Risk Assessment and Reduction

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Outline

• Major and Minor Risk Factors
• Risk Models and Counseling
• Biomarkers for Risk Stratification
• Standard Risk Reduction Strategies
• Interventions Under Study
Risk Factors
Risks Related to Breast Cancer

- Advancing Age
- Gender
- Close Relative
- Age at First Birth
- Education & Income
- Diet
- Ionizing Radiation
- Benign Breast Disease
- Overweight
- Late Menopause
- Hormone Replacement Therapy
- Alcohol
- Lack of Exercise
- Passive Smoke
- Chemicals
  - Work
  - Home
  - Garden
  - Recreation
- Early Menarche
- Benign Relative
- ???
## Major Factors Absolute & Relative Risk Per Year

<table>
<thead>
<tr>
<th>Factor</th>
<th>Absolute Risk</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA 1/2 &gt; 30</td>
<td>2%</td>
<td>20x</td>
</tr>
<tr>
<td>DCIS</td>
<td>2%</td>
<td>20x</td>
</tr>
<tr>
<td>Breast XRT &lt; 30</td>
<td>2%</td>
<td>20x</td>
</tr>
<tr>
<td>LCIS</td>
<td>1%</td>
<td>10x</td>
</tr>
<tr>
<td>AH + Family HX</td>
<td>1%</td>
<td>8-10x</td>
</tr>
<tr>
<td>AH</td>
<td>0.5%</td>
<td>4-5x</td>
</tr>
<tr>
<td>Prior Inv Cancer</td>
<td>0.75%</td>
<td>5-8x</td>
</tr>
<tr>
<td>Age &gt; 60 (vs 30)</td>
<td>0.33%</td>
<td>10x</td>
</tr>
<tr>
<td>Major (&gt;2 fold increase)</td>
<td>Minor (&gt;1&lt;2 fold)</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>• BRCA1/2 Mutations (20x)</td>
<td>• Early menarche (1.05 year &lt;12)</td>
<td></td>
</tr>
<tr>
<td>• Chest radiation &lt;30 (10-20x)</td>
<td>• None/&gt;30 first birth vs 20 (2x)</td>
<td></td>
</tr>
<tr>
<td>• DCIS (20X)</td>
<td>• No Lactation (0.96 per 12 months breast feeding)</td>
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<td>• LCIS (10X)</td>
<td>• Late menopause&gt; 50 (1.05/year)</td>
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<tr>
<td>• ALH, ADH (4-5x)</td>
<td>• 2\textsuperscript{nd} &amp; 3\textsuperscript{rd} degree relatives</td>
<td></td>
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<tr>
<td>• Age &gt;60 vs 30 (10x)</td>
<td>• 5 years CEE alone HRT (0.75)</td>
<td></td>
</tr>
<tr>
<td>• 1st degree &lt; age 50 (2X)</td>
<td>• 5 years CEE+ MPA HRT (1.25)</td>
<td></td>
</tr>
<tr>
<td>• Prior breast Cancer (&gt;2x)</td>
<td>• Obesity (1.3 BMI &gt;30 vs&lt;25)</td>
<td></td>
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Risk Models and Counseling
Risk Assessment Tools Should Consider All Major Factors, Minor if Possible

NCCN Guidelines Genetic Testing

Gail Model

Tyrer–Cuzick (IBIS)
Gail Model (II) Considers

- Current age
- Age at menarche
- Age at first live birth
- Number of 1st degree relatives
- Number of biopsies
- Presence of Atypical Hyperplasia
- Race

- Discriminatory accuracy is suboptimal (C statistic ~ .63)

www.cancer.gov/bcrisk/tool/

References:

Rockhill JNCI 93:358, 2001
Tice Breast Cancer Res Treat 94:115, 2005
Gail et al. JNCI 81:1879, 1989,
Tyrer Cuzick Model Considers More Factors
Woman's age is 52 years.
Age at menarche was 11 years.
Age at first birth was 27 years.
Age at menopause was 51 years.
Height is 1.67 m.
Weight is 80 kg.
Woman has never used HRT.

