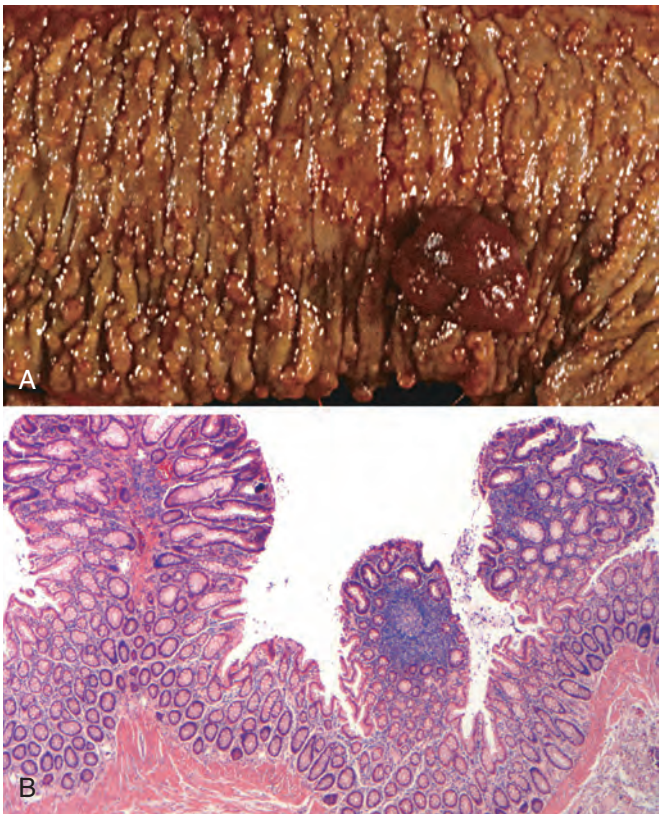

Figure 17-48 Familial adenomatous polyposis. **A,** Hundreds of small polyps are present throughout this colon with a dominant polyp (right). **B,** Three tubular adenomas are present in this single microscopic field.

mutations, are frequently present in MUTYH-associated polyposis.

Hereditary Non-Polyposis Colorectal Cancer

Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome, was originally described based on familial clustering of cancers at several sites including the colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, pancreas, and skin. HNPCC is thought to account for 2% to 4% of all colorectal cancers, making it the most common syndromic form of colon cancer. Colon cancers in HNPCC patients tend to occur at younger ages than sporadic colon cancers and are often located in the right colon (Table 17-11). Just as identification of *APC* mutations in FAP has provided molecular insights into the pathogenesis of the majority of sporadic colon cancers, unraveling the defects in HNPCC has shed light on the mechanisms responsible for most of the remaining sporadic cases. **HNPCC is caused by inherited mutations in genes that encode proteins responsible for the detection, excision, and repair of errors that occur during DNA replication** (Chapter 7). There are at least five such mismatch repair genes, but majority of patients with HNPCC have mutations in *MSH2* or *MLH1*. Patients with HNPCC inherit one mutant gene and one normal allele. When the second copy is lost through mutation or epigenetic silencing, defects in mismatch repair lead to the accumulation of mutations at rates up to 1000 times higher than normal, mostly in regions containing short repeatings sequences referred to as microsatellites. The human genome contains approximately 50,000 to 100,000 microsatellites, which are prone to undergo expansion during DNA replication and represent the most frequent sites of mutations in HNPCC. The consequences of mismatch repair deficiency and the resulting microsatellite instability are discussed next in the context of colonic adenocarcinoma.

Adenocarcinoma

Adenocarcinoma of the colon is the most common malignancy of the GI tract and is a major cause of morbidity and mortality worldwide. In contrast, the small intestine, which accounts for 75% of the overall length of the GI tract, is an uncommon site for benign and malignant tumors. Among malignant small intestinal tumors, adenocarcinomas and well-differentiated neuroendocrine (carcinoid) tumors have roughly equal incidence, followed by lymphomas and sarcomas.

Epidemiology. Approximately 1.2 million new cases of colorectal adenocarcinoma, and 600,000 associated deaths, occur each year worldwide. Thus, colorectal adenocarcinoma is responsible for nearly 10% of all cancer deaths. The

Table 17-11 Common Patterns of Sporadic and Familial Colorectal Neoplasia

Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis	APC/WNT pathway	*APC*	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
MYH-associated polyposis	DNA mismatch repair	*MYH*	Autosomal recessive	None	Sessile serrated adenoma; mucinous adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	*MSH2, MLH1*	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (70%-80%)	APC/WNT pathway	*APC*	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%-15%)	DNA mismatch repair	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (5%-10%)	Hypermethylation	*MLH1, BRAF*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma