OUTLINE
- Risk Assessment
- Risk Reduction
- Tests at Diagnosis

Case: Maria
- 35 yo white woman, has 2 children ages 1 and 4. She started menstruating at age 11 and took birth control pills from age 19 to 26.
- She recently had a biopsy for a breast lump which was benign (cyst)
- Her mother diagnosed BC at age 69
- She is an advertising executive and drinks 2-3 glasses of wine/night.
Maria’s questions

• What is my risk for developing breast cancer?
• What can I do to lower my risk?

Why risk assessment?

• Breast cancer is most commonly diagnosed cancer in U.S. women
  – 1 in 8-9 women will be diagnosed in her lifetime
• 2nd most common cause of cancer death in women
  – >49,000 deaths (ACS, Surveillance Research, 2014)
• Risk assessment tools are available
• Risk reduction is possible

Risk factors for breast cancer

• Strong
  – Age
  – Breast density
  – Atypical hyperplasia
  – LCIS
  – BRCA mutation
• Moderate
  – Family history
  – Breast biopsy
  – Race / ethnicity
  – Hormone therapy
  – Hormone levels (E2, T, IGF-1)
  – Benign breast disease
• Weak
  – Age at first birth
  – Menarche age
  – Height, weight, BMI
  – Bone mineral density
  – NAF/Lavage
  – SNPs
  – Age of diagnosis for family history
  – 2nd degree relatives
  – Alcohol intake
  – Diabetes
  – Physical activity
  – Breast feeding
  – Menopause age
Factors Considered in The Gail Risk Model

- Current age
- Race / Ethnicity
- Age at menarche
- Age at first live birth
- Number of 1° relatives with BC
- Number of breast biopsies
- Presence of ADH


Gail Model on NCI website

http://www.cancer.gov/bcrisktool/

- 5 year and lifetime estimates by race

Validated for populations; but modest discriminatory value for the individual

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What is Maria’s 5-year risk for BC?

1. < 0.5%
2. 0.5 to 1.49%
3. 1.5 to 2.49%
4. ≥ 2.5%
### Maria’s risk using the Gail model

- **5 years:** 1.0%
- **Lifetime (to age 90):** 25.8%

### Average 35 year old woman

- **5 years:** 0.3%
- **Lifetime (to age 90):** 12.6%

### Risk factors not in Gail model

- **Strong**
  - Age
  - **Breast density**
  - Atypical hyperplasia
  - LCIS
  - **BRCA mutation**

- **Moderate**
  - Family history
  - Breast biopsy
  - Race / ethnicity
  - **Hormone therapy**
  - Hormone levels (E2, T, IGF-1)
  - Benign breast disease

- **Weak**
  - Age at first birth
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  - Alcohol intake
  - Diabetes
  - **Physical activity**
  - Breast feeding
  - Menopause age

### Mammographic Breast Density

- **BI-RADS**
  - 1: Almost entirely fat
  - 2: Scattered densities
  - 3: Heterogeneously dense
  - 4: Extremely dense

- **RR**
  - 1.0
  - 2.0
  - 2.8
  - 4.1

- **Prevalence:** 40-45% (BI-RADS 3 and 4 density)
- **About 10%** for BI-RADS 1 and 10% for BI-RADS 4

Kuninovskaya JNCI 2007
Sprague JNCI 2014

### SB 1538: California’s Breast Density Law

- For women with BI-RADS 3 and 4 BD, radiologists must inform women
  - that they have dense breasts
  - that dense breasts make it harder to detect breast cancer
  - That dense breasts are associated with a higher risk of breast cancer
BCSC breast density model
- Age, race, BD, family history, breast biopsy

https://tools.bcsc-scc.org/BC5yearRisk/

Maria’s 5-year risk comparing models

<table>
<thead>
<tr>
<th>Model</th>
<th>Risk</th>
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<tbody>
<tr>
<td>Gail Model</td>
<td>1.0%</td>
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<tr>
<td>BCSC Model</td>
<td></td>
</tr>
<tr>
<td>- Almost entirely fat</td>
<td>.24%</td>
</tr>
<tr>
<td>- Scattered densities</td>
<td>.50%</td>
</tr>
<tr>
<td>- Heterogeneously dense</td>
<td>.77%</td>
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<tr>
<td>- Extremely dense</td>
<td>1.0%</td>
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Risk Reduction