Risk after 10 years is 9.755%.
10 year population risk is 2.674%.
Lifetime risk is 23.93%.
Lifetime population risk is 7.802%.
Probability of a BRCA1 gene is 5.86%.
Probability of a BRCA2 gene is 1.509%.
Tyrer Cuzick (IBIS) Advantages and Disadvantages Compared To Gail Model

**Advantages**
- Estimates Risk even if < 35
- Estimates Risk even if LCIS
- Estimates risk of BRCA1/2
- Considers Factors Gail II doesn’t
  - Height and Weight
  - 2nd and some 3rd degree relatives
  - Age of relatives diagnosis
  - HRT use
  - Ovarian Ca & Oophorectomy
  - Age at menopause

**Cons**
- May overestimates risk especially if patient has a dx of Atypical hyperplasia or LCIS

Boughey J CO 2010;28: 3591*
How Well Does Gail vs Tyrer Cuzick Perform in a High Risk Cohort?

• Mayo Clinic Cohort of 9376 women with biopsies followed for median of 14 years (331 atypia)

• Concordance Statistic for 10 year risk
  – Gail Model atypia .45
  – Tyrer Cuzick atypia .54
  – Tyrer Cuzick no atypia .57

Boughey J Clin Oncol. 2010;28:3591
Would Adding Biomarkers Predictive of Short Term Risk Improve Model Accuracy or Increase Uptake of Chemoprevention?
Mammographic Density Adds Modestly to Gail Model Predicted Risk

- Density Largely Inherited Trait
  - Weakly correlated with progesterone and SHBG
- >50% density occurs in
  - 12 % Postmenopausal
  - 37 % premenopausal women
- Concordance Statistic
  - increase from ~.60 Gail to .66 Gail + Density
  - ~ = Gail when used alone

Vachon Breast Cancer Res. 2007;9:217
Warren CEBP 2006 15: 1502
RPFNA: Non-Lesion Directed Sampling

Local Anesthesia

2 areas per breast;

21 gauge, 1-1/2 in needle

3-4 slides Thin Prep Pool

Aspirates in Fixative

Morphology

ER
Ki-67

Molecular Markers
RPFNA Atypia Increases Relative Risk of Breast Cancer by 5-Fold

Cumulative Frequency, Percent

Time from Entry on Study, months

Total High Risk Cohort (N=480)

FNA Atypia (N=102) P<0.0001

No FNA Atypia (N=378)

Risk Based Approach to Surveillance
Women at Increased Risk with + FH

Start Mammography 10 years before Youngest Affected Relative
Use of More Sensitive Screening Techniques in Addition to Digital Mammography Risk and Density Dependent

MRI
> 20-22% Lifetime Risk Based on FH

Tomosynthesis
> 25-50 % density

Automated or Hand Held Breast Ultrasound
> 50 % density

Berg et al. JAMA 307:1394
Additional Imaging  Women with Normal Mammogram & Dense Breasts Add to Cancers Detected

• Breast Ultrasound  3.2-3.7/1000 Screens
• Breast MRI ~ 14.7/1000
• Tomosynthesis : Decrease call backs

MRI and US also Increase Number to False Positive Exams and Biopsies

Hooley Radiology 265:59
Berg et al. JAMA 307:1394–1404
## Risk Based Suggestions for Screening

