Hereditary Colon Cancer

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Family History of Colon Cancer

• Most colon cancer occurs in patients without a family history
  • 70-80% is sporadic

• Only 20-30% of cancer patient have family history
  • Most have only 1 relative with CRC
  • Not a “syndrome”

• Only 2-5% of CRC patients have “hereditary colon cancer”
Hereditary Colon Cancer Syndromes

• Lynch Syndrome
  • Hereditary Non-Polyposis Colon Cancer (HNPCC)

• Familial Adenomatous Polyposis

• MUTYH-Associated Polyposis
Introduction to Genetics

• Genes = DNA
  • Originally it was thought these mostly coded for amino acids/proteins
    • Structural genes
  • We now realize that the vast majority of DNA is regulatory

• Nearly all cells in an person carry the exact same DNA
  • Which genes get turned on in a given cell at certain time = gene regulation
    • Heart cells and GI mucosal cells carry the same DNA, make very different proteins
    • Grow at very different rates
    • Wide variation in longevity: Mucosal cells - few days, myocardial cells - many decades
Intro to Genetics

• Changes in DNA = mutations

• How mutations occur
  • Damage to DNA (radiation)
  • Most common: mistakes made when cells replicate
    • Repair mechanisms

• Somatic versus Germ-line mutations
  • Somatic mutations occur in cells *after conception*
    • Affect function of that individual cell and its subsequent tissue
    • Not inherited
    • Not passed on
  • Germ-line mutations
    • Present in sperm or ova
    • Inherited, found in essentially all cells of the body
    • Can be passed on to future generations
Dominant vs. Recessive

- Dominant genes: need mutation on only one chromosome to get disease
  - Example: Huntington’s disease
  - Half of all offspring expected to get it
  - Does not skip generations

Therefore, you can inherit the disease only if your parent has it
Dominant vs. Recessive

- Recessive genes: mutations on both copies required to get disease
  - Example: sickle cell anemia
  - Carriers with one bad gene do not have the disease
  - Must receive one bad gene from each parent (both carriers) to get disease
  - Offspring of patients expected to be carriers, but not to get the disease

Can inherit disease without either parent showing signs of the disease
Intro to Genetics

• Genotype vs. Phenotype
  
  • Genotype: the *genes* you inherit
  
  • Phenotype: the actual *expression* of those genes
  
  • Penetrance: how *likely* the gene is to get expressed
    • Sickle cell – High penetrance
      • Most people who have the mutation on both chromosomes get the sickle cell anemia
    
    • Hemochromatosis – Low penetrance
      • Most people who have the mutation on both chromosomes do not get clinical iron overload
What makes cells develop into cancer?

- Disorder of cellular regulation
  - Replicating cells grow too much
    - Inappropriate cellular replication, or too rapid

- Cells don’t know when to die
  - Role of senescence: “programmed cell death”

- Cells don’t stay where they belong
  - Invade surrounding tissues
  - Metastasize
Biology of Colon Cancer

• Adenocarcinoma arises from the colonic mucosa (epithelial cells)
  • Normal mucosa: cells on the surface are mature, not replicating
  • Replication occurs in crypts
Average Colon Epithelial Cell Lives Only 6 Days
Biology of Colon Cancer

• Adenoma-carcinoma sequence:
  • Reproducing cells in epithelial crypts acquire mutations
  • Mutated cells grow to form polyps
  • Further mutations: polyps progress to cancer
  • This process typically takes 10 years
Biology of Colon Cancer

- **“Multi-hit hypothesis”**
  - Multiple mutations are required to turn a colonic cell cancerous
    - Polyps have fewer mutations
    - As they accumulate more mutations, polyps larger, more aggressive

Fully established cancers have at least 4 separate mutations in growth-regulating genes
Why is the Colon Prone to Cancer?

