Breast Cancer

*There are many types of breast cancers, and correctly identifying each one is important to determine the proper treatment.

*Breast cancers can be divided into two **main overarching groups**: the carcinomas and the sarcomas.

Carcinomas	**Sarcomas**
*are cancers that arise from the **epithelial component** of the breast. *The epithelial component consists of the cells that line the **lobules and terminal ducts**; under normal conditions, these epithelial cells are responsible for making milk.	*are rare cancers that arise from the **stromal (connective tissue)** components of the breast. *These stromal component cells include **myofibroblasts and blood vessel cells**, and cancers arising from these **"supportive" cells** include phyllodes tumors and angiosarcoma.
comprise the **vast majority** of all breast cancers, and will be further discussed belo	account **for less than 1%** of primary breast cancers.

In the US, invasive Ca B is **2nd to **lung cancer** as a cause of cancer death in women, & despite advances in diagnosis & treatment, **1/4 of women** who develop Ca B will die of it.

****The lifetime risk of Ca B is one in eight (1/8) for women in the US**, with 75% of cases older than age 50.

Breast Cancer

*Only 5% are younger than the age of 40.

*For unknown reasons (possibly related in some part to earlier detection via mammography) there has been worldwide increase in the incidence of Ca B.

***Is The most common non-skin malignancy of women.**

*2nd most common cause of cancer deaths in women, following **carcinoma of the lung.**

*The worldwide incidence and mortality are increasing at an alarming rate. This trend is due to social changes especially in the developing countries.

*Those social changes Include delayed childbearing, fewer pregnancies, and reduced breastfeeding and with lack of access to optimal health care.

*Since 1980s the mortality rate has dropped from 30% to <20% due to improvement in detecting cancers before they metastasize through screening (mammographic screening) and more effective systemic treatment.

***Almost all breast malignancies are adenocarcinomas (>95%)**

****Classification system**

•The **most clinically used** classification system for breast cancer depends on the expression of hormone receptors

*hormone receptors are:

1-Estrogen receptor (ER),

2-progesterone receptor (PR)

3- human epidermal growth factor receptor 2 (HER2, or ERBB2)

*Can be classified according to expression of hormone receptors into three major groups:

ER positive	HER2 positive	Triple negative
(HER2 negative; 50%–65% of cancers)	(ER positive or negative; 10%–20% of cancers)	(ER, PR, and HER2 negative; 10%–20% of cancers

*The three groups show **striking differences** in patient characteristics, **pathologic features, treatment response, metastatic patterns, time to relapse, and outcome**

*Within each group are additional histologic subtypes, some of which also have clinical importance.

***Eighty** percent of carcinomas that are **both ER-and PR-positive respond to hormonal manipulation**

*__40%__ of CA **positive for only ER** or **PR respond.**

***Strongly ER-positive cancers are less likely to respond to chemotherapy.**

***cancers that fail to express** either ER or PR have a less than 10% likelihood of responding to hormonal therapy but are **more likely to respond to chemotherapy.**

*HER2:

HER2 overexpression is associated with poorer survival

predictor of response to agents that target this receptor

•An alternative classification system relies on **gene expression profiling.**

*used **mainly in clinical research**

*divides breast cancers into four major types:

Luminal A	**Luminal B**	**HER2-enriched**	**Basal-like**.
majority of cases are **lower grade, ER-positive & HER2 negative** cancers	Majority of cases are **higher grade ER-positive +/-HER2 positive** cancers .	**overexpress HER2** and ER-negative.	gene expression profiling resemble basally located myoepithelial cells and are **ER-negative, HER2-negative**

**Risk Factors

RF	Its effects
***Age:**	*It is considered **rare** in women **younger** than 25 and *incidence **increase after** the age of **30**. ***more than two thirds** of women with breast cancer are **older** than the age of **50** and ***only 5%** are **younger** than the age of 40.
***Gender:**	The incidence in **men** is only **1%** of that in women
Family History of Breast Cancer:	
Geographic Factors	•**higher i**n the **Americas** and Europe than in Asia and Africa •The **mortality rates** of breast cancer in America is 5 times greater than japan . •Immigration studies showed that migrance from low incidence to high incidence areas tends to **acquire the rates of their new home countries**. طب شو الاشي يلي موجود بالبيئة وخلا هاد الكانسر يزيد ؟؟ •In this context, **diet, reproductive patterns, and breast feeding practices** are thought to be involved . •Breast cancer rates appear to be raising in parts of the world that are adapting the western habits.
Race/Ethnicity:	•Highest rate in women of **European descent** because of higher incidence of **ER-positive cancers.** •**Hispanic and African** American develop cancer at a **younger** age and develop **aggressive** tumors. •This is thought to result from combination of differences in genetic social factors and access to health care.
***Reproductive History**	•Including **Early age of menarche**, **nulliparity, absence of breastfeeding**, with **older age at first pregnancy** are all associated with increased risk due to increased the exposure of the epithelial cells of the breast to **estrogenic stimulation**
Ionizing Radiation.	•**Chest Radiation especially if the breast is developing.**
Other Risk Factors.	•**Postmenopausal obesity** •**postmenopausal hormone replacement therapy** •**mammographic density** •**alcohol consumption**

