A Dissertation on

A prospective comparative study of Tamoxifen versus standard treatment response in fibrocystic disease of the breast in tertiary health care

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the requirements

For the award of degree of

M.S. (BRANCH-I)

GENERAL SURGERY

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI, TAMILNADU.
MAY 2020

CERTIFICATE

This is to certify that this dissertation titled **A prospective comparative study of Tamoxifen versus standard treatment response in fibrocystic disease of the breast in tertiary health care is** a bona-fide research work carried out by **Dr.Zothanpari Ralte** under our direct supervision and guidance, submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment of the requirements in the award of degree of M.S. (GENERAL SURGERY)Branch -I for the May 2020 examination.

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DECLARATION

I, **Dr.Zothanpari Ralte** solemnly declare that "**A prospective comparative study of Tamoxifen versus standard treatment response in fibrocystic disease of the breast in tertiary health care"** is a bonafide work done by me.

I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any university board either in India or abroad.

This thesis is submitted to The Tamil Nadu Dr .M.G.R. Medical University in partial fulfilment of the rules and regulations for the award of Master of Surgery degree Branch-I (General Surgery) to be held in May 2020.

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I wish to thank all my co-post graduates for helping me in this work.

I gratefully acknowledge all patients and participants who gave their consent and co-operation for this study.

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INTRODUCTION

Introduction

Due to high prevalence of benign breast diseases and their impact on the quality of life of a woman, they are clinically as well as culturally significant. The clinical importance is further augmented by the proclivity of the benign breast disease towards transforming into a neoplasm. From the epidemiologist and clinician's point of view, it is essential to understand the etiology and the pathogenesis of the disease in addition to the understanding of the risk factors for designing preventive strategies of the disease. The research on benign breast disease is not new as we have the luxury of having a wide knowledge database about the disease. Multiple systematic reviews have been done to summarise and sort the wealth of accumulated knowledge right from etiology till treatment including histopatholoy and molecular biology.

The study of such benign breast diseases are challenging in the light of separating physiologic changes from the pathologic changes clinically as well as in histopathology. The definitions and classifications are not scanty in this disease though the majority of the attention is being attributed to the following;

a) fibroadenoma

b) fibrocystic breast disease

Fibroadenomas are non-neoplastic lesions with pseudoencapsulation macroscopically and sharp delimitation microscopically. Epithelial and stromal components are present. It seems to arise from a single lobule due to distortive hyperplasia.

On the other hand, fibrocystic breast disease is not clearly defined. Fibrocystic breast disease is a condition of breast tissue affecting an estimated 30-60% of women and at least 50% of women of childbearing age. Some studies indicate that the lifetime prevalence of fibrocystic disease of breast may be as high as 70% to 90%.

Any condition that presents with a palpable lump that is ill defined; associated with pain and tenderness and shows cyclical pattern corresponding to the menstrual cycle is considered as fibrocystic breast disease. The disease tends to progress till menopause and tends to decline in incidence and prevalence post that. This disease has conflicting nomenclature where the same condition has been described with different names namely;

1. chronic cystic mastitis
2. cystic disease
3. cystic hyperplasia
4. epithelial dysplasia
5. mastopathia

The histologic analysis shows that the lesions arise from the epithelium. On the other hand, the microscopic analysis reveal microcysts and macrocysts either alone or in conjunction with papillomas, adenosis, epitheliosis, apocrine epithelium and papillomatosis. Schnitt and Conolly elaborated on this nomenclature.

Summarising, cysts are characterised by the following features;

a) They vary in size from being microscopic to macroscopic and present as an apparent lesion

b) They are filled with fluid

c) They are round to ovoid in shape

Haagensen defined gross cyst as a derivation of the end of the ductal lobular unit presenting as a palpable mass. There are two layers of the epithelium namely epithelial layer (inner) and myoepithelial layer (outer). Cysts may be associated with hyperplasia or metaplasia. In metaplasia, the normal epithelium transforms into the type of epithelium present in apocrine glands. In hyperplasia, it can be either adenosis or epitheliosis. Adenosis is the condition where a new ductal or lobular structures are developed accompanied with the proliferation of myoepithelial or epithelial cells. In sclerosing adenosis, there is a predomination of myoepithelial cells. When there are papillae present, it is called as papillomatosis.

It is often periodically related to hormonal influences from the menstrual cycle. The changes in fibrocystic breast disease are characterised by the appearance of fibrous tissue and a lumpy, cobblestone texture in the breasts. These lumps are smooth with defined edges, and are usually free-moving in regard to adjacent structures, The lumps are more often found in the upper, outer sections of the breast (nearest to the armpit), but can be found throughout the breast. Women with fibrocystic changes may experience a persistent or intermittent breast aching or breast tenderness related to periodic swelling. Breasts and nipples may be tender or itchy. Symptoms follow a periodic trend tied closely to the Menstrual cycle. Symptoms tend to peak in the days and, in severe cases, weeks before each period and decrease afterwards. At peak, breasts may feel full, heavy, swollen, and tender to touch. No complications related to breastfeeding have been found.

The exact mechanism of the condition is not fully understood, though it is known to be tied to hormone levels, as the condition usually subsides after menopause and is also related to the menstrual cycle. Post-menopausal women placed on hormone replacement therapy (HRT) have also reported symptoms of fibrocystic disease of breast indicating that hormones may play a role. Fibrocystic breast changes is a cumulative process caused partly by the normal hormonal variation during a woman's monthly cycle. The most important of these hormones are oestrogen and

progesterone. These hormones directly affect the breast tissues by causing cells to grow and multiply. Many other hormones such as TSH, insulin, growth hormone and growth factors such as TGF-beta exert direct and indirect effects amplifying or regulating cell growth. Years of such fluctuations eventually produce small cysts and/or areas of dense or fibrotic tissue.

Diagnosis and Prognostic Factors- An overview

Mammography is usually the first imaging test to be ordered when unusual breast changes have been detected during a physical examination. Ultrasound of the breast is commonly performed in conjunction with mammographies.

Risks- Except for patients with a strong family history of breast cancer, where the risk is two-fold, nonproliferative lesions have no increased risk. Proliferative lesions have approximately a 2-fold risk. Clinical examination of the breast is characterised by detailed history taking, followed by the traditional inspection, palpation and other parameters like mammogram, FNAC, etc. The tests of palpation, imaging and biopsy is known as Triple test.

The role of Tamoxifen in breast disease- what do published literature say?

World Health Organisation have enumerated Tamoxifen as a necessary ingredient in the treatment protocol of breast cancer. Since a quarter of a century, it is been

used as the gold standard endocrine method of treating oestrogen-receptor-positive breast cancer, irrespective of staging. Tamoxifen is known to have saved the lives of around 400,000 women apart from the large number of women who received palliative care and improved quality of life post surgery. It is also the first drug to be approved by the Food and Drug Administration (FDA) as cancer chemopreventive in women who were at higher risk. It is known to reduce the incidence of cancer in premenopausal as well as post menopausal women.

When given as an adjuvant therapy, Tamoxifen is known to be effective in decreasing the recurrence of breast cancer and thereby death. Even in patients with metastasis, it provides adequate palliation. This explains why Tamoxifen is used in both premenopausal and postmenopausal women provided their neoplastic tissue is estrogen receptor positive. The only exception being made on the basis of prognostic factors and with very low risk of dissemination.

For postmenopausal women who present with metastatic breast cancer, tamoxifen is the first treatment of choice in the list of hormonal therapy. The drug is well tolerated and is known to be safe. Even in younger women, it is the used as a first or second choice drug, the risk of endometrial cancer being present. Another reason for preference of Tamoxifen and a number of randomised trials studying its use is

the positive effects of the drug on bone density, risk of contra lateral breast cancer and cardiovascular mortality.

Studies show that there is a relationship between benign diseases of the breast and cancer risk mainly based on their morphological subtypes. The risk severity varies between different histologic subtypes. Proliferative lesions with atypia are known to be having 1.5 to 2-fold risk of getting cancer. There are a number of factors associated with these lesions that determine the progress to cancer namely;

1. type of atypical hyperplasia
2. time since biopsy
3. menopausal status
4. family history
5. postmenopausal hormone use
6. presence of other benign lesions

In a recent study conducted by Tan-Chiu et al in 2003, it is found that Tamoxifen treatment reduces the risk of benign breast disease by 28%. Tamoxifen was found to be effective in reducing pain in women with: cyclical mastalgia and also to a lesser degree in women with non cyclical mastalgia. Women who received Tamoxifen had a 29% reduction in undergoing biopsies. Adverse effects were

reported more frequently with Tamoxifen 20 mg than with Tamoxifen 10mg. However, the overall side effects were reported only in minority of the population. Reported adverse effects included an increase in weight, menorrhagia, hot flashes and vaginal discharge Tamoxifen is a selective estrogen receptor modulator class of drugs that is used to prevent breast cancer in women and men.lt is also being studied for other types of cancer. It is currently used for the treatment of both early and advanced estrogen receptor positive(ER-positive)breast cancer in pre-and post menopausal women. It has been further approved for the reduction of contra lateral cancer. Tamoxifen is also used for the treatment of infertility, gynecomastia, Albright syndrome and other rare conditions of retroperitoneal fibrosis and idiopathic sclerosing mesenteritis.

Salient features of Tamoxifen

Route of administration-mouth

Pregnancy category-US: D (evidence of risk)

Protein binding-99%

Metabolism—hepatic(CYP3A4, 2C9 and 2D6)

Elimination half tife-5-7 days

Excretion-feces 65% urine 9%

Side effects include:

- irregular periods
- weight gain
- hot flashes
- vaginal discharge
- uterine cancer
- stroke
- vision problems
- pulmonary embolism
- deep vein thrombosis
- steatorrhoeic hepatosis

Abstract

Introduction

World Health Organisation have enumerated Tamoxifen as a necessary ingredient in the treatment protocol of breast cancer. Since a quarter of a century, it is been used as the gold standard endocrine method of treating oestrogen-receptor-positive breast cancer, irrespective of staging.

Aims and objectives of the study:

To assess the effectiveness of Tamoxifen in fibrocystic disease(benign breast disease) of the breast.

Methods

It was a Comparative Prospective Single Center Study in the Department of General surgery, Government Stanley Medical College from September-2018 to September- 2019 among Patients who are diagnosed with fibrocystic breast disease are recruited from the surgery department. Based on the lottery method, consecutive patients are randomised into two groups; Each group contains 20 patients with a total sample size of 40.

Results

The mean age of the Tamoxifen group is 35.15 years with a standard deviation of 4.79 years with a median of 37 years ranging from 25 years to 40 years. The mean age of the Primrose group is 31.20 years with a standard deviation of 3.98 years

with a median of 30 years ranging from 26 years to 39 years. In the Tamoxifen group, the disease was present on the right side in eight patients and on the left side in twelve patients. In the Evening Primrose group, the disease was present on the right side in seven patients and on the left side in thirteen patients. All lesions were cystic in nature Majority (n=22) of the patients had grade 3 pain with 10 patients in the Evening Primrose group and 12 patients in the Tamoxifen group. The two groups are comparable and does not differ significantly in the grading of pain. Both the Groups received treatment for three months. The Cardiff Breast Pain Score was comparable between the two groups with no significant differences. The reduction in size of the lump was better in Tamoxifen group with 8 of them showing reduction whereas in the Evening Primrose group only three of them had a reduction in the size of the lump. The difference is statistically significant. Out of 20 patients in the Tamoxifen group, only two of them had side effects while five of them had side effects in the Evening Primrose group. Out of the two patients in the Tamoxifen group with side effects, one of them had Hot flashes while the other one had Menorrhagia. Whereas in the Primrose group, three of them had headache and two of them had diarrhea.

Conclusion

The outcome was better in the group that was treated with Tamoxifen as compared to the treatment with evening Primrose group.

REVIEW OF LITERATURE

Review of literature

It is essential for the surgeon to familiarise with the structure (anatomy) and function (physiology) of breasts for planning proper management. This following section deals with the anatomy of breast, embryology, structural composition and development. Significant asymmetries are present in almost all female patients and might pose significant deformities post-operatively which may be augmented by chest wall deformities or other asymmetries. This explains why pre-operative photos are taken for records.

Surface anatomy of the breast

The shape of breasts varies widely among different women. The surface anatomy is significant than the shape of the breast. The following image shows the surface anatomy of the breast. It extends medially from the body of sternum and intermammary cleft till the anterior axillary fold laterally.

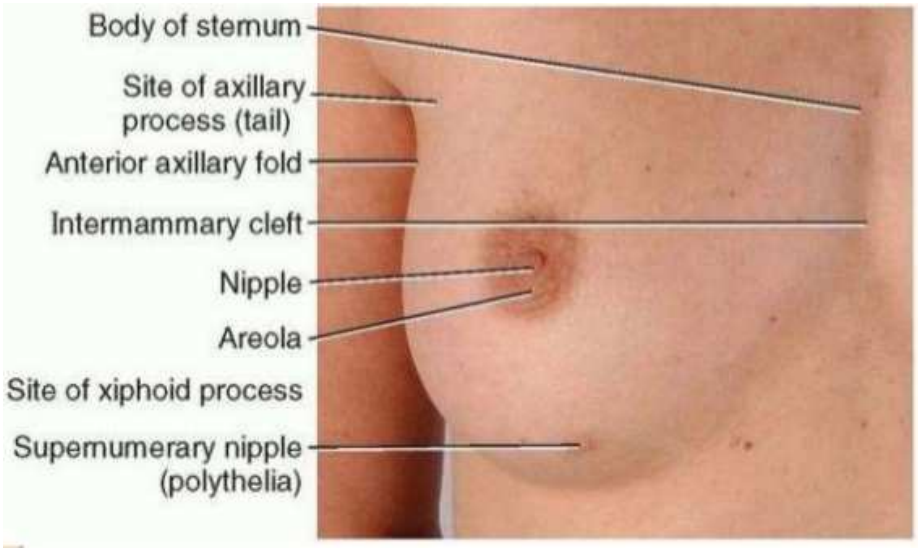
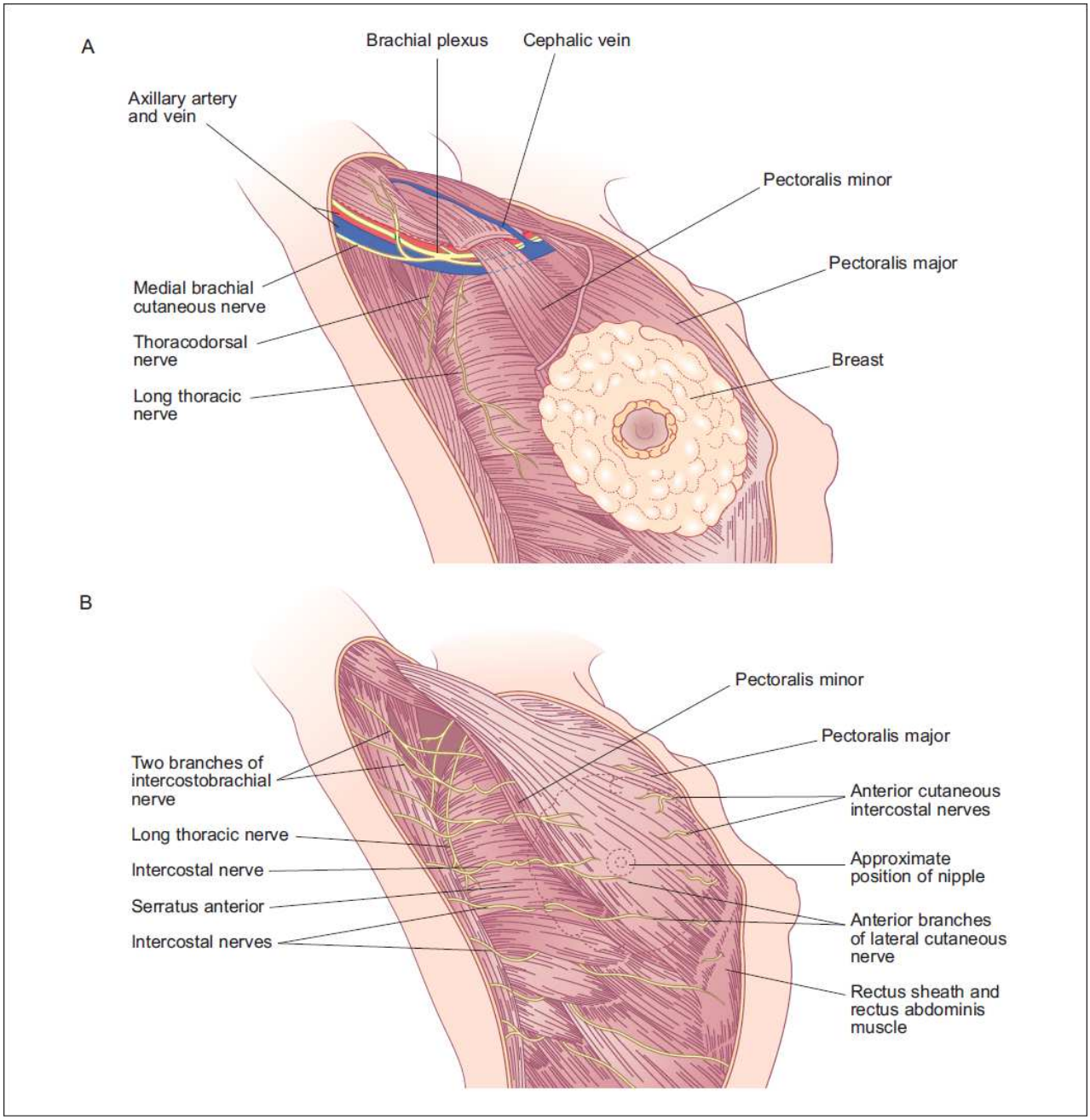
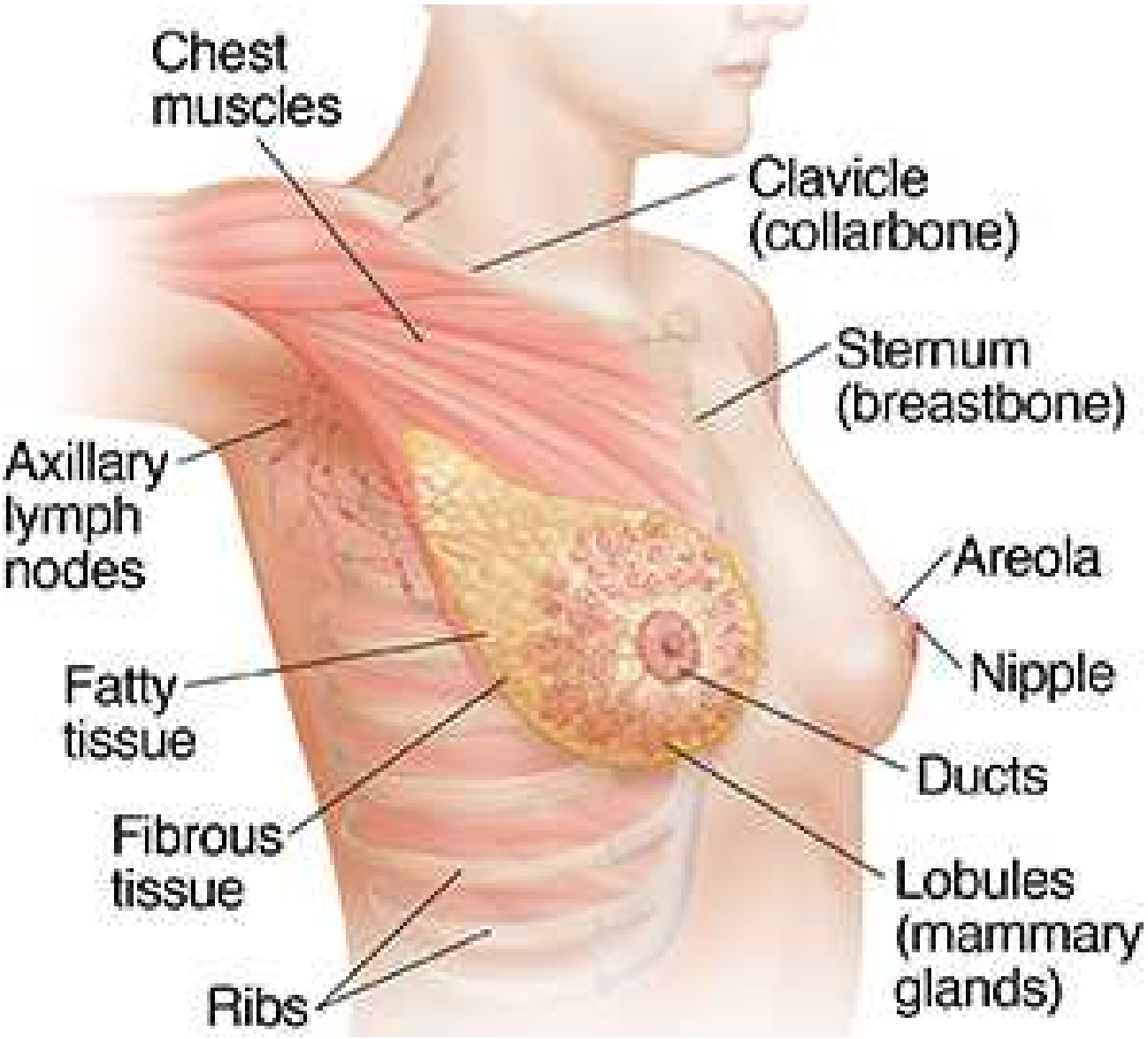


Image 1: Surface anatomy of the breast

At the superior portion, it extends from the clavicle. The anatomical relations of the breast are shown below.

