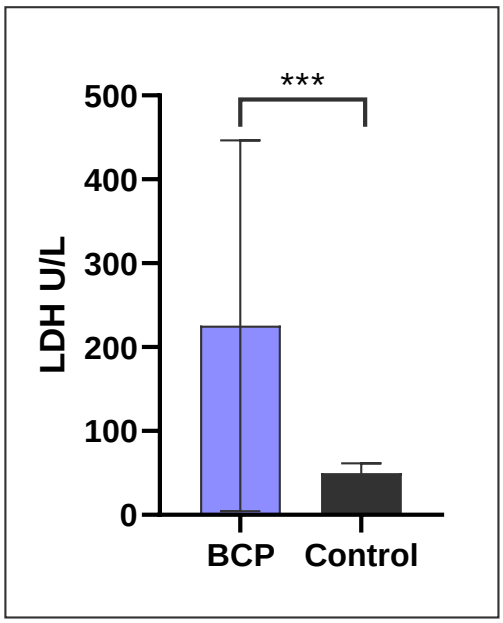


Figure (4.10). liver and protein parameters in BC patients and control groups.

4.5 Association of estrogen receptor, progestrone receptor and HER2 status in BC patients

Expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her2/neu) receptors are very important and useful predictive factors in medical practice nowday. Data were analysed to investigate the distribution of HER2 and ER and PR.

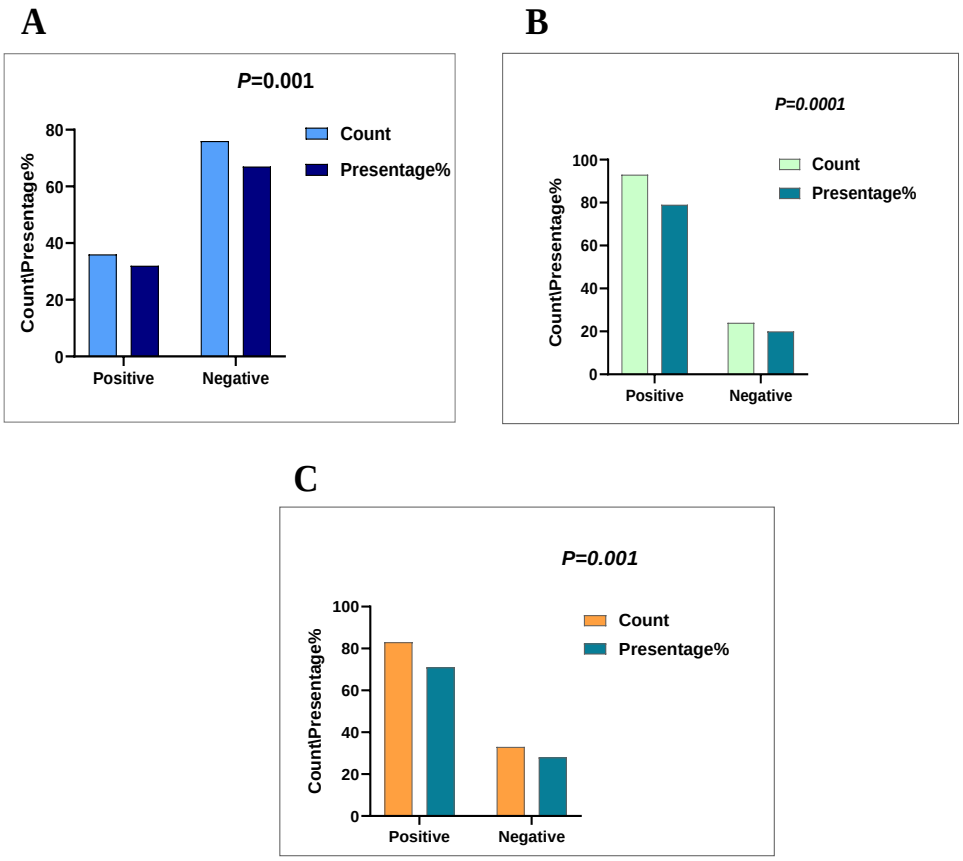
4.5.1. Distribution of estrogen receptor, progestrone receptor and HER2 status in BC patients

Table 4.11 shows that the distribution of ER-positive (79.5%) caseses is highly significantly higher than ER-negative (20.5%), (P<0.0001). Similarly comparison of PR distribution showed PR- positive (71.6) are significantly higher against PR-negative (28.4%), (P< 0.0001). In contrast, distribution of HER-positve (32.1%) showed signifiacly lower than HER-2 negative (67.9%), (P< 0.001) (Figure 4.11).

Table (4.11): Distribution of estrogen eeceptor, progestrone receptor and HER2 Status in BC patients

Variable	Categories	Count	%	Chi square	P value
ER	Positive	93	79.5	40.68	<0.0001
	Negative	24	20.5		
PR	Positive	83	71.6	21.56	< 0.001
	Negative	33	28.4		
HER2	Positive	36	32.1	14.29	< 0.001
	Negative	76	67.9		

Estrogen(ER), Progestron (PR) receptors and human epidermal growth factor receptor-2 (HER2) were analysed and a chi-square test was conducted to determine whether the distribution between them is significal (P<0.0001).



Figure(4.11): Distribution of Estrogen rceptor (A) Progestrone receptor (B) HER2 receptor (C)Status in BC patients.

4.5.2 Association between estrogen receptor (ER) and HER2 status

Table 4.12 presents the relationship between estrogen receptor (ER) status and HER2 expression among breast cancer patients. The results showed that among ER-positive patients, 24.8% were also HER2-positive, while 54.7% were HER2-negative. Conversely, among ER-negative cases, 9.4% were HER2-positive, and 11.1% were HER2-negative. This result indicates that the association was not statistically significant (*P*=0.177) (Figure 4.12).

Table (4.12). Association between estrogen receptor (ER) and HER2 status

ER	HER2				Chi square	P value
	Positive		Negative			
	Count	%	Count	%		
Positive	29	24.8	64	54.7	1.820	0.177
Negative	11	9.4	13	11.1		
Total	40	34.2	77	56.8		

Steroid receptors estrogen (ER) and human epidermal growth factor 2 (HER2) were analyse. A chi-square test of independence was conducted to determine whether there was a significant association.

