Assessment and Management of Hereditary Breast Cancer Risk

Joanne Jeter, MD
February 14, 2013
Objectives

• Who needs genetic evaluation?
• What are some considerations for counseling for genetic testing?
• What are some hereditary cancer syndromes associated with increased risk of breast cancer?
• How are individuals at increased risk for breast cancer managed?
Cancer Incidence, US, 2012

<table>
<thead>
<tr>
<th>Estimation of New Cases*</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>241,740</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,470</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>73,420</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>55,600</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>44,250</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,250</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>38,150</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>28,540</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>26,830</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,090</td>
<td>3%</td>
</tr>
<tr>
<td>All Sites</td>
<td>848,170</td>
<td>100%</td>
</tr>
<tr>
<td>Breast</td>
<td>226,870</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>109,590</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>70,040</td>
<td>9%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>47,130</td>
<td>6%</td>
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<tr>
<td>Thyroid</td>
<td>43,210</td>
<td>5%</td>
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<tr>
<td>Melanoma of the skin</td>
<td>32,000</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>31,970</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>24,520</td>
<td>3%</td>
</tr>
<tr>
<td>Ovary</td>
<td>22,280</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,830</td>
<td>3%</td>
</tr>
<tr>
<td>All Sites</td>
<td>790,740</td>
<td>100%</td>
</tr>
</tbody>
</table>
# Cancer Deaths, US, 2012

## Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>87,750</td>
<td>72,590</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,170</td>
<td>39,510</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,470</td>
<td>25,220</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,850</td>
<td>18,540</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>13,980</td>
<td>15,500</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,500</td>
<td>10,040</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,040</td>
<td>8,620</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,510</td>
<td>8,010</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,320</td>
<td>6,570</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,650</td>
<td>5,980</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>301,820</td>
<td>275,370</td>
</tr>
</tbody>
</table>

CA: A Cancer Journal for Clinicians; 2012
Major Breast Cancer Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germline mutations</td>
<td>10-20</td>
</tr>
<tr>
<td>Chest radiation under 30</td>
<td>5-20</td>
</tr>
<tr>
<td>Age (30 vs 60)</td>
<td>10</td>
</tr>
<tr>
<td>Prior breast/ovarian cancer</td>
<td>2-10</td>
</tr>
<tr>
<td>Intraepithelial neoplasia</td>
<td>2-10</td>
</tr>
<tr>
<td>1° relative dx &lt; 60</td>
<td>2</td>
</tr>
</tbody>
</table>
Breast Cancer Risk Factors

- Older age
- Family history of breast cancer
- Personal history of specific benign breast conditions (e.g., atypical hyperplasia, lobular carcinoma in situ)
- Early menarche, nulliparity/late first birth, late menopause
- Radiation exposure
- Menopausal hormonal therapy
- Alcohol use
- High-fat diet (possible)
Risk Factors for Ovarian Cancer

- Older age
- Personal history of early-onset breast cancer
- Family history of ovarian, breast, endometrial, or colon cancer
- Early menarche, nulliparity, late menopause
- Long-term use of estrogen-only replacement therapy
How Much Breast and Ovarian Cancer Is Hereditary?

Breast cancer
- Sporadic: 85%–90%
- Family clusters: 5%–10%
- Hereditary: 15%–20%

Ovarian cancer
- Sporadic: 90%
- Hereditary: ~10%
Causes of Hereditary Susceptibility to Breast Cancer

