Inherited Colorectal Cancer Syndromes

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ABSTRACT

Colorectal cancer is one of the major causes of cancer deaths in both men and women. It is estimated that ~5% to 10% of patients with colorectal cancer have an inherited germline mutation that predisposes them to cancer. Clinically, hereditary colorectal cancer syndromes can be divided into those associated with colonic polyposis (familial adenomatous polyposis, attenuated familial adenomatous polyposis, and *MYH*-associated polyposis) and those not associated with colonic polyposis (hereditary nonpolyposis colon cancer).

Treatment options for these patients include multiple aggressive screening regimens, chemopreventive medications, and prophylactic surgery. Selection of the appropriate management approach is best made using information obtained from the patient's clinical examination, the family medical history, and genetic evaluation. Compliance is improved when patients completely understand their disease and participate fully in the formulation of the treatment plan. Although not proved, it seems reasonable that this approach may prevent the poor outcomes so frequently associated with inherited cancer syndromes.

KEYWORDS: Familial adenomatous polyposis, attenuated familial polyposis, *MYH*-associated polyposis, hereditary nonpolyposis colon cancer

Objectives: Upon completion of this article, the reader should be familiar with the characteristics of inherited colorectal cancer syndromes and their treatment options.

Colorectal cancer is one of the major causes of cancer deaths in both men and women in westernized societies. In the United States alone, there are ~140,000 new cases and 50,000 deaths annually. It is estimated that ~5% to 10% of patients with colorectal cancer have an inherited germline mutation that predisposes them to cancer. Clinically, hereditary colorectal cancer syndromes can be divided into those associated with colonic polyposis (familial adenomatous polyposis [FAP], attenuated familial adenomatous polyposis [aFAP], and *MYH*-associated polyposis [MAP]) and those not associated with colonic polyposis (hereditary nonpolyposis colon cancer [HNPCC]).

DIAGNOSIS

Most patients with an inherited colorectal cancer syndrome are not diagnosed until the development of a colorectal neoplasm. Specific criteria for the diagnosis of the various syndromes are included in the discussion of the specific entities, but, in general, a hereditary colorectal cancer syndrome should be suspected in patients with either an unusually large number of colon polyps or a young age of occurrence or in patients with a colorectal cancer and a history of a previous colorectal cancer or extracolonic malignancy that is associated with inherited colorectal cancer syndromes, particularly if they occurred at an unusually young age.

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As important as the patient's medical history is the family medical history. A history of multiple family members and generations afflicted with colorectal cancer or associated malignancies should suggest the possibility of a hereditary cancer syndrome. As a rule, the likelihood of an inherited cancer syndrome increases as the number of affected individuals and generations increases and the age of the affected individuals decreases.

Despite the importance of the family medical history, it is frequently omitted or inaccurate. The family medical history is usually obtained at the initial physician encounter and is incorrect in 10% to 30%.[1–4] Possible reasons for this include separation from the family, distress over the more immediate medical problem, and poor memory. The most accurate means of obtaining a family medical history is with a questionnaire that the patient and the patient's family complete and return later.

The family medical history can provide valuable information regarding the natural history and manifestations of the problem in the family. Although not perfect, predictions about the age of onset and severity of the disease can be made as well as the risk for and sites of extracolonic manifestations. Occasionally, the family medical history shows no evidence to suggest a hereditary colorectal cancer syndrome in a patient whose clinical history and physical examination are highly suspicious for such a problem. Possible explanations include a recessive mode of inheritance, a new mutation, and questions of paternity, adoption, or denial.

GENETIC COUNSELING

The initial management of any patient with a suspected inherited cancer syndrome is genetic counseling. Genetic counseling should be performed by a trained individual who can investigate the family medical history, resolve any ambiguities, and construct a pedigree. After examination of the pedigree, if indicated, the patient can be educated about the natural history of the disease, the implications of a hereditary disease for the patient's family, and issues of employment and insurance. The diagnosis of an inherited cancer syndrome is a calamitous event, and the psychological impact on the patient and the family can be addressed and referrals made for counseling and to local and national support groups. Optimal management of hereditary cancer syndromes requires a lifetime of aggressive surveillance and screening. The best outcomes are obtained when the patient is educated about the disease, participates in the decision-making process, and is fully compliant with the treatment plans. Genetic counseling appears to be the best method to deal with the potential for denial and noncompliance and prevent the bad outcomes that can result from delays in evaluation and treatment.

