Cancer Risks and Management Options for Genetic Mutation Carriers

Allison W. Kurian, M.D., M.Sc.
Director, Women’s Cancer Genetics Clinic
Associate Professor of Medicine and Health Research & Policy
Stanford University School of Medicine
## Disclosure Slide

<table>
<thead>
<tr>
<th>Company</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambry Genetics</td>
<td>Research collaboration, no funding</td>
</tr>
<tr>
<td>Color Genomics</td>
<td>Research collaboration, no funding</td>
</tr>
<tr>
<td>GeneDx</td>
<td>Research collaboration, no funding</td>
</tr>
<tr>
<td>Invitae</td>
<td>Research collaboration, no funding</td>
</tr>
<tr>
<td>Myriad Genetics</td>
<td>Research funding to my institution</td>
</tr>
</tbody>
</table>
Objectives

• Present cancer risks with inherited mutations
  – BRCA1 and BRCA2 (BRCA1/2)
  – Other newly identified gene mutations

• Outline risk-reduction options
  – Surgery
  – Screening
  – Medications

• Discuss strategies for decision-making
## Established Breast/Ovarian Cancer Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Relative Risk</th>
<th>Ovarian Relative Risk</th>
<th>Other Cancer Risks</th>
<th>U.S. Clinical Practice Guidelines (NCCN, ACS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>2 to 3-fold</td>
<td>Potential increase</td>
<td>Ataxia Telangiectasia Syndrome in homozygotes; maybe colon, pancreas, prostate</td>
<td>Screening breast magnetic resonance imaging (MRI), start at age 40; insufficient evidence to recommend risk-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(insufficient evidence)</td>
<td>reducing salpingo-oophorectomy (RRSO)</td>
</tr>
<tr>
<td>BARD1</td>
<td>Potential increase</td>
<td>Insufficient evidence</td>
<td>Uncertain</td>
<td>Insufficient evidence to guide management</td>
</tr>
<tr>
<td>BRCA1</td>
<td>10-fold</td>
<td>20 to 40-fold</td>
<td>Pancreas, prostate; melanoma</td>
<td>Breast MRI at 25, recommend RRSO by 40, discuss RR mastectomy (RRM)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>10-fold</td>
<td>10 to 20-fold</td>
<td>Pancreas, prostate; melanoma</td>
<td>Breast MRI at 25, recommend RRSO by 45, discuss RRM</td>
</tr>
<tr>
<td>BRIP1</td>
<td>Insufficient evidence</td>
<td>2 to 3-fold</td>
<td>Autosomal recessive risk to offspring</td>
<td>Consider RRSO at 45-50</td>
</tr>
<tr>
<td>CDH1</td>
<td>5-fold (lobular)</td>
<td>No increased risk</td>
<td>Gastric</td>
<td>Breast MRI at 30, discuss RR gastrectomy</td>
</tr>
<tr>
<td>CHEK2</td>
<td>2 to 3-fold</td>
<td>No increased risk</td>
<td>Colon; maybe thyroid (insufficient evidence)</td>
<td>Breast MRI at 40, earlier/more frequent colonoscopy</td>
</tr>
<tr>
<td>MLH1,</td>
<td>Insufficient evidence</td>
<td>5 to 10-fold</td>
<td>Colon, uterine, pancreas, others</td>
<td>Consider RRSO and hysterectomy, annual colonoscopy, biannual endoscopy</td>
</tr>
<tr>
<td>MSH2,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH6,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS2,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPCAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>2 to 3-fold</td>
<td>Insufficient evidence</td>
<td>Nijmegen Breakage Syndrome in homozygotes</td>
<td>Breast MRI at 40</td>
</tr>
<tr>
<td>NF1</td>
<td>2 to 3-fold</td>
<td>No increased risk</td>
<td>CNS, peripheral nerve sheath, GIST</td>
<td>Breast MRI at 30</td>
</tr>
<tr>
<td>PALB2</td>
<td>4 to 6-fold</td>
<td>Insufficient evidence</td>
<td>Pancreas</td>
<td>Breast MRI at 30, discuss RRM</td>
</tr>
<tr>
<td>PTEN</td>
<td>At least 5-fold</td>
<td>No increased risk</td>
<td>Thyroid, colon, renal, endometrial</td>
<td>Breast MRI at 30, discuss RRM, discuss hysterectomy</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Insufficient evidence</td>
<td>2 to 3-fold</td>
<td>Uncertain</td>
<td>Consider RRSO at 45-50</td>
</tr>
<tr>
<td>RAD51D</td>
<td>Insufficient evidence</td>
<td>2 to 3-fold</td>
<td>Uncertain</td>
<td>Consider RRSO at 45-50</td>
</tr>
<tr>
<td>STK11</td>
<td>At least 5-fold</td>
<td>Non-epithelial: 2 to 3-fold</td>
<td>Pancreas, colon, ovarian sex cord-stromal</td>
<td>Breast MRI at 25, discuss RRM</td>
</tr>
<tr>
<td>TP53</td>
<td>At least 10-fold</td>
<td>No increased risk</td>
<td>Sarcoma, leukemia, adrenocortical, brain, etc.</td>
<td>Breast MRI at 20, discuss RRM; whole-body MRI, colonoscopy/endoscopy, complete blood count, etc.</td>
</tr>
</tbody>
</table>
Cancer Risks with \textit{BRCA1/2}, Clinic-Based

