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Modern Approaches to the Diagnosis and Complex Treatment of the Development of Fibrocystic Mastopathy against the Background of Ovarian Cysts in Women

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Abstract: The aim of this literature review is to enhance the theoretical knowledge of obstetricians-gynecologists, general practitioners, master's students, and clinical residents regarding cystic changes in the ovaries in the context of fibrocystic mastopathy, based on data from foreign and domestic sources.

The occurrence of a huge ovarian cyst in pregnancy is an uncommon clinical finding, with an incidence of less than 1% of pregnancies. These cysts, especially those greater than 10 cm in diameter, present serious maternal-fetal dangers, including torsion, rupture, preterm labor, and, in some few cases, malignancy. Our patient had an ovarian cyst of 27.4 cm in diameter diagnosed in the first trimester, which underlines the significance of timely diagnosis. The patient's presentation with abdominal pain, on-and-off pain, and bloating was typical of a large ovarian mass, but still, her 13-week gestation complicated the clinical picture.

Keywords: clinical, rupture, preterm labor, malignancy.

Introduction

Since most benign (non-cancerous) ovarian masses are asymptomatic, it is important to do a thorough evaluation of the adnexa during antenatal sonography so as to maximize the chances of early diagnosis and hence early intervention of ovarian cysts in pregnancy. In our patient, the diagnostic imaging through sonographic scanning and MRI was a cornerstone in evaluating the size of the cyst, and its origin and nature. The MRI findings, with their clear delineation of the cystic structure, helped guide the decision for surgical intervention. The management of large ovarian cysts in pregnancy can be difficult due to the need to weigh the benefits and risks to maternal health with the preservation of fetal well-being. Surgery, in the form of ovarian cystectomy, remains the gold standard of management of huge ovarian cysts. The cyst in this case met clinical indication for surgical intervention (cystectomy) due to its large size, the need for fetal viability preservation, and potential for complications, and the fact that the majority of ovarian torsion in pregnancy occurs between 8 and16 weeks of gestation. Laparotomy was the preferred method due to the size of the cyst and the gestational age. The surgery was successfully performed, thanks to the team, and even though the right ovary was removed, the left ovary was thoroughly inspected, and it appeared normal and so preserves future fertility for this woman, given her young age and needs for future fertility. It is comforting that there were no complications intraoperatively and the fact the gravid uterus was preserved.[11]

Though CA-125 was elevated at 62.97 U/mL, it could be due to expansion of the cystic epithelium, though there is no significant correlation between the size of the cyst and CA-125. However, it was further evaluated pathologically and was found to be within the normal range. This case contributes to the growing body of evidence that highlights that, despite the rarity of huge ovarian cysts in pregnancy,

they can be safely managed with prompt surgical intervention, underlining the significance of customized care. Further study is needed to focus on the optimal timing for surgical intervention, with the purpose of minimizing associated risks both to the mother and the fetus.

This case illustrates the successful management of a rare presentation of a huge ovarian cyst in early pregnancy. It underscores the rarity of ovarian cysts in pregnancy and the challenges in the management of a huge ovarian cyst in pregnancy in resource-limited settings. Early diagnosis, careful imaging, and individualized multidisciplinary management are key to optimizing outcomes for both mother and fetus. Besides the rarity of huge ovarian masses in pregnancy, they can be safely managed with good maternal and fetal outcomes, given timely diagnosis, appropriate surgical intervention, and close monitoring of the pregnancy.[9]

The results demonstrate that EnCor VAE is a safe and effective treatment for benign breast lesions, with low complication rates and high patient satisfaction. The minimally invasive nature of the procedure, combined with its short procedure duration and excellent cosmetic outcomes, contributes to its psychological benefits, as evidenced by the significant reduction in anxiety scores post-procedurally. These findings align with previous studies highlighting the advantages of vacuum-assisted

Our multimodal network is designed with both an image encoder and a text encoder as feature extractors, leveraging the strengths of both modalities for comprehensive analysis. For the image encoder, the framework utilizes the tiny Swin Transformer V2 in PyTorch pretrained on the ImageNet dataset. For the text encoder, the multi-qa-mpnet-base-dot-v1 model (MQM) from Sentence Transformers [46] fine-tuned from MPNet encodes the radiology reports illustrates our multimodal model architecture, where image and text encoders independently extract features in dimensions of 768 from their respective modalities. Swin Transformer utilizes shifted windows to conduct self-attention between non-overlapping windows and connect across windows. The hierarchical structure has linear complexity with respect to image size and achieves excellent performance on several benchmarks. The second version, Swin Transformer V2, available in PyTorch, further improves the performance by moving layer normalization to after the attention and feedforward layers, upgrading the original attention with cosine attention, and incorporating relative position bias. As shown, the pretrained model is frozen and its very last layer is replaced with a custom network that includes a transformation layer, concatenation, and one hidden layer. Each of the radial and anti-radial images is passed through the pretrained model to extract features which are projected to a common space as the textual features for alignment. The image features are obtained as below: where and are the radial view, the anti-radial view, and their respective features.

MQM is fine-tuned from MPNet which adopted permuted language modeling and position compensation, retaining the advantages of BERT and XLNet [9] while avoiding their limitations. The fine-tuning was conducted on question and answer pairs and designed for semantic search. The frozen model extracts features by processing each report as follows: where is the radiology report and corresponds to the textual features. For each breast mass input, their features are projected to a common space in dimension through an affine transformation and concatenated in the first dimension as follows:where and are the projected features respectively and is the resulting vector concatenating all the projected features. This is similar to the use of a linear projector in many multi-modal large language models[20], except that having an offset results in better performance for our task. The concatenated vector passes through a two-layer perceptron for binary classification. The image and text features are projected into 64 dimensions, optimized within the choices of [8, 16, 32, 64, 128, 256]. The hidden layer has a size of 48, which is followed by the activation function and a dropout layer with a probability of 0.3. For data augmentation, images are applied vertical and horizontal flipping with a probability of 0.35. Data pre-processing follows that of the tiny Swin Transformer V2, which resizes the input image to a size of 260 by 260 and crops the 256 by 256 in the middle before normalization. The shorter side of the images is padded to match the length of the longer side to maintain the aspect ratio. The model is trained with a learning rate of 0.0004, optimized within the

range of, for 100 epochs under a batch size of 128. Opposed to benign cases, malignant cases are assigned a weight of two in the loss function to overcome the issue of data imbalance.

Pioneered by CLIP, foundation models have emerged for their capability to transfer pretrained knowledge to a variety of tasks. They were trained to maximize the similarity between matching pairs of images and texts. MedCLIP [13], another example, specialized in chest X-ray and medical reports. Of particular interest to the radiologist community is their feature for zero-shot classification, which produces a classification output for any image to belong to any custom-defined category. It was claimed to have competitive performance without any fine-tuning by the user. While the traditional transfer learning approach requires further training, this feature of foundation models lowers the barrier for radiologists to utilize deep learning. Due to this potential, CLIP and MedCLIP are considered our baseline models to gain insights on how foundation models perform compared to models fine-tuned in the domain of breast cancer classification. Performance comparisons between multimodal and image-only models, along with the physician's BIRADS ratings categorized at different probability thresholds. Performance evaluation: Multimodal model vs. Unimodal model compared to physician's BIRADS ratings, To validate the effectiveness of our multimodal model, presents a comparison with the unimodal models, shown in the second, third, and fourth columns. The test set consists of a total of 58 masses, with 37 being benign and 21 malignant. Our multimodal model, incorporating both images and text data, achieved outstanding results with the highest accuracy at 86%, specificity at 86%, precision at 78%, recall at 86%, and an F1 score of 82% on the test set, outperforming the image-only and text-only models on most metrics and with little variation from the training performance. For AUC, the multimodal model exhibited a higher value of 0.8533 (SD = 0.0589) than the image-only model with marginal significance (p= 0.087) and underperformed the text-only model with no statistical significance (p= 0.692). By evaluating performance at the optimal threshold for each model, the indicated that the multimodal model outperformed the unimodal models. These findings highlight the effectiveness of the multimodal model in enhancing classification performance over the image-only model in our analysis.