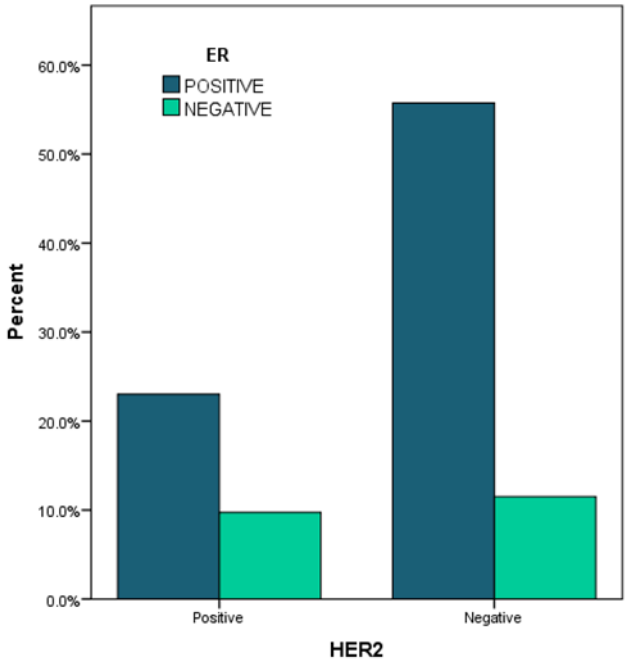


Figure (4.12) Association between estrogen receptor (ER) and HER2 Status

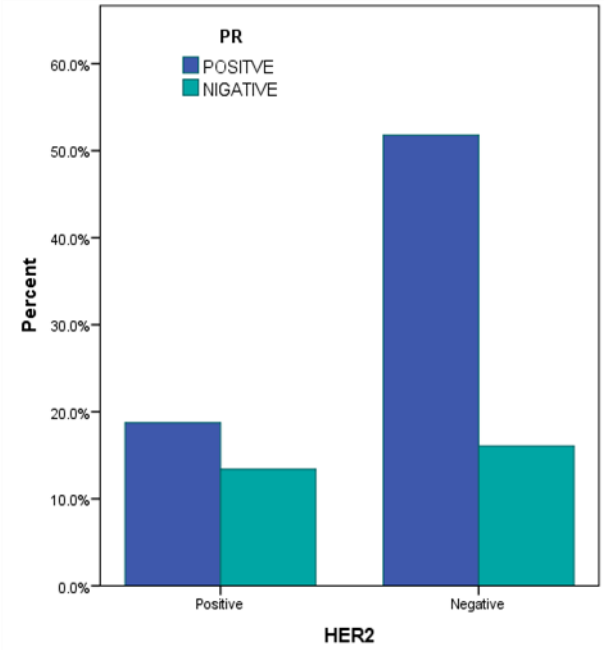
4.5.3 Association between progesterone receptor (PR) and HER2 status

Table 4.13 displays the relationship between progesterone receptor (PR) status and HER2 expression in breast cancer patients. Among individuals with PR-positive status, 21.4% were also HER2-positive, and 50.94% were HER2-negative. In contrast, among PR-negative individuals, 12.8% were HER2-positive and 15.4% were HER2-negative (Figure 4.13).

Table (4.13). Association Between Progestron Receptor (PR) and HER2 Status

PR	HER2				Chi square	P value
	Positive		Negative			
	Count	%	Count	%		
Positive	25	21.4	59	50.94	2.894	0.089
Negative	15	12.8	18	15.4		
Total	40	34.2	77	56.8		

Steroid receptors progestron (PR) and human epidermal growth factor 2 (HER2) were analyse. A chi-square test of independence was conducted to determine whether there was a significant association.



Figure(4.13) Association between progestron receptor (PR) and HER2 status.

4.5.4 Association between estrogen receptor ER , PR , HER2 and side of cancer

Table 4.14 presents the distribution of estrogen receptor (ER) status in relation to the side of breast cancer occurrence (left, right, or bilateral). Among patients with ER-positive status, 35.9% had cancer on the left side, 41.9% on the right, and 1.7% had bilateral cancer. For those with ER-negative status, 10.3% had left-sided and 10.3% had right-sided cancer, with no cases of bilateral involvement. The results indicate that there is no statistically significant association between ER status and the side of breast cancer (*P*=0.726).

Table (4.14): Association between estrogen receptor (ER) and side of cancer

ER	Side of cancer						Chi square	P value
	Left		Right		Both			
	Count	%	Count	%	Count	%		
Positive	42	35.9	49	41.9	2	1.7	0.639	0.726
Negative	12	10.3	12	10.3	0	0.0		
Total	54	46.2	61	52.1	2	1.7		

A chi-square test of independence was performed to assess the association between ER status and cancer laterality. no statistically significant association between HER2 expression and the side of breast cancer.

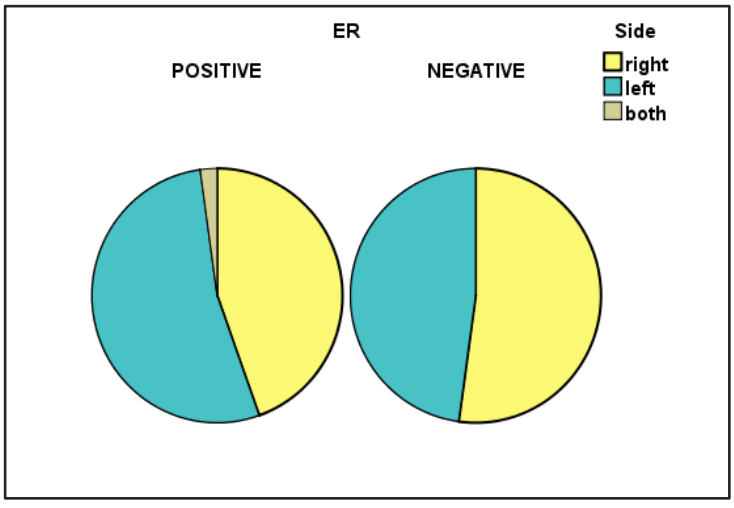


Figure (4.14). Association between estrogen receptor (ER) and side of cancer.

Table 4.15 present the association between PR receptors and side of cancer.

The results revealed no statistically significant association between PR status and whether the tumor was located in the left, right, or both breasts (*P* = 0.758). PR-

positive tumors were slightly more common on the left side (53.7%) compared to the right (45.1%) and bilateral cases (1.2%). Similarly, PR-negative tumors were almost evenly distributed between the left (50.0%) and right (46.9%) sides, with a small proportion presenting bilaterally (3.1%) (Figure 4.15).

Table (4.15): Association between progestrone receptor (PR) and side of cancer

PR	Side of cancer						Chi square	P value
	Left		Right		Both			
	Count	%	Count	%	Count	%		
Positive	44	53.7%	37	45.1%	1	1.2%	0.553	0.758
Negative	16	50.0%	15	46.9%	1	3.1%		
Total	60	52.6%	52	45.6%	2	1.8%		

