Genetics in Breast Cancer

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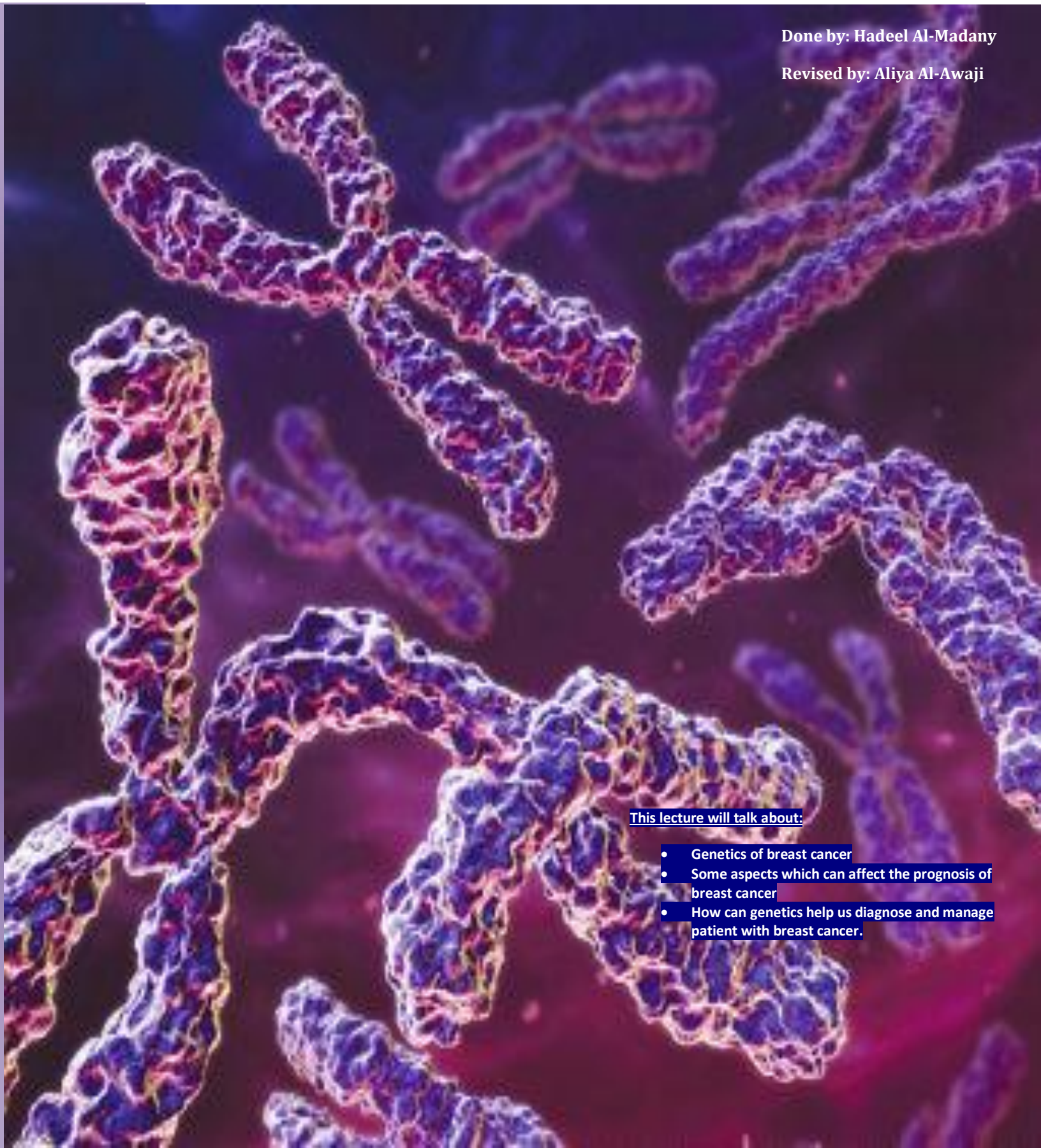


This lecture will talk about:

- Genetics of breast cancer
- Some aspects which can affect the prognosis of breast cancer
- How can genetics help us diagnose and manage patient with breast cancer.