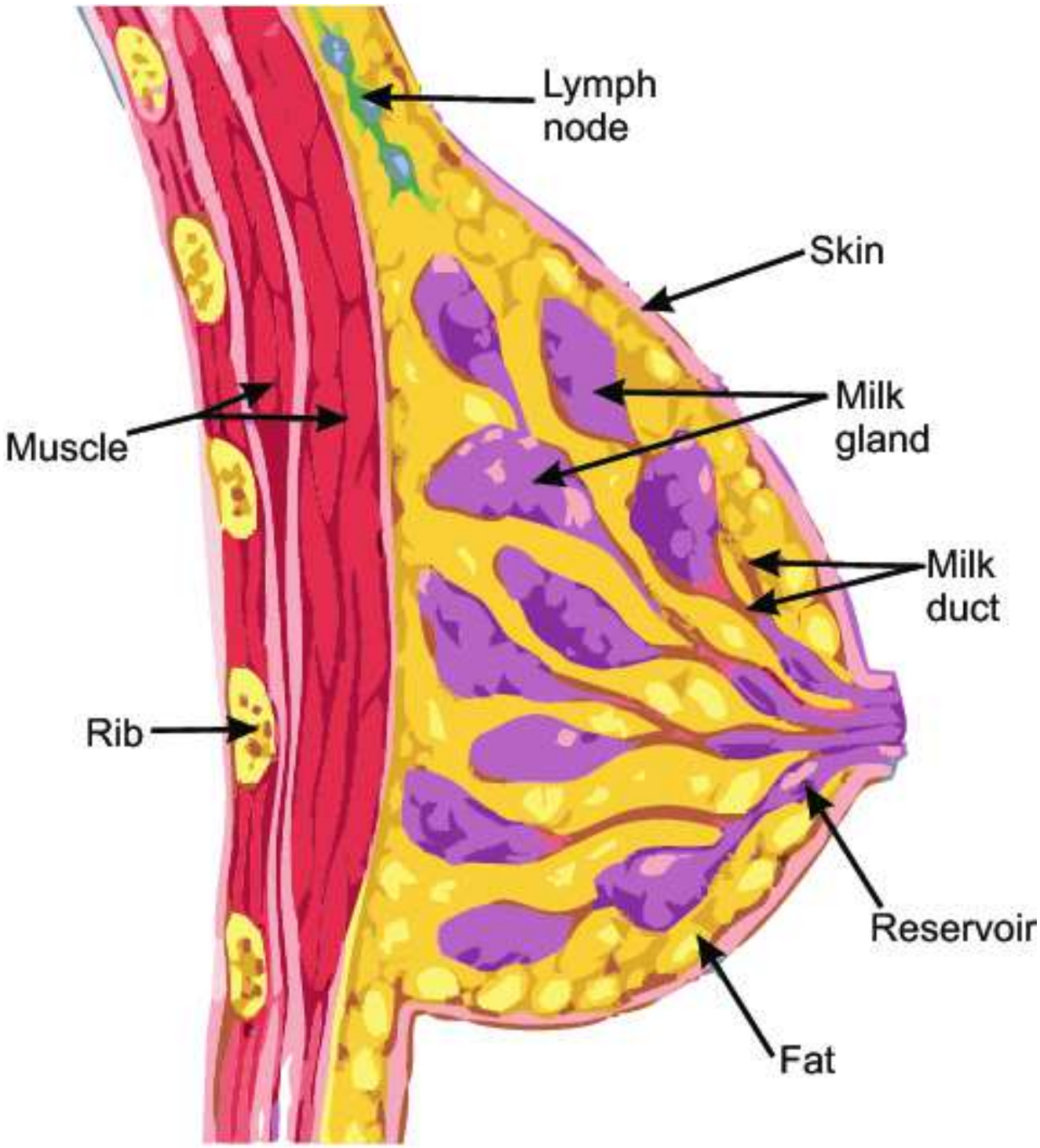


Source: M.D. Barber, Jeremy St J. Thomas, J. Michael Dixon:
Breast Cancer: An Atlas of Investigation and Management



Composition of the breast

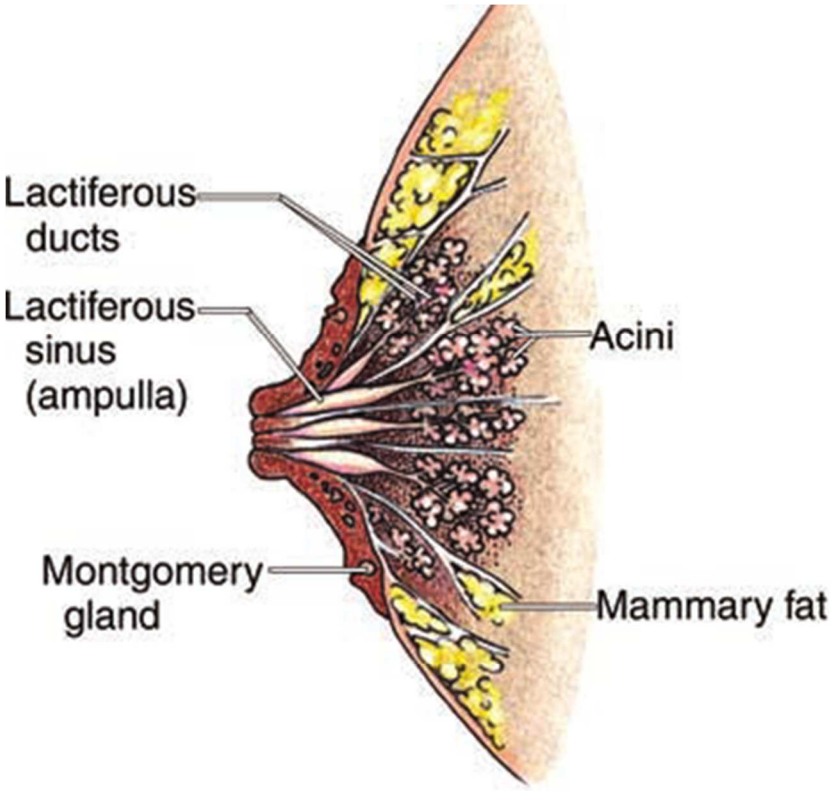
The breast is a collection of glands with fatty and fibrous tissues interspersed with the glands. The mass is freely mobile on the top of the pectoral muscles that form the part of the chest wall. They are attached to the underlying chest wall by Cooper's ligaments that are fibrous strands. The soft consistency of the breast comes from the fatty composition of the breast.

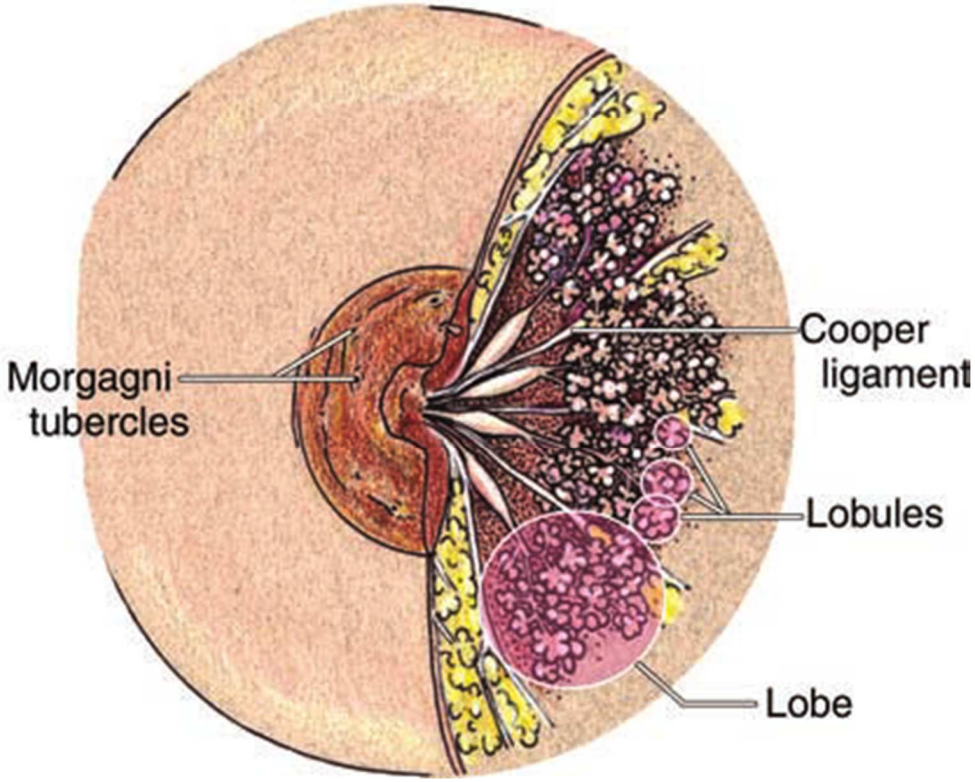


The glands of the breast contain the lobules and ducts. Lobules are milk producing glands that are present at the end of the lobes while the ducts are milk passages. As

the duct approaches the nipple, it enlarges into a sac called the ampulla. When a woman is lactating, the lobules produce milk that are carried by ducts to the nipples. Thus, a breast contains the following;

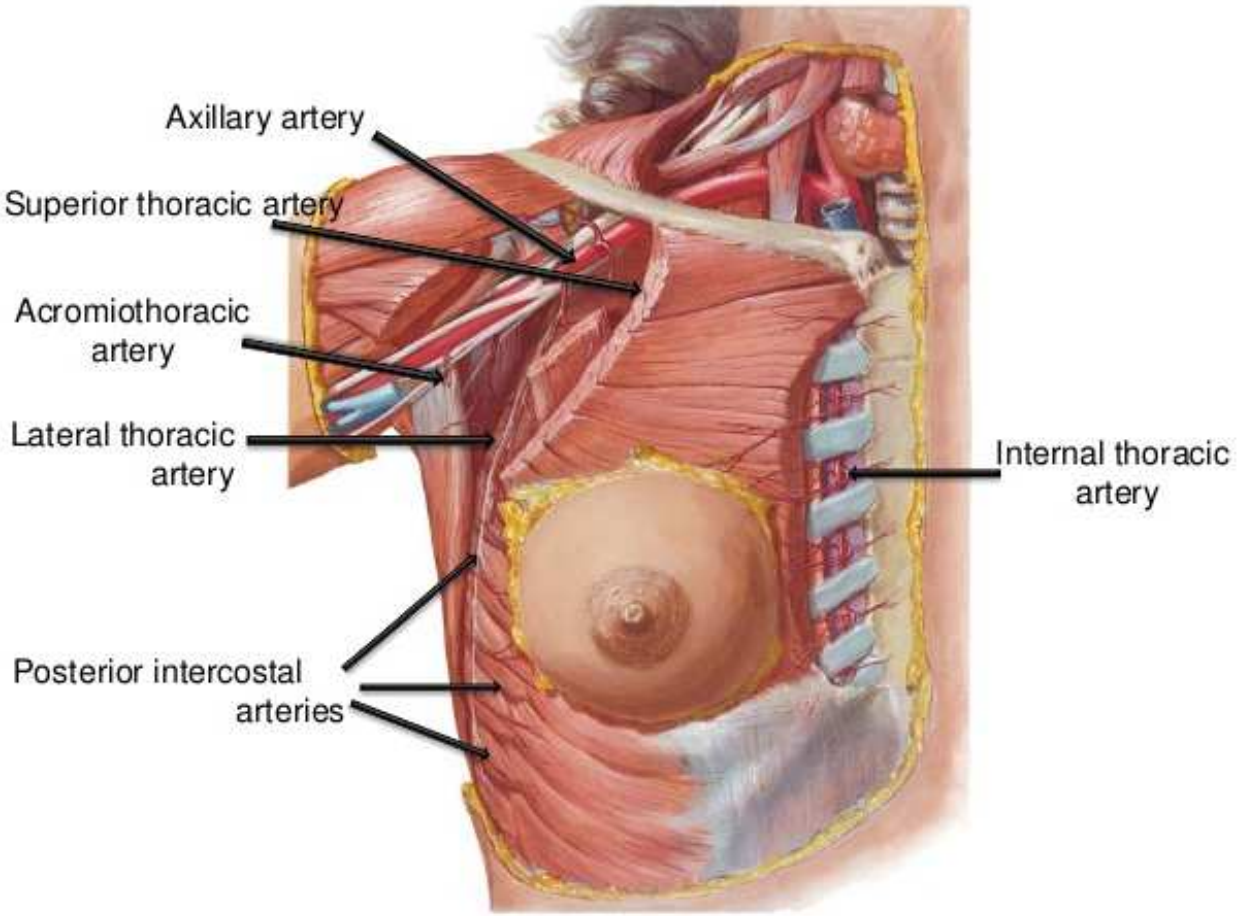
a) Lobules or milk glands that produce milk
b) Ducts
c) Nipple
d) Areola (the area surrounding the nipple that is pink or brown in colour with pigmentation)
e) Fat
f) Fibrous connective tissue surrounding the ducts and lobules

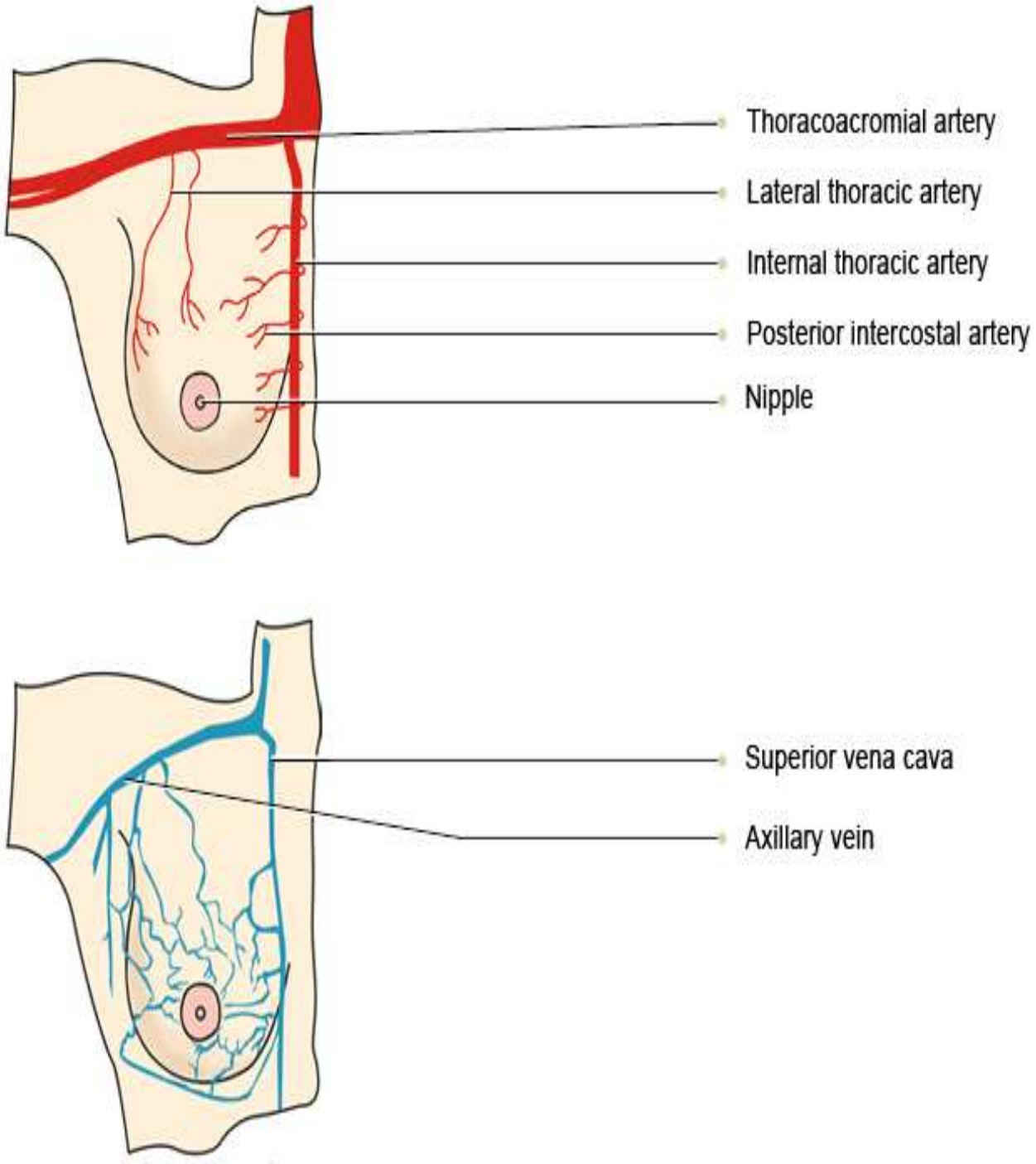

Lactiferous ducts
Lactiferous sinus (ampulla)
Acini
Montgomery gland
Mammary fat


Morgagni tubercles
Cooper ligament
Lobules
Lobe

Arterial Supply and Venous Drainage

The following image shows the blood supply of the breast. The axillary artery extends from the armpit and supplies blood to the outer half of the breast while the internal mammary artery starts from the neck and supplies the interior part of the breast.

