Revised & Approved
Bassam Alasmari
Rania Almutiri

HUMAN GENETICS

Objectives :

- Recognize carcinoma of the female breast as the leading cause of cancer morbidity and mortality among women.
- Know the risk factors of breast cancer with special emphasis on the genetics and importance of family history.
- Know the role of molecular prognostic and predictive factors in breast cancer with special emphasis on hormonal receptors and HER2-neu status.

Special thanks to
Human genetics Team #438

Team leaders:
Sarah alqahtani
Faisal AlFadel

Dr's notes
Important
Extra notes
** Only in girls slides
** Only in boys slides

Breast Cancer

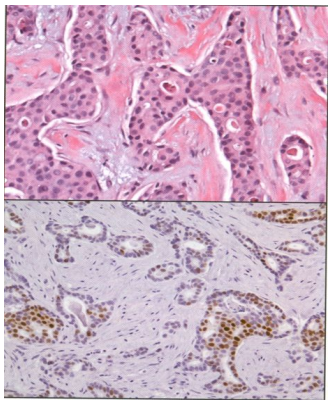
- ★ Breast Cancer is a disease of women who are > 50 years of age.
- ★ There are predisposing factors that may lead to breast cancer, which are:
  - **The Age:** The older the women the most likely to have a breast cancer.
  - **Family History:** Especially first degree relatives & people who carry theses two genes (BRCA1 & BRCA2) & also p53 gene (the guardian of the genome) which also involved in breast cancer (we can't do screening for this gene) & also p10 gene also involved in breast cancer.
  - When there is a breast cancer in the contralateral breast, that a predispose the patient to cancer in the other breast.
  - **Obesity:** The people who have high BMI will predispose the patient to breast cancer because the adipose tissue when it is present in high amount it will secrete Estrogen and breast cancer is hormone dependent (that's mean need estrogen to grow, need the estrogen to multiply & when they have other source of estrogen because of obesity the cancer will grow).
  - **Epithelial Hyperplasia:** Typical & Atypical types (likelihood to have a breast cancer).
  - **Consistency (Density) of breast tissue:** The more the stroma of breast the greater to have breast cancer.
  - **Nulliparous women (Never have children):** Have increase incidence of breast cancer.
  - **Women who get menarche at early age:** Is a predisposing factor to breast cancer (may more exposure to estrogen hormone).
  - **Late Menopause:** Is a predisposing factor to breast cancer (long-period exposure to estrogen hormone).
  - **Alcohol:** May increase incidence of breast cancer.

BRCA Genes

- ★ About 5% to 10% of breast cancers are related to specific inherited mutations.
- ★ Those mutations happen in those genes:
  - BRCA1 and BRCA2 which are mutated in familial breast cancers are involved in DNA repair.
  - BRCA1 is located on chromosome 17q 21.3 - Mutation in this gene will increase the risk of ovarian cancer.
  - BRCA2 is located on chromosome 13q 12-13 - Mutation in this gene will increase the risk of estrogen dependent breast cancer.
  - 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.
  - When they are mutated, their function of stopping breast cancer will stop.

Estrogen (ERs) , Progesterone (PRs) receptors

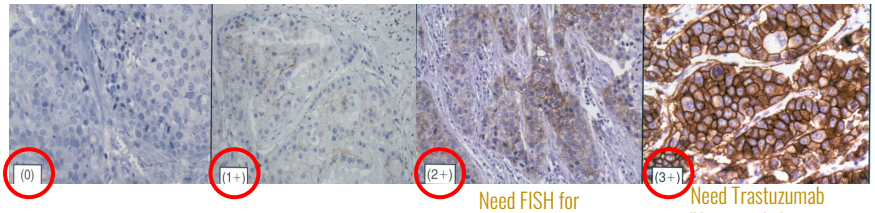
- ★ 60% to 70% of breast carcinomas express estrogen receptors (ERs) and progesterone receptors (PRs).
- ★ The presence of ERS in breast cancer is a weak prognostic factor, however, it is optimally useful as a predictive factor for the benefit of adjuvant tamoxifen or aromatase inhibitor therapy.
- ★ The positivity of tumor to (estrogen or progesterone receptors):
  - Positivity to Estrogen: We use Immunohistochemical stain for estrogen - If the number of cell stained by this stain and become brown in color and more than 10% thats mean it is estrogen receptor cancer (positive).
- ★ Tamoxifen (Aromatase inhibitor or Anti-estrogen): Therapy for the tumor who is positive to estrogen receptor - stopped the growth of the tumor.