<table>
<thead>
<tr>
<th>Risk</th>
<th>Mammogram Start/Frequency</th>
<th>SONO</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>40-50</td>
<td>1-2 Years</td>
<td>No</td>
</tr>
<tr>
<td>Moderate FH (&gt;2 fold for age-1%/year)</td>
<td>10 years before youngest affected</td>
<td>Yearly</td>
<td>If &gt; 20-22% lifetime based on FH</td>
</tr>
<tr>
<td>High Density</td>
<td>Tomosynthesis</td>
<td>Yearly</td>
<td>No, if not &gt;20-22% lifetime based on FH</td>
</tr>
<tr>
<td>High (1-2%/year)</td>
<td>After pre-cancerous biopsy or 10 years before youngest affected</td>
<td>Yearly</td>
<td>ABUS if &gt;20-22% lifetime based on FH</td>
</tr>
<tr>
<td>Very High (BRCA1/2 mutation)</td>
<td>25-30</td>
<td>Yearly</td>
<td>If no MRI, sono ABUS if 50% or higher density</td>
</tr>
</tbody>
</table>

**References**

Berg JAMA. 2012; 307: 1394
Lourenco Radiology. 2014; 140; 317.
Ho AJR Am J Roentgenol. 2014;203:449
Hendrick AJR Am J Roentgenol. 2011;196:W112
Cancer Epidemiol Biomarkers Prev. 2012;9:1458
Risk Reduction:
Standard Approaches
Type of Prevention Intervention Suggested Varies With Risk Level

- **Prophylactic Surgery**: Very High Risk
  - $\sim 2\%$/year ($BRCA1/2$)
- **Anti-Hormones**: High Risk
  - 1-2%/year ($LCIS, AH + FH$)
- **Healthy Lifestyle/ Anti-hormones**: Moderate Risk
  - 0.33-1%/year ($FH$, Reproductive Factors)
- **Healthy Lifestyle**: Average Risk
Standard Risk Reduction Interventions

• Pre-menopausal Women Gail Risk of >1.66 AH, LCIS, DCIS
  – Tamoxifen for 5 years beginning after age 35

• Postmenopausal Women Gail Risk >1.66 AH, LCIS
  – Tamoxifen for 5 years
  – Raloxifene for 5 years or more
  – Exemestane or Anastrozole for 5 years

• Women from Hereditary Breast/Ovarian Families (BRCA ½ )Family
  – Removal ovaries and tubes @ 35-40
  – Prophylactic Mastectomy

Visvanathan J Clin Oncol 2013;10:2942
Kurian J Clin Oncol. 2010; 10;28:222
Risk Reduction from Chemoprevention

- Tamoxifen Meta-Analysis (Cuzick) 33% NSABP P-1 50%
- Raloxifene 40%
- Anastrozole 50%
- Exemestane 65%
- No survival Benefit
- Patient Choice as whether to take

Cuzick Lancet. 2013;381:1827
Fisher J Natl Cancer Inst 1998; 90:1371
Vogel Cancer Prev Res .2010; 3:696
Cuzick Lancet. 2014;383:1041
## Side Effects Of Preventive Agents

<table>
<thead>
<tr>
<th>Tamoxifen</th>
<th>Exemestane/Anastrozole</th>
</tr>
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<tbody>
<tr>
<td>Hot Flashes, Vaginal Discharge</td>
<td>Hot Flashes</td>
</tr>
<tr>
<td>Uterine surgery &amp; cancer</td>
<td>Vaginal Dryness</td>
</tr>
<tr>
<td>DVT, PE, Cataracts</td>
<td>Joint &amp; Muscle pain</td>
</tr>
<tr>
<td></td>
<td>Bone Density Loss</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
</tbody>
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- **Tamoxifen**
  - Hot Flashes, Vaginal Discharge
  - Uterine surgery & cancer
  - DVT, PE, Cataracts

- **Raloxifene**
  - Hot Flashes, Vaginal Dryness
  - DVT, PE

- **Exemestane/Anastrozole**
  - Hot Flashes
  - Vaginal Dryness
  - Joint & Muscle pain
  - Bone Density Loss

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*References*

- Fisher *J Natl Cancer Inst* 1998;90:1371
- Cuzick *Lancet* 2003; 361:296
- Vogel *JAMA* 2006;295:2727
- Goss *NEJM* 2011; 363:2381
- Cuzick *Lancet* 2014;383:1041
Tamoxifen or Raloxifene
Contraindicated if

- Prior Deep Venous Thrombosis
- Prior Stroke
- Inherited Clotting Disorder
Tamoxifen should be discussed with a premenopausal or postmenopausal woman at increased risk for Breast Cancer with a 5 year Gail model or equivalent risk of >1.66 %.

