Hereditary Aspects of Colon Cancer

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Inherited colorectal cancer syndromes are responsible for a small percentage of all colorectal cancers, but affected individuals are at increased risk of gastrointestinal and extraintestinal malignancies. Gene testing plays an important diagnostic role and guides continued care to the patient and family members. Predisposition to colorectal cancer outside these inherited syndromes is less well defined, but recently established screening guidelines should prove to reduce the incidence of colorectal cancer in those with a familial risk. Colorectal cancer is preventable through recognition, treatment, and proper screening of those at risk.

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Worldwide, an estimated half a million new cases of colorectal cancers are diagnosed each year (1). In the United States colon cancer is the third most common cancer and the second leading cause of cancer-related deaths after lung cancer with an estimated 129,400 new cases and 56,600 deaths annually (2). The etiology is multifactorial, but environmental and genetic factors play key roles. Next to age, family history is the most common risk factor. Approximately one-third of colon cancer cases arise from inherited predisposition. For only a small fraction of these inherited syndromes is the genetic etiology known. Responsible genes are being sought, however, and screening recommendations have been established to accommodate the higher risk observed in this population.

Polyps

Polyps are defined histologically within two broad categories: epithelial and hamartomas. Epithelial polyps develop from abnormal growth of the surface epithelium, while hamartomas arise from the overgrowth of some element of the lamina propria. Polyps may be pedunculated (having a stalk) or sessile (flat), and their surfaces are often described as either smooth or lobulated.

Epithelial Polyps

Adenomatous Polyps

Adenomatous polyps, by definition, exhibit dysplasia, or features of precancer. They are divided into three subtypes: tubular, tubulo-villous, and villous. Each of these subtypes of adenomatous polyps may also exhibit mild, moderated, or severe dysplasia. The risk of an adenoma containing malignant tissue or becoming malignant, especially in the colon, relates to polyp size, amount of villous tissue in the polyp, and the degree of dysplasia.

Endoscopically, polyps become visible at 1-2 mm in diameter. As they enlarge to centimeter size, they usually become more pedunculated, although they may remain sessile. The change to malignancy takes, on average, 10 years, although the variation in duration is substantial.

Of the 30% to 50% of adults who eventually develop small adenomas of the colon, approximately 5% will experience colonic adenomas that enlarge and become malignant. The inherited adenoma syndromes of colon cancer account for only a small fraction of persons with adenomas overall (about 3% to 5%). Nonetheless, the inherited conditions remain a very important part of clinical medicine because of the high risk of colon cancer in affected persons and the inherited nature of the conditions in families.

Table 1. Main inherited polyposis syndromes: distinguishing features.

Syndrome	Gene (frequency of mutation)	Colon Cancer Risk (average age at diagnosis)	Polyp Histology	Polyp Distribution	Age of GI Symptom Onset, If Untreated	Most Prominent Extra-Intestinal Features	
						Benign	Malignant
Familial adenomatous polyposis	APC (90%)	100% (39 years)	Adenomatous, except stomach: fundic gland polyps	Stomach: 23%-100% Duodenum: 50%-90% Jejunum: 50% Ileum: 20% Colon: 100%	33 years	Desmoid tumors, Epidermoid cysts, Fibromas, Osteomas, CHRPE, dental abnormalities	Duodenal or periampullary: 3%-5%, Rare pancreatic, thyroid, gastric, CNS, hepatoblastoma
Peutz-Jeghers syndrome	STK11(LKB1) (50%-60%)	39% (46 years)	Peutz-Jeghers	Stomach: 24% Small bowel: 96% Colon: 27% Rectum: 24%	22-26 years	Orocutaneous melanin pigment spots	Pancreatic 36%, Gastric 29%, Small bowel 13%, Breast 54%, Ovarian 21%, Uterine 9%, Lungs 15%
Juvenile polyposis	SMAD4 (DPC4), BMPRA1 (53%)	9% - 68%	Juvenile	Stomach: may occur Small bowel: may occur Colon: usually	18.5 years	Macrocephaly, hypertelorism, 20% congenital abnormalities in sporadic type	Stomach and duodenum combined up to 20%
Cowden syndrome	PTEN (80% - 90%)	Little, if any	Juvenile, lipomas, inflammatory, ganglioneuromas, lymphoid hyperplasia	Esophagus: 66% Stomach: 75% Duodenum: 37% Colon: 66%	Not determined	Facial trichilemmomas, oral papillomas, multinodular goiter, fibrocystic breast disease	Thyroid 3%-10% Breast 25%-50%, Uterine 2%-5%

CHRPE = congenital hypertrophy of the retinal pigment epithelium; CNS = central nervous system

Hyperplastic Polyps

Hyperplastic polyps are a type of non-neoplastic epithelial polyp almost always found in the colon. They are characterized by a saw-toothed appearance of the surface epithelium thought secondary to inadequate sloughing of the cells. Endoscopically, they are usually one to several millimeters in diameter and appear to have little if any malignant potential. Only rarely do they grow larger. These tiny polyps account for about half of the polyps found in the colon, and the primary concern is distinguishing them from adenomas. Hyperplastic polyposis syndrome, on the other hand, does have some malignancy risk.