HER2 Gene

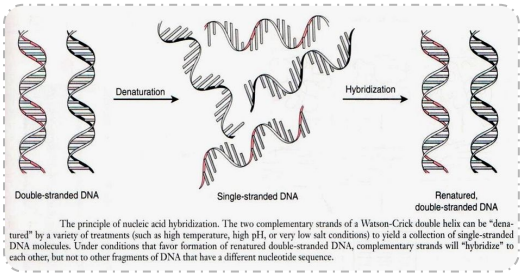
- ★ HER2 (Human epidermal growth receptor 2) gene: Located in chromosome 17, Control tissue growth - if it is get mutated and the patient has breast cancer this cancer is going to spread and grow and multiply very quickly.
- ★ If this gene is present in the tumor cell more than one copy (overexpression), the tumor will grow quicker, will multiply and spread more, will produce worse prognosis.
- ★ Normal cells have one copy of the HER 2 (HER2-neu) 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.
- ★ In approximately 15% to 25% of breast cancer, the HER2 gene is found to be amplified 2 fold to greater than 20 folds in each tumour cell nucleus.
- ★ As a result, HER2 positive breast cancers tend to be aggressive.
- ★ The positivity of tumor to (HER2 receptors). We use Immunohistochemistry for the assessment of the level of HER2 expression at the tumor cell membrane, If the number of cell stained by this stain and become **slightly** brown in color (+2) that's mean it is NOT enough (equivocal). but if it is full of brown color (+3) that's mean it is HER2 receptor cancer (Positive).
- ★ **Treatment of HER2 mutation:**
  - 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 (stop the growth of the tumor).

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



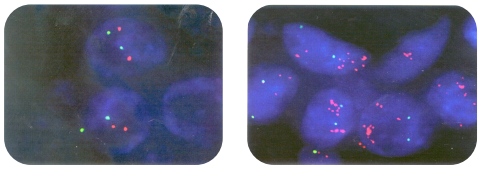
Principles of Hybridization

- ★ DNA is double stranded.
- ★ Bonds between complementary bases hold strands together (Cytosine → Guanine; Adenine → thymine).
- ★ Heat/alkalinise DNA – separation of strands ('denaturation') occurs.
- ★ Cool separated strands – *complementary* double strands re-form.
- ★ Labelled complementary single-strand DNA can identify a DNA sequence (e.g. a gene) in intact cells or disrupted cell preparations.
- ★ FISH (Fluorescence in situ hybridization) technique (molecular technique): We use it if we can determine the tumor positivity to the HER2 receptors - for the (+2) patients ONLY.
- ★ FISH denature dsDNA to ssDNA (break the bonds between various proteins) and then hyperdizate them to dsDNA again (bring hybride stranded that has fluorophore "radiant stain" and tagging of it, after that impeding of the hybride DNA with the patient DNA to become a "Double Stranded DNA").
- ★ SISH: (Silver in situ hybridization) technique (molecular technique): Same as FISH but we use silver stain.



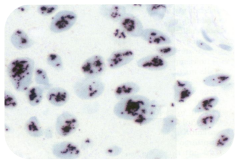
The principle of nucleic acid hybridization. The two complementary strands of a Watson-Crick double helix can be "denatured" by a variety of treatments (such as high temperature, high pH, or very low salt conditions) to yield a collection of single-stranded DNA molecules. Under conditions that favor formation of renatured double-stranded DNA, complementary strands will "hybridize" to each other, but not to other fragments of DNA that have a different nucleotide sequence.

