

HEREDITARY COLON CANCER

Sporadic disease, accounts for approximately 70 percent of all colorectal cancer:

- -older than 50 years of age
- -dietary factors
- -environmental factors.

Fewer than 10% is an inherited predisposition to colorectal cancer-

- with polyposis:
 - familial adenomatous polyposis (FAP)
 - the hamartomatous polyposis syndromes (eg, Peutz-Jeghers, juvenile polyposis)
- without polyposis:
 - hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome I)
 - the cancer family syndrome (Lynch syndrome II).
 - high risk of developing colorectal cancer
 - the genetic mutations

"Familial" colorectal cancer- up to 25% of cases

- a family history of colorectal cancer, but the pattern is not consistent with one of the inherited syndromes
- increased risk of developing colorectal cancer, although the risk is not as high as with the inherited syndromes.
- Having a single affected first-degree relative (ie, parent, child, or sibling) increases the risk of developing colorectal cancer 1.7-fold.
- The risk is further increased if two first-degree relatives have colorectal cancer
- If the case is diagnosed before 55 years of age.

The clinical features that raise the suspicion for one of the familial forms of cancer:

- cancer that occurs at an unusually young age compared with its usual presentation
- The development of multiple tumors in a single organ, or bilateral development in tumors in paired organs
- The development of more than one primary tumor of any type
- A family history of cancer of the same type in first-degree relatives
- A high rate of cancer occurrence in the family
- Cancer occurring in an individual or within a family with congenital anomalies or birth defects

Familial Adenomatous Polyposis (FAP)

Hereditary Non-Polyposis Colorectal Cancer (HNPCC):

- Hereditary site specific colon cancer or Lynch syndrome
- Cancer family syndrome or Lynch syndrome II

Peutz-Jeghers syndrome (PJS)

Familial juvenile polyposis coli (FJP)

Familial Adenomatous Polyposis and variants:

- Turcot's syndrome (FAP associated with brain tumors),
- Gardner's syndrome (FAP with associated extraintestinal manifestations)
- attenuated familial adenomatous polyposis

- an autosomal dominant disease
- mutations in the adenomatous polyposis coli (APC) gene (chromosome 5q21-q22)
- one-third of patients with FAP have no family history -new germ-line APC mutations?
- 1/10,000 to 1/30,000 live births
- less than 1% of the total colon cancer risk in the United States.
- The diagnosis -more than 100 adenomatous colorectal polyps
- Polyposis typically develops in the second or third decade of life.

Specific APC mutations with a clinical phenotype:

- the classic form of FAP- mutations between codons 169 to 1393
- the attenuated form of APC mutations that are more 3' or 5'
- increased risk of colorectal cancer among Ashkenazi Jews
a mutation of I1307K
- profuse colorectal polyposis mutations between codons 1250 and 1464
- extraintestinal manifestations mutations in codons 1465, 15465, and 2621
- Retinal lesions mutations in codons 463 to 1444
- desmoid tumors mutations between codons 1445 and 1578
- periampullary lesions mutations downstream from codon 1051
- duodenal polyposis mutations in the central part of the APC gene (codons 279 to 1309)

An **attenuated** form of the disease (attenuated familial adenomatous polyposis coli):

- mutations in the APC gene
- presence of fewer colonic adenomas
- lower cancer penetrance
- an older age distribution of adenomas and cancer.

Turcot's syndrome -an association between brain tumors (primarily medulloblastomas and gliomas) and FAP.

Gardner's syndrome -extraintestinal lesions:

- desmoid tumors
- sebaceous or epidermoid cysts
- lipomas
- osteomas (especially of the mandible)
- supernumerary teeth
- gastric and duodenal polyps
- juvenile nasopharyngeal angiofibromas.