Inflammatory Polyps

Inflammatory polyps are actually pseudo polyps consisting of normal tissue, often with increased inflammatory elements. They are mostly associated with the chronic inflammatory conditions of the bowel including ulcerative colitis and Crohn's disease. They do not have malignancy risk, but the inflammatory conditions themselves do.

Hamartomatous Polyps

Hamartomatous polyps are benign lesions with overgrowth of some constituent of the lamina propria, submucosa, or muscular tissue. The surface mucosa or epithelium is normal and corresponds to the location of the polyp in the gastrointestinal tract. The most common hamartomas involved in inherited conditions include Peutz-Jeghers polyps (arborizing pattern of muscular tissue) and juvenile polyps (overgrowth of the

Table 2. Other rare miscellaneous conditions that exhibit hamartomatous and other polyp types.

- Syndromes where polyps contain neural elements
  - Neurofibromatosis type I (NFI)
  - Multiple endocrine neoplasia type II (MEN2)
- Syndromes of uncertain etiology
  - Cronkhite-Canada syndrome
  - Hyperplastic polyposis
- Conditions in which inflammatory polyps form
  - Inflammatory bowel disease
  - Devon polyposis
  - Cap polyposis
- Polyposis conditions arising from lymphoid tissue
  - Nodular lymphoid hyperplasia
  - Multiple lymphomatous polyposis (MLP)
  - Immunoproliferative small intestinal disease
- Miscellaneous non-inherited polyposis syndromes
  - Leiomyomatosis
  - Lipomatous polyposis
  - Multiple lymphangiomas
  - Pneumatosis cystoids intestinalis

lamina propria often with cysts). Other hamartomatous polyps that occasionally occur include lipomas, leiomyomas, neurofibromas, and ganglioneuromas. All of these polyps may be either sessile or pedunculated.

Although the hamartomatous polyps themselves are considered non-neoplastic and therefore benign lesions, most of the inherited hamartomatous polyposis conditions exhibit substantial malignancy risk. Furthermore, adenomatous change has been noted to sometimes occur in both Peutz-Jeghers and juvenile polyps.

Hamartomatous polyps are much less common than adenomatous polyps but more commonly involve the upper gastrointestinal tract in the inherited syndromes. Hamartomas account for substantially less than 5% of colonic polyps overall. Sporadic juvenile polyps of the colon occur in 2% to 3% of children, and sporadic Peutz-Jeghers polyps are very unusual. Polyposis syndromes exhibiting hamartomatous polyps are distinctly rare and are summarized in Tables 1 and 2.

The Polyposis Syndromes

Inherited colon cancer syndromes include the polyposis syndromes and hereditary nonpolyposis colorectal cancer (HNPCC). The polyposis syndromes are categorized by polyp histology (3,4). More recently, elucidation of the underlying genetic etiology has allowed further refinement of syndrome classification. Several polyposis syndromes that are not premalignant, and others that are not inherited, must be distinguished from the inherited, precancerous ones.

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is characterized by the development of hundreds to thousands of colonic adenomatous polyps (3-6). It occurs in approximately 1 in 10,000 births. The average age of adenoma development is 16 years, whereas the average age of colon cancer is 39 years. If the colon is not removed, cancer will inevitably develop in all FAP patients; 87% will develop colon cancer by age 45, and 93% by the age of 50. Symptoms occur, on average, at age 33 and include bloody bowel movements, change in bowel habits, diarrhea, abdominal pain, and weight loss. Unfortunately, by the time symptoms occur, two-thirds of cases will already have colon cancer.

Extracolonic gastrointestinal findings are common in FAP. Gastric polyps occur in up to 90% of patients but rarely cause symptoms (4). The polyps are fundic gland polyps histologically with very little malignant risk (0.5%). Duodenal polyps also occur in up to 90% (7). These are adenomatous polyps and do have malignant potential with 5% to 10% of persons with FAP developing duodenal cancer. The duodenal papilla is particularly prone to the development of adenomatous polyps and cancer. Small bowel adenomas also occur distal to the duodenum, but the risk of malignancy appears to be very low.

