Genetics in Oncology

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Disclosers

• None relevant to this talk
• I am not involved in any sinister projects of genetic manipulation for world dominance
Outline/Objectives

• Review any “red flags” or clinical “pearls” that might signify that a patient or family may harbor a genetic mutation

• Discuss how to assess a patient with cancer for a possible genetic etiology of their primary

• Provide an update on the more common genetic syndromes seen in oncology practice
Cancer is a Genetic Disease

• If there were no errors in DNA, cancer would not occur. On the other hand, it is hard to imagine copying $10^{27}$ nucleotides over a lifetime without making many, many errors. Why don’t cancerous cells arise every few minutes? The extremes – no cancer at all and cancer occurring so often as to not permit human life – are philosophical boundaries that we can only contemplate.

  • Ross, 1998. Introduction to Oncogenes and Molecular Cancer Medicine
Cancer Arises from Gene Mutations

Germline mutations

- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Parent

Mutation in egg or sperm

Child

All cells affected in offspring

Somatic mutations

- Occur in nongermline tissues
- Are nonheritable
- Acquired alterations common for all cancers

Somatic mutation

(eg, breast)
Red flags for a hereditary cancer syndrome

- Early age of onset
- Bilaterality, multifocal, multiple primaries
- Rare tumor types
- Cancers that cluster together
  - In an individual or a family
  - Breast or Colon <50
  - Medullary thyroid Cancer
  - Breast and ovarian OR colon and endometrial (more later)

- Associated non-malignant manifestations
The Key to Cancer Genetics Assessment

1) Family History
2) Family History
3) Family History
Taking a Cancer Family History

- Obtain at least a three-generation pedigree
- Ask about all individuals in the family and record the following:
  - Age at cancer diagnosis, age at and cause of death
  - Distinguish primary from metastatic sites
  - Precursor lesions, bilateral multiple cancers
  - Pertinent prophylactic surgeries
  - Associated congenital abnormalities
- Record ethnicity and race

**Sporadic Cancer** = single occurrence in a family
- majority of cancer cases
- onset later in life
- inherited risk unlikely

Gen Pop Risk = 11%
Risk to Female First Degree Relatives = 8.8% (not elevated)
Cluster of cancer in families
- cancers not known to be related to each other in a hereditary syndrome
- could be explained by chance alone as cancer is a common disease
  (general population risk is 1/3 to the age of 80)
Familial Cancer

- 2 or more 1st or 2nd degree relatives with cancer
- onset later in life
- unilateral disease
- unclear pattern
  - chance, common environment, genetic factors?
- genetics consult not indicated

![Family Tree Diagram]
Hereditary Cancer = inherited cancer predisposition

- 5-10% of breast/ovarian cancer
- Young ages at diagnosis (under 50)
- Bilateral/multifocal cancers
- Multiple generations
Update – Cancer Predisposition Syndromes

• All are rare HOWEVER:
• All are very important to recognize
  – Very high risk of cancer development if not-detected
  – Often many family members at risk
  – Early screening/prophylaxis saves lives
  – Treatments may be (very) different
Hereditary Breast Cancer

- Sporadic
- Hereditary (10%)
- PTEN
- P53
- BRCA1
- BRCA2
Causes of Hereditary Susceptibility to Ovarian Cancer

Hereditary (~10%)

Undiscovered single genes (<5%)

HNPCC genes (7%)

BRCA1 (~75%)
- 65% breast/ovarian
- 10% site-specific ovarian

BRCA2 (<15%)
- 10% breast/ovarian
- < 5% site-specific ovarian
Hereditary Breast and Ovarian Cancer (HBOC)

• Mutation in *BRCA1* or *BRCA2*
• Risk of multiple cancers however breast and ovary by far most common
• More common in Askenazi Jew’s due to founder mutations
**BRCA1 and BRCA2-Associated Cancers: Lifetime Risks**

Breast cancer: 40%–85%  
(often early age at onset)  
Contralateral breast cancer: 40%–60%  
Ovarian cancer: 15%–40%

Breast and Ovarian Cancer Risks
BRCA

• Large prospective cohort

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast cancer risk (70y)</th>
<th>Ovarian Cancer (70y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>60%</td>
<td>59%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>55%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Mavaddat JNCI 2013
BRCA – Additional Cancers

• Other than prostate cancer most have lifetime risks less than 10%
  – Pancreas
  – Melanoma
  – Male breast
  – Fallopian Tube
Management – Current Standard

• Surveillance
  – Annual Breast MRI and mammogram
  – Consider annual ca-125/TVUS¹

• Surgery
  – Bilateral Salpingo-oophrectomy (ideally by age 40y)
    • Reduce risk of ovarian cancer by >90% and breast cancer by 50%²
  – Prophylactic mastectomy reduced BC risk >90%

1) Rosenthal JCO 2013  2) Mavaddat JNCI 2013
Tamoxifen chemoprophylaxis

• Reduces risk in high risk populations including BRCA carriers
• Much debate in literature thus far about whether as effective in BRCA1 carriers as BRCA2 carriers
  – Recent data eludes to possible benefit in both groups
    • Eg. Tamoxifen used as adjuvant treatment reduced risk of contralateral breast cancer in both BRCA1 and 2 carriers by >60%. Independent of ER/PR status of first primary

1) Phillips JCO 2013
Salpingectomy in BRCA carriers

• Suggestion that most OC arises in distal tube
• Modeling studies have suggested initial salpingectomy at 40y followed by oophrectomy at 50y might result in optimal QOL and survival (see Editorial Foulkes Current Oncology 2013)

• EXPERIMENTAL at this point
High Risk Referral Criteria

1- First-degree relative of a BRCA1/2 mutation carrier (who has not had genetic testing).

