Introduction

In the United States, colorectal cancer is the second most common cause of cancer mortality after lung cancer. Its mortality rate is declining, probably as a result of improved public and professional health awareness as well as better primary detection. Primary detection depends on the physician's ability to recognize the earliest neoplastic lesion. This review analyzes some of the disease processes and corresponding pathologic lesions representing the early changes thought to be the precursors of colorectal cancer.

Miller et al have recently confirmed the preexisting belief that the risk of developing colorectal cancer increases with age. They reported incidence rates of 19.2 per 100,000 patients under 65 years of age and 337.1 per 100,000 among those over 65 years of age. Only 3% of colorectal cancers arise in patients under 40 years of age. It is possible that this correlation is the reflection of the time needed for the adenoma-carcinoma sequence to be completed. The origin of this hypothesis can be traced back to Crohn and Rosenberg, who first described the association of colon cancer and chronic ulcerative colitis (CUC). Since then, cumulative evidence has proven the importance of dysplasia as an intermediary in the progression of CUC to neoplastic disease.

Colon Cancer and Inflammatory Bowel Disease

Approximately 1% of colorectal cancer patients have a history of CUC. In a follow-up of 401 patients with CUC over a period of 22 years, the cumulative risk of colorectal cancer was 3%, 5%, and 9% at 15, 20, and 25 years of age, respectively. The risk of developing colorectal cancer is inversely correlated with the age of onset of the colitis but is directly correlated to the extent and duration of active disease. Since distant foci of dysplasia are usually found in specimens of colon cancer arising in CUC, the use of colonoscopic surveillance for dysplasia seems a reasonable choice. However, CUC-related colon cancer is associated with dysplasia in only 50% of cases, thus decreasing the effectiveness of the prophylactic screening. A prospective study reported a 20% to 25% incidence of dysplasia in cases of CUC examined in surveillance studies that were initiated after seven years from the diagnosis of CUC. In a report by Nugent et al, colon cancer developed in five (28%) of 23 patients 10 years after the onset of their inflammatory bowel disease.

Genetic Factors

Approximately 95% of colon cancers are sporadic. However, at least 15% of patients with colorectal cancer have a positive family history of similar tumor in a first-degree relative. These are autosomal dominant inherited conditions that probably reflect a common genetic abnormality and/or a similar environmental exposure. Familial adenomatous polyposis (FAP) is one of these conditions. Patients with FAP have hundreds or thousands of colorectal adenomas, usually of the tubular type (Fig 1), with obligatory conversion to malignant disease (usually by 40 years of age) and autosomal dominant penetrance. In Gardner’s syndrome, colorectal adenomas in the same patient are associated with mandibular osteomas, childhood epidermal inclusion cysts, desmoid tumors, and mesenteric fibromatosis. In 1987, the common genetic defect of FAP and Gardner’s syndrome was identified in the loss of a presumed suppressor gene on chromosome 5q21-q22. The loss of both alleles at 5q21-q22 is required for the phenotypic expression of FAP since the inheritance is dominant at the cellular level but is recessive at the molecular level.

Hereditary nonpolyposis colon cancer syndrome (HNPCC) also is a familial form of colon cancer. Lynch et al described two variants - Lynch syndrome I is characterized by colon cancer alone, and Lynch syndrome II exhibits the association between colon cancer and endometrial, ovarian, breast, gastric, and pancreatic cancers. Patients with HNPCC develop colon cancer at a young age, and the tumor is usually multifocal, high-grade (often mucinous), and located in the right colon. The incidence of recurrences is high. HNPCC is a misnomer, since as many as 20% of these cases exhibit polypoid adenomas, and flat adenomas have been described by Lynch himself in HNPCC.

