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Physiologic Influences on Breast Cancer Risk

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Disclosures

- Delphinus–Clinical Advisory Committee
- Seno Medical–Medical Advisory Board
- Siemens Ultrasound–Research support, consulting, and speaker

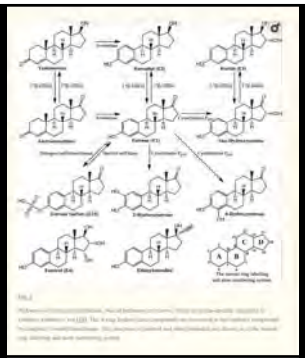
OBJECTIVES

- Review physiologic changes from infancy to adulthood
- Appreciate density as an imaging indicator of hormonal effect
- Discuss modifiable risk factors
- Suggest diagnosis and management utilizing ACR appropriateness criteria where applicable

Hormones and the breast: estrogen

Estrogens: group of steroid hormones with biological target: estrogen receptors (ERα, ERβ)

- primary female sex hormone
- development and regulation of the female reproductive system and secondary sex characteristics
- 4 endogenous estrogens:
  - estradiol (E2)–estrogen reproductive years; produced by ovaries
  - estriol (E3)–estrogen during pregnancy; produced by the placenta
  - estrone (E1)–estrogen during menopause; produced by ovaries and adrenals
  - estetrol (E4)–produced only during pregnancy by the fetal liver



Hormone Receptors and Risk

- Endogenous and exogenous estrogens
- ERs in benign processes: fibroadenomas
- ER % in tissue changes with age: most numerous puberty, decreasing > 35y; postmenopausal, 0.
- Most postmenopausal cancers ER+
- High grade ER- cancers not estrogen dependent; paradoxically found during high estrogenic states e.g. pregnancy and at any age
- Triple negative–higher % in African Americans

Hormone Receptors and Risk

Study of ERα in normal breast epithelium of 376 women may augment estrogen sensitivity and risk of breast cancer

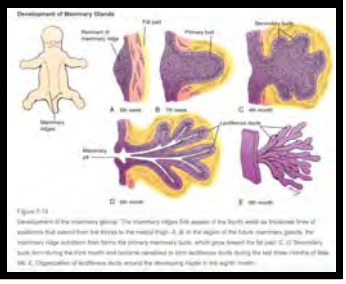
- 2 groups: women with newly diagnosed breast cancer (case) vs women with benign breast disease (control)
- Postmenopausal: ERα positivity, 18.7% higher in case vs control cohorts. Other risk factors additive: lactation, early menarche, late menopause, alcohol use
- Premenopausal: 17.6% greater ERα positivity in case than control. ERα expected to decline in luteal phase (25-28 d) but continues to increase in breast cancer cohort. Interaction with other factors not significant in the premenopausal group.

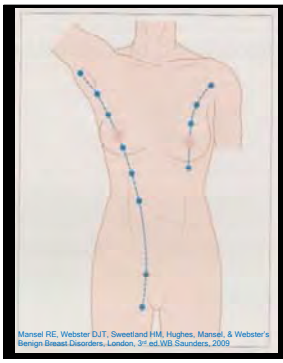
Khan SA, Rogers M, Khurana KK et al. Estrogen Receptor Expression; JNCI 1997; 89:37-42

Breast Development

- Mammary ridges 4th week
- Ridges disappear except at site of breasts
- Ridge remnant produces primary bud by 7th week
- Bud grows down into dermis beneath, toward fat pad that will induce bud to branch
- Secondary buds by 12th week, which lengthen and branch throughout time of gestation; ducts canalize
- Stroma-ingrowth of connective tissue; partitions between primitive alveoli; specialized fat cells
- At birth, 15-25 lactiferous ducts opening into small depression, mammary pit
- Underlying mesoderm proliferates, and pit becomes everted nipple within few weeks
- Skin surrounding nipple proliferates to form areola, which contains circular and smooth muscle fibers

Schoenwolf, G.C. Larsen's Human Embryology. 5th ed., 2015. Philadelphia:Elsevier





Mansel RE, Webster DJT, Sweetland HM, Hughes, Mansel, & Webster's Benign Breast Disorders, London, 3rd ed.WB Saunders, 2009

Birth

- Transient secretory changes in both sexes - "witches milk"
- Neonatal prolactin levels elevated briefly (80-90% of neonates have colostrum)
- Maternal luteal and placental hormones
  - stimulate fetal breast until birth
  - breast development may be asymmetric
  - do not remove "mass" particularly in girls

