1. INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. Each year approx 130,000 Americans are diagnosed with the disease and 50,000 will die of it (1). The cumulative lifetime risks of CRC and mortality from CRC are approx 3–6% and 2%, respectively. The majority of CRCs occur in individuals over 60 yr old, whom have no previous personal or family history of the disease. The major risk factors for these sporadic cases are advancing age and environmental exposures, most importantly diet. Approximately 20–25% of CRCs are in younger individuals or in those with a personal or family history of cancer, suggesting a heritable susceptibility (2).

The genetic predisposition to CRC falls into two major groups, common familial CRC (15–20% of CRC) and hereditary CRC (5% of CRC) (Fig. 1) (3). In common familial CRC, first-degree relatives of persons with CRC or adenomatous polyps have an approximately twofold risk of developing CRC, and the risk increases with the number of relatives affected and the earlier the age of onset in the family (4). Increased risk for CRC in common familial CRC is conveyed by the inheritance of one or more, of the likely many, low penetrance susceptibility alleles, most of which have yet to be identified (5). Carriage of these susceptibility alleles increases the risk of acquiring CRC, but by no means is the development of CRC certain. In fact, in the large majority of allele carriers, CRC does not occur.

More than 5% of CRCs are hereditary in etiology, meaning that they are caused by carriage of a highly penetrant, dominantly inherited, susceptibility allele. Hereditary CRC is conventionally divided between the polyposis syndromes and hereditary nonpolyposis colorectal cancer (HNPCC) (Table 1) (3). The polyposis syndromes are defined by the presence of multiple polyps in the gut lumen, and have conventionally been categorized by polyp histology. The most common and important of the polyposis syndromes is familial adenomatous polyposis (FAP). FAP carries a life-time risk of CRC approaching 100% if the colon is not removed (6).

The other major category of hereditary polyposes is the hamartomatous polyposis syndromes, most importantly Peutz-Jeghers syndrome (PJS), hereditary juvenile polyposis, and Cowden syndrome. There are a number of other very rare hereditary polyposis syndromes, as well as several nonhereditary polyposis syndromes that may or might not confer an increased risk for CRC.

Much more common than any of the polyposis syndromes is HNPCC. At least 2–3% of all CRC is secondary to HNPCC (7,8). In HNPCC, the lifetime risk of CRC approaches 70–80%, but not as a consequence of an increased number of colorectal adenomas (6).

The primary importance of familial and hereditary colorectal cancer is the increased risk of CRC, and often, other cancers, for individuals with these conditions. Failure to recognize common familial CRC, or more importantly, one of the hereditary syndromes, will lead to inadequate cancer screening and surveillance in individuals at risk, with subsequent premature loss of life. Recently, the elucidation of the genes responsible for many of these syndromes has revolutionized the care of at-risk individuals and families. Genetic testing has the potential...
to greatly improve the efficiency and reduce the costs and morbidity of cancer screening and surveillance. Genetic testing is now commercially available and is often offered to individuals and families with, or suspected of having, FAP or HNPCC (9,10). Genetic testing will most likely affect the management of individuals at risk for common familial CRC as well. However, genetic testing raises a number of vexing clinical, ethical, legal, and psychosocial questions.

This chapter discusses the clinical features, genetics, diagnosis, and management of common familial and hereditary CRC, specifically the polyposis syndromes and HNPCC.

2. POLYPOSIS SYNDROMES

2.1. FAMILIAL ADENOMATOUS POLYPOSIS

2.1.1. Clinical Features: Intestinal

FAP is an autosomal-dominant disorder that affects about one in 10,000–15,000 individuals and accounts for probably less than 0.1% of CRCs (11). In classic FAP, affected individuals develop hundreds to thousands of colonic adenomas by the mid to late teens, with more than 95% of affected individuals demonstrating polyposis by age 35. CRC is inevitable in untreated patients, with the majority of cancers appearing by age 40 and more than 90% by age 45 (12,13). Variants of FAP are now recognized in which polyps are greatly reduced in number, are predominantly or exclusively located in the right colon, and colon approximately a decade later than in classic FAP. This latter condition has been termed attenuated adenomatous polyposis coli (AAPC) or attenuated FAP (14,15).

In addition to colonic polyps, up to 90% of individuals with FAP will develop small bowel adenomas, most commonly at or near the ampulla of Vater (16–19). These lesions are usually multiple and sessile, often forming carpet-like lesions. Because the ampulla of Vater is almost invariably involved, to assess the full extent of duodenal polyposis, duodenoscopy, in addition to routine upper endoscopy, is required (20). The lifetime risk for small bowel carcinoma is approx 5%, and duodenal cancer is the leading cause of cancer death in FAP patients that have undergone a colectomy (13,21–23).

Most FAP patients also will develop gastric polyposis. Gastric polyps are usually of the fundic gland histological type, but adenomas rarely do occur (19). Gastric carcinoma risk is not much increased in Western families, but is reported to be increased three- to fourfold in Japanese and Korean families with FAP. Overall the lifetime risk of gastric cancer in individuals with FAP has been reported at 0.5% (19).

2.2. CLINICAL FEATURES: EXTRAINTESTINAL

Approximately two-thirds of FAP patients will have congenital hypertrophy of the retinal pigment epithelium (CHRPE). Although CHRPE does not affect vision or have any malignant potential, it is important as an early marker to identify susceptible individuals, as it can be detected at birth. In CHRPE-positive families nearly all individuals with FAP in the family will have CHRPE. Thus, an examination of the fundus can identify susceptible family members at a young age (24).

Other benign extraintestinal manifestations of FAP include dental abnormalities, osteomas, lipomas, epidermoid cysts, and desmoid tumors (12,17). Desmoids develop in about 9–17% of individuals with FAP. Approximately half are intra-abdominal and involve the small bowel and its mesentery. The rest occur in the abdominal wall or other extraabdominal sites such as the neck, thigh, breast, axilla, or back (17,25–27). Although desmoids are not malignant, they may cause considerable morbidity and mortality by local invasion. Surgical treatment of intraabdominal desmoids is associated with high morbidity and mortality and therefore is reserved for those who have severe symptoms (25,28). FAP in conjunction with soft tissue tumors, osteomas, and dental abnormalities is often referred to as the Gardner syndrome.

FAP is associated with increased risk for extraintestinal cancers, including hepatoblastoma in young children, medullloblastoma, papillary carcinoma of the thyroid, and pancreatic cancer (12,29,30). The association of FAP and central nervous systems tumors, primarily medulloblastoma, has been termed Turcot syndrome (31,32).

2.3. GENETICS

The great majority of cases of FAP are caused by a germline mutation of the tumor suppressor APC gene located on chromosome 5q21 (33–35). Individuals with FAP only have one functional copy of APC per cell, and mutation or loss of this functional copy can initiate the pathway of colonic neoplasia (36–42). The specific location of a germline mutation in APC may determine in part the disease phenotype (43–55). Such genotype–phenotype correlation will prove useful in increasing the accuracy and effectiveness of screening, surveillance, and treatment (56–58).

Recently, a small number cases of FAP have been attributed to inherited defects of the base excision repair gene MYH (59,60). MYH is responsible for repair of G:C to T:A mutations that occur as a consequence of oxidative DNA