Familial Cancer Predispositions

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Outline

• Familial cancer genetics overview

• Psychosocial implications of genetic testing and genetic mutation carriage

• Role of genetic counsellors
All cancer is genetic

SPORADIC CANCER
- Accumulation of gene faults in one cell over time

http://kintalk.org/genetics-101/
All cancer is genetic
Most cancers are NOT hereditary
Genes and cancer

- **Common**
- **Low penetrance**
- **Population frequency**
  - Rare
  - High penetrance: BRCA, MMR, TP53, PTEN
    - RR: 6 - >10
  - Uncommon
    - Moderate penetrance: CHEK2, ATM, PALB2
    - RR: 2-4
  - Common
    - Low penetrance
Genes and breast cancer risks

- Untested
- Mutation negative
- BRCA1 positive
- BRCA2 positive
- PALB2 positive
- CHEK2 positive
- ATM positive

Breast cancer risk (%) vs. Age (years)
Familial Cancer Predisposition Genes

Tumour suppressor, DNA repair, mismatch repair genes
Familial Cancer Predispositions
Mostly autosomal dominant inheritance

Cancer predisposition (50%)  Not at risk (50%)
Hereditary Cancer Predispositions

• **Well known:**
  - Hereditary Breast and Ovarian (BRCA1, BRCA2)
  - Lynch syndrome (mistmach repair genes MMR)

• **Rarer, not as well known:**
  - Li-Fraumeni syndrome
  - Familial Adenomatous Polyposis
  - MUTYH-associated polyposis
  - PTEN-hamartoma syndrome (Cowden)
  - Multiple Endocrine Neoplasia (MEN)
  - Hereditary paraganglioma-pheochromocytoma
  - ...

• **Implications for management** (*increased risk of other cancer/manifestations, specific treatment options*)

• **Implications for other family members** (other relatives may be at increased risk of cancer)
When to suspect Hereditary Cancer Predispositions

• **Rule of thumb:**
  - **EARLY**
  - **MULTIPLE**
    - Family history of $\geq 2$ other relatives with similar or related cancer
    - Multiple cancer in one person
  - **UNUSUAL / RARE**
    - Type of cancer (ovarian cancer, sarcoma, rare tumour)
    - Histopathology (triple negative/positive breast cancer, MSI high CRC/endometrial tumour, high-grade serous ovarian cancer)
    - Ancestry (Jewish)
When to suspect Hereditary Cancer
Predisposition: Breast cancer

• **EARLY:**
  - Breast cancer <35yo

• **MULTIPLE:**
  - Family history of ≥ 2 other close relatives with breast cancer or associated cancer (ovarian)
  - Bilateral breast cancer, breast and ovarian cancer, breast and other cancer

• **“UNUSUAL”:**
  - ER, PR, HER2 positive \((triple \ positive)\) breast cancer <40
  - ER, PR, HER2 negative \((triple \ negative)\) breast cancer <60
  - Basal phenotype (CK5/6 basal markers positive)
  - “Medullary” breast cancer
  - Male breast cancer
  - Jewish ancestry
When to suspect Hereditary Cancer
Predisposition: ovarian cancer

• **EARLY:**
  - Ovarian cancer <60yo

• **MULTIPLE:**
  - Family history of $\geq 2$ other close relatives with cluster of ovarian, breast or CRC
  - Family history of cancers at a young age

• **Particular histopathology:**
  - High-grade serous (regardless of age), endometrioid tumours
Hereditary Breast and Ovarian Cancer (HBOC): BRCA1 and BRCA2

• **Account for:**
  - around 5% of all breast cancer
  - around 20% of high-grade serous ovarian cancer

• **Implications for cancer management:**
  - PARP inhibitors
BRCA1 and BRCA2

• **BRCA1**
  - Risk of breast cancer: **70%**
  - Risk of controlateral breast cancer: up to **40%**
  - Risk of ovarian cancer: up to **44%**
  - Breast cancer more likely to be
    - Poorly differentiated (grade 3)
    - Hormone receptors ER, PR, HER2 negative *(triple negative)*
    - CK5/6 marker positive *(basal phenotype)*

• **BRCA2**
  - Risk of breast cancer: **70%**
  - Risk of controlateral breast cancer: up to **26%**
  - Risk of ovarian cancer: around **17%**
  - Risk of male breast cancer: around **7%**
  - Risk of prostate cancer: **15%**, earlier onset, higher grade
Li-Fraumeni syndrome

- **Significantly increased risk of cancer:**
  - Childhood: 15-20% risk by age 20
  - Women: 50% by 30 yrs >90% by 60 yrs
  - Men: 35% by 30 yrs >90% by 60 yrs

- **Wide tumour spectrum:**
  - adrenocortical tumour, brain tumours, sarcoma, leukemia, young breast cancer
  - other cancer: lung, colorectal, pancreatic,...

