

BREAST CANCER

Keywords

EPIDEMIOLOGY
GENETICS
SPREAD
RISK FACTORS
CLINICAL FEATURES
DIAGNOSIS
TREATMENT

EPIDEMIOLOGY

Incidence By Age

Staging and Survival Rates

Breast cancer remains one of the most common malignancies in women and is leading cause of mortality due to cancer. Though there is decline in breast cancer deaths, the overall survival rate of patients with breast cancer has not significantly increased inspite of many advances in treatment and concept of breast disease. Many recent epidemiological studies coupled with the basic mechanisms of molecular genetics, is paving way to disclose the basic mechanisms of breast carcinogenesis and allow development of novel treatment and prevention strategies. As in classical epidemiological model many Agent, Host and Environmental factors affect the presence and occurrence of breast cancer in society.

Host factors : Age of individual,
Family history,
Menstual history,
Obstetric history,
Dietary habits,
Smoking history.
Genetic factors

Agent factors : Breast cancer type,
Stage of cancer,
Grade of disease,
Response to adjuvant treatment

Environmental factors : Organochlorine pesticides,
Geographic area,
Other pollutants.

Incidence By Age

Each woman's breast cancer risk varies, depending upon a several factors, including family history, genetics, age of menstruation, and other factors that have not yet been identified. But in general the incidence with age increases and is as follows,

A Woman's Chances of Breast Cancer Increases With Age	
By age 30	1 out of 2,212
By age 40	1 out of 235
By age 50	1 out of 54
By age 60	1 out of 23
By age 70	1 out of 14
By age 80	1 out of 10
Ever	1 out of 8

Source: Feuer EJ, Wun LM. DEVCAN: Probability of Developing or Dying of Cancer. Version 4.0. Bethesda MD: [National Cancer Institute](#). 1999.

While breast cancer is less common at a young age (*i.e.*, in their thirties), younger women tend to have more aggressive breast cancers than older women, which may explain why survival rates are lower among younger women.

Five Year Survival Rate By Age	
Younger than 45	81%
Ages 45-64	85%
Ages 65 and older	86%

Staging and Survival Rates

Staging is the process physicians use to assess the extent of a patient's cancer. This information helps determine the most appropriate form of treatment. Breast cancer stages range from Stage 0 (very early form of cancer) to Stage IV (advanced, metastatic breast cancer). The five-year survival rate for breast cancer is calculated based on averages. Each patient's individual tumor characteristics, state of health, genetic background, etc. will impact her survival. In addition, levels of stress, immune function, will to live, and other unmeasurable factors also play a significant role in a patient's survival.

STAGE	5 YEARS	10 YEARS
I	90%	80%
II	60%	50%
III	40%	25%
IV	20%	<5%

Breast cancer survival also continues to decline after five years. Survival after ten years depends on the stage; early stage breast cancers are associated with high survival rates than late stages cancers.

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GENETICS

Oncogene induced Syndromic type

Tumour suppressor gene related

Breast cancer genetics is about the effect of different activities and alterations (mutations), of the variety of genes in the cells, which in practice influences the clinical aspects of breast cancer such as inborn (familial) risk of getting cancer, severity of disease, treatment pattern and prognosis (outcome) in terms of longevity of life and response to treatment.

Genetic mechanisms predisposing to breast cancer can be broadly stratified as :

1. Oncogene induced
2. Tumour suppressor gene related and
3. Syndromic type.

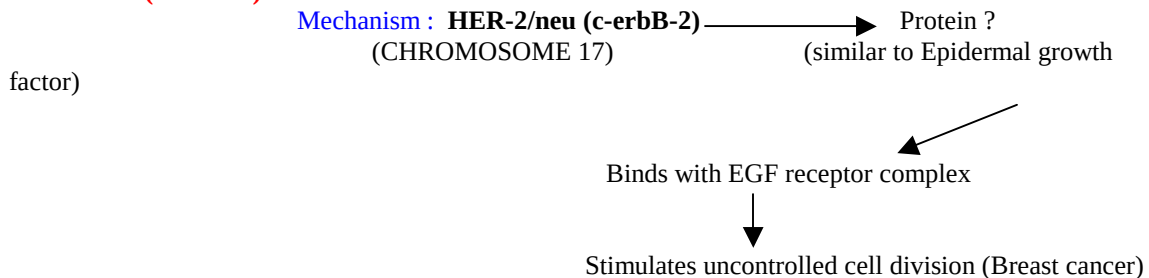
Oncogene induced:

Oncogenes are the genes derived from activation of pre-existing proto-oncogenes in the cells. The activated oncogenes are unstable and makes the cell cycle of hosting cells unstable, which if transmitted to subsequent cells i.e., if heritable are called mutations. The unstable cells of the breast tissue, divide unstoppably due to loss of the cell control mechanisms of the body, which thus forms a cancer mass. So oncogenes exert stimulatory influence on breast cancer formation and progression. The mechanism by which these genes cause cell proliferation is by producing its oncoprotein products.

The two main oncogenes thus far studied in human breast cancer are :

HER-2/neu (c-erbB-2) and bcl2

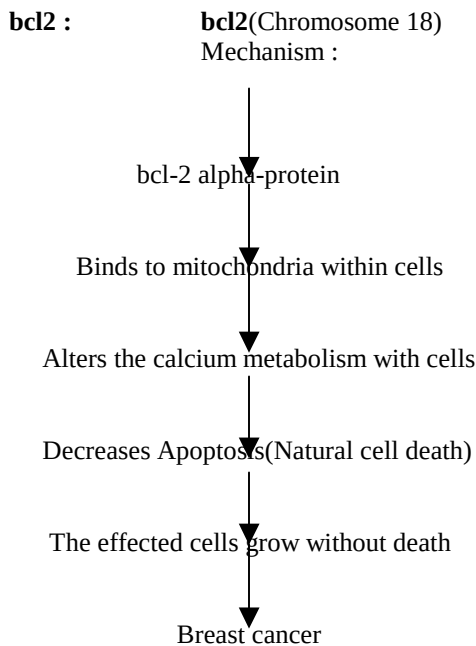
HER-2/neu (c-erbB-2):



Practical implications :

- ❖ HER-2/neu is an established marker of poor prognosis in breast cancer.
- ❖ Powerful predictor of the risk of recurrence
- ❖ Correlates with early spread to lymph nodes and metastasis.

- ❖ This oncogene also helps in guiding the type and number of cycles of chemotherapy.



Though its role in breast cancer is not fully known and under research, certain generalizations from available data is

- ❖ The presence of bcl-2 expression in tumour cell is associated with favourable prognosis.
- ❖ The absence of bcl-2 has poor prognosis
- ❖ They have better response to hormonal therapy.

