Genetics of Breast & Ovarian Cancer

Reproductive Block

MED 443
King Saud University

GENETICS
TEAM 443

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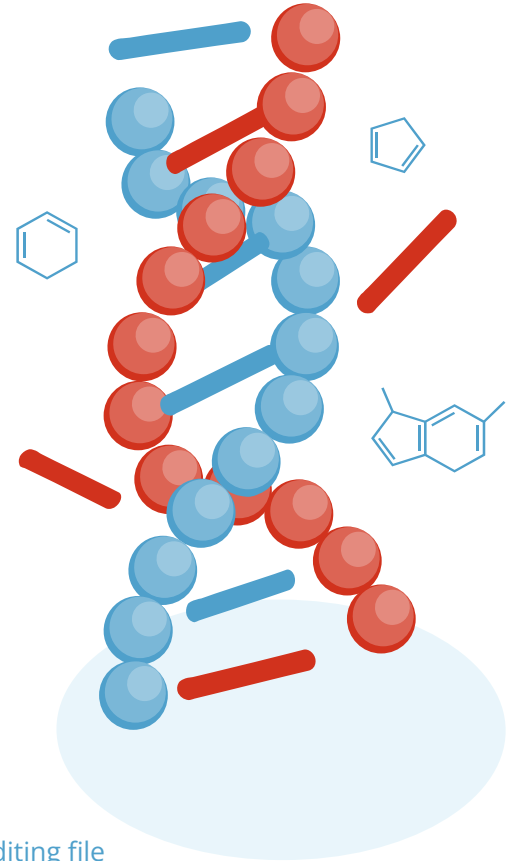
Contents

Genetics of Breast cancer

❖ It is believed that one-quarter to one-third of breast cancers occur due to inheritance of a susceptibility gene or genes.

BRCA genes

1 Mutations in **BRCA1** and **BRCA2** are responsible for **80%** to **90%** of single gene familial breast cancers and about **3%** to **6%** of all breast cancers.

2 **BRCA1** (located on chromosome **17q 21.3**)

3 **BRCA2** (located on chromosome **13q 12-13**).

4 Those genes, which are mutated in familial breast cancers, are involved in **DNA repair**.

Most common

Table 23.3 Most Common Single Gene Mutations Associated With Hereditary Susceptibility to Breast Cancer

Gene (Syndrome)	% of Single Gene Cancers[a]	Risk of Breast Cancer to Age 70[b]	Other Cancers	Comments
High Penetrance Germline Mutations (>4-fold increased risk; 3%–7% of breast cancers)				
BRCA1 (familial breast and ovarian cancer)	~55%	~40%–90%, females; 1%, males	Ovarian (~20%–40%), fallopian tube, pancreas, prostate, others	Majority of cancers are TNBC
BRCA2 (familial breast and ovarian cancer)	~35%	~30%–60%, females; 6%, males	Ovarian (~10%–20%), pancreas, prostate, others	Majority of cancers are ER positive. Biallelic mutations cause a form of Fanconi anemia.

Triple negative breast cancer

In <u>female</u> breast cancer: **BRCA1** is more common
In <u>males</u> breast cancer: **BRCA2** is more common

The second most common cancer associated with BRCA1 mutations Is **ovarian cancer**

Prognostic and predictive factors

## Estrogen (ERs), Progesterone (PRs) receptors

Around **50-65%** of breast carcinomas express **estrogen receptors (ER) "luminal"** and **progesterone receptors (PgR).**

Luminal cancers are further divided into two **groups, A** and **B**, that differ mainly in terms of **proliferation** which **,** is **low** in **group A** and **high** in **group B**.

The presence of **ER** in breast cancer is a **weak prognostic** factor; however, it is a **predictive** factor for the benefit of adjuvant **Tamoxifen** or **Aromatase inhibitor** therapy.
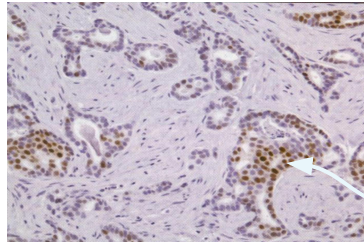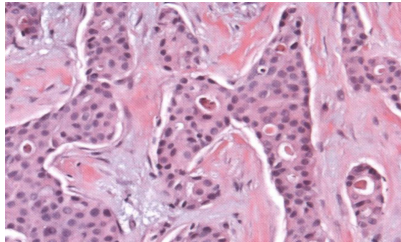
Immunohistochemistry for the evaluation of estrogen receptor (ER)

Immunohistochemistry
Ab for estrogen receptors
اذا كان الريسبتور موجود بيصبغ بني (dye)نحط صبغه

★HER2 (Human epidermal growth receptor 2) gene:
Normally it is Responsible for growth and division
(but within the normal range and it is regulated)

But when it is over expressed or amplified it will lead
to abnormal number of divisions in the cell

HER2 Gene

Normal cells have one copy of the **HER2** gene on each chromosome 17 **(CHR17)** and when this gene is expressed in normal epithelial cells, it is transmits signals regulating **cell growth and survival.**

Around 15-25% of breast carcinomas express HER2-neu. In HER2-positive breast cancer, the **HER2 gene** is found to be amplified **2-fold** to **greater than 20-folds** in each tumor cell nucleus. As a result, **HER2 positive** breast cancers tend to be **aggressive**.

