



Sir William Osler (1849-1919)

The Osler Institute

*Excellence in Continuing Medical
Education*

Radiation Oncology Notes

Disc 1

Disc 2

Disc 3

Disc 4

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Radiation Oncology Disc 1 Notes

Breast Cancer

Brain & Bone Metastases

Spinal Cord & Other Metastases

Soft Tissue Sarcomas

Hodgkin's Lymphoma & Plasmacytoma

Non-Hodgkin's Lymphoma

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Breast Cancer

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Breast Anatomy

- **Mammary gland, fat, blood vessels, nerves, and lymphatics**
- **Cooper's ligament**
- **Mammary gland lies over pec. major muscle and extends from the 2nd to 6th rib vertically and laterally from the sternum to ant. or mid –axillary line**
- **Lymphatic drainage:**
 - **Axillary or principal pathway: lateral chain of LNs b/ 2nd and 3rd intercostal space**
 - **Transpectoral: pec. major muscle to s/c LNs**
 - **Internal mammary: passes through the midline, through the pec. major and intercostal muscle to IM LNs**

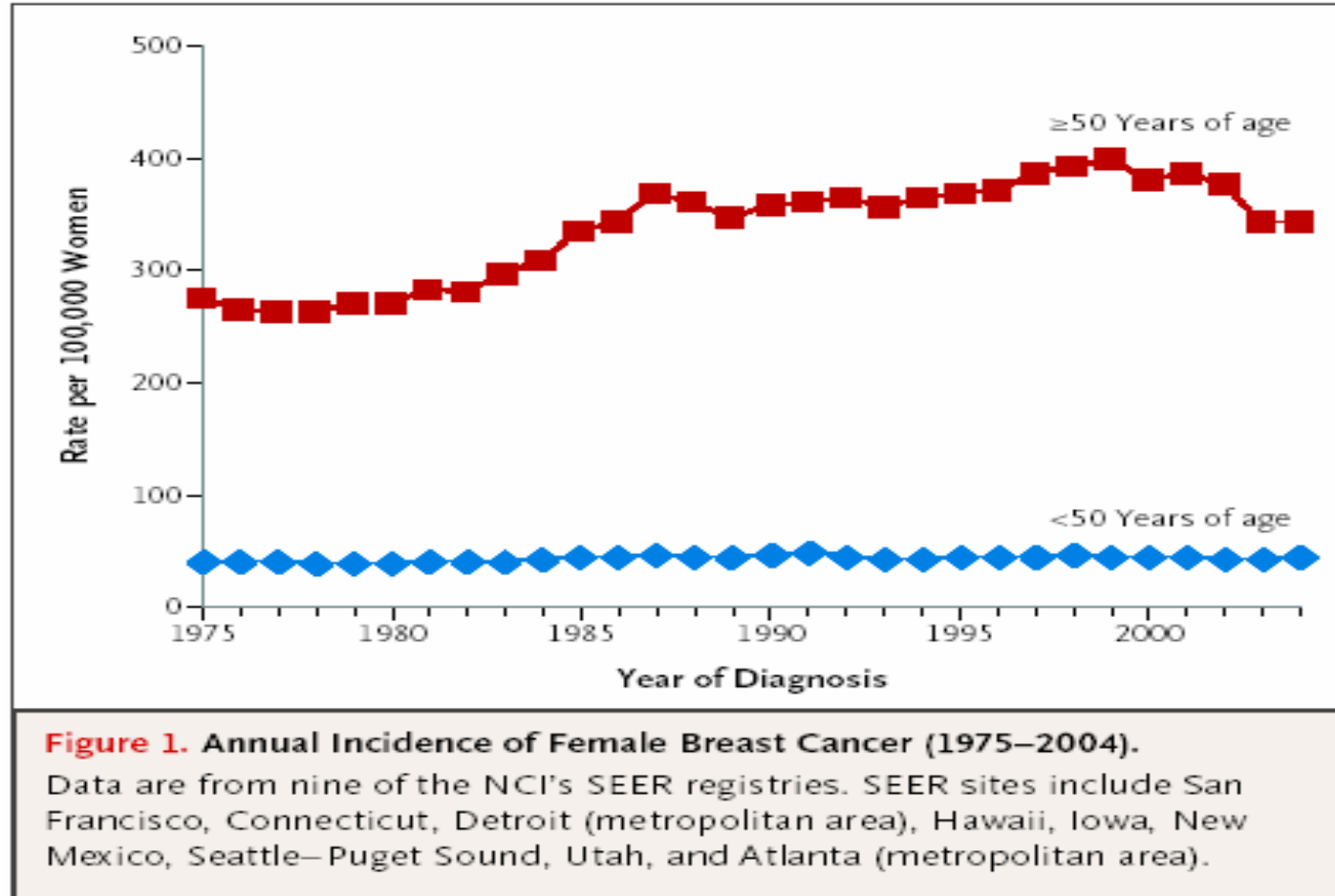
Breast Cancer Epidemiology

- **183,000 cases/yr**
- **41,000 deaths/yr**
- **SEER data:**
 - **Lifetime risk of developing breast ca**
 - **13.1% in white American female**
 - **9.6% in African-American female**
 - **Lifetime risk of dying from breast ca**
 - **3.4% in both white and AA female**
- **1-2% rate of b/l breast ca at presentation**
- **5-8% metachronous b/l breast ca**