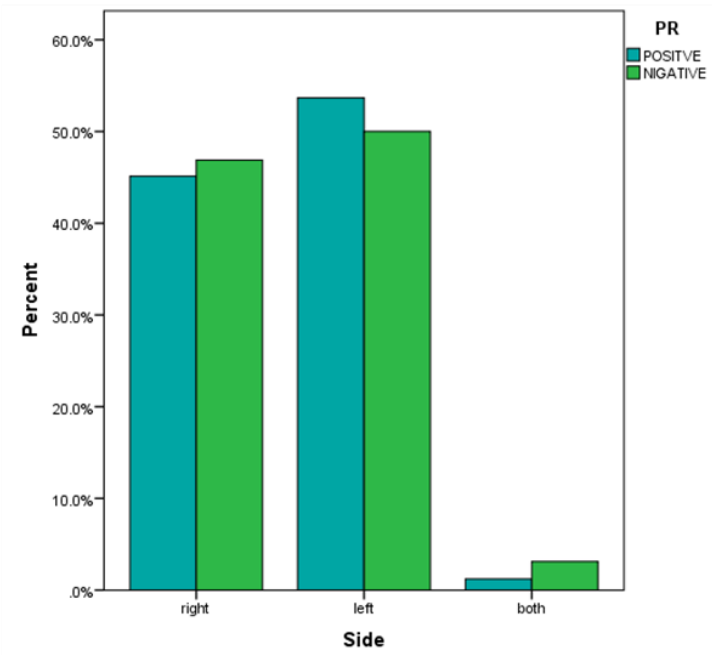


Figure (4.15): Association between progestrone receptor (PR) and side of cancer

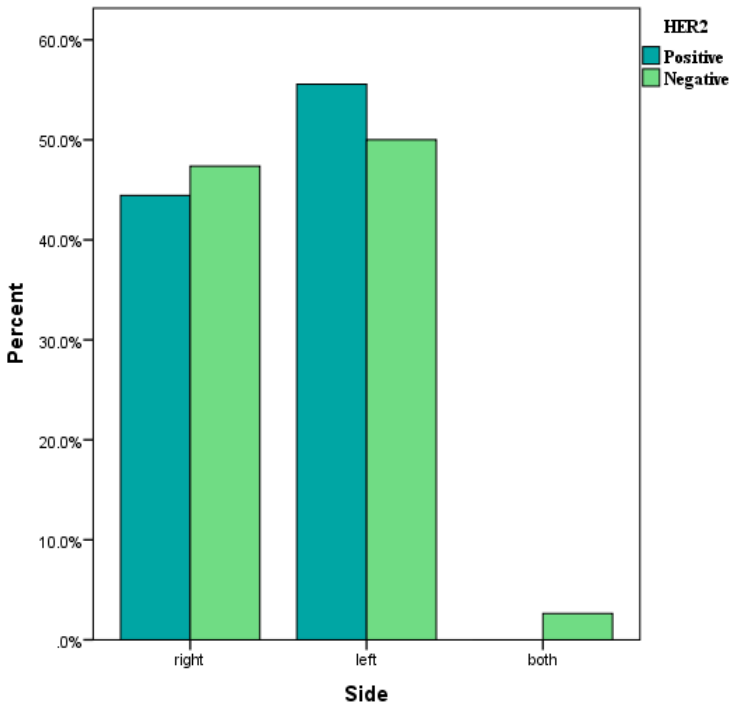
Table 4.16 examines the association between HER2 receptor status and the side of breast cancer (left, right, or bilateral). Among patients with HER2-positive status,

14.5% had cancer in the left breast and 19.7% in the right breast, with no bilateral cases reported. In comparison, HER2-negative cases were 13.6% left-sided, 32.5% right-sided, and 1.7% both sides. The result indicates no statistically significant (*P*=0.461) association between HER2 expression and the side of breast cancer (Figure 4.16)

Table (4.16): Association between HER2 status and cancer side

HER2	Side of cancer						Chi square	P value
	Left		Right		Both			
	Count	%	Count	%	Count	%		
Positive	17	14.5	23	19.7	0	0.0	1.550	0.461
Negative	37	13.6	38	32.5	2	1.7		
Total	54	46.2	61	52.1	2	1.7		

A chi-square test of independence was performed to assess the association between HER2 status and cancer laterality. no statistically significant association between HER2 expression and the side of breast cancer.



Figure(4.16) Association between HER2 status and cancer side

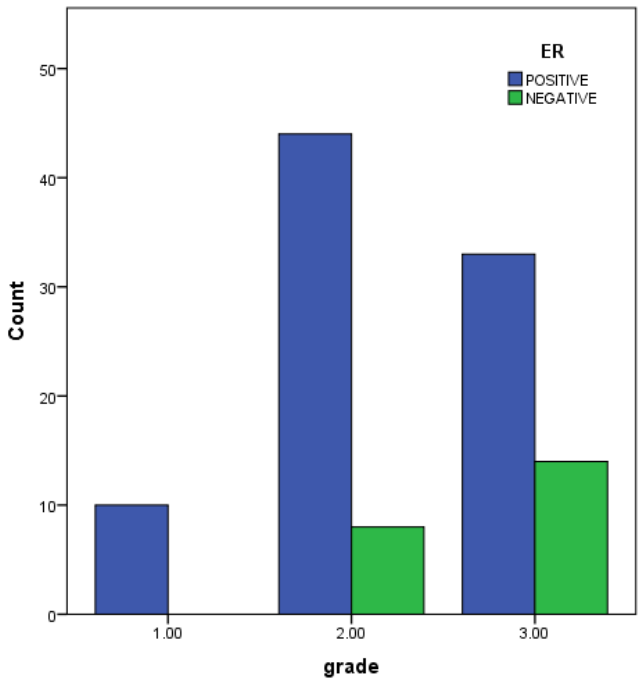
4.5.5 Association between grading of tumor with hormonal receptors

Tumor grading includes I.II.III indicates the extent of cancer spread, and it may be closely linked to hormone recptor status. Therefore, an analysis was established to find out the association between the grading of tumors and hormone receptors.

Table (4.17) Association between grading of tumor and ER

Grade	ER		Chi square	P value
	Positive	Negative		
I	10 (9.2)	0 (0.0)	5.573	0.062
II	43 (39.4)	8 (7.3)		
III	34 (31.2)	14 (12.8)		
Total	87 (79.8)	22 (20.2)		

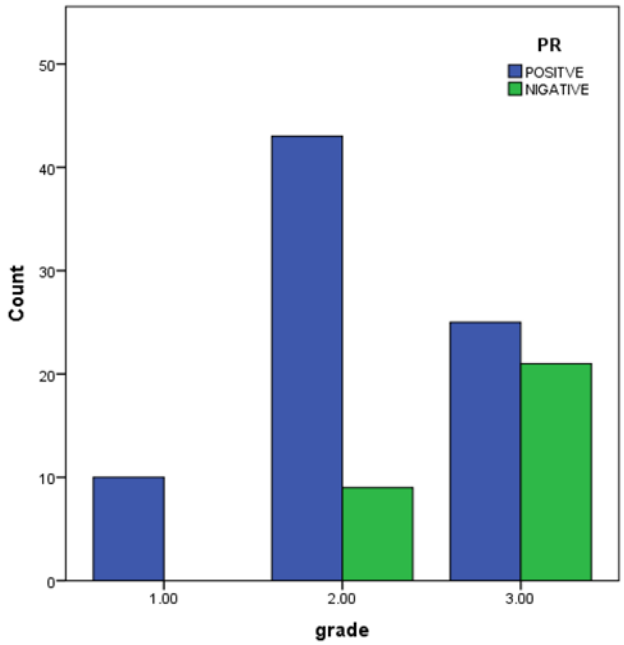
Table (4.17) shows that among those with grade I tumors, 9.2% were ER-positive and none were ER-negative. For grade II, 39.4% were ER-positive and 7.3% ER-negative. In grade III, 31.2% were ER-positive and 12.8% ER-negative. $P = 0.062$, indicating that the result approached but did not reach statistical significance at the conventional level of $P < 0.05$ (Figure 4.17).



Figure(4.17):Association between tumor grading and ER

Table (4.18) Association between grading of tumor and PR

Grade	PR		Chi square	P value
	Positive	Negative		
I	10 (9.2)	0 (0.0)	12.627	0.002
II	42 (38.5)	9 (8.3)		
III	27 (24.8)	21 (19.3)		
Total	79 (72.5)	30 (27.5)		



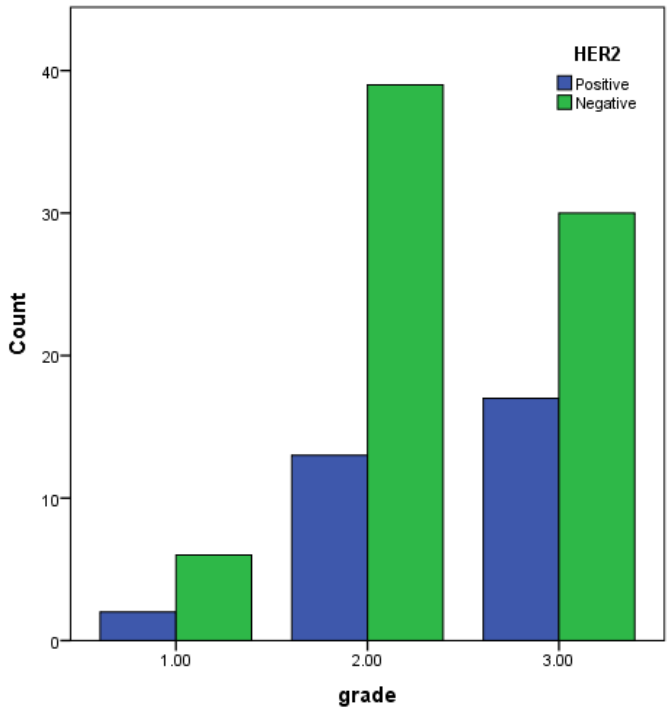
Figure(4.18):Association between grading of tumor and PR

Table (4.18) shows that among grade I patients, 9.2% were PR-positive and none were PR-negative. In grade II, 38.5% were PR-positive and 8.3% were PR-negative. In contrast, grade III patients included 24.8% PR-positive and 19.3% PR-negative cases. P = 0.002. This result indicates that PR status is significantly associated with the grade of breast cancer at diagnosis. The findings suggest that PR positivity is more common in earlier grades of breast cancer, particularly grade I and II, while PR negativity is more frequent in advanced (grade III) tumors (Figure 4.18).

