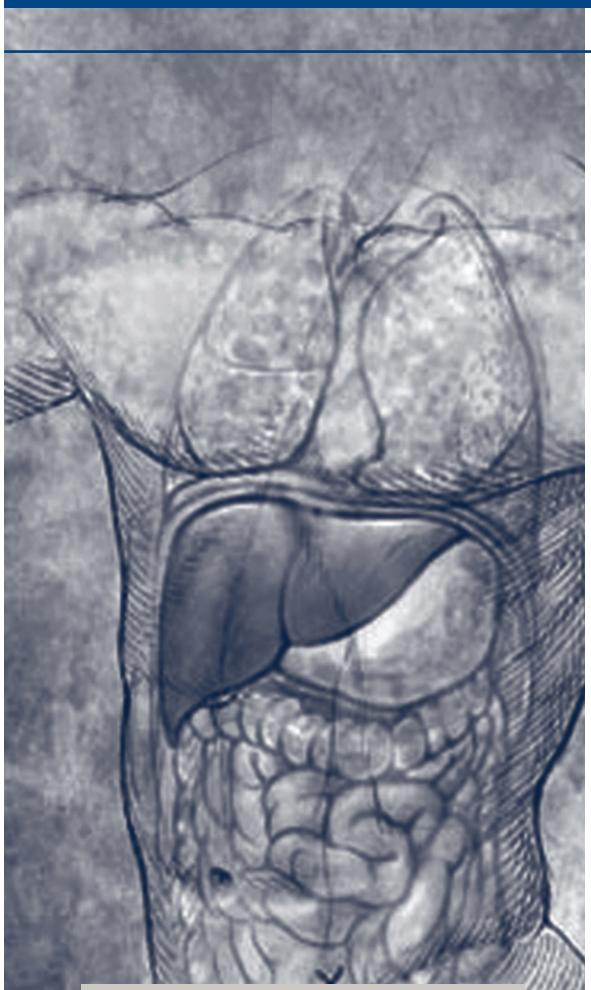
LOS ANGELES

COLON AND RECTAL SURGICAL ASSOCIATES

Norman N. Hoffman M.D., Inc. | Gary H. Hoffman M.D. | Eiman Firoozmand M.D. | Liza M. Capiendo M.D. | Stephen Yoo M.D.

www.lacolon.com



The Genetics of Hereditary Colon and Rectal Cancer:

Understanding is the First Step Toward Treatment

PART II, FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

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DIAGNOSIS AND TREATMENT

Approximately five per cent of patients with colorectal cancer have an inherited or hereditary mutation in the APC gene, a gene known to be associated with cancer development. Many of the high risk mutations which lead to colorectal cancer can be located on individual genes using genetic sequence testing. At present however, clinical genetic manipulation cannot reduce the risk of disease development in individual patents. Fortunately, the process of a genetic mutation leading to a malignancy may take many years, thus providing physicians with a large window of opportunity to detect, prevent or treat colonic disease while it is at a curable stage. In selected patients, we can reduce the risk of developing a malignancy by removing the susceptible end organ.

Two disease groups constitute the majority of inherited cases of colorectal cancer: Familial Adenomatous Polyposis (FAP) and Hereditary Nonpolyposis Colon Cancer (HNPCC).

FAMILIAL ADENOMATOUS POLYPOSIS

Occurring in one per cent of colorectal cancer patients, Familial Adenomatous Polyposis is an autosomal dominant disorder characterized by the pancolonic formation of hundreds or thousands of polyps which develop at an early age. Attenuated Familial Adenomatous Polyposis (AFAP) is characterized by the formation of fewer, more proximal polyps developed at a later age. The causative genetic mutation is located on the adenomatosis polyposis coli tumor gene (APC), a tumor suppressor gene located on the long arm of chromosome five. Six hundred mutations have been discovered in this gene. Any one of these mutations can lead to disease through the production of a defective suppressor protein, which leads to unchecked cellular division with subsequent polyp and tumor growth. The mutation has a high penetrance rate, and individuals with the mutated gene (genotype) will almost surely develop polyps (phenotype). **As colonic polyps precede a colonic malignancy, there is an almost one hundred per cent risk of developing colon cancer if these patients remain untreated.**

DIAGNOSIS: FROM GENOTYPE TO PHENOTYPE

Eighty per cent of patients with FAP or AFAP will have a known family history making the diagnosis straightforward. However, twenty per cent will have a de-novo germ-line mutation. In this group, presentation is usually secondary to rectal bleeding and a thorough history and review of systems must be obtained. In FAP, there is

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a lifetime risk of developing associated desmoid tumors (15%), duodenal cancer (4%), thyroid cancer (2%), brain cancer (2%), ampullary cancer (1.7%), pancreatic cancer (1.7%), hepatoblastoma (1.6%) or gastric cancer (0.6%), and early diagnostic questioning must focus on these areas. A social history should be obtained, as Ashkenazy Jews have a predilection to develop colonic malignancies because of genetic alterations in the APC IL307K allele.