Raloxifene or exemestane should be discussed in a postmenopausal woman with a 5 year Gail model or equivalent risk of >1.66 %.

Visvanathan et al JCO 2013
10% Uptake Tamoxifen Risk Eligible Premenopausal Women

- No significant increase in blood clots or endometrial cancer
- Not used < age 35
- Marked increase in estradiol, ovarian cysts.
- Reduction in BMD
- Hot flashes and menstrual abnormalities

Donnelly and Cuzick Br J Cancer. 2014;110:1681
Overall Uptake Chemoprevention Estimated at 4% Risk Eligible Women

Ropka J Clin Oncol. 2010; 28:3090
What Screening/Prevention Interventions Have Demonstrated Survival Advantage?

- Screening Mammography
  - Average to high risk cohorts
- Prophylactic Surgery/Breast MRI
  - BRCA1/2 Carriers
    - MRI added to Mammography
    - Prophylactic Oophorectomy
    - Prophylactic Mastectomy (BRCA2)
    - Oophorectomy + Mastectomy or Oophorectomy + Screening MRI

Berg JAMA, 2012; 307:1394
Gareth Breast Cancer Res Treat 2014;145:663
Kurian J Clin Oncol. 2010;28:222
Early Surgical Menopause Associated with Increased Cardiovascular Death and Dementia

• Oophorectomy < age 45
  – ~80% increased cardiovascular death, and early cognitive impairment
  – No increase in these events if given estrogen until age 45-50.
• Breast Cancer Risk reduction from oophorectomy at age 35-40 not attenuated with add back estrogen

Olmstead County Trial Rivera 2009, Rocca 2007
Rebbeck JCO 2005; 23:7804
Domchek et al ASCO 2011 Abstract 1501
Hot Flash Free Interventions Under Study

Anti-Hormonal +

Letrozole for Women on HRT
Bazedoxifene (SERM) + CEE
Curcumin
Polyphenols
Lignans
Vitamin D

Anti-Inflammatory: ER+/-

Weight Loss
Metformin
ASA
Omega-3 FA
70% Tumors ER+, ER Proliferation Generally Increases with Atypical Morphology

<table>
<thead>
<tr>
<th>Normal</th>
<th>Hyperplasia</th>
<th>Atypia</th>
<th>In Situ Cancer</th>
</tr>
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<tr>
<td>Normal</td>
<td>Hyperplasia</td>
<td>Atypia</td>
<td>In Situ Cancer</td>
</tr>
<tr>
<td>Ki-67</td>
<td>2X</td>
<td>5X</td>
<td>10X</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>2-15%</td>
<td>Relative Risk</td>
<td>2X</td>
</tr>
<tr>
<td>20</td>
<td>60</td>
<td>90</td>
<td>60</td>
</tr>
</tbody>
</table>

ER

Relative Risk

Ki-67

2-15%

20

60

90

60
Role of Inflammation In Breast Cancer
Activated Macrophages Progressively Increased in Proliferative Breast Disease and Cancer

Hussein J Clin Pathol 2006;59:972
In Obesity, Activated Macrophages Move Along Connective Tissue Paths, to Remove Dying Fat Cells

Crown Structures in obesity

Chronic Inflammation From Macrophages, Cytokines, Increased Risk of Cancer

90% obese, 1/3 Normal BMI

How Much Does Weight Loss Does It Take to Reduce Breast Cancer Risk? Don’t Know

- Bariatric Surgery 20-30% loss reduces risk
- Observational studies suggest 10% associated with reduced risk if maintained.
- Tissue/Serum Risk Biomarker studies: 10 % or higher for marker change