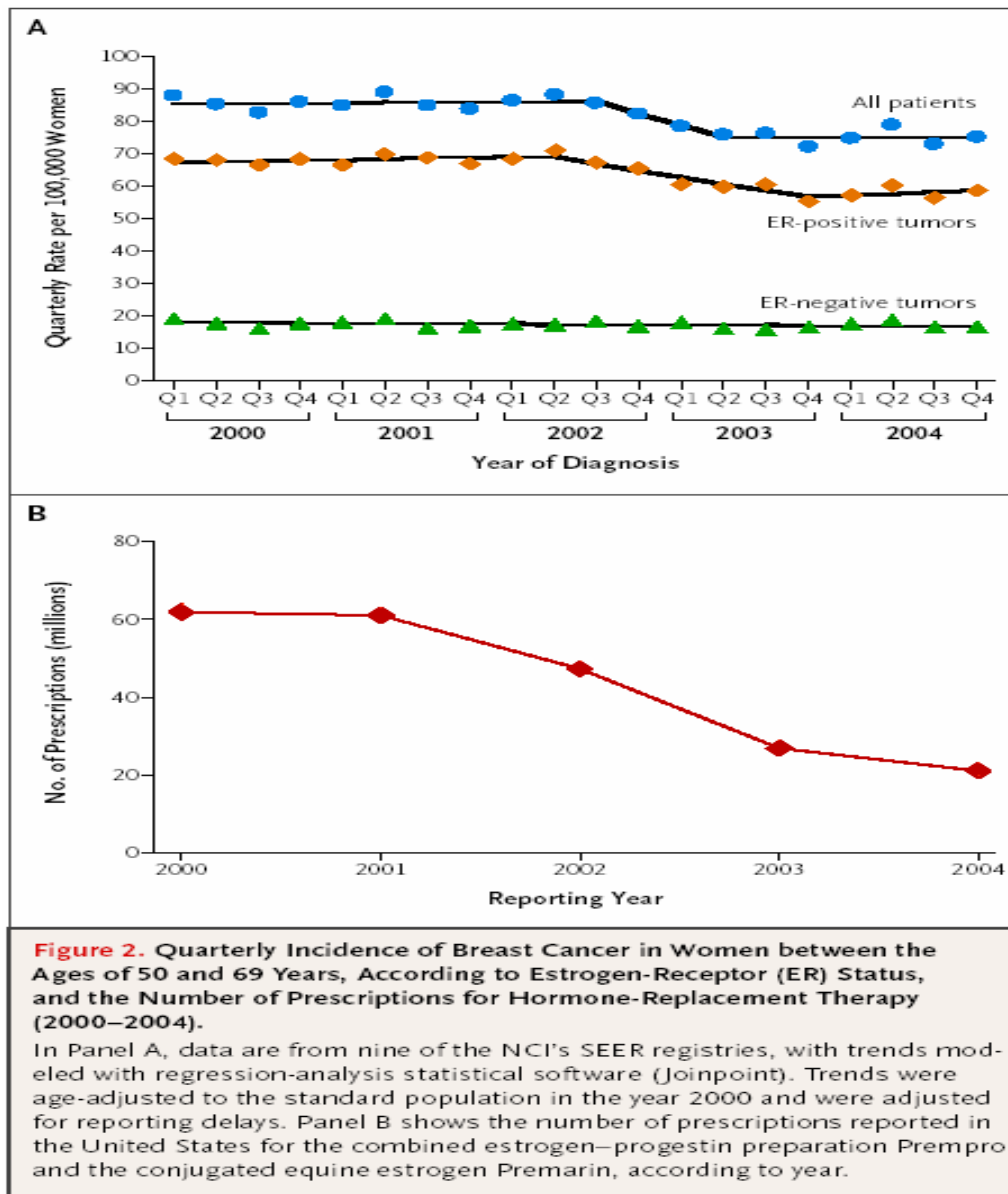
Breast cancer: Incidence

- **NCI – SEER registries**
 - Age adjusted incidence rate of breast cancer fell sharply by 6.7% in the year 2003
 - Decrease only in women >50 yrs of age or older
 - ER+ breast cancer
 - Drop in use of HRT in post-menopausal
 - Ages 50-69 yrs with ER+ tumors
 - Reduction was 14.7%
 - Ages 50-69 yrs with ER- tumors
 - Reduction was 1.7%
 - For 2004, incidence is leveling off

Breast cancer: Incidence



Breast cancer: Incidence



Risk Factors for Breast Ca

- **Age (>50yrs)**
- **Female sex**
- **Family history**
 - First degree relatives
- **Nulliparity**
- **First child after 30 yrs of age**
- **Inherited Factors**
 - Ashkenazi Jews; BRCA genes
- **Hormones**
 - Early menarche, late menopause
- **Dietary Factors - alcohol**
- **Benign breast disease - ADH**
- **Environmental factors – radiation exposure**
- **Benign breast disease**
 - 70% nonproliferative, 30% proliferative (3.6% atypical hyperplasia)

Mammographic Density and the Risk and Detection of Breast Cancer

- **Extensive mammographic density ($\geq 75\%$)**
- **Increased risk persisted for at least 8 years**
- **For younger women, 26% of all breast cancers and 50% of cancers detected less than 12 months after a negative screening test were attributable to density in 50% or more of the mammogram.**

Family history of breast ca

First degree relative with breast ca	RR of developing breast ca
Premenopausal	3.2
Postmenopausal	1.5
