Assessment and Management of Women with an Increased Risk of Developing Breast Cancer

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Objectives

- Assess familial and non-familial risk factors for development of breast cancer
- Discuss various statistical models for assessing breast cancer risk factors
- Describe options for management of increased breast cancer risk including screening, chemoprevention, and surgery
- Cite the NCCN guidelines
What is risk?

- Risk is defined as “the probability that an event will occur”
  - Usually stated as a percentage chance for a set period of time
- Most breast cancers are attributable to nothing more than female gender and advancing age
- Baseline risk for developing breast cancer in a woman who lives to age 90 is 1 in 8 or 12.5%
Why try to estimate risk?

- Breast cancer is the most common cancer diagnosed in women
  - 234,190 new cases in 2015
  - 40,290 deaths in 2015
- Identification of women at higher than average risk can lead to implementing interventions to manage or reduce the risk
- Identification of women who *think* they are high risk but are actually *average* risk can lead to providing assurance and avoiding unnecessary intervention
Challenges in risk estimation

- Estimating risk for an individual patient at a given point in time is very difficult
- Few risk factors can be modified
- Interventions to modify risk have side effects and a risk and benefits must be balanced for each individual
- The NCCN offers Breast Cancer Risk Reduction guidelines
  - www.nccn.org/professionals/physician_gls/f_guidelines.asp
Challenges in risk estimation

- Who should not undergo a risk evaluation?
- Patients with a history of invasive breast cancer or DCIS
  - May need to be evaluated for presence of hereditary cancer
- Patients with a life expectancy of less than 10 years
  - Age or life-limiting medical problems
  - Minimal if any benefit
Risk Factors

- Familial/Genetic factors
  - Family history
  - Known or suspected BRCA 1/2 mutation
  - Other gene mutation associated with increased breast cancer risk
    - TP53, PTEN
- Demographics
  - Age
  - Ethnicity
- Reproductive history
  - Age at menarche
  - Age at first live birth
  - Age at menopause
- Environmental factors
  - Prior thoracic radiation
  - Hormone therapy
  - Alcohol consumption
- Other
  - ADH, LCIS
  - Number of biopsies
  - BMI
  - Breast density
Outline for risk estimation

- Evaluate for hereditary breast cancer
- Evaluate for prior thoracic radiation or proliferative breast disease (LCIS, ADH)
- Estimate breast cancer risk based on statistical models
<table>
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<tr>
<th><strong>Hereditary</strong></th>
<th><strong>Familial</strong></th>
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<tr>
<td>Mutations with high chance of cancer</td>
<td>More frequent, but not characteristic of hereditary cancer</td>
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<tr>
<td>Vertical transmission through mother or father</td>
<td>Combination of</td>
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<td>Autosomal dominant</td>
<td>Chance clustering of genes</td>
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<td>Multiple cancer types</td>
<td>Genetic variation with lower penetrance</td>
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<td>Characteristics</td>
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<td>Number of relatives</td>
<td>Close relatives</td>
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<tr>
<td>Young age</td>
<td>Young age</td>
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</table>
Criteria for further risk evaluation

- An *affected individual* with:
  - Early onset breast cancer defined as Age < 50
  - Triple negative breast cancer
  - Two breast primary cancers
  - Ovarian cancer

- Close blood relative with:
  - Breast cancer <50 years old
  - Ovarian cancer at any age
  - >2 relatives with breast cancer
Criteria for further risk evaluation

- An *affected individual* with (continued):
  - Thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, others
  - Male breast cancer
Criteria for further risk evaluation

- An *unaffected individual* with a family history of:
  - 2 or more breast primaries from same side of family
  - 1 or more ovarian cancers from same side of family
  - A family member with breast cancer plus cancers listed above
  - Male breast cancer
  - Population at risk
    - Ashkenazi Jews
Evaluation for hereditary cancer

