An overview of familial cancer and genetics

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Tuesday 28th March 2017
An overview of familial cancer and genetics

- Principles of inherited predisposition to cancer
- How to take a family history
- Approach to inherited breast cancer
- Approach to inherited bowel cancer
- Approach to genetic testing
- Familial Cancer Program at Genetic Services of Western Australia (GSWA)
All cancer is genetic (acquired genetic).

But most cancers are not inherited.
Somatic mutation

Germline mutation
Mutations in tumour suppressor genes or DNA repair genes cause inherited predisposition to cancer.

Oncogenes: Accelerate

Mismatch repair genes: Repairs keep the car running smoothly
Tumour suppressor gene requires a second mutation in the other copy to cause cancer.
Knudson’s 2-Hit Hypothesis

Gene Mutations May be Inherited or Acquired During a Person’s Life

Sporadic Cancer: 2 acquired mutations

Hereditary Cancer: 1 inherited and 1 acquired mutation

(c) 2005, Lori Demmer
Genes that cause inherited cancer predisposition are passed on in an **autosomal dominant** manner
Guide to family history taking

- 3 generation family tree
- Clusters of the same cancer type
- Clusters of known associated cancers
  - E.g. breast/ovarian cancer
- Young-age of onset of cancer
- Multiple cancers of the same type in a young individual
- Multiple cancers of different types in a young individual
- Limited family information \(\rightarrow\) low threshold to refer
APPROACH TO INHERITED BREAST CANCER
Breast cancer genes

Contribution of known genes to familial aggregation of breast cancer

- BRCA1
- BRCA2
- TP53
- PTEN
- ATM
- CHEK2, BRIP1, PALB2
- Other genes familial risk factors
- 79 common SNPs

Only 5% to 10% of cases of breast and ovarian cancer are due to an inherited predisposition.

- Due to inherited faulty BRCA1 and BRCA2 genes
- Due to other unknown inherited faulty 'cancer protection' genes

90% to 95% are not inherited.

Cases of breast and ovarian cancer in Australia not involving an inherited predisposition.
Indicators of a possible BRCA mutation in the family

- Multiple* breast cancers in the family
  - Young age of onset (<40)
  - Certain types of breast cancer ("triple negative")
  - Multiple primary breast cancers in an individual
  - Male breast cancer
  - Ashkenazi Jewish heritage

- Breast and ovarian cancer in the family
  - Young age of onset (<60 for ov ca)
  - Certain types of ovarian cancer
  - Individual with primary breast and ovarian cancer
  - Ashkenazi Jewish heritage

*3 or more
# Manchester Score

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Age</th>
<th>BRCA 1</th>
<th>BRCA 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Breast Cancer</td>
<td>&lt;30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Female Breast Cancer</td>
<td>30-39</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Female Breast Cancer</td>
<td>40-49</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Female Breast Cancer</td>
<td>50-59</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Female Breast Cancer</td>
<td>&gt;59</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Male Breast cancer</td>
<td>&lt;60</td>
<td>5*</td>
<td>3</td>
</tr>
<tr>
<td>Male Breast cancer</td>
<td>&gt;59</td>
<td>5*</td>
<td>5</td>
</tr>
<tr>
<td>Ovarian Cancer #</td>
<td>&lt;60</td>
<td>8</td>
<td>5**</td>
</tr>
<tr>
<td>Ovarian cancer #</td>
<td>&gt;59</td>
<td>5</td>
<td>5**</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>Any</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>&lt;60</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>&gt;59</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**NB:** Cancers occurring through two unaffected females at >60 years of age are not counted

* If BRCA2 already tested

** If BRCA1 already tested

# Ovarian cancer  Do not include in scoring: Mucinous, Borderline, germ cell tumours

**Manchester Score Unadjusted:**

\[ M = \]
Breast cancer pathology

• BRCA1
  – Mostly invasive ductal ca (74%)
  – Poorly differentiated (Grade 3) (66-100%)
  – ↑proportion medullary or atypical medullary carcinoma
  – ER, PR, HER2 negative (triple negative)
  – CK 5/6 (basal markers) positive (basal-like)
  – HER2 expression infrequent (0-3%)