Extraintestinal lesions are common in FAP and appear to correlate with the location of the mutation in the adenomatous polyposis coli (APC) gene (4,6). Osteomas occur in 20% of FAP patients, most frequently at the angle of the mandible and on the skull, but may occur on any bone surface of the body, including the long bones. Epidermoid cysts occur in 20% of patients, typically along the legs, face, scalp, and arms, but potentially on any cutaneous site. The osteomas and epidermoid cysts are always benign but may cause cosmetic problems as they vary in size from millimeters to centimeters. Asymptomatic sclerotic bone lesions of the mandible or maxilla occur in over 90% of FAP patients. Supernumerary teeth and odontomas are unusual. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) occurs in some families but is always asymptomatic.

Desmoids, benign fibroblastic tissue growths, occur in 10% of FAP patients (8). Symptoms occur in half of these through local invasion or compression of other organs, particularly in the abdomen. Lesions in the mesentery are often referred to as mesenteric fibromatosis and appear to be stimulated by surgery, trauma, and estrogens. Extraintestinal cancers are sometimes observed in FAP. Pancreatic and thyroid cancers occur in 2% of patients, usually later in life. Hepatoblastomas develop in 1.6% of children, usually within the first 5 years of life. In the FAP variant Turcot syndrome, central nervous system tumors may occur (typically cerebellar medulloblastomas) at any age in <1% of patients.

Genetics

FAP is inherited as an autosomal dominant disease with near 100% penetrance in terms of colonic polyps and cancer (6,9). In at least 95% of affected families, mutations occur on chromosome 5q21 of the APC gene. The APC gene is a tumor suppressor gene whose normal function is to control cell proliferation and apoptosis. Most mutations reported give rise to a premature stop codon through either a single base pair substitution or one or two base pair deletions or additions (10,11). Some large chromosomal deletions have been reported. Approximately 30% of newly diagnosed cases, not belonging to families with known disease, appear to represent new mutations.

Normally, the APC gene functions as a negative regulator in the Wingless-type (WNT) signaling pathway (10,11). Together with several other molecules, it binds to and phosphorylates soluble beta-catenin leading to cytosolic degradation of the beta-catenin. The stimulation of the WNT signaling pathway leads to the uncoupling of the beta-catenin from the complex and, therefore, no phosphorylation occurs. As beta-catenin traverses the nuclear membrane, it binds to Tcf-Lef transcription regulators giving rise to the transcription of various proteins (c-Myc, cyclin D1, and others). The result is increased cell proliferation and decreased cell apoptosis. Therefore, aberrant function with the mutated APC gene results in a constant failure of

Table 3. Cancer risk and screening recommendations in familial adenomatous polyposis.

Cancer	Cancer Risk	Screening Recommendation
Colon	Nearly 100%	Sigmoidoscopy annually, beginning at age 10-12 years
Duodenal or periampullary	5% - 10%	Upper GI endoscopy (including side-viewing examination) every 1-3 years, start at age 20-25 years
Pancreatic	About 2%	Possibly periodic abdominal ultrasound after age 20 years
Thyroid	About 2%	Annual thyroid examination, starting at age 10 to 12 years
Gastric	About 0.5%	Same as for duodenal
CNS, usually cerebellar meduloblastoma (Turcot syndrome)	<1% but RR 92	Annual physical examination, possibly periodic head CT in affected families
Hepatoblastoma	1.6% of children <5 years of age	Possible liver palpation, hepatic ultrasound, a-fetoprotein annually during first decade of life

RR = relative risk

beta-catenin/phosphorylation and unregulated nuclear transcriptional stimulation leading to unregulated cell proliferation and unregulated suppression of apoptosis.

Genetic Testing

Genetic testing is now considered part of the standard management of families with FAP. Several testing methods are used to confirm the diagnosis of FAP in suspected cases and to determine the gene carriers in families with FAP (6,12). An in vitro protein truncation assay detects the presence of truncated mutations. It is 80% to 90% successful in diagnosing patients in families known to have FAP. Once the mutation has been found in an affected person, the test is nearly 100% effective in detecting the presence or absence of mutation in other family members. The cost is $750 to $1,000 to examine for an unknown mutation and about $500 per person in relatives once a mutation is known to be present. Gene sequencing, now increasingly used as a genetic diagnostic approach, is often preceded by single-strand conformational polymorphism (SSCP) or denaturing gradient gel electrophoresis (DGGE) to narrow the area of the gene where sequencing is to be performed. It is up to 95% effective in finding a disease-causing mutation if present and, once such is found, is nearly 100% effective in detecting the mutation in family members. The cost for sequencing is $800 if the mutation is not known and about $200 once the mutation has been identified.

If these two methods are unsuccessful, gene linkage testing can be performed if DNA can be obtained from two or more affected persons from two generations. Once obtained, linkage can be effective in >95% of families with >98% accuracy. The cost is about $245 to $260 per person tested. A number of genetic testing laboratories now perform genetic testing for FAP and other inherited conditions. (More information can be found at www.genetests.org.)