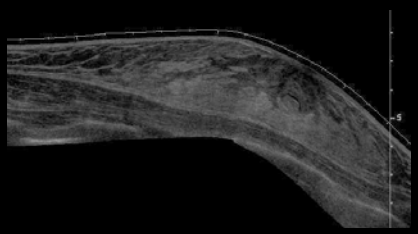
ANDI: CLASSIFICATION OF BENIGN BREAST DISORDERS

Aberrations of Normal Development and Involution

- Developmental: adolescent hypertrophy, fibroadenoma (early reproductive; 15-25 y)
- Cyclical change: mastalgia, nodularity; epithelial hyperplasia of pregnancy (mature reproductive, 25-40y)
- Involution (35-55y)
  - lobular: cyst formation, sclerosing adenosis
  - ductal: duct ectasia/periductal mastitis
  - epithelial turnover–ranging from hyperplasia to atypia
- Non ANDI: conditions with well-defined etiology; e.g. lactational abscess, traumatic fat necrosis

Mansel RE, Webster DJT, Sweetland HM, Hughes, Mansell, & Webster's Benign Breast Disorders, London, 3rd ed.WB Saunders, 2009

Puberty: developing female breast resembles gynecomastia



Hormone-related Risk Factors

Non-modifiable

- Genetic density pattern–similarity in identical twins
- Menarche–each year of onset before age 12 adds 4-5% to b.c. risk
- Menopause–natural menopause before 45y has 50% of risk of menopause occurs at or after 55y; each additional yr adds 4%
- Higher numbers of menstrual cycles until 1st live birth increases risk

Modifiable

- Age at 1st term pregnancy–younger than 20y can reduce b.c. by 50% compared with those of 35y
- Breast feeding 1st live birth for >1year is a risk reducer compared with > 3 children and < 1 year breast feeding
- Related to hepatic steroid metabolism
  - Obesity; alcohol
- Oral contraceptives–benefit may exceed risk especially women with children over age 25
- HT: Women's Health Initiative-conjugated estrogens; 26% excess cancer; risk > benefit

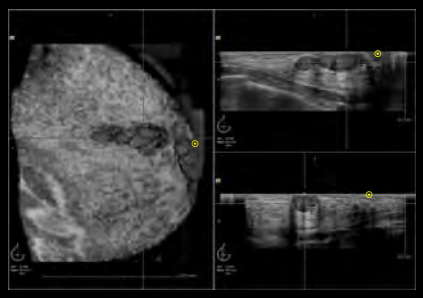
Lipton A. Hormonal influences on Oncogenesis of breast cancer in Roses D. Breast Cancer. ed. 2. 2005

Imaging Hormonal Effects: Density

- Modifiable risk factor: perceptible decrease in density and BPE with tamoxifen (less effect with aromatase inhibitors, arimidex)
- Reflects both epithelial and stromal components
- May suggest physiologic age range by anatomic pattern: relative proportions of ducts and stroma

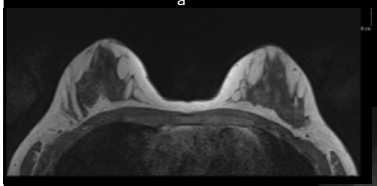
19y RIGHT BREAST, LAT VIEW - bx proven fibroadenomas

Tissue comp density equivalent: BI-RADS d, young, ductal proliferative pattern

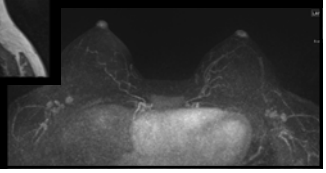


\The amount of FGT may not correlate with the degree of BPE. 54-year-old woman with heterogeneous FGT (a) has minimal BPE (b).

a



b



Courtesy D.Gupta, MD

Breast Masses (11-30y)

Fibroadenoma	166	(67%)
Carcinoma	4	(2%)
Fibrocystic Change	28	(11%)
Sclerosing Adenosis	11	(4%)
Other Benign Disease	40	(16%)

Ligon, Stevenson, Diner. Breast masses in young women. AJSurg 1980; 140:779-782.

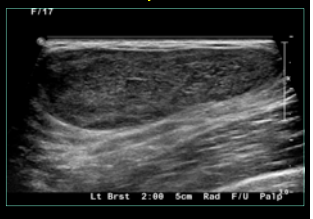
Similar findings: Seltzer, Skiles. Diseases of the breast in young women. SGO 1980; 150:360-361.

