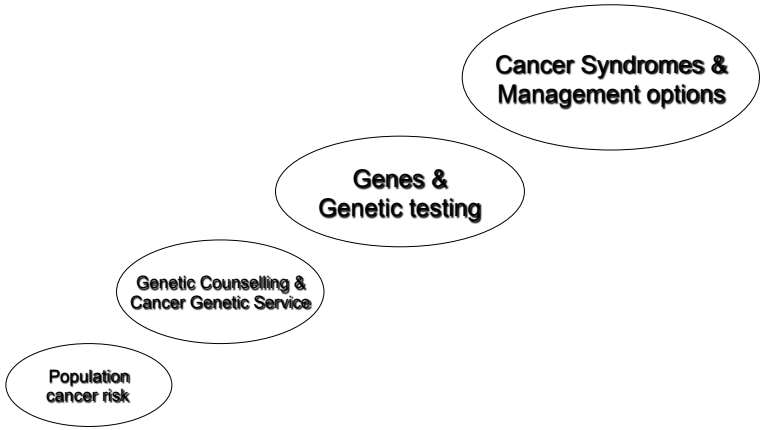
Introduction to Cancer Genetics

Overview



What are the cancer risks for the general population?

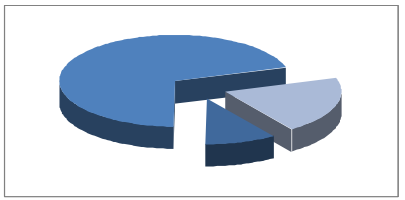
- 1 in 3 people will develop cancer at some point in their lives

– Prostate:	17%
– Female Breast:	12-13%
– Lung:	6-8%
– Colorectal cancer:	6%
– Melanoma:	1-2%
– Ovarian:	1.5%
– Stomach / Pancreas:	1%
– Male breast:	0.1%

SEER Figures. NCI 2001-2003

How Many Cancers are Genetic?

Sporadic (~85%)

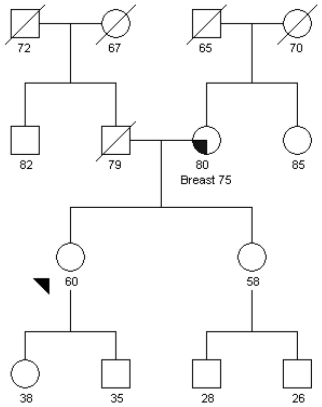


Familial (~10%)

Hereditary (~5%)

Sporadic Cancer

- **Many patients may have a similar FHx**
- **Age of diagnosis typically later in life**
- **Usually not inherited**
- **Can be reassuring**



Aims of Genetic Counselling

Help patients to…

- Understand the information about the genetic condition
- Appreciate inheritance patterns and risk of recurrence
- Understand available options
- Make informed choices appropriate to their personal and family situation
- Make the best possible adjustment to the condition and risk

Do Genes Affect Cancer Risk?

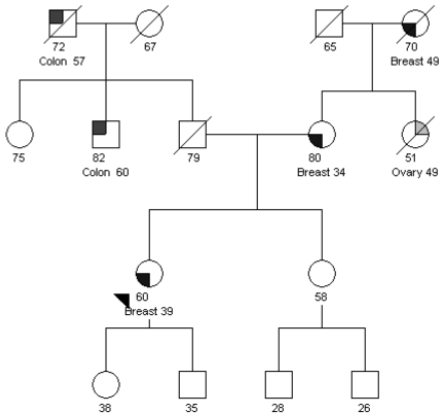
Risk Assessment Tools

- Referral guidelines / NICE guidelines
- Family History form
- Comprehensive 3 generation pedigree
- Confirmation of cancer pathology
- Pedigree assessment
  - Manchester score
  - BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm)
  - Amsterdam I/II Criteria
  - Bethesda Criteria

Genetic Cancers

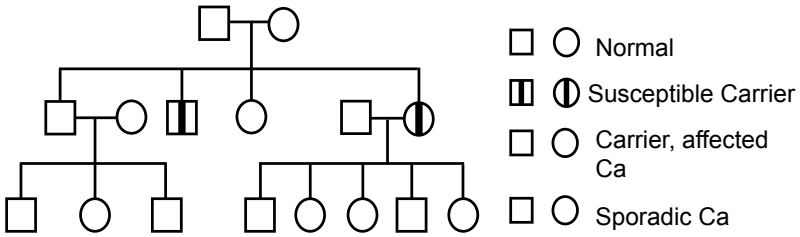
- Breast and ovarian
- Colon cancers
- Cowden syndrome
- Gastric cancer
- Gorlin Syndrome
- Li-Fraumeni
- Multiple endocrine neoplasia (MEN)
- Neurofibromatosis
- Peutz-Jeghers syndrome
- Phaeochromocytoma
- Retinoblastoma
- von Hippel-Lindau disease
- Wilm's tumour