Tumour suppressor gene related:

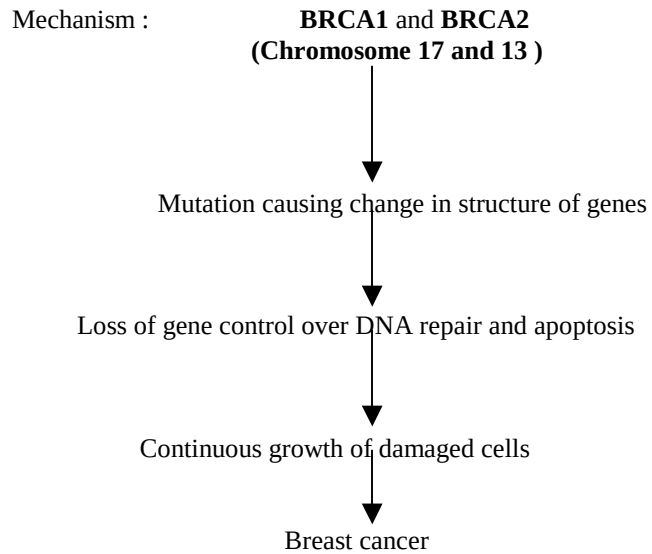
These are unique genes characterised by their protective effect, if normally functioning. they normally control uninhibited cell division by process called Apoptosis. Apoptosis is a process of programmed cell death, where by unwanted ,excess and tired cells are removed and disposed by the body these genes mediate the process by producing the protein product which interacts with cell receptors or cell metabolism and identifies the cells destined to be not useful for the body and which are to be removed. This way it influences along with many other factors to maintain normal cell turnover and maintains optimal quantity and quality of cells in the body. Any deviation from this normalcy manifests in the form of uncontrolled growth of cells with loss of their quality (i.e., normal function), to various degrees depending on the various gene anomalies – which is nothing but cancer and in this context it is **Breast cancer**

The two main oncogenes thus far studied in human breast cancer are :

BRCA
and
p53 genes

BRCA :

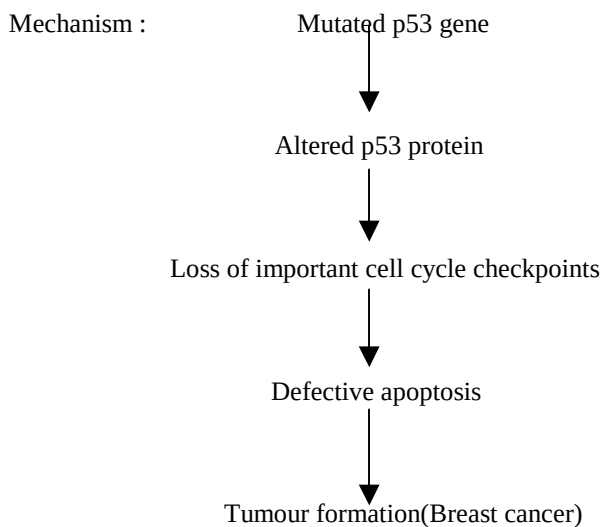
There are two distinct subtypes of BRCA genes i.e., **BRCA1** and **BRCA2**.



Practical implications :

1. BRCA 1 gene is associated with development of breast cancer and ovarian cancer.
2. BRCA 2 gene in addition to breast, ovarian cancer, is associated with pancreatic, Liver, prostate and particularly male breast cancer.
3. BRCA gene mutations are seen in both familial and sporadic breast cancers.

p53 gene :



Practical implications :

1. p53 mutations are involved hereditary types of breast cancer and also ovarian cancer.
2. They also play a role in syndromic type of breast cancer.

Syndromic type :

There are many types of tumors and cancers occurring in same individual at the same or different time periods, due to instability in DNA (basic genetic material), caused by variety of environmental and genetic events. All these syndromes which also includes p53 gene, are characterised by inability of DNA repair mechanisms to correct the damaged DNA. Also in some syndromes due to mutations of normal functioning genes of cell cycle. All these syndromes are rare, but cause significant problems both for patient and treating doctor.

Different syndromes in relation to breast cancer are :

- ❖ Li-Fraumeni Syndrome
- ❖ Cowden syndrome
- ❖ Lynch syndrome
- ❖ Ataxia-Telangiectasia
- ❖ Xeroderma pigmentosa

Li-Fraumeni Syndrome:**Different features of it are :**

Premenopausal breast cancer
Childhood sarcoma
Brain tumours
Leukemia
Lymphomas
Lung cancer
Adrenal carcinoma

Cowden syndrome :**Different features of it are :**

- ❖ Breast cancer
- ❖ Gastrointestinal malignancies
- ❖ Thyroid disease
- ❖ Skin conditions like papillomas, fibromas, palmar and plantar keratosis

Lynch syndrome :**Different features of it are :**

- ❖ breast cancer
- ❖ ovarian cancer
- ❖ gastrointestinal tumours
- ❖ sarcomas

Ataxia-Telangiectasia :**Different features of this are :**

- ❖ Immunodeficiency
- ❖ Hypersensitivity to ionizing radiation
- ❖ Neurological disease
- ❖ Telangiectasias
- ❖ Breast cancer

Xeroderma pigmentosa :**Different features of this are :**

- ❖ Skin cancer
- ❖ Leukemias
- ❖ Breast cancer

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SPREAD

The breast cancer has remarkable capacity to reach different sites which aggravates the poor prognosis. The aim of knowing about spread is to prevent/intervene/treat the cancer. The spread of cancer beyond breast tissue is called METASTASIS. The different patterns of spread are :

Local spread

Regional spread

Distant spread

Local spread: In this the cancer process in the form of microscopic focus/small lump grows and infiltrates the remaining breast parenchyma, overlying skin and underlying pectoralis muscle, fascia and bony chest wall. This local process of invasion is called Infiltration. The different clinical ways of presentation of this local invasion are :

- ❖ Tethering/adherence to skin through ligaments of Cooper.
- ❖ Peau d' Orange (due to blockage of dermal lymphatics with cancer cells)
- ❖ Ulceration of skin over tumour
- ❖ Nodules over the skin of breast
- ❖ Fixity to pectoralis fascia
- ❖ Fixity to bony chest wall

According to local spread the tumour staging in TNM staging is

T4 – Any size of lesion with spread

4a – fixity to chest wall

T4b – Involvement of skin – nodules, ulceration, peau d' Orange

T4c – Both T4a and T4b

T4d – Inflammatory carcinoma.

Regional spread : This includes the extension of cancer to draining lymph nodes of breast. The most common and first region involved are Axillary lymph nodes. The other regions are internal mammary and supraclavicular lymph nodes. The nodal status is the most important prognostic indicator of survival and recurrence.

The axillary lymph nodes are divided into : Level I – anterior, lateral, posterior groups lateral to pectoralis minor muscle Level II – central group behind pectoralis minor muscle Level III – Apical group medial to pectoralis minor muscle

The supraclavicular lymph nodes are located in lower neck, which is next station after axillary lymph nodes, and usually signals harbinger of distant metastasis. The internal mammary lymph nodes are located in medial aspect of intercostal spaces in the chest. The presence of node enlargement with cancer deposits seen in histology alters the treatment approach to a more aggressive variety with use of adjuvant treatment.

According to regional spread the nodal staging in TNM staging is :

N0 – No lymph node involvement

N1 – presence of ipsilateral mobile axillary lymph nodes.

N2 – Matted/fixed ipsilateral axillary lymph nodes.

N3 – Ipsilateral internal mammary/supraclavicular lymph nodes.

Distant spread : This is the most threatening feature which occurs in very early stages of breast cancer in the form of micrometastasis, but clinically/ radiologically manifests itself in later course of cancer and signifies terminal stage of disease. It is important that they are recognized early to plan the treatment ,as in this case surgery is not the 1st option or in many cases never. The distant spread can occur through lymphatics or through blood stream.