Genotype-phenotype correlations have not yet been found to be of precise use in clinical settings. At this time, the following correlations have been made (6).

1. CHRPE: present in families with mutations distal to exon 9 of the APC gene
2. Dense polyposis: present with mutations in the mid portion of exon 15
3. Attenuated Adenomatous Polyposis Coli (AAPC): found with mutation in the extreme proximal or distal end of the APC gene
4. Osteomas and desmoids: more commonly found with mutations in the distal portion of exon 15

Genetic testing will first be clinically useful, and should be considered, between the ages of 10 and 12. There may be a role for earlier screening for hepatoblastoma.

Cancer Screening

In gene carriers and all at-risk persons, sigmoidoscopy should be performed every 1-2 years beginning at age 10–12 if genetic testing is not done or not informative. In families with AAPC, colonoscopy should be done every 2 years beginning at age 21 or earlier, depending on the age of polyp emergence in other family members.

Upper gastrointestinal endoscopy should begin when colon polyps emerge or by age 25 and should be repeated every 1-3 years depending on polyp size, number, and histology. Side viewing should be performed as part of the examination to carefully identify and examine the duodenal papilla. Small bowel x-ray should be performed if numerous or large adenomas are present in the duodenum, and before planned colectomy. The number and size of polyps found determine follow-up. Overall cancer-screening recommendations for FAP are provided in Table 3.

Surgical Management

Surgery should be considered once polyps emerge, although one can often wait until a person finishes high school. Surgery should not be delayed if the polyp number nears 100, if any polyps approach 1 cm in diameter, or if advanced histology is detected. If surgery is delayed, colonoscopy should be performed at least annually.

Surgical options include subtotal colectomy with ileorectal anastomosis or total colectomy with mucosal proctocolectomy, ileal pouch construction, and ileo-anal anastomosis (3,13). The former is single-stage and much less complicated, but the later is a more definitive surgery that eliminates the risk of rectal cancer. The subtotal colectomy still requires surveillance of the remaining rectum every 6-12 months for polyp ablation. Total colectomy also requires surveillance of the ileal pouch every 2 years, as polyps sometimes recur there. Because total colectomy is a more complicated surgery, it should be performed only by specialized colon and rectal surgeons.

Chemoprevention

Chemoprevention as primary therapy for FAP is still experimental. Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to suppress rectal adenomas and possibly colonic adenomas, especially in FAP. Sulindac, in particular, is effective, but upper gastrointestinal side effects are of concern with prolonged use (14). Other more selective agents, such as the COX-2 inhibitors or sulindac metabolites, are currently being evaluated as they also decrease the size and number of polyps throughout the colon, possibly with fewer side effects (15). At this time, only celecoxib is approved for preventive treatment of the remaining rectum in persons with a subtotal colectomy, although its effect appears to be quite modest (16).

Disease Variants of FAP

Gardner Syndrome is identical to FAP but includes the extraintestinal manifestations outlined above. It is mainly of historical interest, as it is now known to be allelic to FAP. These common extracolonic manifestations include osteomas, odontomas, epidermoid cysts, fibromas, and desmoid tumors.

Turcot Syndrome is another variant of FAP with the same colonic findings coupled with central nervous system malignancies. Two-thirds of Turcot syndrome families represent a subset of FAP and typically exhibit cerebellar medulloblastomas (17). The other one-third develops glioblastomas, and the syndrome arises from mutations in mismatched repair (MMR) genes and is thus categorized as a part of hereditary nonpolyposis colorectal cancer (HNPCC).

Table 4. Clinical criteria for the diagnosis of hereditary polyposis colorectal cancer.

Classic or Amsterdam I Criteria (21)

There should be at least 3 relatives with colorectal cancer with the following criteria also met

1. One should be a first-degree relative of the other 2
2. At least 2 successive generations should be affected
3. At least 1 colorectal cancer should be diagnosed before age 50
4. Familial adenomatous polyposis should be excluded
5. Tumors should be verified by pathological examination

Amsterdam II Criteria (recent modification of the original criteria) (22)

There should be at least three relatives with an hereditary nonpolyposis colorectal cancer-associated cancer (colorectal, endometrial, small bowel, ureteral, and renal pelvis)

Attenuated Adenomatous Polyposis Coli (AAPC). The average number of colonic adenomas is 30, usually distributed throughout the proximal colon (18). The appearance of both colonic adenomas and cancer is delayed approximately 10 years compared with FAP. The upper gastrointestinal findings, when they do occur, are not attenuated. The risk of cancer is somewhat lower than that observed in FAP.