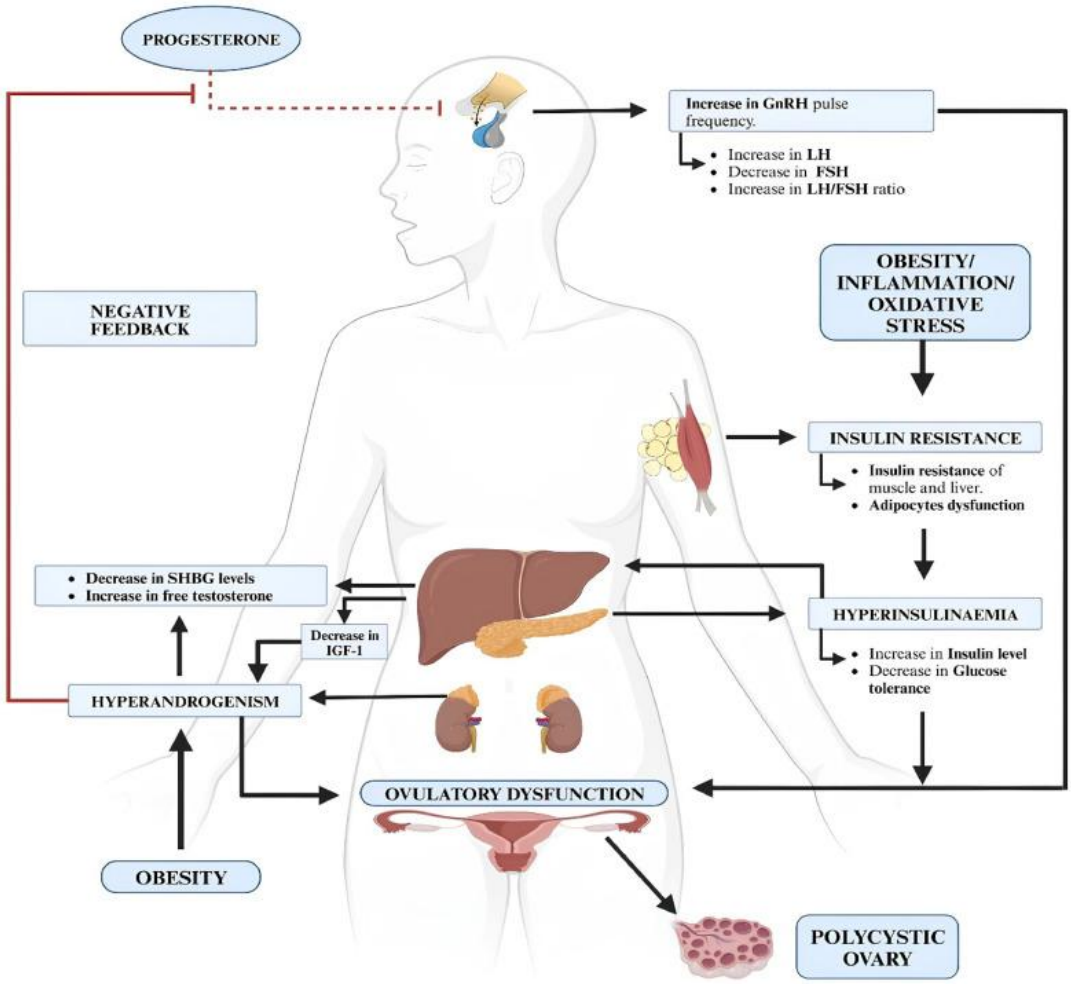
After showcasing the effectiveness of multimodality, the model is compared against the physician's evaluation based on the assigned BIRADS categories using different cutoffs for malignancy probability. When considering only category 5 as malignant, corresponding to probabilities of malignancy of 95%, the physician's assessment achieved perfect precision and specificity but showed a significant deficiency in recall, resulting in a low F1 score of 0.55 (not listed). However, including subcategory 4c (cutoff at 50%; sixth column) in the malignancy class led to a decrease in precision and specificity to below 50%, while recall increased to 90.48%. When further incorporating subcategories 4b and 4a as malignant (cutoffs at 10% and 2% respectively; https://www.sciencedirect.com/science/article/pii/S0010482525008170 - tbl1 last two columns), both precision and specificity further decreased without any corresponding increase in recall, showing the significant discrepancy between BIRADS scores and biopsy outcomes. The F1 score for all groupings of malignant categories remained below 0.65, which is more than 15% lower than the performance of the multimodal model. The same figure marks the sensitivity (recall) and 1-specificity, or false positive rate (FPR) derived from the BIRADS ratings at three distinctive cutoffs: 2%, 10%, and 50%, denoted by star, triangle, and circle, respectively. All models outperformed the physician's BIRADS evaluation. Notably, the multimodal model matched the physician's best recall rate of 90.48% at a 25% cutoff for malignancy probability. At this threshold, the model exhibited an FPR of 46%, outperforming the physician's best result (FPR of 57% at the 50% cutoff) and resulting in an 11% reduction in false positive predictions. This improvement is even more significant against the physician's ratings at cutoff thresholds of 10% and 2%, leading to 26% and 45% fewer false positives, respectively. A major factor in low-grade chronic inflammation is obesity. The buildup of adipocytes in visceral fat results in a low level of oxygen and subsequent death of tissue or cells that triggers the release of inflammatory cytokines. An inflammatory condition results from the death of adipocytes owing to hypertrophy. Adipose tissue mononuclear cells release cytokines that promote inflammation. The inflammatory state is also brought on by excess belly fat.

Moreover, obesity contributes to the onset of insulin resistance (IR), hypertension (HA), and elevated levels of insulin in the bloodstream (hyperinsulinemia). Blood concentration of non-esterified fatty acids (NEFAs) rises in relation to visceral obesity. NEFAs are absorbed by skeletal muscles in place of glucose as an energy source. Hyperinsulinemia and a pancreatic fast response are the results of this hyperglycemia. Furthermore, visceral fat's lipolytic reaction to catecholamines results in lipotoxicity and a decrease in insulin clearance and activity as shown in. Free fatty acid (FFA) decreases tyrosine phosphorylation while increasing IRS-1 serine/threonine phosphorylation. In intramyocellular lipids, elevated FFAs decrease insulin and glucose absorption sensitivity. Notably, because visceral fat has a more severe lipolytic reaction to catecholamines than abdominal or subcutaneous fat, visceral fat weighs more in insulin resistance (IR). The cause lies in the enhanced activity of the β3 and increased expression of β1 and β2 receptors. Furthermore, cortisone is converted to active cortisol by type 1 isoenzyme of 11β-hydroxysteroid dehydrogenase (11β-HSD), which is abundantly expressed in adipose tissue. In omental adipocytes, glucocorticoids decrease insulin signaling and glucose absorption. Furthermore, adiponectin secretion from visceral fat is lower than subcutaneous fat, and this phenomenon results in a reduction in adiponectin production in obesity. Adipokines, also known as adipocytokines, are substances secreted by adipose tissue that have endocrine properties. Adipocytes generate leptin, which, in high concentrations, prevents granulosa cells from expressing aromatase mRNA and inhibits the conversion of androgens to estrogen. Furthermore, it has been proposed that a lack of folliculogenesis is associated with elevated leptin levels.