Fluorescence in situ hybridization image

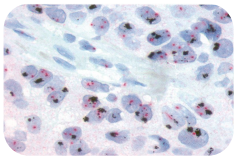


Negative for HER2 receptor | Positive For HER2 receptor

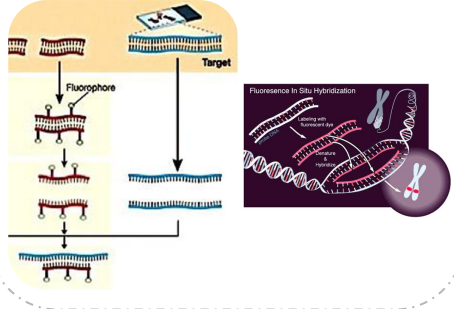
Silver in situ hybridization image



Dual-color silver in situ hybridization (SISH) image



Schematic illustration of FISH technique



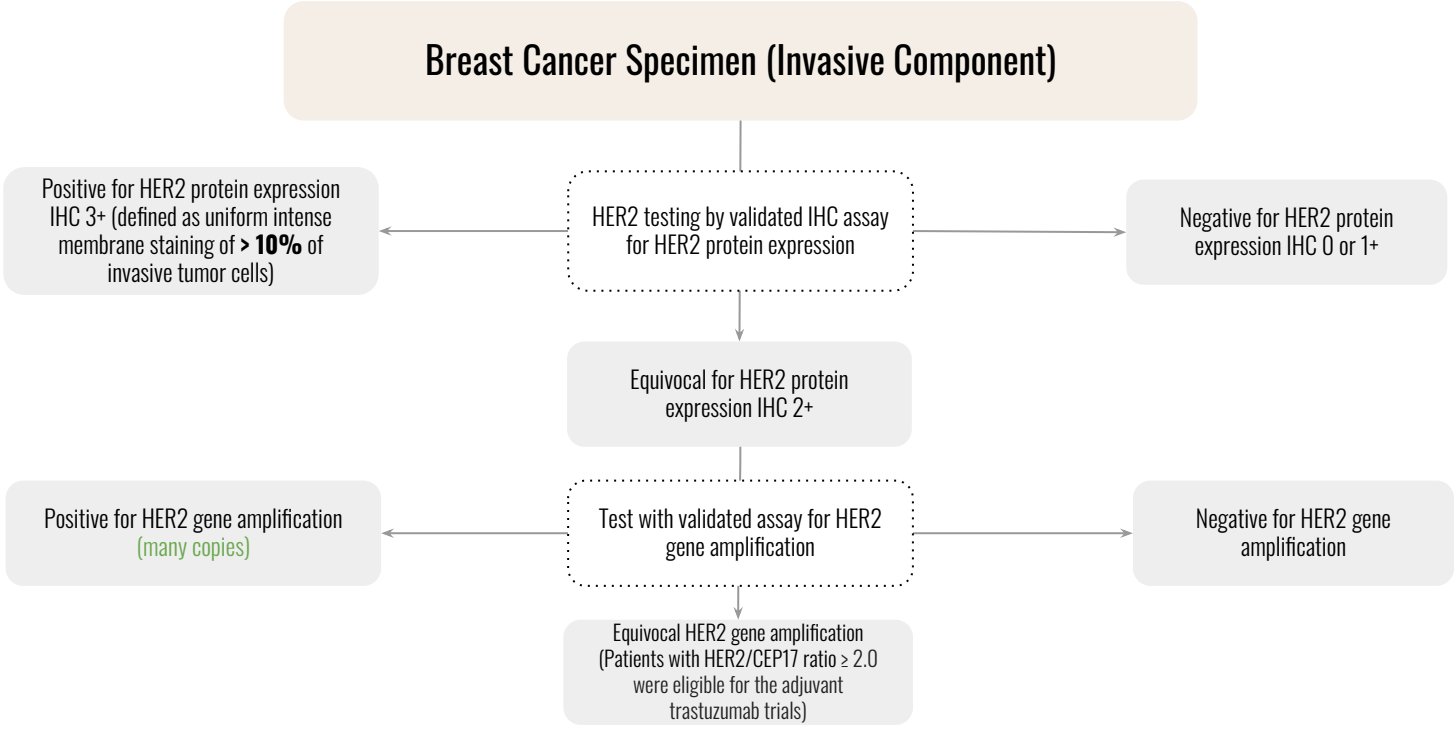
Classifications (Types) of Breast Cancer IMP

Immunophenotyping as a Surrogate for Molecular Category Using Estrogen Receptor and HER2 Status				
Molecular Category				
	Luminal A	Luminal B	HER2	Basal-like
ER (Estrogen Receptor)	+	+	-	-
PR (Progesterone Receptor)	+	+	-	-
HER2	-	+	+	-

★ Four types of breast cancer:

- **Luminal A:** Estrogen & Progesterone Positive but HER2 Negative. The treatment is Tamoxifen (Anti-Estrogen) therapy.
- **Luminal B:** Estrogen, Progesterone & HER2 Positive. The treatment is Tamoxifen (Anti-Estrogen) & Herceptin Molecule or Trastuzumab (HER2 receptor antagonist) COMBINED therapy.
- **HER2:** Estrogen & Progesterone Negative but HER2 Positive (should be High grade +3). The treatment is Herceptin Molecule or Trastuzumab (HER2 receptor antagonist) therapy.
- **Basal-like:** Estrogen, Progesterone Negative & HER2 Negative (Triple-Negative). The treatment mainly is Aggressive Chemotherapy, Have the worst prognosis.

ASCO/CAP Guideline Recommendations for The Optimal Algorithm for HER2 Testing By IHC IMP



DR. RIKABI'S NOTES

- ★ Breast cancer used to be cancer no 1 in females but still very common right now, Lung cancers in women are nowadays at an increasing rate due to many women smoking and changing their lifestyle.
- ★ Family history is a major non modifiable risk factor.
- ★ Many women choose to stay nulliparous nowadays and that is especially with the increasing responsibilities and occupations they choose to take and this means get married late and bear children late.
- ★ Regular mammogram screenings starting at a young age and especially with women with family history of breast cancer is very important.
- ★ If breast cancer appears at 20-30 years of age this raises suspension of very strong familial history.
- ★ +1 IHC result is considered negative and so the drug won't bring any benefit in such cases.
- ★ Brown stain is on the antibodies and only when the Ab reacts with these antigens (HER2 receptors) it releases this stain.
- ★ SISH an be used as an alternative or combination with FISH.
- ★ Luminal A and B make up 60%-65% of breast cancer cases, while HER2 make up 15%-20% and the basal like cancers make up 5%-10% of cases.
- ★ PCR is DNA extraction technique used to identify if genes are mutated or not but we use FISH here.
- ★ Use a combination of treatment if the patient is positive for both ER/PR and HER2.
- ★ only give medication when indicated.
- ★ So the steps of management are:
  Step 1 → Benign/malignant
  Step 2 → pleomorphism (Shape and size of cells)
  Step 3 → TNF
  Step 4 → ER and PR status
  Step 5→ HER2 status
- ★ And also investigate family history.