GENETIC TESTING

The role of genetic testing in the diagnosis of an inherited cancer syndrome is often misunderstood. The diagnosis of these syndromes is made on the basis of a patient's history and clinical examination and the family medical history. Although the discovery of a genetic defect by genetic testing can provide valuable diagnostic and prognostic information for a patient and the patient's family, the failure to identify an abnormality does not mean that one is not present and does not exclude the diagnosis of an inherited cancer syndrome.

For the affected patient, determination of the specific genetic abnormality can provide helpful prognostic information. Even though attempts to correlate genotypic information with the phenotypic manifestations of the disease have not been completely successful, certain specific patterns can be discerned. Mutations in the APC gene located before codon 157 or after codon 1464 are associated with the milder form of the disease, aFAP,[5,6] and abnormalities located between codons 1250 and 1464 are associated with an earlier age of onset, a very large number of polyps, and more severe manifestations of FAP.[7–9] There appears to be an increased risk of desmoid tumors in patients with a mutation between codons 1403 and 1578 in the APC gene[10–12] and endometrial carcinoma in patients with an abnormality in the *MSH6* mismatch repair gene.[13]

After the specific genetic mutation has been identified in an affected family member, genetic testing for that specific defect can be offered to other members of the family who are at risk for inheriting the defect. In this circumstance, discovery of the abnormality in a patient who has yet to exhibit the disease can indicate the need for early and frequent screening for the manifestations of the disease and the possibility of passing the defect to the patient's offspring. A family member who can be conclusively proved not to have inherited the defect that is associated with the increased risk of malignancy in the family is at no greater risk for cancer than the general population and does not need aggressive screening for cancer, nor is there a potential for that person's children to inherit the defect.

POLYPOSIS SYNDROMES

Polyposis syndromes are rare entities that account for ~1% of colorectal carcinomas. They are identified by the presence of numerous polypoid lesions in the gastrointestinal tract. Although several polyposis syndromes have been identified to date, the most common are familial adenomatous polyposis coli (FAP), attenuated familial adenomatous polyposis coli (aFAP), and *MYH*-associated polyposis coli (MAP).

Genetics

FAMILIAL ADENOMATOUS POLYPOSIS AND ATTENUATED FAMILIAL ADENOMATOUS POLYPOSIS

FAP and aFAP result from a mutation in the APC gene. The APC gene is a tumor suppressor gene located on chromosome 5q21[14,15] that is involved with apoptosis or programmed cell death.[16,17] Most commonly, the mutation results in the termination of translation, resulting in a truncated protein. The functional consequences of the mutation are dependent on the location of the abnormality. Whereas two normal APC protein molecules bind together to form a biologically active homeodimer,[18] truncated APC proteins may bind to normal APC proteins to form an inactive homeodimer. This binding is dependent on the length of the abnormal protein. A very truncated protein resulting from a proximal mutation is unable to bind effectively with a normal molecule, resulting in the mild manifestations of aFAP. The proteins produced from more distal mutations can effectively bind a normal APC protein molecule. If the truncated APC protein is only minimally shortened from a very distal mutation, the homeodimer does retain some activity, also resulting in the mild manifestations of aFAP.[5,6] If the mutation is more in the midportion of the gene, the resulting intermediate-length protein can effectively bind a normal APC protein, resulting in an inactive homeodimer and the severe manifestations of FAP.[7–9] Cancers associated with germline mutations of APC develop through the chromosomal instability pathway and are microsatellite stable.

MYH-ASSOCIATED POLYPOSIS

Germline mutations in the base-excision-repair gene *MYH* have been associated with a syndrome of multiple colorectal adenomas.[19,20] Patients with *MYH* mutations have an excess of somatic mutations consisting of the substitution of a thymine-adenine pair for a guanine-cytosine pair in the APC and K-ras genes.[21,22] The specific defects in the *MYH* gene are ethnicity specific, with the missense mutations Y165C and G382D preponderant in patients of European descent and the nonsense mutations E466X and Y90X most common in patients of Indian and Pakistani descent.[22,23] Cancers associated with biallelic defects of *MYH* may develop along a novel pathway. They are most commonly nearly diploid and microsatellite stable.[24,25]

