incidence of these tumors is highest in North America, with the United States accounting for approximately 10% of worldwide cases and cancer deaths. This represents nearly 15% of all cancer-related deaths in the United States, second only to lung cancer. Australia, New Zealand, Europe, and, with changes in lifestyle and diet, Japan, also have high incidences of colorectal adenocarcinoma. In contrast, rates are lower in South America, India, Africa, and South Central Asia. Colorectal cancer incidence peaks at 60 to 70 years of age, with fewer than 20% of cases occuring before age 50.

The *dietary factors* most closely associated with increased rates of colorectal cancer are low intake of unabsorbable vegetable fiber and high intake of refined carbohydrates and fat. Although these associations are clear, the mechanistic relationship between diet and risk remains poorly understood. It is theorized that reduced fiber content leads to decreased stool bulk and altered composition of the intestinal microbiota. This change may increase synthesis of potentially toxic oxidative by-products of bacterial metabolism, which would be expected to remain in contact with the colonic mucosa for longer periods of time as a result of reduced stool bulk. High fat intake also enhances hepatic synthesis of cholesterol and bile acids, which can be converted into carcinogens by intestinal bacteria.

In addition to dietary modification, *pharmacologic chemoprevention* has become an area of great interest. Several epidemiologic studies suggest that aspirin or other NSAIDs have a protective effect. This is consistent with studies showing that some NSAIDs cause polyp regression in FAP patients in whom the rectum was left in place after colectomy. It is suspected that this effect is mediated by inhibition of the enzyme cyclooxygenase-2 (COX-2), which is highly expressed in 90% of colorectal carcinomas and 40% to 90% of adenomas. COX-2 is necessary for production of prostaglandin E_2, which promotes epithelial proliferation, particularly after injury. Of further interest, COX-2 expression is regulated by TLR4, which recognizes lipopolysaccharide and is also overexpressed in adenomas and carcinomas.

Pathogenesis. Studies of colorectal carcinogenesis have provided fundamental insights into the general mechanisms of cancer evolution. These were discussed in Chapter 7; concepts that pertain specifically to colorectal carcinogenesis will be reviewed here.

The combination of molecular events that lead to colonic adenocarcinoma is heterogeneous and includes genetic and epigenetic abnormalities. At least two genetic pathways have been described. In simplest terms, these are the *APC/β-catenin pathway,* which is activated in the classic adenoma-carcinoma sequence; and the *microsatellite instability pathway*, which is associated with defects in DNA mismatch repair and accumulation of mutations in microsatellite repeat regions of the genome (Table 17-11). Both pathways involve the stepwise accumulation of multiple mutations, but differ in the genes involved and the mechanisms by which mutations accumulate. Epigenetic events, the most common of which is methylation-induced gene silencing, may enhance progression along either pathway.

- **The classic adenoma-carcinoma sequence, accounts for up to 80% of sporadic colon tumors and typically includes mutation of *APC* early in the neoplastic process** (Fig. 17-49)**.** Both copies of the *APC* gene must be functionally inactivated, either by mutation or epigenetic events, for adenomas to develop. *APC is a key negative regulator of β-catenin, a component of the Wnt signaling pathway* (Chapter 7)**.** The APC protein normally binds to and promotes degradation of β-catenin. With loss of APC function, β-catenin accumulates and

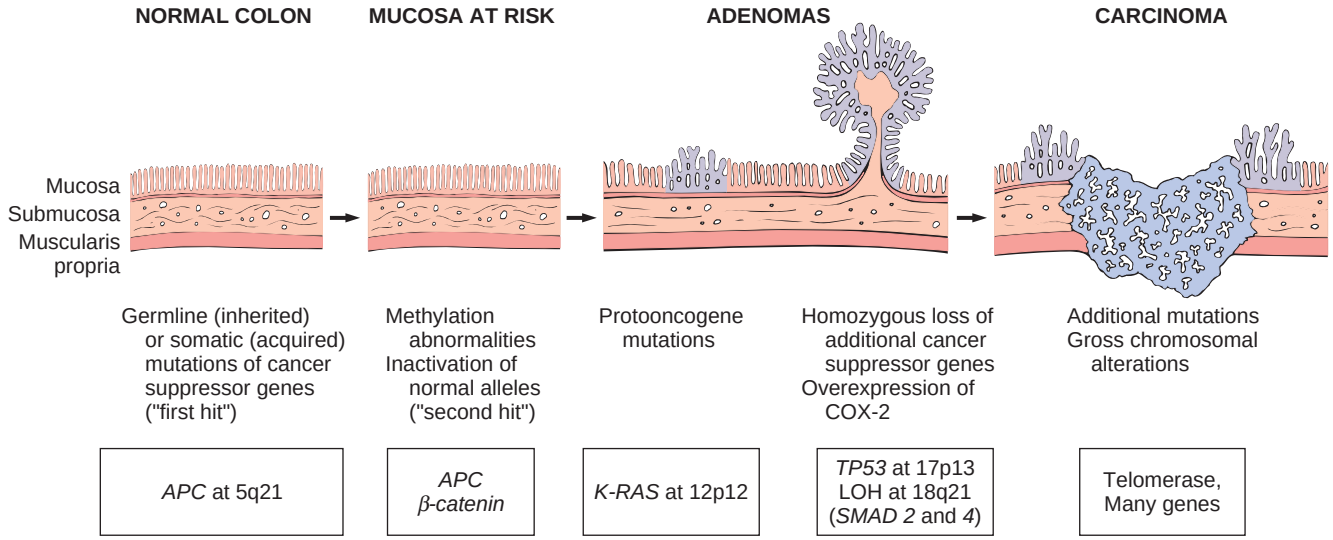

Figure 17-49 Morphologic and molecular changes in the adenoma-carcinoma sequence. Loss of one normal copy of the tumor suppressor gene *APC* occurs early. Individuals born with one mutant allele are therefore at increased risk of developing colon cancer. Alternatively, inactivation of *APC* in colonic epithelium may occur later in life. This is the "first hit" according to the Knudson hypothesis (Chapter 7). The loss of the intact second copy of *APC* follows ("second hit"). Other changes, including mutation of *KRAS*, losses at 18q21 involving *SMAD2* and *SMAD4*, and inactivation of the tumor suppressor gene *TP53*, lead to the emergence of carcinoma, in which further mutations occur. Although there seems to be a temporal sequence of changes, the accumulation of mutations, rather than their occurrence in a specific order, is most critical.