Hereditary Intestinal Polyposis Syndromes

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SUMMARY Background: *Colorectal cancer is one of the most common cancers in the world, with overall mortality exceeding 40% even with treatment. Effective efforts for screening and prevention are most likely to succeed in patient groups identified as high risk for colorectal cancer, most notably the hereditary intestinal polyposis syndromes. In these syndromes, benign polyps develop throughout the intestinal tract prior to the development of colorectal cancer, marking the patient and associated family for precancer diagnosis followed by either close surveillance or preventive treatment.* **Purpose:** *This review article was undertaken to discuss the most recent developments in the knowledge of hereditary intestinal polyposis syndromes, emphasizing the clinical approach to diagnosis and treatment relative to preventing the development of cancer.* **Results:** *The most common of the hereditary polyposis syndromes is familial adenomatous polyposis (FAP), which is characterized by the development of hundreds to thousands of adenomatous polyps in the colon followed at an early age by colorectal cancer. Colorectal cancer can be prevented in this autosomal dominant condition by prophylactic colectomy, though a risk for other tumors, including periampullary cancers, remains throughout life. Variant of FAP associated with fewer and smaller polyps (hereditary flat adenoma syndrome), or even CNS tumors (Turcot's syndrome) also carry this high risk of colorectal cancer. Hereditary hamartomatous polyposis syndromes such as juvenile polyposis and Peutz-Jeghers syndrome (also autosomal dominant) are characterized by less frequent polyps. Though these are generally benign polyps, they are also associated with a significant risk of colorectal and other cancers. Other polyposis syndromes, including neurofibromatosis and Cowden's disease, do not carry this increased risk of colorectal cancer, and therefore affect different treatment strategies. Analysis of genetic factors responsible for these and other hereditary syndromes with predisposition to colorectal cancer has*

RESUMEN Antecedentes: *El cáncer colorrectal constituye uno de los tumores más frecuentes en el mundo, con una mortalidad global que sobrepasa al 40%, incluso con tratamiento. Los esfuerzos efectivos para escrutinio y prevención tienen más probabilidad de lograr éxito en grupos de pacientes identificados con un mayor riesgo de cáncer colorrectal, principalmente los síndromes de poliposis intestinal hereditarios. En estos síndromes, se desarrollan pólipos benignos en el tubo digestivo previo al desarrollo de malignidad, permitiendo que el paciente y sus familiares sean estudiados y diagnosticados antes del desarrollo de cáncer, ya sea por seguimiento cercano o tratamiento preventivo.* **Objetivos:** *Este artículo de revisión se realizó para discutir los desarrollos más recientes en el conocimiento de los síndromes de poliposis intestinal hereditarios, enfatizando el abordaje del clínico para el diagnóstico y tratamiento preventivo del desarrollo de cáncer.* **Resultados:** *El más común de los síndromes de poliposis hereditaria es la poliposis adenomatosa familiar (PAF), que se caracteriza por el desarrollo de cientos a miles de pólipos adenomatosos en el colon, con subsecuente desarrollo de cáncer colorrectal a temprana edad. El cáncer colorrectal puede prevenirse en esta enfermedad autosómica dominante por colectomía profiláctica, aunque persiste un riesgo de por vida para el desarrollo de otras neoplasias, incluyendo tumores periampulares. Otras variantes de PAF asociadas con menos y más pequeños pólipos (síndrome hereditario del adenoma plano), o con tumores del SNC (síndrome de Turcot) también conllevan un mayor riesgo de cáncer colorrectal. Síndromes de poliposis hamartomatosa hereditaria, como poliposis juvenil y síndrome de Peutz-Jeghers (también autosómico dominante) se caracterizan por pólipos menos frecuentes. Aunque generalmente son pólipos benignos, pueden también asociarse a un riesgo significativo de cáncer colorrectal y de otra localización. Otros síndromes de poliposis que incluyen la neurofibromatosis y enfermedad de Cowden, no conlle-*

not only contributed to our molecular understanding of colorectal cancer, but opened the door to DNA testing and treatment strategies for these diseases. **Conclusions:** The treatment advances that are discussed and careful screening in appropriate families will effectively reduce the risk of death from colorectal cancer.

van aumento en el riesgo para cáncer colorrectal y por ello tienen diferentes estrategias terapéuticas. El análisis de los factores genéticos responsables para estos y otros síndromes hereditarios con predisposición al cáncer colorrectal ha contribuido al entendimiento del cáncer colorrectal a nivel molecular, pero también ha abierto el panorama para las pruebas del DNA y nuevas estrategias terapéuticas. **Conclusiones:** Los avances terapéuticos que se discuten y el escrutinio meticuloso en familias apropiadas reducirán efectivamente el riesgo de muerte por cáncer colorrectal.

