Gynecological Genetics

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Objectives

• Understand the difference between sporadic, familial and hereditary causes of cancer and why it is important.

• Overview of hereditary breast cancer syndromes

• Causes of other gynecological cancers

• Advances in genetics of oncology and genetic testing.
Understanding genetics of cancer
Hereditary versus Sporadic
Sporadic (environmental, by chance)

- No other family history
- Age of onset is typical

Breast @ 65
Hereditary

- Pattern of breast, ovary and other cancers
- Age of onset is early
- Multiple generation
- Multiple primary cancers

- Breast @ 52
- Left Breast @ 42
- Right Breast @ 67
- Breast @ 34
- Breast @ 77
- Prostate @ 52
- Melanoma @ 42
- Ovarian @ 77
- Breast @ 52
- Breast @ 34
- Breast @ 77
Familial

- Clustering of breast cancer in same lineage
- Age of onset is typical
- Environment? Genetic? Both?

Breast @ 77
Breast @ 82
Breast @ 61
Most cancer is not due to hereditary causes.

- Inherited: 10%
- Familial: 20%
- Sporadic: 70%

Legend: Inherited, Familial, Sporadic
Goal: Classification
Who needs what?

Assessment  Risk Classification  Intervention

Family Hx  Average (Sporadic)  Standard prevention recommendations

Moderate (“Familial”)  Personalized prevention recommendations based on family history

High (Hereditary)  Referral for genetic evaluation with personalized prevention recommendations based on the hereditary syndrome
Sporadic

At birth

Hereditary
Sporadic

~10-25 years

Hereditary
Sporadic

~30-40 years

Hereditary

DNA REPAIR GENE(S)

Malignancy
Sporadic

~60-80 years

Hereditary

Malignancy
Summary

Hereditary causes of cancer

- Earlier onset
- Higher risk
- At risk for more than one type of cancer
Somatic vs. Inherited “germline” Genetic testing

• Hereditary “germline” genetic testing:
  – Ie. BRCA, TP53, PALB2
  – Test is done on blood
  – To determine if a person was born with a predisposition to cancer.

• Somatic genetic testing:
  – Ie. Her2neu, KRAS, BRAF, OncotypeDX
  – Test is done on the tumor cells.
  – To determine specific characteristics of the tumor for treatment decisions.
Hereditary cancer genes are good genes to have.
BRCA1 and BRCA2 mutation carriers

Hereditary Breast and Ovarian Cancer Syndrome (HBOC)
Classic BRCA family

- Breast @ 44
- Melanoma @ 67
- Prostate @ 52
- Breast @ 77
- Ovary @ 64
- Breast @ 52
- Left Breast @ 42
- Right Breast @ 67
- BRCA1 positive
- Breast @ 34
- 29
## Risks for cancer for BRCA1 and 2 carriers

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>General Population</th>
<th>BRCA1 mutation</th>
<th>BRCA2 mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (women)</td>
<td>12%</td>
<td>50-80%</td>
<td>40-80%</td>
</tr>
<tr>
<td>Breast (men)</td>
<td>Less than 1%</td>
<td>1-2%</td>
<td>6%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.4%</td>
<td>40-50%</td>
<td>10-30%</td>
</tr>
<tr>
<td>Fallopian tube, primary peritoneal</td>
<td>&lt;1%</td>
<td>2-3%</td>
<td>2-3%</td>
</tr>
<tr>
<td>Colon</td>
<td>5%</td>
<td>Possibly increased for women</td>
<td>Unknown</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%-15%</td>
<td>Increased</td>
<td>20%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1%</td>
<td>1.4%</td>
<td>3%-7%</td>
</tr>
<tr>
<td>Melanoma, stomach, buccal/pharynx</td>
<td>Various</td>
<td>-</td>
<td>1-2%</td>
</tr>
<tr>
<td>Gallbladder/bile ducts</td>
<td>-</td>
<td>-</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

Women with BRCA1 or BRCA2 mutation who have had breast cancer and did not have bilateral mastectomies have a 40—60% risk for a new breast cancer in the opposite breast.
Medical Management

For Women:

• **Breast**: Annual MRI @ 25. Annual mammogram @ 30
• **Ovarian**: Consider screening versus surgical risk reduction
• **Risk reducing surgery**:
  – Bilateral mastectomy
  – Salpingo-oophorectomy ideally between 35 and 40 and after childbearing or earlier depending on earliest ovarian cancer in family
• **Risk reducing agents**: (Chemoprevention): tamoxifen/raloxifene

For Men:

• **Prostate cancer**: Adhere to screening guidelines. Consider baseline digital rectal exam (DSE) and PSA level at age 40.
• **Breast cancer**: monthly self-breast examination and education starting at 35 and clinical breast exam twice a year starting at age 35. Consider baseline mammogram at age 40.
Don’t be fooled
• Study Shows Third Gene as Indicator for Breast Cancer

PALB2

The next “BRCA3” gene???
Fig. 6.