The flat adenoma syndrome (Fig 2) is also predominantly right-sided, but carcinomas develop later, usually in the seventh decade. Small flat adenomas containing foci of cancer have been reported. These lesions are slightly elevated with a reddish central depression. Yao et al recently described "depressed flat adenomas" as a variation on the theme. For these investigators, the interest in a flat adenoma syndrome is based on its potential as an early form of colorectal cancer.
The study of familial forms of large bowel cancer has fostered the preexisting belief that in the colon, as in other clinical models (eg, cervix, breast, bladder, bronchus), carcinoma usually arises from a precursor, the adenoma. This is usually represented by a polypoid growth, but flat adenoma and focal adenomatous changes do occur and may explain why many colon cancers fail to exhibit residual elements of a precursor neoplastic polyp. This consideration and several reports of small, pure adenocarcinomas have led to the proposal that at least some carcinomas arise de novo. Wada et al recently presented data suggesting that 70% to 80% of superficial-type early colorectal carcinomas develop from a de novo carcinoma and only 20% to 30% from a preexisting adenoma. They also found p53 oncogene product expression in 63% of the intramucosal adenocarcinomas but in 88% of the adenocarcinomas with invasion in the submucosa. The authors suggested that p53 may be related to the enlargement and deeper invasion of the adenocarcinomas regardless of the sequence of development. Conversely, an even earlier preneoplastic lesion in mice treated with colon carcinogens was described by Bird and named "aberrant crypt foci." These lesions are not grossly visible but can be observed in whole-mount preparations of colon tissue, before they are embedded and sectioned, especially after staining with methylene blue. Furthermore, these lesions are not defined by their histologic features but by their surface luminal features. When compared with normal crypts, they are deeper in color, are larger in size, and have an oval-shaped luminal opening. When "dysplastic," aberrant crypt foci can be microscopically identified as a single or a few glands exhibiting apical branching, crowding of nuclei, and loss of mucin. When "dysplastic," aberrant crypt foci can be microscopically identified as a single or a few glands exhibiting apical branching, crowding of nuclei, and loss of mucin (Fig 3). Subsequently, this lesion was described in human colons. It remains unclear whether these minute lesions are hyperplastic or dysplastic and whether they are precursors of colon cancer. However, provocative reports of K-ras activation but absent p53 protein accumulation in aberrant crypt foci indicate that, although histologically hyperplastic, these lesions are genetically monoclonal and could represent the earliest change along the cascade of events leading to colorectal cancer (Table). At the molecular level, the malignant transformation arises through sequential genetic abnormalities and activation of cell receptors and/or cellular oncogenes. These alterations are phenotypically translated into the cytologic and architectural features of cancer.

Adenoma

**Definition**

Neoplastic adenoma describes an advancing, nonreparative cellular proliferation characterized by the thymidine incorporation and clonogenic activity of all levels of the mucosal glands. These glands are lined by cytologically abnormal, dysplastic epithelium. Adenomas are by definition dysplastic. In this dynamic evolving process, the initially low-grade dysplasia may progress to a higher degree of cellular and nuclear atypia and eventually to frank carcinoma. The morphologic changes correspond to genetic and molecular changes represented, for example, by aneuploidy and c-ras oncogene expression, which translate into nuclear proliferation, enlargement, hyperchromasia, and presence of macronucleoli. When these features associate to architectural changes such as bridging (gland-within-gland morphology), a carcinoma in situ is formed.

**Types of Adenomas**

Colonic adenomas may present as polypoid or nonpolypoid mucosal growths. A colonic adenoma that preserves the mucosal tubular gland morphology is called tubular, and if a metaphasic villous appearance is evident, it is termed villous. Adenomas that have both tubular and villous components are called tubulovillous. The growth pattern of an adenoma influences its malignant potential. In one study, the incidence of invasive cancer was approximately 2% to 3% in tubular adenomas, 6%...
Adenomas may be stalked (pedunculated) or sessile (flat). Usually, tubular adenomas are pedunculated and villous adenomas are sessile (Fig 4). The size of an adenoma has been associated to its malignant potential. Most tubular adenomas (75%) measure 1 cm or less in diameter. These adenomas exhibit approximately 1% to 3% incidence of transformation to carcinoma. Conversely, 60% of the villous adenomas are 2 cm in diameter and have an estimated 25% incidence of carcinomatous transformation. This observation correlates with the finding that most of these polyps are aneuploid. This finding may explain their larger size and rapid growth.

Gross and Microscopic Findings

Microscopically, tubular adenomas usually exhibit tubules that are regular with minimal branching or tufting and are separated from each other by normal lamina propria. The epithelial cells exhibit cigar-shaped, hyperchromatic nuclei with prominent stratification. Mucin is usually decreased. Adenomas can show advancing degree of dysplasia up to carcinoma in situ. Carcinoma in situ or severe dysplasia is characterized by a glandular cribriform pattern, increased mitoses, and cellular atypia (large, polygonal, vesicular nuclei with prominent nucleoli). The incidence of adenomas containing carcinoma in situ is approximately 12.3%, and invasive adenocarcinoma arising in colonic adenoma has an incidence of 5%. The probability of residual disease and/or tumor metastasis correlates with the level of invasion, the approximation of the tumor to the stalk resection margin, high-grade cytologic and architectural dysplasia, and local lymphovascular invasion. Haggitt et al proposed a system to classify degrees of invasion within an adenoma undergoing malignant transformation (Fig 5):

Level 0: adenoma with intramucosal carcinoma (in situ)
Level 1: penetration of malignant glands through the muscularis mucosa into the submucosa, within the polyp head
Level 2: the same submucosal invasion, but present at the junction of the head to the stalk
Level 3: invasion of the stalk
Level 4: invasion of the stalk’s base at the connection to the colonic wall (this level corresponds to stage Dukes A)