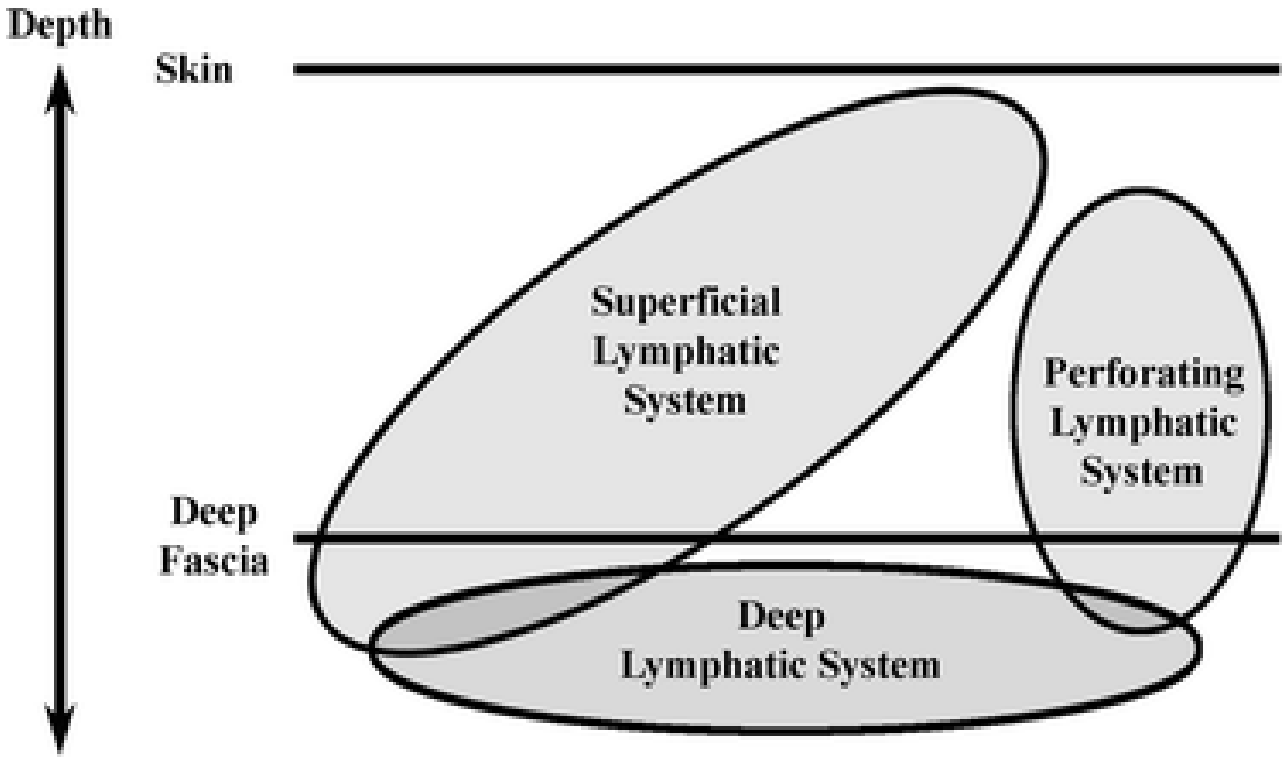


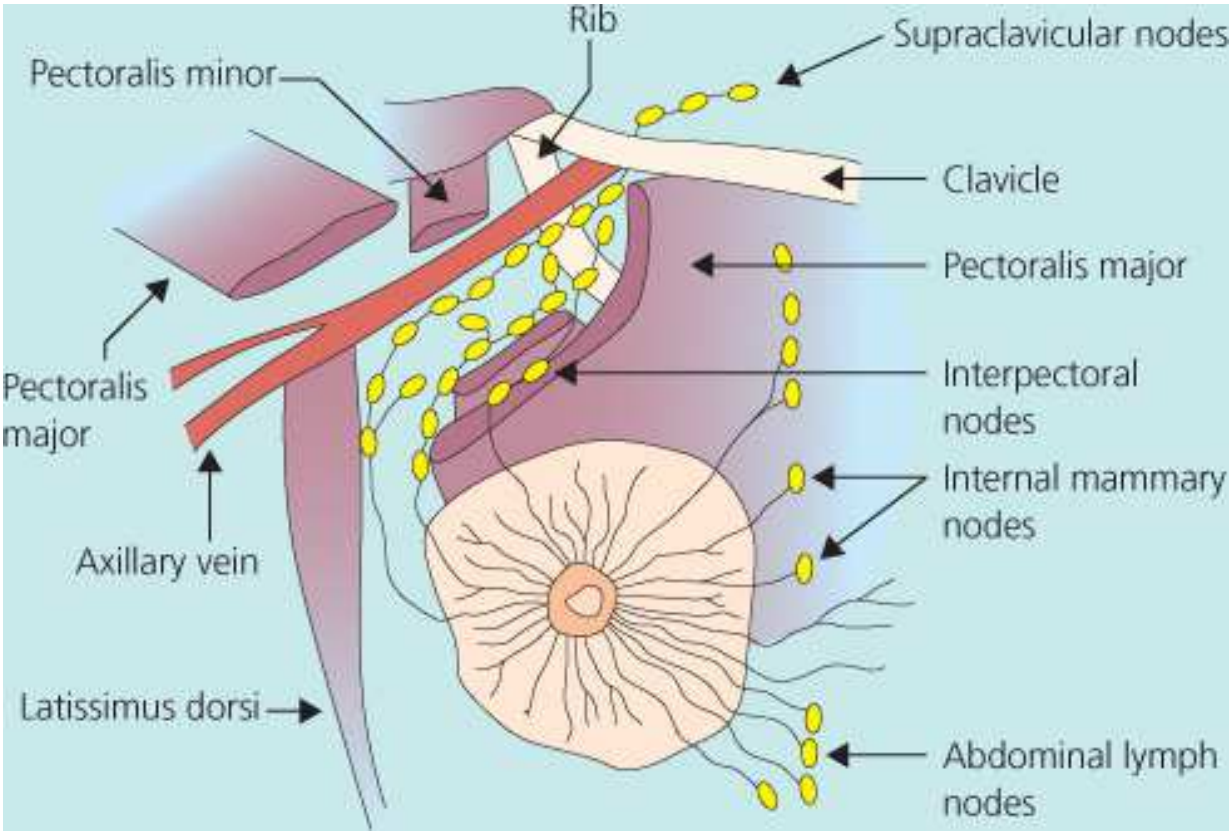


The venous drainage is through the axillary vein into the superior vena cava.

Lymphatics

The important aspect of breast anatomy is the lymphatic drainage. This is essential from the management perspective especially when they are involved in malignancy and metastasis. It forms an important component of staging. It contains superficial and deep lymphatic system. The following images show the lymphatic drainage of the breast.

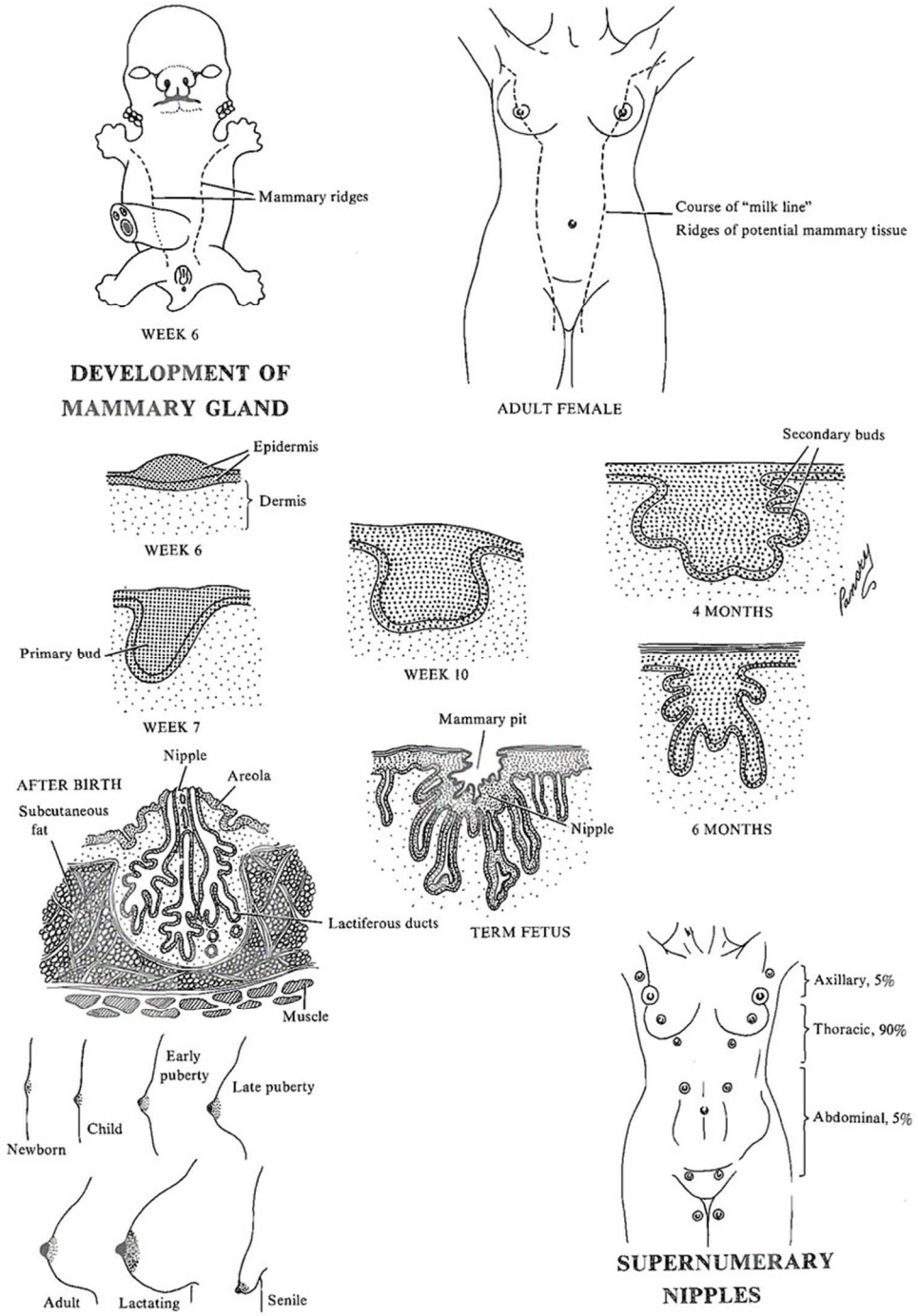


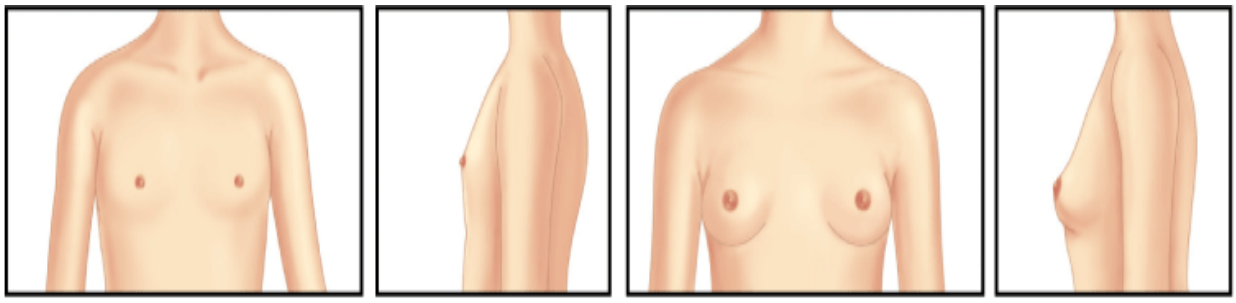


Development of breast

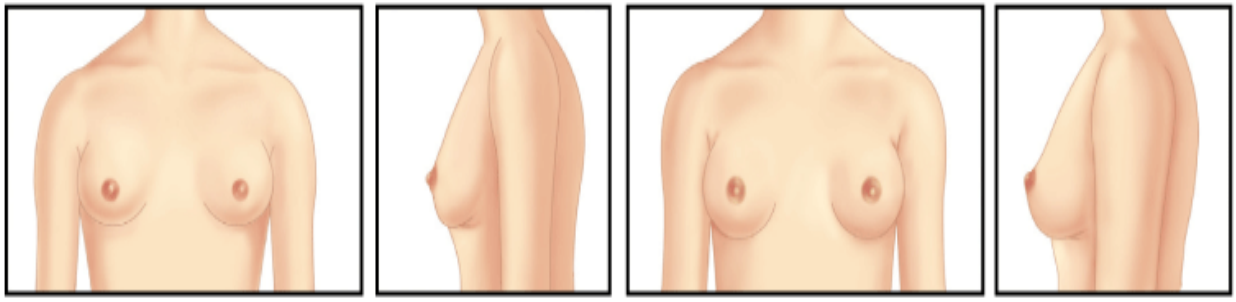
Breast comprises of galndular tissue that are a type of sweat gland but highly specialised. Towards the 5th and 6th intrauterine life, embryo shows mammary ridges that are thickened ectoderm. These ridges extend from the axilla to the inguinal region. Then mammary buds start developing as downgrowths of epidermis and penetrate the underlying mesenchyme. These ridges disappear as the fetus matures and when it persists, leads to accessory breasts and accessory nipples.

During puberty, there is an enlargement of the breast due to the deposition of fat and growth of the mammary glands.

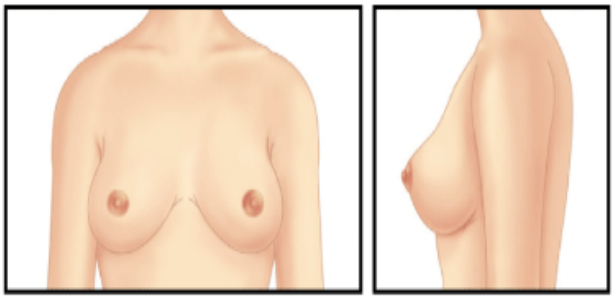




Stage 1 Stage 2



Stage 3 Stage 4



Stage 5

Stage 1 Preadolescent: juvenile breast with elevated papilla and small flat areola.

Stage 2 The breast bud forms under the influence of hormonal stimulation. The papilla and areola elevate as a small mound, and the areolar diameter increases.

Stage 3 Continued enlargement of the breast bud further elevates the papilla. The areola continues to enlarge; no separation of breast contours is noted.

Stage 4 The areola and papilla separate from the contour of the breast to form a secondary mound.

Stage 5 Mature: areolar mound recedes into the general contour of the breast; papilla continues to project.

Source: Patel DR, Greydanus DE, Baker RJ: *Pediatric Practice: Sports Medicine:* www.accesspediatrics.com

Benign breast conditions

Benign breast diseases are a group of disorders that are non-cancerous in nature. These disorders range from requiring no attention to those that require clinical interventions. They may be painful or painless. Some of the commonly encountered benign breast diseases are cysts, fibroadenomas and hyperplasias. Hormones play an important role as a risk factor. Genetic causes like BRCA1 and BRCA2 mutations are also known.

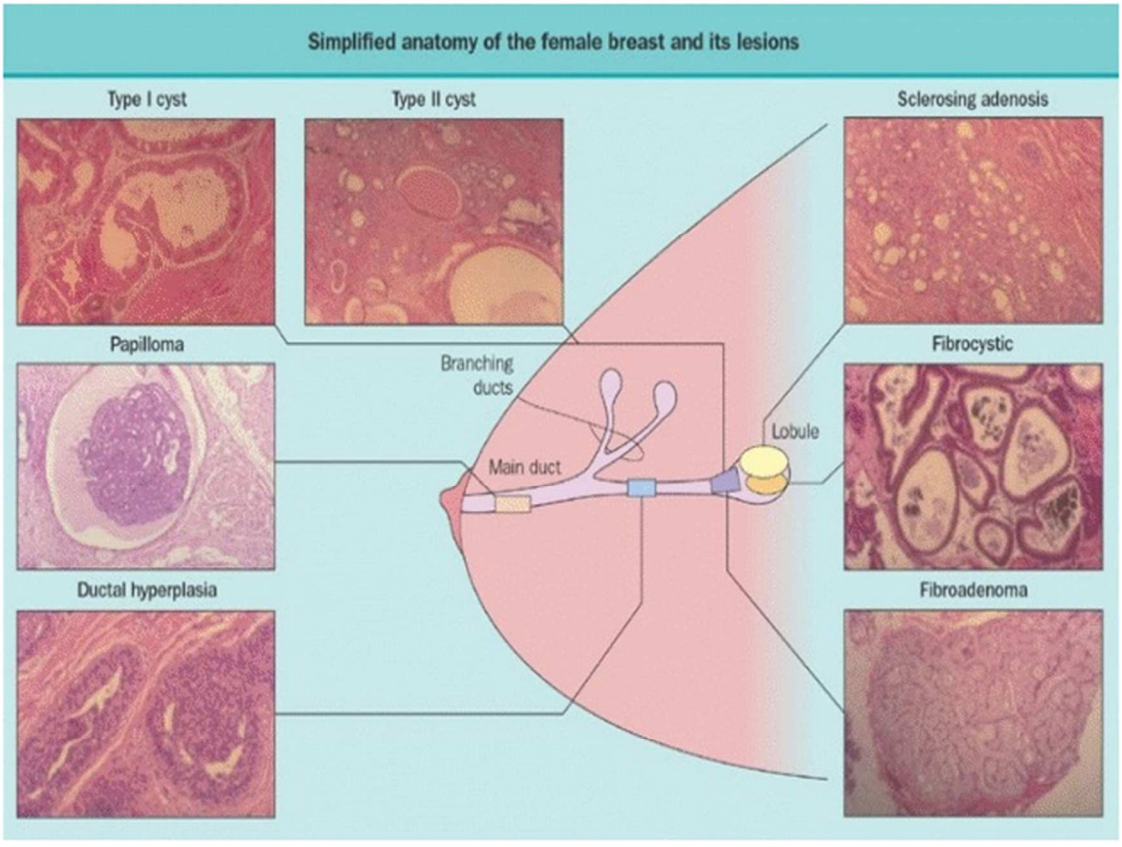


Figure 2 Simplified anatomy of the female breast illustrating the major structural components of the breast, the anatomic location of various lesions, and the histology of those lesions and corresponding sites of origin of potential lesions.

Hyperplasia

The excessive accumulation and build up of cells which is typically found in the lobules and ducts are known as hyperplasia.

Cysts

These are fluid filled sacs that are palpable and painful at times. The etiology of these cysts are unknown though hormonal changes are implicated.

Fibroadenomas

These are benign lumps of the breast that have almost no cancerous potential.

Sclerosing Adenosis

This is common in women in their 30s that present as small nodules. Histologically, it comprises of elongated and distorted cells. The risk of carcinoma is high with sclerosing adenosis.

Radial Scars

These lesions are usually incidental findings in the breast tissue that was biopsied for tumor.

Intraductal papillomas

These small projecting mass are present in the lactiferous ducts of the breast which may present with nipple discharge.

Other conditions that are worth mentioning are Benign Phyllodes Tumor and Sclerosing Lymphocytic Lobulitis.

Etiology of benign breast diseases

Due to high prevalence of benign breast diseases and their impact on the quality of life of a woman, they are clinically as well as culturally significant. The clinical importance is further augmented by the proclivity of the benign breast disease towards transforming into a neoplasm. From the epidemiologist and clinician's point of view, it is essential to understand the etiology and the pathogenesis of the disease in addition to the understanding of the risk factors for designing preventive strategies of the disease. The research on benign breast disease is not new as we have the luxury of having a wide knowledge database about the disease. Multiple systematic reviews have been done to summarise and sort the wealth of accumulated knowledge right from etiology till treatment including histopatholoy and molecular biology.

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-cystic disease

-cystic hyperplasia

-epithelial dysplasia

-mastopathia

The histologic analysis shows that the lesions arise from the epithelium. On the other hand, the microscopic analysis reveal microcysts and macrocysts either alone or in conjunction with papillomas, adenosis, epitheliosis, apocrine epithelium and papillomatosis. Schnitt and Conolly elaborated on this nomenclature.

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a) They vary in size from being microscopic to macroscopic and present as an apparent lesion

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c) They are round to ovoid in shape

Haagensen defined gross cyst as a derivation of the end of the ductal lobular unit presenting as a palpable mass. There are two layers of the epithelium namely epithelial layer (inner) and myoepithelial layer (outer). Cysts may be associated with hyperplasia or metaplasia. In metaplasia, the normal epithelium transforms into the type of epithelium present in apocrine glands. In hyperplasia, it can be either adenosis or epitheliosis. Adenosis is the condition where a new ductal or lobular structures are developed accompanied with the proliferation of myoepithelial or epithelial cells. In sclerosing adenosis, there is a predomination of myoepithelial cells. When there are papillae present, it is called as papillomatosis.

Table 2. Common Benign Breast Disorders in Women.