Introduction

- Carcinoma of the breast is one of the leading causes of cancer morbidity and mortality among women worldwide. However, It may rarely occur in men
- In the United States alone, there are more than 200.000 newly diagnosed cases of invasive breast cancer.
- Out of those 200,000, about 40,000 died from the disease.

When a new diagnosis of breast cancer is made, the most immediate issues for each patient involve what the diagnosis means for her future, whether or not she will survive, and whether therapies beyond primary surgery might be of additional benefit.

There has been an encouraging decline in mortality from breast cancer over the past years, what are the causes of this decline?

- This can be attributed to several factors:
  1- Public education and screening programs that lead to the discovery of the disease at an earlier and more treatable stage.
  2- Significant and important **treatment advanced** with;
    a) improvements in hormonal therapies
    b) The development of more effective combination chemotherapy regimes
    c) The development of biologic therapeutics such as the targeted therapy against the human epidermal growth factor receptor 2 (HER2) receptor tyrosine kinase.

This evolution of therapeutic modalities for breast cancer has yielded an increasingly complex array of treatment option, both local and systemic, necessitating the development of some rational way of stratifying patients as to the most appropriate treatment regimen based on an assessment of the likelihood for disease recurrence after completion of local-regional therapy. Or in other words, it gives more options for treating patients according to their stage of the disease.

- 5-10% of the cases are related to specific inherited mutations, the rest are sporadic.
- These individuals (who have genetic mutations and didn't develop cancer yet) need to be identified because they will need mammography and checkups more than others in order to diagnose them early due to their increased risk of developing breast cancer.
- How to know if a certain patient had a genetic-mutation-related cancer? What are the signs?
- 1) age "under the age of 40"
- 2) bilateral breast cancer
- 3) Family history "first degree relative", this is also considered for ovarian cancer because they are related.
- If the previous factors were present then the patient should be screened for gene mutations (BRCA-1 AND BRCA-2). However, it is not necessary that her cancer is due to genetic mutation but it is most likely the cause.

What are the BRCA-1 and BRCA-2?

- These are DNA repair genes. Hence, when they are mutated, we may get an abnormal DNA which may lead to the creation of clone of cells which are malignant cells.
- BRCA-1 is situated on chromosome 17q21.3
- BRCA-2 is situated on chromosome 13q12-13
- The screening for these genes should be done in molecular genetics lab and it cost a lot of money. It shouldn't be done unless they present with a highly suggesting history.
- Most carriers of those mutant genes will develop breast cancer by the age of 70 years, as compared with only 7% of women who do not carry a mutation.
- Mutations in BRCA-1 are more common than BRCA-2

The doctor didn't mention this

- BRCA-1 and BRCA-2 act as tumor suppressor genes. Each gene is composed of two alleles. Cancer arises when both alleles are inactive or defective. One mutation of an allele is caused by a germ-line mutation "during development, this gene is formed incorrectly" and the second by a subsequent somatic mutation "during somatic division (growth)".
- The role of these genes in nonhereditary sporadic breast cancer is less clear, because mutation affecting BRCA-1 and BRCA-2 are infrequent in these tumors.
- Less common genetic diseases associated with breast cancer are:
  1) Li-Fraumeni syndrome: caused by germ-line mutations in **p53**; which is another tumor suppressor gene.
  2) Cowden disease: caused by germ-line mutations in PTEN; another tumor suppressor gene as well.
  3) Carries of the ataxia-telangiecatasia gene. (Further info on the last page, not important, just for you to understand)

ASSEMENT OF BREAST CANCER : What should be done after receiving a biopsy of breast cancer?

1- Diagnosis (histologic type)
2- Prognostic indicators (Grade and stage) and evidence of vascular or lymphatic invasion.