LIFESTYLE
No association with breast cancer
- Fruits & vegetables
  - Smith-Warner, JAMA, 2001
  - Pooled prospective studies
  - 7377 cases in 351,825 women
- Carotenoids; Vitamins A, C, E
- Selenium

Mixed results on dietary fat intake
- WHI dietary study: post-intervention follow-up: non-significant decrease in breast cancer incidence in low-fat diet group

Obesity
- Premenopausal – small decreased risk
- Postmenopausal – increased risk

Alcohol and breast cancer risk:
- Meta-analysis

<table>
<thead>
<tr>
<th>Total Alcohol Intake g/d</th>
<th>Multivariate Relative Risk</th>
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<tr>
<td></td>
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<tr>
<td>0</td>
<td>1.0</td>
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<tr>
<td>1-3 hours brisk walking/week</td>
<td>0.8</td>
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</table>

Smith-Warner, 1998

Exercise and risk of breast cancer
- Overall 25-30% decreased risk
- Lifetime exercise matters
- Modest amounts: 1-3 hours brisk walking/week

Hormone Therapy
Women’s Health Initiative
- E + P
  - 1.24 (1.01-1.54) ITT
  - 1.49 (as treated)
- E
  - 0.77 (0.59-1.01)

- Survival curves do not separate until 3 years on treatment
- Risk is lower if started at least 5 years after menopause
- Risk dropped to baseline within 2 years of stopping therapy

CHEMOPREVENTION

SERMs Reduce the Risk of Breast Cancer

Adverse Events From Prevention Trials of Tamoxifen & Raloxifene

- DVT/PE: 1.9 (1.4-2.6)
- Endometrial cancer: 2.4 (1.5-4.0)
- ↑ risk fatal stroke
- ↑ risk cataracts
- ↑ risk hot flashes

** Majority of adverse events in women ≥ 50 years


- SERMS
  - BCPT 1998:
    • 5-yrs tamoxifen reduced risk of invasive breast ca 49% -- increased endometrial CA, VTE, cataracts
  - STAR trial 2006:
    • raloxifene equal to tamoxifen in reducing risk of invasive breast cancer -- significantly less thromboembolism and cataracts
USPSTF Draft Recommendation

- “...clinicians engage in shared decision-making with women at increased risk of breast cancer regarding medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications such as tamoxifen or raloxifene.”

- “In general, women with an estimated 5-year breast cancer risk of 3% or greater are more likely to benefit from tamoxifen or raloxifene.”

http://www.uspreventiveservicestaskforce.org/

SERM Risk Benefit Ratio Likely To Be Favorable For ...

<table>
<thead>
<tr>
<th>5 yr Gail</th>
<th>Age &lt;50</th>
<th>Age &gt;50</th>
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<tr>
<td></td>
<td>^1.5 – ^1.67%</td>
<td>&gt;2.5%</td>
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<td>&gt;2.5%</td>
<td>&gt;5.0%</td>
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Raloxifene vs. Tamoxifen

- **Pro raloxifene**
  - Equivalent reduction in IBC
  - Less thromboembolism, uterine cancer, and cataracts
  - Primary care comfort with therapy

- **Con raloxifene**
  - No reduction in DCIS/LCIS: long-term follow-up concerns
  - Post-menopausal women only
  - Generic tamoxifen less $$$

Case: Ana

- 34 year old woman born in Mexico
- My mother’s fine and I don’t have a sister.
- But my dad had 4 sisters, 2 of whom developed breast cancer and my paternal grandmother also had breast cancer
- 5-year Gail risk = .31%