Symptom or Finding	Possible Causes or Disorders
Breast pain	
Cyclic pain	Hormonal stimulation of normal breast lobules before menses
Noncyclic pain	Stretching of Cooper's ligaments Pressure from brassiere Fat necrosis from trauma Hidradenitis suppurativa Focal mastitis Periductal mastitis Cyst Mondor's disease (sclerosing periphlebitis of breast veins)
Nonbreast pain	
Chest-wall pain	Tietze's syndrome (costochondritis) Localized lateral chest-wall pain Diffuse lateral chest-wall pain Radicular pain from cervical arthritis
Non–chest-wall pain	Gallbladder disease Ischemic heart disease
Nipple discharge	
Presence of galactorrhea	
From multiple ducts bilaterally	Hyperprolactinemia from pituitary tumor, hypothyroidism, drugs*
Absence of galactorrhea	
From one duct — elicited or spontaneous and bloody, with occult blood, or serosanguineous	Intraductal papilloma Ductal carcinoma in situ Paget's disease of breast
From multiple ducts — elicited and bloody or nonbloody, bilateral, black or clear	Fibrocystic changes Ductal ectasia
Discrete solitary lump	
Age <30 yr	
Firm, rubbery lump	Most common lesion: fibroadenoma
Age 30–50 yr	
Firm, discrete lump	Most common lesions: fibroadenoma, cyst, fibrocystic changes, usual ductal hyperplasia, atypical ductal hyperplasia, atypical lobular hyperplasia†
Age >50 yr	
Firm, discrete lump	Most common lesions: cyst, ductal carcinoma in situ, invasive cancer
Diffuse lumpiness ("lumpy-bumpy")	
Absence of discrete lump	Fibrocystic changes

It is often periodically related to hormonal influences from the menstrual cycle. The changes in fibrocystic breast disease are characterised by the appearance of fibrous tissue and a lumpy, cobblestone texture in the breasts. These lumps are smooth with defined edges, and are usually free-moving in regard to adjacent structures, The lumps are more often found in the upper, outer sections of the breast (nearest to the armpit), but can be found throughout the breast. Women with fibrocystic changes may experience a persistent or intermittent breast aching or breast tenderness related to periodic swelling. Breasts and nipples may be tender or itchy. Symptoms follow a periodic trend tied closely to the Menstrual cycle. Symptoms tend to peak in the days and, in severe cases, weeks before each period and decrease afterwards. At peak, breasts may feel full, heavy, swollen, and tender to touch. No complications related to breastfeeding have been found.

The exact mechanism of the condition is not fully understood, though it is known to be tied to hormone levels, as the condition usually subsides after menopause and is also related to the menstrual cycle. Post-menopausal women placed on hormone replacement therapy (HRT) have also reported symptoms of fibrocystic disease of breast indicating that hormones may play a role. Fibrocystic breast changes is a cumulative process caused partly by the normal hormonal variation during a woman's monthly cycle. The most important of these hormones are oestrogen and progesterone. These hormones directly affect the breast tissues by causing cells to

grow and multiply. Many other hormones such as TSH, insulin, growth hormone and growth factors such as TGF-beta exert direct and indirect effects amplifying or regulating cell growth. Years of such fluctuations eventually produce small cysts and/or areas of dense or fibrotic tissue.

Diagnosis and Prognostic Factors- An overview

Mammography is usually the first imaging test to be ordered when unusual breast changes have been detected during a physical examination. Ultrasound of the breast is commonly performed in conjunction with mammographies.

Risks- Except for patients with a strong family history of breast cancer, where the risk is two-fold, nonproliferative lesions have no increased risk. Proliferative lesions have approximately a 2-fold risk

Clinical examination of the breast in benign breast conditions

Clinical examination of the breast is characterised by detailed history taking, followed by the traditional inspection, palpation and other parameters like mammogram, FNAC, etc. The tests of palpation, imaging and biopsy is known as Triple test.

Table 3. Clinical Examination of a Patient with Benign Breast Disease.

History

Characterize symptoms

Identify risk factors for breast cancer
- Age
  - At menarche
  - At first live birth
- Number of relatives with breast cancer or ovarian cancer
  - Age at diagnosis
- Number of previous breast biopsies
- Presence of atypical hyperplasia or lobular carcinoma in situ on previous breast biopsy
- Weight gain after menopause
- Waist-to-hip ratio
- Results of bone-density testing

If patient is postmenopausal
- Age at menopause
- Duration of use of estrogen or progestin therapy

Physical examination

Palpate the four breast quadrants while patient is sitting and lying down
- Identify discrete lumps and examine for regional nodes
- Determine whether consistency is doughy with vague nodularity — findings consistent with fibrocystic changes
- Determine whether a discrete lesion has distinctly marginated borders — a finding consistent with fibroadenoma

Examine overlying skin, areola, and axilla

Determine degree of symmetry (asymmetry suggests underlying disease)

Examine nipple and seek to elicit discharge
- Determine whether galactorrhea is present
- Determine whether discharge is from one duct or from multiple ducts
- Determine whether discharge is viscous, watery, serosanguineous, grossly bloody, clear, blue–black, or green
- Determine whether occult blood is present

Seek to elicit chest-wall pain
- Examine costochondral junctions (Tietze's syndrome)
- Examine lateral chest wall while patient is lying on her side (at 90 degrees), to move breast away from chest wall
- Compare pain elicited by squeezing breast tissue with pain elicited by palpation of chest wall

Management of benign breast conditions

The gold standard treatment for benign breast conditions have been under study for a long time. Studies how that Tamoxifen, Danazol and Bromocriptine are effective while the treatment using Linoleic acid as primrose oil is still uncertain due to the failure in a large trial. Iodine and vaginal progesterone are considered to b effective while Vitamin E is ineffective. One of the drawbacks is the lack of generalised multi centric trials for finding out the efficiency of caffeine avoidance, progesterone and Medroxyprogesterone acetate. Pain relief is brought about by well-fitted bras. A temporary post-menopausal state can be reached by using GnRH agonist analogues. Menopause is therapeutic in managing breast pain. The following image shows the effectiveness of various treatments. Lack of data or single center studies is a major limitation of these studies.

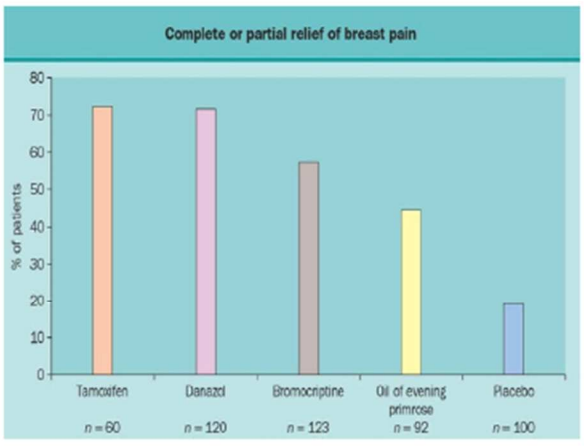


Figure 15

Relative efficacy of agents to treat breast pain. These data are from the Breast Clinic in Cardiff, Wales and represent observational studies and not randomized, controlled efficacy trails.

The role of Tamoxifen in breast disease- what do published literature say?

World Health Organisation have enumerated Tamoxifen as a necessary ingredient in the treatment protocol of breast cancer. Since a quarter of a century, it is been used as the gold standard endocrine method of treating oestrogen-receptor-positive breast cancer, irrespective of staging. Tamoxifen is known to have saved the lives of around 400,000 women apart from the large number of women who received palliative care and improved quality of life post surgery. It is also the first drug to be approved by the Food and Drug Administration (FDA) as cancer chemopreventive in women who were at higher risk. It is known to reduce the incidence of cancer in premenopausal as well as post menopausal women.

When given as an adjuvant therapy, Tamoxifen is known to be effective in decreasing the recurrence of breast cancer and thereby death. Even in patients with metastasis, it provides adequate palliation. This explains why Tamoxifen is used in both premenopausal and postmenopausal women provided their neoplastic tissue is estrogen receptor positive. The only exception being made on the basis of prognostic factors and with very low risk of dissemination.

For postmenopausal women who present with metastatic breast cancer, tamoxifen is the first treatment of choice in the list of hormonal therapy. The drug is well tolerated and is known to be safe. Even in younger women, it is the used as a first

or second choice drug, the risk of endometrial cancer being present. Another reason for preference of Tamoxifen and a number of randomised trials studying its use is the positive effects of the drug on bone density, risk of contra lateral breast cancer and cardiovascular mortality.

In a recent study conducted by Tan-Chiu et al in 2003, it is found that Tamoxifen treatment reduces the risk of benign breast disease by 28%. Tamoxifen was found to be effective in reducing pain in women with: cyclical mastalgia and also to a lesser degree in women with non cyclical mastalgia. Women who received Tamoxifen had a 29% reduction in undergoing biopsies. Adverse effects were reported more frequently with Tamoxifen 20 mg than with Tamoxifen 10mg. However, the overall side effects were reported only in minority of the population. Reported adverse effects included an increase in weight, menorrhagia, hot flashes and vaginal discharge Tamoxifen is a selective estrogen receptor modulator class of drugs that is used to prevent breast cancer in women and men.lt is also being studied for other types of cancer. It is currently used for the treatment of both early and advanced estrogen receptor positive(ER-positive)breast cancer in pre-and post menopausal women. It has been further approved for the reduction of contra lateral cancer. Tamoxifen is also used for the treatment of infertility, gynecomastia, Albright syndrome and other rare conditions of retroperitoneal fibrosis and idiopathic sclerosing mesenteritis.

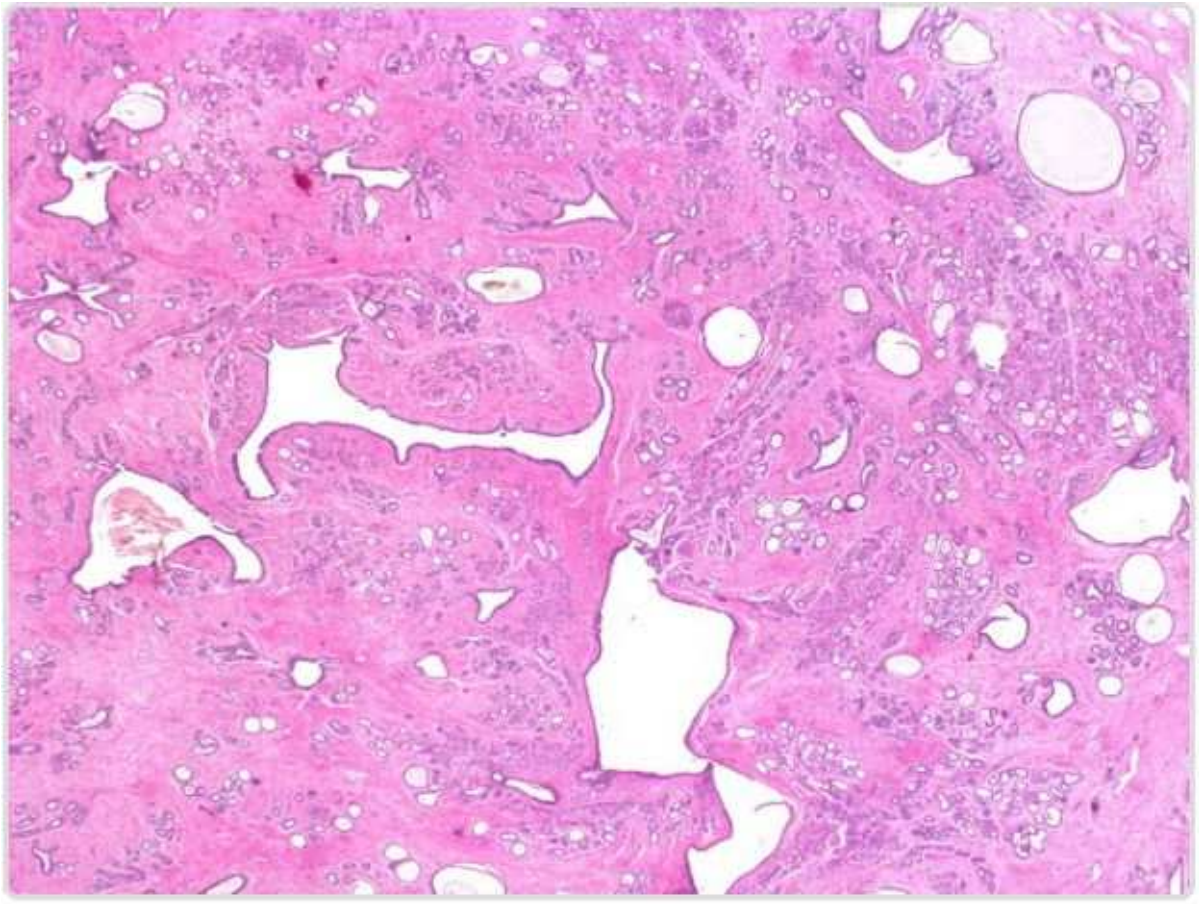
The correlation between benign breast disease and risk of breast carcinoma.

Studies show that there is a relationship between benign diseases of the breast and cancer risk mainly based on their morphological subtypes. The risk severity varies between different histologic subtypes. Proliferative lesions with atypia are known to be having 1.5 to 2-fold risk of getting cancer. There are a number of factors associated with these lesions that determine the progress to cancer namely;

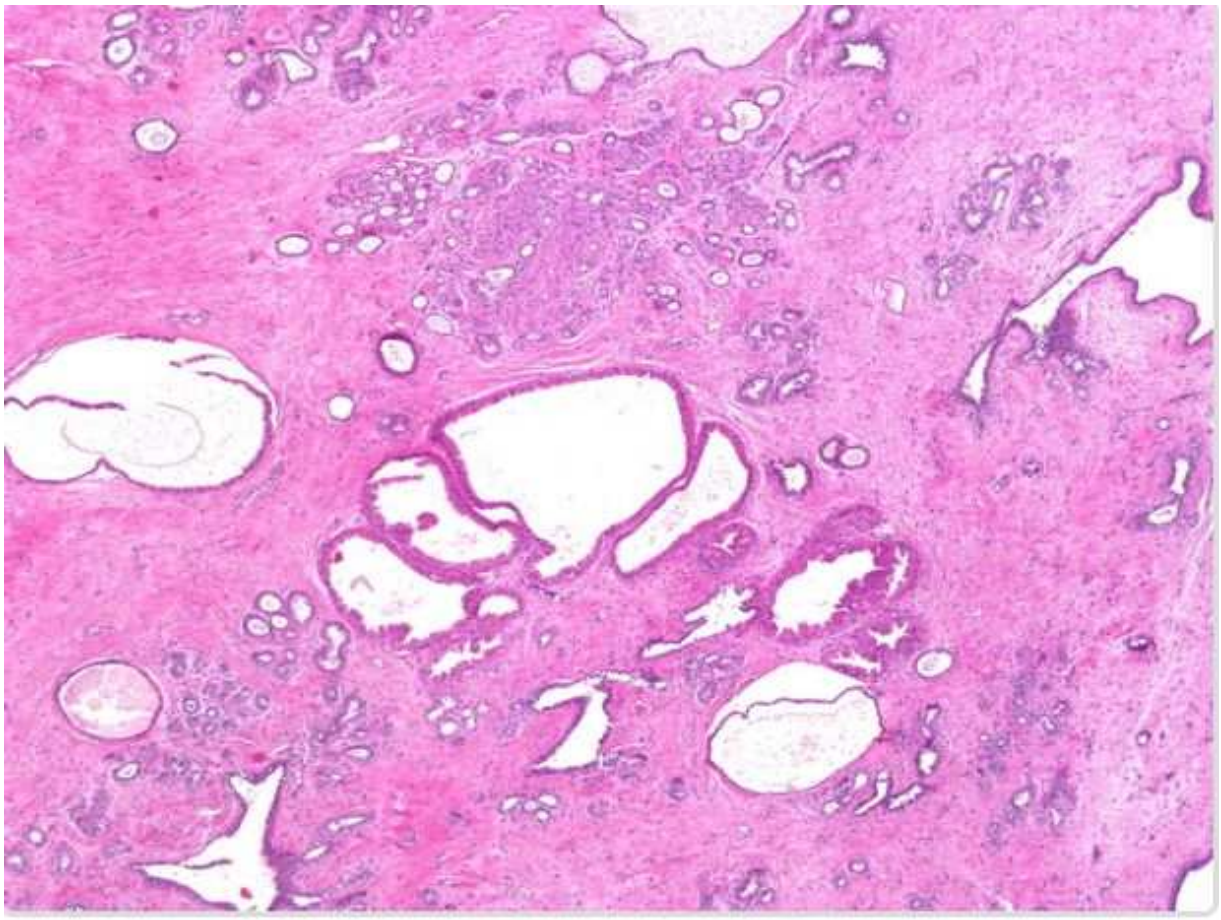
7. type of atypical hyperplasia
8. time since biopsy
9. menopausal status
10. family history
11. postmenopausal hormone use
12. presence of other benign lesions

Fibrocystic Change : Gross Pathology and Histologic features

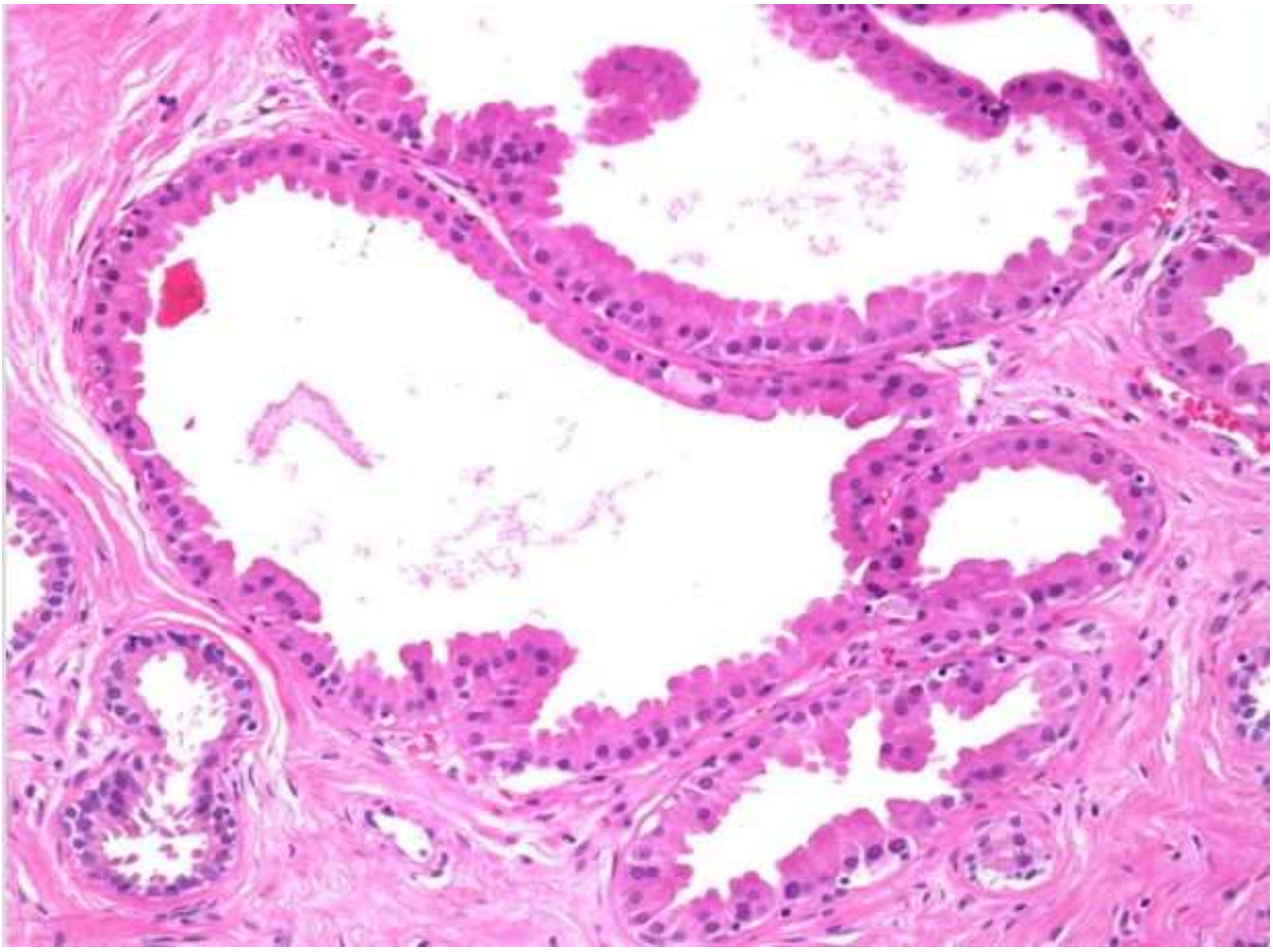
The cut surface of **fibrocystic change** is characterized by **variably-sized cysts scattered in fibrotic breast tissue**. The cysts are filled with straw-colored to dark brown fluid. Given their appearance when intact, the larger cysts are referred to as **blue dome cysts**.