• BRCA2
  – Same histological types and ER/PR expression as sporadic breast tumours
  – HER2 expression infrequent (0-3%)
Ovarian cancer pathology

- Epithelial, not germ cell
- High-grade serous or endometrioid
- Fallopian tube primary is suspicious
- Not mucinous
- Not lesions of borderline malignant potential
Modified Manchester

<table>
<thead>
<tr>
<th>Pathology</th>
<th>BRCA1 Adjustment</th>
<th>BRCA2 Adjustment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast index case</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her2+</td>
<td>-4</td>
<td>0</td>
<td>No other alteration to score on the basis of pathology needed</td>
</tr>
<tr>
<td>Lobular</td>
<td>-2</td>
<td>0</td>
<td>Add or subtract ER status</td>
</tr>
<tr>
<td>DCIS only (No invasive cancer)</td>
<td>-1</td>
<td>0</td>
<td>Add or subtract ER status</td>
</tr>
<tr>
<td>LCIS only (No invasive cancer)</td>
<td>-4</td>
<td>0</td>
<td>No other alteration to score on the basis of pathology needed</td>
</tr>
<tr>
<td>Grade 1 Invasive Ductal Carcinoma</td>
<td>-2</td>
<td>0</td>
<td>Add or subtract ER status</td>
</tr>
<tr>
<td>Grade 2 Invasive Ductal Carcinoma</td>
<td>0</td>
<td>0</td>
<td>Add or subtract ER status</td>
</tr>
<tr>
<td>Grade 3 Invasive Ductal Carcinoma</td>
<td>+2</td>
<td>0</td>
<td>Add or subtract ER status</td>
</tr>
<tr>
<td>ER pos</td>
<td>-1</td>
<td>0</td>
<td>Add or subtract grade</td>
</tr>
<tr>
<td>ER neg</td>
<td>+1</td>
<td>0</td>
<td>Add or subtract grade</td>
</tr>
<tr>
<td>Grade 3 Triple neg</td>
<td>+4</td>
<td>0</td>
<td>No other alteration to score on the basis of pathology needed</td>
</tr>
<tr>
<td>Ovary index case</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>0</td>
<td>0</td>
<td>No adjustment to ovarian score</td>
</tr>
<tr>
<td>Granulosa</td>
<td>0</td>
<td>0</td>
<td>No adjustment to ovarian score</td>
</tr>
</tbody>
</table>

*Manchester score of 15 gives a detection rate of about 10%*
Meta-Analysis of BRCA1 and BRCA2 Penetrance

- BRCA1 breast (57%)
- BRCA2 breast (49%)
- BRCA1 ovary (40%)
- BRCA2 ovary (18%)

Chen et al, JCO April 2007
The **cumulative risk** of an unaffected carrier of a specified age developing breast and ovarian cancer by the age of 75 years.
Mx of BRCA-associated cancer risk

• **Surveillance:**
  • 6 monthly clinical breast exam
  • Yearly imaging - mammography + MRI (+ ultrasound)
  • Start at 5 years younger than youngest age or 30 years of age for mutation carriers
  • Chemoprevention (Tamoxifen) should be considered

• **Risk-reducing bilateral mastectomy**

• **Risk-reducing bilateral salpingo-oophorectomy**
  
  BRCA1 – from 35-40  
  BRCA2 – from 40-45
Other genes causing Hereditary Breast Cancer

- Tp53 (Li-Fraumeni syndrome)
- PTEN (Cowden syndrome)
- STK11 (Peutz-Jeghers syndrome)
- CHD1 (HDGC & Lobular Br Ca)
- ATM (Ataxia-Telangiectasia)
- PALB2
- CHEK2
- BRIP1 (Fanconi anaemia)
# Li Fraumeni syndrome (Tp53)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>TP53 mutation carrier</th>
<th>General population to age 85 yrs</th>
</tr>
</thead>
</table>
| Cancer (female)         | 15% by 20 yrs  
50% by 30 yrs  
80% by 40 yrs  
>90% by 50 yrs | 33% (female) |
| Cancer (male)           | 15% by 20 yrs  
20% by 30 yrs  
30% by 40 yrs  
60% by 50 yrs | 50% (male) |