**Pathogenesis : Factors that contribute directly to the development of breast cancer can be grouped into:

•**Genetic**	**BRCA1 and BRCA2: Are classic **tumor suppressor genes** and the cancer only occur if both alleles are **defected** **هاد الجين حلو و بمنع ظهور الكانسر فلو صار فيه طفرة او كان deleted م هون المشكلة** >encode **proteins** that are required for **repair of DNA damage.** >**most carriers** develop **breast cancer by the age of 70 years** *For unclear reasons, ***BRCA2*** mutations are primarily associated with **ER-positive tumors**, whereas **BRCA1** mutations are associated with **triple-negative cancers** **Other mutated genes: *TP53*and *PTEN* P53 AKA guardian of the genome **The pathways in which familial breast cancer genes function also are often disturbed in sporadic cancers **HER2 gene amplification : *Cancers that **overexpress** HER2 are **highly proliferative.** هاد الجين مو حلو وشرير لانه لو كان موجود وحصله expression هون المشكلة بتتزكروا ؟؟ حكينا انه حساسية الخلايا لل GF بتزيد وبزيد النمو تبعها *In the past they had a **poor** prognosis; Nowadays, the availability of **therapeutic agents** targeting HER2 has **improved the prognosis.** It is a **receptor tyrosine kinase** that promotes the cell proliferation and suppress apoptosis
•**Hormonal**	*Estrogens are considered an important hormonal factors since they stimulate the production of growth factors promoting the tumor development. **Estrogen receptors **regulate other genes** in an estrogen dependent fashion. Some of those genes are **important for the tumor development or growth.** **Estrogens also drives the proliferation from **precursor** regions to a fully malignant and **metastatic carcinoma**. **Estrogen antagonists: **reduce** the development of **ER-positive cancers** in women at high risk and are mainstays in the treatment of established ER-positive tumors.
•**Environmental**	

Morphology

Location:

1-Upper outer quadrant (50%)

2-Central portion(20%).

3- Lower outer quadrant 10%

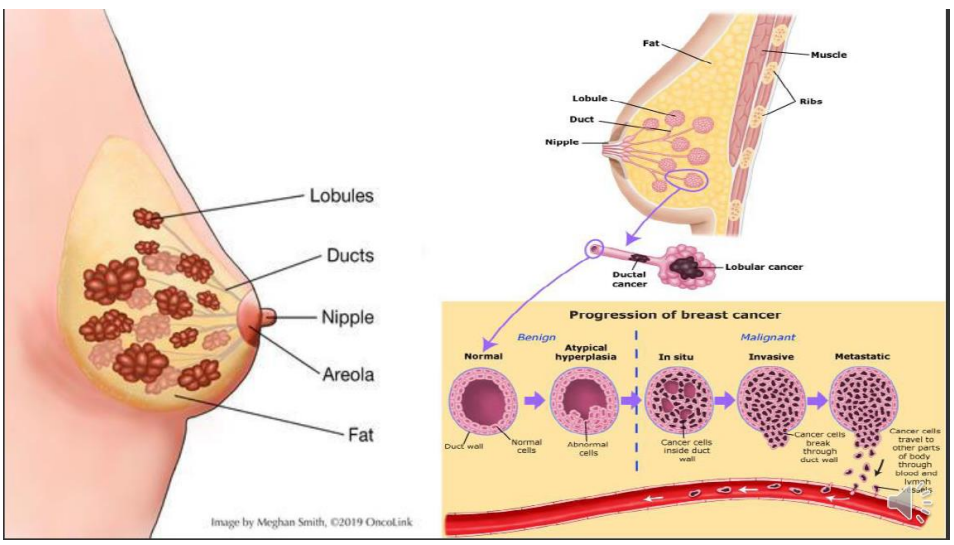
4- Upper inner quadrant 10%

5- Lower inner quadrant 10%

4% have **bilateral** primary tumors or **sequential** lesions in the same breast

