The Non-Cancerous Human Breast
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Disclosures
• I have no conflicts of interest to disclose.
• The views expressed here are mine alone and may not represent the views of the University of Utah, the State of Utah, or the Huntsman Cancer Institute

Goals
• Label the parts of the human breast using correct nomenclature
• Describe the stages of development of the breast and how they relate to breast cancer risk
• Recognize normal breast variants
• Recognize non-cancer diseases and symptoms of the breast
• Recognize who can and cannot have mammograms
• Incorporate DCIS into breast cancer risk assessment
The normal breast

- Structure of the human breast
- Development of the human breast
- Breast variations, natural and unnatural
- The male breast

Breast lies over pectoralis major

Lymphatic drainage of the breast

First, what is a lymph node?
Breast internal anatomy

- Luminal cells: ER/PR positive
- Basal cells: ER/PR/Her2 negative, "Triple negative"

Breast ducts microanatomy

- Luminal cells: ER/PR positive
- Basal cells: ER/PR/Her2 negative, "Triple negative"

Breast under the microscope

- Pink = stroma
- Purple = cell nuclei
- Duct
- Lobe
- Lobule
- Clear = Fat cell
Pop quiz

Breast lobules are:
A. Tubes that carry milk to the nipple
B. The inner lining of cells around a duct
C. A terminal ductule and all the acini attached to it
D. Connective tissue that elevates the breast

Question 1

Which statement best describes the lymphatic drainage of the breast?
A. Lymph can drain either to the axilla or internal mammary chain lymph nodes depending on a complex network of lymphatic channels
B. Lymph drains first to lymph nodes in the axilla
C. The upper breast drains to the axilla while the lower breast drains to the internal mammary chain
D. Lymph from the breast cannot drain to the inferior mammary lymph nodes
The normal breast

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External breast development

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Breasts during childhood. The breasts are flat and show no signs of development.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>Breast bud stage. Milk ducts and fat tissue form a small mound.</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Breasts continue to grow. Breasts become rounder and fuller.</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Nipple and areola form separate small mound. Not all girls go through this stage. Some skip stage 4 and go directly to stage 5.</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Breast growth enters final stage. Adult breast is full and round shaped.</td>
</tr>
</tbody>
</table>

Breasts through the ages

• Birth
  • Breast rudiment = 10-12 immature ductal elements (not canalized) under the nipple
• Prepuberty
  • Ducts canalize, grow slowly and isomorphically, and branch
• Puberty
  • Increase in estradiol, progesterones, growth hormone, and prolactin
  • Increase growth and branching of ducts
  • Formation of terminal end buds and alveolar buds (primitive acini)
  • Formation of type I lobules
    • 11 alveolar buds/ductules/lobule
      • Most proliferative
    • Most estrogen receptors
Breasts through the ages

Nulliparous women
- Menstrual cycling stimulates branching and differentiation of type 1 lobules into type 2 lobules (~20-30%)
- Type 2 lobules have ~42 ductules/buds per lobule
  - Less proliferative
  - Fewer estrogen receptors

Pregnant women
- hCG stimulates differentiation into type 3 and type 4 lobules
- Type 3 lobules have secretory glands forming from each bud, ~80 per lobule
- Type 4 lobules have large acini and large cells within each acinus
  - Able to make colostrum/milk
  - Breast is mainly ducts with little stroma

Breasts through the ages

For the visual learner

Types of Breast Lobules

Type 1: Breast at birth
Type 2: Breast after puberty
Type 3: Breast after pregnancy after 32 weeks
Type 4: Breast with milk

Breasts through the ages

After pregnancy
- Glandular involution/regression
- Type 4 lobules become type 3 lobules, which predominate until the late 30’s
- 40’s: type 3 lobules regress into type 1 lobules
  - Greater fibrosis of stroma
  - Less proliferation in both stroma and lobule than nulliparous type 1 lobules
  - These type 1 lobules are less “dense” than nulliparous type 1 lobules

Menopause
- Regression of breast structures to type 1 lobules
- Glands atrophy and the NUMBER of lobules decreases
- Lobules may disappear, leaving only ducts
- Fibrous connective tissue/stroma decreases, leaving breasts mostly with adipose tissue = fatty replacement
Which hormone stimulates breast growth and development during puberty?

