Malignant tumors of the small intestine are rare. In fact, one of the more puzzling aspects of small-bowel tumors is the surprisingly low frequency with which they occur. Although the small intestine constitutes three-fourths of the length and approximately 90 percent of the surface area of the gastrointestinal (GI) tract, it is the site of less than 5 percent of GI malignancies.1,2 In the United States, approximately 140,000 colorectal cancers and 22,000 gastric cancers occur annually whereas only 4,500 to 5,000 small-bowel cancers are seen each year.

Due to the rarity of these tumors, detailed knowledge of the epidemiology of small-bowel cancer is limited. Small-bowel cancer has been the subject of only a small number of population-based descriptive epidemiologic studies.3–10 Detailed information and subpopulation analysis within these population-based studies are also limited. Hospital case studies, most requiring several decades to accumulate data, generally contain more detail than is available from cancer registries, and these studies (however flawed) have been the prime source of descriptive data regarding these rare cancers.

INCI DENCE

Four histologic tumors make up 90 percent of all small-bowel malignancies: adenocarcinoma, carcinoids, lymphoma, and sarcoma.6 The relative frequencies of the differing histologies vary from reported studies. In general, however, adenocarcinoma and carcinoids have similar relative frequencies, and each constitute from 30 to 40 percent of all small-bowel malignancies. Small-bowel sarcomas and lymphomas are somewhat less common, each representing 10 to 20 percent of the total3,5–7 (Figure 18–1).

The differing histologic forms of small-bowel cancer tend to occur in particular locations along the length of the small intestine. Adenocarcinomas most frequently occur in the duodenum, particularly in the vicinity of the ampulla. Sixty-two percent of the small-bowel adenocarcinomas reported in the Los Angeles County tumor registry were located within the duodenum,7 and other studies also indicate a predominance for adenocarcinoma in the duodenum.11 Carcinoids and lymphomas are typically more distal in the small bowel, being predominantly ileal or jejunal. Sarcomas appear to be evenly distributed throughout the small bowel.

The Surveillance, Epidemiology and End Results (SEER) data (1973 to 1991) indicate an overall annual rate of 9.9 cases per million population for all the histologic subtypes of small-bowel malignancies.8,12 Combined statistics from the cancer registries of western Canada show a similar rate of 11 cases per million population.5 This is approximately one-thirtieth of the incidence of colorectal carcinomas within the same population groups. Most population-based studies have indicated a slightly higher risk among men than among women, with the male-female ratio being approximately 1.2:1.12 This higher incidence among males is consistent throughout all four of the more common histologic subtypes. The risk for small-bowel malignancies increases with age, with most occurring in individu-
als who are 60 to 70 years of age. Over 90 percent of small-bowel malignancies occur in patients older than 40 years of age. In the industrialized countries, correlation with age occurs in all histologic subgroups although the mean age for the diagnosis of lymphoma and sarcoma is somewhat less than for carcinoids and adenocarcinoma. In the developing world, however, small-bowel lymphomas seem to occur more frequently in young adults.13

Few data exist describing the relative rates of small-bowel malignancies among people of differing races living within the same geographic location. Analysis of the SEER data by Chow and colleagues indicates that white individuals have a slightly increased risk for small-bowel malignancies when all histologic subtypes are taken into account.4 The SEER data indicate an increased risk among African Americans for adenocarcinomas when compared to whites. The University of Southern California Cancer Surveillance Program also noted an increased age-adjusted risk for small-bowel adenocarcinoma among African Americans.7 Small-bowel lymphomas, on the other hand, are somewhat less common among African Americans.

Population-based studies within the United States indicate a trend over time for an increasing incidence of small-bowel malignancies4,6,8 (Figure 18–2). This increase in incidence has been for adenocarcinomas and carcinoids but is most pronounced for lymphomas, which have risen from approximately 0.1 per million in 1973 to 3 per million in 19904 (Figure 18–3). This increase in small-bowel lymphomas parallels an increase in cases of gastric lymphoma over the same time period. This observation has led some to suggest a common etiology for small-bowel and gastric lymphomas. Immunosuppressive states, such as those that occur in acquired immunodeficiency syndrome (AIDS) and transplant patients, are an established risk factor for lymphomas in general; yet, it is not known

Figure 18–2. The incidence of small intestinal malignancies in the United States, as a function of time.
whether such immunosuppressive states contribute specifically to the increased incidence in lymphomas of the small bowel. *Helicobacter pylori* has been associated with gastric lymphomas, but any relationship between *Helicobacter pylori* and small-bowel lymphomas is entirely based on conjecture.