Breast carcinoma

Noninvasive:	**Invasive (infiltrating):**
(<u>confined by a basement membrane</u> and do not invade into stroma or lympho-vascular channels)	Beyond BM
Include 1. Ductal carcinoma in situ 2. Lobular carcinoma in situ	(includes all carcinomas that are not of a special type) 70% to 80% 2. Invasive lobular carcinoma 10% to 15% 3. Carcinoma with medullary features 5% 4. Mucinous carcinoma (colloid carcinoma) 5% 5. Tubular carcinoma5% 6. Other types



	Notes	%	Clinical presentation/ gross	Receptor profile:	Microscopically
Invasive ductal carcinoma	**Also called **Carcinomas "not otherwise specified"** **شو معنى الجملة يلي تحتها خط ؟؟ يعني انه الخلايا يلي بتطلع ما الها اشكال مميزة ما في شي بميزها** **Precancerous lesion**: usually DCIS **usually associated with DCIS.	70-80%	هي ما ضلت بس جوا ال duct لا طلعت كمان *a mammographic density; **a hard, palpable irregular mass**. بتكون قاسية كتير وكأنها صخرة طب لي يا ترا ؟؟ بسبب ال fibrous tissue يلي جواها وهي تفسير تحت *Cases with invasive ductal carcinoma produces **desmoplastic(fibrous tissue) response which replaces the normal fat and result in mammographic densities** *Nipple retraction, or fixation to the chest wall can be seen in advanced cancers	•ER (+vein 50-60%) •HER2 (+vein 20%) •15% are negative for both	
Carcinoma with Medullary features	****Precancerous lesions**. usually absent **increased frequency in women with ***BRCA1*****mutations**	**5%**	*typically grow as **rounded masses** بكبر بشكل منظم طب مهو كانسر وبعمل كيف هيك invasion ؟؟ الجواب الجملة يلي تحتها خط *that can be difficult to distinguish from benign tumors on imaging	**Triple negative** lack hormone receptors and **do not overexpress HER2/NEU** معناها هو Not طب hormonal حلو ولا لا ؟؟ اها حلو بنعالجه دايركت بالجراحة	*large anaplastic cells with **pushing, well-circumscribed borders** **هو بعمل invasion بس مؤدب مو مرة وحدة زي باقي الكانسرز .... بعمل مجموعة من خلايا بتضغط على يلي حواليها وتوسع** *with a pronounced **lymphocytic infiltrate.** وهاي الشغلة كويسة لانه بتعمل immune reaction ضد الكانسر

	Notes		Clinical presentation/ gross	Receptor profile:	Microscopic picture
Colloid mucinous Carcinoma		**a rare subtype	****Grossly** the tumors are usually **soft and gelatinous.** mucin مهو في بالتالي رح يكون طري جدا	****ER-positive/HER2-negative cancer >>>>>good prognosis** prognosis هاد ال تبعه بجنن ليه ؟؟ estrogen لانه dependent بنعطيها Anti estrogen غير هيك ما عندها الجين يلي مو حلو	The tumor cells produce abundant quantities of extracellular **mucin** that dissects into the surrounding stroma.
Tubular carcinoma	***Lymph node metastases are rare,** *Sometimes mistaken for benign sclerosing lesions. *Calcification may present in the tumor lumen	10% of invasive carcinomas	irregular mammographic densities	**ER-positive/HER2-negative cancer >>>prognosis is excellent** زي يلي فوقه	**well-formed tubules** with low-grade nuclei.
Inflammatory Carcinoma	**•True inflammation is minimal or absent. •Most of these T have distant metastases •mimics the surface of an orange peel, an appearance referred to as peaud'orange.**		**يبان وكأنه التهاب وفي اعراض التهاب •clinically present as an enlarged, swollen, erythematous breast (resulting from the blockage of dermal lymphatic spaces by ca cells) يعني هي بتيجي واصلا منتشر *usually without or, with ill-define palpable mass or presents with breast erythema and skin thickening**	**the prognosis is extremely poor.** عشانه بعمل invasion to lymphatics and blood	**generally poorly differentiated & diffusely invading the breast tissue.**

Invasive lobular carcinoma

*10-15%

***Precancerous lesion**. associated with LCIS.

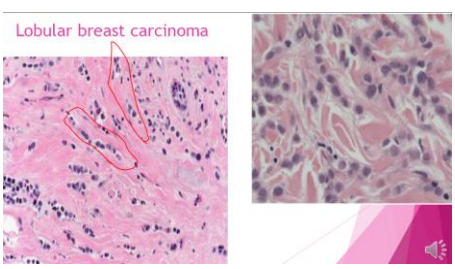
*10% to 20% are **multicentric and bilateral**

في اكتر من منطقة وفي ال 2breasts

***Clinical presentation**. Most present as palpable masses or mammographic densities

*cells invade stroma i**ndividually** and often are aligned in **“single-file”**

ماشية بطوابير



*Almost **all of these carcinomas express hormone receptors (hormone dependent) ,** but **HER2 overexpression is very rare or absent.>>> good prognosis**

***Metastasis** of lobular carcinoma **is unique since it frequently reaches the CSF, serosal surfaces, bone marrow , ovary, and uterus**

SCREENING:

1- mammographic screening

2- Magnetic resonance imaging, MRI

Spread of breast cancer

through **lymphatic and **hematogenous** channels.