Hereditary Cancer



- Several affected family members
- Earlier than average age of onset
- Multiple generations are affected on one side of the family
- A particular pattern of cancers noted
- Individuals with more than one primary tumour site
- 5-10% of Cancer Cases

Most Cancer Susceptibility Genes Are Dominant With Incomplete Penetrance



- You only need one altered copy of the gene to have an increased risk of cancer
- Gender is irrelevant
- It is not possible to "skip" generations
- Penetrance can be incomplete
- All offspring are at 50:50 risk

Genetic Testing

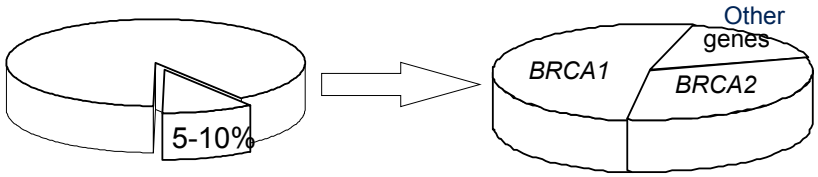
- Genetic testing is usually carried out on DNA from a blood sample
- Technically difficult to locate the mutation in a cancer gene for a particular family
  - Can take up to three months
- Usually need to first test a living relative who has already developed cancer
- Is only offered to high risk families (>20% chance of mutation)
- Often cannot locate a mutation in a family (only identified in about 20% of families)

Genetic Testing cont…

- Genetic testing is NOT usually possible if there are no living affected relatives
  - Exception is populations with founder mutations eg Ashkenazi Jewish population
- Once a mutation is found, testing can be offered to other at-risk family members
- Individuals who DO NOT carry the family mutation ARE NOT at increased risk of developing the cancers, but are still at population risk
- Individuals who DO carry the family mutation ARE at increased risk of developing cancer but there is still uncertainty. . .

However, testing enables us to identify individuals who may be at higher risk of developing certain types of cancer

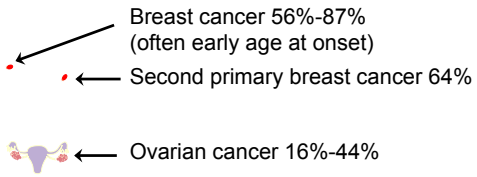
Hereditary Breast and Ovarian Cancer



- Sporadic
- Hereditary

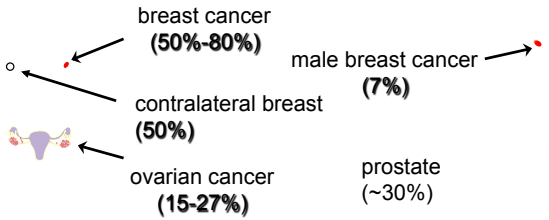
- **Most cases caused by a mutation in *BRCA1* or *BRCA2* gene**
- ***BRCA1 / 2* are tumour suppressor genes, which are involved in the repair of DNA**
- **Accounts for about 5% of breast cancer cases and about 12% of ovarian cancer cases**

BRCA1 -Associated Cancers: Lifetime Risk



Increased risk of other cancers, eg about double population risk for prostate cancer in men

BRCA2-Associated Cancers: Lifetime Risk



Other cancers:
pancreatic
malignant melanoma

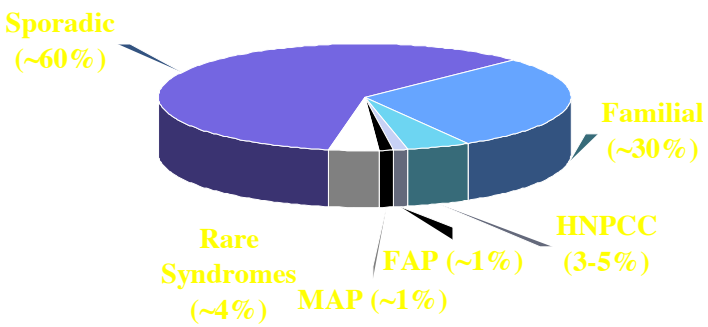
Options for BRCA1/2 Carriers

- Cancer Screening
  - Additional breast screening by mammography / MRI
  - Ovarian screening through UKFOCSS research trial
- Prophylactic bilateral mastectomy
  - ~90% reduction in breast CA risk
- Prophylactic bilateral salpingo-oophorectomy
  - ~up to 96-98% reduction in ovarian CA risk
  - ~50% reduction in breast CA risk (age dependant)
- ? Chemoprevention in the future
- ? Tailoring of treatment for carriers in the future