Key words: Intestinal polyposis.

Palabras clave: Poliposis intestinal, herencia.

INTRODUCTION

Cancer of the colon and rectum is one of the most common cancers affecting both men and women in the Western World, with a lifelong risk of nearly one in fifteen in the normal population[1]. Even with optimal treatment, mortality is as high as 40%, thus, the most effective method of treatment available for these life-threatening cancers is detection and removal at premalignant or early malignant stages, which is the goal of screening and surveillance efforts. The vast majority of colorectal cancers (>90%) are the result of an unpredictable series of sporadic genetic alterations (mutations) which occur too infrequently to make routine screening of the general population both reliable and cost effective with current techniques[2]. In the remaining cases, cancer is associated with a genetically defined risk factor, most without signs or symptoms prior to the development of cancer, such as the hereditary nonpolyposis colorectal cancer syndrome (Lynch syndromes)[3]. In contrast, a small but significant minority of colorectal cancers arise in patients with a familial predisposition associated with polyposis syndromes[4]. Benign polyps develop throughout the intestinal tract (predominantly colon) prior to the development of cancer in these patients, allowing precancer diagnosis, close surveillance, or preventive treatment.

Though these hereditary polyposis syndromes are uncommon, two important factors make them important for all clinicians treating diseases of the gastrointestinal tract to recognize. First, the presence of multiple polyps in these syndromes indicates a significant and defined risk of subsequent colorectal or other cancer development, and treatment or surveillance strategies must be understood by both

physician and patient to minimize the risk of cancer mortality. Secondly, the hereditary nature and high frequency of cancers in these syndromes have important implications not only for the affected patient, but for asymptomatic family members as well. It is in these patients and their families, that screening, surveillance, and cancer prevention techniques will have the greatest impact on cancer survival.

This article will focus on the most thoroughly studied and understood of the polyposis syndromes, familial adenomatous polyposis (FAP), and emphasize recent developments in our understanding of the clinical approach to diagnosis and treatment relative to

TABLE 1
COLON POLYPOSIS SYNDROMES AND CANCER

Non Polyposis
    Hereditary nonpolyposis colorectal cancer
    (Lynch syndromes)

Adenomatous Polyps
    Familial adenomatous polyposis
    Muir-Torre syndrome
    Hereditary flat adenomas syndrome
    Turcot's syndrome

Hamartomatous Polyps
    Juvenile polyposis
    Peutz-Jeghers syndrome
    Cowden's disease
    Cronkhite-Canada syndrome

Miscellaneous Polyposis
    Neurofibromatosis
    Lymphomatous polyposis
    Pseudopolyposis

preventing the development of cancer. The salient clinical features of FAP will be contrasted with other hereditary polyposis syndromes, including variants of FAP, juvenile polyposis, Peutz-Jeghers syndrome, and other less common polyposis syndromes to present a framework for approaching the patient with multiple intestinal polyps (Table 1). While it is beyond the scope of this article to provide an exhaustive review of all familial predisposition to colorectal cancer, the reader is referred to a number of excellent recent reviews, summarizing both hereditary nonpolyposis[3] and polyposis[4-8] syndromes for more information.

FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis (FAP) is the most common hereditary polyposis syndrome, and is characterized by the development of greater than 100 adenomatous polyps throughout the colon and rectum[7]. The polyps vary in size from microscopic adenomas to several centimeters, but most polyps are typically <2 cm in size[9]. They may be either pedunculated or sessile, and may have tubular, tubulovillous, or villous histologic features. Polyps are usually evenly distributed throughout the colon, but in rare cases may spare the rectum early in the disease[10].