*LN metastases are present in about 50% of ca presenting as palpable masses, but… in fewer than 15% of cases found by mammography.

* **Outer quadrants & centrally located ca**	**Ca B** in the **inner quadrants**	The supraclavicular LN are usually become involved only after the axillary & internal mammary LN are affected, but… sometimes are the primary site of spread (Skipped).
typically spread first to the axillary LN.	often involve the LN along the internal mammary arteries.	

Favored metastasis are the **bone, **lungs**, **skeleton**, **liver**, and **adrenals** and (less commonly) the brain, spleen, and pituitary.

*More **distant dissemination** eventually follows, with metastatic involvement of **almost any organ or tissue in the body. Favored** locations are the lungs, skeleton, liver, & adrenals & (less commonly) the brain, spleen, & pituitary. However, **no site is exempt!**

****Metastases may appear many years after apparent therapeutic control of the primary lesion that's why we use screening program**

*Metastases may appear many years (sometimes 15 years) after apparent therapeutic control of the primary ca!

Clinically, Ca B is often discovered by the woman or her physician as a **solitary, painless, & not movable mass(fixed , hard in consistency). At this time, the ca is typically **2 to 3 cm** inØ, with involvement of the **regional LNs**(most often axillary) in about **50% of patients**

Breast cancer Prognosis

The outcome for women with breast cancer depends on the **biologic features of the carcinoma (molecular or histologic type)**and the extent to which the cancer has spread (**stage**) at the time of diagnosis

Prognostic Factors

Tumor stage	**Tumor size. The**risk of axillary lymph node metastases increases with the size of the primary tumor, but both are independent prognostic factors. **Locally advanced disease. Carcinomas** invading into skin or skeletal muscle are usually large and may be difficult to treat surgically.
Invasive carcinoma versus carcinoma in situ	
Distant metastases.	**Once** distant metastases are present, cure is unlikely,
Lymph node metastases.	**Axillary lymph node status is the most important prognostic factor for invasive carcinoma in the absence of distant metastases.** biopsy is necessary for accurate assessment. With no lymph involvement the ten years survival is 70-80% 1 -3 lymph involvement 35-40% If more than 10 lymph nodes 10-15%
Tumor size.In cm	
Locally advanced disease	
Inflammatory carcinoma	Discussed
Lymphovascular invasion	strongly associated with the presence of lymph node metastases. poor prognostic factor

Molecular subtype		
Special histologic types.	women with **tubular, mucinous, lobular, papillary, and adenoid cystic**	The **survival rate** is **greater than that of women with cancers of no special type**.
	Women with **metaplastic carcinoma or micro papillary carcinoma**	have a **poorer prognosis**
Histologic grade	**All invasive carcinomas are graded using Histologic Score composed of Nuclear grade, tubule formation, and mitotic rate ****Proliferative rate:** *measured by **mitotic** counts. ***Highly proliferative** tumors have **poorer prognosis** but **may respond better to chemotherapy**	
Estrogen and progesterone receptors and HER2 expression	Discussed	

Stages of breast ca

Stage 0: DCIS or LCIS, with 5-year survival rate (5YSR):**92%**

Stage I: Invasive ca up to **2 cm**Ø(including ca in situ with micro invasion) without LN involvement **(**5YSR:**87%).**

Stage II: Invasive ca up to **5 cm**Ø**with up to 3 involved axillary LNs** or invasive ca more than 5 cm without LN involvement **(**5YSR:**75%).**

Stage III. Invasive ca up to **5 cm**Ø**with 4 or > involved axillary LNs**; invasive ca more than 5 cmØwith LN involvement; invasive ca with 10 or more involved axillary LNs; invasive ca with involvement of the ipsilateral internal mammary LNs; or invasive ca with skin involvement (edema, ulceration, or satellite skin nodules), chest wall fixation, or clinical inflammatory ca (5YSR:**46%).**

Stage IV. Any Ca B with **distant metastases**(5YSR: **13%**).

Why some cancers **recur** following postoperative therapy whereas others do not? Remains unknown & a **mystery**.