دعائي لكل مريض

أ. م. د. وئـــام أحمـــد العـامـلـــي

MOLECULAR SUBTYPES OF BREAST CANCER

BY

Assist. Prof.

Dr. Wiaam Ahmed Al- Amili

Cancer

Cancer is the abnormal, uncontrollable , continuous replication of cells which will inevitably lead to the formation of a tumor.

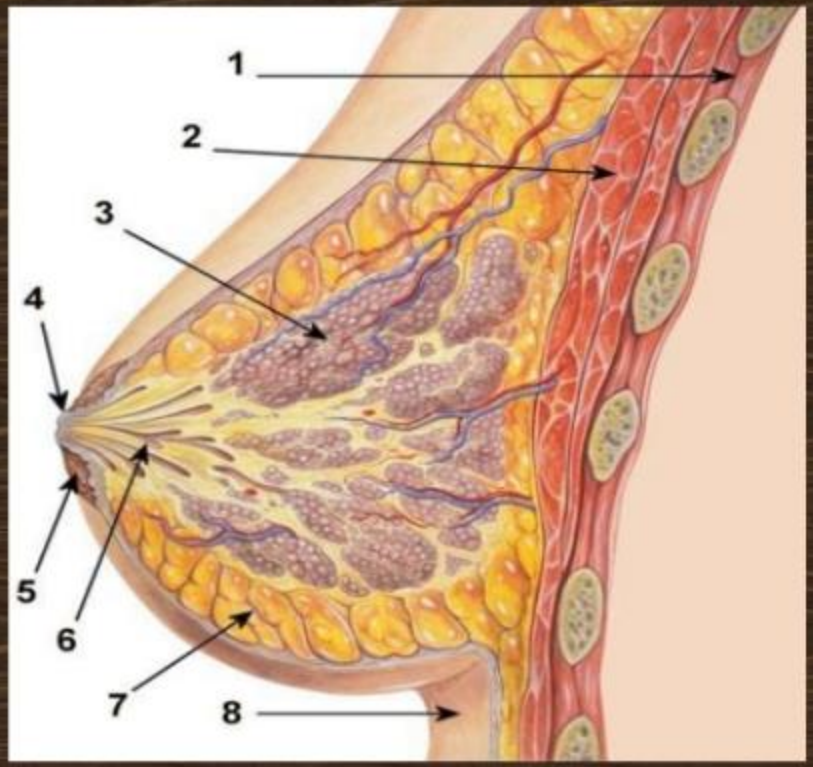
Breast Cancer

Breast cancer

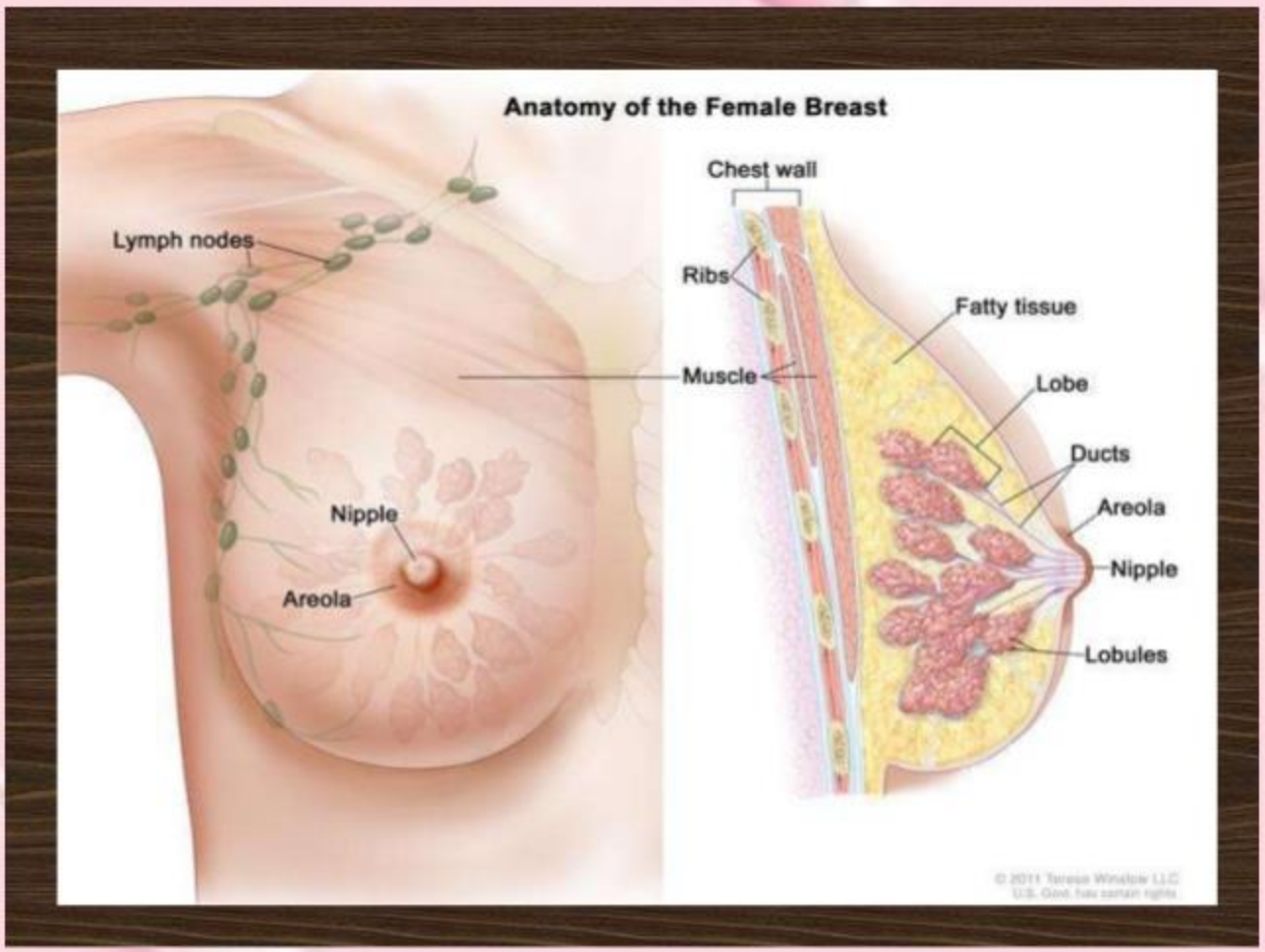
Forms in the tissues of the breast

Spreads mainly through the Lymphatic system

THE NORMAL BREAST



1. *Chest wall.*
2. *Pectoral muscles.*
3. *Lobules (glands that make milk).*
4. *Nipple surface.*
5. *Areola.*
6. *Lactiferous duct tube that carries milk to the nipple*
7. *Fatty tissue.*
8. *Skin.*


Anatomy of the Female Breast
Lymph nodes
Nipple
Areola
Chest wall
Ribs
Muscle
Fatty tissue
Lobe
Ducts
Areola
Nipple
Lobules