5-year Gail比例可能对…有利

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<th>5 年Gail</th>
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<th>年龄 &gt;50</th>
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<td>&gt;=1.5 – &gt;=1.67%</td>
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<td>&gt;=2.5%</td>
<td>&gt;=5.0%</td>
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The Gail Model Can Underestimate Hereditary Risk of Breast Cancer

Features that indicate increased likelihood of BRCA mutations
- Multiple cases of early onset breast cancer
- Ovarian cancer
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer

BRCA1/2 Mutations Increase the Risk of Early-Onset Breast Cancer

Population Risk  | 0.5%  | 2%  | 7%
Hereditary Risk  | 10%-20%  | 33%-50%  | 56%-87%
Surgical strategies for women with BRCA mutations

- Risk-reducing oophorectomy (RRSO)
  - 50% reduction in breast cancer
- Risk-reducing mastectomy (RRM)
  - 90% - 95% risk reduction

Rebbeck, NEJM 2002
Kauf, NEJM 2002
Rebbeck, JNCI 1999
Rebbeck,

Abnormal Mammogram

- Cumulative risk of false positive result: 49% after ten mammograms
  Elmore et al NEJM 1998
- False positive rates highest for women in their 40’s and 50’s

<table>
<thead>
<tr>
<th>Age Group</th>
<th>40-49y</th>
<th>50-59y</th>
<th>60-69y</th>
<th>70-79y</th>
<th>80-89y</th>
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Case

- Your patient AH, a 56 yo woman, goes for her screening mammogram. A few days later, you get a call from the radiologist. The mammogram shows increased density and possibly a calcification on the right. The radiologist says they are reading it as a BIRADS 0 and the patient should get follow-up, could you please let her know?
What kind of follow-up does this patient need next?

1. A repeat mammogram in 3-6 months
2. A mammogram at the usual screening interval
3. A diagnostic mammogram with spot-compression views
4. A referral to the breast surgeon/clinic for a biopsy

American College of Radiology BIRADS category (breast imaging reporting and data system)

Normal
1: negative routine follow-up
2: benign finding routine follow-up

Abnormal
0: indeterminate immediate follow-up
3: low chance malignancy (~2%) short interval follow-up (3-6 months repeat mammogram)
4: >2-95% chance malignancy (a: low; b: intermediate; c: moderate) biopsy
5: ≥95% chance invasive malignancy biopsy

MQSA: Mammography Quality Standards Act
• Passed by U.S. Congress in 1992
• Mammography facility must send patient written report of her mammogram within 30 days of exam
• Report must be in words she can easily understand
• For BIRADS 4 or 5 results, facility expected to contact patient as soon as possible – ‘expectation’ within 5 days
• If verbal contact, still need to send letter

Communication Matters
• Adequate communication of abnormal results improves receipt of appropriate follow-up
  Poon et al, JGIM 2004
• Minority women report lower rates of adequate communication, and are less likely to know their abnormal mammogram results
  Zapka et al, Prev Med 2004
• Women who received their results verbally (in person or over the telephone) more likely to know that their mammogram was abnormal
  Karliner et al, JGIM 2005
Delays in Diagnosis

- 20-40% women undergoing breast cancer diagnosis experience delays to diagnosis or treatment
- Delay of ≥3 months (symptoms to treatment) associated with 12% lower 5-year survival
  - Most of this attributable to later stage disease
  Richards et al, Lancet 1999
- African-American women are more likely to suffer delays than White women
  Elmore et al, Med Care 2005
- Hospitals disproportionately serving non-English speaking and minority women have longer delays
  Karliner et al, Med Care 2011

Causes of Delay

- Mammogram Facility
  - Resource issues
  - Tracking systems
  - Appointment access
- Communication
  - Physician inaction (not contacting patient; not ordering follow-up tests)
  - Inadequate communication of abnormal results and need for follow-up
  - Language barriers
- Patient
  - Patient inaction (lack of knowledge / understanding, fear, anxiety)

Case: Gwen

- You are seeing Gwen, a 50-year-old Chinese-American woman, for her routine annual exam. She tells you about a new lump she found in her breast, which you feel and find to be firm with regular borders.
- You send her for a diagnostic mammogram which shows an area of calcification BIRADS 4 and next she undergoes a core biopsy.