Clinical-Pathologic Features

FAMILIAL ADENOMATOUS POLYPOSIS AND ATTENUATED FAMILIAL ADENOMATOUS POLYPOSIS

FAP is a syndrome characterized by the presence of over 100 colonic adenomas. Review of the family medical history usually reveals an autosomal dominant pattern of inheritance, although up to 30% of patients appear to develop the disease from a new APC mutation.[26,27] Although all areas of the colon are involved in the fully developed syndrome, there appears to be a predilection for the rectum and left colon with a greater number of polyps and an earlier age of onset. For patients affected by FAP, adenomatous polyps are present in 15% of patients by 10 years of age, 50% at age 15 years, and 75% by 20 years of age. The lifetime risk of colorectal malignancy in patients with FAP is nearly 100% with a median age of 39 years. However, 7% of affected patients develop cancer before age 21 years.[28–31]

In contrast to patients with FAP, those with aFAP have an average of 30 polyps with the polyps more likely to be right colonic. The onset is also later, with the polyps developing after 25 years of age.[6] As with FAP, the lifetime risk of colorectal malignancy in patients with aFAP is nearly 100%, but the median age of cancer diagnosis is 59 years.[9,28] Also as with FAP, the family medical history usually reveals an autosomal dominant pattern of inheritance.

MYH-ASSOCIATED POLYPOSIS

It is usually impossible to distinguish MAP from FAP and aFAP clinically in an individual patient. On evaluation of the family medical history, however, the distinction is obvious. Whereas FAP and aFAP have an autosomal dominant pattern of inheritance, MAP is inherited in an autosomal recessive manner. The number of polyps in MAP is variable, having a reported range of 5 to 750, with a median of $\sim$50 polyps and 36% of patients having over 100 polyps.[20,21] To date, patients with MAP have been diagnosed at a median age of 48 years with a range of 13 to 65 years. Colorectal cancer has been present at diagnosis in 48% at a mean age of 50 years and a range of 30 to 65 years. The cancers are usually left sided, with multiple colorectal cancers present in 24% of the patients at diagnosis.[21] A comparison of the clinical features of FAP, aFAP, and MAP is shown in Table 1.

Extracolonic Manifestations

Any APC gene mutations can also result in extracolonic findings. The most common of these are listed in Table 2. Duodenal adenomatous polyps develop in 80% to 90% of patients with FAP with a 12% risk of duodenal or periampullary cancer, which occurs an average of 16 years after the diagnosis of FAP.[32–36] Adenomas can also develop in the jejunum and ileum, but the malignant potential of these lesions is not known.[37]

Gastric polypoid lesions are also present in the majority of patients with FAP. Most commonly, these are small sessile lesions that on histologic evaluation

Table 1 Comparison of Familial Adenomatous Polyposis, Attenuated Familial Adenomatous Polyposis, and *MYH*-Associated Polyposis

	FAP	aFAP	MAP
Number of polyps	> 100	Average 20–30	Median ~50
Age of onset (yr)	< 21	25–30	?
Location of polyps	Distal colon	Proximal colon	Throughout
Average age at cancer diagnosis (yr)	39	59	50
Manner of inheritance	Dominant	Dominant	Recessive

are composed of dilated fundic glands. These polyps are considered to be hamartomas with no malignant potential.[38–42] Gastric adenomas have been associated with FAP, but there seem to be regional differences in the incidence of the lesions, with these neoplasms being much more common in Japanese than non-Japanese patients.[33,38,43]

Desmoid tumors consist of masses of fibroaponeurotic tissue with an incidence of 12% to 38% in patients with FAP.[12,44–46] An increased risk of desmoids has been described in premenopausal women, during pregnancy, and following abdominal trauma or surgery.[47–52] These desmoids usually arise within 2 to 3 years of the event and are located intra-abdominally in 80% of patients, within the abdominal wall in 18% of patients, and extra-abdominally in 2% of patients.[51,53] Multiple desmoids are present in 5% to 38% of patients.[52,54] In contrast to sporadic desmoids, those associated with FAP have a variable clinical course. Whereas 47% remain stable or grow slowly after diagnosis, 10% regress completely, 29% undergo cycles of growth and regression, and 10% grow rapidly.[53] Intra-abdominal desmoids can obstruct the small intestine or ureters or cause occlusion of the mesenteric blood vessels with resultant intestinal ischemia and sepsis. Surgery for a desmoid-related complication is required in 27% of patients with an intra-abdominal desmoid.[55,56]

Extracolonic manifestations have also been associated with *MYH* mutations and include two reported cases of gastric cancer, one at 17 years of age, and two cases of duodenal polyps. Congenital hypertrophy of the retinal pigment epithelium and osteomas have also been reported.[21–23]

MANAGEMENT

As discussed earlier, the initial management of any suspected inherited cancer syndrome is genetic counseling. Management options include aggressive screening regimens, chemopreventive agents, and prophylactic surgery. Regardless of the treatment modality chosen, a lifetime of surveillance is needed.