- **BRCA1** Breast: 72%
- **BRCA2** Breast: 69%
- **BRCA1** Ovarian: 44%
- **BRCA2** Ovarian: 17%

- Prospective study of \textit{BRCA1/2} mutation carriers
- 94\% ascertained from high-risk clinics: may over-estimate risks of average patient
Cancer Risks with BRCA1/2, Population-Based

• Others: pancreas, melanoma, bile duct (<5%); prostate (20%); male breast (6%)
• Risks may vary with other genes (polygenic risk scores), mutation type

Chen J Clin Oncol 2007, Rebbeck JAMA 2015, Kuchenbaecker JNCI 2017
Changes in Remaining Risk with Age

Women “outlive” some of their lifetime cancer risk as they age

Chen J Clin Oncol 2007
Risks for Breast Cancer Survivors

- 25-year risk: 47% (39-56%)
  - \textit{BRCA1}: 1.6-fold > \textit{BRCA2}

- Earlier 1\textsuperscript{st} cancer: higher risk
  - Under age 40: 63% (50-75%)
  - Over age 50: 20% (5-34%)

Graeser J Clin Oncol 2009
Prophylactic Mastectomy (PM)

- Reduces breast cancer risk by 90-95%; mortality reduction reported
- Little data on comparative effectiveness of nipple or skin-sparing

Rebbeck J Clin Oncol 2004; Domchek JAMA 2010
Prophylactic Salpingo-Oophorectomy (PO)

- PO reduces ovarian cancer by 80%, death by 77%
- Estimated to reduce breast cancer risk by around 50% (age-dependent)

Finch JAMA 2006; Domchek JAMA 2010; Metcalfe J Clin Oncol 2014
Breast Cancer Screening

38 year old woman with a *BRCA1* mutation:

- Mammograms: sensitivity in range of 50%; many false-negatives
- Breast MRI: sensitivity in range of 80%; most cancers Stage 0-1

Mammogram: Dense tissue, no cancer seen

MRI: Central lesion, cancer on biopsy

Ovarian Cancer Screening?

- Ultrasound plus CA125, once or twice a year

- No benefit for the general U.S. population
  - Recent large PLCO trial showed no advantage

- No benefit for women with BRCA1/2 mutations
  - Does not find ovarian cancers earlier
  - Demonstrated by multiple studies

Preventive Medications

- **Tamoxifen**
  - Blocks estrogen stimulation of breast tissue; also used as treatment
  - 5 years’ use reduces breast cancer risk by 30-50%
  - Rare (0.1-0.8%) serious side effects: blood clots, uterine cancers

- **Raloxifene**
  - Similar efficacy to tamoxifen; better tolerated?
  - Little information about use by women with *BRCA1/2* mutations

- **Exemestane**
  - Aromatase inhibitor, also a treatment, for post-menopausal only
  - 3-5 years’ use reduced breast cancer by 65% in a recent trial
  - Little information about use by women with *BRCA1/2* mutations