Bilateral	5.4
Premenopausal, b/l	8.8
Postmenopausal, b/l	4.0

Long-Term Risk of Breast Cancer in Women with Fibroadenoma

Benign breast disease	RR of inv. breast ca
Fibroadenoma	2.17 (95%CI)
Complex Fibroadenoma (w/ cysts, sclerosing adenosis, epithelial calcifications, or papillary apocrine changes)	3.1
Benign proliferative disease	3.88
Fhx (breast ca) + complex fibroadenoma	3.72

Benign Breast Disease and the Risk of Breast Cancer

Benign breast disease	RR of inv. breast ca
Nonproliferative lesions (67% incidence)	1.27 (95%CI)
Proliferative disease without atypia (30% incidence)	1.88
Atypical hyperplasia (4% incidence)	4.24
FHx + atypical hyperplasia (postmenopausal women)	3.3
FHx + atypical hyperplasia (premenopausal women)	11
Calcification + proliferation	1.3

Hartmann LC, et al., NEJM 2005;353(3):229-37

Hormonal Factors

- **Increased estrogen exposure**
 - **Early age at menarche (age <12)**
 - **Late menopause (age >55; with >40 menstrual yrs)**
 - **Nulliparity**
 - **Late age at first full-term pregnancy (age>30)**
 - **Obesity**
 - **Hormone replacement therapy**

Protective Risk Factors

- **First birth (<20yrs of age)**
- **Breast feeding**
- **Oophorectomy (<40yrs)**

Inherited Predisposition to Breast Ca

- **Sporadic breast cancers: 50%**
- **Hereditary breast cancers: 5%-10%**
- **Two tumor suppressor genes:**
 - **BRCA 1 and 2**
 - **Increased incidence in Ashkenazi Jewish women**
 - **Autosomal dominant**
 - **5-6% of all breast cancer**