The natural history of FAP has been well characterized through the development of a number of registries[4,7,11]. Polyps usually become apparent endoscopically by the late teens or early twenties, and if untreated, will typically become symptomatic by the mid thirties. Most affected patients will demonstrate polyps by mid forties, though in rare patients development of polyps may be a late manifestation of the disease, and may not appear until after the mid fifties[10]. Though often asymptomatic, bleeding is the most common symptom, but vague abdominal discomfort, diarrhea, tenesmus, mucus discharge, and obstructive symptoms can also occur. Cancer may precede the development of polyp symptoms, and is high in probands of FAP patients in the absence of a polyposis registry[12]. In untreated patients, cancer may develop as early at the late teens, or early twenties, but more typically occurs in the mid thirties. Without treatment, the mean age of death from colorectal cancer is 42.

Genetics of FAP

FAP is an autosomal dominant condition with high, but not 100% penetrance[10]. The gene responsible for FAP has been identified and is called APC (for adenomatous polyposis coli). This gene is on the long arm of

chromosome 5 (5q21 locus)[13-15] and the abnormalities in families with FAP include a variety of mutations, most commonly point mutations and microdeletions, all resulting in an abnormal gene product[16]. The importance of this gene in colorectal cancer is underscored by the fact that mutations not only occur in all families with FAP, but occur in over 65% of all sporadic colorectal polyps and cancers as well[17].

The precise mechanism of colorectal tumorigenesis resulting from APC mutation is currently under intense study. A large number of different mutations lead to FAP and the development of colorectal cancer, though some mutations occur more commonly than others[18]. Certain APC mutations appear to favor the development of more severe colonic disease[19], while other mutations may result in fewer polyps but none the less lead to the development of cancer[20]. The phenotypic expression of certain common mutations, however, appears to be strongly affected by environmental factors, resulting in significant clinical variation[9]. While more accurate genetic mapping may eventually lead to better genetic diagnosis[18,21], other factors play a critical role in the disease expression.

The genetic abnormality associated with APC appears to result in increased proliferation of the mucosa throughout the gastrointestinal tract and other epithelial tissues, which has been postulated to be secondary to disruption of a tumor suppressor protein produced by the APC gene[15]. This concept is supported by the finding of increased DNA synthesis in the colonic mucosa in patients with FAP[22], and suggests that more rapid epithelial cell proliferation may be a common mechanism for the development of both FAP and sporadic colorectal cancer[17,23]. Attempts to decrease this proliferative rate have been the target of medical treatment strategies for FAP[24], as will be discussed in a later section. Further identification of the function of the APC gene product should provide a more accurate therapeutic target for the treatment of colorectal tumorigenesis.

Extracolonic manifestations

Since the original report of Gardner identifying a family with polyposis, epidermoid cysts, and osteomas, which was subsequently shown to result from the same genetic mutation as other forms of FAP[25], a number of extracolonic manifestations of FAP have been identified (Table 2). It appears that most or all of these manifestations are due to a common genetic defect at the APC locus which results in a generalized growth disorder with variable phenotypic expression[9].

TABLE 2
EXTRACOLONIC MANIFESTATIONS OF FAMILIAL
ADENOMATOUS POLYPOSIS

Benign	Malignant
Osteoma	Desmoid tumors *
Epidermoid cyst	Periampullary carcinoma
CHRPE	Gastric carcinoma
Gastric fundus polyps	Hepatoblastoma
Duodenal polyps	Papillary carcinoma (thyroid)
Small bowel tumors	Medulloblastoma/Glioblastoma
Endocrine adenomas	

Histologically benign, biologically malignant tumors.

A number of benign tumors are common in FAP[26]. Osteomas occur in over 50% of patients, and are typically found on the face, particularly the mandible. Epidermoid cysts, as originally described in Gardner's syndrome, are also common, most often on the limbs and scalp. Pigmented retinal lesions commonly seen in FAP patients were originally thought to be congenital hypertrophy of the retinal pigment epithelium (CHRPE), but the lesions in FAP are different than those that appear in the normal population[27], and are thought to be hamartomas of the pigmented epithelium[7]. Since these CHRPE lesions are apparent at or shortly after birth, they may represent an early screening marker for FAP in selected patients[23], as discussed later.