- The grade is related to the degree of differentiation of the cells, it is done according to a score (Grade 1, 2 and 3 or well, moderate and poorly differentiated), Women with poorly differentiated cancer are likely to have more aggressive breast cancer.
- Stage depends on 3 things (tumor size, lymph nodes and the presence or absence of metastasis)
- Breast cancer usually goes to axillary and mediastinal lymph nodes.

Hormone Receptors:

- ***60% to 70% of breast carcinomas express estrogen receptors (ERs) and progesterone receptors (PRS).***
- The first of the prognostic and predictive in breast biomarkers in breast cancer to enter routine clinical use, the steroid hormone receptors.

Previously, women with an advanced stage (stage 3 or 4) of breast cancer were treated by bilateral oophorectomy (surgical removal of the ovaries) or removal of the pituitary gland or bilateral adrenalectomy to cause regression of the cancer. The problem with these 3 previous surgeries is that they cause major side effects including musculization. However, these methods lead us to the fact that breast cancer is estrogen responsive (not all types) due to the presence of estrogen and progesterone receptor on the cancerous cells surfaces which propagate and increase in number after binding to either hormone estrogen or progesterone.

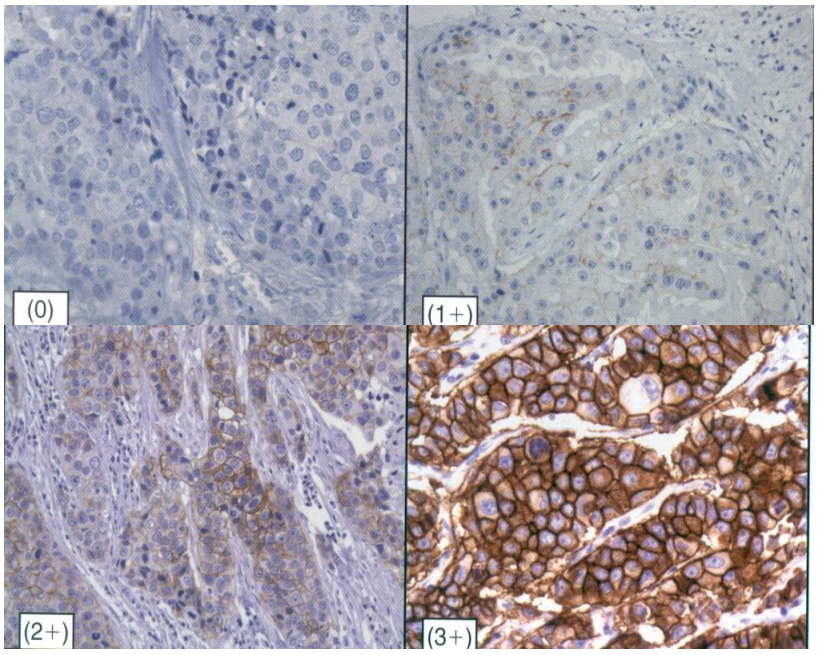
Nowadays, estrogen and progesterone receptors present on the malignant cell surfaces can be identified by other means (such as immunohistochemistry) and give drugs against estrogen and progesterone without the need to the oophorectomy, Hypophysectomy or adrenalectomy.

How? We do immunohistochemistry for estrogen and progesterone (it depends on antigen antibody reaction) if the reaction was there, it means the antigen is there (the antigen in this case is the estrogen receptor, or the estrogen molecules which encode for this receptor). For this to be seen under the microscope; it should be labeled by a dye which will stain brown in estrogen positive tumor cell. In this case, the patient will benefit from ***anti-estrogenic drugs*** such as ***tamoxifen*** and ***aromatase inhibitors***.