Fibroadenoma

- Estrogen responsive tumor, developing puberty
- Younger patients 15-35
- Pregnancy and lactation may stimulate growth
- No malignant potential
- Hyalinization; coarse calcifications
- Surgery if severe cyclical pain

Solitary (BI-RADS 3); multiple in 10-20% (consider BI-RADS 2)

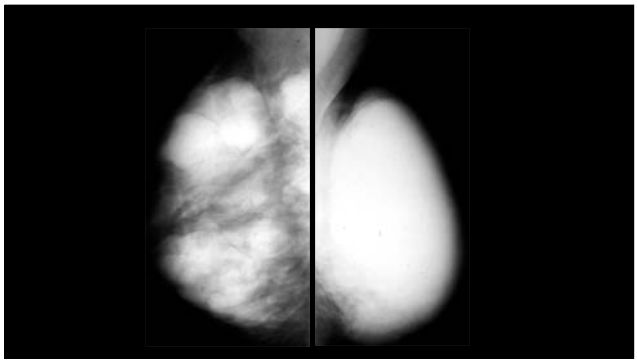
BI-RADS probably benign: **Oval** (including 3-4 gentle lobulations), **circumscribed**, and **parallel**



GIANT FIBROADENOMA

- Large size: FA > 5-10 cm in diameter
- Juvenile: younger age group (11-20 years) than phyllodes tumor
- May be multiple and bilateral
- US: benign features
- Lack of malignant potential
- Management difficult: hormonal agents; surgery including skin-sparing, function-retaining mastectomy

Imaging large masses: sweep (extended FOV); automated US

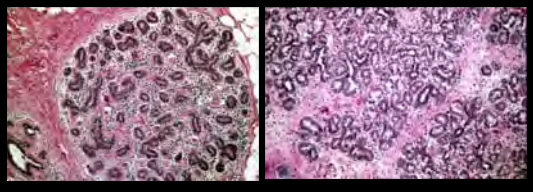


PHYSIOLOGIC CHANGES IN PREGNANCY

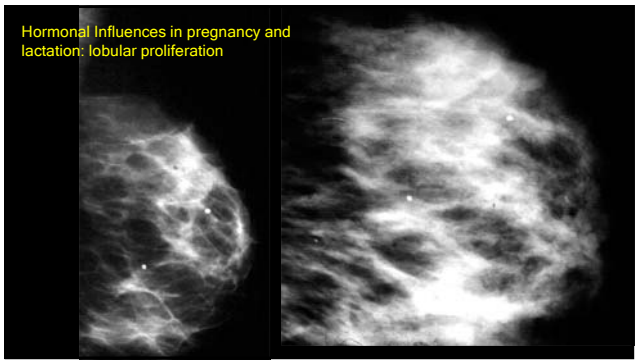
- Lobuloalveolar growth
  - Luteal and placental sex steroids
  - Placental lactogen and chorionic gonadotropin
  - Prolactin - increases during pregnancy for milk production

BREAST IN PREGNANCY

- Nonpregnant breast - 200 g
- Early - ductal and lobular development - weeks 1-4; lobular proliferation - weeks 5-8
- Alveoli enlarge; colostrum formation - from 12th week
- Angiogenesis with new capillary development and at term 180% increase in blood flow
- Breast weight doubles
- Alveoli dilate, filled with fat droplets
- Two-layer alveolar epithelium becomes one layer

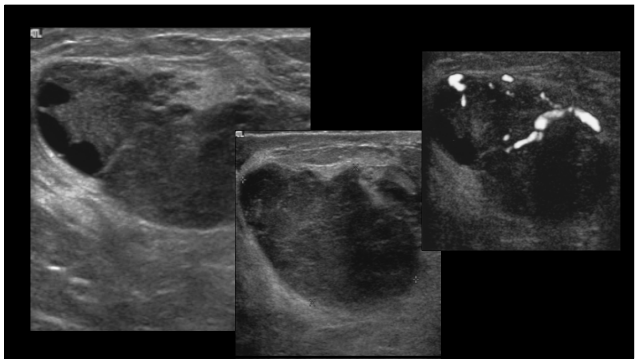


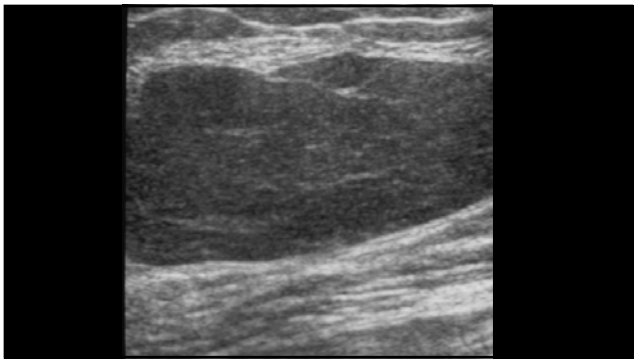
Non-Pregnant 3rd Trimester



PREGNANCY-ASSOCIATED MASSES

- Lactating adenoma/lobular hyperplasia of pregnancy
  - Crowding of lobules; mass-forming aggregations
  - Hormonal influence of luteal and placental sex steroids; placental lactogen and chorionic gonadotropin
  - 2nd and 3rd trimester of pregnancy with regression after delivery