2- A personal or family history (paternal or maternal) of at least one of the following:

- Multiple cases of breast cancer (particularly where diagnosis occurred at ≤50 years) and/or ovarian* cancer (any age) in the family – especially in closely related relatives, on the same side of the family.
- Both breast and ovarian cancer in the same woman.
- Breast cancer at ≤35 years.
- Invasive serous ovarian cancer.
- Breast and/or ovarian cancer in Ashkenazi Jewish families.
- An identified BRCA1 or BRCA2 mutation in any blood relative.
- Male breast cancer.
Epidemiology of Colon Cancer

Sporadic (~60%)

Familial (~30%)

Rare Syndromes (~4%)

FAP (~1%)

MAP (~1%)

Hereditary syndromes
Colon and Endometrial Cancer Risk in HNPCC

![Graph showing Colon and Endometrial Cancer Risk in HNPCC]
Lynch syndrome (HNPCC)

• Colon cancer:
  – often right sided tumors
  – Characteristic histology
    • Mucinous, signet ring, lymphocyte infiltration, Crohn’s like reaction
Ovarian and Gastric Cancer Risk - HNPCC

![Bar chart showing cancer risk comparison between General Population and HNPCC patients.](chart.png)
HNPCC Increases Risks of Other Cancers

- Additional cancers that have a lifetime risk of <5%
  - Ureter/renal pelvis
  - Biliary tract
  - Small bowel
  - Pancreas
  - Brain (Turcott's syndrome)
  - Sebaceous adenoma (Muire Torre syndrome)
Lynch syndrome

• Mutations in mismatch repair (MMR) genes
• Faulty MMR genes leads to propagation of DNA error → mutations → cancer
• Four genes: MLH1, MSH2, MSH6, PMS2
• Criteria for LS genetic testing are complex and generally family history based.
<table>
<thead>
<tr>
<th>Amsterdam Criteria</th>
<th>Revised Bethesda Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. At least 3 family members affected by CRC or</td>
<td>1. Colorectal cancer diagnosed in a patient &lt; 50 years</td>
</tr>
<tr>
<td>2. Two family members affected by CRC and one affected by endometrial or gastric</td>
<td>2. Presence of synchronous, metachronous colorectal or other</td>
</tr>
<tr>
<td>3. Affected cases must span at least two generations</td>
<td>HNPCC associated tumours regardless of age</td>
</tr>
<tr>
<td>4. One must be a first degree relative of the other two</td>
<td>3. Colorectal cancer with MSI-H histology diagnosed in a patient</td>
</tr>
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<td>5. One case must present under 50</td>
<td>younger than age 50</td>
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<td></td>
<td>4. Colorectal cancer or HNPCC associated tumour diagnosed at</td>
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<td>younger than age 50 years in at least one first-degree relative</td>
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<td>5. Colorectal cancer or HNPCC associated tumour diagnosed at</td>
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<td>any age in 2 first or second degree relatives</td>
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“Pre-tests” for HNPCC

• Micro Satellite Instability (MSI)
• 90% of tumors from patient with HNPCC show microsatellite instability

• Immuno-Histochemical Staining (IHC)
HNPCC Surveillance/Management Recommendations

- Colonoscopy q1-2 years begin 20-25
- Consider yearly renal ultrasound/urinalysis
- Consider UGI endoscopy concurrent with colonoscopy
- Endometrial U/S and sampling q1-2 years begin 30-35
- Consider TAH and BSO
What’s new in LS?

ASA may be useful in preventing LS associated cancers\(^1\)

- CVD trials meta-analysis show decreased CRC
- Randomized trial of high dose ASA vs placebo
  - 600mg ASA for >2 years reduced LS related cancers

1) Burn Lancet 2011
Two or more years of ASA

Colorectal cancer

HR 0.41 (95% CI 0.19–0.86)
p=0.02
All LS associated cancers

![Graph showing the proportion of patients diagnosed with Lynch syndrome cancers over years since CAPP2 entry. Two lines represent Aspirin placebo and 600 mg aspirin. The graph indicates a significant difference with HR 0.45 (95% CI 0.26–0.79) and p=0.005.](image-url)
Additional tidbits LS

• Universal screening for LS on all incident CRC (+/- Endometrial cancer) will become reality in next decade

• Cancer spectrum is evolving
  – ?Include breast cancer, prostate, renal cell
Conclusions

• Syndromes like LS and HBOC are rare but important to recognized for patient and ESPECIALLY family members
• The key to recognition is some knowledge of syndromes but more importantly TAKE A GOOD FAMILY HISTORY
• Refer to genetics clinic if any doubt