Proposed model for the role of PALB2 in linking MRG15 and the BRCA complex into a pathway of HR. We propose that by directly binding PALB2, BRCA1 and MRG15 independently regulate site selection and chromatin accessibility, respectively, in PALB2 recruitment to sites of DNA damage. Once it is localized, PALB2 is proposed to be responsible for the recruitment of BRCA2 and RAD51.
PALB2

• Breast cancer: 2-6 fold risk

• Pancreatic: “increased”

• Other: ???
ATM

Autosomal Recessive:

Ataxia Telangiectasia (AT)

- Cerebellar ataxia
- Oculomotor apraxia
- Choreaathetosis
- Telangiectasias
- Immunodeficiency
- Leukemia/lymphoma
- Sensitive to ionizing radiation
Increased risk for pancreatic, breast, leukemia/lymphoma. Sensitive to radiation like the homozygotes?
No Breast or Ovarian cancer in the family. BRCA1/2 negative.
Do not limit your questions to just breast and ovarian cancer.

- Brain @ 45
- Bone @ 52
- Breast @ 29
- Leukemia @ 62
- Leiomyosarcoma ≤ 45
- Choroid plexus carcinoma @ birth
Other syndromes: LFS

- Li Fraumeni (TP53):
  - breast, sarcoma, leukemia/lymphoma, adrenocortical tumor, brain (colon, choroid plexus carcinoma, and others)
  - LFS classic criteria: <45 with sarcoma + FDR under 45 + FDR/SDR under 45 or sarcoma at any age.
  - Management:
    - High risk breast screening similar to BRCA carriers.
    - Annual physical exam with skin and neurological exam
    - Colonoscopy every 2-5 years starting at 25
    - Full body MRI
    - Educate patients on signs/symptoms of cancer
    - Counsel about limitations of testing,
    - Sensitive to ionizing radiation?
# Lynch Syndrome Cancer Risks

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Lynch Syndrome Risk by Age 70</th>
<th>General Population Risk by Age 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>80%</td>
<td>5%</td>
</tr>
<tr>
<td>Uterine</td>
<td>60%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>12%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Stomach</td>
<td>12%</td>
<td>1%</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>1-4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ureter/Renal Pelvis</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Brain (glioblastoma)</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Pancreatic/Biliary</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

“I don’t wanna do the prep doc?”
# Lynch Syndrome Surveillance

<table>
<thead>
<tr>
<th>Site</th>
<th>Procedure</th>
<th><em>Begin at</em></th>
<th>How often?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>colonoscopy</td>
<td>20-25*</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Stomach/sm. bowel</td>
<td>Upper EGD/capsule</td>
<td>30-35</td>
<td>1-5 years</td>
</tr>
</tbody>
</table>

*Or 5-10 yrs prior earliest dx in family, whichever comes first

- Consider annual urinalysis
- Yearly physical exam

NCCN 2013
Other Syndromes: Cowden

- **Cowden Syndrome (PTEN)**
  - Breast, uterine, thyroid (papillary, follicular)
  - Criteria: 2 major or 1 major + 2 minor
    - Major: breast/uterine/thyroid cancer, mucocutaneous lesions, macrocephaly (>97th percentile), multiple GI hamartomas/ganglioneuromas
    - Minor: RCC, fibroids, lipomas, fibroma, MR, autism, thyroid nodule/goiter/adenoma, single hamartoma/ganglioneuroma
Management for Cowden Disease

– Management:
  • Mammo/MRI starting 30-35
  • BSE at 18/ Clinic breast exam at 25 1-2 times per yr
  • Endometrial cancer screening (efficacy unknown)
  • Risk reducing agents/surgery
  • Annual physical with attention to associated tumors/cancer begin at 18 (skin, thyroid)
  • Baseline thyroid ultrasound at 18
  • Colonoscopy starting at 35 or 5-10 years earlier if symptoms or polyps found.

NCCN 2014
Genes linked to GYN cancers

- **OVARIAN**
  - SMARCA4
  - RAD50
  - PALB2
  - BRCA1
  - BRCA2
  - MSH2
  - MSH6
  - PMS2
  - MLH1
  - EPCAM

- **BREAST**
  - CDH1
  - ATM
  - NF1
  - CHEK2

- **UTERINE**
  - TP53

Gene targets for GYN cancers.
THE GOLD RUSH BLUES

One day in the KANSAS settled KANSAS at the
spring, brought in some MILL. Was it from
some rare place far back in the past? Was it
from some small town in the KANSAS and
PACIFIC PLAINS RUSH. No matter how
they got it, they dug it up and put it on the
farm next to the mill.
Gene Panel testing

• Test multiple genes linked to cancer with one sample.
• Advantage
  – Lower cost
  – Ability to test multiple rare genes for lower cost
  – Decrease need for additional testing in future
  – Identify gene mutations that were not expected
• Disadvantage
  – More uncertain variants
  – Incidental findings
  – Emotional impact
  – Complex answers
Penetrance vs. Prevalence of hereditary susceptibility genes

- High Risk: BRCA1, BRCA2, CDH1, TP53, PTEN,
- Moderate Risk: ATM, BARD1, BRIP1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, RAD50, RAD51C, RAD51D,
- Average Risk: Cox11, ESR1, LSP1, TOX3, FGR2