The **Herceptin molecule (Trastuzumab)** has been shown to demonstrate a high specificity and affinity for the **HER2 receptor** and also acts as a biologic targeted therapeutic agent **against HER2** receptors.

(0)　(1+)
(2+)　(3+)
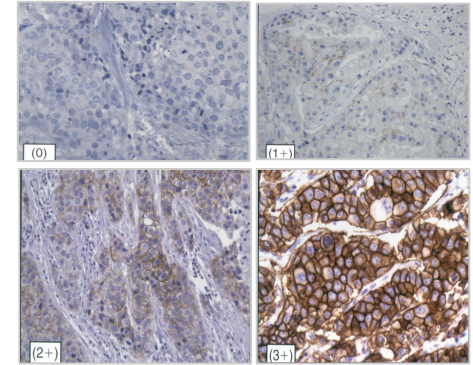
Immunohistochemistry (IHC) for the assessment of the level of HER2 protein expression at the tumor cell membrane.

Triple negative breast carcinomas (TNBCs)

❖　Arise through an **estrogen independent** **pathway** that is **not** associated with **HER2 gene amplification.**

It's not associated with (Er ,PR, HER2)

FISH Technique (principles of Hybridization)

1 DNA is double stranded. Bonds between complementary bases hold strands together (Cytosine-Guanine; Adenine-thymine).
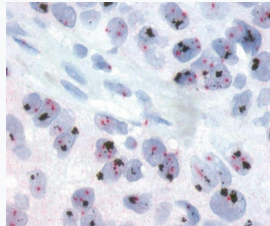
2 Heat alkalinizes DNA leading to the separation of the strands ('denaturation').

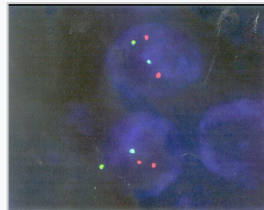**3** Cool separated strands bond with complementary ones forming double strands.

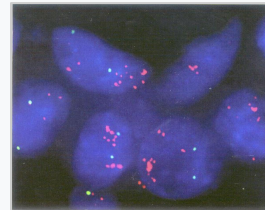**4** Labelled complementary single-strand DNA can identify a DNA sequence (e.g., a gene) in cells.
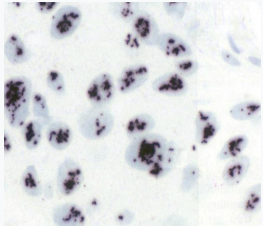
Silver in situ hybridization image.
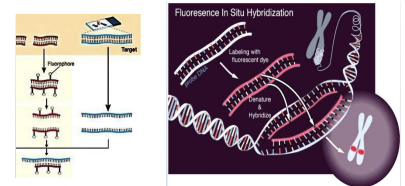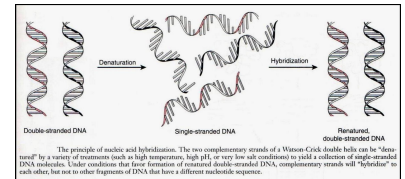
Dual-color silver in situ hybridization (SISH) image.

Normal HER2

Over expression

Fluorescence in situ hybridization image

Table 23.4 Molecular Subtypes of Invasive Breast Cancer

Grade3   High grade

Defining Features	Luminal (ER-Positive/HER2-Negative)		HER2 (HER2 Positive)	TNBC (ER-Negative/ HER2-Negative)[a]
Percent of breast cancers	~40%–55% (low to moderate proliferation)	~10% (high proliferation)	~20%	~15%
Most similar group defined by mRNA profiling[b]	Luminal A	Luminal B	HER2-enriched (ER-negative), luminal B (ER-positive)	Basal-like
Most common gene mutations	PIK3CA (45%), TP53 (12%)	PIK3CA (29%), TP53 (29%)	PIK3CA (39%), TP53 (70%–80%)	PIK3CA (9%), TP53 (70%–80%)
Typical special histologic types	Tubular, grade 1 or 2 lobular, mucinous, papillary	Grade 3 lobular	Some apocrine, some micropapillary	Medullary features, metaplastic[c]
Typical patient groups	Older women, men, cancers detected by mammographic screening	BRCA2 mutation carriers	Young women, TP53 mutation carriers (ER positive)	Young women, women of African heritage, BRCA1 mutation carriers
Complete response to chemotherapy	<10%	~10%	ER positive ~15%; ER negative ~30%–60%	~30%
Metastatic pattern	Bone (70%), more common than viscera (25%) or brain (<10%)	Bone (80%) more common than viscera (30%) or brain (10%)	Bone (70%), viscera (45%), and brain (30%) all are common	Bone (40%), viscera (35%), and brain (25%) all are common
Relapse pattern	Low rate over many years, long survival possible with bone metastases	Early peak at <10 years, late recurrence possible	Bimodal with early and late (10 years) peaks	Early peak at <8 years, late recurrence rare, survival with metastases rare