DR. RIKABI'S NOTES

- ★ Breast Cancer is very important & common in female.
- ★ Breast Cancer is a fatal disease in women.
- ★ Breast Cancer is more common in Europeans and Americans.
- ★ Breast Cancer affects younger women in saudi arabia.
- ★ Breast Cancer is a disease of women who are > 50 years of age.
- ★ There are predisposing factors that may lead to breast cancer.
- ★ Women who do not have any predisposing factors, what's the incident of breast cancer in this women? 3%
- ★ Women who have a predisposing factor, e.g. family history (mutation is certain gene), what's the incident of breast cancer in this women? 3-90%.
- ★ The two genes is BRCA1 & BRCA2 - mutated in familial breast cancer & involved in DNA repair.
- ★ When they are mutated, their function of stopping breast cancer will stop.
- ★ Not only increase their chances to develop breast cancer but also ovarian cancer.
- ★ These predisposing factors are:
    - The Age: The older the women the most likely to have a breast cancer.
    - Family History: Especially first degree relatives & people who carry theses two genes (BRCA1 & BRCA2) & also p53 gene (the guardian of the genome) which also involved in breast cancer (we can't do screening for this gene) & also p10 gene also involved in breast cancer.
    - When there is a breast cancer in the contralateral breast, that a predispose the patient to cancer in the other breast.
    - Obesity: The people who have high BMI will predispose the patient to breast cancer because the adipose tissue when it is present in high amount it will secrete Estrogen and breast cancer is **hormone dependent** (that's mean need estrogen to grow, need the estrogen to multiply & when they have other source of estrogen because of obesity the cancer will grow).
    - Epithelial Hyperplasia: Typical & Atypical types (likelihood to have a breast cancer).
    - Consistency (Density) of breast tissue: The more the stroma of breast the greater to have breast cancer.
    - Nulliparous women (Never have children): Have increase incidence of breast cancer.
    - Women who get menarche at early age: Is a predisposing factor to breast cancer (may more exposure to estrogen hormone).
    - Late Menopause: Is a predisposing factor to breast cancer (long-period exposure to estrogen hormone).
    - Alcohol: May increase incidence of breast cancer.
- ★ BRCA1 gene is located in chromosome 17q (long arm) & the locus is 21.3.
- ★ BRCA2 gene is located in chromosome 13q (long arm) & the locus is 12-13.
- ★ **Mammography** for the follow-up the patients who have breast cancer.
- ★ Patients who have mutation in BRCA2: The tumor more likely to be estrogen dependent & BRCA1 is not.
- ★ Most people who have mutation in these genes will develop cancer by the age of 70.
- ★ People who do not have a mutation in these genes and no family history of gene mutations the percentage of cancer to develop is 7% instead of 70% with mutation in these genes of family history related them.
- ★ If we have source of estrogen & progesterone & also a receptors for them, the patients are more likely to develop breast cancer (the tumor should be positive for the estrogen receptor to grow).

DR. RIKABI'S NOTES

- ★ How we can determine the prognosis & how we treat the patient who has breast cancer?
  - 1. Tumor MALIGNANT or BENIGN.
  - 2. The grade (degree of differentiation) of the tumor is determined by HISTOLOGY.
  - 3. The stage of tumor is determined by clinical examination & investigation which depend on 3 things (TNM):
  - T: Describes the size of the original (primary) tumor and whether it has invaded nearby tissue - The larger the tumor the more aggressive it is.
  - N: Describes nearby (regional) lymph nodes that are involved (metastasize) - axillary lymph nodes is first likely to be involved. We determine the number of lymph nodes by radiology methods (imaging techniques), biopsy, clinical examination.
  - M: Describes distant metastasis (spread of cancer from one part of the body to another).
  - 4. The positivity of tumor to (estrogen or progesterone receptors):
    - Positivity to Estrogen: We use Immunohistochemical stain for estrogen - If the number of cell stained by this stain and become brown in color and more than 10% thats mean it is estrogen receptor cancer (positive).
- ★ Tamoxifen (Aromatase inhibitor or Anti-estrogen): Therapy for the tumor who is positive to estrogen receptor - stopped the growth of the tumor.
- ★ HER2 (Human epidermal growth receptor 2) gene: Located in chromosome 17, Control tissue growth - if it gets mutated and the patient has breast cancer this cancer is going to spread and grow and multiply very quickly.
- ★ If this gene is present in the tumor cell with more than one copy (overexpression), the tumor will grow quicker, will multiply and spread more, will produce worse prognosis.
- ★ The positivity of tumor to (HER2 receptors). We use Immunohistochemistry for the assessment of the level of HER2 expression at the tumor cell membrane, If the number of cell stained by this stain and become **slightly** brown in color (+2) that's mean it is NOT enough (equivocal). but if it is full of brown color (+3) that's mean it is HER2 receptor cancer (Positive).
- ★ Herceptin Molecule or Trastuzumab (HER2 receptor antagonist): Therapy for the tumor who is positive to HER2 receptor - stopped the growth of the tumor.
- ★ FISH (Fluorescence in situ hybridization) technique (molecular technique): We use it if we can determine the tumor positivity to the HER2 receptors - for the (+2) patients ONLY.
- ★ FISH denature dsDNA to ssDNA (break the bonds between various proteins) and then hyperdizate them to dsDNA again (bring hybride stranded that has fluorophore "radiant stain" and tagging of it, after that impeding of the hybride DNA with the patient DNA to become a "Double Stranded DNA").
- ★ Four types of breast cancer:
  - **Luminal A:** Estrogen & Progesterone Positive but HER2 Negative. The treatment is Tamoxifen (Anti-Estrogen) therapy.
  - **Luminal B:** Estrogen, Progesterone & HER2 Positive. The treatment is Tamoxifen (Anti-Estrogen) & Herceptin Molecule or Trastuzumab (HER2 receptor antagonist) COMBINED therapy.
  - **HER2:** Estrogen & Progesterone Negative but HER2 Positive (should be High grade). The treatment is Herceptin Molecule or Trastuzumab (HER2 receptor antagonist) therapy.
  - **Basal-like:** Estrogen, Progesterone Positive & HER2 Negative. The treatment mainly is Aggressive Chemotherapy, Have the bad prognosis.
- ★ SISH: (Silver in situ hybridization) technique (molecular technique): Same as FISH but we use silver stain

