Beating Bowel Cancer Patient Day

Family history of bowel cancer

Laura Boyes
Lead Consultant Genetic Counsellor
West Midlands Regional Genetics Centre
Birmingham Women’s and Children’s NHS Foundation Trust
Causes of colorectal cancer

>30,000 cases/year
Lifetime risk 1 in 25-30

- **Sporadic** (65%–85%)
- **Familial** (10%–30%)
- **Hereditary Non-Polyposis Colorectal Cancer (HNPCC)** (5%)
- **Familial Adenomatous Polyposis (FAP)** (1%)
- **Rare CRC syndromes** (<0.1%)

Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996
Why do we get cancer?

- Chance or bad luck
- Environmental effects
- Genetic effects
The cancer in your family is more likely to be inherited if:

- People have been unusually young when they had cancer
  - Bowel cancer under 50
  - Endometrial cancer under age 50
  - Ovarian cancer under age 60
The cancer in your family is more likely to be inherited if:

- There have been several people with the same sort of cancer
- Or with related cancers
  - Bowel/Endometrial/Ovarian
    - Stomach/ Ureter/ Renal

On the same side of the family
The cancer in your family is more likely to be inherited if..

- Anyone has had more than 1 primary cancer of related types
  - Bowel and womb cancer
  - Bowel and ovarian cancer
  - Womb and ovarian cancer
Likely to be a genetic predisposition.....

Possible Lynch syndrome gene
The cancer in your family is less likely to be inherited if:

• Only 1 or 2 people have had cancer

• Especially at older (or more typical) ages

• The cancers have recognised environmental causes
  – Lung Cancer
  – Skin cancer (Basal Cell Carcinoma)
  – Cervical Cancer
Unlikely to be a genetic predisposition

Not an increased risk
What hereditary bowel cancer do we know about
Causes of colorectal cancer

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Hereditary Colorectal Cancer

• ~5% of all CRCs are due to a strong inherited predisposition
• Occur due to inherited alteration in a gene usually protecting against cancer
• Cancer syndromes
  – Lynch Syndrome (HNPCC)
  – Familial adenomatous polyposis (FAP)
  – MYH associated polyposis (autosomal recessive)
  – other rare cancer syndromes
    • Pol D/E, Juvenile polyposis, Peutz Jehgers
Lynch syndrome (HNPCC)

- 3-5% bowel cancers due to Lynch Syndrome

- Increased chance of
  - bowel cancer (50-80%)
    - Can be young ages (25-55)
  - Endometrial cancer (30-60%)
    - Can be premenopausal
  - Ovarian cancer (10%)
    - Epithelial, endometrioid, not borderline

- Others
  - Duodenal, pancreatic, stomach, transitional cell bladder/renal tract.
How is Lynch syndrome inherited?

- Inherited in a dominant way
- Risk of inheriting mutation is 50% (1/2), but...
- Mutations are not 100% penetrant, so not all mutation 'carriers' will develop cancer
- 4 genes involved: MLH1, MSH2, MSH6, PMS2
How can we diagnose Lynch syndrome?

- Immunohistochemistry on tumour sample
  - NICE guidelines recommend testing all bowel cancers
How can we diagnose Lynch syndrome?

• If cancer tissue tests suggest Lynch syndrome
  – Additional tests of BRAF and promoter methylation should be done to rule out sporadic cases

• Proceed with genetic testing

• Test blood sample (or saliva) from someone who has had bowel cancer for alterations in Lynch syndrome genes
  – MLH1, MSH2, MSH6, PMS2

• Can identify specific gene alteration for the family & confirm Lynch syndrome

• Can enable other family members to then be tested for that specific gene alteration.
Surveillance in Lynch Syndrome

- Known gene carriers and 50% risk
- Bowel cancer
  - Colonoscopy every 2 years from 25
  - or 5 years before youngest case if <25
- Endometrial cancer
  - Annual screening from 35
  - US-scan
  - Pipelle biopsy (endometrium)
- Ovarian cancer – consider ovary removal
- Refer for other sites if cases in family
Surveillance Reduces Risk of Colorectal Cancer

% of subjects with CRC

Years of follow-up

No surveillance

Surveillance

11.9%

4.5%

ASCO
## Lower risk cancers

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>lifetime risk(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal (m)</td>
<td>50-80</td>
</tr>
<tr>
<td>Colorectal (f)</td>
<td>30-70</td>
</tr>
<tr>
<td>Endometrial</td>
<td>30-60</td>
</tr>
<tr>
<td>Ovarian</td>
<td>10</td>
</tr>
<tr>
<td>Gastric</td>
<td>10</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1-4</td>
</tr>
<tr>
<td>Small bowel</td>
<td>4-7</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>3</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>2</td>
</tr>
<tr>
<td>Ureter, renal pelvis</td>
<td>4-6</td>
</tr>
<tr>
<td>Other urinary tract</td>
<td>?</td>
</tr>
</tbody>
</table>

*Image: Aarnio M et al., Int J Cancer 64:430, 1995*
Familial Adenomatous Polyposis (FAP)
colorectal polyposis
Familial Adenomatous Polyposis (FAP)