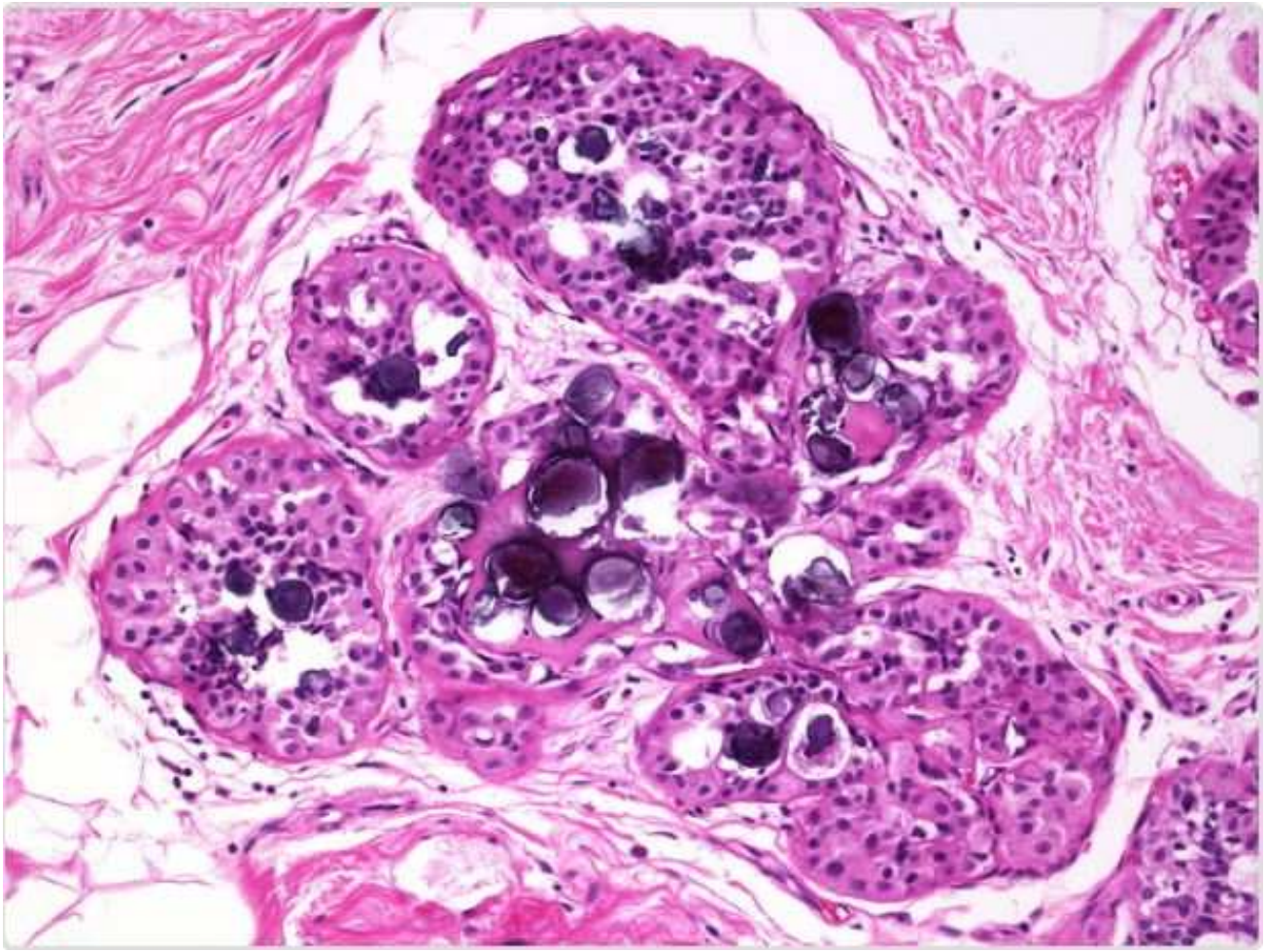
The importance of fibrocystic change lies in its ability to **mimic clinical, radiographic, gross, and microscopic features of carcinoma**. It is seen most frequently **between the ages of 25 and 45 years**. The image shows numerous **variably sized cysts** surrounded by foci of adenosis.



Some of the larger cysts in fibrocystic change may have a bluish appearance from outside (**blue-domed cysts**). The **cyst lining is flattened or absent** in some cases. In the center of this image, cysts are lined by **apocrine epithelium**. Note the focus of adenosis above it.



Apocrine metaplasia is a **frequent finding** in fibrocystic change. The lining cells have **abundant eosinophilic granular cytoplasm, prominent nucleolus and apocrine snouts**. Immunostain for **GCDFP-15** is **strongly positive**. Presence of cytologic atypia in apocrine metaplasia is not a risk factor for carcinoma.



Microcalcifications tend to be less common in fibrocystic change than in carcinoma. They tend to be **coarse and irregular**.

MATERIALS

AND METHODS

Materials and Methods

Aims and objectives of the study:

To assess the effectiveness of Tamoxifen in fibrocystic disease(benign breast disease) of the breast.

Study design

Comparative Prospective Single Center Study

Place of study

Department of General surgery, Government Stanley Medical College

Study period

September-2018 to September- 2019

Study population & Sampling Methodology

1) Patients who are diagnosed with fibrocystic breast disease are recruited from the surgery department

2) Based on the lottery method, consecutive patients are randomised into two groups

3) Each group contains 20 patients

4) Total sample size=40

Inclusion criteria:

1) Newly diagnosed patients with fibrocystic disease of the breast

2) Age group of 20-40 years.

Exclusion criteria:

1. Patients who had received Tamoxifen drugs
2. Age group <20 and >40 years
3. Post hysterectomy patients
4. Post menopausal patients
5. Ovarian cancer patients
6. Endometrial cancer patients
7. Endometrial hyperplasia patients
8. Pregnancy
9. Patients planning for pregnancy
10. Patients unwilling to undergo treatment

Methodology

There will be two groups;

Group A: Consisting of patients receiving

Tamoxifen (10mg OD from 5th day to 25th day of menstrual cycle for a period of 3 months)

Group B: Consisting of patients receiving

Standard treatment evening primrose 1000 mg BD daily for 3 months)

- Patients who are newly diagnosed with fibrocystic disease of the breast either by USG breast, X-RAY mammogram, FNAC of the breast will be taken up for the study.
- USG of the breast will be used to ascertain the size of the lump at the beginning of the therapy
- A repeat USG of the breast will be done after completing 3 months of the proposed treatment to record the post treatment lump size.
- The difference between the two lump sizes will be recorded.

All patients will be categorized before receiving treatment as

GRADE 1-no pain

GRADE 2-mild pain

GRADE 3-moderate pain,

GRADE 4a-severe pain without effecting daily activities

GRADE 4b-severe pain effecting daily activities

After completing the proposed treatment patients will be asked for the effectiveness of the drug in reducing the pain which will be expressed in terms of CARDIFF BREAST PAIN SCORE(CBS);

CBS I-excellent response with no pain,

CBS II-substantial response

CBS III-poor response

CBS IV-no response.

Investigations

a. HB%, TC, DC, ESR.

b. Blood urea, Serum creatinine, Blood sugar.

c. Blood grouping and Rh typing.

d. BT, CT.

e. Urine routine examination.

f. Screening for HIV, Hbs Ag and VDRL after informed consent

g. Specific Investigations

1. USG BREAST
2. FNAC OF THE BREAST
3. X-RAY MAMMOGRAM

Statistical Analysis

Data were analyzed according to history, clinical examination and investigation. Data were entered in excel sheet and analyzed using SPSS v23. Frequencies and percentage analysis were done. Cross tabulation and Chi-square analyses were done to find the relationship and association between various variables.

Methods:

Reports of following formats were aggregated, data extracted and entered;

RESULTS

Results

The mean age of the Tamoxifen group is 35.15 years with a standard deviation of 4.79 years with a median of 37 years ranging from 25 years to 40 years. The mean age of the Primrose group is 31.20 years with a standard deviation of 3.98 years with a median of 30 years ranging from 26 years to 39 years. In the Tamoxifen group, the disease was present on the right side in eight patients and on the left side in twelve patients. In the Evening Primrose group, the disease was present on the right side in seven patients and on the left side in thirteen patients. All lesions were cystic in natureMajority (n=22) of the patients had grade 3 pain with 10 patients in the Evening Primrose group and 12 patients in the Tamoxifen group. The two groups are comparable and does not differ significantly in the grading of pain. Both the Groups received treatment for three months. The Cardiff Breast Pain Score was comparable between the two groups with no significant differences.The reduction in size of the lump was better in Tamoxifen group with 8 of them showing reduction whereas in the Evening Primrose group only three of them had a reduction in the size of the lump. The difference is statistically significant. Out of 20 patients in the Tamoxifen group, only two of them had side effects while five of them had side effects in the Evening Primrose group. Out of the two patients in the Tamoxifen group with side effects, one of them had Hot flashes while the other one

had Menorrhagia. Whereas in the Primrose group, three of them had headache and two of them had diarrhea.

Age Distribution of the two groups

The mean age of the Tamoxifen group is 35.15 years with a standard deviation of 4.79 years with a median of 37 years ranging from 25 years to 40 years. The mean age of the Primrose group is 31.20 years with a standard deviation of 3.98 years with a median of 30 years ranging from 26 years to 39 years.

	Tamoxifen Group	**Primrose Group**
N	20	20
Mean	35.1500	31.2000
Median	37.0000	30.0000
Mode	40.00	28.00[a]
Std. Deviation	4.79336	3.98154
Minimum	25.00	26.00
Maximum	40.00	39.00

Table 1: Age Distribution of the two groups

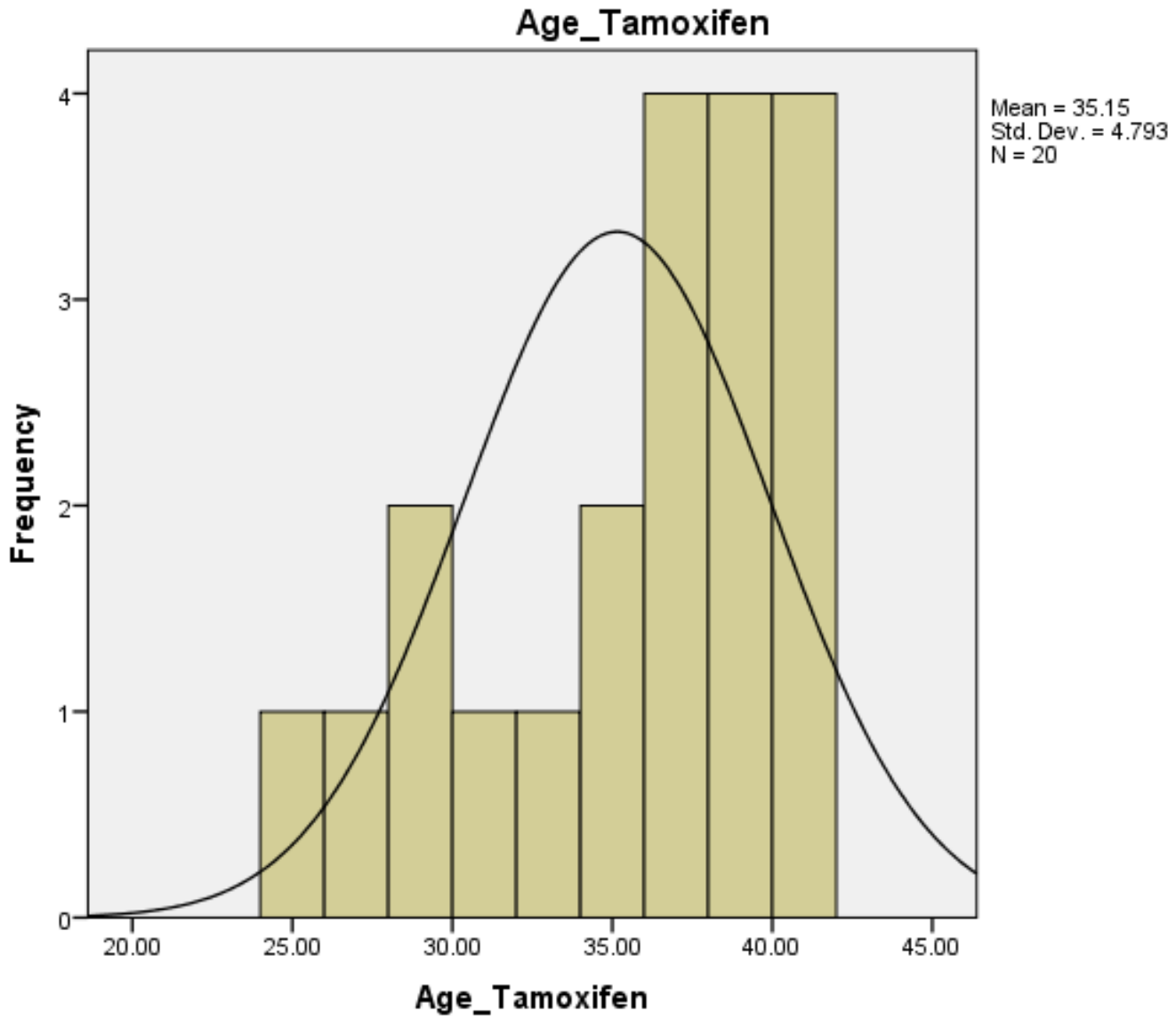


Figure 1: Age Distribution of Tamoxifen

Figure 2: Age Distribution of Primrose

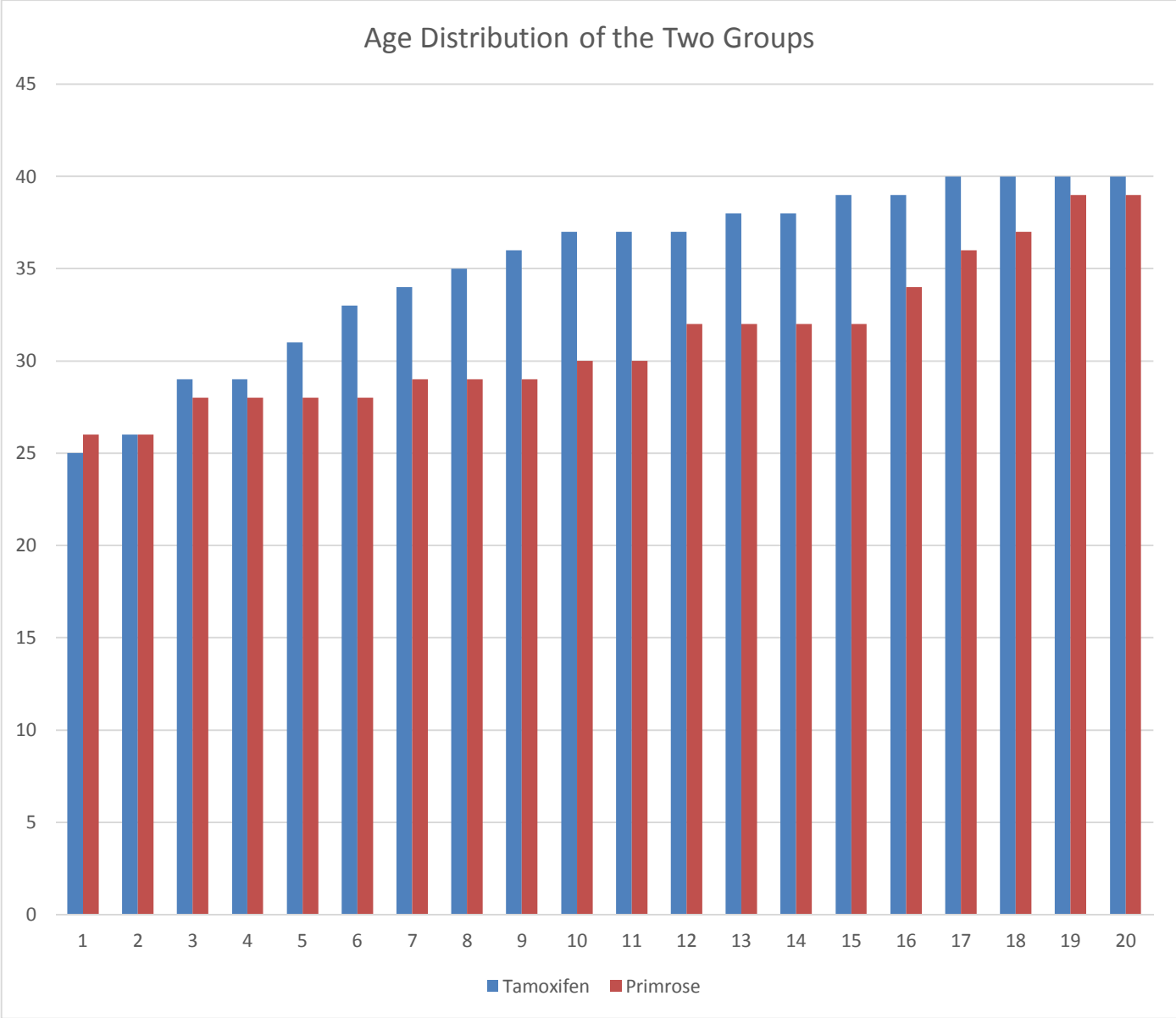


Figure 3: Age Distribution of the two groups

FNAC Diagnosis

In the Tamoxifen group, Fibroadenosis was present in 17 patients (right breast=5; left breast=12) and Fibrocystic disease right breast=3 patients. In the Evening Primrose group, Fibroadenosis was present in 12 patients (right breast=4; left breast=8) and Fibrocystic disease was present in eight patients (right breast=3 patients; left breast=5 patients).