Test Yourself! MCQs

Q1: What is the main cause of Breast Cancer?

A. Genetics
B. Radiation
C. Smoking
D. Multi factorial

Q2: Which of the following is related to higher risk of developing breast cancer?

A. Smoking
B. Menarche at>17
C. First degree relative with breast cancer
D. Increased androgen levels

Q3: Gene BRCA1 is found on which chromosome?

A. 17q 21.3
B. 13q 12.13
C. 17p 21.3
D. 13p 12.13

Q4:Aromatase inhibitor can benefit?

A- HER2 positive cancer
B- Triple negative breast carcinoma
C- PRs positive cancer
D- ERs positive cancer

Q5: Which one of the following is considered as the prognosis of HER2 gene mutation?

A- Good prognosis
B- Treated by Tamoxifen
C- Treated by Herceptin
D- Highly metastasize

Q6: HER2 positive breast cancer tend to be?

A- Benign
B- Aggressive
C- Metastasized
D- Good prognosis

Textbook Questions !

Q1: A 54-year-old woman sees her physician after feeling a lump in her left breast. The physician palpates a firm, irregular mass in the lower outer quadrant just beneath the lateral margin of the areola. A mammogram shows a 2-cm density with focal microcalcifications. Excisional biopsy shows both intraductal and invasive components of a breast carcinoma.Immunohistochemical staining shows that the cells are positive for ERBB2 (HER2/neu) expression but negative for estrogen receptor and progesterone receptor expression. Flow cytometry shows a small aneuploid peak and a low S-phase. When combined with doxorubicin, which of the following drugs is most likely to be useful in treating this patient?

A. Hydroxyurea   **B.** Raloxifene   **C.** Tamoxifen   **D.** Trastuzumab

Q2: A 29-year-old woman and her 32-year-old sister were diagnosed with infiltrating ductal carcinoma of the breast (breast cancer in very young women)**, and both had bilateral mastectomies. Which of the following risk factors is most significant for this type of cancer?**

A. Oral contraceptive use   **B.** Inheritance of a mutant p53   **C.** Obesity   **D.** Smoking cigarettes

Q3: A study of women with breast carcinoma is performed to determine the presence and amount of estrogen receptor (ER) and progesterone receptor (PR) in the carcinoma cells. Large amounts of ER and PR are found in the carcinoma cells of some patients. These receptors are not present in the cells of other patients. The patients with positivity for ER-PR are likely to exhibit which of the following traits?

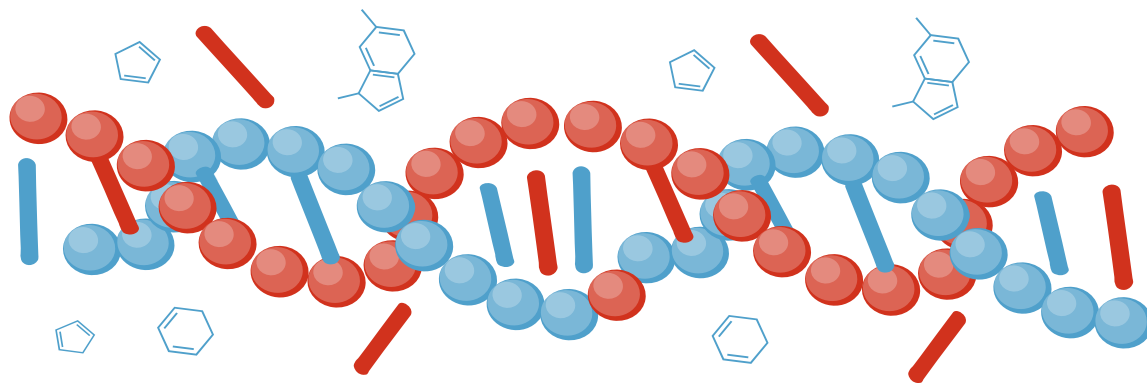**A.** Higher response to therapy   **B.** Greater likelihood of metastases   **C.** Higher tumor grade   **D.** ↑immunogenicity

Team Leaders

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Wish You All the Best !!