Hereditary Multifocal Breast Cancer

Farin Amersi M.D., F.A.C.S
Division of Surgical Oncology
Department of Surgery
Cedar Sinai Medical Center
CASE STUDY

- 30 year old Ashkenazi Jewish woman
- Nulliparous
- Felt left breast mass while showering
- Gynecologist referred for mammo and U/S
- Mammogram: no architectural distortion or mass
- Ultrasound: solid mass in left breast at 3 o’clock
CASE STUDY

- Physical Examination:
  - Palpable 5 cm mass left breast
  - No left axillary adenopathy
  - No masses right breast or axillary adenopathy
- core biopsy of palpable mass
Left breast core biopsy

- High grade ductal carcinoma in situ
Case Study

- **Core biopsy:**
  - DCIS
    - High grade, without necrosis
    - ER 96%/ 3+ and PR 69%/2+

- **Risk factors:**
  - Multiple family members with breast and ovarian cancer
  - BRCA testing: positive for BRCA 2 mutation

- **Further Imaging:**
  - Breast MRI
  - PET/CT
CASE STUDY

- MRI and PET/CT findings:
  - 4 or 5 lesions suspicious for invasive cancer

- Next Steps?
  - Biopsy all other lesions in breast?
  - Proceed to mastectomy?
    - Unilateral vs bilateral?

- Procedure: bilateral mastectomy – pathology
Mass #1

- **Upper Inner**
- **Size = 1.1 cm**
- **ER+/ PR-/ Her2 +**
- **MBR = II/III**
  - Tubules 1
  - Grade 3
  - Mitosis 2
Mass #2

- Lower Inner
- Size = 1.5 cm
- ER-/PR-/Her2 -
- MBR III/III
  - Tubules 3
  - Grade 3
  - Mitosis 3
Mass #3

- Mid lateral
- Size 3.0 cm
- ER+/PR+/HER2-
- MBR III/III
  - Tubules 2
  - Grade 3
  - Mitosis 3
Mass #4

- Upper Outer
- Size 3.0
- ER+/PR+/Her2+
- MBR
  - Tubule 1
  - Grade 3
  - Mitosis 2
DCIS

- Intermediate and high grade, solid and cribriform
- Multifocal admixed with and away from invasive components
- Margins negative
- Lymph nodes negative
Right breast
4 separate primary breast cancers, LN-

- 3cm, grade III – ER+/PR+/Her2 +
- 3cm, grade II- ER+/PR+/Her2 -
- 1.5 cm, grade III- ER-/PR-/Her2 -
- 1.1 cm, grade II- ER+/PR-/Her2 +
CASE STUDY

- **Risk of distant recurrence at 10 yrs** *(AdjuvantOnline)*
  - A) 3cm, grade III - 60% (or 40% no recurrence)
  - B) 3cm, grade II - 50%
  - C) 1.5 cm, grade III – 44%
  - D) 1.1 cm, grade II – 35%

- **What is her risk of any recurrence?**
  - Metastatic spread of any tumor (independent events)
  - Probability of no recurrence \( p(A) \times p(B) \times p(C) \times p(D) \)
  - Probability of any recurrence = 1 - p

(courtesy of Jim Mirocha, Biostatistics)
CASE STUDY

- Risk of distant recurrence at 10 yrs (AdjuvantOnline)
  - A) 3cm, grade III - 60% (or 40% no recurrence)
  - B) 3cm, grade II - 50%
  - C) 1.5 cm, grade III – 44%
  - D) 1.1 cm, grade II – 35%

- What is her risk of any recurrence?
  - Probability of no recurrence $p(A) \times p(B) \times p(C) \times p(D)$
    - $.4 \times .35 \times .56 \times .65 = .07$
CASE STUDY

- Risk of distant recurrence at 10 yrs (AdjuvantOnline)
  - A) 3cm, grade III - 60% (or 40% no recurrence)
  - B) 3cm, grade II - 50%
  - C) 1.5 cm, grade III – 44%
  - D) 1.1 cm, grade II – 35%

- What is her risk of any recurrence?
  - Probability of no recurrence $p(A) \times p(B) \times p(C) \times p(D)$
    - $.4 \times .5 \times .56 \times .65 = .07$
  - Probability of ANY recurrence = .93, or 93%
CASE STUDY

- Risk of distant recurrence at 10 yrs (AdjuvantOnline)
  - A) 3cm, grade III - 60% (or 40% no recurrence)
  - B) 3cm, grade II - 50%
  - C) 1.5 cm, grade III – 44%
  - D) 1.1 cm, grade II – 35%

