Dr Marion Harris (Medical Oncologist)

1. Cancer genetic testing and surveillance for familial breast and colorectal cancer

What does an FCC do?

- Collect , assess and VERIFY a FHx of cancer
- Questionnaire and consent forms mailed to patients to confirm the family history
- Information verified by Victorian cancer register or individual patient consent form (delay-2-3mths)
- Determine cancer risk category (low /mod/high)
- Assess likelihood of a hereditary predisposition
- Offer genetic testing or not (mutation detection Vs predictive)
- Suggest surveillance
- Annual mutation follow up program for mutation carriers
- Research study

What to look for?

- Collect a 3 generation family tree
- Note tumour site and age of onset
- Assess the number of people with breast or ovarian cancer on each side of a family who are first or second degree relatives of each other
- Ages of BC onset (<40 or <50)
- Autosomal dominant inheritance (paternal FHx IS important)
- Ethnicity – Jewish (relevant for breast cancer risk where 1/40 carry Ashkenazi founder mutation in BRCA genes)
- Family histories change with time

Causes of familial Breast cancer

- Unknown 50%
- BRCA 1/2 mutations 15%
- Known SNPs 15%
- Predicted SNPs 14%
- Moderate risk genes 4%- CHEK 2, ATM
- Other high risk genes 3% p53, PALB2,

BRCA 1 and BRCA2

- Hereditary Breast-Ovarian Cancer Syndrome
- mutation frequency each 1 in 500
- Early age of BC onset
- Bilateral disease(2nd primary risk at 30 yrs 25-40%)
- Male breast cancer
  - Invasive epithelial non mucinous OC (esp serous)
- Ashkenazi Jewish ancestry (1 in 40 carry founder mutation)
- Tumour suppressor genes , role in DS DNA repair

BRCA 1

- Breast cancer risk to 80 72% R(65-79)
- Ovarian cancer risk to 80 44%R(36-53)
- Prostate cancer risk for males increased RR 1.5-2.0
- Typical histology-high grade, hormone receptor negative (75%), medullary /atypical medullary histology, basal epithelial phenotype (CK 5/6+)

BRCA 2

- Breast cancer risk to 80 69% R(61-77)
- Ovarian cancer risk to 80 17% R(11-25)
- Male breast cancer 6%
- Pancreatic cancer 3.5%
- Prostate cancer RR4+, high stage/grade
- Melanoma risk increased
- No classic phenotype for BC

p53

- Premenopausal breast cancer – her 2+
- Sarcoma (non Ewing)
- CNS tumours – GBM
- Leukemia
- Adrenocortical cancer and other paediatric tumours
- (breast –sarcoma syndrome)

PALB 2

- Partner and localiser of BRCA2-
- On chromosome 16 p with 13 exons
- Interacts with BRCA 2 and 1 and acts in DS –DNA repair
- Is a gene in which loss of function mutations cause increase in breast cancer risks like BRCA 2
- Mutations – truncating /deletion or splice site
- Many different mutations , Canadian , Finnish founders
- Esp common PALB2 c3113G>A
- BC risk <40 yo 8-9 X increase in BC risk
- 40-60 6-8 X increase risk
- >60 yo 5X increase in risk
- Avge risk BC to 50 yo is 14%
- Risk to age 70 35%
- Cancer risk influenced by birth cohort and family BC history

PALB2

- Absolute cancer risk to 70 yo 33% if no Fhx
- 58% if ≥ 2FDR with BC by 50
- 75% of tumours are ER +
- 25-30 % are TN (commonest cause TN BC after A1/2)
- Non-significant increase in OC risk (RR 2.0)
- No significant increase in male BC
- No significant increase in pancreatic cancer
- Moderate to high risk breast cancer predisposition gene
- In vitro tumours have sensitivity to parp inhibitors
- Thought to explain 1-3 % of families with a history of BC depending on the population

Genetic testing

- Next generation sequencing –fast, can test multiple(all) genes at once , cheaper
- Whole exome sequencing – test exons=1% of genome but codes 85% of proteins produced
- Whole genome sequencing – test introns and exons = entire genome