Lymphogenous route disseminates cancer cells to :

1. Opposite breast and internal mammary lymph nodes.
2. Liver
3. Retroperitoneal lymph nodes.
4. Peritoneal surface
5. Ovaries in premenopausal women
6. Skin of chest wall and arm and upper abdomen.
7. lungs

Hematogenous route spreads cells by either permeation/embolisation to :

1. Liver
2. lungs
3. peritoneum
4. brain
5. bones
6. Adrenal glands
7. Opposite supraclavicular lymph nodes
8. Distant skin

Sometimes the breast cancer patient presents with distant visceral metastasis and the outlook in these patients is gloomy. These patients are usually treated with palliative chemotherapy and irradiation of solitary metastasis like painful/fractured bone deposits or brain deposits. Very rarely in few individuals the tumour responds and downstages in which case surgery is planned. Based on presence of distant spread staged in TNM classification as ;

M0 – No metastasis

M1 – presence of metastasis.

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RISK FACTORS FOR BREAST CANCER

Many factors can influence a woman's risk of getting breast cancer, but having one or more risk factors does not necessarily mean that a woman will get breast cancer. Some women with one or more breast cancer risk factors never develop the disease, while the majority of women with breast cancer have no apparent risk factors. Even when a woman has a risk factor, there is no way to prove that it was the actual cause of breast cancer.

Common risk Factors for Breast Cancer include :

- ❖ Old age
- ❖ Sex female >Male
- ❖ Family history of breast cancer – Mother,sisters,daughter
- ❖ H/o cancer in opposite breast
- ❖ Benign proliferative disease with atypia.

Risk Factors for Breast Cancer Include Both modifiable and non-modifiable.

Age: As a woman ages, her risk of breast cancer also increases. But the tumours in younger age group are more aggressive with poorer prognosis and survival rates.

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Genetics: Over expression/mutation of certain genes such as BRCA,p53,HER-2/neu cause predisposition to breast cancer than in those with normal gene activity.

Menstrual periods: Women who begin menstruating at an early age (before age 12) and those who reach menopause after age 50 have an increased risk of breast cancer.Because of long menstrual history,these women have increased exposure to hormonal fluctuations which is the reason for increased for breast cancer risk.Also those women who do not breast feed their children have enhanced risk as they are exposed to more number of menstrual cycles, as the lactation has a beneficial effect of delaying the restart of menses.

Delayed childbirth: Women who have their first child after age 30 or who never have a child are at a higher risk for develop breast cancer.

Personal habits: Most health care providers agree that regular alcohol intake increases breast cancer risk. A recent study on alcohol and breast cancer revealed that women who consume two to five alcoholic beverages each day were found to have a slightly higher risk of developing invasive breast cancer compared to women who do not drink alcohol.Smoking increases a woman's chance of developing several types of cancer, including breast cancer.

Diet: Though there is controversy , most clinicians in the agree that increased high fat consumption as in western diet is associated with increased risk as it leads to estrogen excess.Also good quality of nutrients such as fresh fruits which consists of vitamins,minerals and trace elements are shown to be protective and prevent breast cancer.

Weight: The link between weight and breast cancer risk is controversial. Several new studies suggest that overweight (obese) women who gained weight as adults are at an increased risk of developing breast cancer, but women who have been overweight since childhood are not at any significantly higher risk.

Previous radiation therapy: Women whose breast/chest area have been exposed to radiation therapy during childhood are at higher risk of developing breast cancer, especially if radiation was used to treat Hodgkin's disease. In general, the younger the woman was exposed to radiation, the greater the risk that she will develop breast cancer.

Hormone replacement therapy (HRT): HRT does not increase the breast cancer risk as it is used after menopause , but after prolonged use after 5 years does increase the risk .

How Do Women assess their Risk For Breast Cancer?

A questionnaire is issued for use by the general public which helps in early referral to treating physicians.

❖ When did she had menarche is it below 12 years ?	Yes	No
❖ When did she give birth to First child was it after 30 years?	Yes	No
❖ Are you childless?	Yes	No
❖ Did she had breast cancer in opposite breast?	Yes	No
❖ Did her family members(mother,sisters,daughter) suffer from breast cancer or lumps?	Yes	No
❖ Did she undergo breast biopsy?	Yes	No
❖ Was she told by any doctor that she has suspicious lumps or suspicious biopsy report?	Yes	No

If response to any of the above questions is “yes” which is 5 or above, then the woman should consult health care provider/counsellor/physician for examination and early diagnosis/or ruling out the suspicion.

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CLINICAL FEATURES

The clinical presentations of breast cancer are protean. They can be divided broadly as **Local**, **Regional** and **Systemic** varieties. Among all, lump felt by the patient or physician, in the breast is the most common presentation.

Local presentation : In 70 to 85% of breast cancer cases, lump in the breast is the presenting symptom. Though most of lumps in breast, if all breast diseases are considered are benign

- Change in size/shape of breast
- Dimpling, puckering of breast
- Skin induration
- Redness
- Nipple discharge
- Nipple retraction
- Found on investigation for breast pain
- No symptoms

The different signs found on clinical examination are :

- ❖ Nipple retraction
- ❖ Visible lump
- ❖ Irregular scar
- ❖ Palpable hard, irregular, non tender lump
- ❖ Peau d' orange (blockade of subdermal lymphatics with cancer cells)
- ❖ Nodules over the breast skin
- ❖ Ulceration
- ❖ Tethering/puckering
- ❖ Lumps fixed to chest wall with restricted mobility.
- ❖ Induration of skin over chest wall and arm

Regional presentation :

In certain case breast cancer is only suspected with finding of palpable lymph nodes in axilla and/or internal mammary lymph nodes and/or same side supraclavicular lymph nodes. Regional spread signals subsequent distant spread or metastasis. The findings on examination based on extent of disease may be

- Firm to hard/hard, mobile lumps
- Hard multiple, matted lymph nodes together
- Fixed lymph nodes to chest wall
- Ulcerating axillary lymph nodes

Systemic presentation :

The breast cancer, especially in younger women, men and moderate/high grade tumours spreads to distant sites and breast cancer is one of the cancers which spreads very early during the course of disease in its natural history. In fact by the time symptoms of breast cancer manifest, there are distant micro-metastasis. Based on the sites of deposits, the symptoms can be varied as follows :

Liver secondaries : Pain abdomen, jaundice and bleeding episodes.

Lung secondaries: Hemoptysis, pleural effusion, pleurisy.

Bone secondaries : Bone pain, fractures, spinal cord compression.

Brain secondaries : Stroke, cranial nerve palsies

Adrenal secondaries : Adrenal crisis, shock

Peritoneal secondaries : Ascites, cachexia.

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DIAGNOSIS

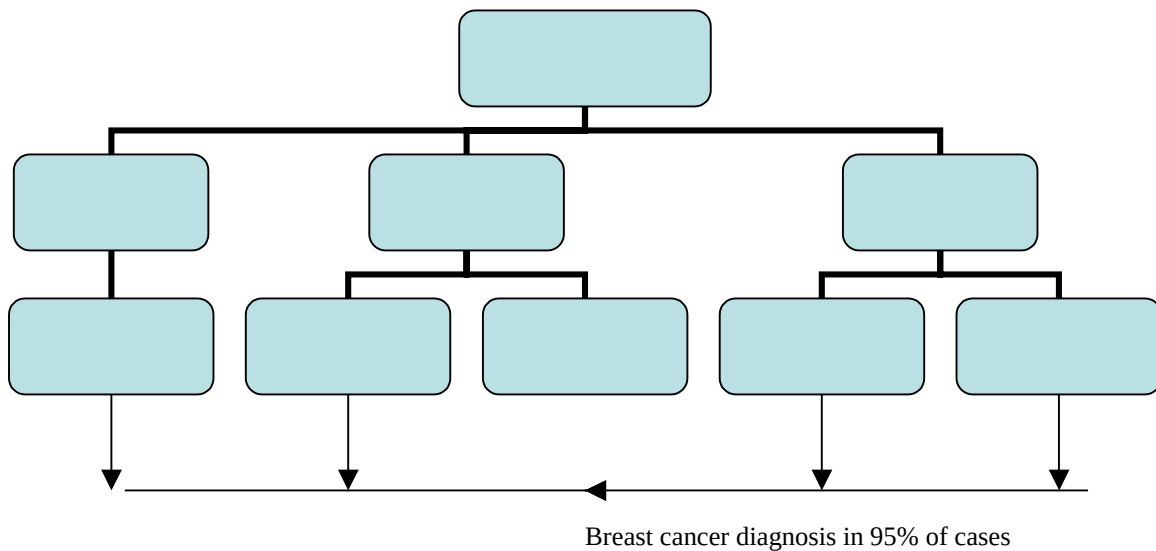
The methods used to come to a diagnosis of breast cancer include :