• Mucosal crypt cells reproduce rapidly
  • Mutations are likely to occur as mistakes made with constant DNA replication
    • Repair of replication errors critical

• Normal cells have high turnover
  • Average lifespan only 6 days
    • Regulatory genes for senescence (programed cell death) critical
    • If these are knocked-out, cells become “immortalized”

• Exposure to mutagens is common
  • Constant exposure to stool
    • Fat-soluble carcinogens
  • Longer “dwell time” compared to other parts of the GI tract
    • Esophagus: seconds, stomach: minutes, small bowel: hours, colon: days
Biology of Colon Cancer

• Sporadic colon cancer
  • These mutations must occur at random (somatic mutations)
    • Typically don’t accumulate to form a cancer until 50’s or later

• Hereditary colon cancer
  • Patient born already with some mutations
    • Has “head start” on forming polyps or accumulating more mutations
    • Cancers much more common, develop at younger age
Incidence of colorectal cancer by age

FAP: familial adenomatous polyposis; HNPCC: hereditary nonpolyposis colorectal cancer.
Hereditary Colon Cancer Syndromes

• Familial Adenomatous Polyposis
  • Classic FAP
  • Attenuated FAP

• Lynch Syndrome (HNPCC)

• MUTYH-Associated Polyposis

• Other:
  • Serrated polyposis syndrome
  • Juvenile polyposis
  • Peutz-Jeghers syndrome
  • Other germline mutations associated with increased risk of colon cancer
Familial Adenomatous Polyposis

• Not the most common cause of hereditary cancer
  • Affects only 1/10,000 people in the US
  • < 1% of all colon cancers due to FAP
  • Most dramatic, best understood of CRC syndromes

• Mutation in single gene: APC
  • Affects early stage of polyp formation
  • Patients form *lots* of polyps
    • Typically > 100, often >1,000
FAP

• Patients born with one mutated APC gene
  • Rapid cell replication in crypts: second somatic mutations eventually occur
    • Usually in teens or twenties
  • Once APC knocked out, polyps form

Head-start on polyp formation

Polyps first appear at age 10-25, become more numerous over time
Due to the sheer number of polyps, colon cancer follows inevitably
FAP – Classic Form

• As only 1 copy of the mutation needed for disease, FAP is dominant
  • Each child of affected parents has 50/50 chance of inheriting it
  • Does not skip generations

• Has high penetrance
  • Essentially 100% will eventually develop CRC (complete penetrance)
  • Hundreds or thousands of adenomatous colon polyps
    • These polyps are not any more aggressive individually
    • Strength in numbers
      • Eventually some will turn malignant
    • Start at early age

• Average age of cancer in 40’s, but can develop cancer in teens.
FAP - besides colon cancer

• **Extracolonic manifestations** *(Gardner’s syndrome)*
  • Duodenal, ampullary adenomas and cancers develop in > 50%
  • Gastric polyps found in nearly all FAP patients
    • Fundic gland, sometimes with low-grade dysplasia, rarely progress to cancer
  • Thyroid Cancer – 3%
  • Ileal cancer, cancer in J-pouch
  • Desmoid tumors
  • Other:
    • osteomas of jaw
    • brain tumors
    • retinal lesions
    • benign adrenal tumors
Management of Familial Polyposis (Classic)

• Suspect it if numerous polyps found, especially > 100
  • Genetic counselling and testing for APC mutation
    • Also test first-degree relatives
      • Second-degree testing unnecessary, will not skip generations

• Total colectomy or proctocolectomy
  • If rectum left in place, will need lifelong rectal surveillance
  • Delay in colectomy can result in metastases

• Role for NSAIDs?
  • Sulindac and celecoxib (Celebrex) can reduce number of polyps
    • They do not reduce the overall incidence of cancer, or need for colectomy
    • May have role in reducing duodenal or rectal adenomas
Management of Familial Polyposis (Classic)

• Survey UGI tract
  • Duodenal adenomas common, all require removal
    • Most common cause of cancer death following colectomy in FAP
    • Side-viewing duodenoscope to find ampullary lesions
      • Frequency of EGD surveillance depends on adenomas found (Spiegelman score)
  • Gastric polyps
    • Typically fundic gland, numerous but not pre-malignant
    • Low-grade dysplasia fairly common, but progression to gastric cancer is rare
      • Polypectomy not required in most cases
      • Consider polypectomy for antral, large gastric polyps

• Survey J-pouch, ileostomy, rectum

• Yearly thyroid exam + ultrasound
Desmoids in FAP

• Benign fibrotic tumors, usually abdominal or abdominal wall
  • Do not metastasize, not cancer
  • Locally aggressive
    • Infiltrate mesentery, encase nearby vital organs, nerves or vessels
• Occur in ~20% of FAP patients
  • More common in women
  • Often appear 2-3 years following abdominal surgery
    • Laparotomy thought to trigger their development
• Major cause of morbidity and mortality
  • 10 year prognosis: > 60% survival
  • Ultimate cause of death in 10% of FAP patients
• Difficult to treat
  • NSAIDs
  • Anti-estrogens (tamoxifen)
  • Chemotherapy
  • Radiation
  • Surgery – usually not feasible or curative
Attenuated FAP