A. Follicle Stimulating Hormone (FSH)
B. Anti-Mullerian Hormone (AMH)
C. Estradiol
D. Testosterone
E. Human chorionic gonadotropin (hCG)

Which of the following is correct about breasts after pregnancy?

A. Type 1 lobules identical to those in nulliparous women predominate
B. Type 4 lobules persist
C. Fatty replacement occurs
D. Lobules have more stroma and less proliferation than before pregnancy
The normal breast

- Structure of the human breast
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“...condition called ‘good health.’ Frankly, I’m not sure how to treat it.”

What’s wrong with this picture?

Extra nipple in center
Extra nipples along mammary ridge

Terminology

- Polythelia – Accessory nipple
- Poymastia – Accessory breast tissue
- Hypoplasia – Underdeveloped breast
- Amastia – Congenital absence of the breast
- Amazia – Nipple is present but breast tissue is absent
  - Most common cause is iatrogenic due to biopsy or radiation

Which one does Zac Efron have?
Accessory breasts occur along the mammary ridge

Breast pain
- 45% of women have breast pain, and 21% have severe pain.
  - Most never tell their doctor.
- 95% of women who see a doctor for breast pain do not have cancer
- Cyclic breast pain
  - Occurs between ovulation and menses
  - Due to estrogen stimulation of ducts, progesterone stimulation of stroma, and prolactin stimulation of secretion
  - Associated with Fibrocystic change
    - Not a disease, as 50% of women have fibrocystic breasts
    - Not a single pathologic lesion
    - Combination of fibrous tissue, usually in the upper outer quadrant, and cysts that respond to hormones, sometimes with pain

Fibrocystic change
Breast pain

- Noncyclic breast pain
  - Cooper ligament strain, particularly with pendulous breasts
  - Ductal ectasia = distension of duct with surrounding inflammation.
  - May have a fever
  - Mastitis/abscess, usually during lactation
  - Hidradenitis suppurativa
  - Chronic occlusion and swelling of sweat glands
  - Traumatic necrosis
  - Referred pain
    - Chest wall
    - Ribs or costochondritis
    - Pectoralis major strain
    - Spine
    - Gall bladder (right)
    - Heart disease (left)

Benign breast “diseases”

- Nonproliferative = no risk of cancer
  - Simple cysts
  - Papillary apocrine (sweat) change
  - Epithelial calcifications
  - Mild hyperplasia
  - Simple fibroadenoma
    - No relationship to fibrocystic change
    - Rubbery, mobile tumor, common in adolescents and women under 30
    - May grow and shrink with hormonal changes

Benign breast “diseases”

- Proliferative = increased risk of cancer
  - Without atypia = not precancer, small increased risk (1.5-2X)
    - Usual ductal hyperplasia
    - Solitary papilloma
    - Sclerosing adenosis
    - Radial scar
    - Complex fibroadenoma
    - Marker of carcinogen exposure or predisposition to cancer
  - With atypia
    - Atypical ductal hyperplasia
      - Pre-pre-cancer because turns into DCIS
    - Atypical lobular hyperplasia
      - Not precancer but risk factor for cancer
Nipple discharge

- Milky = Galactorrhea
  - Usually bilateral
  - Excess stimulation of milk production
  - Hormonal
  - Mechanical
- Pus = Mastitis
  - Infection of the duct

Clear, bloody, or blood-tinged

- Usually single duct
- 50-60% caused by papilloma
- 15-30% other benign lesion, such as ductal ectasia
- 10% DCIS
- Up to 20% of pregnant women can have blood-tinged discharge
- Some other color
- Probably medication-induced change

Non-milky discharge is concerning for breast cancer if there is a mass, woman over 40, or particularly bloody.