- ❖ Breast self examination
- ❖ Clinical suspicion
- ❖ Clinical Examination
- ❖ FNAC
- ❖ Biopsy
- ❖ Mammography
- ❖ Breast ultrasound
- ❖ Newer techniques : MRI, nuclear scan.
- ❖ Metastatic workup

The most important, practical and time tested method of using the available gadgets to come to clinical diagnosis is TRIPLE ASSESSMENT

TRIPLE ASSESSMENT

The main components of triple assessment are clinical examination, radiological imaging of breasts and pathological examination of tumour.

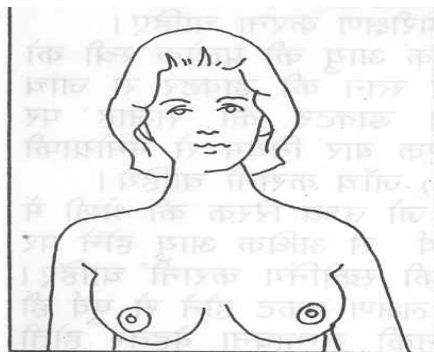


Breast self examination :

The importance of self examination is it saves lot of patient and doctor's time and once any suspicion or abnormality is noticed by the woman, she should consult the physician, for proper evaluation of the complaint.

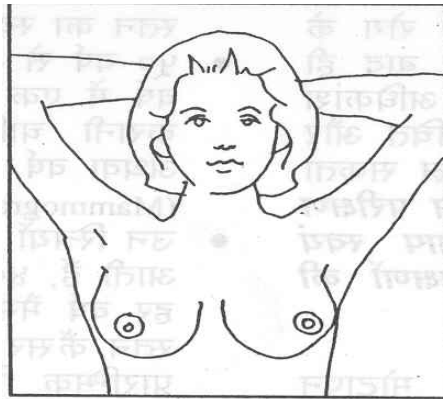
How Should I Examine My Breasts?

- Examine in standing and lying down, both breasts, with flat of your hands.
- Size and shape
- Puckering of skin, discoloration.
- Alteration of nipple.
 - 1) Stand in front of a mirror & inspect both the breasts for any abnormality like change in shape, nipple discharge, dimpling of skin or redness.



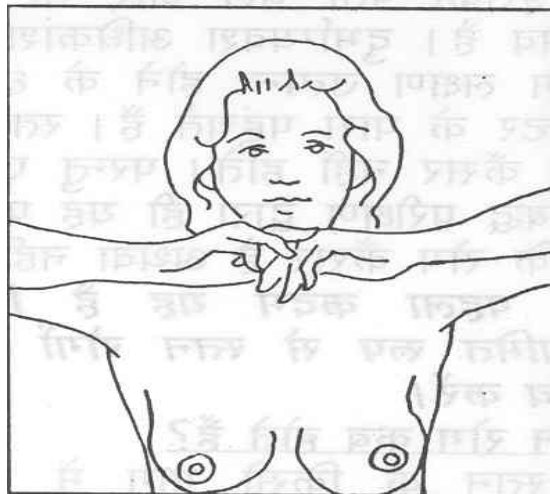
1. एक आईने में अपने स्तनों की जांच करें। क्या एक स्तन दूसरे की अपेक्षा बड़ा अथवा नीचा तो नहीं हो गया है ? क्या एक स्तनाग्र भीतर की ओर मुड़ा है ? क्या पानी या रक्त बहता है ? क्या त्वचा में झुर्रियाँ, छोटे-छोटे गड्ढे या अन्य परिवर्तन हैं?

2. Watching closely in the mirror clasp both hands behind the head and press. Look for any dissimilarity between both breasts in movement, texture, any skin or nipple change.



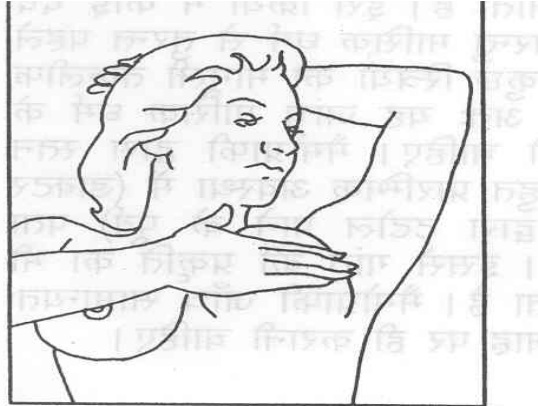
2. बाँहों को सिर से ऊपर उठाकर प्रत्येक स्तन का बगलों तक परीक्षण करें। कोई सूजन अथवा झुर्रियाँ तो नहीं हैं? अपने स्तनाग्रों को देखते-देखते हाथों को ऊपर और नीचे कीजिए। क्या वे एक बराबर हिले हैं ?

3. Now bend forwards and clasp both hands in front again examine both breasts for any abnormality.



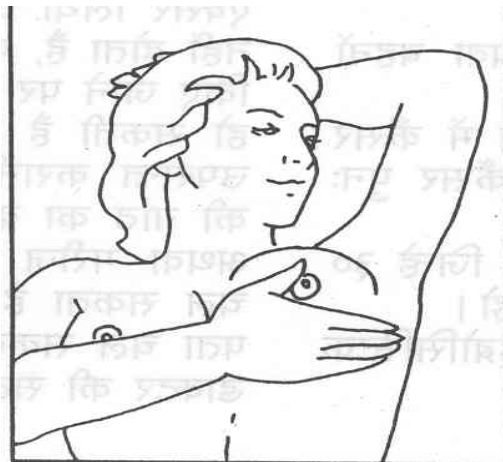
3. आगे झुककर प्रत्येक स्तन का छोटे-छोटे गड्ढों के लिए, झुर्रियों के लिए तथा स्तनाग्र के अन्दर की ओर मुड़े होने के लिए परीक्षण कीजिए। अब विश्राम की अवस्था में लेट जाइये।

4. Raise your left arm and with the right hand carefully and gently explore the left breast in small circles starting at the outer edge and gradually moving towards the nipple and areola to find any lumps. Exploration is done in several methods i.e., spirally, radially, obliquely, and in small circles. The same action is performed on the right breast.