Table (4.19)Association between grading of tumor and HER2

Grade	HER2		Chi square	P value
	Positive	Negative		
I	4 (3.7)	6 (5.5)	1.533	0.465
II	13 (11.9)	38 (34.9)		
III	17 (15.6)	31 (28.4)		
Total	34 (31.2)	75 (68.8)		

Table 4.19 shows that among grade I patients, 3.7% were HER2-positive and 5.5% were HER2-negative. In grade II, 11.9% were HER2-positive and 34.9% HER2-negative, while in grade III, 15.6% were HER2-positive and 28.4% HER2-negative. No statistical significant $P = 0.465$, indicating no significant relationship between HER2 expression and breast cancer grade in this sample (Figure 4.19).



Figure(4.19):Association between grading of tumor and HER2

4.6 The relationship between grades and tumor markers (CEA) and (CA 15-3).

This section explores the relationship between breast cancer grades and the serum tumor markers (CEA) and (CA 15-3). Tumor grade reflects the level of cellular differentiation and aggressiveness, while these markers may indicate tumor activity

and burden. Understanding their association can provide useful insights into prognosis and disease monitoring.

4.6.1 Analysis of CEA and CA 15-3 Levels Across Breast Cancer grades

Table 4.20 presents the mean levels of carcinoembryonic antigen (CEA) and cancer antigen (CA 15-3) across breast cancer grades (grades I, II, and III). For CEA, mean levels increased across grades : grade I(M = 3.72, ,grade II (M = 5.88, and grade III (M = 11.07). Despite this trend, there was no statistically significant ($P = 0.607$).

For CA 15-3, the mean levels were higher in grade I (M = 162.49), but decreased in grade II (M = 78.45) and grade III (M = 61.20). Again, the variation among the three grades was not statistically significant ($P = 0.548$). Although average CEA levels appeared to rise with cancer progression and CA 15-3 levels decreased, the differences were not statistically significant, suggesting that CEA and CA 15-3 alone may not reliably distinguish among grades in this sample. The large standard deviations—especially for CA15-3 indicate substantial inter-patient variability, which may have obscured any true differences.

Table (4.20): Analysis of CEA and CA 15-3 Levels Across Breast Cancer grades

Parameters	grades	N	Mean	Std	F value	P value
CEA (ng/mL)	**I**	5	3.72	2.136	0.507	0.607
	II	13	5.88	6.779		
	III	15	11.07	23.977		
CA153 (U/mL)	**I**	7	162.49	275.730	0.611	0.548
	II	16	78.45	228.899		
	III	16	61.20	136.591		

Tumor markers carcinoembryonic antigen (CEA) and cancer antigen(CA 15-3.was analyse inrelation to grade. One -way along with their standard deviations, F-values, and significance levels of p-value.

4.6.2 Association of serum tumor markers (CA15-3 and CEA) with ER, PR, and HER2 status in breast cancer patients

Table 4.21 shows the mean serum levels of cancer antigen (CA15-3) and CEA in relation to positive and negative statuses of estrogen receptor (ER), progesterone receptor (PR), and HER2 in breast cancer patients.

Table (4.21) . Association of serum tumor markers (CA15-3 and CEA) with ER, PR, and HER2 status in breast cancer patients

Serum tumor marker	Parameters	Case	N	Mean	Std	T value	P value
CA 15-3 (U/mL)	**ER**	**Positive**	34	100.68	216.192	2.261	0.030
		Negative	8	16.94	15.487		
	PR	**Positive**	31	78.72	165.482	-0.317	0.753
		Negative	11	100.91	276.595		
	HER2	**Positive**	12	86.52	201.569	0.041	0.968
		Negative	30	83.74	198.579		
CEA (ng/mL)	**ER**	**Positive**	26	5.56	7.974	-0.841	0.423
		Negative	9	13.91	29.405		
	PR	**Positive**	23	6.16	8.317	-0.591	0.565
		Negative	12	10.67	25.752		
	HER2	**Positive**	10	7.50	11.081	-0.044	0.965
		Negative	25	7.78	18.110		

Analysis of serum tumor markers cancer antigen(CA 15-3) and carcinoembryonic antigen (CEA) for breast cancer patients with the negative and positive ER, PR and HER2. Data were presented as mean and Std. significant are considred at $P<0.001$.

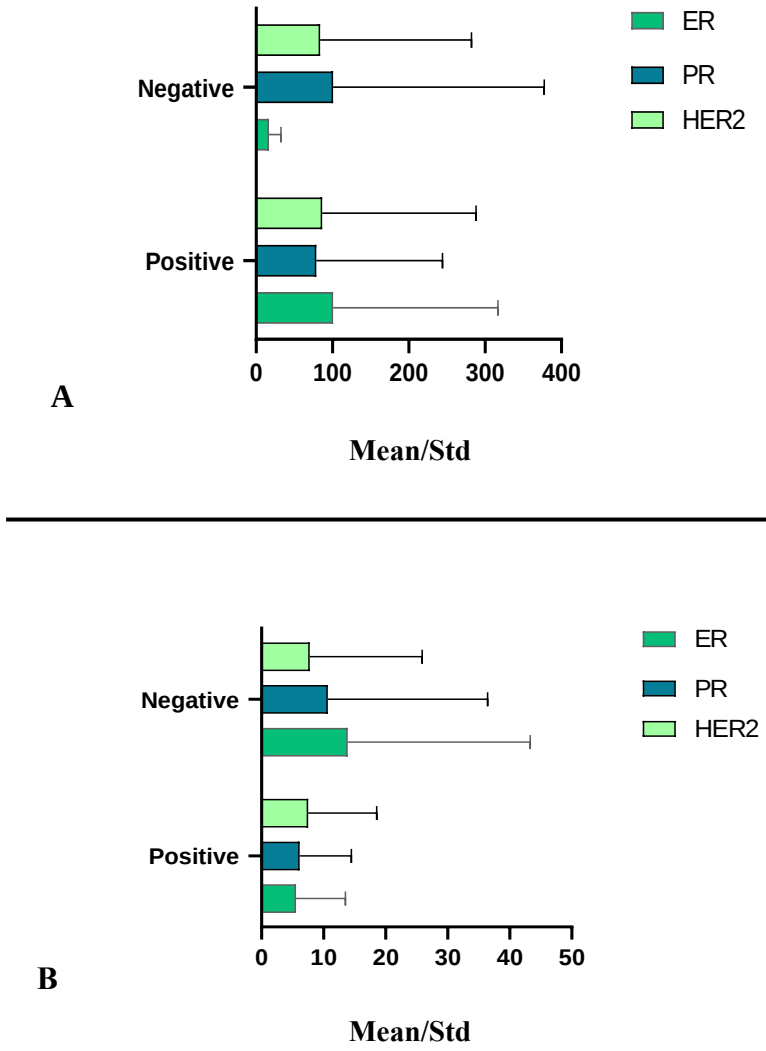


Figure (4.20). Comparison of serum CA15-3 (A) and CEA (B) levels in breast cancer patients with positive and negative ER, PR and HER2 status

Table 4.21 For ER status, the mean CA 15-3 level was significantly higher in ER-positive patients compared to ER-negative (p = 0.030), indicating a statistically significant difference, whereas no significant differences were observed regarding PR status (negative and positive) (P= 0.753). Likewise, HER2- status (negative and positive) showed no significant difference (P = 0.968).