• Polyposis that is less severe and presents later in life than classic FAP
  • Polyps typically > 20 but fewer than 100
  • Average age of diagnosis of polyposis: 44
  • Average age of colon cancer: 56

• Mutation in same gene (APC)
  • Typically found near one of the ends of the gene, rather than in the middle
    • Mutation is less severe/less disruptive of APC gene function
    • Dominant inheritance

• Colon cancer develops in “only” 75%
  • Lower penetrance (attenuated phenotype)
  • Annual surveillance with polypectomy is acceptable
    • Colectomy reserved for cancer or unresectable polyps

• Extracolonic manifestations of FAP similar, but less frequent
  • Surveillance similar
Familial Polyposis – Take Home

• Polyposis that inevitably leads to colon cancer
  • Dominant mutation in APC gene, does not skip generations
• Usually presents in teens or twenties
  • Cancer by 40’s, often sooner
• Treatment is colectomy or proctocolectomy
  • Delaying surgery may lead to metastasis
  • NSAIDs have limited role, cannot prevent need for surgery
• Follow-up
  • Surveillance of UGI tract for duodenal adenomas
    • Surveillance of rectum, j-pouch or ileostomy
      • May be role for capsule endoscopy
  • Thyroid ultrasounds
• Avoid abdominal surgery when possible (desmoids)
Lynch Syndrome

• Most common of hereditary colon cancer syndromes
  • Lynch-associated cancers account for 3% of all colon cancers

• Primarily colon cancers, but associated with other malignancies
  • **Endometrial**: 2% of all endometrial cancers are Lynch-related
  • **Ovarian**, gastric, small intestine, ureteral, skin (Muir-Torre)

• Mutation in mismatch repair genes
  • Multiple genes involved
    • MLH1, MSH2, MSH6, PMS2, EPCAM
    • This makes genetic testing more complicated

• Dominant germ-line mutation
  • Children of affected patients have 50/50 chance of having Lynch themselves
  • Siblings and parents are also at risk
  • Does not skip generations
Mismatch Repair (MMR)

- DNA replication highly regulated
  - DNA unzipped, copied, rezipped each time a cell divides
  - Mistakes made during replication uncommon: 1 per million
    - Given the number of cells this leads to lots of mistakes

- Mismatch repair – recognizes mistakes, clips out errors

- Complicated process, numerous steps, various genes
  Defect in repair genes leads to subsequent new mutations
  Somatic – occur in cells but not passed on to offspring
  Cells descendant from these cells have the new mutations

Mutations particularly likely to occur in areas of repeated sequences, “microsatellites”
  Result is known a microsatellite instability, or MSI
MMR Gene Defect

- Mutation in an inherited gene that leads to more mutations (somatic)
  - When these new mutations affect regulatory genes, cancer can result
- High replication rate of colon cells = high rate of mismatches
- Tend to affect regulation of already-growing polyps
  - Accelerates malignant transformation of polyps, rather than causing more polyps
Lynch Syndrome

• Result of MMR gene defects:
  • Numerous mutations affecting regulation of growth of established polyps
    • Polyps tend to be larger, progress to cancer faster

• Lynch syndrome colon cancers
  • Arise from colon polyps, but this is not *polyposis*
  • Progression from polyp to cancer is more rapid
    • 2-3 years in Lynch vs. 10 years in sporadic cancers
    • Therefore, 5-year surveillance inadequate
  • Develop at younger age (40-60) compared with sporadic cancers (average 69)
  • More often right-sided
  • Tumors usually have microsatellite instability (MSI) due to mismatch repair

• HNPCC: Hereditary Non-Polyposis Colon Cancer syndrome
  • Essentially same thing as Lynch syndrome
    • HNPCC based on family history (pedigree) rather than MMR mutation
Lynch Syndrome

- **Suspect it in a young person (<60) with colon cancer**
  - Especially if 1st degree relative with colon, gynecological, or UGI cancers

- Right-sided colon cancers

- Tumor has microsatellite instability or missing MMR gene products
  - Caveat: 15% of sporadic cancers have MSI or absent MMR *without* Lynch
  - These result from *somatic* mutations in the tumor
    - Especially in patients with BRAF mutations

- Anyone with sebaceous cell adenoma (skin): Muir-Torre syndrome
Sebaceous Adenoma in Muir Torre