BREAST TUMORS

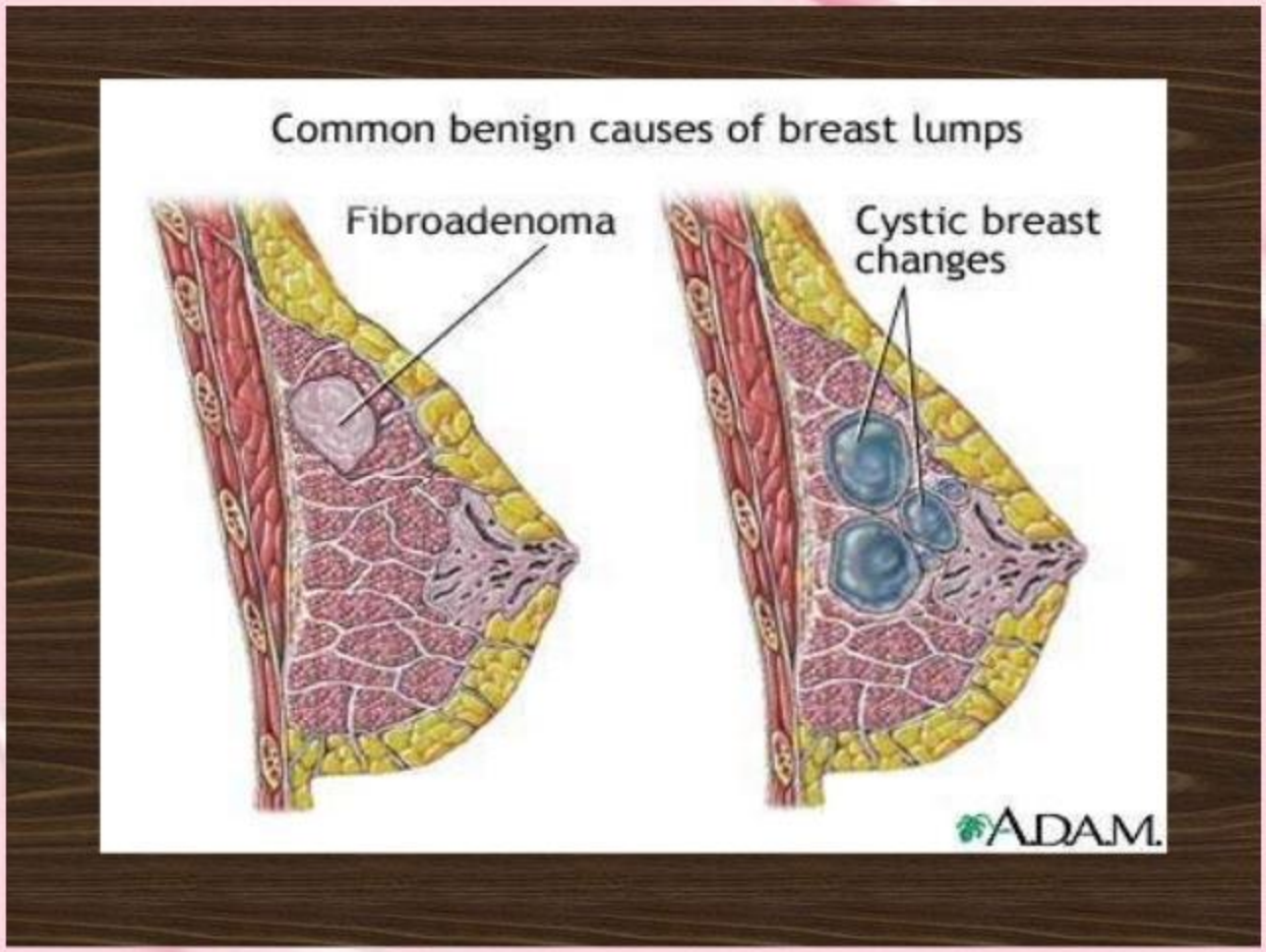
- Malignant
  - Cancerous
- Benign
  - Not - Cancerous

BENIGN TUMORS

- Not cancerous.
- Benign breast tumors are abnormal growths, but they do not spread outside of the breast and they are not life threatening.

BENIGN TUMORS

- Most lumps are caused by the combination of cysts and fibrosis
- *Cysts are fluid-filled sacs.*
- *Fibrosis is the formation of scar - like* tissue.
- These changes can cause breast swelling and pain.


Common benign causes of breast lumps
Fibroadenoma
Cystic breast changes
A.D.A.M.

Breast Cancer

- Breast cancer is a malignant (cancerous) tumor that starts in the cells of the breast. It is found mostly in women, but men can get breast cancer, too.

