# Inherited bowel cancer and other aetiological/predisposing factors

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# Introduction

- Colon cancer affected > 145,000 individuals in 2005 in U.S.
- 3rd leading cause of death due to cancer in U.S.
- Up to 30% of these cases exhibit familial clustering
- Approx. 3-5% of colon cancers are associated with high-risk, inherited colon cancer syndromes.

# Classification

- Inherited colon cancer syndromes classified by polyp histopathology:
  - Adenomatous
  - Hamartomatous

- Syndromes characterised by adenomatous polyps:

  - FAP (which also includes attenuated FAP)
  - Gardner's Syndrome
  - Most cases of Turcot's Syndrome
  - HNPCC (or Lynch Syndrome)
  - MUTYH – associated polyposis (MAP)

# Familial Adenomatous Polyposis

- Autosomal-dominant syndrome

- Characterised by 100s or 1000s of adenomatous polyps in the colon as well as extracolonic tumours of the duodenum, pancreas and thyroid.

# Familial Adenomatous Polyposis (cont)

- Less than 1% of all colorectal cancers.
- Left untreated, virtually 100% with this syndrome eventually develop colon cancer.

# FAP Variants

- Gardner's Syndrome: Osteomas and epidermoid cysts in addition to colon polyps.

- AFAP: milder form of FAP = fewer colon adenomas  and cancer development at older age.
- Turcot's Syndrome: CNS neoplasms (medulloblastomas) in the presence of multiple colonic adenomas.

# FAP Variants

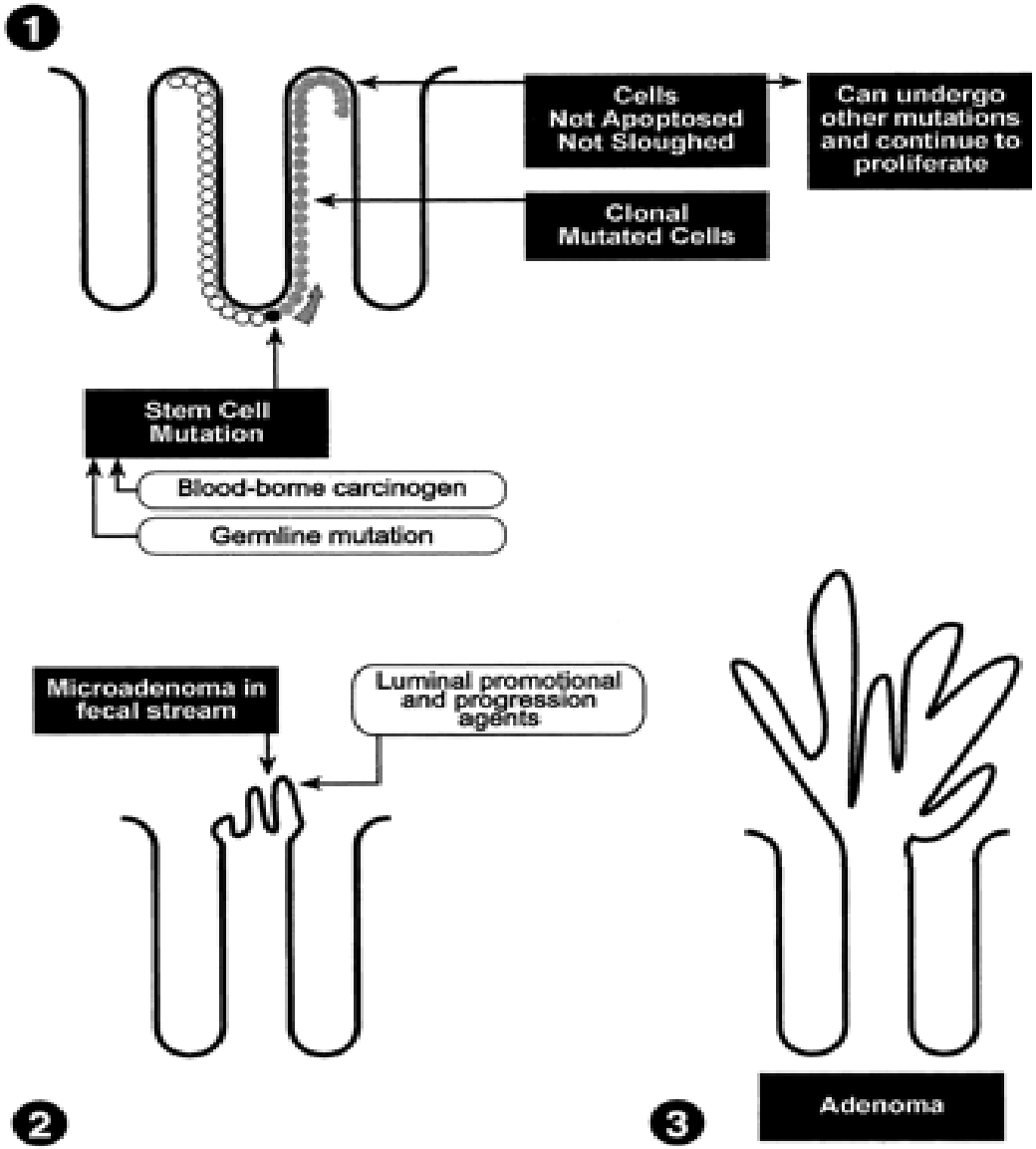
- FAP and its variants result from mutations in the APC gene

