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Learning Series - #15

Making sense of Breast Cancer

Breast Cancer Awareness Month
October

Breast cancer is the second most common cancer in women after skin cancer and remains one of the most prevalent diseases in the western world, with 1 in 8 women predicted to be affected in their lifetime.

Improvements in detection, anti-estrogen therapies, and cytotoxic chemotherapy have led to increased survival rates.

The majority (80%) of the breast cancers that are diagnosed are invasive lesions. The remaining 20% are in- situ lesions and have cells that show malignant changes but have not invaded through the basement membrane.

Types of breast cancer

A) Invasive vs. non-invasive (in-situ)

1) Ductal carcinoma is a common type of breast cancer and it starts in cells that line the milk ducts.
2) Lobular breast cancer starts in the cells of the lobules (groups of glands that make milk).

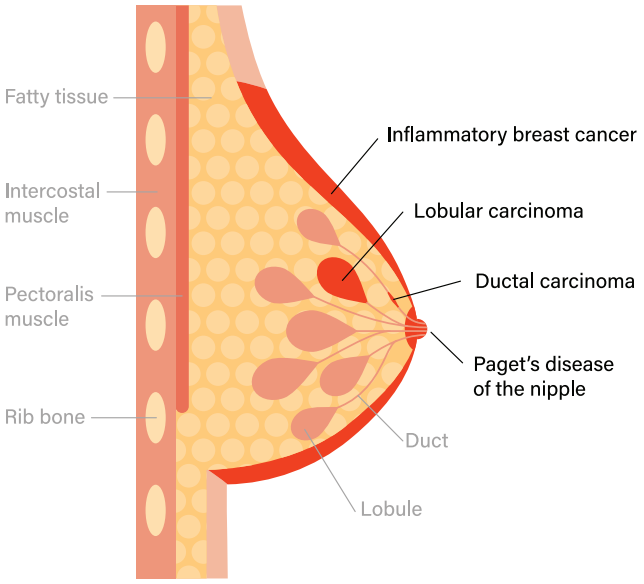
Both ductal and lobular carcinomas can be
- in situ (cancer has not grown into surrounding tissues)
- invasive (cancer has grown into surrounding tissues).

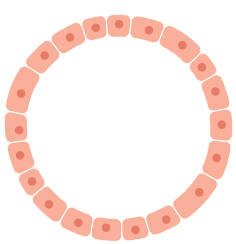
B) Less common types include:

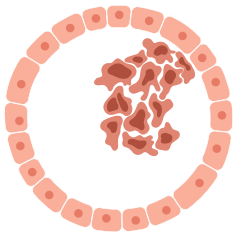
- Inflammatory breast cancer
- Paget disease of the breast
- Triple negative breast cancer (cancer cells don't have estrogen or progesterone receptors nor excess HER2 protein, therefore this type of cancer does not respond to hormonal therapy or medication that target HER2 protein receptors. More common in women younger than age 40, more often in Hispanic and African American women, or who have a BRCA1 mutation).
- Rare types include: angiosarcoma, Phyllodes tumor

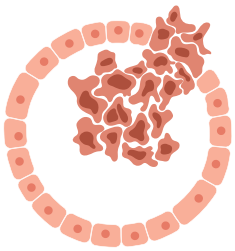
C) Molecular subtypes: based on the genes a cancer expresses and they are different in terms of risk factors; presentation; response to treatments; prognosis.

- Luminal A
- Luminal B
- Basal-like
- HER2-enriched
- Normal-like




Normal duct


Ductal carcinoma in situ


Invasive ductal carcinoma

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Risk factors

- **age:**
  The odds for developing breast cancer for women aged 30-40, 40-50, 50-60, and 60-70 increase sequentially and are 1:252, 1:68, 1:35, and 1:27 respectively.
- **family history:**
  The risk increases with the number of affected relatives and the age at which those relatives developed a tumor. For a history of cancer in first degree relatives (mother or sister), the risk varies depending on whether the onset in the family member was premenopausal or postmenopausal and whether there was bilateral disease. With the combination of bilateral disease and early onset, the risk is increased even further.
- **estrogen exposure:**
  Prolonged exposure to estrogens is important in the development of breast cancer. Factors that increase exposure: early menarche, older age at first pregnancy, and delayed menopause.
- **previous history of breast cancer or certain non-cancerous breast diseases:**
  Women who have had breast cancer are more likely to get breast cancer a second time.
  Some non-cancerous breast diseases such as atypical hyperplasia or lobular carcinoma in situ are associated with a higher risk
- **previous treatment using radiation therapy:**
  Women who had radiation therapy to the chest or breasts (like for treatment of Hodgkin's lymphoma) before age 30 have a higher risk of getting breast cancer later in life.
- **Environmental factors:**
  Alcohol consumption, smoking, obesity in postmenopausal women, lack of physical activity can increase the risk of developing breast cancer