**RISK FACTORS**

A wide variety of potential risk factors for the development of small-bowel malignancies have been investigated. Most data regarding putative risk factors originate from hospital-based studies that review a small number of cases accumulated over many years. The conclusions drawn from these hospital-based studies are at the mercy of their inherent deficiencies. A small number of such studies have used case-control comparisons in an attempt to find an association with certain dietary, social, and health factors. Along with increasing age and male sex, Crohn’s disease and familial adenomatous polyposis (FAP) are clearly recognized as risk factors for small-bowel cancer. Many other factors have been studied, but their impact on the risk of small-bowel cancer is less certain (Table 18–1).

**Crohn’s Disease**

The data clearly support Crohn’s disease as a risk factor for small-intestinal adenocarcinoma. The expected incidence for these two rare conditions occurring in the same individual is approximately one in one billion, yet, over 100 cases of Crohn’s disease–associated small-bowel cancer have been reported in the literature since the initial report of a small-bowel Crohn malignancy by Ginsberg and colleagues in 1956. Unlike sporadic cancers, in whose case adenocarcinomas occur predominantly in the proximal small bowel, adenocarcinomas with Crohn’s disease typically occur in areas of long-standing active disease (most commonly, the ileum).

Many studies have shown a substantial risk for small-intestinal adenocarcinoma among Crohn’s disease patients, but the precise calculated risks vary. In Denmark, a prospective cohort analysis of 373 patients who were diagnosed with Crohn’s disease and who were observed for 10 to 15 years found 2 cases of small-bowel cancer, both in the ileum, compared to an expected 0.04 cases. Thus, in this study, the relative risk of small-bowel cancer in patients with Crohn’s disease was 50 times that of the general population. A similar report from Stockholm found a lower but substantial relative risk of 15.6. In a hospital-based study of patients with inflammatory bowel disease, Greenstein and colleagues estimated the incidence of small-bowel cancer to be increased 86-fold in patients with Crohn’s disease. In a case-control study by Chan and colleagues, 4 of 19 cases of small-bowel adenocarcinoma arose in the ileum, and 3 of these were associated with a history of Crohn’s disease. Although Crohn’s disease patients are at risk for adenocarcinoma of the small bowel, their risk for other histologic subtypes of small-bowel malignancies is not increased.

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<th>Table 18–1. RISK FACTORS FOR SMALL-BOWEL CANCER</th>
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<td><strong>Established factors</strong></td>
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<td>Age</td>
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<td>Crohn’s disease</td>
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<td>Familial adenomatous polyposis</td>
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<td>Hereditary nonpolyposis colorectal cancer syndrome</td>
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<td><strong>Theoretic factors</strong></td>
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<td>High-fat/high-protein diet</td>
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<td>Peutz-Jeghers syndrome</td>
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<td>Radiation injury</td>
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There are three factors known to affect the risk for small-bowel adenocarcinoma in Crohn’s disease patients. The first is duration of disease; the longer the history of active disease, the greater the risk. In fact, long-standing disease seems to be necessary; the appearance of small-bowel carcinoma in patients who have had Crohn’s disease for less than 10 years is virtually unreported. The second established risk factor is male sex. Small-bowel cancer occurs with a male-to-female preponderance of 3:1 among Crohn’s disease patients. The final risk factor is the presence of diverted or excluded segments of small intestine. Although no longer recommended, intestinal bypass with the exclusion of diseased segments of small intestine was commonly performed for cases of active Crohn’s disease. This practice resulted in a high incidence of adenocarcinoma developing in the diseased segment of intestine that was excluded from the normal intestinal stream. For this reason, this type of surgical approach to the management of Crohn’s disease has been abandoned.