What Pathologic Staining Findings are Indicative of the Poorest Prognosis Tumor?

1. ER/PR positive staining
2. ER/PR and HER2Neu positive staining
3. ER/PR/HER2Neu negative staining
Hormone Receptors and HER2
- Assay for estrogen, progesterone receptors and HER2
  - Perform on core biopsy specimen
  - If negative on core specimen, should be repeated at definitive surgery:
    - up to 15% of cases with negative markers on biopsy specimen will be positive on larger surgical specimen
- ER/PR + cancers responsive to anti-estrogen therapy
- Over-expression of HER2/neu oncogene
  - worse prognosis
  - responsive to trastuzumab (Herceptin)

Poor Prognosis Tumors
- Triple negative tumors
  - ER-/PR-/HER2-
  - Unresponsive to anti-estrogen therapy and trastuzumab
  - Neo-adjuvant chemotherapy
  - Clinical trials investigating immune modulators and receptor-blockers for growth factors
- African Americans, Latinas and BRCA1 carriers more at risk for triple negative tumors

Sentinel Lymph Node Biopsy
- Initial standard axillary staging procedure for invasive breast cancer
- SLN: any node receiving drainage directly from the primary tumor (can be >1)
- Technetium-labeled sulfur colloid or vital blue dye injection around tumor / biopsy cavity / subareolar
- Identifies SLN in 92-98% of patients
- 97.5-100% concordance with complete axillary lymph node dissection (ALND)

SLN biopsy and survival
- RCT of 5,611 women with invasive breast CA, 8-years of follow-up

<table>
<thead>
<tr>
<th></th>
<th>ALND in +SLN only</th>
<th>ALND in all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>90.3%</td>
<td>91.8%</td>
</tr>
<tr>
<td>Disease Free Survival</td>
<td>81.5%</td>
<td>82.4%</td>
</tr>
</tbody>
</table>

Krag et al, Lancet Oncology 2010
If SLN negative then can avoid axillary dissection
SLN and Survival

- If SLN positive – medical necessity of ALND is at question –
  - RCT of no further axillary treatment vs. ALND
  - T1-T2 invasive breast cancer, no palpable adenopathy,
    1-2 SLN with mets
  - No difference in 5-year overall or disease free survival
  - Only able to enroll half target (891/1900 women)
    Giuliano et al, JAMA 2011
- When ALND required, standard: removal of at least 6-10 nodes (level I and II dissection)

Gene Expression Profiling

- Goal: improve risk stratification in early stage breast cancer to better tailor use of chemotherapy
- Used to classify tumor according to recurrence risk and to predict response to chemotherapy
- Oncotype Dx best studied
  - HR+, LN- <5cm tumors
  - Recurrence risk low (<18) no benefit from chemo
  - Recurrence risk high (>30) + benefit from chemo
- Ongoing RCTs using Oncotype Dx (TAILORx) and Mammaprint (MINDACT)

Metastatic Work-up

**Mets are rare without symptoms**

- Physical exam: breasts, skin, lymph nodes, abdomen
- Diagnostic bilateral mammography; possible breast MRI
- CBC, LFTs
- Chest x-ray; possibly CT pre-radiation
- Staging CT – liver, pelvis, chest – and bone scan in stage III disease and above

Summary

Risk Assessment & Reduction

- Lifestyle
  - Exercise, weight loss or maintenance
  - Minimize alcohol
  - Avoid/stop HT (2-year max)
  - Low fat diet?
- Use risk assessment to weigh risk/benefit of SERMS
- Assess familial risk
  - Refer to genetic counseling / high risk breast clinic
Summary

Tests at Diagnosis

- Delays in diagnosis are common after an abnormal mammogram
  - Improved communication of abnormal results improves receipt of appropriate follow-up
- SLN biopsy can help avoid axillary dissection and results can help determine need for chemo
- Stay-tuned on gene expression profiling of tumor to help determine treatment
- Metastases are rare without symptoms