Additionally, adipocytes release adiponectin, which has anti-inflammatory, anti-diabetic, and insulin-sensitizing activities. The adiponectin insulin-sensitizing effect leads to lowering FFA uptake and gluconeogenesis. It also contributes to ovulation, reduced GnRH release, and production of progesterone and estrogen. Moreover, adiponectin stimulates the granulosa to secrete estrogen, lowers the pituitary's release of LH, and is related with the production of androgen in ovaries. Another substance produced by adipose tissue, omentin-1, enhances IGF-1 receptor signaling and steroidogenic acute regulatory protein and CYP450 aromatase expression. It also improves the production of estradiol and progesterone in many ways (Watanabe et al., 2017). A number of enzymes found in adipose tissue are also responsible for converting testosterone into dihydrotestosterone and androstenedione into testosterone. Androstenedione is converted into testosterone and estrone to estradiol via 17β-HSD. Adipose tissue expresses this enzyme. Excessive fat accumulation aggravates HA as a result of this procedure.

Moreover, Lipotoxicity, characterized by the excessive storage of lipids in non-fatty tissues, results in endoplasmic reticulum and oxidative stress. This stress is proximately linked to insulin resistance (IR) and inflammation. The increased number of fatty acids in muscles and the liver contributes to insulin resistance through the process of serine phosphorylation of the insulin receptor, a mechanism facilitated by diacylglycerol (Dumesic et al., 2020). Furthermore, hepatic lipid buildup lowers HNF-4α levels, leading to reduce the synthesis of SHBG.

Pathophysiology of PCOS [This figure illustrates the hormonal and metabolic pathways involved in polycystic ovary syndrome (PCOS). It shows how abnormal feedback mechanisms lead to increased GnRH (Gonadotropin releasing hormone) pulse frequency, affecting LH (Luteinizing hormone and FSH (Follicles- stimulating hormone) levels, resulting in an altered LH/FSH ratio. Obesity, inflammation, and oxidative stress contribute to insulin resistance and hyperinsulinemia, which further exacerbate hyperandrogenism and ovulatory dysfunction. This cycle is linked to decreased SHBG (Sex hormone binding globulin) levels, increased free testosterone, and IGF-1 (Insulin- like growth factor 1) reduction, ultimately leading to the development of polycystic ovaries.



The figure highlights the interconnection of endocrine and metabolic dysfunctions in PCOS].Management of PCOS The choice of management approaches and the selection of the most fitting drug therapy are shaped by understanding the specific attributes and needs of the patient being addressed (Zeind and Carvalho, 2017). The challenges might range from trying to conceive, controlling irregular menstruation, losing weight, or getting rid of hyperandrogenic symptoms such as hirsutism, skin breakout, or androgenic alopecia. In fact, the best outcome can only be achieved by tailoring the strategy to each individual The ultrafast protocol showed potential to discriminate between malignant and benign breast lesions with high accuracy using MS.Breast magnetic resonance imaging (MRI) is the most sensitive imaging technique for breast cancer detection and has been shown to detect cancers that are mammographically, sonographically, and clinically occult. The use of breast MRI for screening has increased over the past decade, mostly in women with a high risk of breast cancer. In these women, MRI screening detects the cancers at a lower stage and reduces the incidence of interval cancers. in their recent study, demonstrated that screening MRI improves early diagnosis of prognostically relevant breast cancer in women at average risk with a negative screening mammogram. Common barriers and limitations to breast screening with MRI include claustrophobia, long examination time, high cost, limited patient access, and patient discomfort.

In order to increase the accessibility of MRI as a screening method, an abbreviated MRI screening protocol aims to decrease the magnet, technologist, and radiologist reading time and consequently, make the examination overall more cost efficient. Kuhl *et al* published the first studies in 2014 that proposed a streamlined protocol that reduced breast MRI examination time to approximately 3 minutes. The proposed protocol acquires only the unenhanced and first contrast-enhanced acquisitions and evaluates lesions on the maximum-intensity projections and subtraction series. The information from dynamic enhancement, the T2-weighted (T2W), and diffusion-weighted imaging (DWI), are discarded, yielding a negative predictive value of 99.8% in a screening population. Since then, there

have been several published studies comparing the duration, sensitivity, and specificity of the abbreviated protocol and the standard protocol.

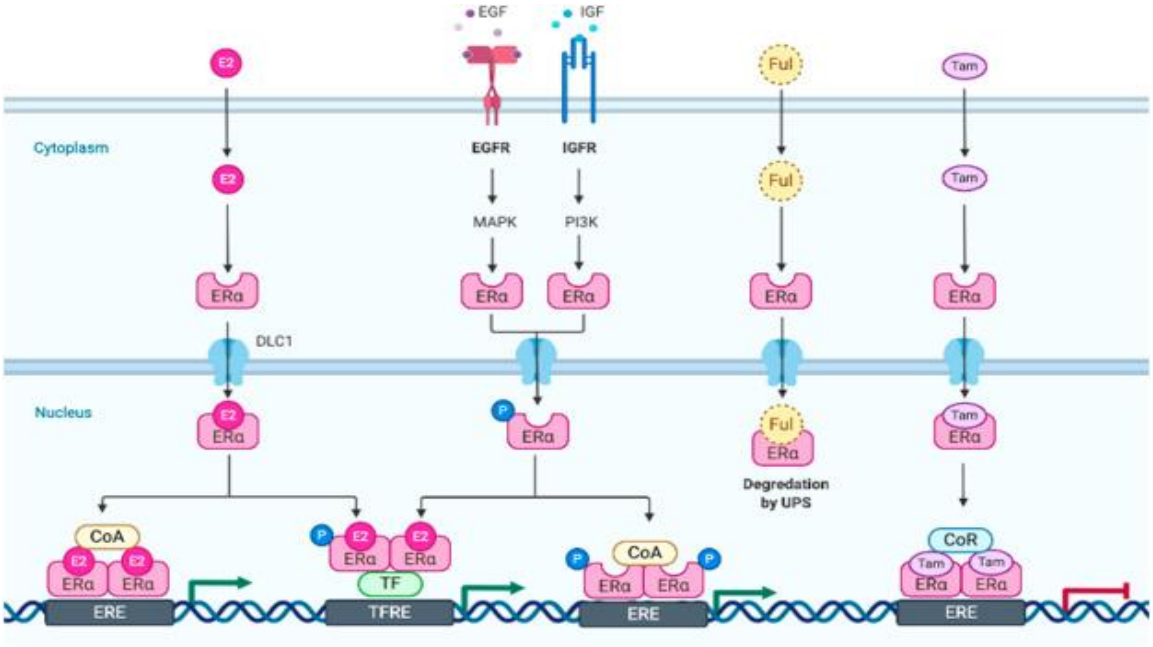
Screening typically finds small lesions at the early stage. By adopting the abbreviated protocol, additional dynamic information, which is important to classify small mass-like lesions, will be lost, causing a diagnostic conundrum. Hence, there is a requirement for a dynamic scan protocol without extending the imaging time.

Ultrafast dynamic contrast-enhanced (DCE) breast MRI sequences re-enable dynamic evaluation of contrast medium inflow during and shortly after contrast agent injection while preserving a diagnostic spatial resolution that allows morphological analysis of breast lesions. Time-resolved angiography with stochastic trajectories (TWIST) is an ultrafast high spatial and high temporal resolution MRI sequence, allowing the acquisition of 20 whole-breast three-dimensional (3D) volumes within 102 seconds. Ultrafast kinetic parameters include maximum slope (MS), time to enhancement (TTE), and arterial and venous visualisation index (AVI). The MS evaluates the upslope of the time–intensity curve, TTE demonstrates the initial time a breast lesion enhances, and the AVI is the time interval at which the breast artery and veins enhance. These parameters have been reported to discriminate between malignant and benign breast lesions.18, 19, 20 The first ultrafast sequence study by Mann *et al.*, in 2014 showed that lesions that enhance ≤10 seconds after the aorta are likely malignant; lesions that enhance between 10 and 15 seconds after the aorta are indeterminate, and lesions that enhance >15 seconds after the aorta are likely benign.[11]

Abbreviated breast MRI with an ultrafast sequence overcomes the limitations of MRI, including high cost, limited availability, and long scanning times, whilst retaining excellent sensitivity and specificity, thus making breast MRI a more accessible and efficient screening method for the general population. The present study aimed to evaluate the diagnostic performances of ultrafast breast MRI sequences using the view-sharing technique to differentiate malignant from benign breast lesions. In particular, the association of ultrafast kinetic parameters, including the MS, TTE and AVI, was compared with histopathological diagnosis.