Families with site-specific breast cancer

- BRCA1: 37%
- BRCA2: 28%
- Other genes or unknown: 35%

Families with breast/ovarian cancers

- BRCA1: 80%
- BRCA2: 15%
- Other genes or unknown: 5%

# Prevalence of BRCA Mutations

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1 in 400 (~0.25%)</td>
</tr>
<tr>
<td>Women w/ breast cancer</td>
<td>1 in 50 (2%)</td>
</tr>
<tr>
<td>Women w/ breast cancer (&lt;40 y/o)</td>
<td>1 in 10 (10%)</td>
</tr>
<tr>
<td>Men w/ breast cancer</td>
<td>1 in 20 (5%)</td>
</tr>
<tr>
<td>Women w/ ovarian cancer</td>
<td>1 in 8 - 1 in 10 (10%–15%)</td>
</tr>
<tr>
<td>Ashkenazi Jewish population</td>
<td>1 in 40 (2.5%)</td>
</tr>
<tr>
<td>Ashkenazi Jewish women w/ breast cancer</td>
<td>1 in 10 (10%)</td>
</tr>
<tr>
<td>Hispanic women w/breast cancer</td>
<td>3.5%</td>
</tr>
<tr>
<td>Cancer</td>
<td>General Population</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Breast</td>
<td>11-12%</td>
</tr>
<tr>
<td>2nd Breast</td>
<td>0.8% - 1.5%/yr</td>
</tr>
<tr>
<td>Ovary</td>
<td>1-2%</td>
</tr>
<tr>
<td>Prostate</td>
<td>5%</td>
</tr>
<tr>
<td>Male Breast</td>
<td>0.1%</td>
</tr>
</tbody>
</table>
“Red Flags” for Hereditary Cancers

• Earlier age than would be expected
• Bilateral disease
• Multiple cancers in the same individual
• More than 2 family members with the same cancer on same side of family
• Evidence of autosomal dominant inheritance of associated cancers in pedigree
# Age at Cancer Diagnosis

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Hereditary Cancers</th>
<th>Sporadic Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>41</td>
<td>62</td>
</tr>
<tr>
<td>Ovarian</td>
<td>40-50</td>
<td>60</td>
</tr>
<tr>
<td>Prostate</td>
<td>63</td>
<td>71</td>
</tr>
</tbody>
</table>
Autosomal Dominant Inheritance

- Each child has a 50% chance of inheriting the mutation
- No "skipped generations"
- Equally transmitted by men and women
When should the family history be taken?

- Initial visit of the patient
- Genetic testing is sometimes used in decision making for the initial management of breast cancer
- Important to check for updates on a regular basis!
Who should be evaluated?

Individuals with:
- Early-onset breast cancer
  - <45 if no relatives
  - <50 if relatives with breast cancer or limited hx
- Two primary breast cancers (1st <50)
- Triple negative breast cancer (<60)
- Breast cancer and close male relative with breast cancer
- Both breast and ovarian cancer
- Breast cancer and >1 close relative with breast and ovarian cancer from the same side of the family
Who should be evaluated?

Individuals with:

• Breast cancer and Ashkenazi Jewish ancestry
• Ovarian/primary peritoneal/fallopian tube cancer
• Male breast cancer
• Breast or ovarian cancer and > 1 relative with pancreatic cancer
• Pancreatic cancer and > 1 relative with breast, ovarian, or pancreatic cancers

## BRCA in Ashkenazim

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1 in 400 (~0.25%)</td>
</tr>
<tr>
<td>Ashkenazi Jewish (AJ) population</td>
<td>1 in 40 (2.5%)</td>
</tr>
<tr>
<td>AJ women w/ breast cancer</td>
<td>1 in 10 (10%)</td>
</tr>
<tr>
<td>AJ Women w/ breast cancer (&lt;40 years)</td>
<td>1 in 3 (30%–35%)</td>
</tr>
<tr>
<td>AJ Men with breast cancer</td>
<td>1 in 5 (19%)</td>
</tr>
<tr>
<td>AJ Women w/ovarian cancer or primary peritoneal cancer</td>
<td>1 in 3 (36%–41%)</td>
</tr>
</tbody>
</table>
BRCA in Ashkenazim

- 3-mutation panel accounts for up to 96% of mutations in Ashkenazim
- Some recommend testing regardless of personal or family history
- NCCN recommends testing of AJ women with breast or ovarian cancer at any age
BRCA & Triple-Negative Breast Cancer

- Triple-negative tumors associated w/BRCA1
- Recent abstract reported ~20% of women w/triple negative tumors had BRCA mutations
- Cost-benefit analyses support testing women with triple-negative breast cancer diagnosed before 50
- No change in NCCN recs to date
BRCA Mutations in Hispanics

- May not be accurately predicted using current models
  - Expected Prevalence: 19.6%
  - Observed Prevalence: 30.9% (Weitzel 2005)
- Are more likely to be variants of uncertain significance
  - Up to 23% of high-risk families
- May not be detected by standard testing by sequencing
  - Deletion of BRCA1 exons 9-12
BRCA Mutations in Hispanics