Desmoid tumors are a special class of benign tumors occurring in 10% of patients with FAP[29]. These tumors histologically are fibromatous lesions occurring most commonly on the abdominal wall and the mesentery, but occasionally found on the extremities[29,30]. Though they are histologically benign, they may exhibit aggressive local growth, causing significant morbidity and mortality due to mesenteric ischemia, small bowel obstruction, ureteral obstruction, and local invasion[30,31]. Patients with FAP who have undergone previous surgery have a higher incidence of desmoid formation[31]. The incidence of desmoid tumors also appears to be higher in premenopausal females[29], and may be associated with pregnancy or oral contraceptives. While they tend to occur more commonly in certain FAP kindreds, there is no direct association with specific APC mutations[29]. Though desmoid tumors also occur

in the normal population, the "malignant" behavior of these tumors is primarily associated with FAP.

While colorectal polyposis is the predominant feature of FAP, gastroduodenal and small intestinal polyps also occur, though their exact incidence is unknown[32]. These tumors appear later than colorectal polyps, and with improved survival following proctocolectomy and elimination of the colorectal cancer risk, they are presenting an increasing therapeutic challenge[32-36]. Gastric polyps occur in over half of the patients with FAP, and are usually fundal gland polyps, hyperplastic polyps, or less commonly, adenoma[32,36]. Gastric carcinoma has been reported, but is uncommon[33,35]. Duodenal polyps, in contrast, occur in virtually all patients with FAP followed long enough, and are nearly always adenomatous polyps[32,36-40]. Unlike their gastric counterparts, these duodenal tumors, primarily periampullary in location, have a high risk of malignant transformation, and (assuming colectomy with removal of the colorectal cancer risk) patients with FAP have up to a 300-fold risk of gastroduodenal cancer compared to the normal population[33,35,40,41]. The high frequency of adenomas and adenocarcinoma in the periampullary region has lead investigators to speculate that altered bile components or altered pH may play a role in the development of these neoplastic changes in FAP[42-44]. Adenomas of the small intestine also occur with advancing age in patients with FAP, primarily in the terminal ileum. Adenomas have been reported in the ileal mucosa after ileostomy, ileorectal anastomosis, ileoanal pouch, and Koch pouch[45-49] but unlike duodenal adenomas, malignant transformation is rare[35,50].

A variety of other tumors can occur in association with FAP, consistent with the proposal that mutation of the *APC* gene removes a tumor suppressor protein, and results in abnormal proliferation of a number of tissues. Hepatobiliary tumors, including hepatoblastoma[51], are thought to be more common than in normal patients, and gallbladder dysplasia has been reported[52]. Papillary carcinoma of the thyroid is also seen with increased frequency in women with FAP[53]. Central nervous system tumors occurring in association with multiple colonic neoplasms is referred to as Turcot's syndrome[54], though because the genetic basis of this syndrome is complex, these tumors will be discussed later as a variant of FAP.

Screening
The recognition of FAP in a kindred has significant implications for screening of all potentially affected individuals. Since FAP is inherited in an autosomal

dominant manner, roughly 50% of susceptible family members will carry the gene and its associated high risk of death from colorectal cancer. The goal of screening in FAP kindreds is not to detect colorectal cancer, but to determine which family members express the altered *APC* gene and initiate preventative treatment prior to the development of colorectal or other cancers. The value of such a screening priority is confirmed by the significant reduction in not only the age at diagnosis of FAP, but most importantly a 10-fold reduction in the incidence of carcinoma (and consequently death due to carcinoma) in asymptomatic patients detected by screening[12,55-57].

With recent localization and enhanced characterization of the *APC* gene, the development of direct DNA testing is the ideal screening tool for family members at risk for FAP[58]. In practice, however, a large number of mutations have been demonstrated in the *APC* gene from different families with FAP[58] making analysis of the abnormal gene difficult on a large scale. A slightly different approach is analysis of the *APC* protein[59]. Unlike gene testing, this approach does not require several first degree relatives for analysis, since abnormally truncated proteins are detected in the majority (82%) of unrelated FAP patients[59]. Ultimately, a combination of *APC* gene and protein analysis is likely to allow for accurate testing of affected individuals at young ages (even prepartum), and will allow focused treatment strategies prior to the onset of any phenotypic expression of the disease. For the present, however, this approach is confined to a few academic medical centers with the individual laboratory expertise for accurate and sophisticated testing, and is not practical for the majority of patients at risk for FAP.