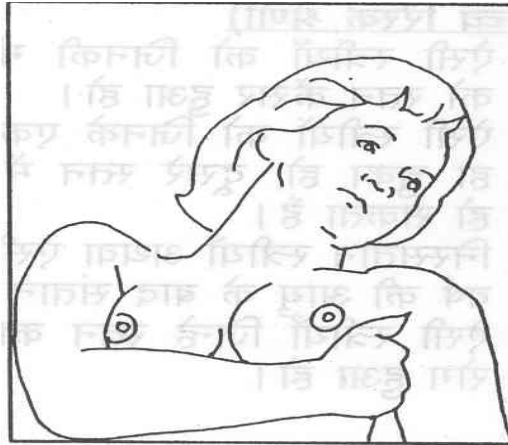
4. अब बायें स्तन से शुरू करें। अपनी ऊंगलियों को सीधा व सटाकर रखते हुए स्तन पर हाथ फेरें। न बहुत जोर से दबायें न बहुत हल्के से। थोड़े अभ्यास के साथ ही आप सही तरीका सीख जायेंगी।

5. Repeat the procedure of exploring the breast with the person lying flat. Both the breast self examination should be done in similar circular motion.



5. बगल से शुरू करते हुए हाथ को स्तन पर स्तनाग्र के ऊपरी हिस्से तक बाहर से अन्दर की ओर फेरिए। स्तन में गाँठें देखने के लिए इस प्रक्रिया को बार-बार कीजिए ताकि स्तन के सारे हिस्सों का परीक्षण पूरा हो।

6. Examine while lying down, the area between the breast and underarm and underarm itself, for any abnormal lump, mass under the skin.



6. कालर बोन के ऊपर और बगल में गाँठों के लिए हाथ फेरिए। इसी प्रक्रिया को दाहिने स्तन पर दोहराइये। यदि आपको कुछ असामान्य लगे तो अपने चिकित्सक से सम्पर्क करिए। पर कृपया याद रखिए कि १० गाँठों में से केवल १ ही कैंसर होती है।

Clinical suspicion

Commonest complaint in breast cancer is lump in the breast identified incidentally or during self-examination. But most of the cancer are advanced by the time are palpable. So breast cancer should be diagnosed at an early stage for curative treatment, for which there needs to be a index of suspicion among women and health care workers. Apart from breast lump which is seen in 85% of cases, other pointers to early detection of breast cancer,

- Lump in armpit
- Change in size/shape of breast
- Dimpling, puckering of breast
- Skin induration
- Redness
- Nipple discharge
- Nipple retraction
- Found on investigation for breast pain
- No symptoms

The importance of these symptoms is once they are persistent, the person should consult the physician for clinical examination and further diagnostic workup and treatment/counseling.

Clinical Examination

Clinical examination is carried out by the physician/surgeon :

It includes

- ❖ Detailed clinical history about duration of symptoms,progress of symptoms,any other associated symptoms.
- ❖ Detailed clinical history about general features like appetite,loss of weight.
- ❖ Detailed clinical history of systemic features like cough,difficulty in breathing,jaundice,bone pain.
- ❖ Past clinical history of other systemic diseases such as Tuberculosis,Diabetes,hypertension,heart diseases,Chronic pulmonary conditions like asthma,all these help in treatment planning and diagnosis.
- ❖ Personal history includes Age at menarche,pattern of menstrual cycles,any cyclical mastalgia,age at having 1st child,breast feeding,parity and smoking history and any drug allergy.
- ❖ Family history is enquired especially,if 1st degree relatives who are affected by breast cancer/ovarian cancer or any G.I/soft tissue tumours.

After detailed clinical history taking,next step is actual examination,

The following sequence is used_:

- ❖ General examination in which the condition of built, nutrition, eyes, skin, hands, feet are examined to see for any anemia, jaundice, edema, lymphadenopathy, pulse, Blood pressure changes.
- ❖ Inspection, in which the breast and axillary regions are exposed from the neck to abdomen around umbilicus, as a 1st step, then these regions are looked at for any signs of disease, such as lumps in both the breast,axillae,chest wall,both arms,neck supraclavicular fossae and abdomen.
- ❖ Palpation is systematic method of feeling all the regions mentioned in inspection for any lumps and to define the additional features of it such as consistency,fixity to surrounding soft tissue, skin and bony structures and lymph nodes in axilla,neck which indicate spread of cancer beyond breast.Palpation is done in different positions such as sitting with arms by the side of body ,sitting with arms raised above the head semi-recumbent,lying down and leaning forward.All these help in exactly identifying the characteristics and extent of lump and thus in diagnosis.
- ❖ Abdomen is palpated for any liver enlargement,other lumps and any free fluid.
- ❖ Lungs are percussed and auscultated for any pleural effusion
- ❖ Skeletal system is examined for bone pain,tenderness or muscle weakness,which suggests extensive metastasis(spread) to distant sites from breast and also has poor prognosis.
- ❖ After clinical examination a provisional diagnosis is made and decision to carry out relevant tests and investigations is planned.

Mammography

This is the method in which soft tissue X – ray is taken by placing breast in direct contact with the film and exposing to the source radiation.It has advantage that it is painless,quick and safe technique.Avoids expensive and toxic treatment of advanced cancer or it gives re-assurance if negative.The amount dose delivered by mammography less than normal plain X-ray.

Commonest type used is film-screen mammography. The different varieties of mammography used, based on utility are :

Standard mammography
Diagnostic mammography
Additional mammographic views
Specimen mammography

Standard mammography :

A screening mammogram includes craniocaudal (CC) and mediolateral oblique views of each breast, the combination of these two images should almost the entire breast volume. In CC view, the breast is compressed in a horizontal plane. The lateral most part of breast including axillary tail, may not be visualized properly due to curved shape of breast. The MLO view includes the axillary tail and breast is compressed side to side. Compression helps to decrease motion of breast and overlap of surrounding tissues thus improves quality. It also hastens the total procedure of imaging.

Diagnostic mammography:

This is used to evaluate the patient with clinical symptoms and signs of breast cancer such as palpable lump, pain, nipple discharge and to visualize and localize further abnormalities detected on screening mammography. It is done in various views and sometimes supplemented by breast ultrasound. Other indications of diagnostic mammography are history of breast cancer and prior benign breast disease and biopsy.

Additional mammographic views:

There are several other mammographic views that aid in better imaging of certain areas of breast tissue. The exaggerated craniocaudal lateral (XCCL) view is also known as internally rotated CC view because breast is internally rotated in relation to the compression plate and the film. This helps to include lateral most breast tissue in CC view which is usually seen in MLO views. Likewise most medial lesions of breast can be included in externally rotated CC view or a Cleavage (valley) view as it is near cleft between the breasts. This also images medial portions of both breasts. The axillary tail view is performed at an angle between CC and MLO views and helps to look into deeper regions of axilla that are covered in routine views. Lateromedial view in combination with standard views helps to exactly localize the lesion.

Specimen mammography:

Specimen mammography is done on the excised tumour tissue after breast conservative surgery in the form of lumpectomy or wide local excision. In this a 'j' tipped wire is inserted through the breast tissue under mammographic guidance into the tumour. Then the lump along with 1 cm surrounding breast tissue is excised at operation and specimen is submitted to mammography to confirm that the same lump seen in prior mammogram is excised.

There are four general types of breast tissue for mammographic interpretation :

1. Almost entirely fat
2. Scattered fibroglandular densities
3. Heterogeneously dense
4. Extremely dense

The different types of findings seen in mammography are:

Masses described in terms of shape, margins and their density in comparison to adjacent breast tissue. Calcifications with respect to their size, shape and distribution within breast. Architectural distortion of parenchyma of breast. Other findings like skin retraction, ligamentous thickening and axillary adenopathy. Most prominently stated finding of importance is calcification. In benign disease are usually large (>1 mm), confluent, diffuse and scattered. In cancers, they are mostly small (<0.5 mm), focal and clustered.