- So panels of gene tests have largely replaced one gene test

Cancer Panels

- Previously BRCA 1 and 2 – cost $2400
- Now breast cancer gene panel – 5 genes for $600
- Larger panels $800
- With price drop increase in patients self-funding testing

Panel Testing

- Patients may have 2 mutations
- May have unexpected findings ie p53
- Many variants of uncertain significance- more than 3000 in BRCA 1 /2 alone
- These are missense , intronic or inframe deletions and insertions
- 8-20 % of variants in any one gene are VUS, so if test for multiple genes see many
- VUS <95% probability of pathogenicity

CHEK 2 (Var)

- Particular mutation 1100del C
- truncating mutations doubles BC risk RR 2.5-3 (30% lifetime BC risk)
- Missense mutations lower RR 1.5
- Mutation carried by 1% of individuals in Northern and Western Europe

ATM (var)

- Truncating variants cause a moderate increase in BC risk (30% lifetime risk)
- ATM missense c7272T>g is high risk (60-80%lifetime BC risk)
- Importance cell cycle checkpoint kinase
- Down regulates p53, CHEK 2 and BRCA 1
- Can have standard MG and therapeutic RT

RAD 51 c/d

- Clear evidence of association with OC risk
- Together found in around 1% of OC cases esp serous
- Risk of oc to age 70 6% and 12 % respectively , 20 % of cases between 40 and 50, seldom <40
- Are DS DNA break repair genes
- Consider BSO, parp and platinum

- Evidence of association with BC risk is limited

Polygenic Breast Cancer Risk

- SNP= single base change that is present in >1% of the population
- Individual SNPs combine/interact together to increase or decrease risk of diseases
- These can modify effects of high risk variants ie BRCA mutation
- For BC combination of 100+ SNPS known to influence BC risk
- Each in its own confer small increase in BC risk <1.5 X as high as general population
- c/w variants with mod to high increase in risk
- Those at highest quartile of polygenic risk have a 2nd BC risk as high as a BRCA carrier and have earlier age of onset

Polygenic BC risk

- Those at lowest quartile of risk have less than an average woman's risk of BC
- These SNP profiles believed to contribute to around 15% of familial BC risk
- Role in management subject of ongoing research in Victoria (P James et al)

Risk Management Strategies

- MRI screening program + mammography
- Starting 25-35 yo or 5-10 yrs before youngest affected, stop ? 50-69
- MRI- proven high sensitivity (80-90%) in detecting BC in high risk women <50 (c/w MG 40%) BUT no OS data
- Increasing data that all ages benefit
- Problems –claustrophobia and lower specificity (false+)
- ? PALB 2-start at 35 unless strong Fhx – start 30
- ? CHEK 2 start 40
- Australian guidelines reimburse only for women <50 who carry a high risk breast cancer mutation or who meet certain high risk family history criteria for BC/OC

Medical Prevention

- Risk reducing medication -underutilised
- Tamoxifen for premenopausal and Raloxifene (or aromatase inhibitor) in post menopausal women taken daily for 5 yrs
- Reduce risk of hormone positive BC by 35-40% but no proven OS benefit
- SE (tamoxifen DVT/endometrial cancer) for 5 yrs but benefit up to 20 yrs (IBIS 1)

Preventive Surgery

- Prophylactic bilateral mastectomies with breast reconstruction (best protection from BC but residual risk 1-5%)
- Maximal OS gain if done at 30yo
- Prophylactic bilateral salpingo-oophorectomy
- Remove tubes as well b/c of tubal hypothesis of OC(OC starts in distal fallopian tube rather than the ovary)
- Done once childbearing is complete around 40 (BRCA1) or 45 (BRCA2) as the risk of OC increases from these ages
- BSO reduces OC risk by 80-95%
- Having a premenopausal BSO halves BC risk with optimal benefit if done by 40 yo.(at least in BRCA 2 carriers - recent data suggests no benefit in BRCA 1 carriers)