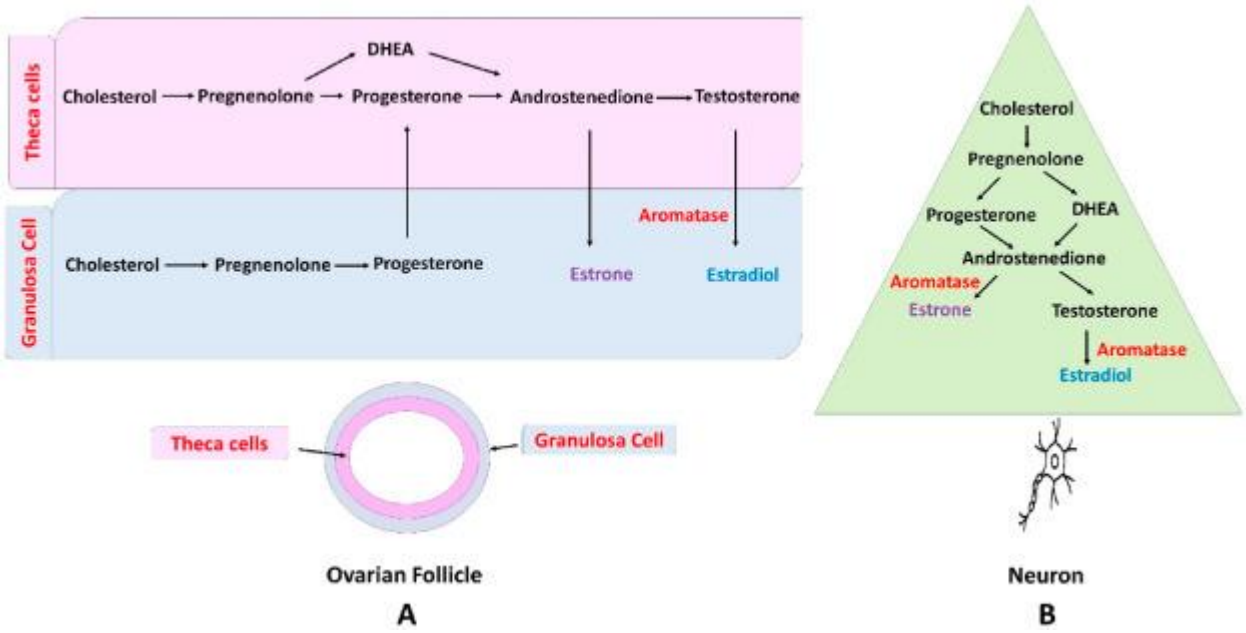
She was soon referred to a breast surgeon, in order to do ultrasound-guided core biopsy of the breast, which was performed 5 days after her first presentation. The hystopathologic examination revealed a benign breast tissue with acute and chronic inflammation, and micro abscess formation. Breast magnetic resonance imaging (MRI) was performed 25 days after the breast biopsy, and it demonstrated the presence of a small round “mass-type” lesion with homogeneous enhancement of 8 mm in diameter in the left retroareolar region. The MRI finding was given BI-RADS category 4 B (moderate suspicion for malignancy, >10% to 50%), because of the enhancement time-intensity kinetic curve (type II: progressive contrast enhancement with initial uptake of gadolinium, followed by the plateau phase - plateau pattern). In the case that we report here, medical treatment was not considered for our patient because despite the histological outcome, MRI was still quite concerning. Breast surgeon by agreement with the radiologist decided for surgical excision of the lump, and the hystopatological result was a fibrous tissue-producing subacute-chronic inflammatory process, with aspects of a foreign body-associated giant cell granulomatousis, showing a prevalent periductal disposition. In female mammals, the development and regulation of the reproductive system and non-reproductive system are significantly influenced by estrogens (oestrogens). In addition, lipid metabolism is another physiological role of estrogens. Estrogens act through different types of receptors to introduce signals to the target cell by affecting many estrogen response elements. Breast cancer is considered mostly a hormone-dependent disease. Approximately 70% of breast cancers express progesterone receptors and/or estrogen receptors, and they are a good marker for cancer prognosis. This review will discuss estrogen metabolism and the interaction of estrogen metabolites with breast cancer. The carcinogenic role of estrogen is discussed in light of both conventional and atypical cancers susceptible to hormones, such as prostate, endometrial, and lung cancer, as we examine how estrogen contributes to the formation and activation of breast cancer. In addition, this review will discuss other factors that can be associated with estrogen-driven breast cancer. Estrogens also known as oestrogens, are key hormones responsible for the progression and regulation of mammal females’ reproductive system and

have an essential role in the non-reproductive system [1,2]. In addition, they are pleiotropic steroids that play a regulatory role in a myriad of physiological processes from reproduction to lipid metabolism [3]. Estrogens perform their action through two different types of receptors: First, classical nuclear estrogen receptors (ER) with two various isoforms known as (ERα and ERβ) that are encoded by genes on chromosomes 6 and 14, respectively. Second, novel cell surface membrane receptors (GPR30 and ER-X). Both kinds of estrogen receptors are expressed in the brain and periphery with cell and tissue-specific circulations [4,5]. Estrogen receptors are a component of the superfamily of nuclear transcription factors with a classical pathway of estrogen-dependent function. The action of estrogen receptors achieves in the cytoplasm by binding lipophilic hormone molecules and transferring the compound to the nucleus, dimerization, and interaction with suitable https://www.sciencedirect.com/topics/medicine-and-dentistry/dna-responsive-element in gene promoters region, which initiates transcription after co-activators binding as demonstrated in [6,7]. Due to the significant role of ER in signaling transduction, the current review aimed to summarize the mechanism of action of estrogen in cancer development, particularly in breast cancer.