Though these are general features, they may be vice-versa, so these findings are to be interpreted in the light of clinical presentation and clinical findings. Serial images with comparison of previous films are more useful in difficult cases eg., previous breast surgery/trauma.

Assessment categories based on the different combinations of above features are :

1. Normal
2. Benign
3. Probably benign
4. Suspicious
5. Highly suggestive of malignancy(cancer)

FNAC(Fine needle aspiration cytology)

Procedure

Advantages

Disadvantages

This is the most commonly and early done definitive investigation test done in palpable breast lumps and even in impalpable lumps (under ultrasound guidance).

Steps of procedure :

- ❖ Patient is first explained about the procedure and its purpose.
- ❖ Then the breast region with lump is cleaned with antiseptic
- ❖ 21 to 23 gauge needle fitted to a 10 ml syringe is used
- ❖ the lump is fixed between the fingers of non-dominant hand
- ❖ Under sterile precautions the needle with syringe is passed in to lump
- ❖ With negative pressure exerted on piston of syringe needle is passed in multiple directions
- ❖ Then the syringe is withdrawn and the aspirated material is immediately released on to the series of slides kept ready before in hand
- ❖ The slides are either air-dried or wet-fixed in isopropyl alcohol for subsequent staining and pathological(microscopic) examination.

Advantages of FNAC :

- ❖ Simple procedure and can done on OPD basis
- ❖ Relatively atraumatic to the patient
- ❖ It may help in cure of a simple cyst
- ❖ First line of investigation in a breast lump.
- ❖ Sensitivity is 80 -97 %

Disadvantages of FNAC :

- ❖ Needs a experienced cytopathologist for reliable report.
- ❖ Inability to distinguish invasive from in situ cancer.
- ❖ Sample inadequacy in 10 to 30 % of cases

The specimen obtained is examined and based on findings is characterised as

1. Benign
2. Atypical/indeterminate
3. suspicious for carcinoma
4. malignant
5. insufficient sample for diagnosis

If findings are beyond category 2 from above, then other forms of biopsy ranging from core needle biopsy to excision biopsy or sometimes mastectomy is considered after evaluation of other components of **TRIPLE ASSESSMENT** (mammographic, sonographic and clinical findings) in addition to FNAC.

Biopsy

Biopsy is a procedure of obtaining partial specimen or entire cancerous lump by various techniques for histological diagnosis/ruling out of cancer. The advantages of having more sample of tissue is increased accuracy of diagnosis.

The various methods of biopsy techniques are :

1. FNAC
2. Core needle biopsy
3. Stereotactic biopsy
4. Incisional biopsy
5. Excisional biopsy

Core needle biopsy : This method in many ways resembles FNAC, but has more yield of diagnosis as larger amount of material is obtained. It is better understood if compared with FNAC and read.

<i>Core/Trucut biopsy</i>	
❖ <i>21 to 23 G size needle</i>	❖ 14 to 18 G needle
❖ <i>Bevelled tipped needle</i>	❖ Cutting needle
❖ <i>OPD procedure</i>	❖ Done in admission or under observation after procedure
❖ <i>Loose cells and stroma are sampled</i>	❖ Tissue cores are obtained
❖ <i>Material may inadequate or not representative of whole lump</i>	❖ Complete pathological assessment
❖ <i>Sensitivity rates are 75 to 98 %</i>	❖ Sensitivity rate is almost 100%
❖ <i>It is relatively painless and atraumatic procedure</i>	❖ Main disadvantage is greater trauma and bruising to the breast
❖ <i>Used as a first line test in all cases</i>	❖ Useful in suspicious FNAC reports.

Stereotactic biopsy :

It is method of image guided biopsy technique in which images obtained are paired and the lesion is accurately localized in three dimensional conformation by computer first. Then under this guidance a needle can be passed in to the lesion to obtain the material. This method is used in impalpable lumps. This

procedure helps in detection of cancer at very early stages thus helps in better cure rates and conservative breast surgeries.

Incisional biopsy :

This is simpler form of open surgical biopsy technique in which a portion of lesion is incised and taken for pathological examination. With improved percutaneous needle biopsy methods, incisional biopsy is rarely used except in large lumps but suspicious of DCIS and core needle method is not available. The other form of incision biopsy is edge biopsy in ulcerated breast cancer masses.

Excisional biopsy :

Any breast lesion that requires definitive histopathological evaluation can subjected to excisional biopsy. If needle biopsy is not technically feasible or when the findings of lesser methods are not conclusive then open diagnostic biopsy is indicated. But the essential precaution before and after it is to ensure that the palpable lesion correlates with mammographic / ultrasonographic abnormality. The skin incision site is placed over the lump and precaution to be taken that this scar lies within the incision site of subsequent mastectomy if it is needed later.

Breast ultrasound :

Breast ultrasound is a cost effective and useful alternative or complementary imaging investigation to mammography. Breast ultrasound is done with a high frequency 7 to 10 MHz hand held transducer probe. The scanning is done with the patient in supine position usually, though it can be done in sitting up, reverse oblique positions. Breast ultrasound has 100% accuracy in distinguishing a simple cyst from solid mass. In addition, it helps in guided FNAC/needle biopsy of small impalpable lesions or small lumps in large breasts

Indications of Breast ultrasound :

- ❖ To differentiate cysts from solid nature of palpable or non-palpable breast masses.
- ❖ As a initial screening test of palpable lumps in young (usually <30) or pregnant women.
- ❖ Helps in guided biopsies.
- ❖ To evaluate doubtful mammographic abnormalities

Newer techniques :

Many new investigations are being tested for early detection of breast cancer. One of them is MRI (Magnetic Resonance Imaging). So far the only approved indication for MRI breast is to evaluate the integrity of breast implants. But the other potential indications for MRI are clinically palpable but mammographically and sonographically negative lumps, for further details of lump characteristics and to investigate cases with nipple discharge. But at present MRI is still investigational tool and not widely used as it is not cost effective, availability of cheaper alternatives and not available in many centres. Other newer techniques of breast imaging like Technitium-99m isotope scanning and PET(positron emission tomography), are being tested with encouraging results in some experimental studies, but again they are not widely available and not cost effective. But in future they may find place in diagnostic work up of breast cancer.

Metastatic workup:

Metastatic workup is systematic search for secondaries (metastatic deposits), which spread from the primary site of cancer in breast, once breast cancer is diagnosed. The metastatic search is important in a case of breast cancer, because it significantly alters the treatment plan, adversely affects the prognosis, recurrence and survival rates of the patient. Sometimes breast cancer presents clinically with the symptoms related to secondaries and breast cancer is diagnosed retrospectively. For example,

Liver secondaries : Pain abdomen, jaundice and bleeding episodes.

Lung secondaries : Hemoptysis,pleural effusion,pleurisy.
Bone secondaries : Bone pain,fractures,spinal cord compression.
Brain secondaries : Stroke,cranial nerve palsies
Adrenal secondaries : Adrenal crisis,shock
Peritoneal secondaries : Ascites,cachexia.

In metastatic workup the following investigations are carried out :

1. Chest X-ray (for Lung secondaries)
2. Ultrasound abdomen and/or CT scan Abdomen.
3. Plain X-rays of long bones,spine and skull.(for Bone secondaries)
4. If X-rays are suspicious,Tc-99m skeletal scan is done(for Bone secondaries)
5. CT skull if brain secondaries are suspected clinically.