Molecular Prognostic and Predictive Factors: HER-2

- It is located on chromosome 17
- It is found in all normal cells
- It encodes for cell proliferations
- This gene is amplified (2 o more than 20- folds) in these patients (15- 25% of breast cancer patients), therefore, there likely to have more aggressive tumor (larger tumor size, positive axillary nodes, higher nuclear grade, and higher proliferative index).
- Herceptin molecule (Trastuzumab) used to treat this type of breast cancer, is an-anti HER-2 receptors, it makes the receptor unresponsive to the genetics guidance coming from the gene, and therefore, it stops its effect.
- Herceptin molecule (Trastuzumab) is known as biological targeted therapy.

- Women with estrogen and progesterone positive receptors are herceptin negative and vice versa.
- There are some tumors known as triple negative breast cancer, those are negative for estrogen, progesterone and herceptin. These are treated by aggressive chemotherapy.



Immunohistochemistry (IHC) for the assessment of the level of HER2 protein expression at the tumor cell membrane.

(0) → no stain → negative→ won't response to herceptin

(1+) → Granular staining on the cytoplasm → regarded as negative → no herceptin treatment is given

(2+) → membranous staining but staining is not complete → may be herceptin positive or negative (will be discussed later).

(3+) very clear staining → given herceptin → usually estrogen and progesterone negative.

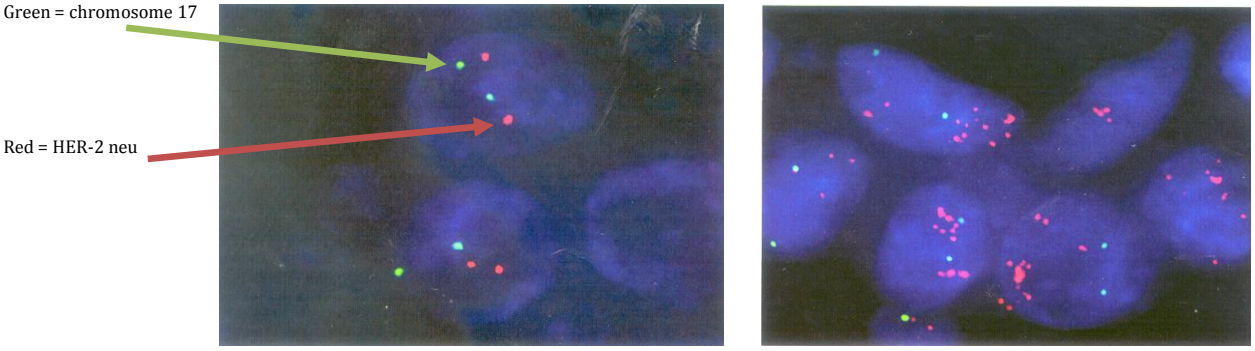
What is the next step in patient with (2+) result for HER-2 receptors?

- We do Fluorescent or silver in situ hybridization (FISH or SISH), which is a molecular genetic technique with higher specify and sensitivity to sort out these patient to either negative or positive.

What is the principle of FISH?

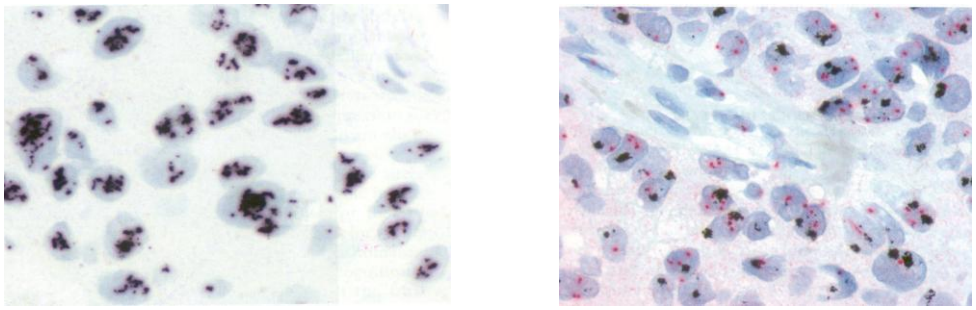
1- The DNA is double stranded (composed of double strands or double helix)
2- Those strands are made out of proteins (amino acids) in certain sequence to make up genes which encodes certain protein and the transform their orders via mRNA
3- Between those double strands are bonds between complementary bases hold stands together (cytosine↔ Guanine; Adenine↔ Thymine).
4- So we take the tumor tissue sample that we want to examine and heat it or alkaline fluid to it to break the bonds and separate the strands from each other.
5- Then we get a complementary strand and label the chromosome 17 "the site of HER-2 receptor" with Fluorescent stain.
6- We mix those the strands (the labeled one and that of the patient) and cool them. This is called hybridization.
7- By this, we can identify the DNA sequence of the HER-2 receptors