Dome-shaped, < 5 mm
Lynch Syndrome: diagnosis

- **Refer patients for genetic counselling as well as genetic testing**
  - Merely sending out for genetic testing is inadequate
  - Many different genes to check
  - Interpretation of results is complicated
    - If no gene defect identified, have not ruled-out HNPCC
  - Genetic testing expensive, not always covered by health insurance
  - Concerns about insurability once results available

- **When strong family history, but patient does not yet have cancer**
  - Test the affected *family member with cancer first*, when possible
    - If specific mutation found (MLH1, MSH2, MSH6, PMS2, EPCAM)
      - Test your patient for that mutation
    - If no mutation found in member with cancer, no point in testing your patient
Cancer Risks in Lynch Syndrome

![Graph showing cancer risks in Lynch Syndrome](image)
Effects of Lynch Syndrome Genotype

• **High penetrance**, but not complete penetrance

• **Lifetime risk of colon cancer is 70%**
  • Men > women
  • Multiple colon cancers common. Second colon cancer develops in 20-60%.
    • Synchronous cancers found in 10%

• **Lifetime risk of endometrial cancer is 25-70%**
  • Younger age (40)

• **Lifetime risk of ovarian cancer 10%**
  • vs. 1.5% in general population
  • Younger age (40)

• Other:
  • stomach, small bowel, urologic, brain, biliary, skin
Lynch Syndrome: management

**Intensive surveillance**
- Colon cancer: colonoscopy every 1-2 years age starting age 25
- Endometrial: yearly age 30, endometrial biopsy and pelvic ultrasound
- Ovarian: annual pelvic US
- Urologic: annual urine cytology
- Sebaceous cell tumors: annual skin exam

**Gastric surveillance: it depends**
- Perform EGD with biopsy ~age 30: assess for risks
  - H. pylori, atrophic gastritis, intestinal metaplasia,
  - Other: Family history of gastric Ca, Asian immigrants
- If no risk factors, no further EGD surveillance
- If risk factors present repeat every 3 years

**? capsule endoscopy**
Lynch Syndrome: management

• Surgical Intervention:
  • Prophylactic hysterectomy with bilateral salpingo-oophorectomy
    • Recommended for all women after done childbearing, or age 40

• Colectomy
  • Not done unless colon cancer or unresectable adenoma found
  • If cancer develops: total colectomy with ileorectal anastomosis
    • Not merely a segmental resection
    • 25% will develop second colon cancer within 8 years
  • Rectum needs continued yearly surveillance
  • Prognosis after resection is good, despite rapid tumor progression
  • Women offered TAH with BSO at same time of colectomy if not already done

• Chemoprevention:
  • Aspirin may reduce risk of cancers, but effect seems to be small
Lynch Syndrome: Take-home

- Dominant genetic syndrome that leads to *inability to repair mutations*
- Mutation can be in one of many different MMR genes
  - Difficult to diagnose with simple genetic testing
- Results in colon, endometrial and ovarian cancers
  - Usually at younger ages
  - 70% will get colon cancer. More than half of women get endometrial or ovarian cancer
- Suspect it: family history, right-sided cancer, young, tumor MSI or MMR defects
- Does not cause polyposis
  - However, sporadic polyps progress much more rapidly to cancer
  - Colonoscopic surveillance should be much more intense, typically every year
- Surgical management
  - Colectomy for colon cancer
  - Prophylactic TAH with BSO for women over 40
- Surveillance for colon, endometrium, ovaries, skin, ureters and high-risk stomach
- Send for genetic counselling, don’t just order genetic testing
MUTYH-Associated Polyposis

• Colonic **polyposis**, but **no APC** mutation
  • Fewer polyps than FAP: at least 10 polyps but usually < 100
  • Generally diagnosed at later age: 40-60
    • More than half present with cancer at initial diagnosis
  • MUTYH associated polyposis: **much more rare** than FAP or Lynch syndrome
    • Responsible for < 1% of all colon cancers.