These findings suggest a significant association between elevated CA 15-3 levels and positive ER status, which may indicate a relationship between this tumor marker and hormone receptor expression in breast cancer.

Regarding CEA in relation to positive and negative statuses of estrogen receptor (ER), progesterone receptor (PR), and HER2 in breast cancer patients. For ER status, the mean CEA level was lower in ER-positive cases compared to ER-negative cases, but this difference was not statistically significant ($P = 0.423$). Also, PR status, and HER2 status mean CEA levels were again not statistically significant ($P = 0.565$) and ($p = 0.965$) respectively. These results indicate no significant association between serum CEA levels and hormone receptor (ER, PR) or HER2 status in this sample (Figure 4.20).

5. CHAPTER V

DISCUSSION, SUMMARY AND RECOMMENDATION

5.1 DISCUSSION

Breast cancer represents a major contributor to cancer-related illness and death globally, especially in developed nations. Numerous risk factors are associated with its development. This study explored the association between age, gender, obesity, and family history, and assessed how blood test parameters, liver and kidney function, as well as steroid hormone levels, relate to the risk of breast cancer.

A retrospective analytical study was carried out to investigate potential risk factors associated with breast cancer over the period from November 9, 2024, to March 20, 2025. Data were collected from breast cancer cases registered at the National Cancer Institute in Sabratha, which served as the primary referral and treatment center during this study.

The findings of this study demonstrate a clear age-related pattern in breast cancer incidence, (33.1%) between age of 45-55 years followed by age of 55-65 years (31.5%), whereas the lowest percentage of patients at age of 25-35 years (4.8%) There was a statistically significant difference between age groups ($p< 0.001$). The calculated mean age at diagnosis was 51 years, underscoring the predominance of the disease among older adults.

A previous study in Brazilian breast cancer patients suggested that postmenopausal status is one factor associated with development of breast cancer (Conde *et al*., 2025). It has been suggested that breast cancer is a disease of older women, and its incidence increases with age. The majority of postmenopausal women having dense breast tissue was a predominant risk factor among all women (Surakasula *et al*., 2014).

The current data are consistent with previous epidemiological data from Libya, which reported similar median age values (Elhawari *et al*., 2025), and are also supported by studies conducted in the Gulf Cooperation Council countries, these data (Al-Shamsi *et al*., 2023) reinforce the established association between older age and an increased risk of breast cancer. The researcher concluded from the results obtained that the incidence of breast cancer was significantly higher among married women compared

to other marital status categories. Specifically, married women accounted for (73.39%) of cases, followed by single women (17.74%), widows (4.84%), and divorcees (4.03%). These findings are similar to previous research conducted in Central Africa, where this previous study concurred with the researcher's findings, It turned out that one possible explanation for these Previous findings is the age distribution pattern typically associated with marital status, as married women are more likely to develop breast cancer. The results of this previous study indicate that marital status—particularly marriage—may be associated with an increased risk of breast cancer. (Balikozo *et al*., 2017).

Analysis of family history of breast cancer revealed a statistically significant association ($P < 0.001$). The statistical results indicated that 65.3% of patients reported no family history of the disease, while 20.9% had a first-degree relative and (13.7%) had a second-degree relative with breast cancer. These results are consistent with a previous study conducted in Iran (Khormada *et al*., 2022), which reported that a family history of breast cancer did not represent a statistically significant association with the disease. Based on these results, the researcher concluded that family history is not associated with breast cancer. However, these results can be justified by the small sample size and the possibility that some cases refrained from disclosing their history due to privacy concerns. Therefore, genetic background, in this context, does not appear to be a significant or reliable risk factor for breast cancer.

In examining the geographic distribution of breast cancer patients attending the National Cancer Institute in Sabratha (NCI), it was observed that a significant proportion of cases originated from specific regions in western Libya. According to the collected data, the highest percentage of patients came from the city of Zawia (29.84%), followed by the Western region of Sabratha (24.19%), and Tripoli (13.71%) The elevated percentages of patients in these locations, as compared to other recorded areas, can likely be attributed to the closer geographic proximity to the (NCI) are naturally more inclined to utilize its services, given the accessibility compared to more distant areas. This explanation is supported by a previous study conducted in Libya (Elzouki *et al*., 2018), which reported higher rates of breast cancer incidence in Western regions when compared to Southern and Eastern parts of the country. Moreover, a previous study conducted in Libya (Gusbi *et al*., 2020) demonstrated that the distribution of breast cancer cases was higher in the Western region compared to

other parts of the country, which further supports the findings observed in the present study.

The results of this study showed a complete absence of self-reported smoking among the recorded breast cancer cases. This may be attributed to strong sociocultural stigmas about female smoking in Libyan society, where such behavior is often deemed inappropriate and conflicting with prevailing cultural norms. Another study has been documented in a study from Saudi Arabia, which also reported a notably low prevalence of smoking among female participants (Alsayer *et al*., 2024). These parallels suggest that societal and cultural constraints play a significant role in influencing the accuracy of self-reported behavioral data in many Arab communities.

Furthermore, this study explored the association between body mass index (BMI) and breast cancer risk, revealing that 55.4% of cases were classified as obese, 24.6% as overweight, and 20% as having a normal BMI. These findings suggest a significant correlation between obesity and an elevated risk of breast cancer, particularly in postmenopausal women. The decline in estrogen levels following menopause is believed to contribute to increased adiposity and elevated BMI, both of which are recognized risk factors. Supporting evidence from an African study also demonstrated a postmenopausal rise in BMI and a corresponding increase in breast cancer risk (Mane *et al*., 2025). Previous studies are inconsistent with our results and have further substantiated this relationship(Chen *et al* ., 2023; Han *et al*., 2024).

Measurement of breast cancer grade indicates how quickly cancer cells may grow and spread compared to the normal cells.The current study investigated the breast cancer grade in BC patients. The findings of this study underscore the significance of tumor grading in the diagnosis and management of breast cancer. The result showed that (45.54%) of cases were diagnosed at grade II and (45.54%) at grade III, whereas only (8.8%) were identified at grade I. This distribution highlights a critical gap in early detection, suggesting that delayed diagnosis remains a major challenge. The results emphasize the essential role of public awareness and timely screening in facilitating early-grade diagnosis and improving treatment outcomes. A study conducted in Libya reported a high prevalence of late-grade diagnoses, which can impact treatment options and survival rate (Abousahmeen 2023). Comparative research involving Libya and other African nations confirmed that breast cancer cases

in Libya are frequently diagnosed at more advanced grades than in other countries, where early detection initiatives have led to improved diagnostic timelines (Boder *et al*., 2011). Moreover, a global comparative study found a higher prevalence of early-grade diagnoses in developed countries, a trend attributed to greater health awareness, organized screening programs, and active educational campaigns by healthcare professionals (Fuentes *et al*., 2024). These disparities underscore the impact of systemic public health measures on early cancer detection and outcomes.