• Have some similarities to those found in Ashkenazi Jews
  • BRCA1185delAG
  • BRCA1 5382insC

• May soon be detected by specific panel of mutations
  • 18-mutation multiplex panel with 57% sensitivity

(Volker 2009)
Li-Fraumeni Syndrome

- Early onset of breast cancer, sarcoma, adrenocortical carcinoma, brain tumors, lung cancer, leukemia
- Associated with mutations in TP53, ?CHEK2
- Specific diagnostic criteria
Tumor Sites in Families with TP53 Germline Mutations

- Breast: 24%
- Bone: 12.6%
- Brain: 12%
- Soft tissue: 11.6%
- GI: 7%
- Gynecol: 5.3%
- Hematol: 4.2%
- Adrenal: 3.6%
- Other: 14.1%

% of all tumors

Cowden Syndrome

- Incidence: 1 in 200,000—although this figure is probably an underestimate
- Autosomal dominant inheritance
- *PTEN* gene on chromosome 10q23
- Pathognomonic mucocutaneous lesions
  - Facial trichilemmomas (Fig 1)
  - Papillomas of face, lips, tongue, oral mucosa (Figs 2 and 3)
  - Acral keratoses (Fig 4)
- Lifetime risk of breast cancer estimated to be between 25% and 50%

Fig 1  Fig 2  Fig 3  Fig 4
Cowden Syndrome Diagnostic Criteria

**Major Criteria**
- Breast cancer
- Thyroid cancer
- Endometrial cancer
- Macrocephaly
- Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma)

**Minor Criteria**
- Other thyroid lesions
- Mental retardation
- Hamartomatous intestinal polyps
- Fibrocystic breasts
- Lipomas
- Fibromas
- GU tumors or malformations
Peutz-Jeghers Syndrome

- Autosomal dominant
- *STK11* gene on chromosome 19
- GI hamartomas
- Characteristic pigmentation
- 93% overall cancer risk by age 65 years
- Cancers include colon, breast, pancreas, stomach, ovaries, and others


Photo courtesy of Patrick M. Lynch, JD, MD.
Other Cancers in Peutz-Jeghers Syndrome

Cost-Effectiveness for Testing for Breast/Ovarian Cancer Risk

- BRCA testing for all breast cancer patients < 50 gave unfavorable ICERs.
- Testing women with TN breast cancers < 50 y/o gave an ICER of $8,027/year of life gained ($9,084/QALY), and could reduce subsequent breast and ovarian cancer risks by 23% and 41%.
- In ovarian cancer patients, BRCA testing based on personal/family history and ancestry could prevent future cases in FDRs with an ICER of $32,018 / year of life gained.
Utilization of Genetic Testing

- 30% of women with breast cancer diagnosed at < 41y/o received BRCA1/2 testing.
- Women of Jewish ethnicity were significantly more likely to be tested (HR= 2.83, 95% CI: 1.52-5.28)
- Black women (HR= 0.34, 95% CI 0.18-0.64) and Hispanic women (HR= 0.52, 95% CI: 0.33-0.81) were significantly less likely to be tested than non-Jewish white women.
- Those in an HMO were significantly less likely to receive testing than those in point of service insurance plans. (HR= 0.73, 95% CI: 0.54-0.99)

Awareness of Genetic Testing

• Percentage reporting awareness of genetic testing:
  • 48% of non-Hispanic whites
  • 31% of blacks
  • 28% of Asians
  • 19% of Hispanics.

• Education, nativity/length of residency, residential region were major factors in this discrepancy.

Guidelines for Genetic Testing

- ASCO Recommends Genetic Testing When:
  - The individual has a personal or family history of features suggestive of a genetic cancer susceptibility condition
  - The test can be adequately interpreted
  - The results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk for cancer
Testing the Right Person

= Breast CA

(Many)

dx. 60

dx. 60

40

Bilateral dx.

45
ASCO Statement

“Oncologists should consider offering genetic testing only if they are able to provide or make available adequate genetic education and counseling as well as access to preventive and surveillance options. Otherwise, they should consider referring the patient and family for these services.”
What should be covered in pre-test counseling?

• Information on the specific test being performed
• Implications of a positive and negative result
• Possibility that the test will not be informative
• Options for risk estimation without genetic testing
• Risk of passing a mutation to children
• Technical accuracy of the test
What should be covered in pre-test counseling?