Annual Screening Breast MRI: Guidelines

• >20% lifetime risk, or two-times the average in U.S.
  – Based on cost-benefit analyses (e.g., false positives)
  – Starting age varies (25 for BRCA1/2; 30-40 for ATM, CHEK2)

• Covered by U.S. insurers (e.g., Aetna, Blue Cross)
  – >20% as calculated by models (BRCAPRO, Tyrer-Cuzick)
  – Certain genes (ATM, BRCA1/2, CHEK2, PALB2, PTEN, TP53)
  – Atypical ductal/lobular hyperplasia or LCIS
  – Chest wall radiation aged 10-30

National Comprehensive Cancer Network, American College of Radiology, American Cancer Society
Prophylactic Surgery: Guidelines

• Discuss bilateral mastectomy:
  – BRCA1/2, PTEN, TP53
  – Insufficient evidence, manage based on family history: ATM, BARD1, BRIP1, CDH1, CHEK2, Lynch Syndrome genes, NBN, NF1, PALB2, RAD51C/D, STK11

• Recommend bilateral salpingo-oophorectomy:
  – BRCA1 (age 35-40), BRCA2 (age 40-45)

• Consider bilateral salpingo-oophorectomy:
  – BRIP1 (age 45-50), Lynch genes, RAD51C/D (age 45-50)
## Weighing the Pros and Cons

<table>
<thead>
<tr>
<th>PREVENTION</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
</table>
| Surgery    | The most effective risk-reduction:  
• PM 90-95%  
• PO: 50% breast, 85% ovarian | Invasive, irreversible; may affect:  
• Body image and sexuality  
• Fertility and menopausal side effects |
| Medications | Effective risk-reduction:  
• 30-50% with tamoxifen | Rare (1-8/1000) serious side effects:  
• Blood clots, uterine cancer |

## BREAST SCREENING

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
</table>
| Mammogram  | The most-studied screening test:  
• Fewer false-positives than MRI  
• Better than MRI for some DCIS? | Radiation exposure  
Misses some cancers:  
• Young, dense breasts, triple-negative |
| MRI  | Best at finding small cancers:  
• 80-90% in young, high-risk  
• Twice-yearly approach studied | Cost: 10 times > than mammogram  
• More false-positives, biopsies |

- No randomized trial has compared options (nor is likely to do so)
- How to compare many specific strategies?
Simulating Risk Reduction Strategies

- We built a computer simulation model to compare strategies:

- Estimated difference in survival between screening MRI and PM: 3-5%
- Consistent with an observational study

Online Tool to Guide Decision-Making

http://brcatool.stanford.edu

Kurian J Clin Oncol 2012
## Program Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>James Ford, M.D.</td>
<td>Director, Cancer Genomics</td>
</tr>
<tr>
<td>Allison Kurian, M.D., M.Sc.</td>
<td>Co-Director, Women’s Cancers</td>
</tr>
<tr>
<td>Uri Ladabaum, M.D.</td>
<td>Gastrointestinal Cancers</td>
</tr>
<tr>
<td>Kerry Kingham, M.S.</td>
<td>Lead Genetic Counselor</td>
</tr>
<tr>
<td>Nicolette Chun, M.S.</td>
<td>Genetic Counselor</td>
</tr>
<tr>
<td>Ashlie Miller, M.S.</td>
<td>Genetic Counselor</td>
</tr>
<tr>
<td>Courtney Rowe-Teeter, M.S.</td>
<td>Genetic Counselor</td>
</tr>
<tr>
<td>Rachel Hodan, M.S.</td>
<td>Genetic Counselor</td>
</tr>
<tr>
<td>Peter Levonian, M.S.</td>
<td>Genetic Counselor</td>
</tr>
<tr>
<td>Meredith Mills</td>
<td>Research Manager</td>
</tr>
<tr>
<td>Cindy Ma</td>
<td>Research Assistant</td>
</tr>
<tr>
<td>Alexandra Ooms</td>
<td>Research Assistant</td>
</tr>
</tbody>
</table>