Hematological parameters were also investigated in this study in order to find out the effect of BC on the blood parameters. A significant alterations in several hematological parameters among (BC) patients compared to healthy controls. These changes may reflect both the pathophysiological effects of malignancy and the impact of therapeutic interventions. (Chinedu *et al*., 2025).

However, platelet (PLT) counts were significantly elevated in the BC groups compared to controls ($P < 0.001$), though values remained within clinically acceptable limits. Thrombocytosis in cancer patients may be driven by tumor-induced inflammatory responses or paraneoplastic syndromes and has been associated with poor prognosis in various malignancies, including breast cancer (Taucher *et al*., 2003).

Furthermore, an elvated level of platelets has an important predictive value for the prognosis of breast cancer patients with ipsilateral supraclavicular lymph node metastasis (ISLN) metastasis, which can be used to distinguish high-risk patients as to gain clinical benefits (Liu S *et al*., 2020).

White blood cell (WBC) counts showed no statistically significant difference between the two groups ($p = 0.293$), though the experimental group exhibited slightly lower mean values. This may suggest mild leukopenia, potentially due to bone marrow suppression related to cancer therapies (Muhammad 2024). The mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) remained within normal reference ranges and did not differ significantly between groups. In breast cancer patients, elevated MCHC likely reflects tumor-related metabolic and inflammatory effects on red blood cells, as well as potential influences of chemotherapy or radiotherapy. Extremely high values may rarely indicate hereditary or endocrine disorders, but in this context, they primarily suggest cancer-associated hematologic alterations.

These results contrast with previous studies that reported changes in red blood cell markers in cancer patients (Chinedu *et al*., 2025), showing significant decreases in hematological parameters, including MCHC, attributed to chronic inflammation and metabolic changes in cancer patients.

This study compared hematological parameters between breast cancer patients and a control group. The results revealed statistically significant differences in several hematological parameters, highlighting the potential diagnostic value of routine blood tests. These findings suggest that basic hematological assessments may serve as supportive tools in the early detection and diagnosis of breast cancer (Divsalar *et al*., 2021).

The biochemical parameter comparison between the breast cancer patients group and healthy controls demonstrated some statistically significant differences alongside several nonsignificant findings.

Lymphocyte was significantly in the patients compared to controls with a p-value of (0.029), this reduction may reflect cancer-associated immune modulation or suppression(Afghahi *et al*., 2018).

Similarly, glucose levels were significantly in the BC ($p = 0.013$). This may indicate metabolic disturbances or fasting sample collection, especially noteworthy in controls.

On the other hand, renal function markers—urea and creatinine—showed no significant differences respectively, with both groups maintaining values within or near normal clinical ranges despite high variability, particularly in urea among patients. This variability may reflect heterogeneous renal function or outlier values (Chauhan *et al*., 2016)

Chloride did not differ significantly in this study. Statistical analysis revealed a significant difference in serum sodium levels among breast cancer patients. This decrease in sodium levels in these patients may reflect cancer-related metabolic changes, treatment effects (such as electrolyte imbalances caused by chemotherapy), or hormonal changes associated with chronic diseases, such as inappropriate antidiuretic hormone secretion(Berardi *et al*., 2019).

In contrast, serum potassium levels showed no statistically significant difference between patients. The absence of significance suggests that potassium balance is

largely preserved in this patient group. These results were consistent with the results of this previous study. (Yadav& Khodke 2015).

Regarding the liver enzyme activity and protein-related biochemical markers GOT, GPT, and ALK in breast cancer patients compared to healthy controls. Most parameters did not show statistically significant differences between the two groups, with the exception of lactate dehydrogenase (LDH), which demonstrated a significan elevation ($P<0.001$) in the BC group. This elevation is consistent with LDH's known role as a marker of tissue breakdown and tumor burden. High LDH activity in cancer patients reflects increased cellular turnover, metabolic stress, or potential metastasis(Malhotra *et al*., 2024). Similarly, uric acid levels, total protein and total bilirubin showed no significant diffrences ($P = 0.618$, $P= 0.851$ and $P = 0.360$, respectively between BC group and the control.

This study compared individuals in breast cancer patients and control groups and reported that only one variable (LDH) showed statistical significance, which is consistent with the results of a previous study(Amin *et al*., 2012). The remaining variables did not show any statistically significant differences in the current results. This consistency enhances the reliability of our results and supports the conclusion that specific blood markers may be more predictive in distinguishing breast cancer cases (Ma *et al*., 2022).

The distribution of hormones and HER2 receptors was analyzed. Estrogen receptor (ER) and progesterone receptor (PR) positive cancers were significantly more frequent than their negative counterparts, whereas HER2-positive cancers were less prevalent than HER2-negative cases.

This study examines the relationship between estrogen receptor (ER) expression and HER2 status in breast cancer patients. No statistically significant association between ER and HER2 expression(P=0.177). Although a greater proportion of HER2-negative cases were ER-positive, the lack of statistical significance suggests that ER and HER2 expression may co-occur independently in this population.This result agree with a previous research indicating heterogeneity among breast cancer subtypes. HER2-positive tumors are often associated with more aggressive behavior and may or may not express hormone receptors. Understanding their co-expression patterns is clinically critical. Although ER and HER2 status are important prognostic and

therapeutic markers individually, this study showed no significant association between them. Further studies with larger sample sizes and molecular subtype classification may help clarify their interaction and clinical implications.

The findings of this study are parallel to a previous investigation conducted in Italy, which evaluated a large cohort of breast cancer patients. It reported that tumors characterized by PR-positive, ER-positive, and HER2-negative expression were associated with the most favorable survival outcomes. Similarly, cases with PR-positive, ER-positive, and HER2-positive profiles also demonstrated relatively high survival rates. In contrast, triple-negative tumors—lacking expression of PR, ER, and HER2—were associated with the poorest prognoses, reflecting their aggressive nature and limited treatment responsiveness. These results underscore the prognostic significance of hormone receptor and HER2 status in stratifying breast cancer subtypes and predicting clinical outcomes (Caldarella *et al*., 2011).

Moreover, the relationship between progesterone receptor (PR) expression and HER2 status in breast cancer patients indicates no statistical significance (P=0.089). Among patients with progesterone receptor-positive tumors, these ratios indicate that HER2 positivity is more frequently associated with HER2-negative status, while HER2 positivity tends to occur slightly more frequently in PR-negative cases (Utsumi *et al*., 2021).

Although the association did not reach statistical significance, the observed pattern may be of clinical importance. Progesterone receptor-positive and HER2-negative tumors are often classified as lumin A, which is associated with a better prognosis and response to hormonal therapy. They may respond better to HER2-targeted therapies than hormonal therapy alone (Yersal & Barutca ., 2014).

A study found that young breast cancer patients (under 40 years) with low or negative progesterone receptor (PR) expression had more aggressive tumors and significantly worse survival outcomes compared to those with strong PR expression, Low PR levels were linked to higher risk of metastasis and poorer prognosis, suggesting PR expression is an important prognostic factor in ER-positive/HER2-negative breast cancer (kwak *et al*.,2023).

The association between estrogen receptor (ER) status and tumor location was also assessed. The result showed no statistically significant association between ER status and breast cancer (P=0.726). Estrogen receptor-positive tumors appeared more common on the right side (41.9%), but the distribution did not differ significantly between the two sides.

These results suggest that ER expression is independent of tumor side . This supports previous studies suggesting that hormone receptor status (including ER positivity) is determined by the molecular characteristics of the tumor rather than by external or anatomical factors. Furthermore, the nearly equal distribution of tumors between the left and right sides in both the ER-positive and ER-negative groups reinforces the idea that tumor location is likely a random occurrence and not biologically driven by receptor status(Amer,2014).