Hereditary Nonpolyposis Colorectal Cancer (HNPCC), or Lynch syndrome, accounts for 2%-3% of all colon cancer cases (6,19,20). It is characterized by the presence of colorectal and other cancers in multiple family members. This is not a polyposis syndrome in the strict sense, as multiple adenomatous polyps may form but usually only a few appear. It is inherited as an autosomal dominant disease of primarily colon and endometrial cancer. The colonic polyps that form are larger, occur earlier, and more often contain advanced histology when compared to age-matched controls. Although usually only one or several adenomatous polyps form, the average lifetime risk of developing colon cancer is still 80% in those affected. The average age of cancer diagnosis is 44.

Diagnosis. The clinical criteria for the diagnosis of HNPCC are called the Amsterdam criteria (Table 4). When the classic Amsterdam criteria are met, 50%-70% of families will be found to have a mutation of one of the MMR genes (23). About 8% of families with multiple cases of colon cancer but who do not meet the classic Amsterdam criteria will be found to have a mutation in one of the MMR genes and, therefore, will have HNPCC. An elevated risk for cancer exists at many other sites and screening is recommended (see Table 5).

Table 5. Cancer risk and screening recommendations for hereditary non-polyposis colorectal cancer.

Cancer	Cancer Risk	Screening Recommendation
Colon	> 80%	Colonoscopy every 1-2 years starting at age 20 to 25 years or 10 years younger than earliest case in the family, whichever earlier.
Endometrial	43% - 60%	Pelvic examination, transvaginal ultrasound and/or endometrial aspirate every 1-2 years starting at age 25 to 35 years
Ovarian	9% - 12%	Same as for endometrial
Gastric	13% - 19%	Upper GI endoscopy every 1-2 years starting age 30 to 35 years
Urinary Tract	4 %-10%	Ultrasound and urinalysis every 1-2 years starting age 30 to 35 years
Renal Cell Adenocarcinoma	3.3%	Same as for urinary tract
Biliary Tract and Gall Bladder	2% - 18%	Uncertain, possibly liver function tests annually after age 30 years
Central Nervous System, usually Glioblastoma (Turcot Syndrome)	3.7%	Uncertain, possibly annual physical examination and periodic head CT in affected families
Small Bowel	1% - 4%	Uncertain, at least small bowel x-ray if symptoms occur

Table 6. The modified Bethesda criteria for hereditary non-polyposis colorectal cancer.

1. Individuals with cancer in families that meet the Amsterdam criteria
2. Individuals with 2 synchronous or metachronous HNPCC related cancers*
3. Individuals with colorectal cancer *and*
   A first-degree relative with colorectal cancer and/or HNPCC related extracolonic cancer* and/or colorectal adenoma *and*
   A cancer diagnosed before age 50 years *or*
   An adenoma diagnosed before age 40 years
4. Individuals with colorectal and endometrial cancer diagnosed before age 45 years
5. Individuals with right-sided undifferentiated colon cancer diagnosed before age 45 years
6. Individuals with signet-ring cell type colorectal cancer diagnosed before age 45 years
7. Individuals with adenomas diagnosed before age 40 years

* Colon, rectum, stomach, small bowel, endometrium, ovary, ureter and others

Genetics. HNPCC is an inherited autosomal dominant disorder with at least 80% penetrance by age 70. It arises from mutations in one of the six known MMR genes (11) with mutations in either MLH1 or MSH2 accounting for over 95%. Genetic errors that accumulate when the MMR genes are mutated and dysfunctional are quite specific and include genes such as TGFbeta and BAX.

MMR genes are responsible for the repair of errors that occur during DNA replication. When one of these genes is damaged, a certain type of DNA mutation called a replication error accumulates throughout the genome of the involved tumors. Replication errors are common during cell division but are usually repaired by the MMR system. When an MMR gene itself is damaged or inactivated, replication errors persist and accumulate through repeated cell divisions. Such mutations are most easily identified in segments of DNA called microsatellites, which are sequences of repeating DNA bases found throughout the human genome. When multiple microsatellite errors are present, the tumor tissue is said to exhibit microsatellite instability (MSI) (6). Almost all (> 90%) colon cancers in HNPCC exhibit MSI, which is found in only 15% of sporadic colon cancer where it occurs by a different mechanism. Because MSI is easily detected in tumor tissue, it is used as a marker for HNPCC. It has been suggested that MSI testing on tumors should be done when any of the Bethesda criteria are met (Table 6) (24). The Bethesda criteria are more complex and inclusive rules, but they may detect a greater number of HNPCC families.

Genetic Testing. Testing for MSI instability is done on the tumor tissue. To find mutations in the MMR genes, sequencing is most commonly used with DNA from the white blood cells of peripheral blood samples. Gene sequencing is often preceded by SSCP or DGGE to narrow the area of the gene where sequencing is to be preformed (6). This is successful in 50% to 70% of families who meet the Amsterdam criteria. Once a disease-causing mutation is found in an index case, testing in other family members approaches 100% accuracy.