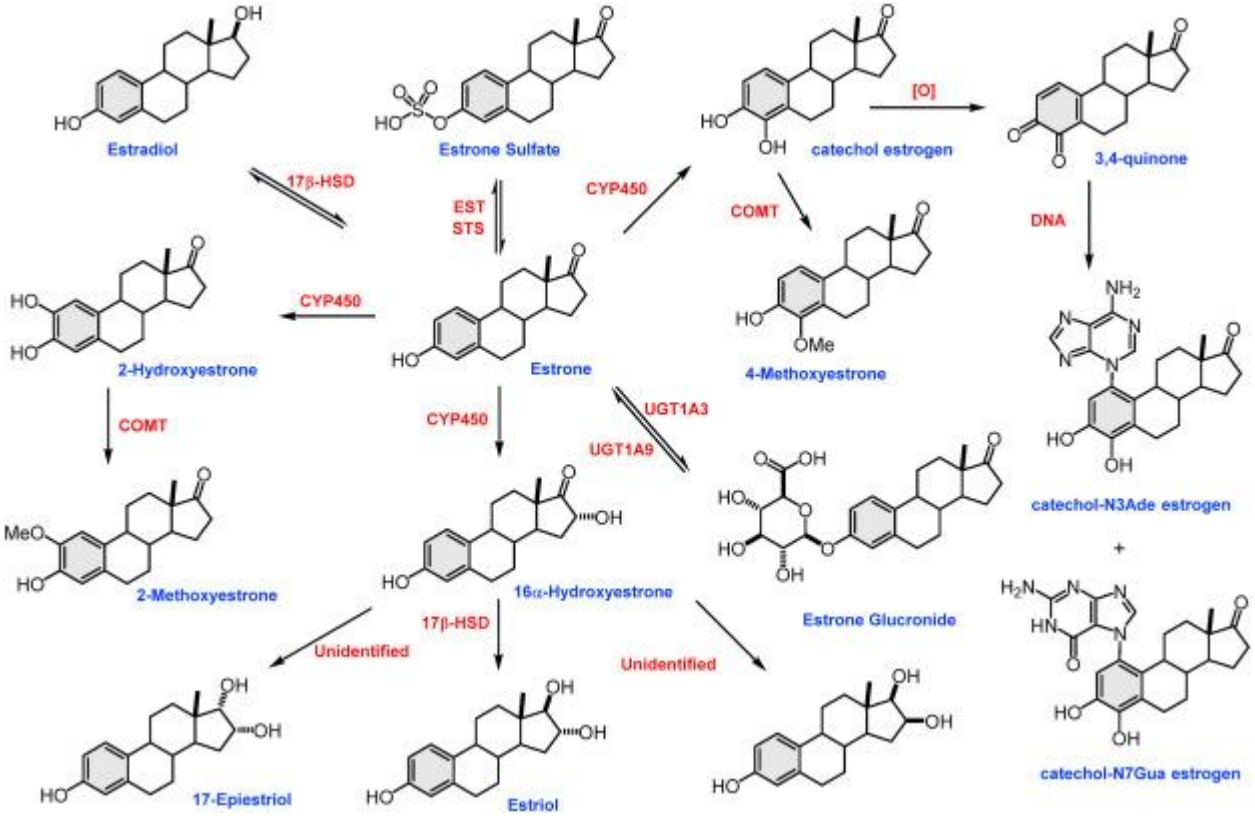


Signaling Pathway of Estrogen Receptor. Estrogen can cross the plasma membrane, where it interacts with intracellular ER and ER to affect DNA directly. The GPER1 and/or ER and ER can interact with estrogen to cause it, to activate intracellular signaling cascades as an alternative. Estrogen-mediated signaling events can be classified as genomic and non-genomic due to differences in the cellular and molecular processes regulating gene expression, in which estrogen-receptor complexes can bind to DNA directly or indirectly. The migration of estrogen-receptor complexes into the cell nucleus and direct contact with chromatin at particular DNA sequences known as estrogen response elements are two examples of genomic impacts (EREs). More than one-third of human genes controlled by estrogen receptors are reported to lack ERE sequence elements, although EREs have been found in multiple gene promoters and regulatory regions. Contrarily, non-genomic impacts entail the indirect control of gene expression via a range of intracellular signaling occasions. Below is a description of the known ways through which estrogens regulate both genomic and non-genomic aspects of Receptor Signaling. Retrieved Estrogen synthesis. In premenopausal women, estrogens are synthesized primarily in theca cells in the ovaries,placenta, and corpus luteum. A noteworthy quantity of estrogens can also be created by non-gonad organs, like the liver, skin, brain, and heart. The synthesis process ends with the conversion of androgens to estrogens in granulosa cells by the aromatase enzyme as illustrated in A and B [8]. There are three main endogenous forms of physiological estrogens in women: estrone (E1), estradiol (E2), and estriol (E3). After menopause, E1 has an important role as it is formed in adipose tissue from adrenal dehydroepiandrosterone. While E2 which is also called estradiol, considers the major and most potent product of the estrogen biosynthesis process. E3 form is the least prevalent

estrogen and is formed from the E1 or E2. Additionally, it plays a larger role during pregnancy when it is produced in large quantities by the placenta [[9], [10], [11]].



Estrogen synthesis pathway in the ovary and brain. (A) Synthesis of estrogens begins with the production of pregnenolone from cholesterol, catalyzed by the cytochrome P450 side-chain cleavage enzyme (P450scc). The pregnenolone is transformed into progesterone by 3 b-hydroxysteroid dehydrogenase (3 b-HSD) in both thecal and granulosa cells. Progesterone is transformed to androgens by cytochrome P450 17a-hydroxylase (P45017a) and 17 b-hydroxysteroid dehydrogenase (17 b-HSD) in the thecal cells throughout the follicular phase. The transformation of E2 is enhanced by the aromatase enzyme (P450Arom) in granulosa cells. (B) Neurons express all of the mandatory enzymes for the production of estrogen to create brain estrogen [12].



Estrogen metabolism pathway in humans. The diagram shows the metabolism of estradiol and other natural estrogens such as estrone and estriol. It demonstrates that conjugation (e.g., sulfation and glucuronidation) occurs in the case of estradiol and metabolites of estradiol that have one or more available hydroxyl (–OH) groups. Catechol and quinone formation from estrone is shown and how the derivatives are reacting with DNA to form depurination DNA adducts (adapted from Ref. [16]).

Estrogens are metabolized via hydroxylation and conjugation. Hydroxylation is achieved by cytochrome P450 enzymes such as CYP1A1 and CYP3A4, while conjugation is performed by estrogen sulfotransferases (sulfation) and UDP-glucuronyltransferases (glucuronidation). Moreover, estradiol is dehydrogenated by 17β-hydroxysteroid dehydrogenase into the less common estrogen estrone as shown in These reactions take place primarily in the liver, but also in other tissues [[13],[14], [15]]. Hydroxylation pathway

2-hydroxylation is the main hydroxylation pathway. CYP1A1 and CYP1B1; cytochrome P-450 enzymes which are expressed in breast and liver tissues are major phase I enzymes [17]. C2 hydroxylation for parent estrogens to catechol estrogens is catalyzed by cytochrome P-450 enzymes including CYP1A2 [18].2-Hydroxylated estrogens have a low binding affinity for the estrogen receptor [19]. Compared with estradiol these metabolites reduce hormonal potency and are the cause of non-estrogenic and anti-estrogenic activities. Some studies showed that 2-hydroxyestrone and 2-hydroxyestradiol can inhibit cell growth and proliferation [20]. Also, they have a role in normal cell differentiation and apoptosis [21]. Therefore, some researchers define 2-hydroxyestrone as a “good estrogen” [22]. The low potency or non-tumorigenic effect of the 2-hydroxy metabolites can be attributed to the high clearance rate, O-methylation by the COMT enzyme, which may inhibit tumor cell proliferation and angiogenesis [19]. In addition, it has been demonstrated that when COMT is blocked or when 2-hydroxyestrogens undergo redox cycling, they can cause DNA damage and release free radicals [23]. Moreover, some studies showed that methoxyestrogens like 2-methoxyestradiol inhibit carcinogenesis through microtubule destabilization [24,25]. Hydroxylation pathway In liver microsomes, the 4 hydroxylations of estradiol primary start with the CYP3A4/3A5 enzyme [26]. 4-Hydroxylated catechol estrogens showed a carcinogenic potential because of their ability to damage the DNA by depurination adducts and oxidative damage that may initiate breast cancer [16,17]. As a biochemical marker, the ratio of 4-/2-hydroxyestradiol is used to differentiate malignant breast tumors because the production of 4-hydroxyestradiol is four times higher than 2-hydroxyestradiol in adenocarcinoma [14]. Additionally, it has been demonstrated that, as compared to control women, women with breast cancer or at high risk of developing breast cancer had much greater ratios of quinone-estrogen DNA adducts to their parent or conjugated catechol estrogens [15]. Moreover, some studies showed that the 4-methoxyestrogens prevent the oxidative metabolism of estradiol and oxidative DNA damage [30]. Although other studies showed that inhibition of the COMT enzyme was linked with higher levels of depurination 4-hydroxyestrone linked with higher levels of depurination 4-OH Estrone/Estradiol-DNA adducts [31].

