Role of DNA in Cancer Development and Treatment: Tumor Genomics and Hereditary Mutations

PSONS Spring 2017 Fundamentals of Oncology
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Licensed Certified Genetic Counselor

Discussion Topics

- Impact of genes on tumor development
- Environmental impact and epigenetics
- Sporadic vs familial vs hereditary cancer
- Hereditary Breast and Ovarian Cancer (HBOC)
- BRCA and PARP inhibitor use

Background: Education and Experience

- Bachelor of Arts in biology and psychology from SUNY Potsdam
- Master of Science in Genetic Counseling from the University of Pittsburgh
- Clinical roles:
  - University of Arkansas for Medical Sciences/Arkansas Children's – pediatric, adult, and cancer genetic counselor
  - Cook Children’s Hospital – pediatric and cancer genetic counselor
  - Overlake Hospital – cancer genetic counselor
- Consultative roles:
  - Clinical program design and development – AR, OR, TX, WA
  - Cleveland Clinic (Oncology and Genetics)

What is genetic counseling?

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.
Cancer Genetics 101

- All cancers are genetic – result of accumulation of mutations
  - Add, remove, switch around, multiply base pairs
  - Development of mutations in the tumor can uncover pathways
    - May unlock medications that target certain pathways
  - 10-15% have a hereditary or inherited component

Rosalind Franklin

- Double helix structure
- Ladder formed – A>T and C>G
  - Adenine, thymine, cytosine, guanine
- Proteins produced have particular functions
  - Oncogenes, tumor suppressors
Gene functions in Oncology

- **Proto-oncogene**
  - A normal gene, that when function is altered by a mutation it becomes an oncogene that can contribute to cancer; many different normal functions within the cell
- **Oncogene**
  - Causes a cell to divide in an unregulated manner; key feature – single altered copy leads to unregulated growth
- **Tumor suppressor**
  - Makes proteins that slow or inhibit progression through a specific stage of the cell cycle, that arrest the cell cycle if DNA is damaged or chromosomes are abnormal, proteins that promote apoptosis (cell death), and DNA repair enzymes.

Impact of Genes on Tumor Development

- Genes regulate cell growth, death, protein role in the body, among other functions
- Understanding which pathways are defective leads to:
  - Steps of tumor development
  - Opportunities to impact defective pathways

### Gene Function

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Familial</th>
<th>Sporadic</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT1</td>
<td>Tumor suppressor</td>
<td>Wilm's tumor</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Rb1</td>
<td>Tumor suppressor</td>
<td>Retinoblastoma</td>
<td>Small-cell lung cancer</td>
</tr>
<tr>
<td>P53</td>
<td>Tumor suppressor</td>
<td>Li-Fraumeni syndrome</td>
<td>Breast, colon, and lung cancer</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>Tumor suppressor</td>
<td>Hereditary Breast and Ovarian Cancer (HBOC)</td>
<td>Breast, ovarian, prostate cancer</td>
</tr>
<tr>
<td>RET</td>
<td>Oncogene</td>
<td>Multiple Endocrine Neoplasia 2</td>
<td>Thyroid cancer</td>
</tr>
</tbody>
</table>

Timing of mutation has impact
Epigenetic markers

- Literally means "above" or "on top of" genetics
- Refers to external factors that modify DNA so that genes are turned on or off
- DNA sequence is not affected or mutated, rather they affect how cells read genes

Sporadic vs Familial vs Hereditary Cancer

- Typical age of onset – breast cancer in early 60s; colon cancer late 60s to early 70s
- When more than one case dx in family, no distinct pattern of inheritance
- General population risk for cancer development
Sporadic Pedigree

- More cases of a specific type(s) of cancer within a family than statistically expected, but no specific pattern of inheritance
- Variable ages of diagnosis
- May result from chance clustering of sporadic cases
- Possible common genetic background (e.g., Ancestry), similar environment and/or lifestyle factors
- Does not usually exhibit classical features of hereditary cancer syndromes

Familial Pedigree

- Autosomal dominant inheritance of specific cancers
- Earlier age of onset of cancers than average (expected)
- Multiple primary cancers in an individual
- Clustering of rare cancers among blood relatives
- Bilateral or multifocal cancers

BOTTOM LINE: History of common cancers at an uncommon age or frequency within the family
Hereditary Pedigree

Hereditary cancer development

Impact of Hereditary Breast and Ovarian Cancer (HBOC) Syndrome

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Impact of Hereditary Breast and Ovarian Cancer Syndrome

Angelina Jolie made the courageous decision to have her ovaries removed after a recent cancer scare but this was not her first warning sign. Eight members of the star's family have also fallen victim to the killer disease, it has emerged.