Most screening strategies in use presently take advantage of the natural history of FAP: development of colorectal polyps 10-20 years prior to detection of cancer in most patients. Flexible sigmoidoscopy should begin by 14 years of age in at-risk relatives, and be repeated every 2 years until polyps are detected or at least until age 50, since late appearance of polyps has been reported in a number of patients[10]. Rigid proctosigmoidoscopy can be used in substitution, since polyps rarely if ever spare the rectum, but patient comfort is critical for compliance, since in many patients the procedure will need to be repeated multiple times to prove absence of disease. Barium enema or colonoscopy as a screening tool are inappropriate because of cost and morbidity. If polyps are detected, a full colonoscopy is appropriate, and should be repeated frequently until colectomy is undertaken.

In addition to endoscopy, interest has been strong in the application of CHRPE lesions of the eye for early (even infancy) detection of affected patients[60]. These lesions have the advantage of being detected in the presymptomatic stage, and may assist in focusing endoscopic screening to patients more suspect for the development of FAP. These lesions are found in the general population, however, and are not necessarily associated with FAP or the development of colorectal cancer[27]. In addition, not all mutations of the *APC* gene are associated with CHRPE lesions[61], thus not all patients with FAP have these retinal lesions. With increased availability of genetic testing, the role of CHRPE lesions in screening for FAP is rapidly diminishing. The principle value of this test is that if CHRPE lesions are present in the original proband or index patient of a kindred, offspring lacking these lesions will not develop polyposis.

Treatment

Once polyposis has been detected in an individual, surgical resection of the colon is the only acceptable treatment option to eliminate the nearly absolute risk of developing colorectal cancer. Multiple polypectomy for removal of large colon polyps is not reasonable, not only because of the impossibility of removing all polyps even with frequent colonoscopy, but because of the possibility of cancer developing in even small or microscopic adenomas. Timing and nature of the surgical therapy is somewhat variable, however, depending on the age at detection and other psychosocial issues, and in young patients may be delayed until the late teens with reasonable risk.

Two major categories of surgical treatment exist: colectomy with ileorectal anastomosis, and total proctocolectomy. In the past, colectomy with ileorectal anastomosis had been a popular treatment option, because of the preservation of a short segment of rectum (typically 6-10 cm). In young patients this has the advantage of avoiding proctectomy and the associated low, but socially significant risk of sexual dysfunction. Rectal polyps may regress after ileorectal anastomosis[62], but the polyps return in most patients, and the risk of rectal cancer is unacceptably high after age 50[63,64]. In certain situations, colectomy with ileorectal anastomosis may be appropriate in young patients concerned about sexual function after pelvic surgery, though it should only be considered a "bridge" to eventual proctectomy with ileostomy or ileoanal pouch. If desmoid tumors occur after ileorectal anastomosis, proctectomy may not be possible, however, and

patients may die from unresectable rectal cancer[31,65]. Ileorectal anastomosis may also be appropriate for patients who are debilitated at the time of surgery, those who are older and have very few rectal polyps, or those with advanced colon cancer at the time of primary surgery. In patients who have an ileorectal anastomosis, consideration should be given to a trial of sulindac to facilitate polyp regression since this agents appears to reduce the number and size of rectal polyps after colectomy[66-68]. In spite of this effect on rectal polyps, however, abnormal rectal epithelial proliferation persists[24,69], and the risk of rectal cancer continues to be a concern[70,71]. Thus even with treatment, close surveillance of the remaining diseased rectum is mandatory, and the inability to perform continuous surveillance is a contraindication to ileorectal anastomosis.

The treatment of choice for patients with FAP is total proctocolectomy. By removing the entire colon and rectum, the risk of colorectal cancer is completely eliminated. Options for reconstruction after proctocolectomy include end (Brooke) ileostomy, continent ileostomy (Koch pouch), and ileoanal pouch. While each of these are acceptable, the ileoanal pouch is the optimal procedure for these young and otherwise healthy patients to maintain normal functional lifestyles and avoid the necessity for a stoma appliance. Function of the ileoanal pouch for FAP is as good or better than in ulcerative colitis[72-74], and pouchitis rarely if ever occurs in FAP[75]. In patients with an ileorectal anastomosis, conversion to ileoanal pouch can be safely offered, with functional results as good as for primary ileoanal pouch[65]. Care should be taken to remove all the rectal mucosa with the ileoanal anastomosis to prevent the occurrence of rectal cancer in the pouch cuff[76]. Results of the ileoanal pouch performed in children are excellent in experienced hands, and this procedure remains the procedure of choice even when operation must be performed at a young age[77].