In the 16-hydroxylation pathway, 16α-hydroxyestrone is the main product. 16α-hydroxyestrone showed a potential tumor stimulation by catalyzing unprogrammed DNA synthesis and promoting independent growth in mammary epithelial cells [32,33]. Some animal studies showed that urinary concentration of 16α-hydroxyestrone is accompanied by an elevated proliferation of mammary cells and mammary tumor incidence [34,35]. Another study shows that there is a relation between estradiol 16α-hydroxylation and increasing the risk of developing breast cancer in humans, the levels of 16α-hydroxyestrone were eight times higher in the cancerous units of mammary terminal duct lobular in comparison with the nearby mammary fat tissue, which suggests a critical role of 16α-hydroxyestrone production in breast cancer induction [36].

Biological function of estrogen in the human body Estrogens are found in both males and females; they are usually present at higher levels in women during reproductive age. They control the improvement of women's secondary sexual characteristics, such as breasts, and are elaborated in the thickening of the endometrium and other features of regulating the menstrual cycle. In men, estrogen regulates specific functions of the reproductive system essential to sperm maturation [8,37]. Estrogen

receptors are responsible for mediating estrogen actions and functions; a dimeric nuclear protein binds to DNA and has a role in controlling gene expression. Similar to the principle of the other steroid hormones, estrogen moves in passively into the cell and binds to it then activates the ER [11]. Estrogen receptor (positive and negative) ER-positive tumors overexpress the ER while tumors that contain a small number of receptors and sometimes no receptors are called ER-negative which is directing the treatment options [8]. Patients with ER-negative have lowersurvival rates in the first few years and their tumors are usually more aggressive [5,7]. However, 10 years after the initial diagnosis of the tumor without being associated with other health problems, the possibility of relapse is more in patients who have ER-positive [9]. In addition, other factors affect the life of a breast cancer patient, such as the infiltration of lymphocytes, especially for patients who have the disease before the age of forty, as the presence of a large number of $CD8^+$ T lymphocytes contributes to the high survival rates of the patient, and this shows It is more clearly in patients who have ER-negative compared with patients with ER-positive [4].

Estrogen and estrogen receptors role in cancer development. The α and β isoforms of estrogen receptors exhibit similar structural and functional organization [3]. Both receptors interact in the same way with endogenous estrogens, mostly with 17β-estradiol (E2) [6]. E2 plays an essential role in the development and malignant progression of multiple cancers. The oncogenic function of estrogens is considered in both classical and non-classical hormone-sensitive carcinomas such as prostate, breast, endometrial, lung, colon, and ovarian cancers [2]. The molecular basis of cancer initiation by estrogen has been suggested through the production of aromatic estrogen metabolites (catechol estrogens quinones) that are derived from normally formed catechol estrogens. Chemically, depurinating DNA-adducts are formed by the reaction of 4-$OHE_{1/2}$ or 2-$OHE_{1/2}$ with Adenine/Guanine bases which leads to DNA mutations (Fig. 3) [16].

Endometrial cancer

Tumoral ER expression is mentioned in approximately 30 different kinds of cancer, predominately in hormone-sensitive tumors like ovarian, breast, prostate, and endometrial cancers [5]. By utilizing immunohistochemistry (IHC), studies were able to compare ER protein expression with clinicopathological characteristics in tumor tissue and illustrated differential relations to the prognosis of disease based on the localization of cells and cancer type [48]. Endometrial cancer which is considered the most popular type of uterine cancer, using histopathology, can be subdivided into two types [51]. Type I endometrial tumors, also called low-grade endometrioid, form most of the endometrial cancer cases around 85%, usually express high levels of α estrogen receptor (αER), and are supposed to be hormonally driven [52]. Type II tumors contain high-grade endometrioid tumors, clear-cell, serous tumors, carcinosarcomas, and tumors with diverse histology. These tumors are expressing ER at low levels, have a worse prognosis, and have combined molecular features with serous ovarian cancer and triple-negative breast cancer such as a high prevalence of p53 mutations and a high number of copies of a variation [3]. Extensive research in epidemiology has illustrated that hormonal and reproductive exposures are linked with a high risk of ovarian cancer. However, how these factors impact ovarian carcinogenesis and lead to tumor development is still not fully understood. Epithelial ovarian cancers are heterogeneous in their morphology, gene and protein expression [6]. These variations are mandatory to understand the etiology, prognosis, and treatment of ovarian cancer [59]. Studies have demonstrated differential associations between the risk factors of ovarian cancer and α-ER and progesterone receptor (PR) status, while no previous research has observed associations of ovarian cancer risk factors with β-ER expression [7]. Some reports suggested tumor suppression activity of ERβ in ovarian tissues and showed low expression in malignant transformation; with cell localization pattern [9]. A study done by De Stefano and colleagues to distinguish between normal and cancer ovarian cells found that; ERβ staining was more likely to be localized in the nucleus in normal ovarian tissue while it was more likely to be localized in the cytoplasm in ovarian cancer cells [6]. Additionally, higher levels of expression of the ERβ protein have been linked with enhanced progression-free survival, furthermore, the probability of metastasis of

lymph nodes has declined in serous tumors [67,68]. A recent study showed alterations in expression and localization of ERβ noticed to be essential for causing ovarian cancer [59].

Estrogen and estrogen receptors and risk of breast cancer

Breast cancer is the m ost common female cancer with no decline in the incidence, prevalence, or mortality. In 2023, it has been estimated that about 300 000 new cases of BC will appear with more than 43 000 deaths in the USA [4]. In 2020, breast cancer surpassed lung cancer to become the most frequently diagnosed cancer and ranked fifth among the leading causes of cancer-related fatalities worldwide. During that year, there were approximately 2.3 million reported cases and 685 000 documented deaths attributed to breast cancer [5]. In combination with growth hormone (GH) and its secretory product insulin-like growth factor 1 (IGF-1), estrogen is important in mediating breast development during puberty and breast maturation during pregnancy to prepare for lactation [26,77]. Estrogen is highly involved in breast development and it is primarily responsible for making the ductal component of the breast as well as for causing growth in fat deposition and connective tissue [[7], [9], [8]]. Moreover, it is indirectly elaborated in the lobuloalveolar component, via increasing the expression of progesterone receptors in the breasts and by inducing prolactin secretion. After working with estrogen, progesterone, and prolactin together, they can complete the growth of the lobuloalveolar during pregnancy [8].