DR. RIKABI'S NOTES

- ★ Major factors of breast cancer are delayed childbearing, fewer pregnancies and reduced breastfeeding with the lack of access to optimal health.
- ★ Almost all breast malignancies are adenocarcinomas.
- ★ Breast cancer is divided based on the expression of hormone receptors: estrogen receptor (ER) and progesterone receptor (PR),
- ★ The expression of the human epidermal growth factor receptor 2 (HER2 — that is also known as ERBB2) into three major groups:
    - ER positive (HER2 negative; 50%-65% of cancers).
    - HER2 positive (ER positive or negative; 10%-20% of cancers).
    - Triple negative (ER, PR and HER2 negative; 10%-20% of cancers).
- ★ An alternative classification system with substantial overlap relies on gene expression profiling which is used in clinical research, it divides breast cancer into 4 major types:
    - **Luminal A:** the majority are lower-grade ER-positive cancers that are HER2 negative.
    - **Luminal B:** the majority are high-grade ER-positive cancers that may be HER2 positive.
    - **HER2 enriched:** the majority over-express HER2 and do not express ER.
    - **Basal-Like:** the majority by gene expression profiling resemble basally located myoepithelial cells and are ER-negative, HER2-negative.
- ★ **Breast cancer risk factors:**
    - Age and gender (increases in women with age).
    - Family history of breast cancer.
    - Geographic factors (high in America and Europe over Asia and Africa).
    - Race/Ethnicity.
    - Reproductive history.
    - Ionizing radiation.
- ★ **Pathogenesis:**
    - genetically it can be divided into inherited and acquired.
    - The major germ-line mutations conferring susceptibility to breast cancer affect genes that regulate genomic stability or that are involved in progrowth signaling pathways.
    - BRCA1 & BRCA2 are classic tumor suppressor genes, in that cancer arises only when both alleles are inactivated or defective. BRCA2 is associated with ER-positive tumors while BRCA1 with triple negative tumors.
    - TP35 & PTEN (an important negative regulator of the progrowth PI3K-AKT pathway) are associated with familial breast cancer.
- ★ The pathways in which familial breast cancer genes function also are often disturbed in sporadic breast cancer. somatic mutations in BRCA1 & BRCA2 are rare in sporadic cancers. Somatic mutations in TP35 are common in breast cancer particularly triple negative and HER2 positive tumors.

Our team based on their amazing work!

438 LEADERS : JUDE ALOTAIBI + ABDULRAHMAN BEDAIWI

Hidden REVIEWERS :

QUIZ

Q1. Which one of the following is FALSE regarding BRCA1 gene?

A. It is a DNA repair gene.
B. It is located on the chromosome 17q.
C. It is only involved in breast cancer.
D. Mutation in it is more aggressive than BRCA2.

Q2. A 39 years female presented for a routine check up, on examination a mass was found in her right breast, a biopsy was taken from the mass and ERs was seen ,some degree of mitosis in the ductal cells. Which one of the following is the best to be used for the treatment?

A. Trastuzumab.
B. Aromatase inhibitor Thereby.
C. Tamoxifen.
D. B&C.

Q3. Immunohistochemistry for HER2 gene from a breast specimen was found to be (2+). What should be the next step?

A. Start trastuzumab.
B. Chemotherapy.
C. Use FISH method.
D. Start Tamoxifen.

Q4. How many copies of HER2-neu gene is normally expressed on cells?

A. One copy.
B. Two copies.
C. Five copies.
D. 20 Copies.

Q5. Normal function of HER2-neu gene is ?

A. Tumor suppressor gene.
B. DNA Repair gene.
C. Sex determination gene.
D. Regulates cell growth by protein production.

Q6. BRCA2 gene is located in which chromosome?