- If criteria for further testing *are met:*
- Referral to cancer genetics professional
- Genetic testing
- Risk reduction counseling if:
  - Lifetime risk for cancer >20%
  - Pedigree strongly suggestive of hereditary
  - Known gene mutation
  - AND Lifetime expectancy > 10 yrs
Statistical models

- Determine if lifetime risk > 20%
  - Claus tables
  - Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)
  - BRCAPRO
  - Cuzick–Tyrer model

- Determine chance of BRCA 1/2 mutation
  - Probably only 4-5% of all breast cancer is due to specific mutation, thus not every diagnosis requires genetic eval
  - However, 20% of breast cancer in patients less than 30 due to specific mutation

breast-cancer-research.com/content/9/5/213
Evaluation

- If criteria for further testing for hereditary cancer are *not* met then...

- Patient undergoes evaluation for:
  - Prior thoracic radiation
  - Proliferative disease (LCIS, ADH)
  - Primarily based on history and results of previous biopsies
Prior thoracic radiation

- Women treated with thoracic radiation (mantle radiation) for Hodgkin’s disease
  - Not commonly used today
- For a woman treated at age 25 the absolute risk of developing breast cancer at age 55 is 29%
- Patients are at high risk based on history of radiation alone

Lobular carcinoma in situ

- Non-invasive pathologic finding
  - Cells heaped up in lobules of the breast
- Often an incidental finding on a biopsy
- Marker lesion
Lobular carcinoma in situ

- Increased breast cancer risk
  - 21% at 15 years
  - 25% over lifetime
  - Risk is conferred throughout both breasts
    - Area containing LCIS does not need to be excised with clear margins

- Long-term outcome good
  - Second invasive lesions tend to be favorable
  - Deaths from cancer in patients diagnosed with LCIS are unusual
  - Risk reduction interventions are available
Evaluation

- If criteria for further testing for hereditary cancer are *not* met...
  - No BRCA 1/2, PTEN, or TP53 mutation
  - No strong family history breast cancer
- AND there is no history of thoracic radiation or proliferative disease then...
- Patient undergoes an evaluation of risk based on the Gail model
  - www.cancer.gov/bcrisktool
  - www.breastcancerprevention.com
Gail model

- Well validated statistical model that uses a woman’s own:
  - Personal medical history (number of previous breast biopsies and the presence of atypical hyperplasia in any previous breast biopsy specimen)
  - Reproductive history (age at the start of menstruation and age at the first live birth of a child)
  - Family history of breast cancer among her first-degree relatives (mother, sisters, daughters)
- Estimates risk of developing invasive breast cancer over specific periods of time
  - Typically reported as five year and lifetime
The Breast Cancer Risk Assessment Tool is an interactive tool designed by scientists at the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) to estimate a woman’s risk of developing invasive breast cancer. The tool has been updated for African American women based on the Contraceptive and Reproductive Experiences (CARE) Study, and for Asian and Pacific Islander women in the United States based on the Asian American Breast Cancer Study (AABCS). See About the Tool for more information.

<table>
<thead>
<tr>
<th>Results (Breast Cancer Risk)</th>
<th>New Risk Calculation</th>
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Reminder: The Breast Cancer Risk Assessment Tool was designed for use by health professionals. If you are not a health professional, you are encouraged to discuss these results and your personal risk of breast cancer with your doctor.

Race/Ethnicity:
White

5 Year Risk

This woman (age 70): 2.4%
Average woman (age 70): 2.2%

Explanation
Based on the information provided (see below), the woman’s estimated risk for developing invasive breast cancer over the next 5 years is 2.4% compared to a risk of 2.2% for a woman of the same age and race/ethnicity from the general U.S. population. This calculation also means that the woman’s risk of NOT getting breast cancer over the next 5 years is 97.6%.