When to refer

- 2 first or second degree relatives with breast cancer < 50 yr
- 3 first or second degree relatives with breast cancer <60yr
- 4 relatives with breast cancer at any age
- 1 ovarian cancer at any age + 1 breast cancer < 50yr
- 1 ovarian cancer + 2 breast cancer both < 60y
- 2 ovarian cancer any age
- Patients who are thought to be of Ashkenazi Jewish heritage with at least one first degree relative with breast cancer <50 years or ovarian cancer any age
- **NB** bilateral breast primaries equivalent to 2 relatives

Colorectal Cancer



HNPCC or Lynch syndrome

Hereditary non-polyposis colorectal cancer (HNPCC)

- 3-5% of all colorectal cancer cases
- Autosomal dominant – multiple generations affected
- High penetrance
- Typical age of CA onset is 40-50 yrs
- 60-70% right-sided/proximal CRC tumors
- Polyps may be present, multiple primaries common. Can overlap with AFAP

HNPCC

- **Lifetime cancer risks:**
  - Colorectal 80%
  - Endometrial 20-60%
  - Gastric 13-19%
  - Ovarian 9-12%
  - Biliary tract 2%
  - Urinary tract 4%
  - Small bowel 1-4%
  - Brain/CNS 1-3%

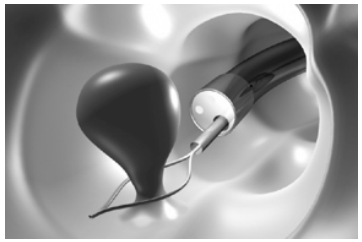
HNPCC

Caused by mutations or deletions in mismatch repair (MMR) genes

MMR genes are like spell checkers in our DNA.

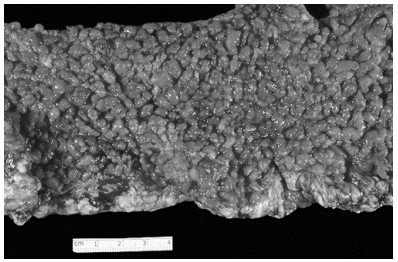
- MSH2, MLH1, MSH6, PMS2
- 90% of detectable mutations in MSH2 and MLH1
- 7-10% of detectable mutations in MSH6

Options for individuals with HNPCC



- 1-2 yearly colonoscopy
- Ovarian and endometrial screening (not proven to be effective)
- ? renal/upper GI screening effective (if have history of gastric/renal cancers)
- Surgery
  - Prophylactic bowel surgery not often chosen
  - Total abdominal hysterectomy and salphingo oophorectomy for females

Familial adenomatous polyposis (FAP)



- 1 in 10,000 incidence
- 100's to 1000's of colonic adenomas by teens
- 7% risk of CRC by 21 yrs; 93% by 50 yrs
- 20-25% no history in parents
- Extra-colonic features
- Screening
  - 1 – 2 yearly flexible sigmoidoscopy from age 10 – 12
  - Upper GI endoscopy 1 –3 yearly from age 25

MAP syndrome/*MYH* gene

- **MYH associated Polyposis (MAP) syndrome**
  - Autosomal recessive; mutations in the *MYH* gene
  - Median number of polyps = 55
  - Mean age of polyp diagnosis = 30-50 years
  - Polyps mainly small, mildly dysplastic tubular adenomas. Some tubulovillous, hyperplastic, serrated adenomas, microadenomas
- 30% of individuals with 15-100 polyps have homozygous mutations in the *MYH* gene
- Genetic testing should be offered if >10-15 polyps (and APC gene testing negative)

When to refer

- Patient or 1 first degree relative affected with
  - Colorectal cancer <50yrs
  - 2 or more colorectal primary cancers any age
  - Colorectal cancer and a related cancer* any age.
- 2 first degree relatives affected with colorectal cancer or related cancer* at any age
- 3 relatives affected with colorectal cancer or related cancer* at any age, one of which must be a first degree relative.
- History of Polyposis (e.g. Familial adenomatous Polyposis)

  - *related cancers- endometrial, ovarian, small bowel, ureter, renal pelvis and stomach

Genetics and Uncertainty

- Cancer genetics is not relevant for most people
- Cancer genetics is not a crystal ball

But cancer genetics can have a great impact on those families most at risk of familial cancer

What Can You Do?

- Recognise patterns of cancers in families
  - Young onset
  - Lots of one or two particular types of cancer
  - Jewish?
- If not sure ask
  - Don't be afraid to contact genetics for advice
- Take a blood sample for DNA banking

DNA Banking

- DNA banking provides families with the chance to pursue genetic testing at a later point in time.
  - where there is currently no genetic test available. DNA banking will allow the family to take advantage of future advances in genetic testing technology.
  - A family member diagnosed with cancer who is terminally ill and there is no time for traditional a genetic assessment and/or testing. The family can then focus their attention on their loved one and defer the process of genetic counselling and testing to a time when they are ready.