Diseases of the breast
(2 of 2)...Breast cancer

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Epidemiology & etiology

• The most common type of cancer & the 2nd most common cause of cancer death in women

• 1 of 8 women in USA

• Affects 7% of women

• Peak at 80 years of age

• 75% of women with breast cancer are older than 50 years of age, and only 5% are younger than 40
Epidemiology & etiology, cont’d

• The highest rate of breast cancer is in non-Hispanic white women. However, Hispanic and African American women tend to develop cancer at a younger age and are more likely to develop aggressive tumors that present at an advanced stage.

• Prolonged exposure to exogenous estrogens postmenopausally is also a risk factor.

• Oral contraceptives have not been shown to affect the risk of breast cancer.

• Ionizing radiation to the chest increases the risk of breast cancer.
  ...the magnitude of the risk depends on the radiation dose, the time since exposure, and age.
  ...only women in whom irradiation occurred before age 30, during breast development, seem to be affected.

• The low doses of radiation associated with mammographic screening have no significant effect on the incidence of breast cancer.
Pathogenesis

- Overexpression of the HER2/NEU proto-oncogene...poor prognosis...30% of breast cancer cases

- RAS and MYC genes

- RB and TP53 mutations

- Steroid receptors
Pathogenesis, cont’d

- Gene expression profiling can separate breast cancer into four molecular subtypes:

  1. luminal A (estrogen receptor–positive, HER2/NEU-negative)

  2. luminal B (estrogen receptor–positive, HER2/NEU overexpressing)

  3. HER2/NEU positive (HER2/NEU overexpressing, estrogen receptor–negative)

  4. basal-like (estrogen receptor–negative and HER2/NEU-negative)
10% of breast cancers are related to specific inherited mutations

• Women who carry a breast cancer susceptibility gene are more likely:
  ...to have bilateral cancer
  ...to have other familial forms of cancer (e.g., ovarian cancer)
  ...to have a positive family history (i.e., multiple first-degree relatives affected before menopause)
  ...to develop breast cancer before menopause
  ...to belong to certain ethnic groups (e.g., people of Ashkenazi Jewish descent)

• One third of women with hereditary breast cancer have mutations in BRCA1 (at chromosomal locus 17q21.3) or BRCA2 (located on chromosomal band 13q12-13)

• mutations affecting BRCA1 and BRCA2 are infrequent in sporadic tumors
Other less common hereditary conditions

• Li-Fraumeni syndrome

• Cowden syndrome

• Ataxia telangiectasia
Pathogenesis, cont’d

• Estrogens stimulate the production of growth factors, such as transforming growth factor-α, platelet-derived growth factor, and fibroblast growth factor and others, which may promote tumor development through paracrine and autocrine mechanisms

...in addition to the previously mentioned risk factors (slide #2), ovarian tumors which secrete estrogen may also be risky
Morphology

- The most common location of tumors within the breast is in the upper outer quadrant (50%), followed by the central portion (20%)

- 4% have bilateral or metachronous tumors

A. Noninvasive
   1. Ductal carcinoma in situ (DCIS)
   2. Lobular carcinoma in situ (LCIS)

B. Invasive (infiltrating)
   1. Invasive ductal carcinoma ("not otherwise specified"), the most common subtype of invasive carcinoma
   2. Invasive lobular carcinoma
   3. Medullary carcinoma
   4. Colloid carcinoma (mucinous carcinoma)
   5. Tubular carcinoma
   6. Other types
DCIS & LCIS

- Both types usually arise from cells in the terminal duct lobular unit
- DCIS tends to fill and distort duct-like spaces
- LCIS usually expands but does not alter the acini of lobules
- Both are confined by a basement membrane and do not invade into stroma or lymphovascular channels
DCIS

- The comedo subtype of DCIS is distinctive and is characterized by cells with high-grade nuclei with extensive central necrosis...most frequently detected as radiologic calcifications

- Calcifications frequently are associated with DCIS

- DCIS only rarely manifests as a palpable or radiologically detectable mass

- When invasive cancer does develop, it usually is in the same breast and quadrant as the earlier DCIS

At least one third of women with small areas of untreated DCIS of low nuclear grade will eventually develop invasive carcinoma

The prognosis with DCIS is excellent, with greater than 97% long-term survival after simple mastectomy...antiestrogenic therapy may be used to prevent recurrence
Paget disease of the nipple

• Caused by the extension of DCIS up the lactiferous ducts and into the contiguous skin of the nipple

• A bilateral crusting exudate over the nipple and areolar skin
  ...clinically as eczema, but unilateral

• In almost all cases, an underlying carcinoma is present, and approximately 50% of the time this carcinoma is invasive

• Presence of Paget disease doesn’t increase the stage of the underlying carcinoma (doesn’t affect the prognosis)
LCIS

- LCIS is virtually always an incidental finding, because unlike DCIS, it is only rarely associated with calcifications.