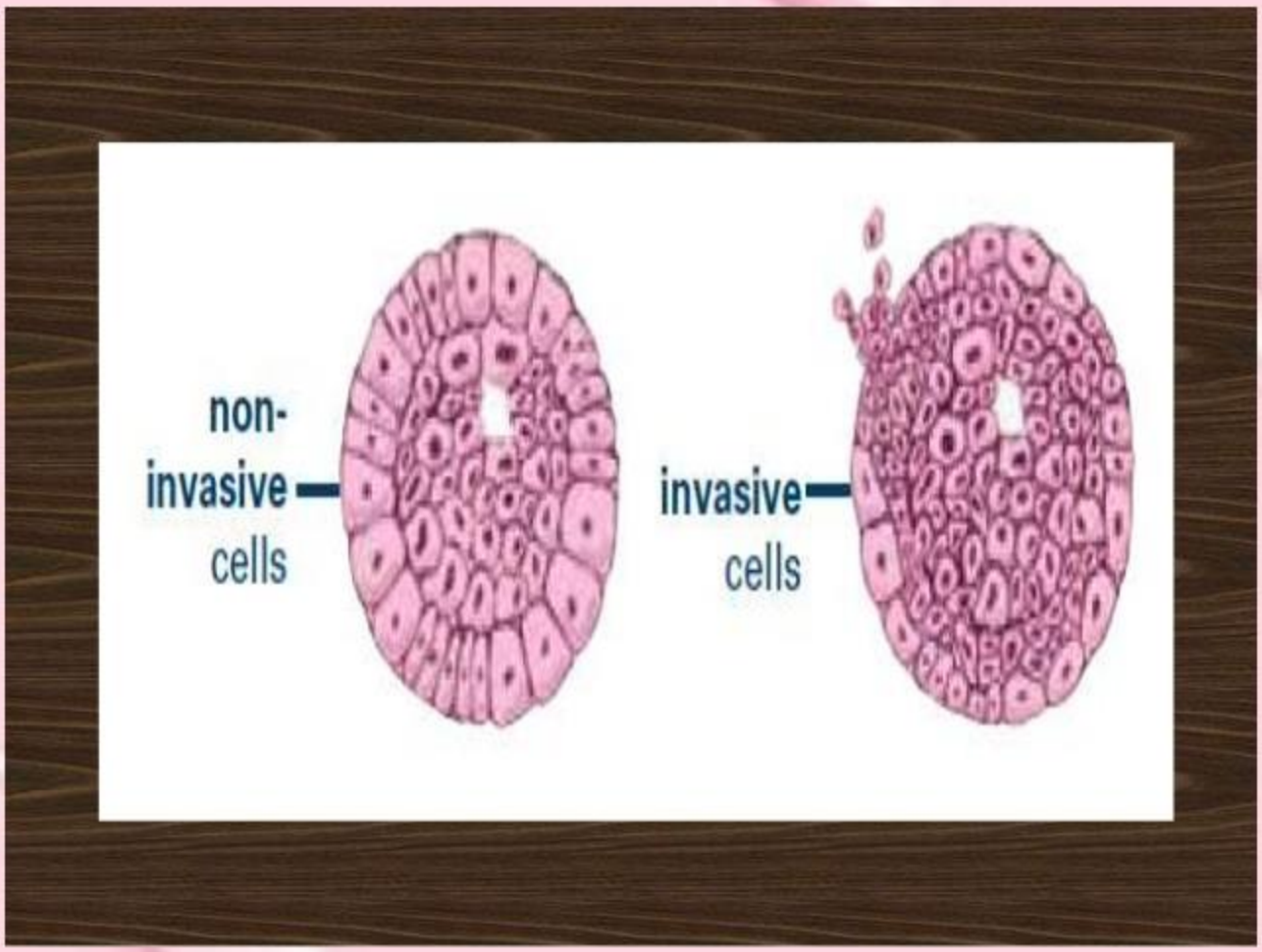
Breast Cancer

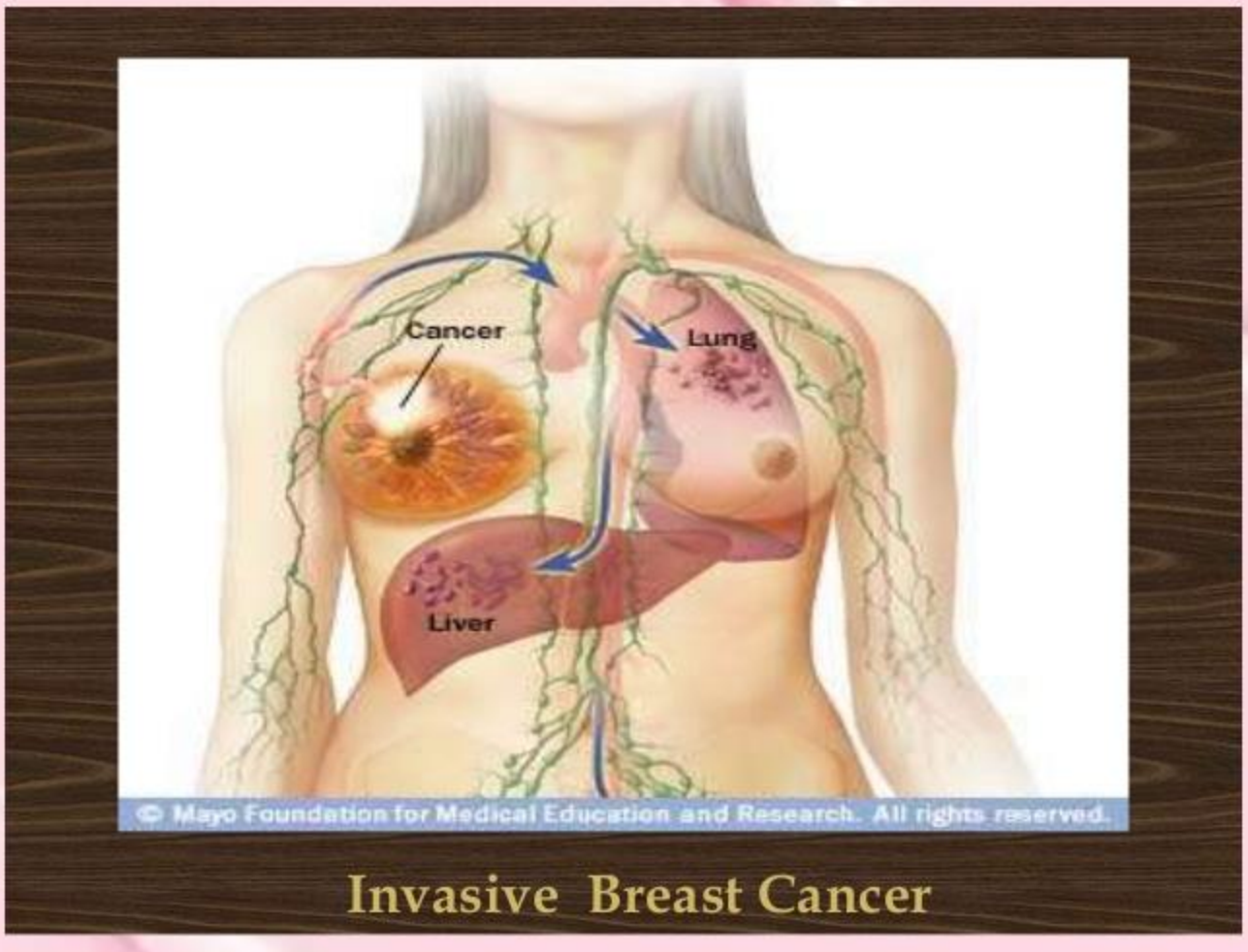
Invasive

- Cancerous
- Malignant
- Spreads to other organs (metastasis)

Non - Invasive

- Pre – Cancerous
- Still in its original position
- Eventually develops into invasive breast cancer.


non-
invasive
cells
invasive
cells



Invasive Breast Cancer

Breast Cancer

- The inner lining of milk ducts.
  - Ductal Carcinoma
- The lobules – Milk producing glands.
  - Lobular Carcinoma

TYPES OF BREAST CANCER

- Ductal Carcinoma
  - Invasive Ductal Carcinoma
  - Ductal Carcinoma in situ (DCIS)
- Inflammatory Breast Cancer (IBC)
- Lobular Carcinoma
  - Invasive Lobular Carcinoma
  - Lobular Carcinoma in situ (LCIS)

FACTORS THAT CONTRIBUTES TO BREAST CANCER

- Gender
- Age
- Genetic risk factors
- Family history
- Personal history of breast cancer

FACTORS THAT CONTRIBUTES TO BREAST CANCER

- Race/ethnic background
- Dense breasts tissue
- Certain benign (not cancer) breast problems
- Menstrual periods
- Breast radiation early in life

Despite surgery, cytotoxic chemotherapy, hormonal therapy, and/or regional radiotherapy, ~ 30% of patients will eventually experience disease recurrence and resistance to treatment are poorly understood .

Predict Chances of Relapse

Tumor Markers

- Tumor markers are substances that can be found in abnormal amounts in the blood, urine and tissues of some patients with cancer .
- Markers are needed to predict cancer progression and the risk of late recurrence .

➢A small number of single biomarkers, including

- Estrogen receptor (**ER**)

- Progesterone receptor (**PR**)

- Human Epidermal growth factor Receptor-2 (**HER2**)

- proliferation marker **Ki-67**

-These markers have been used for to predict the prognosis of breast cancer and guide effectiveness of therapy

Ki 67

- It's a protein in cells that is involved in cell replication, so if many cells are expressing it, the tumor is growing quickly; if very few cells express it, then it is growing slowly.

- Ki-67 is an excellent marker to determine the growth fraction of a given cell population

- A special stain that gives a sense of how aggressive a tumor is. The pathologist takes the biopsy or surgical specimen, prepares it, puts it on to a glass slide, stains it for this protein, and look at it under the microscope.
- The pathologist needs to count about a thousand cells and determine the percentage of cells that are Ki67 positive.