Commercially available tests of whole blood can identify and confirm the diagnosis in asymptomatic patients with a family history of the disease. This is especially useful in young patients or in those who do not wish to undergo an intensive clinical screening process. If positive, more specific gene sequencing tests can identify the specific mutation and subsequent cancer risk. The affected codon, or tri-nucleotide sequence, may code for different forms of FAP and also code for the development of extra-colonic tumors. The clinician must search for these abnormalities. As the entire gastrointestinal tract may be affected by FAP, a thorough evaluation must be performed using standard diagnostic techniques, including laboratory testing, endoscopic surveillance and suitable radiographic examinations such as CT scanning or MRI evaluation.

The clinical diagnosis of FAP is confirmed upon finding more than one hundred colorectal adenomatous polyps on colonoscopic surveillance. The diagnosis of AFAP is more challenging but must be considered in younger patients with between ten and one hundred proximally located colonic polyps. An upper gastrointestinal examination must be performed in patients with FAP or AFAP, as eighty to ninety per cent will develop duodenal or periampullary adenomas. Thirty five per cent of these patients will develop advanced disease including a malignancy.

SURVEILLANCE

In patients with known Familial Adenomatous Polyposis, routine endoscopic surveillance should begin at puberty and should be performed every two years for lifetime. If adenomas are discovered and the patient refuses operative intervention, colonoscopy should be performed annually for life, as the penetrance of the mutation is one hundred per cent, and the risk of malignant transformation is certain. In first-degree relatives without an identified mutation, screening should be continued until age forty and then performed every three to five years if the examinations are normal. After age fifty, national colorectal cancer screening recommendations can be followed. The rationale for continuing screening in relatives without a detected mutation on blood testing is that there are believed to be many, as of yet unknown mutations which cannot be detected through genetic testing.

In AFAP, full colonoscopic screening should begin at age twenty as this entity has a later age of onset, with polyps found more commonly in the proximal colon. The screening interval is similar to those in patients with FAP.

Upper gastrointestinal screening should begin at age twenty and continue for the lifetime of the patient at intervals between one and five years, depending upon the findings. If surgical intervention is to be undertaken, the entire gastrointestinal tract must be evaluated prior to the intervention.

PREVENTION AND TREATMENT: SURGICAL PROPHYLAXIS

It is now recommended that operative intervention be undertaken as soon as polyposis is discovered. Without treatment, there is close to a one hundred per cent risk for the development of colorectal cancer. In patients undergoing an early prophylactic procedure, long term, disease free survival rates are between eighty seven to ninety four per cent. In patients presenting with an established malignancy, ten year survival rates are forty per cent.

With operative intervention, the goal is to remove as much of the colon and rectal mucosa as possible. Currently, three operations are available to treat FAP. A total abdominal proctocolectomy with an end ileostomy provides the most complete risk reduction but requires the creation of a permanent stoma. A total abdominal colectomy with an ileorectal anastomosis may be used in patients with AFAP or in those with few rectal adenomas. Advantages include restored intestinal continuity with better functional outcomes. Risks include the development of rectal cancer in the remaining rectal mucosa in fifteen per cent of patients at fifteen years postoperatively. Continued endoscopic surveillance is necessary. The third option is a laparoscopic total abdominal proctocolectomy with an ileal pouch anal anastomosis (IPAA), with or without a rectal mucosectomy. This type of pouch is also known as a J-pouch. Potential advantages include restored intestinal continuity with a new rectal reservoir, or neo-rectum, in those patients who do not want an end-ileostomy. This approach is favored in situations where there is extensive polyposis, including rectal polyps, that cannot be controlled endoscopically, in patients with a history of desmoid tumors, or in those patients with APC mutations associated with an increased rectal cancer risk. However, patients must be carefully selected as those with poor preoperative sphincter function may have poor functional results after IPAA. Additionally, anatomic considerations may make the creation of an IPAA technically difficult or impossible. The theoretical advantage of a rectal mucosectomy is that all susceptible areas of rectal tissue are removed. Disadvantages include the potential for the unsuspected retention of rectal mucosa and the new, potentially occult development of rectal polyps, or, the possibility of postoperative anal stenosis with troublesome functional symptoms. In patients undergoing an IPAA, continued endoscopic surveillance is mandatory as pouch adenomas can develop in the small intestinal pouch mucosa in thirty per cent of patients. Additionally, ten to thirty per cent of patients may develop neoplasia at the site of the anastomosis. Continuing lifetime surveillance is mandatory.

In patients with AFAP, a total abdominal colectomy with an ileorectal anastomosis and close endoscopic follow up may be performed in order to preserve the rectum, as AFAP usually spares the rectum.

With advances in early detection, and improvement in survival rates and functional outcomes, operative intervention in patients with known or newly diagnosed familial adenomatous polyposis or attenuated familial adenomatous polyposis is gratifying for the patient, the family, any newly diagnosed relatives, the astute physician who first considers and confirms the diagnosis, and the surgeon who performs a preventative or curative operative procedure. Further improvements in early detection will enhance our ability to diagnose and treat this family of genetic disorders.