Sjostrom Lancet Oncol 2009
Teras Cancer Causes Control 2011,
Byers Diabetes Obes Metab 2011
Sjostrom Arch Intern Med 1998
Fabian Breast Ca Res Treat 2013
**SHAPE-2 RCT: Exercise, Diet, Control**

- Both diet and exercise showed favorable effects on sex hormones compared to control.
- Compared with diet, equivalent weight loss by exercise has more beneficial effects on:
  - Body composition ($\uparrow$ more fat loss & lean mass preserved)
  - Physical fitness ($VO_{2max}$)
  - Trend for more beneficial effects on serum sex hormones (mainly androgens and SHGB)

Exercise induced weight loss preserves lean mass and has more overall benefits

*May et al. Effect of equivalent weight loss, with or without exercise, on breast cancer related sex hormones in overweight/obese postmenopausal women. ASCO 2014*
Connecting epidemiology, biomarkers and interventions

- Tell your patients to lose weight
- Exercise an important component of weight loss regimen
- Biomarker modulation largely coherent with the goals and science
Risk Assessment and Prevention Consultation

- Long and short term risk
- Need for genetic testing
- Risk Based Surveillance
- Prevention Interventions based on risk, life phase, co-morbidities
- Benefits (Survival advantage if any) and side effects of standard prevention
- Discuss clinical trials
- Questions esp Hormones
Can I take Hormonal Contraceptives and Fertility Drugs?

### Oral Contraceptives
- Breast Cancer Risk is slightly and non-significantly elevated in general population (HR 1.08) and BrcA1/2 carriers (HR 1.21).
- Significant Reduction in ovarian cancer risk of ~40% in carriers and 30% in general population.

### Fertility Agents
- 12,000 women evaluated for fertility and followed median of 30 years.
- Ever Use Clomiphene HR 1.05
- Multiple Cycles HR 1.69
- Women who remained nulligravid HR 1.98

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*Moorman JCO 2013; 31: 4188*  
*Brinton CEBP 2014; 23;584*
Can I take HRT? Risk/Side Effects Variable
Breast Cancer Risk Hormone & Replacement

1. If oophorectomy no excess risk to age 50
2. After 50 E+P HRT > Risk than E alone
2. E+ Progestins > Risk E+ Natural Progesterone
3. Risk Higher in Lean women
4. Risk Higher if start first 5-10 yrs after Menopause
   WHI no risk E alone vs inc Million Women
5. Excess risk dissipates within few years of stopping
6. No excess risk vaginal hormones

Minimal Excess Risk to Age 60
Natural Progesterone with Estradiol (E2) May Be Less Risky than Progestins + E2

• Estrogen and Progestins > breast tissue proliferation than estrogen + natural progesterone.

• French Cohort Study: estradiol + natural progesterone did not increase risk of breast cancer

*Baseline  Transdermal E2 + MPA
Baseline  Transdermal E2 + Progesterone

Murkes Fertility and Sterility 2011 95: 1188.
Fournier Breast Ca Res & Treat 2008; 107: 103
Newer SERMs as Alternatives to HRT

Bezadoxifene + CEE (TSEC)
- FDA approved for use for women with a uterus and hot flashes
- Pre-clinical studies decrease estrogen induced MCF-7 proliferation
- Clinical studies: reduction hot flashes, no endometrial proliferation, no change breast density, BMD protection

Ospemiphne
- FDA approved pill for
- approved for treatment of dyspareunia associated with vulvar and vaginal atrophy
- Similar drug class as tamoxifen (triphenylethylene).
- Can cause hot flashes

Komm Steroids 2014
DeGregorio Steroids 2014 90: 82
Future Prevention: Personalized Medicine

- Risk and Biology Based Recommendations
- Biomarkers: Risk, Type of Intervention Likely to Work and Response
- Increased Emphasis on Healthy behaviors and Natural Products
- Save Strong Antihormonal agents for Higher Risk