FNAC DIAGNOSIS	TREATMENT RECEIVED		Total
	EVENING PRIMROSE 1000MG BD	TAMOXIFEN 10MG OD	
FIBROADENOSIS LEFT BREAST	8	12	20
FIBROADENOSIS RIGHT BREAST	4	5	9
FIBROCYSTIC DISEASE LEFT BREAST	5	0	5
FIBROCYSTIC DISEASE RIGHT BREAST	3	3	6
Total	20	20	40

Table 2: FNAC Diagnosis

FNAC Diagnosis- Tamoxifen Group

Figure 4: FNAC Diagnosis- Tamoxifen Group

FNAC Diagnosis- Primrose Group

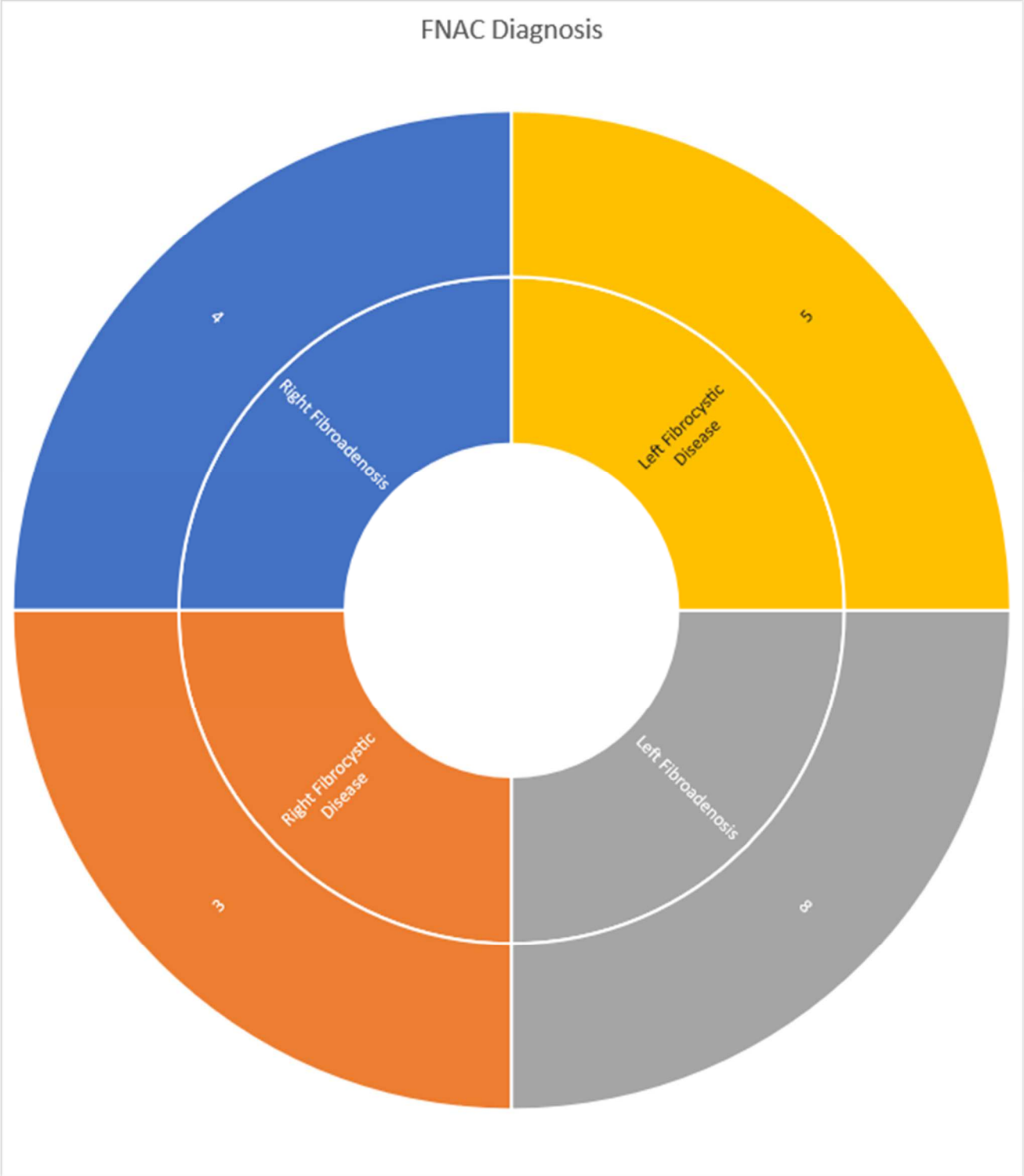


Figure 5: FNAC Diagnosis- Primrose Group

Ultrasound Diagnosis

All lesions were cystic in nature

Size of the lesion

The following table shows the size of the lesions.

SIZE	TREATMENT RECEIVED		Total
	EVENING PRIMROSE 1000MG BD	TAMOXIFEN 10MG OD	
0.8X0.8CM	1	0	1
1.1X0.8CM	1	0	1
1.1X0.9CM	0	1	1
1.3X1CM	1	0	1
1.5X1CM	0	1	1
1.8X1.2CM	1	1	2
1.9X1.2CM	1	0	1
1.9X1.7CM	1	0	1
1X0.7CM	1	0	1
1X0.8CM	4	2	6
1X0.9CM	1	0	1
1X1 CM	1	0	1
1X1CM	2	7	9
2.2X1.5CM	0	1	1
2.3X1.8CM	0	1	1
2.5X2CM	1	0	1
2X1.2CM	1	0	1
2X1.7CM	0	1	1
2X1CM	1	1	2
2X2CM	2	3	5
9.4X7.1MM	0	1	1
Total	20	20	40

Table 3: Size of the lesion

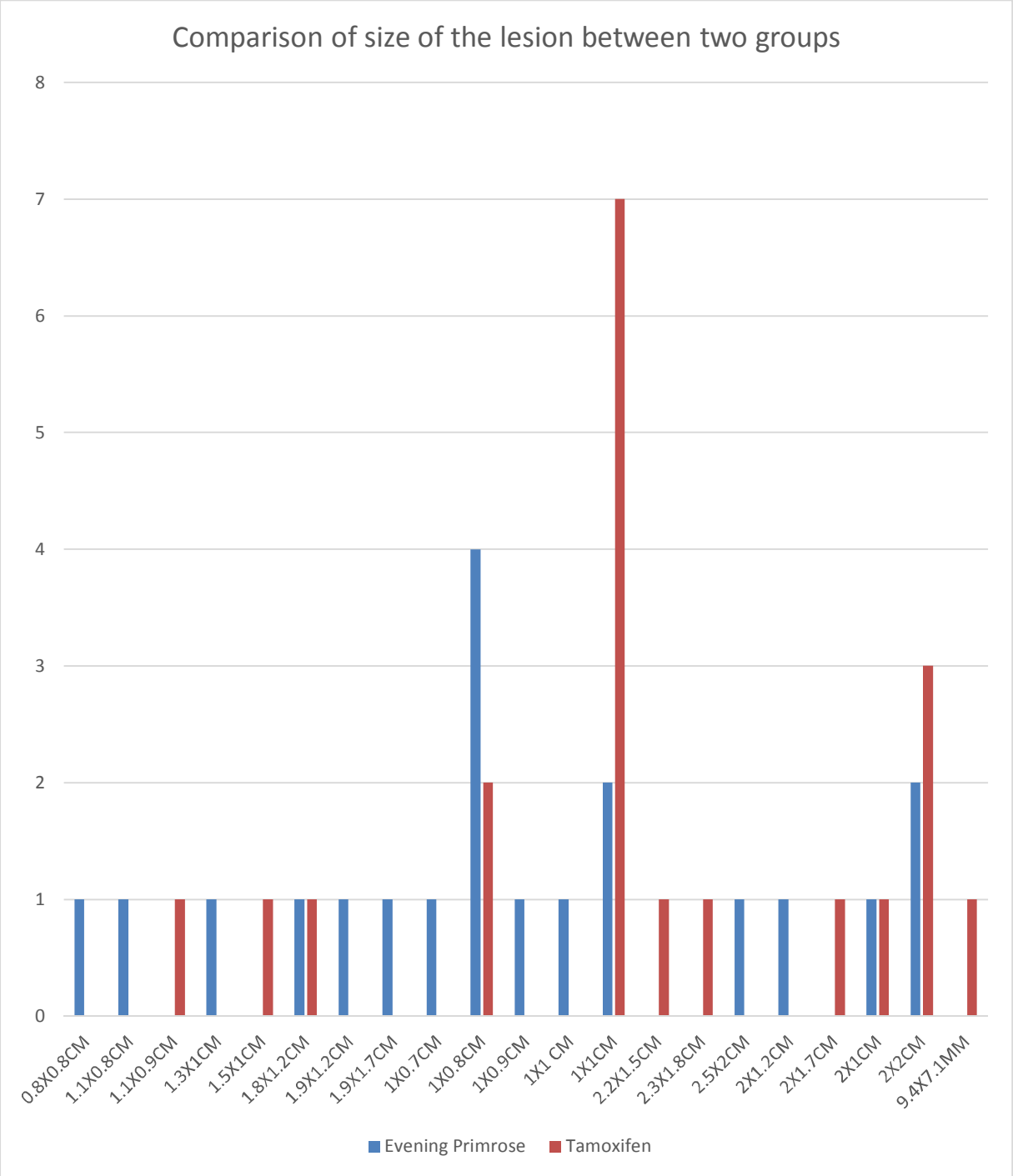


Figure 6: Size of the lesion

Position of the lesion

POSITION	TREATMENT RECEIVED		Total
	EVENING PRIMROSE 1000MG BD	TAMOXIFEN 10MG OD	
2 OCLOCK	3	0	3
2-3 OCLOCK	1	0	1
2-4 OCLOCK	0	2	2
3-4 OCLOCK	1	0	1
4 OCLOCK	0	1	1
4-5 OCLOCK	1	1	2
4-6 OCLOCK	1	0	1
6 OCLOCK	0	1	1
6-7 OCLOCK	1	1	2
6-9 OCLOCK	0	1	1
7 OCLOCK	2	0	2
7-9 OCLOCK	1	0	1
8 OCLOCK	4	4	8
8-9 OCLOCK	1	3	4
9 OCLOCK	2	2	4
9-10 OCLOCK	1	0	1
9-11 OCLOCK	1	4	5
Total	20	20	40

Table 4: Position of the lesion

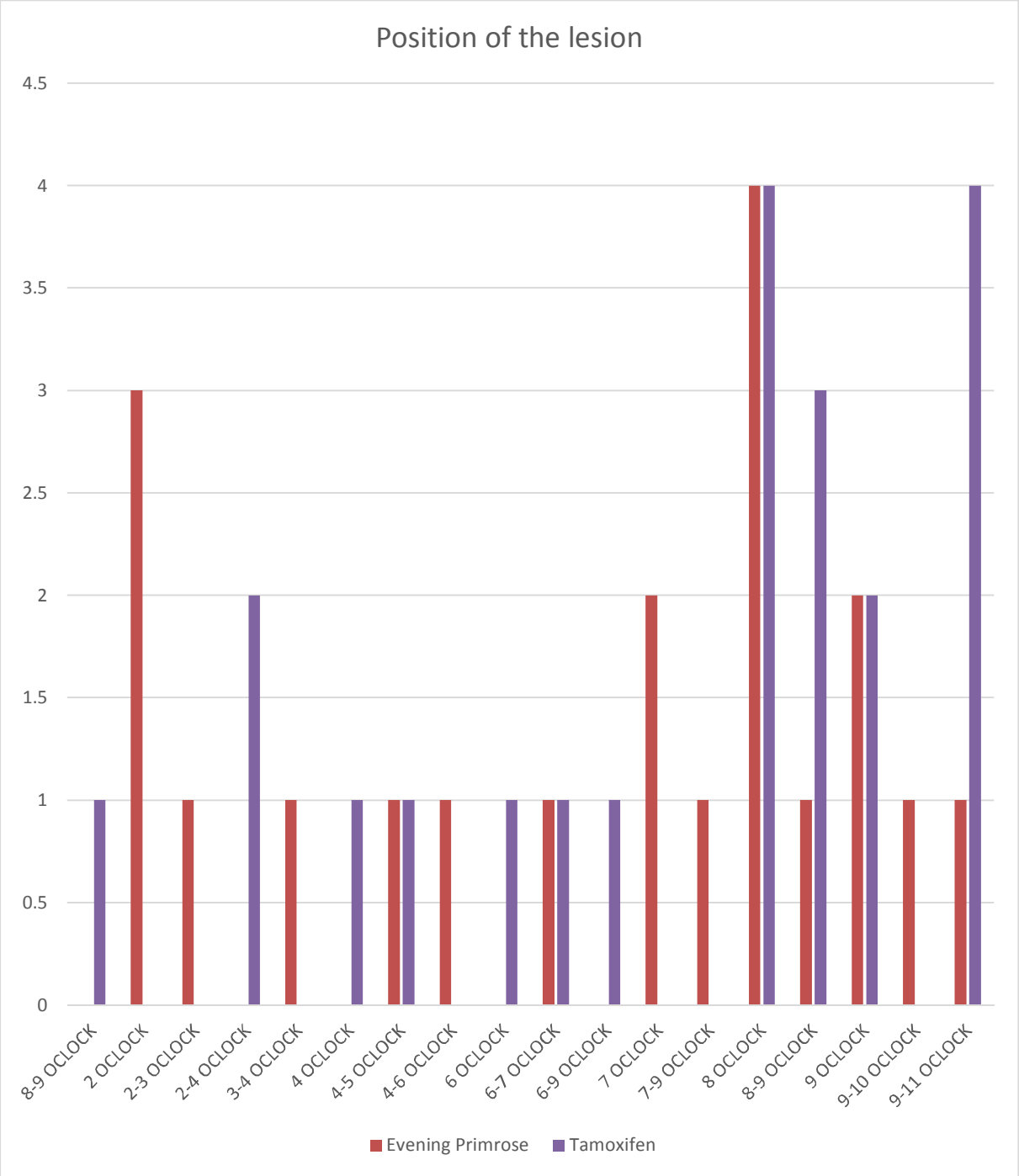


Figure 7: Position of the lesion

Grading of Pain

Majority (n=22) of the patients had grade 3 pain with 10 patients in the Evening Primrose group and 12 patients in the Tamoxifen group. The two groups are comparable and does not differ significantly in the grading of pain.

GRADING OF PAIN	TREATMENT RECEIVED		Total
	EVENING PRIMROSE 1000MG BD	TAMOXIFEN 10MG OD	
GRADE 1	1	0	1
GRADE 2	6	4	10
GRADE 3	10	12	22
GRADE 4	0	2	2
GRADE 4a	3	2	5
Total	20	20	40

Table 5: Grading of pain

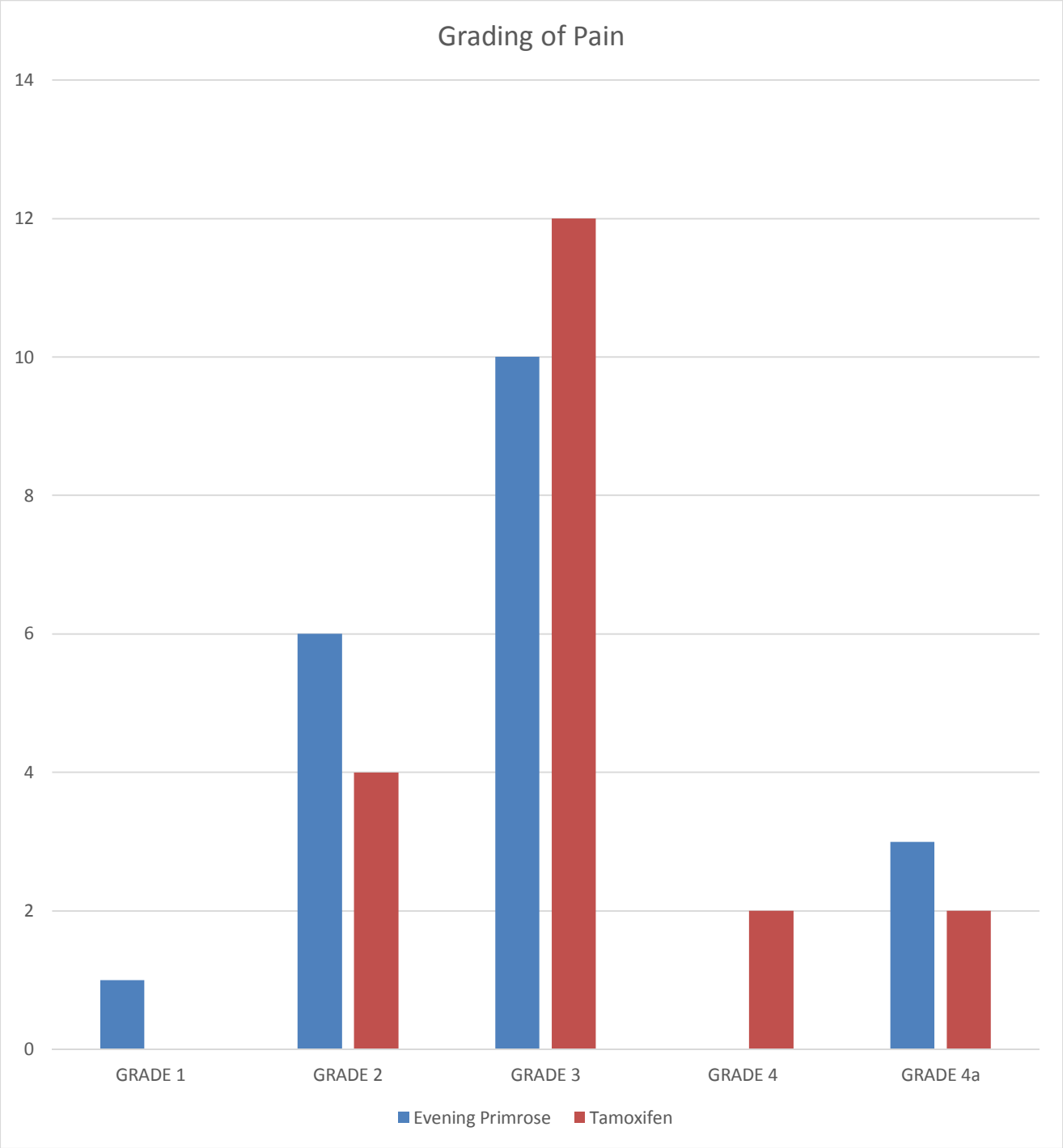


Figure 8: Grading of pain

Duration of Treatment Received

Both the Groups received treatment for three months

Cardiff Breast Pain Score

The Cardiff Breast Pain Score was comparable between the two groups with no significant differences.

Cardiff Breast Pain SCORE	TREATMENT RECEIVED		Total
	EVENING PRIMROSE 1000MG BD	TAMOXIFEN 10MG OD	
1.0	4	4	8
2.0	5	9	14
3.0	5	4	9
4.0	6	3	9
Total	20	20	40

Table 6: Cardiff Breast Pain Score

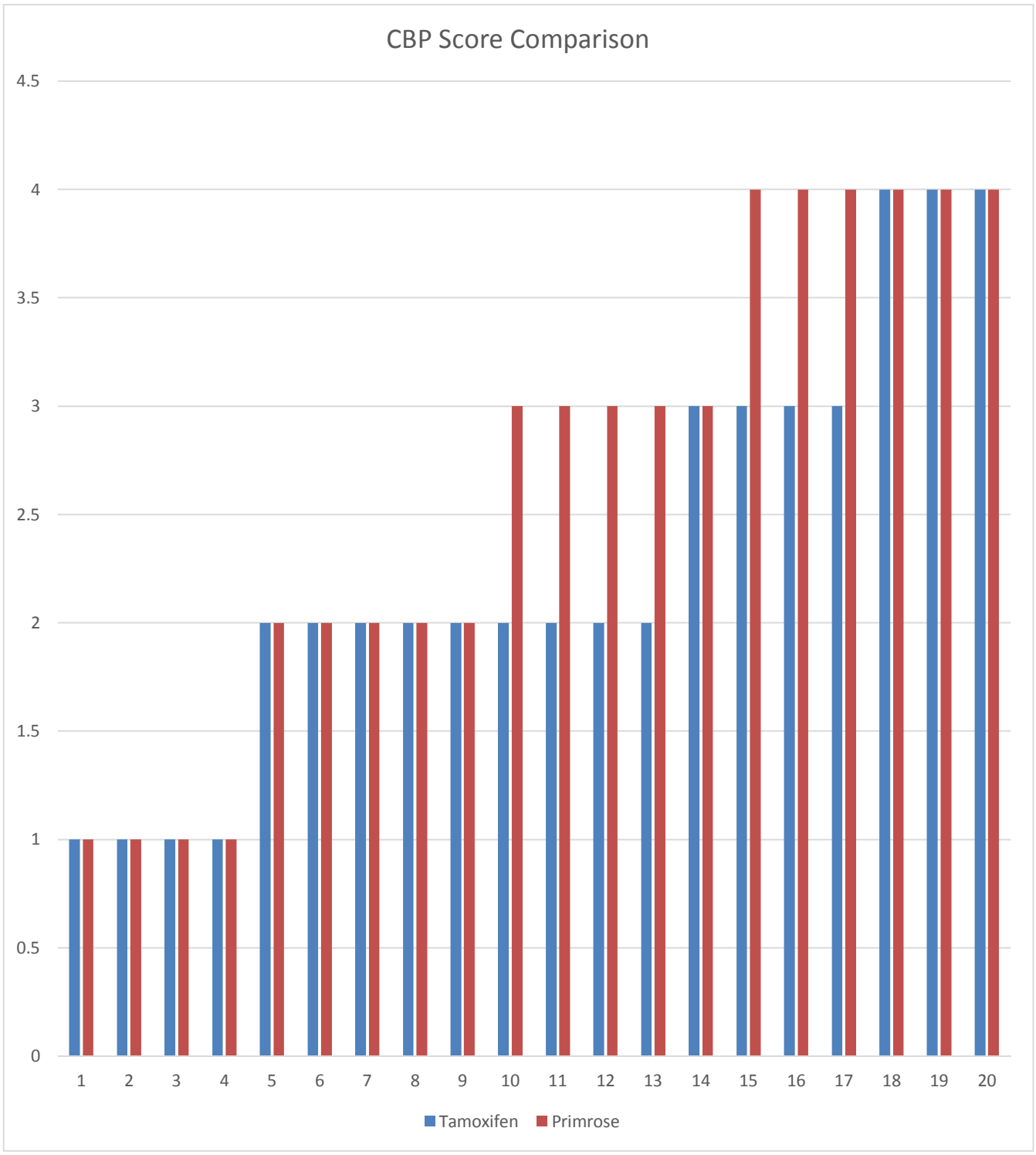


Figure 9: Cardiff Breast Pain Score

USG Findings after treatment

The reduction in size of the lump was better in Tamoxifen group with 8 of them showing reduction whereas in the Evening Primrose group only three of them had a reduction in the size of the lump. The difference is statistically significant.