Bloody Nipple Discharge

- Spontaneous bloody nipple discharge: uncommon but normal condition in 2nd & 3rd trimesters of pregnancy
- Can be unilateral or bilateral
- US and mammography if persistent or suspicious
- Epithelial proliferation

Variant 6: Clinically suspicious nipple discharge during pregnancy. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	O
Digital breast tomosynthesis diagnostic	Usually Appropriate	☢☢
Mammography diagnostic	Usually Appropriate	☢☢
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc-99m sestamibi MBI	Usually Not Appropriate	☢☢☢

Pregnancy-Associated Breast Cancer

Diagnosed during or within 1 year after pregnancy

Incidence during pregnancy: 0.2% to 3.8%

9% diagnosed during 1st pregnancy

More common in 4th and 5th decades as women delay pregnancy and incidence of carcinoma↑

Pregnancy-Associated Breast Cancer

- No significant difference in survival, stage-for-stage, compared with non-pregnant women
- Later stage diagnoses are common in pregnancy - breast changes are expected and women delay seeking help
- 70% are ER-negative
- Can treat with chemo 2nd and 3rd trimester with surgery and radiation after delivery

High grade ER- Cancer in Pregnancy

Pregnancy After Breast Cancer

- Maternal melanoma and choriocarcinoma may extend to fetus
- No documentation of transmission of breast cancer from mother to fetus
- Timing of pregnancy after breast cancer -varied recommendations; studies needed
- Consider egg harvesting

ACR Appropriateness Criteria (2018): *Screen High Risk Pregnant Patients*

Variant 2: Breast cancer screening during pregnancy. Age younger than 30 at high risk. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
Mammography screening	Usually Appropriate	☢☢
US breast	May Be Appropriate	O
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc-99m sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant 3: Breast cancer screening during pregnancy. Age 30 to 39 years at elevated risk (intermediate or high risk). Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
Mammography screening	Usually Appropriate	☢☢
US breast	May Be Appropriate	O
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc-99m sestamibi MBI	Usually Not Appropriate	☢☢☢

Postpartum

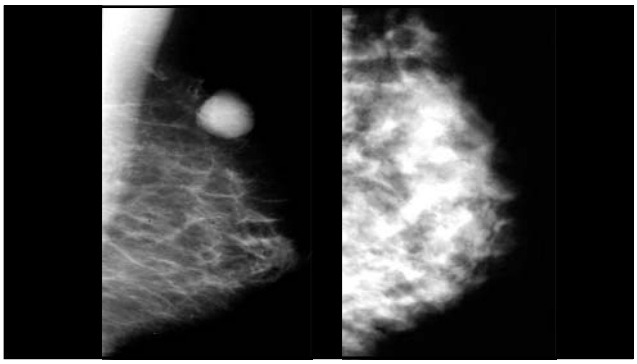
- Decrease in estrogen and progesterone
- Increase in prolactin potentiated by cortisol, insulin, growth hormone, and epidermal growth factor
- Prolactin → RNA synthesis for manufacture of casein and α-lactalbumin

Lactation

- Prolactin stimulates lactose synthesis
- Alveolar cells change shape from columnar to cuboidal
- Upper part of cell extruded
- Fat globules surrounded by membrane
- Milk production
  - Apocrine secretion - fat and protein
  - Merocrine secretion - lactose
- Galactopoiesis maintained by frequent infant feedings–true feedback system