Level 4 invasion was found to be the most reliable predictor of residual and/or recurrent disease and of lymph node metastasis. However, this classification cannot be applied to villous adenomas, since they are devoid of pedicle. In assessing such polyps, any invasion should be considered level 4 (Dukes A). A retrospective study revealed that 1.7% of patients, in whom the endoscopically resected malignant polyp had tumor at the pedicle resection margin, recurred locally and/or had residual disease. The same patients had a 0.3% incidence of positive lymph nodes. Another similar study revealed an incidence of 8.9% recurrence and/or residual disease after endoscopic removal of tubular adenomas with malignant transformation. However, when the tumor grade was considered, the rate of persistent disease was only 0.3% for the well-differentiated tumors. These percentages are useful for clinical decision making with regard to colon resection following endoscopic removal of malignant polyps.

**Differential Diagnosis**

Hyperplastic polyps are small (0.5 cm or less), sessile, polypoid growths arising from the crests of the colonic mucosal folds. Microscopically, these polyps have glands lined by uniform, mucin-rich epithelial cells that are thrown into folds and result in a scalloped or serrated appearance. Hyperplastic polyps show none of the cytologic characteristics of dysplasia, and thymidine-labeling studies show only deep crypt clonogenic activity. Furthermore, mixed hyperplastic adenoma neoplastic polyposis have been described, and it has been suggested that hyperplastic polyps may represent the precursor of some neoplastic adenomas.

Juvenile polyps are usually found in the rectum of children aged 1 to 7 years. They are often pedunculated and composed of cystically dilated glands lined by uniform, benign epithelial cells. Acute inflammation usually is present. Minor rectal bleeding may occur with autoamputation. When found in adults, juvenile polyps are labeled as inflammatory or retention polyps. Neoplastic transformation, through a dysplasia sequence, may occur but is uncommon. The Cronkite-Canada syndrome is characterized by the coexistence of juvenile-type polyps with alopecia, cuticle atrophy, and skin pigmentation.

Peutz-Jeghers polyps are nonneoplastic hamartomatous polyps of variable size that can be sessile or pedunculated. They exhibit an arborizing arrangement of uniform,
Adenoma-Carcinoma Sequence

The association of architectural alterations such as cribriform bridging and severe nuclear atypia constitute intramuscosal malignant transformation. Much has been learned about the sequence of molecular events that takes place in colorectal oncogenesis, but much more remains unclear. Studies of the FAP syndromes and of hereditary nonpolyposis coli syndromes, as noted, have been instrumental in the development of a genetic model of inheritance for this process. The hypothetical sequence of molecular alterations that occurs during the adenoma carcinoma sequence includes the activation of ras oncogene and the loss of suppressor genes, which seem to correlate with each of the steps along the cascade of events leading to colon cancer.  

An MCC (mutated in colon cancer) gene has been identified on the long arm (q) of chromosome 5, adjacent to the gene for familial polyposis coli. This gene is mutated in 15% of patients but not in all the adenomas. The adenomatous polyposis coli (APC) gene also is located on chromosome 5q and is mutated in 60% of colorectal carcinomas and in 63% of adenomas. APC gene mutations have been identified in adenomas as small as 5 mm.  

The molecular biology of colorectal cancer is being unravelled. The use of molecular techniques is allowing the dissection of the multiple molecular changes taking place during the adenoma–carcinoma sequence. The abnormalities described usually translate into the appearance of a malignant phenotype with migratory function, which is capable of producing the enzymes necessary for the invasive process. The migration of tumor cells into the submucosa, usually from the crypt base, has been ascribed to the release of basement membrane-degrading enzymes such as collagenase, urokinase (a plasminogen activator), and collagenolytic cathepsins, inducing weakness of the basement membrane and disorganization of the actin cytoskeleton.  

Conclusions

The molecular biology of colorectal cancer is being unravelled. The use of molecular techniques is allowing the dissection of the multiple molecular changes taking place during the adenoma–carcinoma sequence. Concurrently, molecular findings are being tested as diagnostic tools and prognostic indicators of colorectal tumors. While these developments are exciting for both physicians and biologists, the overwhelming information that becomes available should be evaluated cautiously. Several oncogenes and cell receptors are normally expressed and overexpressed in intestinal tissues, and altered oncogene expression does not always correlate with Duke's stage, tumor progression, or patient survival following resection. It is important to correlate the genetic and molecular data to the histopathology and pathology of the tissues evaluated. Ultimately, prognostic information may rely on both pathologic features and molecular characteristics.

References