- Breast (female)
- Sarcoma
- Brain
- Adrenocortical carcinoma
- Others (leukaemia, malignant phyllodes tumour, Wilms tumour, peripheral nervous tumours, lung, colon and pancreatic cancer)
PTEN mutations (Cowden syndrome)

- Hamartoma tumour syndrome
- Breast, thyroid, endometrial cancer
- Thyroid disease (goitre, thyroiditis)
- Facial papules
- Macrocephaly
- Mucocutaneous lesions (>90%)
### Cowden syndrome (PTEN)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Cowden syndrome</th>
<th>General population to age 85 yrs *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast</td>
<td>25 - 50%</td>
<td>11%</td>
</tr>
<tr>
<td>Thyroid (mostly follicular sometimes papillary)</td>
<td>5 - 10%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>5 - 10%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>
Peutz-Jeghers syndrome

- Intestinal polyposis (hamartomas)
- Mucocutaneous pigmentation
- Colorectal, gastric, pancreatic, breast and ovarian cancer
- STK11 gene mutations
Hereditary Diffuse Gastric Cancer (CDH1)

- Diffuse gastric cancer (histology NB)
- Lobular breast cancer
- Mutations in CDH1 (Ecadherin)
Ataxia-Telangiectasia

- Progressive cerebellar ataxia
- Immunodeficiency
- Telangiectasia of conjunctivae
- Increased risk of malignancy (leukaemia, lymphoma)
- Autosomal recessive condition
- Bi-allelic mutations in ATM gene
- Increased risk of breast cancer in heterozygotes (carriers)?
PALB2 mutations

Breast-Cancer Risk in Families with Mutations in \textit{PALB2}


\textit{N Engl J Med} 371;6  \textit{NEJM.org}  August 7, 2014
What about higher-frequency, but lower penetrance genetic factors?

**GENOME-WIDE ASSOCIATION STUDIES (GWAS)**

Single Nucleotide Polymorphisms (SNPs) in genes associated with breast cancer risk.
3 groups of breast cancer predisposing genes found

79 SNPs recognized
Polygenic risk score

Sawyer et al, JCO 2012
APPROACH TO INHERITED BOWEL CANCER
Adenoma-Carcinoma sequence
Inherited predisposition to bowel cancer

- Mutations in genes that lead to an overwhelming number of polyps (>100)
  - Multiple polyposis syndromes

- Mutations in DNA repair genes $\rightarrow$ polyp-carcinoma sequence is accelerated
  - Lynch syndrome

- Mutations in genes that lead to rare polyps with high malignant potential
  - Juvenile polyposis syndromes
  - Hamartomatous polyposis syndromes
Multiple polyposis syndromes

Familial Adenomatous Polyposis (FAP)
- caused by mutations in the APC gene

**Classic FAP**

- Clinically defined as:
  - > 100 adenomatous colon polyps

- Features:
  - often *thousands* of colon polyps
  - polyps present *throughout* the colon
  - early age of onset:
    - average \( \sim 16 \) yrs
    - range 8-34 yrs
Lynch syndrome

In Men and Women

- **Colon**
  - Risk with Lynch Syndrome: **<25%** by age 50, **82%** by age 70
  - General Population Risk: 0.2% by age 50, 2% by age 70

- **Stomach**
  - Risk with Lynch Syndrome: **13%** by age 70
  - General Population Risk: <1% by age 70

In Women Only

- **Uterine (Endometrial)**
  - Risk with Lynch Syndrome: **~20%** by age 50, **71%** by age 70
  - General Population Risk: 0.2% by age 50, 1.5% by age 70

- **Ovary**
  - Risk with Lynch Syndrome: **12%** by age 70
  - General Population Risk: 2% by age 70

Though the following cancers are rare, their risk also increases with Lynch Syndrome:
- Small Intestine, 7.2%
- Urinary Tract, 4%
- Brain, 3.7%
- Biliary Tract, 2%