- One third of women with LCIS will eventually develop invasive carcinoma. Unlike with DCIS, subsequent invasive carcinomas may arise in either breast.

  ...most of these cancers are invasive lobular carcinomas; however, invasive ductal carcinomas also arise from LCIS.

- Intracellular mucin vacuoles (sometimes forming signet ring cells) are common.

- Current treatment involves either chemoprevention with tamoxifen along with close clinical and radiologic follow-up evaluation or, less commonly, bilateral prophylactic mastectomy.
Invasive ductal carcinoma, not otherwise specified

- Usually is associated with DCIS and, rarely, LCIS

- Most ductal carcinomas produce a desmoplastic response, which replaces normal breast fat (resulting in a mammographic density) and forms a hard, palpable mass

- The microscopic appearance is quite heterogeneous, ranging from tumors with well-developed tubule formation and low-grade nuclei to tumors consisting of sheets of anaplastic cells

- The tumor margins typically are irregular. Invasion of lymphovascular spaces may be seen

- About two thirds express estrogen or progesterone receptors, and about one third overexpress HER2/NEU
Invasive lobular carcinoma

- Fewer than 20% of all breast carcinomas

- The cells morphologically identical to the cells of LCIS

- Two thirds of the cases are associated with adjacent LCIS

- The cells invade individually into stroma and are often aligned in “single-file” strands or chains

- Presence of mutations that abrogate the function of E-cadherin

- Although most manifest as palpable masses or mammographic densities, a significant subgroup may exhibit a diffusely invasive pattern without a desmoplastic response and may be clinically occult

- Lobular carcinomas also are more frequently multicentric and bilateral (in 10% to 20% of cases)

- Almost all of these carcinomas express hormone receptors, whereas HER2/NEU overexpression is rare

They more frequently spread to cerebrospinal fluid, serosal surfaces, gastrointestinal tract, ovary, uterus, and bone marrow

Intracellular mucin vacuoles (sometimes forming signet ring cells) can be seen
Invasive lobular carcinoma, cont’d

Check https://www.library.vanderbilt.edu/the-video-overview for reference.

Check http://medsci.indiana.edu/c602web/602/c602web/breascas/docs/lob1.html for references.
Inflammatory carcinoma

• A clinical term

• Enlarged, swollen, erythematous breast, usually without a palpable mass

• The underlying carcinoma is generally poorly differentiated and diffusely infiltrative

• Characteristically, carcinoma involves dermal lymphatic spaces. The resultant blockage of these channels leads to edema, resulting in the characteristic “inflamed” clinical appearance

• True inflammation is minimal to absent

• Poor prognosis
Medullary carcinoma

- Clinically, they can be mistaken for fibroadenomas...a feature also of colloid (mucinous) carcinoma

- There is invariably a pronounced lymphoplasmacytic infiltrate

- DCIS usually is absent or minimal

- Medullary carcinomas occur with increased frequency in women with BRCA1 mutations, although most women with medullary carcinoma are not carriers

- These are uniformly triple-negative
Clinical features

• Breast cancer often is discovered by the patient or her physician as a deceptively discrete, solitary, painless, and movable mass.

• With mammographic screening, carcinomas frequently are detected even before they become palpable.

• Young patients...more dense, less fat...MRI may be better than mammogram.
Clinical features, cont’d

• Outer quadrant and centrally located lesions typically spread first to the axillary nodes

• Those in the medial inner quadrants often travel first to lymph nodes along the internal mammary arteries

• Distant metastases favored locations: the lungs, skeleton, liver, adrenals, and (less commonly) brain, but no site is exempt

• Metastases may come to clinical attention many years after apparent therapeutic control of the primary lesion, sometimes as long as 15 years later
  …but: with each passing year without disease recurrence, the likelihood of cure increases
Clinical features, cont’d

• With progression:

...skin changes:
- nipple retraction
- skin dimpling
- peau d’orange (“orange peel”) due to lymphedema
Prognostic factors

- Invasive VS in situ
- Size
- Lymph node involvement...the most important
- Distant metastases
- Grade??
- Histologic type??
- The presence or absence of estrogen or progesterone receptors
- Overexpression of $HER2/NEU$??
• Can breast cancer occur in males???
Thank You