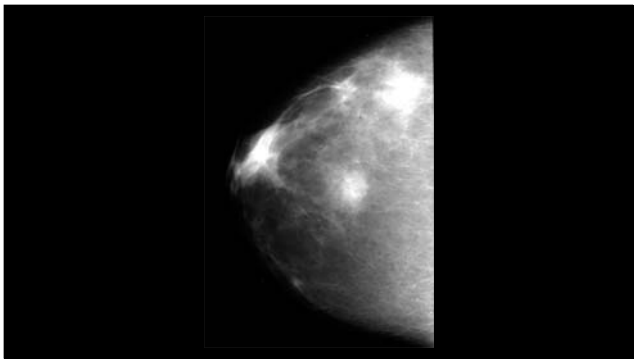
Postlactational Involution

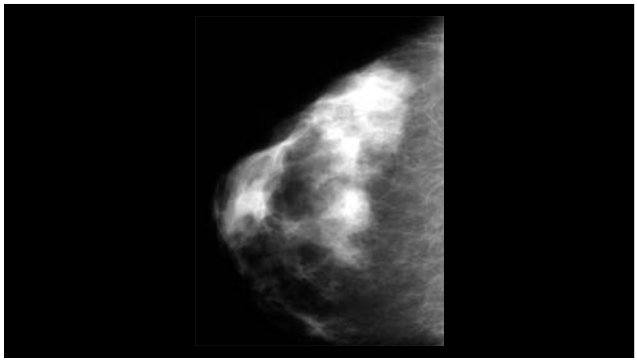
- Lactation ceases 7-10 days after breast feeding stopped
- Phagocytosis removes accumulated secretory products
- Return to resting state 3-4 months–resume screening in patients over 40
- Increase in fat, lobular fibrosis and hyalinization

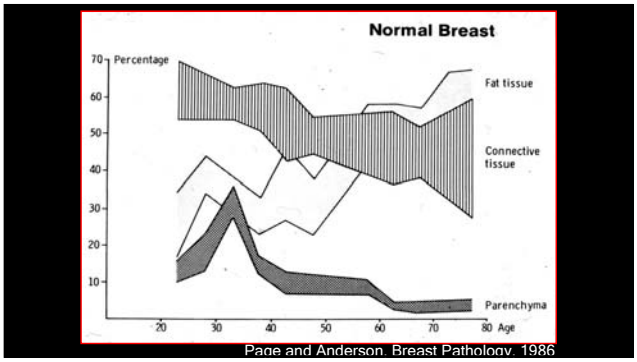


Postmenopausal Involution

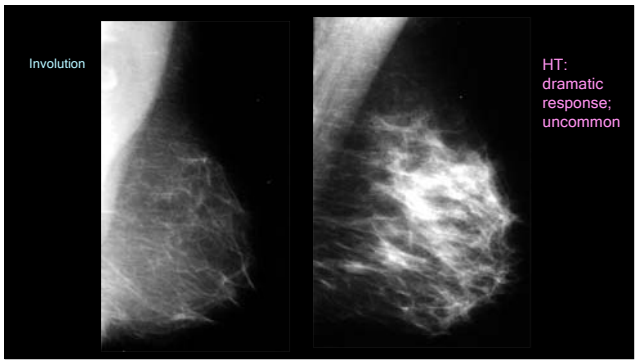
- From age 35 - loss of lobules, collagen replaces loose intralobular connective tissue
- Postmenopausal phase begins at menopause with regression of glandular epithelium
  - Lobule replaced by collagen
  - Microcyst formation as one form of lobular involution
- Compared with postlactational involution, after menopause, both lobules and ducts decrease

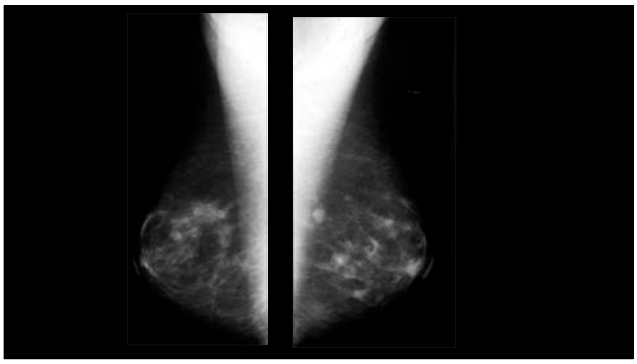






Page and Anderson. Breast Pathology. 1986





Hormonally-mediated Physiologic Changes

- Nonlactating breast - lobules and ducts lined by single epithelial and myoepithelial layers
- Menstrual cycle changes
  - proliferative - estrogen - small lobules, few mitoses, condensed stroma
  - secretory - progesterone - lobules increase, mitoses, loose stroma
  - perimenstrual - ductular epithelium sloughs
- Pregnancy
  - lobular proliferation and enlargement
    - epithelial cells vacuolated; fat droplets
    - 180% vascularity increase
    - breast weight doubles

Hormonally-mediated Physiologic Changes

- Lactation - vacuolated epithelial cells; apocrine secretion (milk); cytoplasm shed (nuclei protrude into lumen); hobnailed appearance
- Postlactational - 3 months to return to nongravid state
- Involution - begins at age 35; takes 3-5 years
- Postmenopausal - lobular atrophy, decreased epithelial and myoepithelial cells; stromal collagenization
  - variable patchy atrophy and formation of dense collagen mimic carcinoma
  - Can contribute to breast density in older women