Inherited Predisposition to Breast Ca

- Two tumor suppressor genes:
- BRCA 1
 - Location: **Chromosome 17q21**
 - Mutation
 - In Female
 - » **80-85% lifetime risk of breast ca(same as BRCA2)**
 - » **54% risk of ovarian ca (higher than BRCA2)**
 - » **High grade and hormone receptor negative breast ca**
 - In male
 - » **increase risk of prostate and colon ca but not breast cancer**

Inherited Predisposition to Breast Ca

- Two tumor suppressor genes:
- BRCA 2
 - Location: **Chromosome 13q**
 - Mutation
 - In Female
 - » 80-85% lifetime risk of breast ca (same)
 - » 23% Ovarian ca (lower than BRCA 1)
 - » No distinct breast cancer features
 - In male
 - » Develop **breast cancer** with an estimated lifetime incidence of 6%

BRCA1 or BRCA2 Mutations

- **Frequency**
 - in North America: 1:150 or 1:800
 - In Ashkenazi Jewish ancestry: 1:50
 - 2 mutations in BRCA1
 - 185delAG and 5382insC
 - 1 mutation in BRCA2: 6174delT
- **After initial dx of breast ca in BRCA1/2 carrier**
 - Risk of cancer to contralateral breast is 3%/yr
 - Contralateral breast cancer incidence is reduced by 50% by oophorectomy and tamoxifen

Genetic Testing should be offered to:

- Familial breast cancer (≥ 2 cases of breast ca <50yrs or ovarian cancer at any age)**
- Invasive (nonmucinous) ovarian cancer**
- Women with Jewish or Polish ancestry with breast ca**
- Unaffected women from a family of the above type where an affected woman is not available**
- Relatives of known mutation carriers**
- Male breast cancer**
- Multiple primary (breast and ovarian) cancer**
- Cancer of the fallopian tube**

Familial syndromes w/ breast ca

- **Li Fraumini Syndrome**
 - p53 mutation in 50%
 - Autosomal dominant
 - **Soft tissue/bone sarcoma, colon ca, early breast ca, brain tumors, leukemia**
 - 25% with b/l breast ca

Familial syndromes w/ breast ca

- **Cowden Disease**
 - **Breast ca, high arched palate, CNS tumors, thyroid ca**
 - **Rare disease**
 - **Chromosome 10q**

Familial syndromes w/ breast ca

- **Ataxia Telangiectasia**
 - **On chromosome 11**
 - **4% of breast ca (<40yrs of age)**
 - **2% of all breast ca b/40-60yrs of age**
 - **Autosomal recessive**
 - **Oculocutaneous telangiectasias, cerebellar ataxia, immune deficiency, predisposition to leukemia, and lymphoma**

Prior RT to breast

- **Mantle RT**
 - Risk of breast ca depends on the age at which she received RT
 - 56% for women ≤ 19 yrs of age at RT
 - 7% for women b/ 20-29 yrs of age at RT
 - 1% for women ≥ 30 yrs of age at RT
 - Cancer develops 10-15 yrs later
 - Usually medial portion of the breast

To determine the risk of developing breast cancer

- **Gail Model**

- Age at menarche
- Age at first live birth
- # of prior breast biopsies
- \pm atypical hyperplasia
- # of first degree female relatives w/ breast ca

- **Claus Model**

- Incorporates both first and second degree relatives

Management of high risk pts

- **Annual mammography after age 40 yrs**
- **If inherited susceptibility gene is present**
 - **Monthly breast self-exam**
 - **Clinical breast exam 1-2 x/yr**
 - **Annual mammogram beginning b/ the age 25 and 30**

Screening Mammography

- **HIP (Health Insurance plan of NY) Study**
 - **61,000 women, age 40-64yrs**
 - **Randomization:**
 - **Screening mammo vs. routine medical care**
 - **Results:**
 - **Mortality rate was reduced by 33% in screened women 50-59 yrs of age**
 - **Survival difference was higher by 7 to 10 yrs after diagnosis in women who had screening mammography**

Screening Mammography Guidelines

- **Average risk**
 - **Baseline mammogram at age 40 yrs**
 - **40-50yrs: mammography q 2yrs**
 - **>50yrs: mammography q 1yr**
- **High risk***
 - **Baseline mammography at age 30 yrs**

