Surveillance for Women at High Risk for Breast Cancer
Overview and Update
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Who is at Risk?

Breast Cancer Risk

How Much Breast and Ovarian Cancer Is Hereditary?

Hereditary Breast and Ovarian Cancer

Sporadic
BRCA1 (52%)
BRCA2 (32%)
Other genes 16%

10%

Hereditary

15%
10%
10%

Breast Cancer
Ovarian Cancer

Sporadic
Family clusters
Hereditary
**BRCA1 and BRCA2 are Tumor Suppressor Genes**

- Protein products of these genes interact with each other in a pathway that repairs damaged DNA
  - Repair of DNA damage prior to cell division is an important way of suppressing tumor development
- **BRCA1** and **BRCA2** mutations are usually present only in hereditary cancers

**BRCA1-Associated Cancers:**
- Breast Cancer 85%
- Second Primary Breast Cancer 3% per year
- Ovarian Cancer 30-54%
- Prostate Cancer 30 to 50%

**BRCA2-Associated Cancers:**
- Breast Cancer (56%–85%)
- Male Breast Cancer (6-8%)
- Ovarian Cancer (20%–30%)

**Breast Cancer Risk**

Terminology BRCA Reports (Myriad)
- Loss of Heterozygosity (LOH) the functional allele become non functional (environmental hit). Loss of tumor suppression.
- Variant of Unknown Significance (VUS) mutation identified but unknown if harmful.
- Variant favor polymorphism is variation believed to be harmless.
- Benign polymorphism-no mutations
Breast Cancer Risk

1. Any women diagnosed with breast cancer under the age of 40 years or multifocal, bilateral breast cancer under the age of 60 years.
2. Any women under the age of 60 and triple Negative ER(−), PR(−), HER-2(−).
3. Any women of Jewish Ancestry (Ashkenazi), Hispanic, Mediterranean, Norwegian diagnosed with breast cancer under the age of 60 years.
4. Breast cancer diagnosis and family history of breast and ovarian cancer including 2nd degree relatives.

Breast Cancer Risk

6. All men with a breast cancer diagnosis should be tested for the BRCA 1 and 2 gene.

Special attention for TP53 mutation in melanoma families and colon carcinoma.

Others to screen are Cowden’s and Li Fraumeni families. Li-Fraumeni strong family history of Leukemia, brain cancer, sarcoma, skin cancers.

Cowden’s Disease (multiple hamatomas) multiple hamatomas on nose by age 20 and in nasal and oral mucosa. Lifetime risk for breast cancer is 81%. Other associated cancers are thyroid, renal, uterine. Benign disorders multinodular goiters and fibroadenomatosis.
Each model has limitations separately; a multi-model assessment has fewer limitations

- **Gail**
  - Limited family history data
  - Well calibrated, but does not discriminate between those who will get breast cancer and those who will not

- **Density**
  - Limited family history data
  - Newer model with limited validation studies

- **Claus**
  - No independent validation
  - Non-family history risk factors not considered
  - Does not include male, bilateral breast cancer, or ovarian cancer

- **BRCApro**
  - Non-family history risk factors not considered

**Flexibility to add as models are they are developed**

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**Breast Cancer Risk**

**Chest Wall Radiation and Risk for Breast Cancer. Special Group.**

- Risk is from radiation exposure at a young age.
- High for women who received mantle radiation for Hodgkin’s Lymphoma under the age of 30 years.
- Chest wall radiation exposure when breast buds are developing are the highest risk.
- Other cancers with radiation at increased risk are Wilms’s tumor, Leukemia, bone cancer, soft tissue sarcoma, Neuroblastoma, and mediastinal tumors.

Breast Cancer Risk

◆ Henderson et al. evaluate 7000 women who receive chest wall radiation (CWR) therapy under the age of 30 years.
◆ A multi-institutional studies (COG) as a cohort study of 14,000 women who receive cancer treatment.
◆ At age 25-30 12-26% of women with CWR developed breast cancer compared to the less than 2% in their cohort.
◆ At age 40-45 13-20% of women with early exposure developed breast cancer.
◆ Risk was highest for Hodgkin’s Lymphoma

Breast Cancer Risk

Recommend women exposed to chest wall radiation under the age of 30 start surveillance 8 years after they complete radiation or at age 25 year.
◆ A similar observation was made by Martens et al. particularly young women and girls are exposed to greater than 20 Gy rads.