Screening

FAP

Endoscopy is the screening method most commonly chosen for patients at risk for polyposis. The initial examination should be performed at 12 years of age for patients at risk for FAP. Complete colonoscopy has been recommended by some,[57] and others, given the predilection for rectal and left colonic polyps in FAP, have recommended flexible proctosigmoidoscopy,[27] Annual flexible proctosigmoidoscopy is the method of choice for subsequent examinations. Screening should be continued until polyps develop or should be lifelong for those with a proven APC gene abnormality. For patients at risk for FAP whose genetic status is unknown, if no polyps have been identified by age 50 years, it is reasonable to conclude that these patients did not inherit the genetic defect and that annual screening can be discontinued, although they still need screening for colorectal cancer as recommended for the general population.

aFAP

For individuals whose family history or APC gene abnormality suggests aFAP, complete colonoscopy is

Table 2 Extracolonic Manifestations of APC Gene Mutations

	Incidence (%)	Significance
Duodenal adenomas	80–90	12% risk of malignancy
Gastric hamartomas	50–70	Must exclude gastric adenoma
Desmoids	12–38	27% risk of complications
Hepatoblastoma	1	Most common before age 2 years
Osteomas	80	Usually less than 1 cm in size
Congenital hypertrophy of the retinal pigment epithelium (CHRPE)	80	Marker for screening purposes

the procedure of choice because of the likelihood of right colonic polyposis in aFAP.[57] Screening examination should begin at age 20 years and be performed every 1 to 2 years. There is no consensus on when to discontinue screening examinations, but given the natural history of aFAP, it would seem that screening of the healthy individual should continue into the eighth decade of life.

MAP

No guidelines for the screening of patients with MAP have been proposed. However, given the clinical features of MAP, it would seem appropriate to follow a screening protocol similar to that used for aFAP.

Extracolonic Manifestations

When a patient is known to have a polyposis syndrome from either the clinical findings of colon polyps or genetic testing, the possibility of extracolonic manifestations must be considered. It can be anticipated that duodenal polyps will develop in 80% to 90% of patients with an APC mutation.[34,58] There is no consensus on screening for duodenal polyps, but as these polyps have malignant potential, screening seems warranted. Given the natural history of duodenal polyps, it would seem reasonable to evaluate the upper gastrointestinal tract with esophagogastroduodenoscopy beginning at age 25 years and every 1 to 5 years thereafter, depending on the endoscopic findings. There is likewise no consensus regarding screening for desmoid tumors. However, given the potential of these tumors for aggressive growth, it would seem appropriate to screen for the development of these tumors by abdominal computed tomography annually for 3 years after a pregnancy or abdominal trauma or surgery. This would seem especially important for patients whose family medical history or genetic defect suggests a propensity for these tumors.

Chemoprevention

Several clinical trials have shown that the nonsteroidal anti-inflammatory drugs (NSAIDs) sulindac, celecoxib, and aspirin can reduce the number and size of colorectal adenomas in patients with FAP.[59–62] What is unclear is whether suppression of the polyps will prevent progression to colorectal cancer. Given the case reports of cancer occurring in patients with FAP whose polyps were suppressed with sulindac,[60–63] chemoprevention cannot be recommended as primary therapy for intestinal polyposis. It can be considered for the special circumstance where surgical therapy has been declined or has an unacceptably high risk of complications.