- APC = tumour suppressor gene – interacts with other intracellular proteins to block DNA transcription that would otherwise lead to uncontrolled cell growth

- APC regulates migration *of enterocytes up the colonic crypt.*

# FAP Variants

- 30% of FAP cases arise *de novo and patient is the first person in the family to be affected*




1. Mutation of APC produces abnormalities in cell proliferation, migration and adhesion.
2. Abnormal cells accumulate at top of crypt
3. Other mutations likely – adenoma formation

# MUTYH-Associated Polyposis

- A significant subset of patients with MAP and a negative genetic test for APC mutations have biallelic mutations in MUTYH
- MAP individuals present at an older age than those with FAP
- Number of adenomas at presentation is variable.
- Associated with rare extracolonic malignancies (incl. Osteomas, gastric & duodenal cancers)

# Hereditary Nonpolyposis Colorectal Cancer

- Autosomal-dominant: mutations in a DNA MMR gene, most frequently in MLH1 or MSH2
- Mutation in one of these genes confers approx. an 80% lifetime risk of developing colorectal cancer.
- Characterised by early onset colorectal, endometrial, gastric and GU cancers in individuals with strong family h/o cancer.

# Amsterdam II Criteria for the Diagnosis of HNPCC

- 3 or more relatives with HNPCC-associated cancer one of whom is a 1st -degree relative of the other two (FAP should be excluded)

- Cancer in at least 2 generations of the same family

- At least one cancer case diagnosed before the age of 50

# Hamartomatous Polyposis Syndromes

- Hamartomas are non-malignant masses of tissues that normally make up the organ in question

- Can occur sporadically, but when in large numbers or with other suggestive features might be part of a cancer-predisposition syndrome:

  - Juvenile Polyposis Syndrome

  - Peutz-Jeghers Syndrome

# Juvenile Polyposis Syndrome

- Autosomal-dominant syndrome

- Diagnosed when 3-10 juvenile polyps are found in colon or any juvenile polyps anywhere else in the GI tract

  - Almost 50% of JPS is caused by SMAD4 mutations, with the rest caused by mutations in BMPR1A, both involved in TGFß signalling

  - Individuals with JPS have a lifetime colon cancer risk of 60%

# Peutz-Jeghers Syndrome

- Rare autosomal-dominant condition
- Histologically distinct polyps in colon, SB and stomach, and pigmentation of perioral and buccal mucosa.
- About 50% of PJS cases are caused by mutations in the LKB1 gene
- PJS is estimated to confer a 40% lifetime risk of colorecta cancer

# Other predisposing factors

- The highly penetrant causative mutations in FAP, HNPCC and the other inherited cancer syndromes underlie cases of colorectal cancer that have a strong hereditary component, with little environmental influence.

- There are also several low penetrance mutations that contribute to CRC susceptibility in an additive way involving gene-environment interactions.

# Other predisposing factors

- Distinction between *'sporadic' & 'familial'* cases & between *'genetic' & 'environmental'* predisposing factors has become blurred.
  - Meat and heterocyclic amines: are important in the aetiology of colon cancer - shown to be carcinogenic in animals.
  - Nitrosamines are also plausible human colon cancer carcinogens.

# Other predisposing factors

- Smoking: tobacco smoke is a major source of many carcinogens incl. heterocyclic amines, polycyclic hydrocarbons & nitrosamines.
  APC is a target for heterocyclic amines in rats.

- Alcohol:
  - known to inhibit DNA repair;
  - may exert its effect through associated deficiencies in nutrients esp. folate.

# Other predisposing factors

- Physical activity & obesity: physical activity might stimulate colon peristalsis, thereby decreasing transit times.

- Vegetable rich diet: is tightly linked to lower risks of almost all epithelial cancers.

- NSAIDs: clearly suppress COX-2 and are capable of inhibiting polyp growth even in FAP individuals.

# Other predisposing factors

- Exposure of the bowel to chronic inflammation associated with UC or Crohn's disease confers significant & substantial increased risk of colorectal cancer.

# Other predisposing factors

- HRT: ER hypermethylation increases with age and is a central feature of colon cancer suggesting that declining levels of oestrogen may be important.

- HRT: The inverse relationship between HRT and both polyps & cancer maybe a consequence of replacing the declining endogenous oestrogen levels.

# Conclusion

The interaction between genes & environment is defined as co-participation in the SAME CAUSAL MECHANISM leading to disease.

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