Henderson et al. Intern Med April 6:152
Martens el al. J NCI 2008:108

Breast Cancer Risk

Tools for Prevention-SERMs
Tamoxifen and Raloxifene
◆ NSABP 1-first clinical trial to look at a medication for otherwise healthy women for chemoprevention.
◆ Goal was to enrolled 13,388
◆ Women identified as high risk by the Gail Risk Model. Risk 1.66%, dx of LCIS/ADH between the ages of 35-59 yrs, any women over the age of 60 yrs.
◆ Tamoxifen was given 20 mg/day. Randomized to Tamoxifen vs. Placebo

Breast Cancer Risk

NSABP P1 After 69 months of follow up
◆ Tamoxifen decreased the risk of an invasive breast cancer by 49% in women identified as high risk for breast cancer.
◆ Tamoxifen reduce the risk of DCIS by 50%.
◆ Tamoxifen reduce the risk of hip, spine, and radial fractures in postmenopausal women.
◆ Tamoxifen increased the risk of cataracts, endometrial cancers (2.34%) increase risk of thromboembolic events.
◆ First drug the FDA approved in 1998 for chemoprevention.

Vogel et al. JAMA 2006:295
Breast Cancer Risk

STAR TRIAL NSABP P2 (Study of Tamoxifen and Raloxifene (Evista) trial)

- Compared breast cancer prevention (invasive and noninvasive) of Raloxifene (2nd generation SERM) to Tamoxifen.
- Randomized 22,000 postmenopausal women identified as high risk for breast cancer.
- Tamoxifen 20 mg/day vs. Raloxifene 60mg/day.

Breast Cancer Risk

STAR TRIAL NSABP P2 (Study of Tamoxifen and Raloxifene (Evista) trial) Results:

- No major difference in prevention of invasive breast cancers. RR 1.02 CI 95%
- Tamoxifen slightly better preventing DCIS. RR 1.40 CI 95%.
- Raloxifene lower incidence of uterine cancer. RR 0.62 CI 95%.
- No difference in other cancers, ischemic heart disease, osteoporosis.

Breast Cancer Risk

STAR TRIAL NSABP P2 (Study of Tamoxifen and Raloxifene (Evista) trial) Results:

- Thromboembolic events less in the Raloxifene group. 0.79 CI 95%.
- Fewer cataracts in Raloxifene group. RR 0.82 CI 95%.
- No difference in the total number of cancer deaths.
- 2005 Raloxifene is approved by the FDA for chemoprevention. Good alternative to Tamoxifen.

The Puzzle of Breast Cancer
Breast Cancer Prevention Framework

Women at risk for breast cancer

- **Family History**
  - Genetic Counseling and/or Testing
    - Genetic Mutation
      - Surveillance
      - Mastectomy
      - Oophorectomy
      - Tamoxifen
  - No Genetic Mutation
    - Standard Risk Assessment
      - Considered to be at high or unknown risk
        - Risk Refinement
          - Atypia/ADH
            - Density
        - Risk Management Plan
          - Surveillance
          - Tamoxifen
          - (Mastectomy)
    - Considered to be at low risk
      - Risk Management Plan
        - Surveillance

No Family History

Risk Management Plan

Surveillance Tools

- **Breast Cancer Risk**
  - **Surveillance Tools**
    - Recommend clinical breast examination every 6 months.
    - Annual Mammogram and Bilateral Breast MRI.
    - If indicated consultation with a genetic counselor.
    - Chemoprevention with Tamoxifen orRaloxifene.
    - Discuss risk reducing prophylactic surgery, mastectomy or BSO.

- **Breast Cancer Risk**
  - **Surveillance Tools**
    - Warner et al. reviewed 11 prospective studies on using Mammogram alone vs. Mammogram and Breast MRI.
      - Mammogram and Breast MRI together are superior to mammogram alone, particularly in young women.
      - Mammogram identified DCIS better than MRI. MRI identified invasive cancers better than mammogram.
    - Impact on survival difficult to get at because low enrollment into a clinical trials and ethics of a trials.

- **Breast Cancer Risk**
  - **Surveillance Tools**
    - Disadvantage of surveillance:
      1. Increased radiation expose for young women may start 15 years earlier with breast imaging compared to other women at age 40. It is not clear if this lead to increase risk of breast cancer or other cancers.
      2. Increase false positive leading to more test and unnecessary biopsies, particularly with breast MRI.
      3. Increase healthcare cost.
      4. Increase stress and anxiety for patients.
Breast Cancer Risk

Breast Cancer High Risk Program:
1. Surgeon with a strong interest in breast disease.
2. Medical oncology to discuss chemoprevention.
3. Gynecology
4. Genetic Counseling services, patient education, and nutrition, exercise counselors.
5. Breast Imaging partnership with the providers.
6. Psychology