What is this a mammogram of?

Breast implants

- Do not affect breast cancer risk
- May increase risk for a very rare kind of breast lymphoma
- Can have mammograms, but need 4 views rather than 2
Question 5

True or False:
Fibrocystic change is the combination of simple cysts and simple fibroadenomas

False

Question 6

Accessory breasts can not appear:
A. On the neck
B. In the armpit
C. Over the ribs
D. Over the abdomen
E. By the groin

Question 7

Which of the following increases the risk of breast cancer?
A. Fibrocystic change
B. Sclerosing adenosis
C. Papillary apocrine change
D. Simple fibroadenoma
The normal breast

- Structure of the human breast
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Can men have mammograms?

- All men have a small amount of breast tissue, equivalent to a woman's breast bud
- Gynecomastia = enlargement of breast tissue in men
- Not the same as increased fatty tissue in the breast
- In adolescents 75% resolve spontaneously
- Caused by excess estrogen-to-testosterone ratio
  - Medications
  - Liver disease
  - Klinefelter's Syndrome
  - Pituitary insufficiency
  - Hyperthyroid
  - Tumors – testicular, adrenal, or pituitary

When men grow breasts . . .
Question 8

Mammograms are not useful for:

A. Men
B. Women who have dense breasts
C. Women who have fibrocystic change
D. Women who have breast implants for breast augmentation
E. Women who have breast implants for post-mastectomy reconstruction

DCIS

• What is DCIS?
• DCIS genetics
• DCIS treatment
• Prevention

DCIS arises from the ducts
Some evidence suggests that not all invasive breast cancer is preceded by DCIS.

### Types of DCIS

- **Comedo** (A) with necrosis and/or calcifications
- **Non-comedo**
  - Cribriform (B)
  - Solid (C)
  - Micropapillary (D)
  - Papillary (E)
- **Comedo necrosis** has a higher recurrence rate
Grades of DCIS

- Grade refers to appearance of the nuclei
- Higher grade = more abnormal
  - Larger nuclei
  - Prominent nucleoli
  - Varied size and shape
- High grade has a higher recurrence risk

DCIS: a pre-cancer

- Natural history studies from misread biopsies
  - Page cohort: 21 of 28 (46%) developed invasive cancer
  - 29% had cancer by year 10
  - All in the same quadrant as the DCIS
  - Nurse's Health study: 6 of 13 (46%) developed invasive cancer
    - Mean time to cancer was 9 years
    - All in the same breast as the DCIS
- Caveats
  - Most of these were palpable and from pre-mammogram era
  - Estimates from autopsy studies suggest that at most about 1/3 of DCIS becomes fatal breast cancer

DCIS: a pre-cancer and a risk factor

- Lumpectomy trials
  - ECOG 5194
    - Low grade DCIS: Risk of invasive cancer: 6% same breast and 3% other breast after 5 years
    - High grade DCIS: Risk of invasive cancer: 13% same breast and 7% other breast after 5 years
  - Observation arms of 4 large randomized trials of radiation
    - Average 8% risk of invasive cancer in the same breast after 5 years
How DCIS is detected

Question 9

DCIS is a:
A. Cancer
B. Pre-cancer
C. Risk factor for cancer
D. B and C
E. All of the above

Question 10

Which of the following presentations would not be seen in a woman with DCIS and not invasive breast cancer?
A. A palpable breast mass
B. Calcifications on a screening breast mammogram
C. Bloody nipple discharge and a palpable breast mass
D. Calcifications on a screening breast mammogram and epithelial cells found in an axillary lymph node

• Which of the following presentations would not be seen in a woman with DCIS and not invasive breast cancer?
• What is DCIS?
• DCIS genetics
• DCIS treatment
• Prevention

How common is DCIS?