- **Therefore, the number that comes back should be a percentage from 0 - 100%.**
- **In general, if the Ki67 is :**

-between 0-2%, then we call it grade 1 or low grade.

-If it is between 2-20%, we call it grade 2 or intermediate grade.

-If it is > 20%, then it is grade 3 or high grade.

-The good, the bad, and the ugly.

Cytokeratins (CK)

- Cytokeratins are keratin proteins found in the intracytoplasmic cytoskeleton of epithelial tissue.
- They are an important component of intermediate filaments, which help cells resist mechanical stress.
- Thus they are used clinically to identify the cell of origin of various human tumors

Cytokeratin (CK)

- Is a Tumor marker .
- The different types of cytokeratins are numbered based on where they are found in the body.
- CK5 positivity helps define a basal-like subtype of triple negative breast carcinoma (TNBC) with poorer prognosis

- Amplification or over-expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer .
- In recent years the protein has become an important biomarker and target of therapy for approximately 30% of breast cancer patients

HER2/neu

- ***HER2/neu:*** growth-promoting protein

➢***HER2*** (from **human epidermal growth factor receptor 2**) or ***HER2/neu*** also known **Receptor tyrosine-protein kinase ERBB-2 (**erythroblastic oncogene B) .

➢HER2 is a member of the human Epidermal Growth Factor Receptor (HER / EGFR / ERBB) family .

Breast Cancer

- **Breast cancer is a very complex, heterogeneous and phenotypically diverse disease.**

- **It's different subtypes have distinct behavior and response to therapy**

Breast tumors are classified by their **hormone-receptor status** and by the presence, or absence, of **certain proteins**.

The type of tumor determines how the disease will be treated.

- **Breast Cancers were divided into:**

- hormone receptor positive

- hormone negative tumours.

Breast carcinomas were classified into four main molecular subtypes :

1- Luminal A: ER/PR(+) / HER2(-)

2- Luminal B/Triple Positive: ER/PR(+) / HER2(+)

3- Non-Luminal/Triple Negative: ER/PR(-) and HER2(-)

4- Non-Luminal HER-2 enriched: ER/PR(-) / HER2(+)

Other phenotypes included:

ER(+)/ PR(-) / HER2(+)

ER(-)/ PR(+) / HER2 (+)

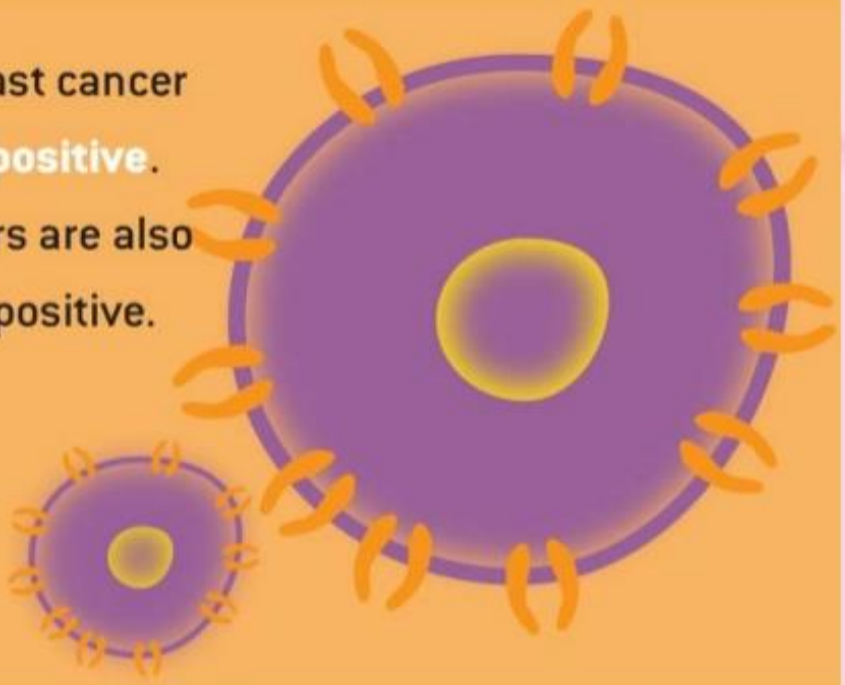
ER (+)/PR (-) / HER2 (-)

ER (-)/PR (+) / HER2 (-).