Genetic testing should be done to confirm an HNPCC diagnosis (12). It should be offered to members of a family with a known mutation or those that meet the Amsterdam criteria. In families not meeting the Amsterdam criteria, the issue is problematic: the phenotype is not distinct in a single individual as it is in other polyposis syndromes. A percentage of families with a history of colon cancer will not meet the Amsterdam criteria but will have HNPCC. Testing should be done to find the MMR mutation. Three approaches have been suggested:

1. Apply MSI testing to the colon cancer tissue in the following situations and, when positive, perform testing on the DNA from peripheral blood to find MMR mutations (25,26).
    a. Colon cancer diagnosis < 50 years
    b. Colon cancer plus one first-degree relative with colon or colorectal cancer
    c. Colon cancer plus a previous colon or endometrial cancer

With this method, 24% of colon cancer cases will undergo MSI testing of the tumor tissue, and MMR mutations will be discovered in 4% of colon cancer cases.

2. Use a specific logistic model applied to an extended family that includes kindred structure and known cancer cases (27).
    a. If the model predicts > 20% chance of HNPCC, go directly to mutation testing.
    b. If the model predicts < 20% chance of HNPCC, do MSI first and go to mutation testing only if MSI is positive on tumor tissue.

3. Go directly to MMR mutation testing if one of the first three Bethesda criteria is positive, but use age < 50 years rather than 45 years (28).

In one study, this approach had 94% sensitivity and 49% specificity (28).

Clinical Management

Colon screening should be performed in all at-risk persons within a family known to have HNPCC either by genetic testing or families meeting the Amsterdam criteria, even if a disease-causing mutation cannot be found (6). It consists of colonoscopy every 2 years starting at age 25, or 10 years earlier than the youngest colon cancer diagnosis in the family, whichever comes first.

Surgical Management

A subtotal colectomy is the procedure of choice to prevent colon cancer and should be done if colon cancer is diagnosed or an advanced adenomatous polyp is found that cannot be adequately treated endoscopically (3). Prophylactic colectomy in those with a disease causing MMR gene mutation is currently being debated. Hysterectomy is indicated only if endometrial dysplasia is found.

Disease Variants

Muir-Torre syndrome

Muir-Torre syndrome is typical HNPCC plus cutaneous tumors such as sebaceous adenomas or epitheliomas, basal cell epitheliomas, keratoacanthomas, or sebaceous carcinomas (usually of the eyelid). This usually arises from mutations in the MSH2 MMR gene.

Turcot Syndrome

Turcot syndrome is HNPCC with central nervous system tumors, especially glioblastomas. This represents the one third of Turcot syndrome families that do not carry the APC gene.

MSH6 Syndrome

MSH6 syndrome is HNPCC associated with mutations in the MSH6 MMR gene. It carries a 60% risk of developing endometrial cancer and 40% risk of colon cancer. Some reported families have later tumor onset than in typical HNPCC (29).

Familial Risk and Colon Cancer

Risk of Colon Cancer in Family Members

The majority of colon cancer cases appear to be sporadic with no evidence of an inherited disorder. Roughly 20% to 30% of colorectal cancer cases can be attributed to a familial or inherited risk with known inherited syndromes accounting for just 1% to 3% (30,31). The average American has approximately a 6% lifetime risk of developing colorectal cancer. But, first-degree relatives of persons with colon cancer have a 2- to 3-fold increased risk of large bowel malignancy compared with control or population incidence (31,32) (Table 7).

A high-risk family history is arbitrarily defined as a first-degree relative with colorectal cancer or adenoma diagnosed earlier than age 60 or two first-degree relatives diagnosed with colorectal cancer at any age (31). The risk in this situation is 3- to 4-fold increased over average risk. Colon cancer even in a second-degree relative (grandparent, aunt, uncle) or third-degree relative (great-grandparent, cousin) increases one's risk for colon cancer, but only about 50% above the average risk (33).

Some familial risk stratification findings related to adenomatous polyps in relatives have also been made. In the National Polyp Study, the risk of colorectal cancer in siblings and parents of persons with any adenomatous polyp was 1.78 (95% CI, 1.18-2.67). The risk of colon cancer, however, was 2.59 (95% CI, 1.64-4.58) in siblings of an adenoma patient diagnosed at < 60 years of age compared with siblings of an adenoma patient diagnosed at ≥ 60 years (34). Therefore, first-degree relatives of patients with adenomatous polyps have an increased risk of colon cancer. Similarly, first-degree relatives of persons with colon cancer have an increased risk of adenomatous polyps. Given what we know about the adenoma-carcinoma sequence, this would seem logical.

Table 7. Summary of familial risk of colon cancer.