Extracolonic malignancies :

- Duodenal ampullary carcinoma
- Follicular or papillary thyroid cancer
- Childhood hepatoblastoma
- Gastric carcinoma
- CNS tumors (mostly medulloblastomas)

DIAGNOSIS

- more than 100 adenomatous colorectal polyps
- Polyposis typically develops in the second or third decade of life.
- Genetic testing
 - affected family member-detectable mutation in APC.
 - The method is protein truncation testing- more than 80 percent of the APC mutations
 - If a mutation is found in an affected family member, then genetic testing of all relatives at risk can provide a true positive or negative result
 - If a mutation is not identified, testing at-risk relatives is useless since the results will be inconclusive - false negative .

Hereditary Non-Polyposis Colorectal Cancer (HNPCC):

- Hereditary site specific colon cancer or Lynch syndrome
- Cancer family syndrome or Lynch syndrome II

- early age of onset
- predominant involvement of the right colon
 - 70% proximal to the splenic flexure
- tumors arising from colorectal adenomas
- the polyps tend to have villous histology
- poorly differentiated tumors
- five-year survival rate is better than that seen in sporadic
- The mean age at diagnosis 48 years (beginning from 20)

Lynch syndrome II

- a high risk of extracolonic tumors
- the most common - endometrial carcinoma (43%)
- ovary, stomach, small bowel, hepatobiliary system, renal pelvis or ureter, and possibly prostate

DIAGNOSIS of HNPCC

- The Amsterdam I and II criteria
- The Bethesda guidelines

Amsterdam Criteria

In 1990, The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer established research criteria for the diagnosis of HNPCC (known as the Amsterdam Criteria I)

- At least three relatives with colorectal cancer, one of whom must be a first degree relative of the other two
- Involvement of two or more generations
- At least one case diagnosed before age 50
- Familial adenomatous polyposis has been excluded
 - restrictive for clinical purposes, particularly in small families
 - Very small families that cannot be further expanded if there are only two first-degree relatives with colorectal cancer, if they involve two generations, and if one occurred under the age of 55.
 - Families with only two first-degree relatives with colorectal cancer if a third relative had a neoplasm at a very early age or there is a third relative with endometrial cancer.

Amsterdam Criteria II:

- With three or more relatives with histologically verified HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other and in whom FAP has been excluded.
- Involvement of two or more generations
- At least one case diagnosed before age 50
- Familial adenomatous polyposis has been excluded

Bethesda Criteria — A 1996 workshop sponsored by the National Cancer Institute proposed guidelines that could be used for identifying patients who should undergo genetic testing for HNPCC.

- Individuals with cancer in families that meet the Amsterdam criteria
- Patients with two HNPCC-related cancers, including synchronous and metachronous colorectal cancer or associated extracolonic cancers (endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell carcinoma of the renal pelvis or ureter).
- Patients with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma with one of the cancers diagnosed before age 45 years, and the adenoma diagnosed before age 40 years.
- Patients with right-sided colorectal cancer having an undifferentiated pattern (solid/cribriform) on histopathologic diagnosis before age 50 years.
- Patients with signet-ring cell type colorectal cancer diagnosed before age 45
- Patients with adenomas diagnosed before age 40.

RECOMMENDATIONS FOR HNPCC SCREENING AND TESTING —

Amsterdam criteria or the revised Bethesda criteria.

- genetic counseling for cancer risk assessment and coordination of genetic testing.
- patients who meet one of the first three Bethesda Criteria have direct genetic sequencing for mutations in MSH2 and MLH1 genes on a blood sample.
 - If this is negative, the tumor tissue should be tested for microsatellite instability (MSI) and/or immunohistochemical analysis (IHC) for protein staining of MLH1/MSH2.

- If the tumor is MSI-H but shows no evidence of loss of MLH1 or MSH2, IHC testing for loss of MSH6 or PMS2 protein can be considered.
- individuals who meet one of the remaining Bethesda criteria have MSI/IHC done on their tumor tissue as a first step with subsequent genetic sequencing on a blood sample if found to have MSI-H or missing protein on IHC
- Families that meet the Amsterdam I criteria (colon only) may benefit from MSI or immunohistochemistry
- It is not recommend routine MSI or IHC testing of all colorectal cancers for the detection of HNPCC.
- Relatives of patients diagnosed with HNPCC should be counseled and undergo screening.