Surgery

Surgery is the primary therapeutic modality in the management of colonic polyposis syndromes. Selection of the appropriate timing of the intervention and the choice of the surgical procedure to be performed must take into account the manifestations of the disease in the patient and the patient's family and the genetic abnormality, if known. APC mutations between codons 1250 and 1464 are associated with an earlier onset and a larger number of polyps. Although colorectal cancer is unusual before 20 years of age, the risk for patients with more than 1000 polyps is twice that for patients with fewer polyps.[31,64] In contrast, APC mutations before codon 157 are associated with much fewer polyps and a very low risk of colorectal cancer before age 21 years.[5,6] The risk of colorectal cancer before age 21 years also seems very low in MAP.[20]

Desmoid tumors are more common in patients with APC mutations between codons 1403 and 1578.[10–12] The polyposis associated with mutations in this region seems to be less severe. Given the potential for desmoids to be induced by surgery, the risk of desmoid-related complications, and the difficulty in managing desmoids, it would seem prudent to delay surgery as long as possible.

With these considerations, it has been recommended that surgery be performed at age 12 to 15 years for patients with severe disease by clinical examination. Surgery can be delayed until age 18 to 21 for those with less severe disease. For patients whose family medical history or genetic test results reveal an increased risk of desmoid disease or who are found to have a desmoid tumor on clinical evaluation, surgery should be delayed until they have an increasing number and size of polyps that cannot be managed endoscopically or develop polyps with severe dysplasia.

Surgical options include total abdominal colectomy with ileorectostomy (TAC), proctocolectomy with ileal pouch anal reconstruction (IPAA), and total proctocolectomy with Brooke ileostomy (TPC). The advantages of a TAC include a single-stage procedure with a low risk of surgical complications, restored bowel continuity with superior functional results compared with the other surgical options, and the avoidance of a proctectomy with the potential for damage to the pelvic nerves and severe urinary and sexual dysfunction.[65–70] Bowel function is influenced by the length of the remaining rectum. Longer rectal remnants are associated with better bowel function but an increased risk of subsequent rectal neoplasia.[71] It appears that 10 to 12 cm of remaining rectum is the optimal remnant, having an adequate reservoir capacity and an acceptable risk of subsequent neoplasia. The risk of subsequent malignancy with 10 to 12 cm of remaining rectum has been reported to be 25% to 37% over 20 years and is the major disadvantage of TAC.[71,72] Clinical and genetic

factors can be used to predict the likelihood that a cancer will develop in the rectal remnant. The presence of over 20 polyps in the rectum or more than 1000 polyps in the colon, a rectal polyp greater than 3 cm in size, and a cancer anywhere in the colon are clinical findings associated with an increased risk of subsequent malignancy in the remaining rectum.[73] As discussed earlier, APC mutations between codons 1250 and 1464 are associated with an increased number of polyps, which would be predictive of an increased risk of subsequent malignancy, and APC mutations before codon 157 are associated with fewer polyps, which would suggest a very low risk of developing cancer in the remaining rectum.[73] The potential also exist for an intra-abdominal desmoid to develop following the TAC, which would limit the surgical options for the patients who may need subsequent proctectomy.[74,75] It seems prudent to avoid TAC in patients whose family medical history or genetic test results reveal an increased risk of desmoid disease or who are found to have a desmoid tumor on clinical evaluation.

Given the risk of subsequent neoplasia after TAC, many surgeons recommend IPAA for most patients with polyposis. With preservation of the anal transition zone, bowel function after IPAA is comparable to that after TAC,[70,76,77] but the risk of subsequent neoplasia in the anal transition zone is reported to be as high as 30%.[78,79] Complete rectal mucosectomy decreases this risk significantly but does not remove it entirely and is associated with diminished bowel function and an increased surgical complication risk.[79–82] The 20% to 40% risk of surgical complications is the major disadvantage of IPAA.[83–87] Another perceived disadvantage of IPAA is the usual need for temporary fecal diversion and a subsequent procedure to close the stoma. Proctectomy is associated with a risk of damage to the pelvic autonomic nerves resulting in impotence and retrograde ejaculation in 2% and 6% of males, respectively.[88] Damage to the pelvic autonomic nerves results in vaginal dryness and dyspareunia in 25% to 30% of women.[88,89] Despite these disadvantages, IPAA is the procedure of choice for patients with an unacceptably high risk of neoplasia after TAC or those with a increased risk of developing desmoid tumors.

Although TPC does not have the risk of subsequent neoplasia that is associated with TAC and IPAA with preservation of the anal transition zone, it is almost never performed as the initial procedure for the management of polyposis because of the resultant permanent stoma.[90] With preoperative counseling, proper selection of a stoma site, and postoperative teaching, a patient with an ileostomy can lead a full and active life. However, the difficulty of convincing a young, asymptomatic patient of this can lead to a delay in treatment with the potential for carcinoma to develop. Currently, TPC is reserved for patients with a contraindication to sphincter preservation such as a low rectal cancer, those with poor sphincter function from previous anorectal conditions or obstetric trauma, or those with technical problems that prevent an ileal pouch from reaching the anus.