USG Findings after treatment	TREATMENT RECEIVED		Total	
	EVENING PRIMROSE 1000MG BD	TAMOXIFEN 10MG OD		Chi-square Analysis' P-value
No reduction in size of the lump	**17**	**12**	**29**	**12.098**
Reduction in size of lump + -2x1cm	0	1	1	**P=0.026**
Reduction in size of lump + 9.8x8.5mm	0	1	1	**Significant**
Reduction in size of lump + 1.2x0.8cm	0	1	1	
Reduction in size of lump + 1.2x1cm	1	0	1	
Reduction in size of lump + 1.8x1.2cm	1	0	1	
Reduction in size of lump + 1x1cm	0	3	3	
Reduction in size of lump + 8.2x7.6mm	0	1	1	
Reduction in size of lump + 9.8x8.9mm	0	1	1	
Reduction in size of the lump + 1.2x0.8cm	1	0	1	
Total	20	20	40	

Table 7: USG Findings after treatment

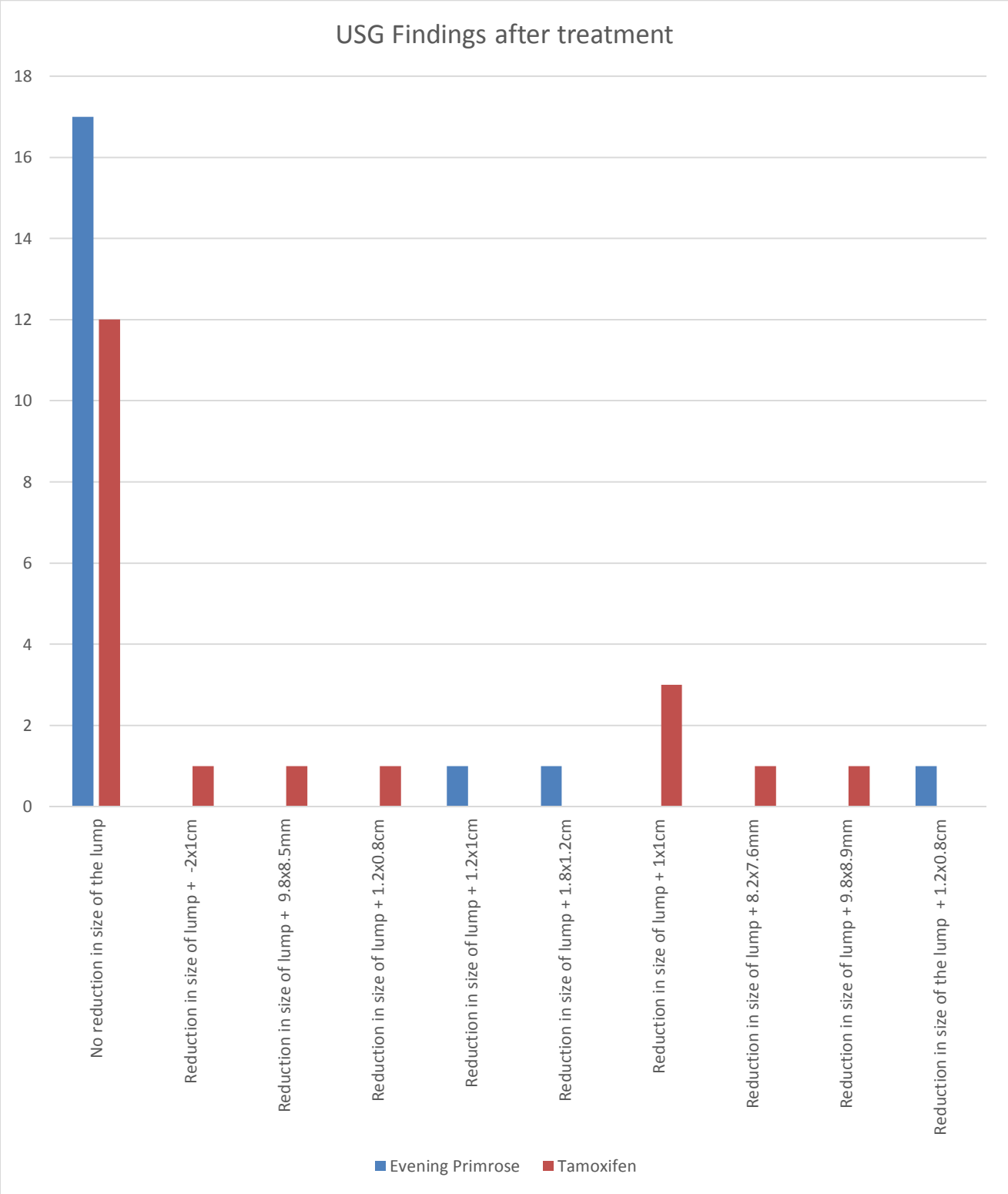


Figure 10: USG Findings after treatment

Side effects

Out of 20 patients in the Tamoxifen group, only two of them had side effects while five of them had side effects in the Evening Primrose group. Out of the two patients in the Tamoxifen group with side effects, one of them had Hot flashes while the other one had Menorrhagia. Whereas in the Primrose group, three of them had headache and two of them had diarrhea.

SIDE EFFECTS	TREATMENT RECEIVED		Total
	EVENING PRIMROSE 1000MG BD	TAMOXIFEN 10MG OD	
DIARRHOEA	2	0	2
HEADACHE	3	0	3
HOT FLASHES	0	1	1
MENORRHAGIA	0	1	1
NIL	15	18	33
Total	20	20	40

Table 8: Side effects

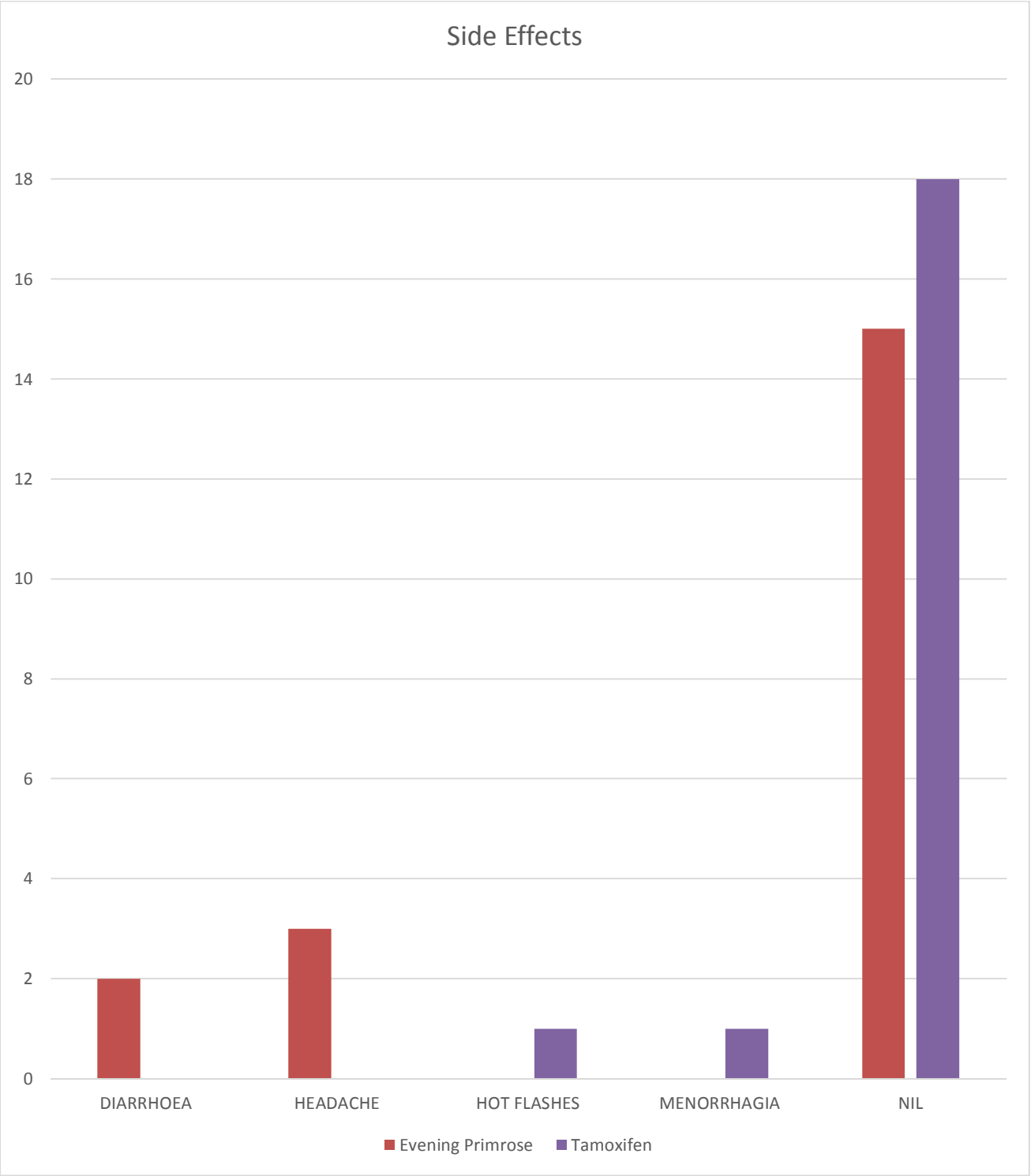


Figure 11: Side effects

DISCUSSION

DISCUSSION

Due to high prevalence of benign breast diseases and their impact on the quality of life of a woman, they are clinically as well as culturally significant. Multiple systematic reviews have been done to summarise and sort the wealth of accumulated knowledge right from etiology till treatment including histopatholoy and molecular biology.

The study of such benign breast diseases are challenging in the light of separating physiologic changes from the pathologic changes clinically as well as in histopathology. The definitions and classifications are not scanty in this disease though the majority of the attention is being attributed to the following; a) fibroadenoma and b) fibrocystic breast disease

Fibroadenomas are non-neoplastic lesions with pseudoencapsulation macroscopically and sharp delimitation microscopically. Epithelial and stromal components are present. It seems to arise from a single lobule due to distortive hyperplasia.

On the other hand, fibrocystic breast disease is not clearly defined. Fibrocystic breast disease is a condition of breast tissue affecting an estimated 30-60% of women and at least 50% of women of childbearing age. Some studies indicate that the lifetime prevalence of fibrocystic disease of breast may be as high as 70% to 90%.

Any condition that presents with a palpable lump that is ill defined; associated with pain and tenderness and shows cyclical pattern corresponding to the menstrual cycle is considered as fibrocystic breast disease. The disease tends to progress till menopause and tends to decline in incidence and prevalence post that.

The histologic analysis shows that the lesions arise from the epithelium. On the other hand, the microscopic analysis reveal microcysts and macrocysts either alone or in conjunction with papillomas, adenosis, epitheliosis, apocrine epithelium and papillomatosis. Schnitt and Conolly elaborated on this nomenclature.

Haagensen defined gross cyst as a derivation of the end of the ductal lobular unit presenting as a palpable mass. There are two layers of the epithelium namely epithelial layer (inner) and myoepithelial layer (outer). Cysts may be associated with hyperplasia or metaplasia. In metaplasia, the normal epithelium transforms into the type of epithelium present in apocrine glands. In hyperplasia, it can be either adenosis or epitheliosis. Adenosis is the condition where a new ductal or lobular structures are developed accompanied with the proliferation of myoepithelial or epithelial cells. In sclerosing adenosis, there is a predomination of myoepithelial cells. When there are papillae present, it is called as papillomatosis.

It is often periodically related to hormonal influences from the menstrual cycle. The changes in fibrocystic breast disease are characterised by the appearance of fibrous tissue and a lumpy, cobblestone texture in the breasts. These lumps are

smooth with defined edges, and are usually free-moving in regard to adjacent structures, The lumps are more often found in the upper, outer sections of the breast (nearest to the armpit), but can be found throughout the breast. Women with fibrocystic changes may experience a persistent or intermittent breast aching or breast tenderness related to periodic swelling. Breasts and nipples may be tender or itchy. Symptoms follow a periodic trend tied closely to the Menstrual cycle. Symptoms tend to peak in the days and, in severe cases, weeks before each period and decrease afterwards. At peak, breasts may feel full, heavy, swollen, and tender to touch. No complications related to breastfeeding have been found.

The exact mechanism of the condition is not fully understood, though it is known to be tied to hormone levels, as the condition usually subsides after menopause and is also related to the menstrual cycle. Post-menopausal women placed on hormone replacement therapy (HRT) have also reported symptoms of fibrocystic disease of breast indicating that hormones may play a role. Fibrocystic breast changes is a cumulative process caused partly by the normal hormonal variation during a woman's monthly cycle. The most important of these hormones are oestrogen and progesterone. These hormones directly affect the breast tissues by causing cells to grow and multiply. Many other hormones such as TSH, insulin, growth hormone and growth factors such as TGF-beta exert direct and indirect effects amplifying or

regulating cell growth. Years of such fluctuations eventually produce small cysts and/or areas of dense or fibrotic tissue.

Studies show that there is a relationship between benign diseases of the breast and cancer risk mainly based on their morphological subtypes. The risk severity varies between different histologic subtypes. Proliferative lesions with atypia are known to be having 1.5 to 2-fold risk of getting cancer. There are a number of factors associated with these lesions that determine the progress to cancer namely; type of atypical hyperplasia, time since biopsy, menopausal status, family history, postmenopausal hormone use, and presence of other benign lesions.

World Health Organisation have enumerated Tamoxifen as a necessary ingredient in the treatment protocol of breast cancer. Since a quarter of a century, it is been used as the gold standard endocrine method of treating oestrogen-receptor-positive breast cancer, irrespective of staging. Tamoxifen is known to have saved the lives of around 400,000 women apart from the large number of women who received palliative care and improved quality of life post surgery. It is also the first drug to be approved by the Food and Drug Administration (FDA) as cancer chemopreventive in women who were at higher risk. It is known to reduce the incidence of cancer in premenopausal as well as post menopausal women.

When given as an adjuvant therapy, Tamoxifen is known to be effective in decreasing the recurrence of breast cancer and thereby death. Even in patients with metastasis, it provides adequate palliation. This explains why Tamoxifen is used in both premenopausal and postmenopausal women provided their neoplastic tissue is estrogen receptor positive. The only exception being made on the basis of prognostic factors and with very low risk of dissemination.

For postmenopausal women who present with metastatic breast cancer, tamoxifen is the first treatment of choice in the list of hormonal therapy. The drug is well tolerated and is known to be safe. Even in younger women, it is the used as a first or second choice drug, the risk of endometrial cancer being present. Another reason for preference of Tamoxifen and a number of randomised trials studying its use is the positive effects of the drug on bone density, risk of contra lateral breast cancer and cardiovascular mortality.

The gold standard treatment for benign breast conditions have been under study for a long time. Studies how that Tamoxifen, Danazol and Bromocriptine are effective while the treatment using Linoleic acid as primrose oil is still uncertain due to the failure in a large trial. Iodine and vaginal progesterone are considered to b effective while Vitamin E is ineffective. One of the drawbacks is the lack of generalised multi centric trials for finding out the efficiency of caffeine avoidance,

progesterone and Medroxyprogesterone acetate. Pain relief is brought about by well-fitted bras. A temporary post-menopausal state can be reached by using GnRH agonist analogues. Menopause is therapeutic in managing breast pain. The following image shows the effectiveness of various treatments. Lack of data or single center studies is a major limitation of these studies.

In this present study, the mean age of the Tamoxifen group is 35.15 years with a standard deviation of 4.79 years with a median of 37 years ranging from 25 years to 40 years. The mean age of the Primrose group is 31.20 years with a standard deviation of 3.98 years with a median of 30 years ranging from 26 years to 39 years. In the Tamoxifen group, Fibroadenosis was present in 17 patients (right breast=5; left breast=12) and Fibrocystic disease right breast=3 patients.

In the Evening Primrose group, Fibroadenosis was present in 12 patients (right breast=4; left breast=8) and Fibrocystic disease was present in eight patients (right breast=3 patients; left breast=5 patients). All lesions were cystic in nature Majority (n=22) of the patients had grade 3 pain with 10 patients in the Evening Primrose group and 12 patients in the Tamoxifen group. The two groups are comparable and does not differ significantly in the grading of pain. Both the Groups received treatment for three months. The Cardiff Breast Pain Score was comparable between the two groups with no significant differences. The reduction in size of the lump

was better in Tamoxifen group with 8 of them showing reduction whereas in the Evening Primrose group only three of them had a reduction in the size of the lump. The difference is statistically significant.

Out of 20 patients in the Tamoxifen group, only two of them had side effects while five of them had side effects in the Evening Primrose group. Out of the two patients in the Tamoxifen group with side effects, one of them had Hot flashes while the other one had Menorrhagia. Whereas in the Primrose group, three of them had headache and two of them had diarrhea.

The outcome was better in the group that was treated with Tamoxifen as compared to the treatment with evening Primrose group.

In a recent study conducted by Tan-Chiu et al in 2003, it is found that Tamoxifen treatment reduces the risk of benign breast disease by 28%. Tamoxifen was found to be effective in reducing pain in women with: cyclical mastalgia and also to a lesser degree in women with non cyclical mastalgia. Women who received Tamoxifen had a 29% reduction in undergoing biopsies. Adverse effects were reported more frequently with Tamoxifen 20 mg than with Tamoxifen 10mg. However, the overall side effects were reported only in minority of the population. Reported adverse effects included an increase in weight, menorrhagia, hot flashes and vaginal discharge Tamoxifen is a selective estrogen receptor modulator class

of drugs that is used to prevent breast cancer in women and men.lt is also being studied for other types of cancer. It is currently used for the treatment of both early and advanced estrogen receptor positive(ER-positive)breast cancer in pre-and post menopausal women. It has been further approved for the reduction of contra lateral cancer. Tamoxifen is also used for the treatment of infertility, gynecomastia, Albright syndrome and other rare conditions of retroperitoneal fibrosis and idiopathic sclerosing mesenteritis.