- **Risk of breast cancer in women**
  - 85% life-time risk
  - Breast surveillance from age 20

- **Increased sensitivity to radiation**

- **Due to mutations in the TP53 gene**
Moderate penetrance genes: risk depends on family history
Breast cancer moderate risk genes
emerging information

• **PALB2** (truncating variants)
  - Breast cancer risk: 33% if no family history, 55% if family history
  - Risk of ovarian cancer: not significantly increased
  - Risk of pancreatic cancer: may be increased

• **CHEK2** (c.1100del)
  - Risk of breast cancer 20-25% if no family history, 35-55% if family history
  - May be increased risk of contralateral breast cancer
  - Cancer tend to be hormone receptor positive (ER, HER2)
  - Risk of ovarian cancer: not significantly increased
  - Risk of prostate cancer: possibly increased

• **ATM** (c.7271T>G)
  - Risk of breast cancer: 47%
  - Risk of pancreatic cancer: may be increased
  - Risk of ovarian cancer: not significantly increased

**RISK MODIFIED BY FAMILY HISTORY**
When to suspect Hereditary Cancer Predisposition: bowel cancer

• **EARLY:**
  – CRC <50yo

• **MULTIPLE:**
  – Family history of ≥ 2 other close relatives with cluster of CRC or associated cancer (uterine/ovarian/uterine/CRC)
  – Multiple polyps, particularly if at a young age
  – More than one cancer in one person

• **UNUSUAL:**
  – Abnormal screening tests (IHC) for Lynch syndrome
Lynch syndrome

- Accounts for about 2-5% of all colorectal cancers
- Most common form of inherited bowel cancer predisposition
- Increased risk of
  - Colorectal cancer
  - Gynaecological cancer (uterine and ovarian cancer)
  - Other cancers
- Due to mutations in one of the mismatch repair genes (MMR) MLH1, PMS2, MSH2, MSH6

Lynch syndrome variants
- Muir-Torre syndrome: Lynch with sebaceous tumours
- Turcot syndrome: Lynch syndrome with brain tumour
Lynch syndrome

Cumulative risk of colorectal cancer

Risk of uterine and ovarian cancer
Colorectal polyposis

- Benign polyposis
  - Hyperplastic
    - Peutz-Jeghers syndrome
  - Hamartoma
    - Juvenile Polyposis
    - PTEN hamartoma tumour syndrome

- Neoplastic polyposis (risk of becoming cancerous)
  - Adenoma
    - FAP
  - Serrated
    - Serrated Polyposis
**Familial Cancer Resources for GP**

- **eviQ:** [https://www.eviq.org.au/](https://www.eviq.org.au/)

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Psychosocial implications of Familial Cancer Predispositions
Psychosocial implications: Physical aspects

- Post or facing surgery
- Self-image/self-esteem
- Sense of identity
Cancer risks for women with faults in BRCA1 and BRCA2 depend both on the precise mutation and the woman’s family cancer history: *EMBRACE study*
Psychosocial implications: living with uncertainty

EMBRACING UNCERTAINTY

HOLD TIGHT
SWIM IN
THE UNRELIABLE
UNPREDICTABLE
RISKY
FICKLE
UNDEFINABLE

DELIGHT
IN THAT
Psychosocial implications: Support and empowerment

- Sense of isolation/belonging

“When I learned I was BRCA positive, I was told ‘your body is the same as it has been for the past 30 years, you are just learning more about it.’ This has helped me so much.”

— Jessica
Psychosocial implications:
Informing other family members

- Family dynamic
- Communication
- Guilt
- Blame
Psychosocial implications:
Predictive Genetic testing of children and young people
Psychosocial implications: family planning

- Prenatal diagnosis
- Preimplantation Genetic Diagnosis
Team GSWA:
Genetic counsellors/clinical geneticists

• Genetic counsellors
  ❖ TRIAGE
    - multidisciplinary meetings (public and private hospitals)
    - Triaging around 50 new referrals/week
  ❖ Genetic testing
  ❖ Follow-up
  ❖ Education/research

• Clinical geneticists:
  ❖ Clinical exam, rarer cancer predispositions

• Team work:
  ❖ Weekly intake meeting
  ❖ Co-counselling (difficult situations, paediatric oncology)
  ❖ Monthly meeting: update on testing (new panels), management (eviQ guidelines)
  ❖ Buddy system/supervision

Not so helpful: “please arrange BRCA testing for Julie with strong FHx of cancer”

Helpful: Histopathology, genetic reports, details of relatives with cancer
Familial Cancer Overview

• Questions?

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