Familial Setting	Approximate Lifetime Risk of Colon Cancer
General population	6%
One first-degree relative with colon cancer	2 - 3 fold increase
Two first-degree relatives with colon cancer	3 - 4 fold increase
First-degree relative with colon cancer diagnosed at < 50 years	3 - 4 fold increase
One second- or third-degree relative with colon cancer	~ 1.5 fold increase
Two second-degree relatives with colon cancer	~ 2-3 fold increase
One first-degree relative with an adenomatous polyp	~ 2 fold increase

NOTE: First degree relatives include parents, siblings, and children; second degree relatives include grandparents, aunts, and uncles; third degree relatives include great-grandparents and cousins.

Table 8. Colon cancer screening recomendations for persons with familial risk.

Familial Risk Category	Screening Recommendation
Two or more first-degree relatives with colon cancer or One first-degree relative with colon cancer or adenomatous polyps diagnosed at age < 60 years	Colonoscopy every 5 years beginning at age 40 years or 10 years younger than earliest diagnosis in the family, whichever is earlier. Double contrast barium enema may be substituted, but colonoscopy is preferred Same as average risk individual
Second- or third-degree relatives with colon cancer or First-degree relative with colon cancer or adenomatous polyp diagnosed after age 60 years	Same as average risk individual but begin at age 40 years

Genetics

The etiology of the commonly observed familial risk is unknown. It likely occurs from both inherited susceptibility and shared environmental factors with genetic determinants increasing the susceptibility to deleterious environmental agents (31). Spouses of persons with colon cancer do not exhibit the increased risk found in first-degree relatives, indicating the small contribution of shared environment. Kindred studies have further found that common familial risk probably arises from mild to moderate penetrance of inherited susceptibility factors. A recent large twin study likewise indicates that common familial risk for colon cancer derives from inherited susceptibility, rather than from shared environmental agents (30).

A number of genes and chromosomal loci have been described that seem to be involved in this manner. I1307K APC mutation in the Ashkenazi Jewish population gives rise to a milder form of colon cancer predisposition than is observed in FAP (35). The degree of predisposition is low to modest at most, with no difference in phenotype from sporadic colorectal cancer. Disease-causing mutations of the MSH6 gene are found in about 7% of patients with a positive family history of colon cancer (29). This mutation may be responsible for a substantial number of familial colon cancers that occur at somewhat older ages but do not fit into the syndrome of HNPCC. A type I transforming growth factor receptor allele, TβR-1(6A), has been found in a higher fraction of colon cancer patients, both homozygotes and heterozygotes (36). A family whose members exhibit frequent colonic adenomas, villous adenomas, serrated adenomas, and colon cancer was found to link to a locus on chromosome 15q (37). Finally, certain polymorphisms of genes involved in the metabolism of both protective and deleterious environmental agents have been associated with predisposition to colon cancer (38). Such genes include methylenetetrahydrofolate reductase and *N*-acetyltransferase 1 and 2.

Screening

The presence of familial risk dictates a more aggressive screening compared with average risk individuals beginning at a younger age. The American Cancer Society recommends full colonoscopy for persons with first-degree relatives with colorectal cancer or adenoma diagnosed prior to age 60 years and for those with two or more first-degree relatives with colorectal cancer (31,39). This screening should start at age 40 or 10 years earlier than the age of diagnosis of the youngest affected relative. Full colonoscopy is recommended every 5 years if no neoplasms are found. Average risk screening is recommended for those with a more modest family history, but should probably start at age 40, rather than 50. Current screening recommendations for persons with increased familial risks are outlined in Table 8.

Conclusion

Colon cancer remains a significant cause of morbidity and mortality worldwide. The proper screening of at-risk individuals is crucial for early detection and cure. Identification of rare syndromes associated with gastrointestinal malignancies is now possible through gene testing, and such tests should be offered to those that meet specific criteria.