Likewise, the association between progestrone receptors status and tumor site showed no significant difference (p=0.55). Nevertheless, positive and negative PR tumors (53.7 and 50.0%) respectively located more on the left side of the breast. These findings suggest that ER expression does not significantly differ based on the laterality of breast cancer. This is consistent with prior studies indicating that hormone receptor status is generally independent of tumor laterality. This asymmetry does not appear to be linked to hormone receptor profiles in the present sample (Rummel *et al*., 2015).

Overall, ER status appears to be uniformly distributed across cancer laterality in this cohort, reinforcing the notion that tumor biology, rather than anatomical factors, predominantly determines receptor expression.

Estrogen receptor status shows no significant association with breast cancer laterality, and therefore, tumor side should not be considered an indicator or correlate of hormonal receptor expression. A prior study demonstrated similar results to what the researchers found, with slight differences in anatomically tumor types and ER/PR/HER2 status by squamous cell type, but they were not clearly influential on survival or final outcomes (kim *et al*., 2022).

Evaluation of the relationship between HER2 gene expression status and the side of breast cancer (left, right, or both) indicated no statistically significant association

between HER2 gene expression status and tumor side (*P*=0.461). Interestingly, the highest incidence of right-sided tumors in HER2-negative patients (32.5%) compared to the left side, as well as compared to the negative HER2 tumors. The lack of correlation between HER2 expression and side of cancer suggests that HER2 overexpression is independent of tumor side, and does not contribute to this variance (Al Saad *et al*., 2022).

HER2 status appears to be equally distributed regardless of tumor location, supporting the concept that molecular characteristics, such as HER2 amplification, are inherent to tumor biology and not influenced by anatomic side. The relationship between breast cancer proliferation and hormonal or HER2 status remains largely unexplored, despite extensive analyses of other clinical characteristics (Al Saad *et al*., 2022).

In this study, analysis of tumor grade and the relationship to estrogen receptor (ER) status revealed a potential trend between disease progression and estrogen receptor expression. ER-positive tumors were predominantly observed in grade II (39.4%) and III (31.2%), with a lower proportion in grade I (9.2%). In contrast, ER-negative tumors were observed in grade III (12.8%) and II (7.3%) respectively.

Although these data suggest an increase in ER-positive tumors with advancing grade, the association did not reach statistical significance (*P*=0.062) suggesting a potential relationship between tumor progression and ER loss, which may reflect more aggressive or treatment-resistant tumor biology in later grades.

Our results are inconsistent with prior studies regarding the risk of estrogen-negative tumors in advanced grades. Patients with ER^-/PR^- breast cancer have a significantly higher mortality rate than those with ER^+/PR^+ tumors, even after adjusting for factors such as age, grade , tumor size, metastasis, and treatment. ER-negative tumors are more commonly diagnosed in advanced grade (II-IV), and more common in younger women, which is associated with a greater number of positive lymph nodes

(Dunnwald *et al*., 2007).

In contrast, the result of this study showed a significant association between progesterone receptor (PR) status and tumor grade in breast cancer patients (*P*=0.002). PR positivity is more common in grade II (38.5) and grade III (24.5%)

whereas PR negative are more common in grade III (19.3%) indicating that PR expression tends to decline as tumor stage progresses(Senel., 2021).

These findings are in agreement with published studies indicating that positivity of hormone receptors, including progesterone receptor (PR), is typically associated with less aggressive tumor biology and earlier disease stages. PR-positive tumors typically respond better to hormonal therapies and are often associated with an improved prognosis. In contrast, the higher incidence of PR-negative tumors in advanced stages highlights the aggressive nature and less promising outcomes typically seen in PR-negative breast cancers (Senel,2021).

There is no doubt that assessing progesterone receptor status remains critical for diagnosis and treatment planning, underscoring the need for early detection strategies that will improve the likelihood of identifying progesterone receptor-positive tumors at a more treatable grade (Kwak *et al*., 2023).

Distribution of HER2 gene expression across different tumor grades in breast cancer patients was also investigated . The results indicate that HER2-negative patients were more prevalent in grades II (34.9%) II and III(28.4%), respectively, while HER2-positive patients were generally more prevalent in stage III (15.6%) and II(11.9). Despite these differences, the data did not show a statistically significant association between HER2 status and tumor grade (P=0.465). This finding suggests that HER2 gene expression may not be directly related to tumor grade progression in this cohort. While HER2 overexpression is known to be an important prognostic marker and is often associated with aggressive tumor behavior, its distribution across grades in this sample did not appear to follow a clear trend. This contrasts with hormone receptor markers such as PR and ER, which typically show a stronger association with tumor progression. This is consistent with a previous study that demonstrated the independence of HER2 expression from prognosis (Cong *et al*., 2020).

Probably factors other than tumor grade, such as tumor biology and molecular subtype, likely play a more important role in HER2 expression. These findings highlight the complexity of breast cancer heterogeneity and suggest that HER2 status alone may not be sufficient to predict tumor progression. Further studies with larger sample sizes and molecular analysis could help clarify the relationship between HER2 and breast cancer grades (Turova *et al*., 2025).

Regarding serum biomarkers CEA and CA 15-3 in different grades of breast cancer, a noticeable trends in mean levels. CEA levels showed a gradual increase from grade I to grade III; however, this pattern did not reach statistical significance (*P*=0.607). Conversely, CA 15-3 levels were highest in grade I and decreased in grades II and III, with similar non-statistically significant differences **(***P*=0.548**)** to serum biomarkers CEA and CA 15-3 in different grades of breast cancer, a noticeable trends in mean levels. CEA levels showe a gradual increase from grade I to grade III; however, this pattern did not reach statistical significance (*P*=0.607). Conversely, CA15-3 levels were highest in grade I and decreased in grades II and III, with similar non-statistically significant differences **(***P*=0.548**)**

These results suggest that both CEA and CA15-3, as measured in this sample, do not provide reliable discrimination between early and advanced breast cancer grades.

While CEA and CA15-3 have been widely studied as potential tumor markers in breast cancer, their sensitivity and specificity remain suboptimal, particularly in the early grades of the disease. These findings are consistent with a previous study that demonstrated that tumor markers are independent and not related to histological grade (Wu *et al*., 2014).

Analysis of serum CA15-3 levels and their relationship to hormone receptor status, ER, PR and HER2 expression revealed a statistically significant association exclusively with estrogen receptor positivity (*P*= 0.030) . This finding suggests a potential link between elevated CA 15-3 levels and estrogen receptor expression, suggesting that CA15-3 may partly reflect tumor biology influenced by hormonal signaling. (Nishimura *et al*., 2003).

In contrast, no statistically significant differences in CA 15-3 level were observed based on PR or HER2 status, indicating limited utility of CA 15-3 in differentiating tumors based on these markers. These findings support the potential diagnostic or prognostic significance of CA 15-3 in estrogen receptor-positive breast cancer subtypes, while emphasizing its limited value in characterizing PR or HER2 status(Dede *et al*., 2013) .

Although CA15-3 is widely used in the monitoring of advanced and recurrent breast cancer, its role as a biomarker of receptor subtype differentiation remains uncertain,

except for the modest association observed with estrogen receptor status in this study. These findings agree with a previous study conducted in Turkey, which also indicated a statistically significant association between CA 15-3 levels and hormone receptors (estrogen receptors and progestrone receptors), but not with HER2 expressio (Atoum *et al*., 2012).

Further large-scale prospective studies are needed to elucidate the biological mechanisms underlying the association between elevated CA 15-3 and estrogen receptor expression, and to determine the clinical significance of CA15-3 in monitoring subtypes, prognosis, or treatment response.