A. Chromosome 11p.
B. Chromosome 17q.
C. Chromosome 13q.
D. Chromosome 13p.

Answers: 1) C, 2) D, 3) C, 4) B, 5) D, 6) C

Table 19.6 Factors Associated With Development of Invasive Carcinoma

Factor	Relative Risk[a]	Absolute Lifetime Risk[a]
Women with no risk factors	1.0	3%
First-degree relative(s) with breast cancer[b]	1.2–9.0	4%–30%
Germline tumor suppressor gene mutation (e.g., *BRCA1* mutation)	2.0–45.0	6% to >90%
Menstrual History		
Age at menarche <12 years	1.3	4%
Age at menopause >55 years	1.5–2.0	5%–6%
Pregnancy		
First live birth <20 years (protective)	0.5	1.6%
First live birth 20–35 years	1.5–2.0	5%–6%
First live birth >35 years	2.0–3.0	6%–10%
Never pregnant (nulliparous)	3.0	10%
Breast-feeding (slightly protective)	0.8	2.6%
Benign Breast Disease		
Proliferative disease without atypia	1.5–2.0	5%–6%
Proliferative disease with atypia (ALH and ADH)	4.0–5.0	13%–17%
Carcinoma in situ (ductal or lobular)	8.0–10.0	25%–30%
Ionizing radiation	1.1–1.4	3.6%–4.6%
Mammographic density	3.0–7.0	10%–23%
Postmenopausal obesity and weight gain	1.1–3.0	3.6%–10%
Postmenopausal hormone replacement	1.1–3.0	3.6%–10%
Alcohol consumption	1.1–1.4	3.6%–4.6%
Alcohol consumption	1.1–1.4	3.6%–4.6%

[a]Relative risk is the likelihood of developing cancer compared to a woman with no risk factors—whose relative risk is 1.0. Absolute lifetime risk is the fraction of women expected to develop invasive carcinoma without a risk reducing intervention. For women with no risk factors, there is about a 3% chance of developing invasive breast cancer.
[b]The most common family history is a mother who developed cancer after menopause. This history does not increase the risk of her daughters.

hyperplasia, increased numbers of both spindled myoepithelial cells and epithelioid luminal cells expand ductal and lobular spaces (Fig. 19.25B).

Proliferative disease with atypia includes atypical lobular hyperplasia (ALH) and atypical ductal hyperplasia (ADH). ALH closely resembles lobular carcinoma in situ (LCIS) and ADH closely resembles ductal carcinoma in situ (DCIS) (both described later), but are more limited in extent. The cells in ADH are uniform in appearance and form sharply marginated spaces or rigid bridges (Fig. 19.25C).

CARCINOMA

Breast carcinoma is the most common malignancy of women globally (excluding nonmelanoma skin cancer) and causes the majority of cancer deaths in women. Although the incidence in the United States decreased slightly in 2002 and then stabilized (changes attributed to a decrease in the use of postmenopausal hormone therapy and a plateau in the number of women undergoing mammographic screening), the worldwide incidence

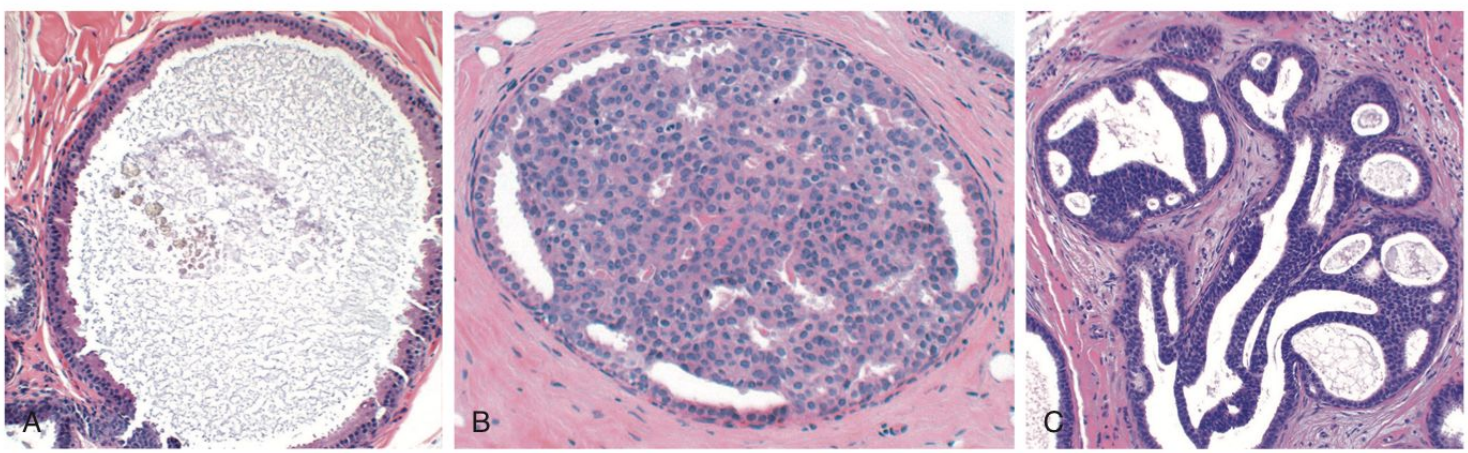


Fig. 19.25 Benign epithelial breast disease. (A) Nonproliferative disease. An apocrine cyst is shown that is a common feature of nonproliferative breast disease. (B) Proliferative breast disease is characterized by increased numbers of epithelial cells, as in this example of epithelial hyperplasia. (C) Proliferative breast disease with atypia. The proliferating epithelial cells are monomorphic in appearance and pile up to form abnormal architectural structures.

and mortality is increasing at an alarming rate. The major factors underlying this trend in developing countries are thought to be social changes that increase breast cancer risk—specifically, delayed childbearing, fewer pregnancies, and reduced breastfeeding—combined with a lack of access to optimal health care.