Screening

- Women between 40 and 44 have the option to start screening with a mammogram every year.
- Women 45 to 54 should get mammograms every year.
- Women 55 and older can switch to a mammogram every other year, or they can choose to continue yearly mammograms.

Screening should continue as long as a woman is in good health and is expected to live at least 10 more years.

Diagnosis

- **self-examination:** palpable lump or nodule, new skin or nipple changes, a bloody nipple discharge, or lymph node enlargement.
- **mammography:** the primary means of diagnosis of breast cancer; detects 80-90% of breast cancers in asymptomatic women. Findings suggestive of cancer are microcalcifications, nodules, or masses. Dense breasts, prior surgery, and the presence of implants reduce the sensitivity of mammography. Not all tumors are detected by mammography so suspicious physical findings should not be ignored if the test is negative.
- **Ultrasound:** evaluate suspicious lesions on mammography. Its primary value is in differentiating cysts from solid lesions and lymph nodes from nodules. It can also be used to direct needle biopsies or cyst drainage. Because ultrasound does not visualize microcalcifications, it is not an effective screening tool.

- **Magnetic resonance imaging (MRI):** more sensitive than mammography. Recommended for women with dense breasts or breast implants and individuals with a high risk of developing breast cancer (i.e., known carriers of BRCA1 and BRCA2 or other genetic high-risk conditions), prior chest irradiation. The disadvantages of MRI are its high false positive rate and cost.

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Staging

The pathologic staging of breast cancer relies on the **TNM** system and uses combinations of the TNM designations

- **T** represents the size and/or local extent of the tumor
- **N** represents the nodal status and is evaluated either clinically or pathologically
- **M** indicates whether distant metastasis is absent (M0) or present (M1).

Staging chart	
Stage	**TNM**
0	DCIS
IA	T1 N0 M0
IB	T0-1 N1mi M0
IIA	T0-1 N1 M0 T2 N0 M0
IIB	T2 N1 M0 T3 N0 M0
IIIA	T0-2 N2 M0 T3 N1-2 M0
IIIB	T4 N0-2 M0 T3 N1-2 M0
IIIC	any T N3 M0
IV	Systemic (any T any N M1)

Hormone Receptor/HER2 Expression/ Hormone status

Evaluating the expression of estrogen receptors (ERs) and progesterone receptors (PRs) in breast cancer is important because selective ER modulators slow the progression of ER-positive and PR-positive tumors. Furthermore, breast cancer is related to several oncogenes including Human Epidermal Growth Factor Receptor 2 (HER2).

- ER/PR/HER2 can be positive or negative. The survival rate is better if both ER & PR are positive.
- The presence of HER2 is associated with a poor prognosis in untreated patients. However, HER2 targeting agents (trastuzumab) improve the prognosis for patients with HER2 positive tumors

New hormone status terminology

- Luminal A: high ER+; low HER2- most common (40%), best prognosis
- Luminal B: lower ER+, variable HER2- worse prognosis
- HER2 enriched indicates HER2 positive
- Basal type: ER-ve and most are triple negative (ER-, PR-, HER2-)
- Ki-67: a new marker for prognosis and carries a worse prognosis (not accepted by all oncology organizations)

Histologic Grade:

Invasive carcinomas are morphologically subdivided according to their growth patterns and degree of differentiation, the latter of which reflects how closely they resemble normal breast epithelial cells. This subdivision is achieved by assessing histological type and histological grade, respectively.

The Nottingham (Elston-Ellis) modification of the Scarff-Bloom-Richardson grading system, also known as the Nottingham Grading System (NGS), is the grading system recommended by various professional bodies internationally.

The grade of a breast cancer is a prognostic factor and is representative of the "aggressive potential" of the tumor.