Table 1. Estimated New Female Breast Cancer Cases and Deaths by Age, US, 2013

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>In Situ Cases</th>
<th>Invasive Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>1,960</td>
<td>10,980</td>
<td>1,020</td>
</tr>
<tr>
<td>&lt;50</td>
<td>15,650</td>
<td>48,910</td>
<td>4,260</td>
</tr>
<tr>
<td>50-64</td>
<td>26,270</td>
<td>84,210</td>
<td>11,010</td>
</tr>
<tr>
<td>65+</td>
<td>22,220</td>
<td>99,220</td>
<td>22,870</td>
</tr>
<tr>
<td>All ages</td>
<td><strong>66,640</strong></td>
<td><strong>232,340</strong></td>
<td><strong>39,620</strong></td>
</tr>
</tbody>
</table>

*Estimated to the nearest 10.
Source: Total estimated cases are based on 1993-2003 incidence data from 40 states as reported by the North American Association for Central Cancer Registries. Total estimated deaths are based on data from US Mortality, 1995-2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Genetics and DCIS

• Previously hypothesized that breast cancer in BRCA1 and BRCA2 carriers occurred faster than in noncarriers and may not have an in situ precursor.
• However,
  • In prophylactic mastectomies from BRCA1/2 carriers, 37% have DCIS and 38% have ADH
  • The majority of invasive cancers in BRCA1/2 carriers have adjacent DCIS
  • Family history of invasive breast cancer increases the risk for DCIS
Myriad data (2002) on prevalence of BRCA1 and BRCA2 mutations:
- 13% in women with DCIS < 50
- 26% in women with DCIS < 40
- 28% in women with Invasive breast cancer < 50
Myriad data (2010):
- Both carriers and noncarriers of BRCA had average of ~8 years between diagnosis of DCIS and diagnosis of invasive cancer.

Breast Cancer Linkage Consortium:
- Recommend adding 10 years to the age of women with DCIS when calculating probability of BRCA mutation.
- Most models developed without consideration of DCIS.
- BRCAPRO, Couch, Shattuch-Eidens, Frank, BOADICEA.
- NCCN recommends NOT correcting for age.
- Considers DCIS equivalent to invasive breast cancer.

http://suzannekesten2.blogspot.com/2010_04_01_archive.html
The relationship between DCIS and BRCA1/2 is:

A. DCIS does not occur in BRCA1 or BRCA2 carriers because cancer develops so fast
B. The time between development of DCIS and development of invasive cancer is the same in BRCA1/2 carriers and noncarriers
C. A 50-year-old woman with DCIS has the same chance of a BRCA1/2 mutation as a 50-year-old woman with invasive breast cancer
D. Men with BRCA1/2 mutations are more likely to get DCIS than invasive breast cancer

**Question 11**

• What is DCIS?
• DCIS genetics
• DCIS treatment
• Prevention

**DCIS**

• What is DCIS?
• DCIS genetics
• DCIS treatment
• Prevention

**Surgery for DCIS**

• Mastectomy is curative
  • 1-2% recurrence risk
  • Further risk reduction for THAT breast is not needed

• Lumpectomy
  • Usually recommend radiation because recurrence rate without radiation is ~15% and half of all recurrences are invasive
  • Age, size, grade, margin size, and presence of necrosis all impact on recurrence risk

• No clinical or molecular criteria have reproducibly identified a group with recurrence risk so low that radiation is not beneficial
DCIS: Estrogen blockade

- Tamoxifen is approved for women with DCIS treated with lumpectomy and radiation
- Based on two randomized trials (NSABP B24 and UKDCIS)
  - In NSABP B24, benefit only seen in ER-positive DCIS
  - In both trials, benefit in women under 50 was higher than in women over 50
- 30% reduction in recurrence in the same breast
- After mastectomy, tamoxifen or exemestane may be used to reduce the risk of breast cancer in the other breast

Chemotherapy & targeted therapy
What is DCIS?
DCIS genetics
DCIS treatment
Prevention