Lifetime Risk

This woman (to age 90): 8.0%
Average woman (to age 90): 6.3%

Explanation
Based on the information provided (see below), the woman’s estimated risk for developing invasive breast cancer over her lifetime (to age 90) is 8.0% compared to a risk of 8.3% for a woman of the same age and race/ethnicity from the general U.S. population.

These results are based upon the following answers:

- Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)? **No**
- What is the woman’s age? **70**
Gail model

- Well validated for white women
- Validated for black women, but may underestimate risk for black women who have undergone a previous biopsy
- Still requires validation for Hispanic women

- Gail model provided the reference for the NSAPB Breast Cancer Prevention Trial and the Study of Tamoxifen and Raloxifene (STAR) trials
- “Elevated risk” defined as 5 yr > 1.7%
Breast density

- Chiu, et.al. followed 15658 ages 45 to 59 from 1997 to 2004 and found an increased incidence of cancer in women with dense breasts (RR 1.57)

- Breast density is not used as a part of any risk estimation model
Now what?

- **Average risk women**
  - Age 20-40: Clinical breast exam every 1-3 yrs
  - Age >40: Yearly mammogram and yearly clinical breast exam
  - Breast awareness

- **Women with elevated risk**
  - Discussion of risk reduction strategies
  - Hereditary Breast and Ovarian Cancer Syndrome
  - Lobular carcinoma in situ/ atypical ductal hyperplasia
  - History of prior thoracic radiation
  - Gail model >1.7% over 5 years
Risk reduction

- Lifestyle modification
- Screening
- Chemoprevention
- Risk reduction surgery
Hereditary Breast and Ovarian Cancer Syndrome

- Individuals who have tested positive for a deleterious mutation in BRCA 1 or 2 or who have a close family member who tested positive

- Breast self exam and education starting at age 18

- Clinical breast exam every 6-12 months starting at age 25
Hereditary Breast and Ovarian Cancer Syndrome

- Annual mammogram and breast MRI starting at 25 or 10 yrs prior to youngest diagnosed relative
- Discussion of risk reduction bilateral mastectomy
- Risk reduction salpingo-oophorectomy
  - Ideally between age 35 and 40
  - After completion of child bearing
  - If no surgery, transvaginal ultrasound and CA-125 every 6 months starting at age 35
Lobular Carcinoma in situ

- Annual mammogram
- Clinical breast exam every 6-12 months
- Consider yearly MRI
  - Young patient
  - Dense breasts
  - Additional risk factors
- Chemoprevention
  - 5 yrs of tamoxifen or raloxifene reduces risk by 48%
- Risk reduction bilateral mastectomy
  - Can be considered but is not the recommended action for most women
  - Young age, additional risk factors, patient anxiety
History of prior thoracic radiation

- Yearly screening MRI in addition to yearly screening mammogram
  - Starting 8-10 years after radiation therapy or at age 25, whichever occurs last
- Clinical breast exam every 6-12 months
- Breast awareness
- There are no data regarding the use of risk reduction bilateral mastectomy or chemoprevention
Screening MRI

- No evidence for use of screening MRI for average risk women
- High risk women
  - BRCA 1/2 mutations
  - Radiation therapy to chest wall
  - Lifetime risk >20% based on statistical model
Chemoprevention

- NSABP Breast Cancer Prevention Trial
- NSABP Study of Tamoxifen and Raloxifene (STAR) trial
NASBP BCPT

- Randomized clinical trial of healthy women aged 60 years or older, aged 35-59 with a 5 yr risk > 1.7%, or LCIS (n=13,388)
- Tamoxifen 20 mg/d 5 years vs placebo
- Initial findings reported in 1998, additional 7 year follow up later published
- 43% reduction in breast cancer incidence
  - 24.8 cases per 1000 vs. 42.5 cases per 1000 across age groups in final report
  - 86% reduction in incidence is subgroup analysis of atypical ductal hyperplasia
NASBP BCPT