In metastasis positive cases,the first line of treatment is chemotherapy(primary chemotherapy) and palliative pain control and nutritional support with loco regional treatment in the form of radiotherapy used for symptomatic isolated secondaries eg., painful bone deposits, isolated brain deposits. Very rarely the cancer may downstage, then surgery to breast is considered or Toilectomy for ulcerating / fungating / bleeding breast cancers.

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TREATMENT

Treatment of Breast cancer is multi-modal type with use combinations of different methods available. The different methods used in Breast cancer management are :

- ❖ SURGERY
- ❖ CHEMOTHERAPY
- ❖ RADIOTHERAPY
- ❖ HORMONAL THERAPY

SURGERY

The many surgical options available for breast cancer treatment are :

- 1) **Wide local excision** : Also called as lumpectomy where the tumour mass with 1cm surrounding normal breast tissue on all sides is excised.This is presently most commonly used [Breast conservative surgery](#)
- 2) **Segmental excision** :It is similar to lumpectomy,but in this form the lump with 1 cm margin is excised from nipple to the base of breast.
- 3) **Quadrantectomy** : Here one quadrant of breast is removed i.e., Same as segmentectomy but with 2-3 cm margin all around the lump.This is not used widely as this causes distortion in shape of breast.
- 4) **Simple mastectomy** : In this whole breast including the nipple,areola ,skin overlying the lump and axillary tail are removed,but axilla is not involved in resection.

5) **Modified radical mastectomy(MRM)** : This procedure goes by the name of Patey's. In MRM in addition to simple mastectomy, the lymph nodes, fatty tissue and fascia of whole axilla is resected in continuity with breast.

6) **Modified Patey's mastectomy** :

This is essentially same as MRM but with slight difference surgical procedure. Three Two types are there .Scanlon modification, where pectoralis minor is cut at insertion ,so that level 3 axillary lymph nodes can be removed effectively. Duncan modification in which pectoralis muscle is just retracted and in Madden type, the muscle is cut but resutured.

7) **MRM with immediate reconstruction** with Latissimus dorsi muscle flap is recent trend in selected cases.

8) **Radical mastectomy** : This is the classical earliest form of breast cancer surgery introduced by Halsted, over a century ago. In this in addition to MRM the pectoralis muscles are removed, which is associated with shoulder stiffness and loss of shoulder contour and weakness of shoulder movements. This is no longer practiced due to better availability of radiotherapy and adjuvant treatment with good loco-regional control.

9) **Toilet mastectomy** : Its only of salvage utility, used in terminal stages, where fungating, bleeding cancers are locally resected and closed.

10) **Axillary clearance** : In this separate incision in axilla is given and lymph nodes are excised along with fat and fascia. It is usually done in conjunction with breast conservative surgery.

Broadly commonly done surgical options can be divided in to :

- ❖ Conservative breast surgery(BCS)
- ❖ Modified radical mastectomy

Breast conservative surgery :

In this form the patient is left with native breast. The different options available are lumpectomy, segmentectomy and quadrantectomy. It is invariably followed by radiotherapy.

Indications for BCS are :

1. Solitary tumour.
2. Ductal carcinoma in situ.
3. Post-operative radiotherapy.
4. stage 1 and 2 tumour.
5. <4 cm.
6. small lump with large breasts.

Contradictions for BCS are :

- ❖ Multicentric tumours.
- ❖ Pregnancy.
- ❖ H/o connective tissue diseases like SLE.
- ❖ H/o of previous irradiation to chest.
- ❖ Small breasts with large lumps.
- ❖ Stage 3 and 4
- ❖ >4 cm.

CHEMOTHERAPY

Chemotherapy is administration of drugs, usually in combination – Polychemotherapy.

They are used either before (Neo-adjuvant) / after (Adjuvant) depending on the stage of cancer. Neo-adjuvant treatment is used in locally advanced disease to downstage the disease/to facilitate conservative breast surgery/to reduce the chances of recurrence/to assess the response to treatment. Adjuvant therapy is used in the setting of early breast cancer, which is operated first, then the drugs are administered to improve the outcome. Though chemotherapy facilitates cancer cure it is associated with many potential toxic side effects. So the patients are chosen with appropriate risk/benefit ratio.

The most common and important factors taken into consideration for giving chemotherapy are :

1. Age of patient-pre or post menopausal
2. Estrogen(ER) and progesterone(PR) receptor status of the tumour.
3. Tumour size
4. Grade of tumour
5. Age of patient <35-high risk and >35 low risk.
6. Lymph nodes in axilla

Adjuvant Treatment in Node-Positive Breast cancer :

Premenopausal

ER/PR positive	Chemotherapy + tamoxifen
ER and PR negative	Chemotherapy

Postmenopausal

ER/PR positive	Tamoxifen + chemotherapy
ER and PR negative	Chemotherapy

Elderly

ER/PR positive	Tamoxifen +/- chemotherapy
ER and PR negative	Consider chemotherapy

Risk factors predicting prognosis

Factor	Low risk	Intermediate risk	High risk
Tumour size	<1 cm	>1 – 2 cm	> 2 cm
Grade	1	1 - 2	2 - 3
Age	> 35	-	< 35
ER / PR status	Positive	Positive	Negative

Adjuvant treatment in Node – positive Breast cancer :

Patient Group	Low risk	Intermediate risk	High risk
Premenopausal ER / PR positive	None / Tamoxifen	Tamoxifen +/- chemotherapy	Chemotherapy + Tamoxifen]
ER and PR negative	Not applicable	Not applicable	Chemotherapy
Post menopausal ER /PR positive	None / Tamoxifen	Tamoxifen +/- chemotherapy	Tamoxifen + chemotherapy
ER and PR negative	Not applicable	Not applicable	Chemotherapy
Elderly ER /PR positive	None / Tamoxifen	Tamoxifen	Tamoxifen
ERand PR negative			
	Not applicable	Not applicable	Consider chemotherapy

- ❖ Premenopausal women usually have a aggressive type of cancer.
- ❖ ER PR positivity guides use of hormonal treatment (Tamoxifen)
- ❖ Elderly people have slow growing variety of tumour and also cant tolerate the toxicity of chemotherapy.
- ❖ High brisk patients usually need chemotherapy because of their metastatic nature.

The note of caution is that the guidelines mentioned above are not followed uniformly in all cases or is advisable. There are many other scientific, institutional and social reasons in using chemotherapy, which are decided upon by the physician. They are condemned to be used by patients or non-doctors.

Once the decision of giving chemotherapy is made there are many regimens that can be used:

CMF

Cyclophosphamide	500 mg/m ² on day 1
Methotrexate	40 mg/m ² on days 1 and 8
5 – Flurouracil	500 mg /m ² on days 1 and 8

Repeat every 28 days , for 6 cycles.

CAF

Cyclophosphamide	500 mg/m ² on day 1
Doxorubicin	50 mg/m ² on day 1
5 – Flurouracil	500 mg/m ² on days 1– 8

Repeat every 3 weeks , for 6 cycles.

CEF

Cyclophosphamide	500 mg/m ² on day 1
Epirubicin	60 mg/m ² on day 1
5 – Fluorouracil	500 mg/m ² day 1

Repeat every 3 weeks , for 6 cycles.

AC + Paclitaxel

Doxorubicin	60 mg/m ² on day 1
Cyclophosphamide	600 mg/m ² on day 1

Repeat every 21 days , 4 cycles , followed by :

Paclitaxel	175 mg/m ² over 3 hrs on day 1
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Repeat every 3 weeks , for 4 cycles.

Before giving each cycle of chemotherapy,patient's blood parameters such as Hemoglobin level,cell counts and cardiac condition are assessed to minimize/avoid the side effects of chemotherapy drugs.