• **Recessive** disorder
  • MUTYH mutations on **both chromosomes** necessary for disease
  • Single MUTYH mutations found in 1-2% of the general population (carriers)
  • No obvious family history of cancer
    • However, siblings should be tested, as each has 25% chance of also having disorder
MUTYH-Associated Polyposis

• MUTYH gene involved in DNA repair
  • Not a mismatch-repair like Lynch, but defect results in increased mutations
  • Typically leads to somatic mutations in APC gene and KRAS: polyposis
MUTYH-Associated Polyposis: management

• Diagnosis:
  • Patient with polyposis (>10 polyps) sent for genetic counselling and testing
  • APC gene mutation negative -> testing for MUTYH mutations
    • Mutations on both copies of MUTYH genes
  • Siblings of patients with MUTYH-associated polyposis
    • Should be offered genetic counselling as well
    • 25% will have the disease, 50% will be carriers

• Prognosis:
  • Risk of colon cancer is high: 75% lifetime
    • Can develop cancer even with few polyps
  • Some risk for FAP-type extracolonic disease, but less
    • Duodenal/gastric polyps, thyroid cancer
    • Rarely: sebaceous adenomas, desmoids
MUTYH-Associated Polyposis: management

• Management
  • Patients with colon cancer or unresectable polyps: total colectomy
    • Followed by yearly surveillance of rectum/pouch
  • Those found to only have polyps:
    • Removal of all polyps found
    • Yearly colonoscopy
  • Asymptomatic MUTYH/MUTYH genotype, no polyps
    • Colonoscopy starting age 25, then every 1-2 years
• Probably should get EGDs like in FAP, check for duodenal adenomas
• Thyroid screening each year
MUTYH-Associated Polyposis: Take-home

• Rare cause of polyposis
  • Patients negative for APC mutations

• Recessive disorder
  • Skips generations
  • Siblings are at risk and should be tested/counselled

• Less aggressive than Familial Polyposis due to APC mutation
  • Fewer polyps, form later
  • Still have 75% chance of getting colon cancer (vs. 100% in FAP)
  • Surveillance with polypectomy is acceptable management
Other Hereditary Polyposis Syndromes

• **Serrated Polyposis Syndrome**
  • More than 20 serrated adenomas, or > 5 large serrated adenomas
  • Thought to be familial, but genetics have not been worked out
    • Patients often with 1st-degree relative with serrated polyposis
    • Colon cancer in family members reported in nearly half
    • No mutation identified
  • Patients with serrated polyposis syndrome should get yearly colonoscopy
    • Family members of patients should start screening age 40, repeat every 5 years

• **Juvenile Polyposis**
  • Polyps usually appear before age 10
    • Hamartomas, not adenomas. Nonetheless, adenomatous change can occur
    • Colon cancer eventually develops in 70%
  • Very rare: 1 per 100,000 in population

• **Peutz–Jeghers Syndrome**
  • Hamartomatous polyps of small bowel, stomach, and colon
    • Usually before age 10, symptomatic in teens and 20’s
  • Freckle-like pigmented spots on lips, gums, palms, and soles
    • Colon cancer risk ~ 40% lifetime
    • Other GI cancers: stomach, small bowel, pancreas
  • Even more rare than juvenile polyposis
Other Inherited Causes of Colon Cancer

• BRCA mutations
  • May be associated with ~ 2-fold increased risk of colon cancer
  • Screening colonoscopy:
    • Generally similar to FHx of sporadic colon cancer in a single 1st-degree relative
      • Start age 40, then every 5 years

• CHEK2 mutations
  • Like BRCA, may be associated with increased CRC risk (1.5 fold)
  • Screening colonoscopy: start age 40, then every 5 years
Hereditary Colon Cancer - Summary

• Most colon cancers are sporadic
  • Only ~ 5% of all colon cancers related to a known hereditary syndrome
    • If you have that syndrome, it is very important

• Most common is Lynch Syndrome
  • Colon cancer in 70%, endometrial/ovarian in > half of women
  • Progression from polyps to cancer is accelerated
    • Should get colonoscopy every year
    • Women screened for endometrial/ovarian. Consider prophylactic TAH/BSO
    • EGDs, urine cytology and skin checks

• Familial polyposis: 100-1000’s of polyps.
  • Cancer is inevitable. Treatment is colectomy
  • After colectomy: surveillance of duodenum and thyroid
  • Can have attenuated form (appears later, less severe)
Hereditary Colon Cancer - Summary

• Main syndromes are dominant
  • Don’t skip generations
    • If your parents don’t have them, it doesn’t matter if you grandparents/cousins did

• Exception is MUTYH-associated polyposis
  • Recessive polyposis

• Most other syndromes are very rare or poorly understood

• BRCA and CHEK2 are not really colon cancer syndromes
  • Associated with slightly increased CRC risk
    • Should be treated like typical family history of colon cancer in terms of screening