Precision Prevention of Cancer: From Nucleotide to Neighborhood

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Equally Applied Cancer Prevention
Only Works if Everyone Is The Same

The Goal Should Be Equity In Outcome
Not All Individuals or Tumors Are the Same

• Complex, Multifactorial Etiology
• Heterogeneity
  • Intra-individual:
    • Genomic (mosaicism)
    • Tumor, metastasis
    • Age-dependent
  • Inter-individual
    • Histopathology
    • Genomic

Vogelstein, *Science* 2013

Lupski, *Science* 2013
What is “Precision” Prevention?

**Low Precision**
- Low Accuracy
- Prostate-PSA

**High Precision**
- Low Accuracy
- BRCA1/2-RRSO

**“Goal”**
- High Precision
- High Accuracy

- Focus: Low inter-individual and intra-tumor heterogeneity
- Usually genomics; could include geography, demographics, risk factors, pathology, residence, etc.
The *BRCA1/2* Example: Cumulative Cancer Risks to Age 70

Breast Cancer

**BRCA1**

- Risk: 57%

**BRCA2**

- Risk: 49%

Ovarian Cancer

**C**

- Risk: 40%

**D**

- Risk: 18%

Chen and Parmigiani *JCO* 2007
Personalizing Risk Assessment

• Risks may vary by:
  • Mutation
  • Modifier genes
  • Modifier exposures
  • Ethnicity

• Goal: Estimate personalized risks for improved decision-making: Discovery > Translation
Mutation-Specific Penetrances to Age 70: Examples

<table>
<thead>
<tr>
<th>BRCA2</th>
<th>Ovary</th>
<th>In-Frame Deletions</th>
<th>18%</th>
<th>43%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ovary</td>
<td>Not Protein-Truncating</td>
<td>6%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>Protein Truncating Mutations in BRC Domains</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>Ovary</td>
<td>In-Frame Deletions</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>Not Protein-Truncating</td>
<td>33%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>Missense Mutations</td>
<td>57%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Rebbeck et al., *JAMA*, 2015
BRCA1/2 Interactors

- **RAD51**
- **BRCA2**
- **BARD1**
- **MRE11**

- **S-Phase/G2 Arrest, HR/RAD51 Localization, Double Strand Break Repair**
- **CHK1 Activation, Checkpoint Regulation**

- **ATM**
- **BRCA1**
- **TOPBP1**
- **BACH1**

- **Homologous Recombination**
- **CHK1 Activation, S-Phase/G2 Arrest, Checkpoint Repair**
BRCA1/2 Interactors: Ovarian Cancer Risks

ABRA1
NBS1
BARD1
MRE11
HR=3.5
HR=4.6 (Rare)
S-Phase/G2 Arrest, HR/RAD51 Localization, Double Strand Break Repair
CHK1 Activation, Checkpoint Regulation
CTIP
ATM
RAD50
Ub
Ub
Merit40
BRCC36
RAD51
BRCA2
PALB2
BRCA1
TOPBP1
BACH1
CHR1 Activation, Checkpoint Repair
Homologous Recombination
ATM
HR=3.5
HR=4.6 (Rare)
HR=10.9 (Rare)
Rebbeck et al., Cancer Research 2011

Rap80
ABRA1
BRCC45
MERIT40
BRCC36
NBS1
MRE11
RAD50
BRCA1
RAD51
BRCA2
PALB2
BARD1
ATM
HR=3.5
HR=4.6 (Rare)
HR=10.9 (Rare)
### Effect of RRSO on Risk and Mortality in BRCA1/2 Mutation Carriers with No Prior Cancer Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Incidence Reduction (HR)</th>
<th>Mortality Reduction (HR)</th>
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</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.63</td>
<td>0.52</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>0.31</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.36</td>
<td>NE</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

Adjusted for year of birth and stratified by center; NE: No Events

What if “lifetime cancer risk” is ≤50% for many carriers?

Which women are undergoing RRSO unnecessarily?
Evidence Academy
- Interviews, Think Tank, Symposium, White Paper(s)

Biomarkers
- Inherited and somatic mutations, other biomarkers

Risk Models
- Risk stratification into actionable groups

Tools and Technologies
- Biosampling, molecular testing, Screening methods

Interventions
- Primary Prevention: (Chemoprevention, Surgery, Vaccination, Exposure Modification)
- Secondary Prevention: (Treatment of pre-neoplasia, chemoprevention, screening & Early Detection)
- Tertiary Prevention: (Survivorship)

Evidence Base
- Knowledge Base
- Knowledge Gaps

Demonstration Projects
- Prioritize by Site: Attributable Risk
  Catchment Area Need
  Shovel Readiness
  Return on Investment

- Prioritize by Gene or Pathway:
  Pleotropic Effects
  Mechanism-Driven Targeted Agents
  Shovel Readiness
  Return on Investment

Implementation, Dissemination, Impact
From Nucleotide to Neighborhood: Precision Prevention Research Framework

What Do We Known About the Disease?
Fundamental Research:
Behavior, Biology, Biomarkers, Epidemiology

What Are the Costs and Benefits?
Health Services/Health Systems Research

Where is the Problem?
Geospatial Research

Who is at Risk?
Genetics, Biomarkers, Epidemiology

Prevention Modalities:
Primary, Secondary, Tertiary

How Do We Get The Intervention to the Relevant Community?
Behavior, Implementation Science, Policy

Lives Saved

Rebbeck, CEBP 2014

DF/HCC Precision Prevention Initiative
Precision Prevention Modality Pipeline

<table>
<thead>
<tr>
<th>Modality:</th>
<th>None/Limited</th>
<th>Inadequate</th>
<th>Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need:</td>
<td>Discovery</td>
<td>Improvement</td>
<td>Implementation</td>
</tr>
<tr>
<td>Examples:</td>
<td>Ovary, Pancreas</td>
<td>Prostate, Breast</td>
<td>Colon, Cervical</td>
</tr>
<tr>
<td>Target:</td>
<td>Modifiable Exposures, Key Early Mutations, Reversible Mutations, Intra-Epithelial Neoplasia, Pre-Neoplasia</td>
<td>Heterogeneity (inter-individual), (intra-tumor), Molecular Subtyping</td>
<td>Communities of Need Cost-Benefit</td>
</tr>
</tbody>
</table>
Precision Prevention

Adapted from Esserman et al. *JAMA* 2009

- Metastatic Disease
- Clinically Detectable Disease
- Subclinical Disease

**Time at Risk**

**Early Aggressive Intervention**

**Weigh cancer risk reduction against long-term consequences**

**Intervene cautiously**

Mortality Not Preventable

Mortality Preventable