Side effects of chemotherapy :

1. Bone marrow suppression which leads fall of leucocyte and platelet counts which usually recovers in 2-3 weeks
2. Nausea and vomitings are frequent frustrating complaints in many patients treated by centrally acting Anti-emetics.
3. Mouth ulcers,gastritis and diarrhea leading to dehydration and undernutrition can occur.
4. Paraesthesias and tingling in hands and extremities can occur.
5. Photosensitive rashes,hair loss can occur in exposed skin.
6. Hemorrhagic cystitis with burning micturition is seen usually with cyclophosphamide drug.
7. Long term toxicity like infertility,heart disease and second cancers can occur.
8. Though most of the side effects are self limiting but permanent/prolonged damage can be seen with high dose chemotherapy especially in patients with pre-existing diseases.

The way to minimizing these effects are proper selection of patients,correct drugs,dosage,duration and monitoring side effects and treating them with symptomatic improvement/change to another regime or withdrawal and using other form of treatment.

RADIOTHERAPY

Radiotherapy constitutes use of high energy particles like neutrons,B-rays,Gamma rays,photons generated from different sources to strike the tumour.These particles cause excitation of the atoms in biochemical processes of tumour cells.this leads to series of changes causing destruction of cancer cells.

Different methods of administering radiotherapy are :

1. External beam irradiation
2. Brachytherapy
3. Intra-operative irradiation

Indications of Radiation in the Breast cancer

- ❖ After conservative breast surgery
- ❖ Mastectomy and axillary dissection in stage 2 and 3
- ❖ Loco-regional recurrence following mastectomy

- ❖ Palliation of bone or brain secondaries including spinal cord compression
- ❖ Following systemic therapy
- ❖ Fungating and bleeding advanced tumours

External beam irradiation :

This is method of giving radiation in which the source of radiation will be outside the patient and at a distance from the target. The target area including the sites to be involved in the field of irradiation is determined first. Then the patient is kept within the striking area of source, which is usually Megavoltage cobalt unit which is used to deliver radiation.

The usual area includes whole breast area, chest wall in front on the side of breast cancer, including lower neck to cover supraclavicular lymph nodal area.

The commonly used dosage is called standard fraction radiation – in which 5000 cGy dose is used over a period of 5 weeks with 5 days/week, daily dose being 200cGy/day. There many other modifications such as hyperfractionation (<200 cGy with more number of doses/day), longer duration (6 to 8 weeks) and larger total doses. All these decisions made by type of tumour, stage and patient general health characteristics. It is usually given about 5-6 weeks after surgery.

Brachytherapy :

In this method, the source of radiation is within the tumour mass. Here usually Iridium-192 needles are inserted in to the breast tumour area and the dose is delivered. The main advantages of this method is ability to deliver high dose to the cancer tissue with sparing of surrounding normal breast tissue. This is said to effectively control local disease and reduce the recurrence rate. The main disadvantage is no proper evidence of brachytherapy effectively treating the cancer because it is not widely used compared to well tested external beam irradiation.

Intra-operative irradiation :

This is the method of delivering radiation to breast area during the actual operation, so that the adjuvant treatment starts early. With all safety precautions to theatre staff, the desired dose is delivered to the tumour bed.

Complications of Radiotherapy :

- ❖ Arm edema (swelling due to lymphoedema)
- ❖ Pneumonitis (lung infection)
- ❖ Rib fractures due to radionecrosis of bone
- ❖ Myocarditis
- ❖ Brachial neural plexopathy
- ❖ Soft tissue necrosis
- ❖ Second malignancy

The most common complication is arm edema due to lymphatic blockade especially if previous breast surgery is done. So it is advised that both surgery and radiation are not given to the axilla. Treatment is arm elevation and compresses and symptomatic treatment. Others are treated symptomatically and with physiotherapy. Rib fractures may need irradiation or rarely surgical reduction and fixation. Lung infection needs aggressive antibiotic treatment and brachial plexopathy may need steroids. All the complications should be dealt in special unit by multimodal team approach including physician, surgeon, radiation oncologist, physiotherapist and good nursing care.

HORMONAL THERAPY

Hormonal therapy includes medical/surgical modification of hormonal activity concerned with breast physiology and breast cancer pathophysiology. It is an important and useful adjuvant treatment in most of patients.

Breast cancer growth and spread is stimulated by excess estrogenic activity, for which the sources are many. In pre-menopausal women mainly it is from ovaries. In post-menopausal women, it is from adrenals and peripheral fatty tissues and conversion of testosterone in men. Estrogens increase the growth of both ductal and glandular components of breast and breast cancer is exclusively sensitive to estrogen especially those with more estrogen receptor positivity on the surface of cancer cells. Even progesterone hormones have similar action like estrogen on breast, but to a lesser extent. Thus decreasing the estrogenic and progestagenic activity in the body forms the basis for hormonal treatment.

Different methods of hormonal therapy includes :

1. Bilateral **OOPHERECTOMY** (ovarian ablation) in **premenopausal women**.
2. **Antiestrogens** : Tamoxifen, toremoxifen and derivatives.
3. **Aromatase inhibitors** : Non-steroidal drugs like Anastrozole, Letrozole.
Steroidal drugs like Exemestane etc.,
4. Progestagens : Medroxy progesterone acetate, Megesterol etc.,
5. Adrenalectomy, hypophysectomy (pituitary) : these have become historical and not used now because of effective adjuvant drugs.

Antiestrogens : They are commonly used drugs in postmenopausal women and even in pre-menopausal women with ER/PR positivity. The usual pattern used is 20 mg daily dose of tamoxifen in 2 divided or once daily dose. It is given for 3 to maximum of 5 years.

The mechanism of action is it is partial (anti-estrogenic) agonist to breast and causes side effects as it is agonist to uterus. So it causes suppression of growth of cancer but may lead to uterine bleeding and endometrial cancer if used for prolonged periods.

The commonest side effect is Hot flushes simulating perimenopausal symptoms. Others are headache, hypertension, uterine bleeding, endometrial cancers.

But its efficacy decreases after 3 years of use and after 5 years it is almost ineffective. But some studies claim its utility in prevention of further cancers if used in low doses even beyond 5 years. Remains the first line of hormonal therapy.

Aromatase inhibitors : They inhibit the enzyme aromatase which is responsible for conversion of many steroids and testosterone on adrenals and in peripheral fatty tissues into estrogens. Thus it acts more proximally than anti-estrogens, while the latter acts on receptors over the cancer cells. The usual dose used is Anastrozole 1 mg and letrozole 2.5 mg. They are used mainly in post-menopausal women and those with ER/PR positivity. Aromatase inhibitors are presently second line drugs to **tamoxifen** and considered in elderly women or in **tamoxifen** resistant cases. Recent studies show these can be used as first line drugs but not practised widely.

In premenopausal women as ovaries are main source of estrogens medical or hormonal ablation is best form of hormonal treatment. The process of ovarian ablation is called OOPHERECTOMY. The various methods of achieving it are :

- ❖ Medical oophorectomy.
- ❖ Radiation oophorectomy.
- ❖ Surgical oophorectomy.

In medical ablation, GnRH (Gonadotropin releasing hormone) analogues/agonists given which suppresses the ovaries. Normally ovaries function by cyclical circadian rhythm pattern of stimulation by hypothalamic GnRH secretions. If it continuously present in circulation ovaries are suppressed.

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Eg., Goserelin – 3.4 mg/day, Buserelin, leuprolide – 3.7 mg /day. [Go to top](#)