- Decrease in bone fractures with tamoxifen
- Complications
  - Hot flashes
  - Invasive endometrial cancer in age >50
    - 3 per 1000 for tamoxifen vs .76 per 1000 for placebo
  - Cataracts
  - PTE in women over age 50
    - 1 per 1000 for tamoxifen vs .3 per 1000 for placebo
- No difference in overall mortality
  - 2.17 per 1000 vs 2.71 per 1000 placebo
  - 2.8 per 1000 vs 3.08 per 1000 placebo over additional 7 years
NASBP BCPT

- Trial resulted in approval of tamoxifen for breast cancer risk reduction by FDA in 1998

Study of Tamoxifen and Raloxifene

- Randomized clinical trial of post-menopausal women aged 35 years or older with 5 yr risk > 1.7% or with LCIS (n=19,747)
- Tamoxifen 20 mg/d vs Raloxifene 60 mg/d for 5 years
- Equivalent for invasive cancer risk reduction (approx 50%) at 5 years but at 8 years raloxifene only 75% as effective as tamoxifen
Study of Tamoxifen and Raloxifene

- Less complications with Raloxifene
  - Endometrial hyperplasia
  - Invasive endometrial cancer
  - DVT and PTE
  - Cataract

- Tamoxifen is a superior risk reduction agent for post-menopausal women, but improved side effect profile might still favor the use of Raloxifene in some women
Contraindications

- History of deep vein thrombosis
- History of pulmonary embolus
- History of thrombotic stroke
- History of transient ischemic attack
- Current pregnancy or pregnancy potential without effective method of contraception
- Known inherited clotting trait

Additionally, hormone replacement therapy should be stopped while taking Tamoxifen or Raloxifene
SERM recommendations

- **Tamoxifen**
  - Women age > 35 pre- or postmenopausal with Gail risk > 1.7%, or ADH or LCIS
  - 20 mg/d for 5 years

- **Raloxifene (Evista)**
  - Women age >35 post menopausal with Gail risk >1.7%, or ADH or LCIS
  - 60 mg/d for 5 years
Aromatase inhibitors

- MAP .3 trial
  - 4560 women randomized exemestane (Aromasin) or placebo
  - 65% risk reduction after 3 years

- IBIS-II trial
  - 3864 post menopausal women randomized anastrozole (Arimidex) or placebo
  - At 7 years cumulative incidence 2.8% treatment vs 5.6% in placebo
Aromatase inhibitors

- Not currently FDA approved
- NCCN recommendations:
  - Indicated for post menopausal women age>35 with Gail risk >1.7 % or LCIS
  - Exemestane 25mg/d
  - Anastrozole 1mg/d
Risk reduction mastectomy

- BRCA 1 or 2 mutation
  - Lifetime risk of developing cancer is 56-84%
  - RRM reduces risk by approximately 90%
- LCIS
  - Only in certain situations
- Prior thoracic radiation
  - No data to support this
- No indication for mammographic screening
- *Risk reduction* mastectomy is different from a *contralateral prophylactic* mastectomy
Lifestyle modification

- “Healthy living” and “breast awareness”
- Alcohol consumption
  - Moderate intake (1-2 drinks/day) associated with increased risk
  - NCCN recommendation is <1 drink/day
- Exercise
  - Women with an activity level exceeding median activity of control group have 20% decreased rate of cancer compared to sedentary women
Lifestyle modification

- Weight
  - Overweight or obese post menopausal women at significantly increased risk
  - Studies also show weight loss to reduce risk

- Breast feeding
  - Every 12 months of breast feeding reduces relative risk by 4.3%
What to do with all this?

- Set up office protocols, templates for risk reduction
- Support screening for high risk individuals by facility that performs mammogram
- Establish referral systems
Breast Care Center

- Average risk women are given reassurance and instructions to continue screening
- Women with elevated risk are to be evaluated by a high risk committee
  - Recommendation for screening, chemoprevention, or surgery
  - Letter to patient and to the primary care physician
Questions?