Prevention vs. treatment

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Given to a person at risk for a disease (DCIS)</td>
<td>• Given after a person already has a disease (DCIS)</td>
</tr>
<tr>
<td>• No disease history in the organ the prevention is aimed at</td>
<td>• Given to prevent recurrence/progression</td>
</tr>
<tr>
<td>• Given to prevent the occurrence of a disease</td>
<td>• Side effects are more acceptable</td>
</tr>
<tr>
<td>• Depending on risk, side effects are less acceptable</td>
<td></td>
</tr>
</tbody>
</table>

Prevention options for DCIS

• Same as invasive breast cancer
  • Ultimately, the goal is to prevent invasive breast cancer
• Prophylactic mastectomy
• Tamoxifen
• Raloxifene
• Exemestane
Tamoxifen: selective estrogen receptor modulator (SERM)

**Blocks Estrogen**
- Breast cancer cells
  - Cancer cells die
- Hypothalamus
  - Hot flushes

**Acts like estrogen**
- Liver
  - Lowers bad cholesterol (LDL)
- Bones
  - Strengthens bones
- Blood vessels
  - Increases risk of blood clots and strokes
- Uterus
  - Stimulates growth of uterine lining
  - Increases risk of low-grade uterine cancer

Tamoxifen pros and cons

- Tamoxifen reduces breast cancer rates by 30-50% in high-risk women
- Consistent in 4 large randomized trials involving 15,000 women
- Giving 1,000 women tamoxifen for a year prevents 8 cases of breast cancer and 3 spine fractures but may cause 4 blood clots and 1-2 uterus cancers

Raloxifene: also a SERM

**Blocks Estrogen**
- Breast cancer cells
  - Cancer cells die
- Hypothalamus
  - Hot flushes
  - Not as much as tamoxifen
- Uterus
  - No risk of uterus cancer

**Acts like estrogen**
- Liver
  - Lowers bad cholesterol (LDL)
- Bones
  - Strengthens bones
- Blood vessels
  - Increases risk of blood clots and strokes
  - But not as much as tamoxifen
**Raloxifene vs. tamoxifen**

- Raloxifene prevents breast cancer in high risk women, but not as much as tamoxifen.
- Raloxifene reduces breast cancer rates by ~30% in high risk women.
- Raloxifene is about 20% less effective than tamoxifen at preventing breast cancer.
- Raloxifene has fewer side effects than tamoxifen.
- Over ~5 years, giving 1000 women raloxifene instead of tamoxifen for a year prevents 2 fewer cases of breast cancer but also prevents 1 blood clot and 1 uterus cancer.
- Raloxifene does not work and is not appropriate for women who have had breast cancer or DCIS (pre cancer).

**Exemestane: aromatase inhibitor**

**Reduces Estrogen**
- Breast cancer cells: Cancer cells die
- Hypothalamus: Hot flushes
- Bones: Increases osteoporosis
- Vaginal lining: Pain and dryness
- Joints: Joint pain

**Acts like estrogen**
- Nowhere

**Which drug to choose?**

<table>
<thead>
<tr>
<th>Tamoxifen</th>
<th>Raloxifene</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous breast cancer or DCIS</td>
<td>Has osteoporosis</td>
<td>Previous breast cancer or DCIS</td>
</tr>
<tr>
<td>History of hysterectomy</td>
<td>No history of breast cancer or DCIS</td>
<td>History of blood clot or stroke</td>
</tr>
<tr>
<td>Low risk of stroke or blood clots</td>
<td>High risk of uterus cancer</td>
<td>Strong bones</td>
</tr>
<tr>
<td>Existing joint pain</td>
<td></td>
<td>High Body Mass Index</td>
</tr>
</tbody>
</table>
Question 12

Tamoxifen:
A. Blocks estrogen throughout the body
B. Prevents DCIS but is not useful once someone has DCIS
C. Can be used after mastectomy for DCIS to reduce the chance of breast cancer in the other breast
D. Is more effective than radiation at preventing DCIS recurrence after lumpectomy

Question 13

• A woman who was treated for DCIS would not have received:
A. Tamoxifen
B. Exemestane (Aromasin)
C. Trastuzumab (Herceptin)
D. Radiation

Thank you

• Questions?