After The BSO

- Consequences of early menopause after BSO for bone health , heart health and general QOL
- Previously did not routinely advise HRT
- Now evidence of adverse CVR outcomes means it is suggested for all to around age 50
- No evidence that use HRT after BSO in this population increases BC risk
- GPs can help – assist with HRT provision
- check Ca intake , Vit D levels , monitor BMD
- follow cholesterol and BP
- Consider need for topical PV lubricants , Venlafaxine for hot flushes or referral to a menopause service – Jean Hailes

Colorectal Cancer

- **Three Broad Categories:** ***Risk***
  - Hereditary CRC <10% High
  - Familial CRC 10-30% Moderate
  - Sporadic CRC 60-80% Average

Familial Colorectal cancer

- Familial Adenomatous Polyposis (FAP)- accounts for < 1% of all CRC
- Hereditary Non Polyposis Colorectal cancer (HNPCC or Lynch Syndrome) accounts for
- 3-5 % of CRC
- MYH polyposis- autsomal recessive inheritance accounts for< 1% of all CRC
- Familial clustering of CRC 80% +

What to look for

- Take a 3 generation family history
- determine the number of affected relatives on each side of the family
- Age of diagnosis and site of primary tumour
- Consider other cancer types – uterine cancer/ ovarian cancer, stomach, pancreas, urinary tract TCC(upper) for HNPCC or other history of multiple polyps

Lynch Syndrome

- LS = 3% of all CRC
- Until recently IHC routinely performed on CRC diagnosed age 50 and under
- Recent US data < 50% of those in this group had routine IHC done
- Now move to IHC screen all ages
- Problem that around 20 % of all CRC have methylation of MHL1 so lack MLH1/PMS2 so False + for LS

MYH Polyposis

- Autosomal recessive condition due to biallelic mutations of the MYH gene that results in multiple colorectal adenomas (15-100).
- Risk of CRC is 60% by age 60
- Mimics attenuated FAP
- 2 specific "common" mutations in this gene have been identified. (gene location 1p)

MYH

- Consider if > 10 polyps
- Heterozygotes? Some increase in CRC risk or not?
- Colectomy at time of polyposis or observation and polypectomy
- Duodenal polyposis in <20%
- Increased risk duodenal cancer approx 4%

POLE and POLD

Encode DNA polymerase enzymes

- are involved in scanning and repairing DNA damage
- cause polyposis or early age onset CRC that is MSI –stable
- up tp 60% lifetime risk CRC

POLE and POLD

- POLD1 also increases risk of endometrial cancer (up to 60%)
- Rare families described
- Somatic mutations in these genes in some sporadic CRC and endometrial cancer
- Will explain some LS like families without mutations

Endometrial Cancer

- 2-3 % of cases have LS
- Lifetime risk in LS 15-60%
- Until recently only some sites did IHC testing routinely 50 and under
- Data suggesting few misses if test 60 and under
- Similar issue to CRC with 20-% absent MLH1/PMS2 due do somatic methylation of MLH1 so need for methylation testing

Hyperplastic Polyps and Polyposis Syndrome

- Assoc with significant lifetime CRC risk
- exact genetic basis unknown
- Definition :
- 1. 5 or more serrated polyps proximal to the sigmoid colon with at least 2 >10mm
- 2. more than 20 serrated polyps of any size throughout the colon

HPS

- Incidence of CRC 15-50%
- Have serrated polyps and conventional adenomas
- Management – 1-2 yrly colonoscopy and removal of all polyps >5mm in size
- First degree relatives 5 yrly colonoscopy from 40 or 10 yrs before age at diagnosis

Surveillance

- Average risk – FOB test 2 yrly from 50 saves lives
- ? Only 40 % uptake
- Moderate risk – 5 yearly colonoscopy from 40 or 10 years prior to age of youngest CRC diagnosed in the family