- Grade 1 (low grade) = well differentiated
- Grade 2 (intermediate/moderate grade) = moderately differentiated
- Grade 3 (high grade/comedo necrosis) = poorly differentiated (worse prognosis)

Pathology

- In-situ carcinomas:

a) DCIS (ductal carcinoma in situ)

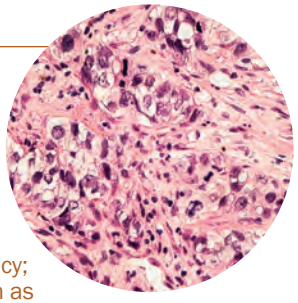
- the most common of in situ lesions;
- can be diagnosed by mammography, by its classic finding of clustered microcalcifications;
- a precursor to invasive breast cancer.

b) LCIS (lobular carcinoma in situ)

- most often an incidental finding (i.e., biopsy that is done for calcifications or another abnormality found on breast imaging. It rarely causes symptoms);
- not detected by mammography;
- tends to occur in younger women and to show diffuse involvement in both breasts;
- a marker for increased breast cancer in either breast, much like family history.

- Invasive cancers:

Most invasive cancers are adenocarcinomas, and the most common of the adenocarcinomas is invasive/infiltrating ductal carcinoma. The next most common type is invasive lobular carcinoma, which tends to be multicentric and to have an increased risk of bilateral disease. Several other subtypes occur with much lower frequency; some of these, such as papillary, colloid, or mucinous tumors and tubular carcinomas, are indolent in character and carry a favorable long-term prognosis.



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Treatment (Tx)

Decision is made after consideration of stage; biological characteristics of the tumor; age; menopausal status; patient and physician preferences based on risks and benefits

- Surgery
- Radiation therapy
- Chemotherapy
- Hormonal therapy
- Immunotherapy

DCIS: Tx directed primarily at preventing local recurrence and generally involves either lumpectomy with local radiation or mastectomy.

LCIS: does not require Tx, the diagnosis increases a patient's risk, so consideration of risk-reducing interventions (prophylactic mastectomy, chemoprevention using hormonal therapy with SERMs like Tamoxifen, or one of the newer aromatase inhibitor drugs) and enhanced breast cancer screening should be discussed.

Invasive cancers: can be treated with lumpectomy, with or without radiation. Individuals with large tumors, an extensive intraductal component, or in whom a lumpectomy would give an unacceptable cosmetic result can require a mastectomy.

Underwriting considerations

- Age of onset: <35 years suggests a worse outcome.
- Mortality varies with the major prognostic factors: lymph node status; tumor size; grade. Invasive breast cancer is a systemic illness at the time of diagnosis. Mortality does not result from degree of local control, but from distant metastasis.
- Tumor size: The larger the size of the lesion, the greater the risk is for metastasis and mortality.
- The histologic grade/degree of differentiation of the lesion: the less differentiated the greater the risk for progression and mortality.
  This grade may be "scored" and noted as Grade I, II or III on the attending physician's statement but if no grade is given consider Grade III.
  A minority of breast cancers are Grade I. In node negative disease, grade may be a better predictor of risk than hormone status.
  Grading depends on the experience of the pathologist, therefore inter-operator inconsistencies amongst pathologist may be present.
- Lymphatic or vascular invasion on the pathologic specimen is associated with a higher risk of local and distant spread.
- Recurrence: once- can consult with MD; 2nd time – RNA
- Determine estrogen (ER) status
  Consider ER positive (ER+) if:
  - Was prescribed anti-estrogen therapy
  - Undergoes ovarian ablation
  - Luminal A; luminal B

  Consider ER negative (ER-) if:
  - Noted ER+ but never taken or prematurely stopped taking anti-estrogen therapy
  - HER2 enriched or Base-like, Triple negative
  - ER status not documented
- The hormone status is an important indicator of risk in breast cancer but may be less so than grade and other factors. The presence of ER+ implies that a more normal cellular mechanism processing estrogen has been maintained despite the malignant change, particularly if the PR is also positive in the tumor cells. Triple negative & node negative disease may be a worse prognosis than a pN1 (TNM) risk where node positive disease is present.
- No offer should be available if: recommended treatment was not performed or completed; had surgical intervention with margin involvement.
- With multiple tumors (in either or both breasts), mortality risk should be considered according to the highest risk classified tumor.
- Inadequate post-treatment follow-up.