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Colon cancer in hereditary syndromes

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A B S T R A C T

Though representing less than 10% of colorectal cancers diagnosed worldwide, inherited colon cancer syndromes are important as their identification allows for screening and early interventions for both patients and their potentially affected family members. Both autosomal dominant and recessive gene mutations have been linked with these syndromes. High-penetrance mutations, such as those involved in tumor suppression or mismatch repair mechanisms, lead to phenotypes with increased colorectal cancer risk. Cancers that develop from hereditary syndromes differ from sporadic cancers in terms of timing, etiology, mechanisms, importance of diagnosis, and surveillance. This article defines these variations associated with the colorectal cancers linked with hereditary colorectal cancer syndromes.

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Introduction

It is estimated that up to 35% of colorectal cancers (CRCs) are associated with a family history of CRC. However, less than 10% are related to a known genetic syndrome, highlighting the need for continued research in this field. Identifying CRCs with a hereditary etiology allows for risk stratification of family members and intensive screening for both the patient and family members (Table 1). The underlying genetic mutations in inherited syndromes can lead to earlier cancer development, increased risk of metachronous cancers, and extracolonic disease manifestations. As such, screening must start earlier and be broadened to include other malignancies. The hereditary CRCs can be broadly divided into the polyposis and non-polyposis syndromes. Within polyposis, there are adenomatous and hamartomatous hereditary syndromes. The non-polyposis syndromes are defined both by clinical criteria and genetic testing. This article provides an overview of the main hereditary colorectal cancer syndromes.

Adenomatous polyposes

Familial adenomatous polyposis (FAP)

Features

Patients with classic FAP develop numerous (< 100) colorectal adenomatous polyps (Fig. 1) that without removal inevitably progress to carcinoma. The condition occurs with a frequency of about 1:10,000 people.[1] Polyps commonly appear in adolescence with the diagnosis of CRC at an average age of 40 years. Historically, FAP accounted for approximately 1% of all CRCs, but further understanding of inheritance patterns, aggressive surveillance, and timely prophylactic surgery have reduced the contribution of FAP to 0.05% of the overall CRC incidence.[2] Extracolonic manifestations of FAP are multiple and include upper gastrointestinal adenomas, desmoid tumors (especially in the mesentery; Fig. 2), papillary thyroid cancer, jaw osteomas, and congenital hypertrophy of the retinal pigment epithelium.

Genetics

FAP is an autosomal dominantly inherited condition caused by mutation of the *adenomatous polyposis coli* (*APC*) gene. The majority of patients have a family history of FAP, but 25% of cases are attributable to a novel *de novo* mutation.[1] The *APC* gene encodes a large protein with multiple cellular functions and interactions, including roles in signal transduction in the wnt-signaling pathway, mediation of intercellular adhesion, stabilization of the cytoskeleton, and possibly regulation of the cell cycle and apoptosis.[3] In both sporadic CRCs as well as those associated with FAP, mutation of the *APC* gene is one of the earliest events. There is a significant variation in FAP phenotypes, ranging from attenuated disease (10–100 polyps) to severe polyposis (> 1000 polyps). This is due both to the position of the mutation within the *APC* gene as well as other genetic modifiers.[4] Patients with a deletion at codon 1309 exhibit a particularly aggressive phenotype with gastrointestinal symptoms and death from CRC occurring about 10 years earlier than in patients with other mutations. The 1309 mutation leads to development of colonic polyps at a

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Table 1
Inherited colorectal cancer syndromes, risk for colorectal cancer, and screening recommendations.

Syndrome	Lifetime risk of colorectal cancer (%)	Endoscopic surveillance	Screening age (years)
FAP	100	Flex sig until polyps identified, then annual colonoscopy	10–12
Attenuated FAP (aFAP)	70	Annual colonoscopy	20–25
MYH-associated polyposis (MAP)	80	Colonoscopy every 1–2 years	25
Peutz–Jeghers syndrome	39	Colonoscopy every 2–3 years	18
PTEN tumor hamartoma syndromes	16	Colonoscopy every 3–5 years	35
Juvenile polyposis syndrome (JPS)	40–50	Colonoscopy every 2–3 years	18
Hereditary non-polyposis colorectal cancer (Lynch)	30–72	Colonoscopy every 1–2 years	20–25
Familial Colorectal Cancer Syndrome Type X	2 × general population	Colonoscopy every 3–5 years	40–45; 5–10 years younger than youngest relative

younger age, thus giving rise to an earlier malignant transformation.[5]