Medical treatment of colorectal polyps should be mentioned for completeness of discussion. With evidence that rectal adenomas regress after colectomy and after treatment with sulindac, medical therapy to facilitate polyp regression throughout the colon became an attractive treatment strategy. Treatment with sulindac has been shown to decrease the number and size of polyps throughout the colon and rectum, but the effect is incomplete and the risk of cancer is unknown[78]. Other agents have also been shown to reduce the rate of mucosal proliferation and may be of interest in the treatment of FAP[79,80]. The relationship between polyp number, mucosal proliferation, and cancer risk is unknown, however[24,69,81] and since the risk of colorectal cancer is eliminated by proctocolectomy, other treatment options must show equal oncologic results to be considered as effective.

The treatment of extracolonic manifestations of FAP is more difficult. Desmoid tumors, when they occur, can be difficult to manage, and may be impossible to remove in many patients[31]. Asymptomatic tumors should generally not be surgically manipulated[30], and thought should be given the pharmacologic treatment of large, non-obstructing mesenteric desmoid tumors, including sulindac, antiestrogen agents, and cancer chemotherapeutics[29,82,83].

Duodenal adenomas in FAP may also be difficult to manage. Because of the significant risk of carcinoma developing in these tumors[33,40], efforts to reduce their number or size using sulindac have been made 66 but have only limited success. Small duodenal adenomas should be excised when possible endoscopically, whereas large polyps can be removed surgically by polypectomy[39,84] or pancreas sparing duodenectomy[85]. Pancreaticoduodenectomy should be reserved for tumors with or highly suspicious for invasive cancer.

VARIANT ADEMONATOUS POLYPOSIS SYNDROMES

Two hereditary adenomatous polyposis syndromes deserve special attention because of confusion surrounding their identity. These include the hereditary flat adenoma syndrome and the Muir-Torre syndrome. Hereditary flat adenoma syndrome is a rare, autosomal dominantly inherited syndrome in which patients have <100 small, flat polyps, primarily in the right colon with the propensity for right colon cancer. This was originally thought to represent a variant of hereditary non-polyposis colorectal cancer, but more recent genetic analysis shows associated mutations in the *APC* gene, suggesting that it is a variant of FAP[20,86]. Upper gastrointestinal tumors similar to those found in FAP support the classification of this syndrome with FAP[36], and treatment should parallel that for FAP.

Muir-Torre syndrome also shows an autosomal dominant inheritance pattern, and is also characterized by the presence of <100 adenomatous polyps, but is also associated with multiple skin lesions[87]. The genetics of this syndrome is unclear, but may be more closely related to hereditary non-polyposis colorectal cancer[4], and treatment should be aimed at removal of polyps and close surveillance.

TURCOT'S SYNDROME

This syndrome is defined clinically by the association between multiple adenomatous colorectal polyps and central nervous system tumors[54]. This syndrome includes a heterogeneous spectrum of findings in which the number of polyps ranges from a few to several hundred, and inheritance patterns vary from autosomal recessive to autosomal dominant[54,88]. Initial genetic studies suggested a linkage to the *APC* gene[89], but recent analysis of several families indicated that at least two distinct types of germ line mutations can lead to Turcot's syndrome[88]. Mutations in the *APC* gene can be associated with multiple colorectal polyps and CNS tumors, primarily meduloblastoma, and represent a variant of FAP. The genetic defect in other families with colorectal cancer, less prominent polyposis, and primarily glioblastomas was found to be in the DNA mismatch-repair genes associated with hereditary nonpolyposis colorectal cancer, and tend toward an autosomal recessive pattern of inheritance. Thus screening and surveillance for families with Turcot's syndrome will depend on the phenotypic expression and likely genetic abnormality associated with the disease.