- Fees involved in testing and counseling
- Psychological implications of test results (benefits and risks)
- Risks of insurance or employer discrimination
- Confidentiality issues
- Options and limitations of medical surveillance and strategies for prevention
- Importance of sharing genetic test results with at-risk relatives
What should be covered in post-test counseling?

• Assess patient response to results disclosure
• Review meaning of result
• Discuss plans for sharing result with family members
• Discuss plan for medical follow-up
• Provide access to updated risk information
Possible BRCA Test Outcomes

Definitive:
- True positive: Deleterious mutation identified
- True negative: Known family mutation not identified in tested individual

Uninformative:
- No mutation found in individual and no mutation identified in family
- Variant of uncertain significance
Benefits of BRCA Testing

- Identifies high-risk individuals
- Identifies noncarriers in families with known mutation
- Allows early detection and risk reduction strategies
- May relieve anxiety
Risks and Limitations of BRCA Testing

• Does not detect all mutations; therefore cannot definitively rule out hereditary risk
• True negatives are still at population risk of breast and ovarian cancer
• Efficacy of some interventions is not well established
• May result in anxiety or survivor guilt
• May heighten concerns about insurance
Insurance Discrimination Legislation

• Health Insurance Portability and Accountability Act (HIPAA)
  • Protects those with group health insurance from being denied coverage or having to pay a higher rate

• Genetic Information Nondiscrimination Act (GINA)
  • Prohibits discrimination by employers and health insurers on basis of genetic tests
  • Effective May 2009

• Life or disability insurance remains an issue
Other Means of Breast Cancer Risk Assessment

• Gail Model (women >34 years old, no history of invasive or in situ cancer)
  http://www.cancer.gov/bcrisktool/

  -- Gives 5-year and lifetime risk
  -- Used to help determine if chemoprevention or MRI screening are appropriate

Caveat: Assessments for Hispanics are based on those for Caucasians in this model and are “subject to greater uncertainty.”
Management of BRCA Carriers Screening

• Breast self-examination
• Clinical breast exam q6mo starting at 25
• Annual mammography starting at 25
• Annual breast MRI starting at 25
• Transvaginal U/S q6mo starting at 35
• CA125 q6mo starting at 35
Management of BRCA Carriers
Surgical
• Prophylactic mastectomy
• Prophylactic oophorectomy
Management of BRCA Carriers
Chemoprevention

• Tamoxifen
• Raloxifene (postmenopausal)
• Other drugs?
Management of BRCA Carriers – Family Education

- Discussion/evaluation of at-risk family members for testing
- Each sibling or child has a 50% chance of having the mutation
- Men can carry the mutation as well
What are some resources?

• FORCE: Facing Our Risk of Cancer Empowered
  • [www.facingourrisk.org](http://www.facingourrisk.org)

• US Surgeon General – Family History Initiative
  • [www.hhs.gov/familyhistory/](http://www.hhs.gov/familyhistory/)

• The National Cancer Institute
  • [www.cancer.gov](http://www.cancer.gov)

• American Cancer Society
  • [www.cancer.org](http://www.cancer.org)
Pedigree – Surgeon General Tool
When to Refer?

- Suspicion of inherited cancer susceptibility syndromes
- Multiple affected family members in successive generations
- Early age of onset
- Multifocal or bilateral tumors
- Questions about cancer risk in offspring or extended family members
- Occurrence of cancer frequently associated with germ line mutations (ie. pheochromocytoma)
Research Studies

• Prevention study with letrozole in postmenopausal women at high risk
• Prevention study with vitamin D in premenopausal women at high risk
• Supplement study for women on tamoxifen for prevention
• Registry of individuals at high risk of cancers
Summary

• Identification of hereditary cancer syndromes can help prevent cancers or detect them early to improve outcomes.
• Decision making for genetic testing is a complex process with many considerations.
• Resources are available to aid in assessment and management of these patients.
• Research is ongoing to help prevent cancers in those at high risk.
Tucson Resources

• Joanne Jeter, MD – Medical Oncologist
• Christina Laukaitis, MD, PhD – Medical Geneticist
• Zoe Powis, MS, CGC and Gail Martino, MS, CGC
  Genetic Counselors 520-694-0800
• UA Cancer Center 520-694-CURE (694-2873)