Postoperative Surveillance

Regardless of the surgical procedure chosen, postoperative surveillance of the rectal remnant after TAC, the ileal pouch after IPAA, and the ileostomy after TPC and screening for the extracolonic manifestations are essential for the remainder of the patient's life. Endoscopy of the rectal remnant or ileal pouch should be performed annually with polyps smaller than 5 mm followed and larger polyps removed without fulguration and examined histologically to exclude dysplasia. For patients who underwent TAC, proctectomy with IPAA can be considered for an increasing number or size of polyps or the development of severe dysplasia.[91–93] Although the significance of polyps in an ileal pouch is uncertain, it has been suggested that these can be managed with the NSAID sulindac or celecoxib.

HEREDITARY NONPOLYPOSIS COLON CANCER

HNPCC is a syndrome characterized by a very high risk of colorectal cancer without an unusual number of colorectal polyps. HNPCC has an autosomal dominant pattern of inheritance and is associated with 5% to 8% of colorectal cancers.

Genetics

HNPCC is associated with mutations of the DNA mismatch repair (MMR) genes. The recognition and repair of mispaired bases in the DNA require multiple gene products that work as a unit. The *MSH2* protein binds with either the *MSH6* or the *MSH3* protein, forming a complex that recognizes and binds to mispaired bases in the DNA. The *MLH1* protein forms a complex with the *PMS2* protein that interacts with the *MSH2/MSH6* or *MSH2/MSH3* complex bound to the mispaired DNA, resulting in excision of the mismatched DNA followed by DNA resynthesis.[94] In addition to repairing errors of replication, the MMR proteins function as a barrier to recombination events between quasi-homologous DNA sequences.[95] Therefore, cells with an MMR deficiency have both a mutator and hyperrecombinant phenotype and are susceptible to tumor formation.

Microsatellite instability (MSI) is the hallmark of MMR deficiency. Microsatellites are mono-, di-, and trinucleotide repeats that are scattered throughout the genome and because of their repetitive nature are susceptible to errors during replication.[96–98] MMR deficiency results in an accumulation of these errors

Table 3 Amsterdam Criteria for the Diagnosis of Hereditary Nonpolyposis Colon Cancer

1. At least 3 relatives with histologically proven colorectal cancer; 1 must be a first-degree relative of the other 2.
2. At least 2 successive generations should be affected.
3. In 1 of the relatives, colorectal cancer should be diagnosed before age 50 years.
4. Familial adenomatous polyposis must be excluded.

of replication and an alteration of the length of the microsatellite sequences within the DNA[99,100] resulting in susceptibility to tumor formation. Both alleles of an MMR gene must be inactive to result in a mismatch deficiency.[101,102] MSI occurs in 15% of sporadic colorectal tumors through inactivation of both alleles of *MLH1* by hypermethylation of the *MLH1* promoter region.[103–105] In patients with HNPCC, there is an inherited mutation that inactivates one allele and an acquired inactivation of the other as described previously.

The two genes most commonly implicated in HNPCC are *MSH2* and *MLH1*, accounting for over 80% of inherited MMR abnormalities. Most *MSH2* defects are frameshift or nonsense mutations and are most common in exon 12. Frameshift and missense mutations in exon 16 are the most common defect of *MLH1*.

Diagnosis

The principles for the diagnosis of an inherited cancer syndrome and the roles of genetic counseling and genetic testing that have already been discussed apply to the diagnosis and evaluation of HNPCC. As opposed to the diagnosis of the polyposis syndromes, in which the clinical finding of colonic polyposis is indicative of a hereditary colorectal cancer syndrome, the diagnosis of HNPCC is based primarily on the family medical history. The initial diagnostic guidelines for HNPCC, the Amsterdam criteria, are shown in Table 3. These criteria were developed to standardize the diagnosis for research purposes and were quite strict.[106] They failed to recognize any of the extracolonic manifestations of HNPCC and had a low sensitivity, especially in families with fewer members. The Amsterdam criteria II (Table 4) were developed to include HNPCC-associated extracolonic tumors, but the value of this has been questioned because comparison of the Amsterdam II with the Amsterdam criteria did not demonstrate improved sensitivity.[107]

The Bethesda guidelines (Table 5) are much less stringent and take into account extracolonic tumors and several other clinical-pathologic findings in patients with HNPCC.[108] They were developed to select tumors that were more likely to have MSI in an attempt to identify patients with HNPCC. Although the Bethesda guidelines are more sensitive than the Amsterdam criteria, they are also much less specific.