Peutz-Jeghers Syndrome (PJS)- autosomal dominant disease.

- The PJ gene in most families has been mapped to chromosomal 19p13.3
- pigmented mucocutaneous macules flat, blue-gray to brown spots 1 to 5 mm in size that look like freckles
- PJS lesions occur most commonly on the:
 - lips and perioral region (94%)
 - hands (74%)
 - buccal mucosa (66%)
 - feet (62%)
- multiple gastrointestinal polyps:
 - polyps contain a proliferation of smooth muscle extending into the lamina propria in an arborization-like fashion;
 - the overlying epithelium is normal
 - Small intestine — 64%
 - Colon — 64%
 - Stomach — 49%
 - Rectum — 32%
 - The number of polyps ranges from 1 to more than 20 per segment of bowel
 - size 0.1-5 cm.
- The overall incidence of cancer was estimated in a study of 240 individuals with known mutations in STK11 .
 - The overall risk of developing cancer at ages:
 - 20-1%
 - 30-3%
 - 40-19%
 - 50-32%
 - 60-63%
 - 70-81%
- Gastrointestinal cancers —
 - Because hamartomatous polyps benign, it is a premalignant condition.
 - The distribution of gastrointestinal cancers is similar to that of the hamartomatous polyps and carcinoma arising in hamartomas has been clearly documented

- The St. Mark's Polyposis Registry and the John Hopkins Registry, which together followed 103 patients with PJS, found that 13 percent of patients developed gastrointestinal malignancy during follow-up.
- Major cancer sites were:
 - Small intestine — 48%
 - Stomach — 24%
 - Colon — 24%
 - Pancreas — 5 percent.
- The reason for the increased risk of gastrointestinal cancer is uncertain

Familial Juvenile Polyposis coli (FJP)

- FJP is a rare (<1/100,000 live births)
- autosomal dominant disease with high penetration.
- Germ-line mutations in a gene (SMAD4 also known as DPC4)
 - located on chromosome 18q21.1
- Children typically develop symptoms between the ages of 4 to 14
 - rectal bleeding and/or anemia (75% of cases)
 - rectal prolapse of polyps
 - abdominal pain
 - intestinal obstruction.
- FJP is associated with an increased risk for the development of colorectal cancer.
- Cancer is thought to arise from adenomatous change within the hamartomas, which has been found in approximately 8 – 47% of hamartomas from subjects with FJP.
- The risk of colon carcinoma in affected patients is unknown, but may be as high as 20%
- The average age of diagnosis of adenoma or adenocarcinoma in one series was 37.
- The risk of developing an adenoma or adenocarcinoma is greatest in patients who had at least three juvenile polyps or a family history of juvenile polyps
- No consensus has been established for optimal screening of asymptomatic individuals at risk for FJP or for the surveillance and clinical management of patients with known juvenile polyposis.
 - A guideline issued by the British Society of Gastroenterology recommends screening of at risk individuals with colonoscopy every one to two years beginning at age 15 to 18 (or earlier in patients who presented with symptoms).
 - Screening intervals can be extended at age 35.
 - Colonoscopic polypectomy with regular surveillance is probably adequate therapy if only a small number of polyps are present
 - Prophylactic surgery can be considered for those with:
 - a large number of polyps
 - multiple polyps that have adenomatous change and high grade dysplasia
 - polyps cannot be removed endoscopically
 - complications (such as bleeding) are not easily controlled
 - colorectal cancer as a feature of the family history
 - Upper gastrointestinal surveillance has been recommended every one to two years beginning at age 25 by upper endoscopy/enteroscopy or UGI with SBFT.

Nikolay Bugaev, M.D.