- What is her risk of any recurrence?
  - Probability of no recurrence $p(A) \times p(B) \times p(C) \times p(D)$
    - $.4 \times .5 \times .56 \times .65 = .07$
  - Probability of ANY recurrence = .93, or 93%
  - Risk reduced by Tam + 3rd gen chemotx + Herceptin~ 70%
Tamoxifen

- Approved 1986
  - Hormone receptor (ER and PR) positive breast cancers
- Antagonistic and agonistic actions on the estrogen receptor (ER)
- Adjuvant endocrine agent of choice for premenopausal, ER/PR positive patients
Her-2/Neu Positive Breast Cancers

- Over expression of Her-2/neu protein or amplification of Her-2 gene occurs in 15 to 25% of breast cancers
  - More aggressive tumor biology

- Herceptin (Trastuzumab) therapy established as beneficial in metastatic disease
  - Monoclonal antibody against anticellular domain of HER2
Breast Cancer

- Most frequently diagnosed cancer in women

- ACS reports 182,460 new cases of invasive breast cancer, and 67,770 cases of in-situ breast cancer in 2008

- 1 in 7 will develop breast cancer in their lifetime

- Second most common cause of cancer death in women
Risk Factors for Breast Cancer

- Age
- Family history of breast cancer
- Inheritance of a genetic mutation
- Radiation to the chest
- History of atypical ductal hyperplasia on a breast biopsy
- Long menstrual history
- Nulliparous (never having children)
- Use of oral contraception/hormonal therapy after menopause
Signs and Symptoms of Breast Cancer

- Abnormality of mammogram
- Palpable, painless mass
- Skin thickening
- Skin dimpling
- Skin redness, ulceration, scaling
- Nipple ulceration, scaling
- Spontaneous bloody nipple discharge
General Features of Hereditary Cancer

- Cancer diagnosed at a young age (<50)
- Uncommon/unusual cancers (e.g. ovarian, male breast)
- Multiple primary cancers in the same individual
- Combination of certain cancers in a family (e.g. breast and ovarian, colon and uterine, melanoma and pancreatic)
Hereditary Breast and Ovarian Cancer

- BRCA1 (52%)
- BRCA2 (32%)
- Other genes
- 15-20% Sporadic
- 15-20% Hereditary

A BRCA Mutation Increases Breast and Ovarian Cancer Risks

- Breast cancer by age 50: 2% (General Population), Up to 50% (BRCA Mutation)
- Breast cancer by age 70: 7% (General Population), Up to 87% (BRCA Mutation)
- Ovarian cancer by age 70: <2% (General Population), Up to 44% (BRCA Mutation)
A BRCA Mutation Increases Risk of Second Cancer

- Ovarian Cancer
  - General Population: ~5%
  - BRCA Mutation: 16%
  - * no statistic available

- Breast Cancer after 5 yrs
  - General Population: ~5%
  - BRCA Mutation: 27%

- Breast Cancer by age 70
  - General Population: ~11%
  - BRCA Mutation: Up to 64%
Prevalence of BRCA Mutations

<table>
<thead>
<tr>
<th>Patient’s History</th>
<th>Family History</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No breast or ovarian cancer</td>
<td>No breast cancer &lt;50 or ovarian cancer</td>
<td>Breast cancer &lt;50, no ovarian cancer</td>
</tr>
<tr>
<td>No breast or ovarian cancer</td>
<td>2.8%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Breast cancer &lt;50</td>
<td>9.8%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Ovarian cancer, no breast cancer</td>
<td>14.8%</td>
<td>23.1%</td>
</tr>
</tbody>
</table>
## Prevalence of Mutations in Ashkenazi Jewish Individuals

<table>
<thead>
<tr>
<th>Patient’s History</th>
<th>Family History</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No breast or ovarian cancer</td>
<td>No breast cancer &lt;50 or ovarian cancer</td>
<td>6.9%</td>
<td>13.7%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Breast cancer &lt;50</td>
<td>Breast cancer &lt;50, no ovarian cancer</td>
<td>14.0%</td>
<td>24.2%</td>
<td>38.8%</td>
</tr>
<tr>
<td>Ovarian cancer, no breast cancer</td>
<td>Ovarian cancer in one relative, no breast cancer &lt;50</td>
<td>22.2%</td>
<td>37.0%</td>
<td>42.0%</td>
</tr>
</tbody>
</table>
“Red Flags” for Hereditary Breast and Ovarian Cancer

- Breast cancer before age 50
- Ovarian cancer at any age
- Male breast cancer at any age
- Ashkenazi Jewish ancestry
- Every woman with simultaneous breast cancers
- Every woman who develops a second breast cancer
- Every first degree relative in a family where a positive test has been found
## Surveillance for Breast Cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age to begin</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast self-exam</td>
<td>18 yrs</td>
<td>Monthly</td>
</tr>
<tr>
<td>Clinical breast exam</td>
<td>25 yrs</td>
<td>Twice a year</td>
</tr>
<tr>
<td>Mammography</td>
<td>25 yrs</td>
<td>Yearly</td>
</tr>
<tr>
<td>MRI</td>
<td>25 yrs</td>
<td>Yearly</td>
</tr>
</tbody>
</table>
Prophylactic Mastectomy