Brave actress Angelina, 39, lost her twin Marcheline Betrand to ovarian cancer. Her cousin Paradiso, great aunt Stella and aunt Debbies died from breast cancer, and Grandad Roland and uncle Raleigh also succumbed to different cancers.

Angelina's grandmother Lois died of ovarian cancer and her great-grandmother, Virginia, was killed by the same disease.

Her uncle Ron told the Sun: "She's very private. In rejecting her medical history she's doing it for a cause. She can save hundreds of thousands of lives."
Red Flags for Hereditary Breast and Ovarian Cancer Syndrome

- Ovarian cancer
- Breast cancer diagnosed ≤ 50 y
- 2 primary breast cancers*
- Male breast cancer
- Triple negative breast cancer
- Pancreatic cancer with an additional HBOC-associated cancer**
- Ashkenazi Jewish ancestry with an HBOC-associated cancer**
- A previously identified BRCA mutation in the family

Degrees of relationship

- General population USA: 1 in 400 to 440
- Individuals of Ashkenazi Jewish decent: 1 in 40
- Breast cancer dx <50 with no further family history of breast or ovarian cancer: 13-15%
- Ovarian cancer diagnosed at any age: 13-15%
BRCA1 and BRCA2

Risks for men with a BRCA mutation

Managing hereditary risk

• Surveillance – aid in detection of cancer at an earlier stage
• Surgery – preventative measure to remove at-risk areas of the body prior to cancer diagnosis
• Medication – used to reduce risk of cancer development
Surveillance

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age to Begin</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Surveillance</td>
<td>30 yrs.</td>
<td>As needed</td>
</tr>
<tr>
<td>Clinical Breast Exam</td>
<td>20 yrs.</td>
<td>Every 2–5 years</td>
</tr>
<tr>
<td>Hereditary and/or Familial</td>
<td>35 yrs.</td>
<td>Annually</td>
</tr>
<tr>
<td>Ovarian Cancer Surveillance†</td>
<td>Complete Blood and CA-125</td>
<td>60-65 yrs.</td>
</tr>
</tbody>
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Prophylactic Surgery

- Hysterectomy
- Salpingo-oophorectomy

Cancer Risk Reduction (%)

- 90%
- As much as 85%

Risk Reducing Agents

Oral Contraceptives
- Up to 60% reduction in risk for ovarian cancer
- No contraindication for birth control use
- Contradictory evidence regarding risk for breast cancer

Tamoxifen
- Reduces risk for contralateral breast cancer by as much as 53%
- Utility for women who have not had a breast cancer diagnosis; risk reduction as much as 45%

Panel Testing: More than just BRCA1 and BRCA2
Case Study

- Woman diagnosed with breast cancer at age 51
- Family History –
  - Mother: breast cancer at age 55
  - Maternal grandmother: breast cancer in her early 60s
  - Father: colon cancer at age 58

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**MSH6 specific cancer risks**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>MSH6 or MSH2?</th>
<th>Male Age of Onset</th>
<th>Female Age of Onset</th>
<th>Risk of Other Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.8%</td>
<td>Yes</td>
<td>40-49 years</td>
<td>30-45 years</td>
<td>5%-20%</td>
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<tr>
<td>Rectum</td>
<td>2.5%</td>
<td>Yes</td>
<td>40-49 years</td>
<td>30-45 years</td>
<td>5%-20%</td>
</tr>
<tr>
<td>Bladder</td>
<td>1%</td>
<td>Yes</td>
<td>50 years</td>
<td>66-85 years</td>
<td>50%</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.8%</td>
<td>Yes</td>
<td>65 years</td>
<td>61-77 years</td>
<td>40%</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>1%</td>
<td>No</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>1%</td>
<td>No</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Breast</td>
<td>1%</td>
<td>No</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Prostate</td>
<td>1%</td>
<td>No</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1%</td>
<td>No</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
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Management specific to genetic result: POSITIVE for MSH6 mutation
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State by State Analysis of BRCA Testing in Patients with Ovarian Cancer

- Since 2008, NCCN recommends hereditary testing for all patients with a diagnosis of epithelial ovarian cancer
- 2013: 27% of newly diagnosed patients were tested

Impact for family members

- 50% chance for first-degree relatives to have inherited same mutation
- Males and females at equal risk of inheriting mutation

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BRCA mutation impact on therapeutics – patients with an ovarian cancer diagnosis

✧ Olaparib
  ◦ Oral PARP-inhibitor
  ◦ Major toxicities: fatigue, nausea, and myelosuppression
  ◦ Has single agent activity in ovarian cancer
  ◦ Indication for third-line therapy for patients with Homologous Repair Deficiency (HRD) as indicated by presence of a BRCA mutation
  ◦ FDA approval in December 2014

Contact Information

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