References

1. Finlay IG, Pickford IR. Colorectal carcinoma. In: Lawson DH, ed. Current Medicine, 4th Edition. Edinburgh, UK: Churchill Livingstone, 1994:51-64.
2. Jemal A, Thomas A, Murray T, et al. Cancer statistics, 2002. CA Cancer J Clin 2002; 52:23-47.
3. Guillem JG, Smith AJ, Calle JP, et al. Gastrointestinal polyposis syndromes. Curr Probl Surg 1999; 36:217-323.
4. Burt RW, Jacoby R. Polyposis Syndromes. Textbook of Gastroenterology. Yamada T, ed. Philadelphia: Lippincott Williams & Wilkins, 1999: 1995-2022.
5. Bussey HJR. Familial Polyposis Coli. Family Studies, Histopathology, Differential Diagnosis and Results of Treatment. Baltimore: Johns Hopkins University Press, 1975.
6. Giardiello FM, Brensinger JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. Gastroenterology 2001; 121:198-213.
7. Kadmon M, Tandara A, Herfarth C. Duodenal adenomatosis in familial adenomatous polyposis coli. A review of the literature and results from the Heidelberg Polyposis Register. Int J Colorectal Dis 2001; 16:63-75.
8. Clark SK, Neale KF, Landgrebe JC, et al. Desmoid tumours complicating familial adenomatous polyposis. Br J Surg 1999; 86:1185-1189.
9. Hampel H, Peltomäki P. Hereditary colorectal cancer: risk assessment and management. Clin Genet 2000; 58:89-97.
10. Goss KH, Groden J. Biology of the adenomatous polyposis coli tumor suppressor. J Clin Oncol 2000;18:1967-1979.
11. Chung DC. The genetic basis of colorectal cancer: insights into critical pathways of tumorigenesis. Gastroenterology 2000; 119:854-865.
12. American Gastroenterological Association medical position statement: Hereditary colorectal cancer and genetic testing. Gastroenterology 2001; 121:195-197.
13. Bülow C, Vasen H, Järvinen H, et al. Ileorectal anastomosis is appropriate for a subset of patients with familial adenomatous polyposis. Gastroenterology 2000; 119: 1454-1460.
14. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J of Med 1993; 328:1313-1316.
15. Goluboff, ET. Exisulind, a selective apoptotic antineoplastic drug. Expert Opin Investig Drugs 2001; 10:1875-1882.
16. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000; 342:1946-1952.
17. Hamilton SR, Liu B, Parsons RE, et al. The molecular basis of Turcot's syndrome. N Engl J Med 1995; 332:839-847.
18. Hernegger GS, Moore HG, Guillem JG. Attenuated familial adenomatous polyposis: an evolving and poorly understood entity. Dis Colon Rectum 2002; 45:127-134; Discussion 134-136.
19. Lynch HT, Lynch J. Lynch syndrome: genetics, natural history, genetic counseling, and prevention. J Clin Oncol 2000; 18(21 Suppl):19s-31s.
20. Lynch HT, de la Chapelle A. Genetic susceptibility to non-polyposis colorectal cancer. J Med Genet 1999; 36:801-818.
21. Vasen HF, Mecklin JP, Khan PM, et al. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 1991; 34:424-425.
22. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology 1999; 116:1453-1456.
23. Wijnen J, Khan PM, Vasen H, et al., Hereditary nonpolyposis colorectal cancer families not complying with the Amsterdam criteria show extremely low frequency of mismatch-repair-gene mutations. Am J Hum Genet 1997; 61:329-335.
24. Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997; 89:1758-1762.
25. Loukola A, de la Chapelle A, Aaltonen LA. Strategies for screening for hereditary non-polyposis colorectal cancer. J Med Genet 1999; 36:819-822.
26. Terdiman JP, Gum JR Jr, Conrad PG, et al. Efficient detection of hereditary nonpolyposis colorectal cancer gene carriers by screening for tumor microsatellite instability before germline genetic testing. Gastroenterology 2001; 120:21-30.
27. Wijnen JT, Vasen HF, Khan PM, et al. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. N Engl J Med 1998; 339:511-518.
28. Syngal S, Fox EA, Eng C, et al. Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations in MSH2 and MLH1. J Med Genet 2000; 37:641-645.
29. Kolodner RD, Tytell JD, Schmeits JL, et al. Germ-line msh6 mutations in colorectal cancer families. Cancer Res 1999; 59:5068-5074.
30. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000; 343:78-85.
31. Burt RW. Colon cancer screening. Gastroenterology 2000; 119:837-853.
32. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 2001; 96:2992-3003.
33. Slattery ML, Kerber RA. Family history of cancer and colon cancer risk: the Utah Population Database. J Natl Cancer Inst 1994; 86:1618-1626.
34. Winawer SJ, Zauber AG, Gerdes H, et al. Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. N Engl J Med, 1996; 334:82-87.
35. Laken SJ, Petersen GM, Gruber SB, et al. Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. Nat Genet 1997; 17:79-83.

36. Pasche B, Kolachana P, Nafa K, et al. TbetaR-I(6A) is a candidate tumor susceptibility allele. Cancer Res 1999; 59:5678-82.
37. Tomlinson I, Rahman N, Frayling I, et al. Inherited susceptibility to colorectal adenomas and carcinomas: evidence for a new predisposition gene on 15q14-q22. Gastroenterology 1999; 116: 789-795.
38. Houlston RS, Tomlinson IP. Polymorphisms and colorectal tumor risk. Gastroenterology 2001; 121:282-301.
39. Smith RA, Cokkinides V, von Eschenbach AC, et al. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin 2002; 52:8-22.

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