Clinical-Pathologic Features

The term "nonpolyposis" in HNPCC is somewhat misleading. Polyps do form in patients with HNPCC; they are simply not present in large numbers. The incidence of polyps in HNPCC is similar to that seen in the general population,[109,110] and just as in patients with sporadic colorectal cancer, the cancers in patients with HNPCC are thought to arise from adenomatous polyps. When compared with sporadic polyps, those associated with HNPCC were more commonly located proximal to the splenic flexure of the colon, were larger, and were more often villous and dysplastic.[111,112] It is also thought that colon polyps associated with HNPCC have a more rapid progression from adenoma to carcinoma.[113–117]

The predominant feature of HNPCC is colorectal cancer. As compared with sporadic colorectal cancer, where 90% occur in patients older than 50 years and 70% are located distal to the splenic flexure of the colon, the mean age at colorectal cancer diagnosis in HNPCC is 44 years with 70% located proximal to the splenic flexure. Patients with HNPCC also have a 7% risk for synchronous cancers, which is threefold higher than the

Table 4 Amsterdam Criteria II for the Diagnosis of Hereditary Nonpolyposis Colon Cancer

1. At least 3 relatives with an HNPCC-associated cancer (colorectal, endometrial, or small bowel adenocarcinomas or transitional cell carcinomas of the ureter or renal pelvis).
2. One should be a first-degree relative of the other 2.
3. At least 2 successive generations should be affected.
4. At least 1 should be diagnosed before age 50 years.
5. Familial adenomatous polyposis should be excluded in the colorectal cancer cases.
6. Cancers should be verified by pathological examination.

Table 5 Bethesda Guidelines

1. Individuals in families that meet the Amsterdam criteria.
2. Individuals with 2 hereditary nonpolyposis colon cancer (HNPCC)-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers (endometrial, ovarian, gastric, hepatobiliary, or small bowel carcinomas or transitional cell carcinoma of the ureter or renal pelvis).
3. Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; 1 of the cancers diagnosed at age < 45 years, and the adenoma diagnosed at age < 40 years.
4. Individuals with colorectal or endometrial cancer diagnosed at age < 45 years.
5. Individuals with a signet-ring cell colorectal cancer (composed of $> 50\%$ signet ring cells) diagnosed at age < 45 years.
6. Individuals with a right-sided colorectal cancer with an undifferentiated pattern on histology (poorly or undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small gland-like spaces) diagnosed at age < 45 years.
7. Individuals with adenomas diagnosed at age < 40 years.

risk in patients with sporadic colorectal cancer, and a 30% to 50% risk for metachronous cancer, which is five- to sevenfold increased compared with patients with sporadic cancers. [118–121]

On histological examination, HNPCC-associated cancers are more likely to be mucinous, signet ring cell, or poorly differentiated.[122] These tumors incite a host immune response marked by an intense peritumor lymphocytic infiltrate that is similar to that seen in the bowel wall of patients with Crohn's disease.[123]

As discussed earlier, HNPCC colorectal cancers arise by the MSI pathway and therefore exhibit MSI. MSI testing is now commercially available. However, 10% to 20% of sporadic cancers have MSI, so this is not diagnostic of HNPCC.[120] Immunohistochemical stains for *MLH1* and *MSH2* are also available. Compared with MSI testing, immunohistochemical testing was found to be 92% sensitive and 100% specific for screening for MMR defects.[124]

Although MSI testing and immunohistochemical testing are useful to screen for defects of MMR and can provide prognostic information, the diagnosis of HNPCC is based on the clinical finding and the family medical history as discussed earlier. Although the lifetime risk of colorectal cancer is 80% for patients with both *MLH1* and *MSH2* gene defects, patients with *MSH2* abnormalities are significantly more likely to have a rectal cancer.[125]

Extracolonic Manifestations

MMR gene defects are also associated with adenocarcinomas of the endometrium, ovaries, stomach, small intestine, and bile ducts and transitional cell carcinomas of the ureter and renal pelvis. For families with HNPCC, endometrial carcinoma is the most common tumor with an incidence of 8%, followed by gastric carcinoma, 6%; pancreaticobiliary cancers, 4%; and uroepithelial malignancies, 2%.[126–130]

Management

As discussed earlier, the initial management of any suspected inherited cancer syndrome is genetic counseling. Management options include aggressive screening regimens, chemopreventive agents, and prophylactic surgery. Regardless of the treatment modality chosen, a lifetime of surveillance is needed.