Roughly **65-75%** of breast cancer patients have **hormone-receptor-positive breast cancer**. These HR+ tumors may be stimulated by either **estrogen** or **progesterone**.

Treatment for HR+ breast cancer usually includes medications such as **tamoxifen** or **aromatase inhibitors**. These **hormonal therapies** block the activity of estrogen.

About **20%** of breast cancer tumors are **HER2-positive**. Half of these tumors are also hormone-receptor-positive.



HER2 stands for **human epidermal growth factor 2**, a gene that expresses the HER2-receptor protein. This receptor is important in the normal growth of breast cells. But, in excess, the HER2 receptor can cause cancer cells to grow.

Treatment for HER2-positive tumors typically includes

- Drugs that target the HER2 receptor, such as **Herceptin** (trastuzumab)
- Chemotherapy

This combination helps block the HER2 signaling pathway, stopping cancer cell growth.

Triple-negative breast cancer means the tumors tested negative for

- Estrogen receptors,
- Progesterone receptors, and
- HER2 receptors

Triple-negative breast cancer affects **roughly 15% of breast cancer patients**, and tends to be **more aggressive** than the other two subtypes.

Younger women, women of African American descent, and those with a *BRCA1* genetic mutation tend to be more likely to develop triple-negative breast cancer.

Since triple-negative tumors lack hormone and HER2 receptors, **chemotherapy** provides the backbone for treatment, particularly **platinum chemotherapy**.

Many new targets for this tumor subtype are being studied in **clinical trials**.

Luminal A

(i)ER and/or PR + , HER2/neu -ve

(ii)Most common

(iii)Luminal A : possess a higher expression of the ER and estrogen-associated genes ESR1, GATA3 and FOXA1

(iv)Ki-67 proliferation index which helps control how fast cancer cells grow- tend to grow slowly low… low-grade.

(v)Associated with a better prognosis

- are likely to benefit from **hormone therapy** and may also benefit from **chemotherapy**.

Luminal B (Triple Positive)

(i)ER and/or PR+ HER2+

(ii)Variable HER2/neu expression

(iii)Increased frequency of TP53 mutations

(iv)Ki-67 proliferation index- high… generally grow slightly faster than **luminal** A **cancers**

(v)Associated with worse prognosis compared to Luminal A

- likely to benefit from chemotherapy
- may benefit from hormone therapy
- may benefit from treatment targeted to HER2.

Basal –Like Subtype (Triple negative)

- ER and PR — and HER2/neu —
- Hormone receptor (ER and PR) and HER2/neu receptor negative .
- Aggressive with a poorer disease-free and overall survival than the other breast cancer subtypes

- This type of cancer is more common in women with *BRCA1* gene mutations. Researchers aren't sure why, but this type of cancer also is more common among younger and Black women .

- They are usually treated with some combination of surgery, radiation therapy and chemotherapy.
- **Triple negative** tumors aren't treated with hormone therapy because they are ER-**negative**
- A standard **triple-negative chemo** regimen is

12 weeks of **taxol**,

followed by four doses of **adriamycin** and **cytoxan**.

In the new study, doctors gave patients an additional **chemo** drug called **carboplatin**

HER2/neu Over Expression

- ER- PR- HER2+

-non luminal / HER2+

-low expression of ER and PR

-HER2-enriched cancers tend to grow faster than luminal cancers and can have a worse prognosis …Poor clinical outcome .

-Associated with a high histological grade,

They are often successfully treated with targeted therapies aimed at the HER2 protein, such as

1- Enhertu (chemical name: fam-trastuzumab-deruxtecan-nxki)

