Few biological puzzles are more intriguing than colorectal cancer. While the disease is common and appears to occur sporadically, familial syndromes are well documented. Tantalizing clues concerning the relationship between diet and colorectal cancer have been studied for years, but the incidence of the disease has not decreased despite widespread public education of these associations. Colorectal cancer has afforded researchers a particular advantage for study because all of the malignant tumors have arisen from a precursor lesion, the adenoma.[1] Yet, only some adenomas develop into cancers, while others stop growing or regress. The adenoma-to-carcinoma sequence has profound implications for screening strategies and early intervention programs. More importantly, the sequence provides a unique opportunity for the molecular biological understanding of the process in which adenomas, and then cancers, arise from normal mucosa. Finally, this sequence of development suggests that chemical intervention in the progression of normal mucosa to cancer may prevent colorectal cancer.[2]

Once a cancer of the large intestine has arisen, there are several characteristics of its tumor biology that are unique. These tumors often release carcinoembryonic antigen (CEA), which can be a useful serum marker for recurrence. Adjuvant chemotherapy affords survival advantage for some stages of the disease. Surgeons have learned that the colon can be removed via the laparoscope. Hospital stays after these less invasive resections are shorter, but concerns about adequacy of resection and tumor recurrence in operative port sites have not yet been resolved by careful prospective study. Finally, a remarkable subset of patients with metastatic colorectal cancer, those with spread limited to the liver, appears to enjoy long-term survival after resection of metastatic deposits.[3]

Most exciting, however, are the genetic changes that have been identified in colon cancer. Several oncogenes have been implicated in the adenoma-carcinoma sequence. Various ras gene mutations have been found in approximately 50% of colorectal cancers, but less than 10% are found in adenomas less than 1 cm in diameter.[4,5] C-myc proto-oncogene products, which appear to increase transcription, are elevated in as many as 70% of colon cancers.[6-8] Tumor suppressor genes also may play a prominent role in the development and spread of colorectal cancer. More than 75% of colon cancers are missing a large segment of chromosome 17p, a region known to contain the p53 gene.[9,10] Another candidate tumor suppressor gene that is located on chromosome 18q is commonly lost in colon cancers and has been named the DCC (deleted in colon cancer) gene.[11,12]

Although the inherited forms of colorectal cancer - familial adenomatous polyposis coli (FAP) and hereditary nonpolyposis colorectal cancer (HNPPC) - together make up only approximately 6% of the colorectal cancers cases occurring each year in the United States, patients with these two disorders have proven to be rich sources of material for genetic study. A tumor suppressor gene associated with FAP has been mapped to chromosome 5q and has been called the adenomatous polyposis coli (APC) gene. Its product appears to bind to catenins, which are proteins that bridge the cytoskeleton to E-cadherin, an intracellular adhesion molecule.[6] The interruption of E-cadherin to catenin-binding might alter cell adhesion and contribute to tissue invasion by cancer. HNPPC appears to be associated with an alteration of normally found mismatch repair genes responsible for detecting and correcting DNA base pair mismatches. A succinct and compelling description of a genetic model for colorectal tumorigenesis has been published by Fearon and Vogelstein.[13]

These findings, and many more like them, provide hope for an eventual understanding of the basic causes of familial and sporadic colorectal cancer. However, to date, the basic understanding of the molecular biology of colorectal cancer, the recognition of the role of diet in the development of these cancers, the observation that several chemicals (nonsteroidal anti-inflammatory drugs, antioxidants, vitamins, and calcium) can prevent colorectal cancer or cause regression of its precursor adenoma, the development of new screening strategies, the routine use of more aggressive operations for primary tumors and metastases, and the aggressive administration of adjuvant chemotherapy have produced neither a significant decrease in the incidence of this disease nor an improvement in the chance of survival of patients who are unfortunate enough to develop it.

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References