This study also investigated serum carcinoembryonic antigen (CEA) levels and their relationship to hormone receptors (ER, PR) and HER2 status. No statistical significant associations in this sample. While the mean CEA level was higher in ER-negative patients compared to ER-positive patients, the difference did not reach statistically significance (P=0.423). Similarly, PR-negative patients showed higher CEA levels than PR-positive patients, but this difference was also not statistically significant (P=0.565). No statistically significant difference was observed between the HER2-positive and HER2-negative groups (P=0.965).

These results suggest that serum CEA levels are not significantly influenced by ER, PR, or HER2 receptor expression in breast cancer patients.

While CEA has been used clinically to monitor treatment response or detect relapse in advanced breast cancer, its diagnostic and prognostic value with respect to molecular subtypes appears limited in this context. These findings support the view that CEA should not be relied upon to assess hormone receptor or HER2 status and should be interpreted with caution when used to characterize the disease. The results we found were consistent with the results of this previous study (Zhang *et al*., 2019).

The results of this study were different to a study by (Zhao *et al*., 2021) demonstrated an elevation of CEA was significantly associated with HER2-positive status ($p < 0.01$), but not with ER or PR status. Multivariate analysis identified HER2 as an independent predictor of elevated CEA. Further research with larger sample sizes and the incorporation of additional biomarkers may help clarify the utility of CEA in more accurately identifying breast cancer subtypes and in clinical decision-making.

5.2 Summary

In this study a total of 124 breast cancer patients were participated, the majority of whom were aged 45–65 years, were married, and had a notable proportion of obesity, with all these demographic factors showing significant differences (P<0.001). Hematological analysis revealed significant reductions in RBC, hemoglobin, hematocrit, and MCV (P < 0.001), while platelet counts were elevated (P < 0.001). Biochemical evaluation showed lower lymphocyte (P = 0.0294) and glucose levels (P = 0.013), with LDH significantly higher in patients (P < 0.001), whereas most liver and metabolic markers were not significantly different. Hormone receptor analysis demonstrated a high ER (79.5%) and PR (71.6%) positivity, and lower HER2 positivity (32.1%), with PR expression significantly associated with tumor grade (P = 0.002), while ER and HER2 associatated with grade were not significant. No significant relationships were observed between receptor status and tumo side. Serum tumor markers showed CA15-3 levels significantly higher in ER-positive patients (P = 0.030), but no significant differences were found for CEA in relation to ER, PR, or HER2. Overall, these findings indicate that PR expression and CA 15-3 may have prognostic relevance, while other markers such as CEA, ER, and HER2 require further evaluation to clarify their clinical significance.

5.3 Recommendations and Limitations

This study highlights the potential relevance of PR expression and CA 15-3 levels in breast cancer prognosis, suggesting that these markers could aid in identifying tumor aggressiveness and guiding clinical management. It is recommended that larger, multicenter studies be conducted to validate these findings and to explore the utility of additional biomarkers, particularly for ER and HER2 subtypes. Early detection strategies should focus on high-risk age groups and obesity as a modifiable risk factor. Limitations of this study include the relatively small sample size, single-center design, and variability in tumor marker levels, which may reduce the generalizability of the findings. Additionally, the cross-sectional design limits causal inferences regarding associations between tumor grade, receptor status, and serum biomarkers.

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المستخلص باللغة العربية

يُعدّ سرطان الثدي من أبرز التحديات الصحية العامة عالميًا وفي ليبيا، حيث يشهد ارتفاعًا في معدلات الإصابة والوفيات، خصوصًا بين النساء الأكبر سنًا. هدفت هذه الدراسة إلى تقييم العوامل الديموغرافية والوراثية وغير الوراثية، بما في ذلك العمر، والحالة الاجتماعية، والسمنة، والتاريخ العائلي، ودراسة ارتباطها بحدوث سرطان الثدي. أظهرت النتائج أن العمر والسمنة والحالة الاجتماعية كانت مرتبطة بشكل معنوي بحدوث المرض، في حين كان للتاريخ العائلي والتدخين تأثير محدود. كما بيّنت المؤشرات الدموية والكيميائية الحيوية تغيرات ملحوظة لدى مرضى سرطان الثدي مقارنةً بمجموعة الضبط. فقد كانت أعداد الصفائح الدموية مرتفعة بشكل معنوي(P<0.001) ، بينما لم تُظهر أعداد كريات الدم البيضاء فروقًا ذات دلالة إحصائية .(P=0.293) انخفضت مستويات الصوديوم في المصل بشكل ملحوظ(P>0.001) ، في حين لم يظهر البوتاسيوم فروقًا ذات دلالة إحصائية (P=0.396). ارتفع إنزيم نازعة هيدروجين اللاكتات (LDH) بشكل معنوي(P<0.001) ، بينما لم تُظهر إنزيمات الكبد الأخرى وحمض اليوريك والبروتين الكلي والبيليروبين الكلي أي فروق معنوية (P=0.618, 0.851, 0.360) على التوالي. كما كانت أعداد الخلايا اللمفاوية ومستويات الغلوكوز أقل بشكل ملحوظ لدى المرضى (P=0.029,0.013) و على التوالي. أما بالنسبة لتوزيع مستقبلات الهرمونات (ER ,PR,HER2)، فقد تبيّن أن الأورام الإيجابية لمستقبلات ER و PR كانت أكثر شيوعًا، بينما كان التعبير الإيجابي لـ HER2 أقل شيوعًا. لم يُسجل ارتباط معنوي بين حالة مستقبل الإستروجين ودرجة الورم (P=0.062)أو جانبية الإصابة (P=0.726) ، في حين وُجد ارتباط معنوي بين حالة مستقبل البروجسترون ودرجة الورم (P=0.002) ، دون ارتباط مع جانب الإصابة(P=0.55). أما تعبير HER2 فقد بدا مستقلاً عن درجة الورم (P=0.465), ومكان الورم (P=0.461). مما يبرز الطبيعة غير المتجانسة لسرطان الثدي وتعقيد أنماطه الجزيئية. أظهرت الواسمات الدموية CEA و CA 15-3أنماطًا متباينة فيما يتعلق بدرجات الورم؛ إذ لم تُسجل فروق معنوية في مستويات CEA بين الدرجات المختلفة (P=0.607) أو فيما يتعلق بحالة ER (P=0.423)أو PR (P=0.565) أو HER2(P=0.965) . كما لم تختلف مستويات CA 15-3 بشكل معنوي عبر درجات الورم (P=0.548) ، لكنها ارتبطت بشكل معنوي مع إيجابية(P=0.030) ER ، دون ارتباط مع PRأوHER2. وبصورة عامة، تؤكد هذه الدراسة على أهمية الكشف المبكر، والتقييم الشامل لحالة مستقبلات الهرمونات وHER2، وزيادة الوعي بالعوامل القابلة للتعديل مثل السمنة. وتشير البيانات إلى أن CA 15-3 قد يحمل قيمة تنبؤية محدودة في الأورام الإيجابية لـER ، بينما يُظهر CEA فائدة ضئيلة في التصنيف القائم على المستقبلات. وتوصي الدراسة بإجراء أبحاث واسعة النطاق تضم الأنماط الجزيئية والواسمات الإضافية من أجل تحسين التقييم التنبؤي وتعزيز إدارة سرطان الثدي سريريًا.

جامعة الزاوية

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عوامل خطر الإصابة لسرطان الثدي ودور مستقبلات الإستروجين والبروجسترون كمؤشرات للتشخيص المبكر "في منطقة غرب الزاوية"

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