2- Herceptin (chemical name: trastuzumab),

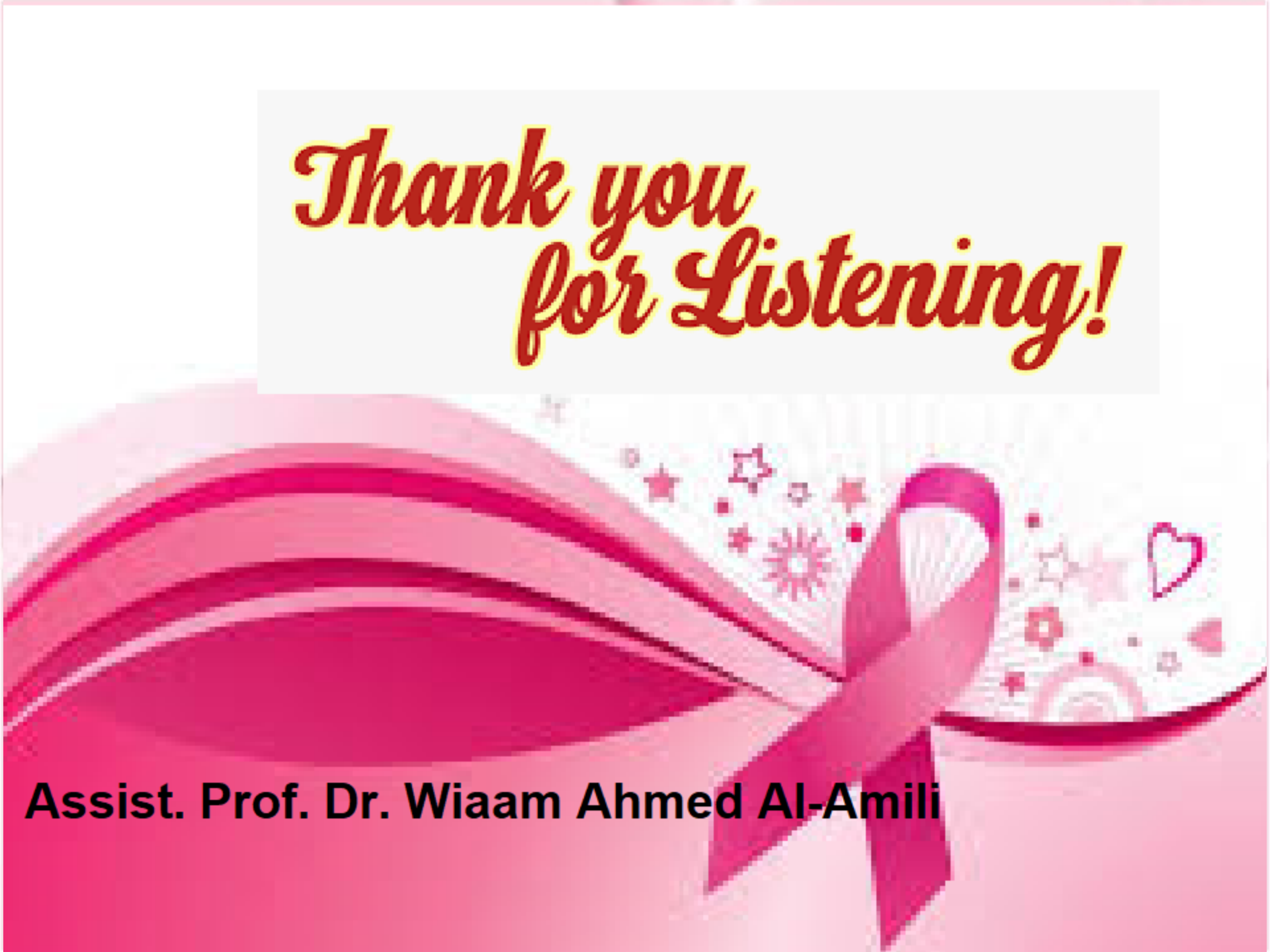
3- Perjeta (chemical name: pertuzumab),

4- Tykerb (chemical name: lapatinib),

5- Nerlynx (chemical name: neratinib),

6- Kadcyla (chemical name: T-DM1 or ado-trastuzumab emtansine).

Subtype	Phenotype	Type of Treatment
Luminal A	**ER + PR +/– , HER2/neu –** **Ki 67 ..low (≤ 14)**	Endocrine therapy alone
Luminal B (HER2 positive)	**ER + PR +/– , HER2/neu +** **Ki 67 ..high (> 14)**	Endocrine + anti-HER2 ± Cytotoxic therapy
Luminal B (HER2 negative)	**ER + PR +/– , HER2/neu –** **Ki 67 .. (> 14)**	Endocrine ± Cytotoxic therapy
Basal-Like (Triple negative) (Ductal)	**ER – PR – and HER2/neu –**	Cytotoxic therapy
HER2/neu Over expression (non- luminal	**ER – PR – and HER2/neu +**	anti-HER2 ± Cytotoxic therapy



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