Adopted from Ambry Genetics Clinician Guide
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Cancer Spectrum/Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAMMM</td>
<td>CDKN2A, CDK4</td>
<td>CDKN2A: 28-76% melanoma, ≤17% pancreas, others CDK4: 74% melanoma, pancreas, breast, others</td>
</tr>
<tr>
<td>FAP/AFAP</td>
<td>APC</td>
<td>Up to 100% CRC, ≤12% duodenum, ≤5% thyroid, pancreas, small bowel, gastric, liver</td>
</tr>
<tr>
<td>HBOC</td>
<td>BRCA1, BRCA2</td>
<td>41-84% breast, 11-54% ovarian, 30% prostate, 3-7% pancreas/male breast</td>
</tr>
<tr>
<td>HDGC</td>
<td>CDH1</td>
<td>40-83% diffuse gastric, 39-52% lobular breast, CRC</td>
</tr>
<tr>
<td>JPS</td>
<td>BMPR1A, SMAD4</td>
<td>40-70% CRC, 21% gastric</td>
</tr>
<tr>
<td>LFS</td>
<td>TP53</td>
<td>73% for male carriers and nearly 100% for female carriers; breast cancer, sarcoma, brain, osteosarcoma, adrenal</td>
</tr>
<tr>
<td>Lynch</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>20-80% CRC, 15-60% uterine, ≤20% ovarian, ≤8% urothelial, ≤7% gastric, ≤4% small bowel, ≤3% brain, sebaceous tumors, breast, pancreas, prostate</td>
</tr>
<tr>
<td>MAP</td>
<td>MUTYH</td>
<td>≤80% CRC, ~4% duodenum, endometrial, ovarian, bladder, breast, and skin</td>
</tr>
<tr>
<td>PJS</td>
<td>STK11</td>
<td>32%-54% breast, 39% CRC, 11-36% pancreas, 29% gastric, 21% ovarian tumors, 15% lung, 13% small bowel, 10% cervical/uterine, 9% testicular tumors</td>
</tr>
<tr>
<td>PTHS</td>
<td>PTEN</td>
<td>25-50% breast, 10% thyroid, ≤10% uterine, melanoma, renal, CRC</td>
</tr>
<tr>
<td>VHL</td>
<td>VHL</td>
<td>70% renal, ≤17% pancreas (neuroendocrine), pheos</td>
</tr>
</tbody>
</table>
## Moderate Risk Genes

<table>
<thead>
<tr>
<th>Syndrome/Pathway</th>
<th>Gene</th>
<th>Cancer Spectrum/Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia-Telangiectasia</td>
<td>ATM</td>
<td>25-30% breast, CRC, pancreas</td>
</tr>
<tr>
<td>DNA Repair</td>
<td>CHEK2</td>
<td>28-38% breast, ≤50% prostate, thyroid, CRC, male breast, ovarian, uterine</td>
</tr>
<tr>
<td>Fanconi Anemia</td>
<td>PALB2</td>
<td>25-50% breast, ≤10% pancreas, ovarian</td>
</tr>
</tbody>
</table>
What to ask your patients

• Who has cancer in your family?
• What type of cancer was it?
• How old were they when they got cancer?
• Does your patient have risk factors for cancer?
  – Atypical ductal hyperplasia, LCIS, other precancerous lesions
  – Dense breast
  – Hormone, oral contraceptive use
  – Menarche < 12, breastfeeding history, age of first child, etc
Who should see a genetic counselor?

- Breast, colon, uterine cancer under 50 (triple negative breast cancer <60)
- Ovarian cancer at any age
- Ashkenazi Jewish with breast or ovarian
- Multiple PRIMARY cancers in one individual
- >3 (or ≥ 2 if premenopausal) family members in same lineage
- Male with breast cancer
- Rare cancers: Medullary thyroid, paraganglioma, pheochromocytoma, adrenocortical carcinoma, choroid plexus carcinoma
- polyposis >20 polyps

(Breast cancer includes invasive and DCIS)
Risk Assessment in the doctor’s office

• Online or tablet based questionnaire patient completes
  – Hughes RiskApps, My Family Health Portrait, MeTree, Progeny

• Online risk programs you input yourself
  – Gail, CaGene, Tyrer Cuzick (IBIS), BRCAPRO
Dr. Schroeder to the rescue!
High Risk Breast Clinic

• Breast C.A.R.E. Program (Comprehensive Assessment and Risk Evaluation)

• Determine risk for breast and/or other cancer:
  – Recommendations prevention and early detection
  – diet, exercise, Vitamin D, stress reduction, smoking cessation
  – for chemoprevention and MRI screening

• Risk for Hereditary Predisposing Gene
  – Offer genetic testing when appropriate
Psych-social issue

• Worry about self
• Worry about family
• Pressure for the young
• Genetic guilt/survivor’s guilt
• Pre-viver: where do I belong?
• Emotional versus logical decision
• Coping strategies
• Financial
• Family reactions
• Dealing with intensive screening, risk reducing surgeries
Logistics
Summary

Hereditary causes of cancer

- Earlier onset
- Higher risk
- At risk for more than one type of cancer

Note: You can be high risk but gene negative
THANK YOU!