*Personal or family hx of breast ca, RT for HD, BRCA+ive women, LCIS, ADH

Breast Imaging

- **Mammography**
 - False –ive rate: 11-25%
 - Sensitivity: 83-95%*
 - Specificity: 90-98%
- **MRI of breast**
 - Same sensitivity and specificity as mammo but costly
 - Sensitivity: 83% for invasive ca**
 - Specificity: 90-95%

*drops to 30% w/ dense breast tissue, hereditary breast ca; 65% w/HRT;

**drops w/ DCIS to 71%; 100% w/ high risk hereditary breast ca

Recommendations for Breast MRI Screening Annually as an Adjunct to Mammography

- **Based on Evidence (nonrandomized)**
 - BRCA mutation
 - First degree relative of BRCA carrier, but untested
 - Life time risk ~20-25% or greater
- **Based on Expert Consensus**
 - RT to chest b/w 10 and 30 years
 - Li-Fraumeni Syndrome and first degree relative
 - Cowden syndrome and first degree relative
- **Insufficient evidence for or against MRI**
 - Life time risk 15-20%
 - LCIS, ALH, ADH
 - Heterogeneously or extremely dense breast on mammography
 - Personal history of breast cancer including DCIS

CA: A Cancer Journal for Clinicians 2007:57;75-89

MRI Evaluation of the Contralateral Breast in Women with Recently Diagnosed Breast Cancer

- **MRI detected clinically and mammographically occult breast cancer in the contralateral breast: 3.1% (30/969)**
- **Contralateral Breast**
 - **Sensitivity of MRI: 91%**
 - **Specificity of MRI: 88%**
 - **Negative predictive value of MRI: 99%**
 - **Positive predictive value of a positive MRI: 21%**
- **Biopsy rate: 12.5%(121/969)**
 - **24.8% (30/121) positive for cancer**
 - **18 invasive ca with negative LN**
 - **12 DCIS**
 - **75.2% (91/121) positive MRI but negative biopsy**
- **Mean diameter of invasive tumor: 1cm**

NEJM 2007;356:1295-303

Breast Cancer Prevention for BRCA mutation

- **Primary Prevention: from occurring**
 - **Prophylactic mastectomy**
 - **Reproductive factors**
 - **Oophorectomy for breast ca risk reduction**
 - **Tamoxifen**
 - **Only if ER+ive tumors**
 - **Selenium**
 - **Reduce rate of chromosomal breakage**
- **Secondary Prevention: early detection**

Oophorectomy for breast cancer risk reduction

- **Tamoxifen**
- **Oophorectomy**
 - **Prevents breast ca in BRCA 1 and 2**
 - **RR reduction is 50% in premenopausal pts**
 - **RR reductions may be higher if done before the age of 40yrs and that the duration of protection is approx. 15yrs**

Breast Cancer Prevention

Reducing the risk of Breast Ca

- **Chemoprevention**
- **Prophylactic Surgery**
 - Bilateral total mastectomy
 - Bilateral oophorectomy
- **Lifestyle and risk reduction**
 - Decrease dietary fat intake
 - Decrease body weight
 - Decrease alcohol intake
 - Increase exercise
- **Environmental factors**
 - Exposure to organochlorines and electromagnetic radiation

Chlebowski, RT NEJM 2000;343(3):191-198

Breast Cancer Prevention

- **Estrogen Receptor Modulators**
 - Tamoxifen(Tam)
 - NSABP P1 Trial (Gail risk \geq 1.67% or >60yrs w/LCIS)
 - Raloxifene (avg risk breast ca; Gail risk \leq 1.66%)
 - MORE Trial*
 - CORE trial
 - STAR Trial (Study of Tam and Raloxifene) (Gail risk \geq 1.67%)
- **Bilateral Prophylactic Mastectomy**
 - Mayo Clinic Retrospective analysis
 - 90% reduction in breast cancer
 - ?increase in survival w/ this if BRCA mutation is present

*Breast Cancer Res Treat 65:125-134, 2001

Breast Cancer Prevention

- **Raloxifene (MORE Trial)***
 - Post-menopausal female with osteoporosis
 - Breast cancer reduction by 62%
 - Invasive breast cancer reduction by 72%
 - Invasive ER+ive breast cancer reduction by 84%
 - No reduction in ER-ive breast cancer
 - Not associated with uterine cancer
 - Side Effects:
 - Increased risk of thromboembolic event
 - 28% hot flashes with raloxifene vs. 21% in placebo
 - » Elevation in FSH and estradiol in premenopausal women
 - » Reductions in FSH and LH in postmenopausal women
 - 40% reduction in cardiovascular events