Greater than 95% breast cancer risk reduction in BRCA carriers
Surveillance for Ovarian Cancer

- CA-125
- Pelvic exams
- Transvaginal ultrasound

*Additional screening techniques under investigation due to limited efficacy of current options*
Prophylactic Oophorectomy

Recommend bilateral salpingo-oophorectomy (BSO) at age 35 or after childbearing is complete

- ~98% ovarian cancer risk reduction in BRCA carriers
- Can reduce breast cancer risk by up to 68% for both BRCA1 and BRCA2 mutation carriers
Surgical Options for the Breast

- Mastectomy
  - Radical Mastectomy
  - Modified Radical Mastectomy
  - Total Mastectomy

- Breast Conservation Therapy (BCT)
  - Quadrantectomy
  - Segmental Mastectomy
Halstedian Theory

- 1890’s

- Breast cancer spreads in step-wise fashion:
  - primary tumor $\rightarrow$ regional lymphatics $\rightarrow$ distant sites

- Radical resections advocated
Radical Mastectomy

- **En bloc resection**
  - Breast
    - Skin
    - Nipple
    - Areola
  - Pectoralis muscle
  - Axilla
    - Full axillary lymph node dissection
Radical Mastectomy
Fisher’s Theory

- 1960’s and 1970’s

- Argument:
  - Systemic disease from inception
  - Challenged necessity of radical procedures
Modified Radical Mastectomy

- **En bloc resection:**
  - Breast
    - Skin
    - Nipple
    - Areola
  - Axilla
    - Full axillary lymph node dissection
- Pectoralis muscle spared
Modified Radical Mastectomy
NSABP B-04

- 1971 to 1974
- 25 year follow-up published in 2002

- Comparison of radical versus total mastectomy
NSABP B-04

- Clinically node negative patients:
  - Radical mastectomy
  - Total mastectomy with axillary radiation
  - Total mastectomy without radiation

- Clinically node positive patients:
  - Radical mastectomy
  - Total mastectomy with axillary radiation
NSABP B-04

- Equivalency among all groups:
  - Disease-free survival
  - Distant-disease-free survival
  - Over-all survival

- “Variations in local and regional treatment—from radical to conservative—all involving removal of the breast, result in the same outcome.”
Total Mastectomy

- **En bloc resection**
  - Breast
    - Skin
    - Nipple
    - Areola

- **Axilla**
  - Sentinel node biopsy
    - Axillary lymph node dissection if SLND positive
Total Mastectomy
Breast Conservation Therapy (BCT)

- Removal of cancer without sacrifice of remainder of breast
  - negative surgical margins
  - radiation therapy to breast

- Terminology:
  - Quadrantectomy
  - Lumpectomy
  - Partial Mastectomy
Segmental Mastectomy
NSABP B-06

- 1976 to 1984
- 3 treatment arms:
  - Total mastectomy and axillary node dissection
  - Lumpectomy and axillary node dissection with/without breast irradiation
- 20 year follow-up published in 2002
NSABP B-06

- Mastectomy and lumpectomy equivalent:
  - Disease-free survival
  - Distant-disease-free survival
  - Overall survival

- Breast irradiation required after lumpectomy
# In-Breast Recurrence

<table>
<thead>
<tr>
<th>Risk</th>
<th>Breast conservation therapy</th>
<th>Mastectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>10 to 15%</td>
<td>1 to 3%</td>
</tr>
</tbody>
</table>
BCT Contraindications

- **Absolute:**
  - Multicentric disease
  - Multifocal disease
  - Prior breast irradiation
  - Persistent positive margins after resection
  - Patient choice
  - History of collagen vascular disease
    - Active SLE
    - Scleroderma

- **Relative:**
  - History of other collagen vascular diseases
  - Large tumor in a small breast
  - Breast size
  - Pregnancy
Post-Mastectomy Reconstruction

- Two main types of constructs:
  - Expander, followed by implant

- Autologous tissue transfers:
  - TRAM flap
  - DIEP flap
  - Latismus dorsi flap
  - Gluteal flaps
Expander Reconstruction
Tissue Reconstruction
TRAM Flap Reconstruction

- Appearance immediately after surgery
- Appearance following nipple reconstruction and tattooing

- Mastectomy scars
- Skin and fat of tram flap
- Tram incision
- Skin from abdomen used to replace missing breast skin