The lifetime risk of breast cancer is 1 in 8 for women living to age 90 in the United States. It is predicted that about 250,000 breast cancers will be diagnosed in 2016 and about 40,000 women will die of the disease—a toll among cancers second only to lung cancer. Since the mid-1980s the mortality rate has dropped from 30% to less than 20%. The decrease is attributed to both improved screening, which detects some cancers before they have metastasized, and more effective systemic treatment.

Almost all breast malignancies are adenocarcinomas (>95%). In the most clinically useful classification system, breast cancers are divided based on the expression of hormone receptors—estrogen receptor (ER) and progesterone receptor (PR)—and the expression of the human epidermal growth factor receptor 2 (HER2, also known as ERBB2), into three major groups:

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

These three groups show striking differences in patient characteristics, pathologic features, treatment response, metastatic patterns, time to relapse, and outcome (Table 19.7 and Fig. 19.26). Within each group are additional histologic subtypes (discussed later), some of which also have clinical importance.

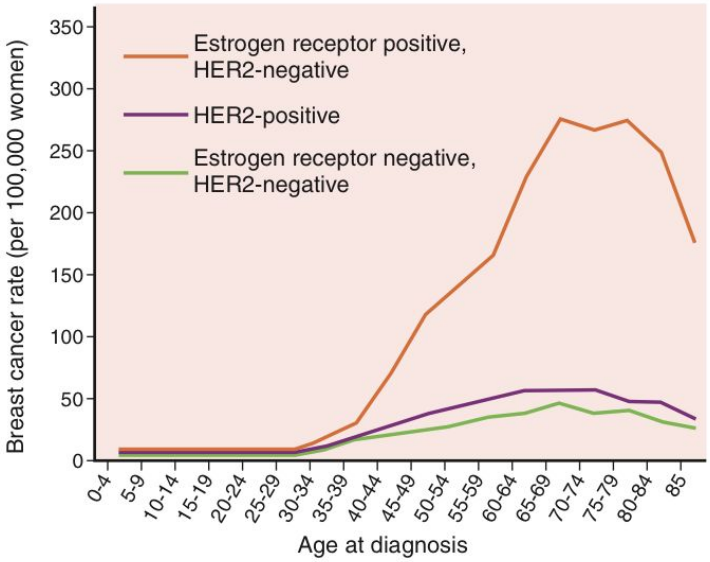


Fig. 19.26 Age and the incidence of breast cancer subtypes.

An alternative classification system with substantial overlap relies on gene expression profiling. This system, which is currently used mainly in the context of clinical research, divides breast cancers into four major types:

- *Luminal A*. The majority are lower-grade ER-positive cancers that are HER2 negative
- *Luminal B*. The majority are higher-grade ER-positive cancers that may be HER2 positive
- *HER2-enriched*. The majority overexpress HER2 and do not express ER
- *Basal-like*. The majority by gene expression profiling resemble basally located myoepithelial cells and are ER-negative, HER2-negative

Table 19.7 Summary of the Major Biologic Types of Breast Cancer

Feature	ER Positive/HER2 Negative	HER2 Positive (ER Positive or Negative)	Triple Negative (ER, PR, and HER2 Negative)
Overall frequency	50%–65%	20%	15%
Typical patient groups	Older women; men; cancers detected by screening; germline *BRCA2* mutation carriers	Young women; germline *TP53* mutation carriers	Young women; germline *BRCA1* mutation carriers
Ethnicity			
European/American	70%	18%	12%
African/American	52%	22%	26%
Hispanic	60%	24%	16%
Asian/Pacific Islander	63%	26%	11%
Grade	Mainly grade 1 and 2	Mainly grade 2 and 3	Mainly grade 3
Complete response to chemotherapy	Low grade (<10%), higher grade (10%)	ER positive (15%), ER negative (>30%)	30%
Timing of relapse	May be late (>10 years after diagnosis)	Usually short (<10 years after diagnosis)	Usually short (<8 years after diagnosis)
Metastatic sites	Bone (70%), viscera (25%), brain (<10%)	Bone (70%), viscera (45%), brain (30%)	Bone (40%), viscera (35%), brain (25%)
Similar group defined by mRNA profiling	Luminal A (low grade), luminal B (high grade)	Luminal B (ER positive), HER2-enriched (ER negative)	Basal-like
Common special histologic types	Lobular, tubular, mucinous, papillary	Apocrine, micropapillary	Carcinoma with medullary features
Common somatic mutations	*PIK3CA* (40%), *TP53* (26%)	*TP53* (75%), *PIK3CA* (40%)	*TP53* (85%)

PIK3CA encodes phosphoinositide 3-kinase (PI3K).

Epidemiology and Risk Factors

A large number of risk factors for breast cancer have been identified (Table 19.6). Some of the more important risk factors are summarized next.