JUVENILE POLYPOSIS

Isolated juvenile polyps are common in children, but must be distinguished from juvenile polyposis, a rare form of hereditary intestinal polyposis[6,90]. Like FAP, juvenile polyposis is a familial premalignant condition characterized by the finding of multiple polyps throughout the gastrointestinal tract. The polyps in juvenile polyposis, however, are hamartomas in contrast to the adenomas characteristic of FAP[91]. Juvenile polyposis is defined as the presence of: a) multiple (>5) hamartomatous polyps in the colon; b) juvenile polyps throughout both the upper and lower gastrointestinal tract; or c) any number of juvenile polyps in a patient with a family history of juvenile polyposis[6]. The number of polyps in juvenile polyposis is variable, but typically ranges between 30 and 200. They are most common in the colon, but can be found throughout the intestinal tract and are occasionally confined to the stomach or small intestine[91].

The clinical presentation of juvenile polyposis is variable depending on the size and number of polyps present. Juvenile polyposis of infancy carries a poor prognosis, presenting with failure to thrive, bleeding, diarrhea, intussusception and rectal prolapse, and usually resulting in death by age 2[92]. Patients presenting later in life typically demonstrate rectal bleeding, ane-

mia, and rectal prolapse or intussusception as late as the early adult years.

The etiology of this polyposis syndrome is unclear. Most patients have a family history of juvenile polyposis with an autosomal dominant inheritance pattern and widely variable penetrance. The underlying genetic abnormality is unknown, but linkage studies have failed to detect abnormalities of the *APC* gene[93]. Though there is an association with other genetic and morphologic abnormalities, no clear familial pattern has emerged to unify these associations. The hamartomas of this syndrome appear to have an inflammatory etiology[91], but the stimulus is unknown.

Though hamartomas are not traditionally thought to be precancerous tumors and solitary juvenile polyps do not have malignant potential[90], it has become increasingly clear that juvenile polyposis is a premalignant condition. The incidence of colorectal cancer in young patients is 15%[94], but is as high as 65% after age 60[95]. These cancers are primarily adenocarcinoma, and are thought to arise from neoplastic transformation of the crypt epithelium in a mixed adenoma/hamartoma juvenile polyp[96-99]. A similar sequence has also been reported with the development of gastric cancer[91,100].

Management of patients with juvenile polyposis depends on the symptoms, and the number and extent of polyps. Infrequent polyps can be treated by endoscopic removal, which is effective at controlling symptoms of the syndrome. Clearance of polyps from the stomach and colon with close follow-up is reasonable since the risk of malignant transformation is primarily in these organs and endoscopic access is relatively easy. For patients in whom the polyps are too numerous to allow complete clearance from the colon, the value of prophylactic colectomy with ileorectal anastomosis has not been established, but is a reasonable option. Screening asymptomatic relatives should be considered, with upper and lower endoscopy probably beginning in the teenage years before the rise in cancer risk[94]. Though tumors can occur in the small intestine, screening and evaluation by small bowel x-ray is of limited value in asymptomatic patients since cancer has not been reported in this portion of the intestine. While the overall prognosis is much better for juvenile polyposis than for FAP, the premalignant nature of these polyps suggests close follow-up is prudent.

PEUTZ-JEGHERS SYNDROME

Like juvenile polyposis, the Peutz-Jeghers syndrome is characterized by a familial predisposition to the

development of hamartomatous polyps, which are associated with distinctive mucocutaneous pigmentations[5]. The polyps in this syndrome are multiple, and though found throughout the gastrointestinal tract, are most common in the small intestine. They tend to be much less frequent than in juvenile polyposis, but are often > 1 cm and frequently cause symptoms related to obstruction or intussusception. Patients may require multiple laparotomies with either small bowel resection or enterotomy and polypectomy to remove the polyps[101], and intraoperative small bowel endoscopy can be useful to identify multiple small bowel tumors and reduce reoperative rates[102].

Though initially thought not to be premalignant, an association between Peutz-Jeghers syndrome and cancer has become increasingly apparent, with the distribution of cancers similar to that of benign polyps[103,104]. As for juvenile polyposis, these tumors are thought to arise from adenomatous areas of a hamartoma[104]. Other tumors are also seen with increased frequency in Peutz-Jeghers syndrome, including ovarian neoplasms, breast cancer, and sex-cord tumors[103,105,106].

The pigmented lesions of Peutz-Jeghers syndrome are distinctive flat, blue-gray to brown macules appearing on the lips, nose, mouth, hands, feet, and occasionally genitals early in childhood. They often fade by puberty, in contrast to normal freckles. Histologically they are caused by pigmentladen macrophages in the dermis, and no association with malignant degeneration is known[4,8].