Lynch Syndrome Management

- Colonoscopy from age 25 years, every 1 year.
- Screening for endometrial and ovarian cancer in women- no proven benefit- NOT DONE . Option of TAH/BSO once age around 40
- Screening for urinary/stomach cancers if these cancers in family (gastroscopy – US/ urinalysis every 1-2 years from 30-35 years) (no proven benefit).
- Consider subtotal colectomy/hysterectomy/oophorectomy if cancer found.
- Aspirin daily ? Dose ? 100mg (CAPP 2 study – see next sl)
- Once CRC occurs better prognosis for same stage
- If MSI high data suggests avoid 5FU adjuvant chemotherapy (no benefit)

FAP Management

- Commence surveillance at puberty (13-16).
- Sigmoidoscopy/colonoscopy every year.
- Proctocolectomy once significant polyposis develops- usu around 18 years.
- Endoscopic screening for duodenal adenomas and rectal carcinoma.
- Predictive genetic testing when available (with appropriate counselling)

MONASH HEALTH FAMILIAL CANCER CENTRE

Correspondence to: Special Medicine Centre, 246 Clayton Road Clayton 3168
Clinic Locations: Clayton, Frankston, Moe, Moorabbin, Prahran
Tel. (03) 9594-2009 Fax. (03) 9594-6046 Email. familial.cancer@monashhealth.org
Dr Marion Harris, Clinical Director/Geneticist/Medical Oncologist
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Cassandra Hoskins, Associate Genetic Counsellor
Dish Johnson, Clinical Genetics Data Manager
Dr Yoland Antill, Dr Prudence Scott, Medical Oncologists
Dr Fiona Nicholson, Gastroenterologist
Dr Matthew Regan, Clinical Genetics Fellow

Monash Health Familial Cancer Centre Referral Guidelines

The following criteria are a guide. Should you have any referral queries or concerns – please contact the Familial Cancer Centre via email familial.cancer@monashhealth.org or by phone: 9594 2009 and ask to speak to the duty counsellor.

Personal History

- Breast cancer ≤ 35 yrs
- Male breast cancer at any age
- Multiple primary tumours, (excluding lung and skin) ≤ 70 yrs e.g. breast and ovarian, fallopian tube, primary peritoneal, endometrial and colorectal.
- Colorectal cancer or endometrial cancer ≤ 50 yrs
- Rare tumour** ≤ 45 yrs
- Multiple colorectal polyps (10 or more)
- Epithelial ovarian, fallopian or primary peritoneal cancer at any age
- Triple negative breast cancer (TNBC) ≤ 60 yrs of age at diagnosis (TNBC: oestrogen, progesterone and HER2 receptor negative)
- Medullary thyroid cancer at any age
- Personal history of breast or ovarian cancer AND Ashkenazi Jewish ancestry
- Diffuse gastric cancer ≤ 40 yrs

Family History

- Blood relative of a known cancer predisposition gene e.g. *BRCA1, BRCA2, APC, MYH, MLH1, MSH2, MSH6, PMS2, PTEN, VHL, SDHA/B/C/D, RET, NF2, CDH1* etc.
- Family history of breast or ovarian cancer in any first or second degree relative **AND** Ashkenazi Jewish ancestry
- First degree relative diagnosed with colorectal or endometrial cancer ≤ 50 yrs (with/without a family history of cancer)
- 2 or more first or second degree relatives on the same side of the family with colorectal, endometrial, ovarian or rare tumour** at any age
- 2 or more first or second degree relatives on the same side of the family with either breast cancer ≤ 60 yrs and/or ovarian cancer at any age.
- **Phaeochromocytoma, paraganglioma, sarcoma, choroid plexus carcinoma, adrenocortical carcinoma, retinoblastoma, diffuse gastric cancer, clear cell renal cancer.

Referrals must be addressed to:
Dr Marion Harris, Monash Health Familial Cancer Centre.
Please send referral via email: familial.cancer@monashhealth.org OR fax: 9594 6046 and include:

- Patient address AND telephone number/s
- Ages of onset and sites of cancer in patient and close relatives on both sides of family*
  **close relative = first degree (parents, siblings & children) and second degree (aunts, uncles, grandparents)*
- If anyone in the family has seen our service before, please provide the relative/s name and date or birth as well as their genetics clinic reference number (where known).