Screening

Because the majority of polyps and cancers in patients with HNPCC are proximal to the splenic flexure of the colon, complete colonoscopy is the screening procedure of choice. Screening should be started at age 20 to 25, or 5 years younger than the youngest affected family member, and be performed every 1 to 2 years for the duration of the patient's life.[131–134] Endoscopic removal of all polyps, if technically possible, has been shown to reduce the incidence of colorectal cancers in HNPCC families.[135]

The cumulative incidence of endometrial carcinoma in women who have not had a hysterectomy and have a documented MMR mutation is 30% to 60%.[136,137] This led to the suggestion that screening for endometrial carcinoma is indicated for at-risk women.

Screening options include annual endometrial aspirate and/or transvaginal ultrasonography beginning at age 25 to 35 years. Although patients with HNPCC have an increased risk for gastric, pancreaticobiliary, and uroepithelial malignancies, routine screening is not recommended unless there is a family member affected with one of these cancers.

Chemoprevention

Several clinical trials have shown that the NSAIDs sulindac, celecoxib, and aspirin can reduce the number and size of colorectal adenomas.[59–62] These agents have

not been studied in patients with HNPCC; therefore, chemoprevention cannot be recommended as primary therapy for HNPCC but may be considered for the special circumstance in which surgical therapy has been declined or has an unacceptably high risk of complications.

Surgery

Surgical intervention is indicated for patients who are proved or strongly suspected to have HNPCC when they develop either a colon polyp that cannot be managed endoscopically or a colon cancer. With the risk of a metachronous colon cancer being reported to be as high as 40% at 10 years after a segmental resection, most would recommend a TAC. Even after TAC, the risk of cancer in the rectal remnant is reported to be 6% to 20%.[138–141]

For patients with HNPCC who develop rectal cancer, proctocolectomy with ileal pouch anal anastomosis (IPAA) should be performed if sphincter preservation is technically possible and does not violate oncologic principles. If sphincter preservation is not possible, TPC will be necessary.[142,143] These three surgical options, TAC, IPAA, and TPC, have already been discussed.

Much more controversial is prophylactic colectomy for patients with MMR mutations and a normal colon. Although prophylactic TAC removes the majority of colon at risk for cancer, allowing screening to be performed by flexible sigmoidoscopy,[142] the lifetime risk of colon cancer in patients with an MMR defect is not 100%. Colorectal cancer does not develop in 15% to 20% of patients during their lifetime, which means that eventual colectomy is not inevitable.[144]

Prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy in female patients with HNPCC are also controversial. With a 30% to 60% lifetime risk of developing endometrial cancer in women with MMR defects, it does not seem unreasonable to consider prophylactic hysterectomy and bilateral salpingo-oophorectomy at the time of colectomy for the patient who is postmenopausal or has completed her family.[142,145] Much more controversial is prophylactic hysterectomy and bilateral salpingo-oophorectomy for patients with MMR mutations and no abnormalities on clinical evaluation. Although prophylactic hysterectomy and bilateral salpingo-oophorectomy remove the organ at risk for cancer, negating the need for screening, which is not 100% effective, to be performed, the lifetime risk of endometrial cancer in patients with an MMR defect is not 100%. Endometrial cancer does not develop in 40% to 70% of patients during their lifetime, which means that eventual hysterectomy and bilateral salpingo-oophorectomy are not inevitable.

Postoperative Surveillance

Regardless of the surgical procedure chosen, postoperative surveillance of any remaining colon and screening for the extracolonic manifestations are essential for the remainder of the patient's life. Endoscopy of the rectal remnant should be performed annually with polyps less than 5 mm followed and larger polyps removed without fulguration and examined histologically to exclude dysplasia. Proctectomy with IPAA can be considered for an increasing number or size of polyps or the development of severe dysplasia.[91–93]

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