If one or more of the following applies to you or a family member, ask your doctor about Lynch Syndrome:
- Colorectal cancer before age 50
- Two or more Lynch Syndrome cancers
- Endometrial cancer before age 50
- A previously identified mutation in the family

References:
Lynch syndrome – mutation in DNA repair genes

Microsatellite Testing (MSI)

Immunohistochemistry (IHC)
Management of Lynch syndrome

- General measures to reduce bowel cancer risk
  - Increase dietary fibre
  - Moderate intake of red wine (5 std drinks/wk)
- Consider aspirin (100mg daily)*
- Annual colonoscopy for the early detection of polyps/cancer
- For women:
  - Consider hysterectomy and removal of ovaries after completion of child-bearing

*To be first discussed with GP
Indicators of a bowel cancer gene mutation in the family

• Multiple* cases of bowel cancer in a family
  – Young age of onset (<50)
  – More than 1 primary bowel cancer in a person
  – Associated with multiple polyps (>100)

• History of bowel, womb and/or ovarian cancer in a family

• Abnormal IHC or MSI on tumour testing
Approach to genetic testing
Principles of genetic testing

• Testing an affected individual to investigate for an inherited predisposition to cancer (diagnostic testing)
• Families/individuals have to be carefully selected to avoid un-interpretable results
• Usually select to test first the individual most likely to carry a genetic cause (youngest or multiple cancers)
• Target only gene/s thought to explain the family history of cancer
Outcomes of genetic testing

1. Mutation identified
   - Explains family history
   - Management decisions can be made
   - Other family members can have **predictive/presymptomatic testing**
   - Reproductive decision-making

2. Uninformative result
   - No mutation identified (none there, limitations of technology, another unknown gene?!)

3. Unclassified Variant/polymorphism
   - Not pathogenic but may be reclassified in future
Predictive genetic testing
testing for a known mutation identified in the family

- **POSITIVE:** *I have* inherited the gene fault
  - I have an increased chance of developing cancer
  - each of my children has a 50% chance of inheriting the same gene fault.

- **NEGATIVE:** *I have not* inherited the gene fault
  - my risk of cancer is **not** increased
  - the gene fault **cannot** be passed on to my children.
Pre-implantation genetic diagnosis (PGD)
Types of genetic testing available

- Sanger sequencing
- Deletion/duplication testing (MLPA)
- Next generation sequencing = Massively parallel sequencing
  - Whole Exome sequencing
  - Whole Genome sequencing
  - Targeted capture (panels)
Cancer panel testing

• Testing a number of genes in a single platform
• Uses next generation sequencing technology (whole exome sequencing)
• Access to TruSight Cancer panel (Illumina)
  – 98 cancer genes
  – 24 pts at a time
Cancer panel testing – clinical perspective

• Advantages
  – Increased diagnostic yield
  – Faster turnaround times
  – Identify genetic syndromes (with known management guidelines) not presenting in a typical way
  – Can select which gene/s to include in analysis (panel within panel)
Cancer panel testing – clinical perspective

• Disadvantages
  – Detect more variants of uncertain significance in genes of known high penetrance
  – Detect so-called pathogenic variants in genes where penetrance is thought to be lower or penetrance is unknown
  – Detect so-called pathogenic variants in genes with no established risk management guidelines
  – Identify genetic syndromes (with known management guidelines) not presenting in a typical way
Drowned in next generation sequencing data

HELP!
Direct-to-consumer testing (DTC)

- SNP-based (polygenic based)
  - Brevagen
- Panel testing
  - My Risk
  - Color
- My advice:
  → do **not** encourage pts to undertake this testing (esp if no family history)
GSWA structure

Obstetrics, Gynaecology and General Service (OGGS)

Genetic Paediatric Service (GPS)

Familial Cancer Program (FCP)

Familial Cancer Registry

- Clinical geneticists
- Genetic counsellors
- Laboratory scientists
- Researchers
- Registry staff
- Administrative staff
Genetic testing in private?

- Yes
- Genetic counselling at WOMEN Centre
- Fee-for-service
- Shorter waiting list
- Faster genetic testing turnaround times
- Access to genetic testing when does not meet criteria for publically-funded testing
- Additional genetic testing options
Thank you!

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