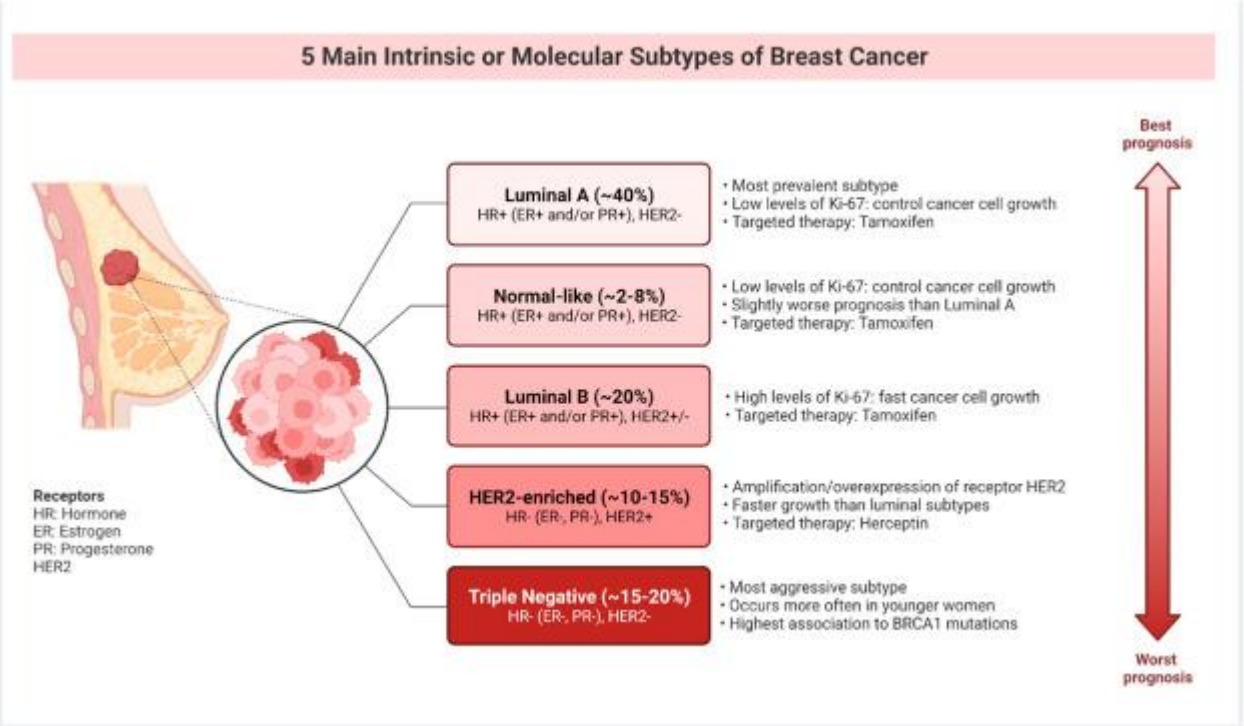
Expression and distribution of ER in the breast

The expression of the individual isoforms of ER is regulated differently in the breast epithelium, compared with other tissues [8]. ERα and ERβ show some distinct expression patterns; ERα is controlled in the luminal epithelial compartment, while ERβ is expressed in myoepithelial cells and luminal, as well as the endothelium of blood vessels and stromal cells [84]. Interestingly, these isoform-specific expression manners can differ between species, for instance, in the rat mammary gland, the ERβ is expressed throughout all stages of development, while ERα demonstrates fluctuating expression, it increases during puberty and declines during pregnancy, as well as increases during lactation, and decreases again in the post-lactating gland [85]. On the other hand, in the rhesus monkey, neither ERα nor ERβ could be noticed in the lactating mammary gland, nor was PR detected, this is a confirmation that observations that are noticed in animal models, may not always be prolonged into the human breast [86]. Therefore, the expression of steroid hormone receptors in normal breast tissue is highly dependent on cell type, the stage of progression, and the exposure to cycling endogenous or exogenous hormone utilization.

7.3. Estrogen and breast cancer

The ovarian hormones of females, estrogen, and progesterone are essential regulators in the development and function of normal breasts, as well as critical in breast cancer. The breast is developmentally infrequent in the fact that the main part of the improvement of the breast happens postnatally, during puberty, and at the onset of pregnancy [7]. Both estrogen and progesterone are censoriously involved in these normal evolving processes, having highly coordinated functions in the development of the ductal structures and amplification of lobules of the normal epithelium. It looks that these behaviors become undermined in the development of breast cancer, connecting both steroids in the enhancement and progression of cancer [3].

Breast cancer is considered mostly a hormone-dependent disease. Approximately 70–80% of breast cancers express progesterone receptors and/or estrogen receptors, and if they are found in a tumor, are a good mark as a promising prognostic biomarker In addition, their expression in malignant cells is mostly associated with other tumor characteristics. The positive association between PR, ER, and prognosis has been identified with the progress of multi-gene prognostic processes that categorize breast cancers into clinically relevant groups, with PR and ER segregating into the better distinguished luminal cancer subtypes as demonstrated in. For managing ER+breast cancer, using agents targeting the signaling pathway of estrogen is still the most effective treatment.



The five main subtypes of breast cancer; are where the best prognosis is when the ER is positive, while the worst is a triple-negative case when ER is negative.

An abundance of clinical and experimental data in various studies has illustrated that estrogen is critical in the progression and proliferation of breast cancer. In different malignant breast cells, the function of an ER signaling pathway is to promote unequal rates of cell proliferation and apoptosis, with pro-survival and proliferation signals devastating pro-death and quiescence signals [5]. Dependable on a pro-proliferative role, there is in vitro proof that estrogen can inhibit apoptosis in breast cancer cells by up-regulation of Bcl-2, an anti-apoptotic proto-oncogene. As a result of its part in the proliferation and growth of tumors in breast cancer cells, the ER signaling network has been considered an attractive agent for the development of therapeutic targets [6].

Menstrual cycle The menstrual cycle is a physiological process that starts in females at ages ranging from 8.5 to 13 years old, and it repeats in a cycle-like pattern that varies in length from 25 to 34 days until they finally stop experiencing it for one year entering a stage called menopause at an average age of 51 years old. The cycle alternates between two phases as it happens each time, a follicular phase that ranges from 10 to 16 days, and a luteal phase that is usually the same in all women that is 14 days. This makes the follicular part of the cycle the usual reason for its length difference between women, what mainly regulates this process are hormones secreted from the hypothalamus, the pituitary gland, and the ovaries like estrogen and progesterone [8], which induce different changes in the reproductive organs leading to the capability of fertility [9].

Understanding the relationship between the menstrual cycle and breast cancer could be beneficial in diagnosing and treating breast cancer since the aggression and poor prognosis characteristics of breast cancer in premenopausal women could be due to the fact of the influence of menstrual cycles on estrogen receptor-positive subtypes of breast cancer, which are the most common in that age group. The age of menarche and time of menopause seem to affect the risk of developing breast cancer, due to their role in the time and amount of exposure to hormones like estrogen and progesterone. An earlier age of menarche induces a rise in breast cancer risk since it causes earlier exposure to the hormonal changes that induce the beginning of menstrual cycles. As well as, a rise in estrogen levels in the first couple of years following early menarche that can remain throughout their fertile years [25]. This risk is limited to hormone receptor-positive subtypes of breast cancer. Moreover, the same concept of increased estrogen exposure is related to the increase of breast cancer risk related to a late age of menopause, due to more exposure to menstrual cycles and their hormones, although the increase in

that risk may be not evident up until 10–20 years after menopause [30]. The regularity and length of the menstrual cycle both have an association with breast cancer risk, a short length, and a regular cycle are associated with breast cancer occurrence since more menstrual cycles result in a shorter follicular phase and therefore more dominant exposure to progesterone and an increased division of epithelial cells in the fixed luteal phase each cycle [22]. Despite some data suggesting no relation betweenmenstrual cycle irregularity and breast cancer with an exception of a precise group of women aged 30–34 years old with a high level of irregularity [10]. Likewise, no relation between irregularity and increased length of menstrual cycles and breast cancer risk again with the exception of longer menstrual cycle length during the age of 18–20 years old decreasing the risk of breast cancer in women younger than 40 years old. Breast cancer that is diagnosed during pregnancy or after it the post-partum period has a poor degree of prognosis [34]. Many factors related to pregnancy are thought to influence breast cancer risk. The first one is the age of the woman when she had her first pregnancy, or "age at first pregnancy". In general, women who first conceive at an older age have a higher risk of developing breast cancer, while younger women have a decreased risk of developing breast cancer. The mechanism behind that is that older women will go through more menstrual cycles and therefore be more exposed to substances like estrogen that can promote the carcinogenesis of breast tissue. Other than that, some changes occur in pregnancy that protective against breast cancer, like the hormonal changes that happen in early pregnancies that secure a gene called p53, which helps in the cessation of the cell cycle, therefore, stopping cell growth, another hormone change is the production of human chorionic gonadotropin, a hormone that differentiates breast cells and makes them less prone to a response by carcinogens [27]. However, age at first pregnancy doesn't affect all breast cancer subtypes in the same way, for example, triple negative and human epidermal growth factor receptor 2 (HER2) subtypes of breast cancer are not affected by it, while the luminal subtype of breast cancer has more prevalence among women who are older than 24 years old when they have their first birth [10]. The second factor is the number of pregnancies that the woman had regardless of whether it resulted in an abortion, stillbirth, successful childbirth, or "parity".