Diagnosis

FAP may be diagnosed either clinically or by genetic testing. Clinical diagnosis begins with identification of the polyposis phenotype on endoscopy. Patients with classic FAP (> 100 adenomatous polyps) and at-risk family members should undergo genetic counseling and consider genetic testing. Genetic evaluation should include full gene sequencing for an *APC* mutation. This will identify *APC* mutations in up to 80% of patients with classic FAP, but only 10–30% of patients with attenuated FAP (see below section). Approximately 20% of clinically diagnosed FAP patients will not have a pathogenic mutation identified in the *APC* gene. If testing is negative, but the patient still expresses a strong FAP phenotype, testing for biallelic mutations in the *MYH* gene should be considered (see below).[6] Patients with polyposis for whom genetic testing fails to identify a mutation should be considered to have indeterminate results. In these families, genetic testing is not informative, and therefore all family members at risk should be encouraged to follow standard FAP surveillance programs.[7]

Colonic surveillance

At-risk family members, *APC* mutation carriers, or members who have not had genetic testing or in whom genetic testing is uninformative should undergo a flexible sigmoidoscopy or colonoscopy (some prefer the latter as the initial screening study) every 12 months starting at age 10–12 years and continuing until age 35–40 years if negative. Once polyps are detected, surveillance should shift to full colonoscopy.[8] Classic FAP almost always involves the rectosigmoid, so sigmoidoscopy alone should be adequate. Screening for extracolonic malignancies, which is detailed in this article, should include scheduled upper endoscopy with a side-viewing scope, thyroid screening, and consideration of hepatic ultrasound for children.

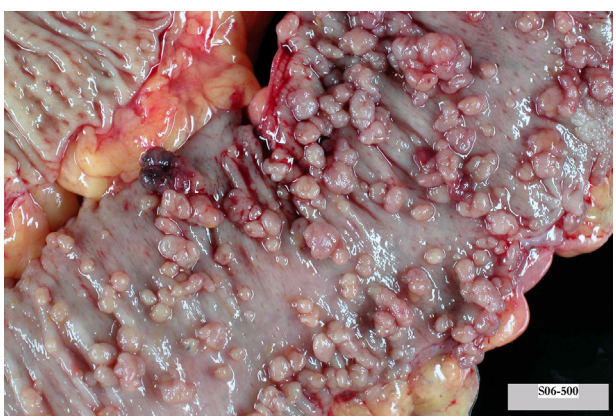

Fig. 1. Colectomy specimen from a familial adenomatous polyposis (FAP) patient.

Surgery

Surgery is indicated for all patients who phenotypically manifest FAP, but the timing and extent of the operation depends on a number of factors. The decision on timing requires dialog between provider and patient as to the extent of polyposis, presence of high grade dysplasia (HGD) or cancer, the patient's understanding of their risk versus quality of life, timing of familial manifestations of the disease (e.g., relatives developed colon cancer at a young age), and the patient's tolerance and availability for further screening procedures. For pediatric patients, the physical and emotional maturity of the child should be considered. Colectomy is mandatory, regardless of age, when the polyp burden becomes too extensive to be managed endoscopically or when HGD or invasive adenocarcinoma is found. To treat the colonic disease in FAP, there are three main operative options as outlined in Table 2. All can be performed using minimally invasive techniques, and avoiding a full laparotomy.

Total proctocolectomy with ileoanal pouch anastomosis (IPAA) is the most widely used procedure for the treatment of FAP and has the advantage of complete removal of the colon and near complete removal of the rectum, resulting in excellent cancer control. However, cancer prevention is not perfect as up to 1.2% of patients will go on to develop neoplasia in the pouch and/or anal transition zone, including reports of HGD and carcinoma.[9] Mucosectomy and handsewn pouch anal anastomosis are no longer thought to always be necessary, as stapled pouches have similar outcomes and provide better functional outcomes.[10] Patients still require surveillance of the anal transition zone and pouch with anoscopy and/or pouchoscopy, although exact timing is unclear and often ranges from every 6 months to every 2 years depending on the patient's phenotype and findings at each exam. Risk of complications and functional results have improved over time, but are still worse than other procedures for FAP.[11] IPAA is the procedure of choice for patients with severe polyposis, significant rectal polyposis, or those known to carry a mutation in codon 1309, assuming that they are a candidate for this complex operation.

Total abdominal colectomy with ileorectal anastomosis (IRA) leaves the rectum in place and is technically easier to perform. Function, both sexual and sphincter (i.e., continence), are superior compared to proctectomy and IPAA.[12,13] Patients who undergo IRA require annual proctoscopy with resection of any polyps larger than 5 mm. Detection of carcinoma in the remaining rectum is an indication for completion proctectomy with either IPAA or end ileostomy. By the age of 60 years, half of the patients who underwent IRA retained their rectum. Rectal polyp count exceeding 20, *APC* mutation in codons 1250–1450, colonic polyp count

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