- Accounts for <1% of CRC
- Affected individuals develop 100s-1000s adenomatous polyps in colon and rectum
- Variable age of onset of polyps, from childhood to 40+
- Inevitable progression to malignancy if untreated
- CRC average age at diagnosis 35
- 30% cases are due to de-novo mutations (No Family History)
- Can get milder ‘attenuated’ form
FAP: age and development of adenomas and carcinomas

% patients

0 20 40 60 80 100

Age

Adenoma
Carcinoma

Bussey HJR. Familial Polyposis Coli, 1975
FAP

- Everyone with FAP gets adenomas 100%
- Untreated - leads to ~100% risk of cancer
- Caused by alterations in \textit{APC} gene
- Autosomal dominant inheritance
FAP management

- Those at 50% risk and family mutation known:
  - offer predictive genetic test age 10-12

- Gene carriers or those at 50% risk where family mutation not known
  - start annual colonoscopy from 10-12 years

- When mutation found/multiple polyps present
  - elective surgery to remove the colon
**Extracolonic manifestations of FAP**

- Desmoid tumours (connective tissue)
  - locally invasive, usually abdominal

- CHRPE (congenital hypertrophy of retinal pigmented epithelium)

- Sebaceous cysts

- Jaw cysts (benign osteomas)

- Upper GI polyps with low malignant potential

- Brain tumours (rare)
MUTYH-Associated Polyposis (MAP or MYH)

- Recessive inheritance
- Fewer polyps than FAP (usually 10-100)
- Later onset than FAP (mean 51 years)
- Genetic test for carriers
  - 4 common mutations in MUTYH
- 25% of cases with >9 polyps but no FH CRC are due to MYH mutations
Autosomal recessive inheritance
If my cancer is genetic, what does it mean for me?

• Will it come back?
  – Genetic cancers are not necessarily more aggressive
    • Staging and response to treatment is more important
  – Some ‘genetic’ cancers respond better to treatment
  – Future targeted treatments

• Will I get another cancer?
  – Risk of certain other cancer types is increased in some predispositions
    • Eg. In Lynch syndrome: Endometrial, ovarian, ureter, pancreatic
What does it mean for my family?

• If you are the only person to have had cancer and at a ‘typical’ age- the risk is not likely to be increased.

• If your cancer is genetic the risk for your relatives may be increased.

• We may be able to arrange extra screening for them.

• Genetic testing may be helpful.
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Colorectal Screening

Population

- Faecal occult blood test (National Bowel Screening, 60-70)

Risk

- Moderate
  - Colonoscopy 5 yearly from 35 – 75
  - Colonoscopy at 35 and at 55yrs
  - Colonoscopy at 55yrs

- Mod-High
  - Colonoscopy 3-5 yearly from 35 – 75yrs
  - Or start 5yrs before age of youngest diagnosed relative

- Lynch Syndrome confirmed
  - Colonoscopy 2 yearly from 25 – 75yrs
  - Gynaecological screening annually from 35yrs
  - Other screening (upper GI/urinary tract) if family history
  - Tissue Studies & Genetic testing?
Screening - Bowel Cancer

• Benefits
  – Early detection cancers
  – Detects + removes precancers (polyps)
  – Reduces risk bowel cancer

• Limitations
  – Unpleasant
  – Small risk of perforating bowel
How do I get referred?

- Every region has a regional genetics centre
- Speak to your GP, surgeon or oncologist about your family history
- Ask for referral if you are concerned.

http://www.bshg.org.uk/
Referral guidelines

- Colorectal cancer (or colorectal polyps)
- 1 first degree relative age under 45
- 2 close relatives (including one first degree) average age under 60 (includes both parents)
- 3 or more close relative with other gastrointestinal, renal, urinary tract, uterine or ovarian cancer at any age
- Familial adenomatous polyposis (FAP) other single gene polyposis disorder
- Individual with 5 or more polyps
What happens next?

- Usually you need to complete a family history form.
  - Gives lots of important details about your family.
  - Fill in what you can, but don’t worry about anything you don’t know.
  - You can ask other relatives for more information if you wish.
  - Let us know if a relative has already done this, or if you are having problems with the form.
What do you do with the form?

- We need to get specific information about cancers occurring in the family
- Permission (consent forms)
- Cancer registry
- Specific hospital reports
- Medical records
What happens next?

- We may write to you to suggest screening for you.
- We may arrange an appointment for you.
  - With a consultant geneticist or genetic counsellor
- Discuss
  - Whether the cancer is likely to be inherited
  - The risk for family members
  - Whether they (or you) should have screening
  - Whether Genetic Testing is helpful
What’s New
Aspirin and bowel cancer

- There is some evidence that taking aspirin at a low dose for 4 years or more could reduce the risk of bowel cancer.

- It may be beneficial for people with Lynch syndrome to take 75mg enteric coated aspirin daily from age 35yrs onwards.

- However aspirin can cause health problems in some people so it is important to discuss this with your GP first.

- CAPP3 research study is now recruiting to gather further evidence of benefit.
100,000 Genomes Project

- Aims to sequence entire genetic material for 100,000 people with rare diseases and cancers
- Sequence of entire human genome
  - Approximately 20,000 genes
  - 3 billion letters
  - Detects genetic alterations causing disease which can help
    - Improve Diagnosis
    - Improve Treatment
    - Screening for family members
Any questions