SUMMARY
AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

A Comparative Prospective Single Center Study to assess the effectiveness of Tamoxifen in fibrocystic disease(benign breast disease) of the breast among forty patients reveals the following;

1) The mean age of the Tamoxifen group is 35.15 years with a standard deviation of 4.79 years with a median of 37 years ranging from 25 years to 40 years.
2) The mean age of the Primrose group is 31.20 years with a standard deviation of 3.98 years with a median of 30 years ranging from 26 years to 39 years.
3) In the Tamoxifen group, the disease was present on the right side in eight patients and on the left side in twelve patients.
4) In the Evening Primrose group, the disease was present on the right side in seven patients and on the left side in thirteen patients.
5) All lesions were cystic in nature Majority (n=22) of the patients had grade 3 pain with 10 patients in the Evening Primrose group and 12 patients in the Tamoxifen group.
6) The two groups are comparable and does not differ significantly in the grading of pain. Both the Groups received treatment for three months.
7) The Cardiff Breast Pain Score was comparable between the two groups with no significant differences.

8) The reduction in size of the lump was better in Tamoxifen group with 8 of them showing reduction whereas in the Evening Primrose group only three of them had a reduction in the size of the lump. The difference is statistically significant.
9) Out of 20 patients in the Tamoxifen group, only two of them had side effects while five of them had side effects in the Evening Primrose group.
10) Out of the two patients in the Tamoxifen group with side effects, one of them had Hot flashes while the other one had Menorrhagia. Whereas in the Primrose group, three of them had headache and two of them had diarrhea.

The outcome was better in the group that was treated with Tamoxifen as compared to the treatment with evening Primrose group.

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ETHICAL COMMITTEE APPROVAL LETTER

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL,CHENNAI -01

INSTITUTIONAL ETHICS COMMITTEE

TITLE OF THE WORK : A PROSPECTIVE COMPARATIVE STUDY OF TAMOXIFEN VRS STANDARD TREATMENT RESPONE IN FIBROCYSTIC DISCASE OF THE BREAST IN TERTIARY HEALTH CENTRE.

PRINCIPAL INVESTIGATOR : DR. ZOTHANPARI RALTE
DESIGNATION : PG IN MS GENERAL SURGERY,
DEPARTMENT : DEPARTMENT OF GENERAL SURGERY, GOVT. STANLEY MEDICAL COLLEGE.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 15.09.2018 at the Council Hall, Stanley Medical College, Chennai-1 at 10am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

1/2/18

MEMBER SECRETARY,
IEC, SMC, CHENNAI

From

The HOD,
Department of General Surgery,
Stanley Medical College,
Chennai.

To

The HOD,
Department of Obstetrics and Gynaecology,
Stanley Medical College,
Chennai.

Respected Sir/Madam,

THROUGH PROPER CHANNEL

(subject:Thesis-"A prospective comparative study of Tamoxifen VRS standard treatment respone in fibrocystic disease of the breast in tertiary health centre")

I hereby informing you,Dr Zothanpari Ralte,II yr Post Graduate in Dept of General Surgery,is doing dissertation on "A prospective comparative study of Tamoxifen VRS standard treatment respone in fibrocystic disease of the breast in tertiary health centre".I request you to grant her permission & acceptance for the said dissertation topic for academic purpose.

Thanking you,

HEAD OF THE DEPARTMENT,
DEPT. OF GENERAL SURGERY,
GOVT. STANLEY MEDICAL COLLEGE,
CHENNAI-01.

Permitted to do the study
K. Kalaimani
15/11/10

PROFORMA

NAME : AGE : SEX :

IP NO: D.O.A:

Wt: Ht:

HISTORY :

- H/o Breast pain
- H/o Nipple discharge
- H/o Presence of lump
- H/o Fever /Evening rise of temperature
- H/o Trauma
- H/o Chest pain/dyspnea
- H/o Loss of appetite/Loss of weight

PAST HISTORY

- Any H/O Diabetes Mellitus /SHTN/PTB/CAD/CKD/Thyroid Disorder/Congenital Disorder/Seizure disorder
- Any H/O malignancy in the past
- Any H/O previous breast surgery
- Any H/O chronic Drugs intake

PERSONAL HISTORY

- Diet
- Allergy history
- Bowel and Bladder Habit

FAMILY HISTORY

- H/o malignancy in the family

MENSTRUAL HISTORY:

Investigation

- ✓ Hb%
- ✓ TC
- ✓ DC
- ✓ RBC
- ✓ PLATELET
- ✓ RBS
- ✓ UREA
- ✓ CREATININE
- ✓ TB
- ✓ DB
- ✓ SGOT
- ✓ SGPT
- ✓ ALK Phos.
- ✓ Total Protein
- ✓ Serum Albumin
- ✓ Sr electrolyte

  Na+/K-

Complete Diagnosis:

USG/FNAC/Xray mammogram Finding:

Treatment given-TAMOXIFEN: YES NO

DOSE-

DURATION-

DANAZOL

EVENING PRIMROSE OIL: YES NO

DOSE-

DURATION-

Treatment response:

GOVT.STANLEY MEDICAL COLLEGE, CHENNAI- 600 001

INFORMED CONSENT

DISSERTATION TOPIC:

"THE STUDY OF TAMOXIFEN RESPONSE IN FIBROCYSTIC DISEASE OF THE BREAST IN TERTIARY HEALTH CENTRE"

PLACE OF STUDY: GOVT. STANLEY MEDICAL COLLEGE, CHENNAI

NAME AND ADDRESS OF PATIENT:

நான், _____

எனதுசொந்தமொழியில்ஆய்வுவிவரங்களைபற்றிதெரிவிக்கப்பட்டது.

நான்முற்றிலும்ஆய்வுவிவரங்களைபுரிந்துகொண்டேன்.

ஆய்வுபங்கெடுத்துக்கொண்டுள்ளநான்,
சாத்தியமானஅபாயங்கள்மற்றும்பயன்களைஅறிந்துஇருக்கிறேன்.

நான்எந்தநேரத்திலும்ஆய்வுஇருந்துதிரும்பமுடியும்மற்றும்அதன்பின்னர்,
நான்வழக்கம்போல்மருத்துவசிகிச்சைபெறதொடரும்என்றுபுரிந்துகொள்ள.

நான்இந்தஆய்வில்பங்குஎடுத்துஎந்தபணம்பெறமுடியாதுஎன்றுபுரிந்து.

நான்ஆட்சேபிக்கிறேன்மாட்டேன்இந்தஆய்வின்முடிவு,
எந்தமருத்துவஇதழில்கிடைக்கும்என்றால்,
என்தனிப்பட்டஅடையாளவெளிப்படவில்லைவழங்கப்படும்.

நான்இந்தஆய்வுபகுதியாகஎடுத்துசெய்யவேண்டும்என்றுஎனக்குநான்இந்தஆய்வுஎன்முழுஒத்துழைப்புநீட்டிக்கஎன்றுஉறுதியளிக்கிறேன்.

பெயர்மற்றும்தொண்டர்முகவரி:

தொண்டர்கையொப்பம் / பெருவிரல்ரேகை

நாள்:

சாட்சிகள்:

(கையொப்பம், பெயர்மற்றும்முகவரி)

நாள்:

பெயர்மற்றும்புலன்விசாரணைகையொப்பம்: (டாக்டர்)

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MASTER CHART

S.NO	NAME	AGE/SEX	FNAC DIAGNOSIS	USG DIAGNOSIS	GRADING OF PAIN	TREATMENT RECEIVED	DURATION OF TREATMENT	FOLLOW UP AFTER 3 MONTH					
								CBP SCORE	ULTRASOUND			SIDE EFFECTS	
1	MANI	28/F	FIBROADENOSIS RIGHT BREAST	WELL DEFINED CYSTIC LESION 2X2CM AT 4-6 OCLOCK	GRADE 3	EVENING PRIMROSE 1000MG BD	3 MONTHS	1	REDUCTION IN SIZE OF LUMP + 1.2X1CM			NIL	
2	SANDHYA	34/F	FIBROADENOSIS RIGHT BREAST	WELL DEFINED CYSTIC LESION 1X0.8CM AT 8 OCLOCK	GRADE 2	EVENING PRIMROSE 1000MG BD	3 MONTHS	2	NO REDUCTIOM OF THE LUMP	TION IN SIZE		NIL	
3	PREETHI	36/F	FIBROADENOSIS LEFT BREAST	WELL DEFINED CYSTIC LESION 0.8X0.8CM AT 2 OCLOCK	GRADE 3	EVENING PRIMROSE 1000MG BD	3 MONTHS	3	NO REDUCTION IN SIZE OF THE LUMP			NIL	
4	ISWARYA	29/F	FIBROCYSTIC DISEASE LEFT BREAST	CYSTIC LESION OF SIZE 2X1CM AT 6-7 OCLOCK	GRADE 3	EVENING PRIMROSE 1000MG BD	3 MONTHS	3	REDUCTION IN SIZE OF THE LUMP+ 1.2X0.8CM			NIL	
5	SOFIA	32/F	FIBROADENOSIS LEFT BREAST	CYSTIC LESION OF SIZE 1.8X1.2CM AT 3-4 OCLOCK	GRADE 3	EVENING PRIMROSE 1000MG BD	3 MONTHS	3	NO REDUCTION IN SIZE OF THE LUMP			NIL	
6	SUMATHI	26/F	FIBROCYSTIC DISEASE LEFT BREAST	WELL DEFINED CYSTIC LESION 1.9X1.2CM 8-9	GRADE 2	EVENING PRIMROSE 1000MG BD	3 MONTHS	1	NO REDUCTION IN SIZE OF THE LUMP			NIL	

				OCLOCK									
7	PRIYA	37/F	FIBROCYSTIC DISEASE RIGHT BREAST	WELL DEFINED CYSTIC LESION 2X2CM AT 7-9 OCLOCK	GRADE 4a	EVENING PRIMROSE 1000MG BD	3 MONTHS	1	NO REDUCTION IN SIZE OF THE LUMP			NIL	
8	PRASHANTHI	30/F	FIBROADENOSIS LEFT BREAST	CYSTIC LESION 1X1CM AT 9 OCLOCK	GRADE 4a	EVENING PRIMROSE 1000MG BD	3 MONTHS	2	NO REDUCTION IN SIZE OF THE LUMP			HEADACHE	
9	VANI	28/F	FIBROADENOSIS RIGHT BREAST	CYSTIC LESION SIZE 2X1.2CM AT 9-10 OCLOCK	GRADE 3	EVENING PRIMROSE 1000MG BD	3 MONTHS	3	NO REDUCTION IN SIZE OF THE LUMP			NIL	
10	VALLI	32/F	FIBROADENOSIS LEFT BREAST	WELL DEFINED CYSTIC LESION 1.3X1CM AT 2-3 OCLOCK	GRADE 2	EVENING PRIMROSE 1000MG BD	3 MONTHS	1	NO REDUCTION IN SIZE OF THE LUMP			NIL	
11	MALLI	30/F	FIBROADENOSIS LEFT BREAST	WELL DEFINED CYSTIC LESION 2.5X2CM AT 9-11 OCLOCK	GRADE 3	EVENING PRIMROSE 1000MG BD	3 MONTHS	2	REDUCTION IN SIZE OF LUMP + 1.8X1.2CM			NIL	
12	EGAVALLI	28/F	FIBROCYSTIC DISEASE LEFT BREAST	WELL DEFINED CYSTIC LESION 1X0.8CM AT 2 OCLOCK	GRADE 2	EVENING PRIMROSE 1000MG BD	3 MONTHS	4	NO REDUCTION IN SIZE OF THE LUMP			HEADACHE	
13	MEGALA	26/F	FIBROADENOSIS LEFT BREAST	CYSTIC LESION OF SIZE 1X0.8CM AT 2 OCLOCK	GRADE 2	EVENING PRIMROSE 1000 MG BD	3 MONTHS	4	NO REDUCTION IN SIZE OF THE LUMP			DIARRHOEA	
14	VANITHA	29/F	FIBROADENOSIS	CYSTIC LESION OF SIZE	GRADE 1	EVENING PRIMROS	3 MONTHS	4	NO REDUCTION IN			DIARRHOEA	

						E			SIZE				
			RIGHT BREAST	1X0.8CM AT 8 OCLOCK		1000 MG BD			OF THE LUMP				
15	KAMALA	32/F	FIBROADENOSIS	CYSTIC LESION 1X1 CM	GRADE 3	EVENING PRIMROSE	3 MONTHS	4	NO REDUCTION IN SIZE			HEADACHE	
			LEFT BREAST	AT 7 OCLOCK		1000 MG			OF THE LUMP				
16	MALA	29/F	FIBROCYSTIC	CYSTIC LESION SIZE	GRADE 3	EVENING PRIMROSE	3 MONTHS	4	NO REDUCTION IN SIZE			NIL	
			DISEASE LEFT	1X0.7CM AT 8 OCLOCK		1000MG BD			OF THE LUMP				
			BREAST										
17	YAZHINI	39/F	FIBROCYSTIC	CYSTIC LESION SIZE	GRADE 2	EVENING PRIMROSE	3 MONTHS	4	NO REDUCTION IN SIZE			NIL	
			DISEASE RIGHT	1.9X1.7CM AT 4-5		1000MG BD			OF THE LUMP				
			BREAST	OCLOCK									
18	YAMUNA	39/F	FIBROCYSTIC	CYSTIC LESION 1X1CM	GRADE4a	EVENING PRIMROSE	3 MONTHS	2	NO REDUCTION IN SIZE			NIL	
			DISEASE RIGHT	AT 9OCLOCK		1000MG BD			OF THE LUMP				
			BREAST										
19	KAVITHA	28/F	FIBROADENOSIS	CYSTIC LESION OF SIZE	GRADE 3	EVENING PRIMROSE	3 MONTHS	2	NO REDUCTION IN SIZE			NIL	
			LEFT BEAST	1.1X0.8CM AT 7 OCLOCK		1000MG BD			OF THE LUMP				
20	ANITHA	32/F	FIBROCYSTIC	CYSTIC LESION OF SIZE	GRADE 3	EVENING PRIMROSE	3 MONTHS	3	NO REDUCTION IN SIZE			NIL	
			DISEASE LEFT	1X0.9CM AT 8 OCLOCK		1000MG BD			OF THE LUMP				
			BREAST										

S.NO.	NAME	AGE/SEX	FNAC DIAGNOSIS	ULTRASOUND DIAGNOSIS		GRADING OF PAIN	TREATMENT RECEIVED	DURATION OF TREATMENT	FOLLOW UP AFTER 3 MONTHS				
1	SARITHA	34/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	CBP SCORE		US G	SIDE EFFECTS	
			LEFT BREAST	2X2CM AT 6-9 OCLOCK			10MG OD		1	REDUCTION IN SIZE OF		NIL	
				POSITION						LUMP + -2X1CM			
2	PARVATHY	26/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	2	NO REDUCTION		NIL	
			RIGHT BREAST	2X1CM AT 2-4 OCLOCK			10MG OD			IN SIZE OF THE			
				POSITION						LUMP			
3	UMA	40/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 2	TAMOXIFEN	3 MONTHS	4	NO REDUCTION		NIL	
			LEFT BREAST	1X1CM AT 9-11 OCLOCK	6 OCLOCK		10MG OD			IN SIZE OF THE			
				POSITION						LUMP			
4	STELLA	33/F	FIBROCYSTIC	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	2	REDUCTION IN SIZE OF		NIL	
			RIGHT BREAST	2X2CM 9-11 OCLOCK			10MG OD			LUMP + 1X1CM			
5	SWATHI	29/F	FIBROCYSTIC	WELL DEFINED CYSTIC LESION		GRADE 4a	TAMOXIFEN	3 MONTHS	3	REDUCTION IN SIZE OF		NIL	
			RIGHT BREAST	1.5X1CM 8-9 OCLOCK			10MG OD			LUMP + 9.8X8.5 MM			
6	JENNIFER	35/F	FIBROCYSTIC	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	2	REDUCTION IN SIZE OF		MENORRHAGIA	
			RIGHT BREAST	2X2CM 8-9 OCLOCK			10MG OD			LUMP + 9.8X8.9 MM			
7	MAGESHWARI 37/F		FIBROADENOSIS	WELL DEFINEDCYSTIC LESION	NED CYSTIC LESION	GRADE 3	TAMOXIFEN	3 MONTHS	1	REDUCTION IN SIZE OF		NIL	
			LEFT BREAST	2X1.7CM 2-4 OCLOCK			10MG OD			LUMP + 1X1CM			
8	MANIMEGALAI40/F		FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 2	TAMOXIFEN	3 MONTHS	4	NO REDUCTION IN SIZE		HOT FLASHES	
			LEFT BREAST	1X1CM AT 6-7 OCLOCK	7 OCLOCK		10 MG OD			OF THE LUMP			

9	UMA	40/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 4a	TAMOXIFEN	3 MONTHS	3	REDUCTION IN SIZE OF		NIL	
			RIGHT BREAST	2.2X1.5CM AT 9-11 OCLOCK			10MG OD			LUMP + 1X1CM			
10	PRIYANKA37/F		FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	2	NO REDUCTION IN SIZE		NIL	
			LEFT BREAST	1X1CM AT 7-9 OCLOCK	8 OCLOCK		10MG OD			OF THE LUMP			
11	SARASWATHY 38/F		FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	3	NO EDUCTION IN THE SIZE		NIL	
			LEFT BREAST	9.4X7.1MM AT 8 OCLOCK			10 MGOD			OF LUMP			
12	JOTHY	39/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	1	REDUCTION IN SIZE		NIL	
			RIGHT BREAST	1.8X1.2CM AT 7-9 OCLOCK	AT 8-9 OCLOCK		10MG OD			OF LUMP + 8.2X7.6 MM			
13	BOMMI	29/F	FIBROADENOMA	WELL DEFINED CYSTIC LESION		GRADE 4	TAMOXIFEN	3 MONTHS	2	REDUCTION IN SIZE OF		NIL	
			LEFT BREAST	2.3X1.8CM AT 9-11 OCLOCK			10MG OD			LUMP + 1.2X0.8CM			
14	GOWRI	39/F	FIROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 4	TAMOXIFEN	3 MONTHS	2	NO REDUCTION IN SIZE		NIL	
			LEFT BREAST	1X1CM AT 8 OCLOCK			10 MG OD			OF LUMP			
15	MUMTAZ	40/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	2	NO REDUCTION IN SIZE		NIL	
			LEFT BREAST	1X0.8CM AT 6 OCLOCK			10 MG OD			OF LUMP			
16	ANITHA	31/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	1	NO REDUCTION IN SIZE		NIL	
			LEFT BREAST	1X1CM AT 8 OCLOCK			10 MG OD			OF THE LUMP			
17	KUMARI	36/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	3	NO REDUCTION IN SIZE		NIL	
			RIGHT BREAST	1.1X0.9CM AT 9 OCLOCK			10 MG OD			OF THE LUMP			
18	PURNIMA	38/F	FIBROADENOSIS	WELL DEFINED		GRADE 2	TAMOXIFEN	3 MONTHS	2	NO REDUCTI		NIL	

				CYSTIC LESION						ON IN SIZE			
			RIGHT BREAST	1X1CM AT 4-5 OCLOCK			10 MG OD			OF LUMP			
19	FATHIMA	37/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 3	TAMOXIFEN	3 MONTHS	2	NO REDUCTION IN SIZE		NIL	
			LEFT BREAST	1X1CM AT 4 OCLOCK			10MG OD			OF THE LUMP			
20	VALLI	25/F	FIBROADENOSIS	WELL DEFINED CYSTIC LESION		GRADE 2	TAMOXIFEN	3 MONTHS	4	NO REDUCTION IN SIZE		NIL	
			LEFT BREAST	1X0.8CM AT 9 OCLOCK			10 MG OD			OF THE LUMP			