Age and Gender. Breast cancer is rare in women younger than age 25, but increases in incidence rapidly after age 30 (Fig. 19.26); 75% of women with breast cancer are older than 50 years of age, and only 5% are younger than 40. The incidence in men is only 1% of that in women.

Family History of Breast Cancer. The greatest risk is for individuals with multiple affected first-degree relatives with early-onset breast cancer. In most families, it is thought that various combinations of low penetrance, "weak" cancer genes are responsible for increased risk. However, approximately 5% to 10% of breast cancers occur in persons who inherit highly penetrant germline mutations in tumor suppressor genes (discussed later). For these individuals, the lifetime risk of breast cancer may be greater than 90%.

Geographic Factors. Significant differences in the incidence and mortality rates of breast cancer have been reported in various countries. The risk is significantly higher in the Americas and Europe than in Asia and Africa. For example, the incidence and mortality rates are five times higher in the United States than in Japan. Some risk factors must be modifiable because migrants from low-incidence to high-incidence areas tend to acquire the rates of their new home countries. Diet, reproductive patterns, and breastfeeding practices are thought to be involved. In line with this, breast cancer rates appear to be rising in parts of the world that are adopting Western habits.

Race/Ethnicity. The highest rate of breast cancer is in women of European descent, largely because of a higher incidence of ER-positive cancers. Hispanic and African American women tend to develop cancer at a younger age and are more likely to develop aggressive tumors. Such disparities are thought to result from a combination of differences in genetics, social factors, and access to health care and are an area of intense study.

Reproductive History. Early age of menarche, nulliparity, absence of breastfeeding, and older age at first pregnancy are all associated with increased risk, probably because each increases the exposure of "at-risk" breast epithelial cells to estrogenic stimulation.

Ionizing Radiation. Radiation to the chest increases the risk of breast cancer if exposure occurs while the breast is still developing. For example, breast cancer develops in 25% to 30% of women who underwent irradiation for Hodgkin lymphoma in their teens and 20s, but the risk for women treated later in life is not elevated.

Other Risk Factors. Postmenopausal obesity, postmenopausal hormone replacement, mammographic density, and alcohol consumption also have been implicated as risk factors. The risk associated with obesity probably is due to exposure of the breast to estrogen produced by adipose tissue. In keeping with this, obesity is only associated with an increased risk of tumors that express ER.

Pathogenesis

The three major subtypes of breast cancer defined by differential expression of hormone receptors and HER2 arise through more-or-less distinct pathways that involve the stepwise acquisition of driver mutations in the epithelial cells of the duct/lobular system (Fig. 19.27). Factors that contribute directly to the development of breast cancer can be grouped into genetic, hormonal, and environmental categories.

Genetic. Driver mutations in cancer genes that contribute to breast carcinogenesis can be divided into those that are inherited and those that are acquired. **The major germline mutations conferring susceptibility to breast cancer affect genes that regulate genomic stability or that are involved in progrowth signaling pathways.** *BRCA1* and *BRCA2* are classic tumor suppressor genes, in that cancer arises only when both alleles are inactivated or defective (Chapter 6). *BRCA1* and *BRCA2* encode proteins that are required for repair of certain kinds of DNA damage. They are normally expressed in many different cells and tissues, and why germline mutations in these genes lead mainly to an increased risk of breast and serous ovarian cancer (discussed earlier) remains mysterious. The degree of penetrance, age of onset, and susceptibility to other types of cancers differ among the many *BRCA1* and *BRCA2* germline mutations, but most carriers develop breast cancer by the age of 70 years, as compared to about 12% of women with an average risk of breast cancer. For unclear reasons, *BRCA2* mutations are primarily associated with ER-positive tumors, whereas *BRCA1* mutations show a strong association with triple-negative cancers (Fig. 19.27). Other mutated genes associated with familial breast cancer include *TP53* (the so-called "guardian of the genome", Chapter 6) and *PTEN* (an important negative regulator of the pro-growth PI3K-AKT pathway), already mentioned earlier as a risk factor for endometrial carcinoma as part of *Cowden syndrome*.

As might be expected, **the pathways in which familial breast cancer genes function also are often disturbed in sporadic breast cancers**. Somatic mutations in *BRCA1* and *BRCA2* are rare in sporadic cancers, but *BRCA1* is inactivated by methylation in up to 50% of triple-negative cancers. Somatic mutations in *TP53* are common in breast cancer, particularly triple-negative and HER2-positive tumors (Table 19.7), whereas mutations that activate PI3K-AKT signaling are frequently found in sporadic ER-positive and HER2-positive breast cancers (Fig. 19.27).

A common clinically important driver mutation in breast cancer is amplification of the *HER2* gene. HER2 is a receptor tyrosine kinase that promotes cell proliferation and opposes apoptosis by stimulating the RAS- and PI3K-AKT signaling pathways. Cancers that overexpress HER2 are pathogenically distinct and highly proliferative. In the past they had a poor prognosis; however, the availability of therapeutic agents that specifically target HER2 has markedly improved the prognosis for patients with HER2-amplified tumors.