Though the inheritance pattern of Peutz-Jeghers syndrome is autosomal dominant with variable penetrance, the underlying genetic abnormality is unknown. Screening of affected family members is of unknown benefit, since the precise incidence of cancer is unknown. Distinctive skin pigmentation will often make screening for the disease phenotype unnecessary. Certainly any family member of an index case with suggestive symptoms should be evaluated, including colonoscopy, upper GI series with small bowel visualization, and probably pelvic ultrasound in females.

OTHER POLYPOSIS SYNDROMES

A number of other polyposis and pseudopolyposis syndromes are important in the differential diagnosis of these hereditary polyposis syndromes and their relevance to cancer. Two other hamartomatous syndromes rarely seen include Cowden's disease and Cronkhite-Canada syndrome. Cowden's disease is

characterized by multiple orocutaneous hamartomas, breast disease, thyroid cancer, and multiple gastrointestinal hamartomas inherited in an autosomal dominant pattern. The skin tumors are the predominant feature of the disease, and though malignant breast, renal, and thyroid conditions can occur, there is no clear predisposition to malignant changes of the gastrointestinal hamartomas, which are typically small[107]. Because of the predisposition to breast and thyroid cancer, screening of patients with the characteristic skin lesions should include frequent mammograms and thyroid examination[108].

Cronkhite-Canada syndrome is also characterized by diffuse gastrointestinal hamartomatous polyps, but unlike the other polyposis syndromes, this is a non-familial condition with onset typically late in life. This may represent an infectious or inflammatory condition, and the natural history is that of progressive deterioration and death due to severe malnutrition and metabolic abnormalities[4].

Other non-classical polyposis lesions can present with a variety of symptoms. Neurofibromatosis can occur in the gastrointestinal tract, presenting with bleeding, obstruction, or intussusception. Typical skin lesions raise the suspicion for this diagnosis, and treatment is based on symptoms. We recently had a patient present with true lymphomatous polyposis, with obstructing symptoms and diarrhea, relieved by chemotherapy for his underlying lymphoma. Pseudopolyposis (metaplastic polyposis) associated with severe, long-standing inflammatory bowel disease can mimic true polyposis endoscopically, but the diagnosis is usually self evident given the symptom complex and extensive ulceration.

CONCLUSIONS

The vast majority of colorectal polyps and cancers seen in the typical practice are sporadic in nature, and extensive screening and prevention efforts will have frustratingly little impact on the incidence and natural history of these diseases. In contrast, recognition and proper treatment of the hereditary polyposis syndromes can profoundly influence the outcomes both on an individual and a family basis, minimizing or eliminating the otherwise high risk of colorectal cancer and death. The appropriate approach to screening is determined by the inheritance pattern for these syndromes, and the pattern of cancer development (Table 3), with emphasis on procedures that will allow for reduction in the cancer risk.

TABLE 3
HEREDITARY PATTERNS AND SCREENING/SURVEILLANCE IMPLICATIONS
FOR POLYPOSIS AND NONPOLYPOSIS SYNDROMES

Syndrome	Inheritance	Cancer Risk	Screening/Surveillance Tests
HNPCC	Autosomal dominant	High	Colonoscopy, pelvic U/S, endometrial biopsy, genetic analysis
FAP	Autosomal dominant	High	Flexible sigmoidoscopy, EGD, APC linkage analysis (if available)
Turcot's syndrome	Autosomal dominant/recessive	High (colon and CNS)	As for FAP + CT or MRI of head is symptoms
Juvenile polyposis	Autosomal dominant	Moderate	Colonoscopy, EGD
Peutz-Jeghers syndrome	Autosomal dominant	Moderate	Unknown; possibly colonoscopy and EGD, mammography
Cowden's disease	Autosomal dominant	Low (breast, thyroid)	Unknown
Cronkhite-Canada	None	Low	None
Neurofibromatosis	Variable	Low	None

With the dramatic leaps in our understanding of the molecular events leading to cancer in hereditary polyposis and non-polyposis syndromes over the past 5 years, the threshold for genetic intervention is fast approaching, and treatment of these rare diseases will have strong implications for the therapeutic approach to the more common sporadic colorectal cancers for which we have much less understanding.

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