*Breast Cancer Res Treat 65:125-134, 2001

Tamoxifen

- **Selective estrogen receptor modulator**
 - Estrogen **antagonist** effects in breast
 - Partial estrogen **agonist** activity in the bone, cardiovascular system and CNS
 - Predominant estrogen **agonist** effects in the uterus, liver, and vagina

Tamoxifen

- **Four completed primary prevention trials using Tamoxifen for ≥ 5 yrs**
 - NSABP P-1
 - International Breast Cancer Intervention Study (IBICIS)-1
 - Royal Marsden
 - Italian
 - **General Results:**
 - 36% reduction of DCIS
 - 46% reduction in invasive breast cancer
 - 48% reduction in ER + tumors
 - no significant reduction in ER-ive tumors
 - **2.4 fold increase in endometrial cancer**
 - 1.9 fold increase in deep venous thrombosis
 - 1.5 fold increase in cerebral vascular accident

NSABP P1 Trial

- Randomized trial of 13,000 pts
- Eligible:
 - 5yr Gail model risk of $\geq 1.67\%$ of developing breast cancer for women age 35 or older
 - Age >60, hx of LCIS
- Tamoxifen vs. Placebo
- Results:
 - Risk reduction of 49% of invasive breast ca in all age groups for ER+ tumors
 - Tam. benefits only apply to ER+ tumors and no diff seen w/ER- tumors
 - Overall risk reductions of 38% in all breast cancer
- Side effects:
 - Increase in endometrial ca(RR:2.53), thrombo-embolic events (DVT, PE, and CVA in >50yrs), bone density
 - No change in rate of ischemic heart disease

Tamoxifen as Prevention Agent

- In ER+ive breast cancer
- Atypical hyperplasia
- Carcinoma in-situ
- 5yr Gail risk >5%
- BRCA2 but not in BRCA1 (usually ER-ive)

NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial

- A prospective, double-blind, randomized study
- N=19,747, post-menopausal, 5yr risk of breast cancer of 1.66% (Gail model)
- Randomization: Tam (20mg/d) or Raloxifene (60mg/d) for 5yrs

	Tam	Raloxifene	
Invasive breast ca	163	168	
Noninvasive breast ca	57	80	
Uterine ca	36	23	
Thromboembolic event		Less	RR=0.7
Cataract		Less	RR=0.79

JAMA 2006;295:2727-41

NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial

- **Conclusion:**
 - **Raloxifene**
 - is as effective as tamoxifen in reducing the risk of invasive breast cancer
 - has lower risk of thromboembolic events and cataracts
 - Nonstatistically significant higher risk of noninvasive breast ca
 - **Tam or Raloxifene:**
 - no difference in risk of other cancers, fractures, ischemic heart disease, and stroke

Questions???

Matching

- BRCA 1 17q
- p53 17p
- RB 13q
- BRCA 2 13q

p=short, q=long

Questions???

Risk factors associated with breast ca?

- a. Fibroadenoma**
- b. Tobacco**
- c. Oral contraceptives**
- d. Age**
- e. a and d**

Answer: e

Questions???

A male with BRCA 1 mutation is at a high risk of developing breast cancer?

True or False

Answer: False

Questions???

What percentage of breast cancers are hereditary?

- a. 5-10%**
- b. 15-20%**
- c. 25-30%**
- d. 35-40%**
- e. 45-50%**

Answer: a

Questions???

What is the risk of developing breast cancer after mantle radiation therapy at age 22?

- a. 1%**
- b. 5-10%**
- c. 15-20%**
- d. 25-30%**
- e. 30-35%**

Answer: b

Questions???

Is oophorectomy a protective factor?

a. yes

b. no

Answer: a

Questions???

Gail model takes the following into consideration except?

- a. Age at first live birth**
- b. # of breast biopsies**
- c. # of second degree relative with breast ca**
- d. Age at menarche**
- e. Atypical ductal hyperplasia**

Answer: c