- As mentioned previously, it is found normally in all cells, but it will be amplified in these patients, so the reaction is going to be 3 to 10 times double the normal.



Fluorescence in situ hybridization image in normal cell, negative for HER-2 receptor.

Fluorescence in situ hybridization image showing amplified reaction, positive for HER-2 receptor.



Silver in situ hybridization image. Black→ HER-2, red→ Chromosome 17

Summary:

The causes of breast cancer mortality decline include:

1- Public education and screening programs that lead to the discovery of the disease at an earlier and more treatable stage.
2- Significant and important **treatment advanced** with;

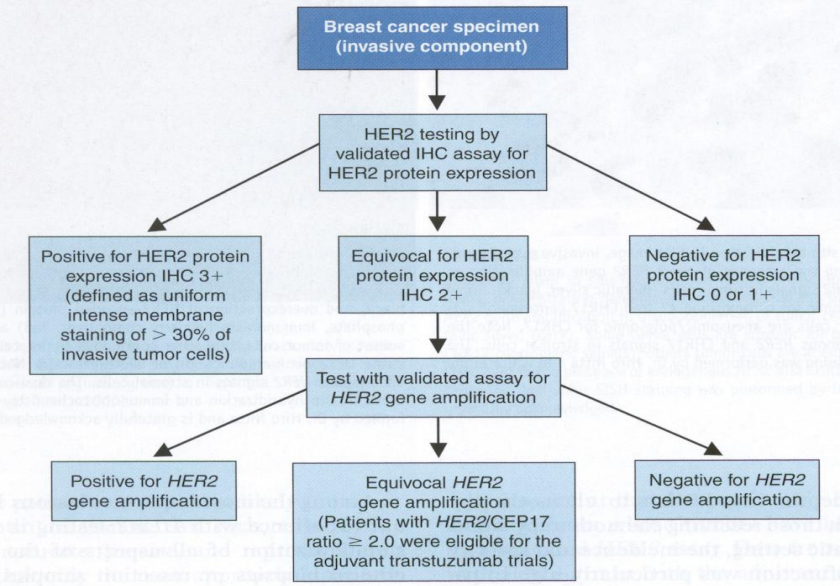
- improvements in hormonal therapies
- The development of more effective combination chemotherapy regimes The development of biologic therapeutics such as the targeted therapy against the human epidermal growth factor receptor 2 (HER2) receptor tyrosine kinase.

Prognostic factors include:

- Traditional morphologic prognostic factors (tumor size, histologic type, grade…etc)
- Hormone receptors (steroid hormone receptors; estrogen and progeterone)
- Molecular (HER-2)

Demonstration of HER-2 neu receptors can be done by:

- Immunohistochemistry antibodies against HER-2 receptors
- FISH or SISH



EXTRAINFO:

Ataxia telangiectasia (A-T) (also referred to as **Louis–Bar syndrome**) is a rare, neurodegenerative, inherited disease causing severe disability. Ataxia refers to poor coordination and telangiectasia to small dilated blood vessels, both of which are hallmarks of the disease.

It affects many parts of the body:

- It impairs certain areas of the brain including the cerebellum, causing difficulty with movement and coordination.
- It weakens the immune system causing a predisposition to infection.
- **It prevents repair of broken DNA, increasing the risk of cancer. Which is why it is involved here.**