The hormone levels during pregnancy, the length of the pregnancy, and the gender of the fetus have been suggested to be related to the development of BC. The hormone levels that decrease breast cancer risk when elevated are the human chorionic gonadotropin hormone (beta-HCG) decreasing it by 30% and the Alpha-fetoprotein hormone (AFP) decreasing it by 50%, while the hormone that increases breast cancer risk while elevated is the estrone hormone increasing it by 2.5 times [28]. Secondly, full-term pregnancy is associated with a lower risk of breast cancer in the long term but a higher one immediately following the birth after the full-term pregnancy is compensated with breastfeeding [29]. Lastly, the sex of the fetus has no relation to the breast cancer risk [34], however, in certain cases like hypertension induced in pregnancy also called "preeclampsia" a male fetus has an impactful decrease in the risk of developing breast cancer for the mother [20].Studies demonstrated that longer breastfeeding duration and protects against breast cancer. For instance, breast cancer risk reduction by 26% and 37% if the duration exceeds a year [121]. Although this protection may only be limited only to postmenopausal women [122]. The mechanism behind this protection that the longer duration of breastfeeding provides is due to the breast cells differentiating after pregnancy to be able to lactate which decreases its responsiveness to substances like estrogen that can stimulate breast cells to become cancerous. Another way is the mechanical flushing of carcinogens and exfoliated DNA-damaged cells and insulin through breast milk, which reduces insulin levels in the blood and prevents the anti-apoptosis effects that insulin can have by increasing the level of substances like insulin-like growth factor [123]. Nevertheless, a recent review proposed there was still an unclarity of the definitive relationship between breastfeeding and breast cancer risk [124]. Polycystic ovary syndrome (PCOS) Polycystic ovarian syndrome (PCOS) is the most common metabolic disease occurring in women at the age of reproduction. Women with the condition are more prone to cardiovascular manifestations as well as insulin resistance, but it also affects fertility, hormone balance, and ovulation [25]. PCOS doesn't have a clear association with an increased breast cancer risk, [29]], despite it causing changes in the body that can lead to breast cancer like the high androgen levels in the blood that results in the absence of ovulation and therefore longer exposure to estrogen [13]. The high levels of insulin that it

causes in the blood, as well as having an intersection with a gene that is also present in breast cancer [31]. Also, it produces high levels of *anti*-Mullerian hormone (AMH) which could suggest PCOS is the original factor responsible for the increased breast cancer risk occurring in women with high levels of (AMH), not the increase in the hormone itself. There are also some data like a population-based case-control study by Kim J, Mersereau JE, Khankari N et al., that does suggest it has a positive relationship with an increased risk of breast cancer occurrence specifically in premenopausal women [33].

Microbiota and breast cancer Dysbiosis was found to make an impact on the effectiveness of chemotherapy drugs and prefer the environment of tumor development, suggesting an association between gut dysbiosis and the progression of cancers, autoimmune disorders of the gut, or inflammatory diseases. Even with the presence of some skeptical concerns about whether breast cancer development is due to this dysbiosis or the natural selection of microorganisms that can survive in a carcinogenic environment with special nutritional requirements [152], a diversity of lipid types suggest lipid signatures for the bacterial growth species in breast cancer compared to healthy breast tissue [153]. Breast cancer environment was reached in higher numbers of Phylum Proteobacteria, families Micrococcaceae*, Caulobacteraceae, Rhodobacteraceae, Nocordioidaceae*, and *Methylobacteriaceae,* and genus *Propionicimonas* compared to benign healthy breast tissue, even with different types of breast cancer like HER2, Luminal A, Luminal B, ER+ the type of microbiome was diverse and different [154]. A shifting of microorganism types was estimated from the healthy breast tissue and cancerous including the presence of microorganisms that will raise the local breast estrogen exposure level by glucuronidation like *S. pyogenes* [15]. To support the role of breast microbiota in breast cancer either as an inducer or consequence of the disease, a study has been done at St. Joseph's Hospital in London, Ontario, Canada by collecting samples from women, aged between 19 and 90 with healthy breasts or with breast cancer. These women underwent breast surgery and the researchers found that breast cancer microbiota was made up of collocation of bacteria that end up with DNA damage and breaks in Vitro including *Bacillus,*Enterobacteriaceae*, Staphylococcus*, and *Escherichia* (a member of the Enterobacteriaceae family) and Staphylococcus epidermidis rising [16]. Fernández et al. support the relationship between the gut microbiota and breast cancer development in many ways. The gut contains many glucuronidase bacteria, including the Clostridium leptum cluster and the Clostridium coccoides cluster, which are members of the Firmicutes phylum. The first method, which included deconjugation of contacted estrogen, came from an endogenous source or even an exogenous source of estrogen through the bile pathway. This deconjugation process will be aided by the Proteobacteria phylum's Escherichia/Shigella bacterial group, which increases the blood level of estrogen. Additionally, the second method involves the function of Firmicutesa nd Bacteroidetes bacteria of the gut, which are in charge of processing the colon. These bacteria discovered that nutrients were present in much higher ratios among obese women, knowing that obesity is an indirect link between breast cancer and the gut microbiome [17]. The gut microbiome, which is thought to play a role in the development of breast cancer, should be the first thing to be targeted during breast cancer treatment or even prevention because there is a clear indication that there is a difference between microbial patterns in healthy breast tissue and women with breast cancer where many DNA breakers are found. Additionally, researchers should discover a means of preventing dysbiosis so that the microbiome balance in breast tissue remains constant and does not change [18,19]. The favorable effects of probiotic therapy on the treatment of breast cancer contradict the idea of the negative effects of microbiota and its function in breast cancer given that this bacterium also contributes to the metabolism of cytotoxic medicines [10]. Another study confirmed the beneficial effects of probiotics in preventing the growth and even genesis of breast cancer. By avoiding dysbiosis, we can improve the balance of the gut's metabolic activity and lower obesity, which is known to increase the risk of breast cancer [11]. Many bacteria found in breast cancer patients have an inverse relationship to the prognosis of breast cancer, a point that should be taken into consideration in the future of breast cancer treatment strategies. These bacteria may affect body weight, chemotherapy agents, and even the potential of neurological side effects [12].

Breast cancer in active or passive smokers can't be negligible knowing that this tobacco smoke included a lot of carcinogens of breast tissue, especially mammary cells. The enzyme N-acetyltransferase 2 (NAT2) was found to play a role in the detoxificationa nd eradication of tobacco smoke chemicals so genetic polymorphisms of this enzyme gene will play a role to determine whether you are a fast or slow acetylators. Moreover, being a slow acetylators with a long history of smoking increases the risk for breast cancer development two times. The onset of smoking was found to increase the risk, like young age or long history of smoking before the first term of pregnancy [13]. Jones et al. reported in their cohort study that the risk of breast cancer and smoking was potentially supported, especially if the onset of smoking was even before the menarche in young girls with a family history of breast cancer [14]. Breast cancer at early stages before lymph node metastasis or organ spread was found to begin at higher rates among smokers of younger age [15]. Another study found that smoking plays a significant role in the prognosis of breast cancer with higher rates of mortality before or after the diagnosis of breast cancer [16].

Conclusion. Thus, the analysis of literature data showed that ovarian cysts and mastopathy, having spread throughout the world, led to an emergency situation. Thanks to the comprehensive measures taken by the international community to combat background and precancerous breast diseases, a stabilization of the global situation has been achieved. The data presented in the review indicate that ovarian cyst against the background of ovarian cyst has fibrous mastopathy.

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