Introduction

Approximately 4,800 new cases of small-bowel cancer are diagnosed in the United States each year, resulting in almost 1,200 deaths [1]. The small intestine constitutes 75% of the length and over 90% of the mucosal surface of the gastrointestinal tract. However, primary adenocarcinoma of the small intestine is rare, accounting for approximately 1% of gastrointestinal neoplasms. Even though the small intestine is located between the stomach and large intestine, which more frequently develop cancer, adenocarcinoma of the small intestine still occurs much less frequently. Factors that play a role in the relative immunity of the small intestine from malignancy are not completely understood. When neoplasms of the small intestine do occur, they present with nonspecific symptoms, and are usually locally invasive at the time of diagnosis.

The principle histologic subtypes of small intestinal cancers are adenocarcinoma, malignant carcinoid, lymphoma, and leiomyosarcoma (stromal cell tumors). Adenocarcinoma is the most common type of small-bowel cancer in the United States, accounting for 50% of cases [2,3]. Despite the rarity of sporadic adenocarcinoma of the small intestine, these tumors do occur in a substantial proportion of persons with FAP. Little is known about risk factors for the development of malignancy in the small intestine.

EPIDEMIOLOGY

The incidence of small-bowel cancer, particularly adenocarcinoma, tends to be higher in Western industrialized countries than in the developing world. It is most commonly diagnosed after the fifth decade of life, with a peak incidence of occurrence in the sixth and seventh decades. There appears to be fairly equal gender distribution, with a slight male predilection [4]. Some series report higher rates in persons of African heritage than in whites [2]. The incidence of adenocarcinoma and cardi-
Adenocarcinoma of the small intestine appears to have increased in recent years [4].

Adenocarcinoma of the small intestine occurs most frequently in the duodenum, with intermediate frequency in the jejunum and least frequently in the ileum. One potential explanation for this observation is that bile, which is mutagenic, is present in highest concentration in the duodenum [5,6].

PATHOGENESIS
The small intestine is relatively resistant to cancer, despite being exposed to many of the same carcinogenic factors as the stomach and colon, which have higher rates of cancers. There are several theories to explain this phenomenon. The relatively sterile environment of the small bowel may be protective because certain carcinogens are dependent upon microbial metabolic activation. The rapid transit of contents through the small bowel is thought to be protective because there is less exposure to luminal carcinogens [6]. Enzymes such as benzopyrene hydroxylase are found in high concentration in the small bowel, and may protect against the effects of carcinogens. The contents of the small bowel are alkaline due to the presence of bile and pancreatic juice, and this alkaline environment may prevent formation of potentially carcinogenic nitrosamines.

ETIOLOGY AND RISK FACTORS
Small-bowel adenocarcinomas share similarities with colorectal cancers. Persons with colorectal cancer are at increased risk of developing small-bowel adenocarcinoma and vice versa [7]. These tumors may present as synchronous or metachronous neoplasms. The adenoma-carcinoma sequence, accepted as the model of cancer development in the colon, appears to hold true for the small bowel as well. Most small-bowel adenocarcinomas contain adenomatous tissue. Patients with small-bowel cancers are older than those with adenomas; thus it appears that malignant degeneration occurs over time. Progression of adenomas to carcinomas is reported to occur over 16 years.

Risk factors associated with small-bowel cancers are shown in Table 1. Persons with FAP have a relative risk of duodenal adenocarcinomas of more than 100-fold, and these are the most common malignancies affecting such persons after colon cancer [8]. Periampullary cancers occur in 3% to 12% of FAP patients. A germ-line mutation of the adenomatous polyposis coli (APC) gene interferes with the apoptotic pathway and imparts cancer risk. In addition, duodenal bile appears to have increased mutagenic properties in persons with FAP. Duodenal and periampullary cancers are generally diagnosed early in the sixth decade of life [9]. Cholecystectomy is associated with an increased incidence of small-bowel adenocarcinoma perhaps due to a more continuous exposure of the gut to bile [7]. Other hereditary colorectal cancer syndromes including Peutz-Jeghers syndrome and hereditary nonpolyposis colorectal cancer (HNPCC) impart an increased risk for small bowel malignancies. Small intestinal adenocarcinomas are also associated with Wilm's tumor, Hodgkins lymphoma, squamous carcinomas, and cancers of the prostate, female genitalia, and lungs.

Many studies have estimated the relative risk of adenocarcinoma of the small intestine in Crohn's disease to range from 15- to 100-fold. This elevated risk begins 10 to 20 years after the onset of the disease, and the cancers generally occur in the ileum [4,10]. Longstanding celiac sprue dramatically increases the risk for adenocarcinoma of the proximal small intestine. Adenocarcinoma of the duodenum and proximal jejunum accounts for more than 20% of small bowel malignancies in sprue patients, with non-Hodgkins T-cell lymphomas accounting for the rest. Adenocarcinoma occurs 10 years after the onset of celiac sprue, and may be multifocal. Gluten restriction does not offer protection from developing small-bowel malignancy in celiac sprue patients [11]. Radiation therapy imparts a two-fold risk for up to 30 years. Cystic fibrosis is also associated with an elevated risk for small-bowel adenocarcinoma.

PATHOLOGY
The most common histologic type of small-bowel cancer is the mucinous adenocarcinoma of varying degrees of differentiation. Genetic mutations or altered expression of erb-B2, K-ras, cyclin D-1, and p53 have been described [12]. Adnab-9 monoclonal antibody staining may have a role as a marker. Adnab-9 staining in the small-bowel epithelium is enhanced in patients who harbor adenocarcinoma, and in FAP patients as well [13].