In addition to the archaic practice of intestinal bypass, other treatments for Crohn’s disease have been studied for their potential to promote small-bowel cancer. Lashner and colleagues found a slight increase of risk for adenocarcinoma among Crohn’s disease patients treated with 6-mercaptopurine. This risk was not seen in patients treated with prednisone or sulfasalazine. Lashner and colleagues also found that patients with jejunal Crohn’s disease seemed to be at higher risk when compared to patients with ileal Crohn’s disease. Some surgeons have expressed concern regarding the use of strictureplasties to treat small-bowel Crohn’s disease. It has been suggested that this new technique may result in the retention of diseased segments for long durations and thus result in an increase in small-bowel cancer. To date, this theoretical concern has not demonstrated such a risk, and only two cases of adenocarcinoma in strictureplasty patients have been reported.

**Familial Adenomatous Polyposis and other Familial Cancer Syndromes**

Patients with FAP are at high risk for small-bowel adenomas and adenocarcinomas, particularly of the duodenum. In fact, duodenal and periampullary adenocarcinomas are the most common extracolonic malignancies in FAP patients and represent the second most frequent cause of death among these patients. Approximately 3 percent of FAP patients will develop small-bowel cancers, almost all of which will occur within the duodenum. Among 1,391 patients in the Johns Hopkins FAP registry, 11 cases of duodenal and ampullary carcinoma occurred. From this registry, the relative risk for duodenal adenocarcinoma among patients with FAP was calculated to be an extraordinary 330.8. Interestingly, however, FAP patients do not appear to have an increased risk for either gastric or nonduodenal small-bowel cancer.

In addition to patients with hereditary FAP, individuals with hereditary nonpolyposis colorectal cancer (HNPCC) also appear to be at higher risk for small-bowel cancer. Two studies have specifically addressed the issue of HNPCC and small-bowel cancer. These studies indicate an estimated lifetime risk of 1 percent for small-bowel cancer among HNPCC patients. This is less than the risk associated with FAP but significantly higher than the risk in the general population.

Small-bowel tumors have been associated with other malignancies, aside from hereditary and non-hereditary colorectal cancers. Even sporadic colorectal cancer may be associated with an increased risk for small-intestinal cancer. From SEER data gathered between 1973 and 1988, Neugut and Santos investigated the association between the 2,581 cases of small-bowel cancer from the database and other second malignancies. This study found relative risks for colorectal cancer following development of small-bowel adenocarcinoma of 5.0 in males and 3.7 in females. The risk of developing small-bowel adenocarcinoma following colorectal cancer was also increased, with risks of 7.1 in males and 9.0 in females.

From the Manitoba and British Columbia registries, 54 of 128 patients with small-bowel cancers also suffered from second malignancies. This translates into a greater than eightfold increase in the incidence of second malignancies with small-bowel cancer. Thirty-eight of these associated tumors were diagnosed prior to the small-bowel cancer, eight were synchronous with it, and six were diagnosed after the
small-bowel cancer. The most common sites for second malignancies were the large bowel, the prostate, the female genitalia, and the lung. In a separate report after a mean follow-up of 6 years, Frost and colleagues found that among 61 patients treated at the Kaiser-Permanente Los Angeles Medical Center for small-bowel cancer, 7 patients developed another primary cancer. These new primary cancers included 3 breast cancers and 1 each of rectal cancer, renal cell cancer, lymphoma, and melanoma. In a study of 49 patients with adenocarcinoma of the small intestine recorded in the Hawaii tumor registry from 1960 to 1989, 11 patients had other cancers. Six males had large-bowel cancer (one of these six also had prostate and stomach cancer; another had cancer of the ureter). Three other males had melanoma, stomach, and ureteral cancer; one male had each of the three cancers. Only two females had second malignancies (one case of colon cancer and one case of breast cancer).

Patients with Peutz-Jeghers syndrome, a rare familial disorder, have mucocutaneous pigmentation and multiple hamartomatous polyps of the GI tract. The risk for the development of invasive adenocarcinoma within these hamartomatous polyps or de novo within the small bowel has been the subject of controversy. Many reports of carcinoma within a Peutz-Jeghers polyp may have been misinterpretations resulting from the incorporation of muscle in the stroma of the polyp, giving the false impression of invasion. Using strict criteria for establishing the diagnosis of malignancy in Peutz-Jeghers patients, Dozois and colleagues reviewed the published reports of 321 cases of Peutz-Jeghers syndrome and found 4 cases of established small-intestinal malignancy (3 of the duodenum and 1 of the ileum) and an incidence of 1.2 percent, suggesting an increased risk for small-bowel cancers in these patients.

**Radiation Therapy**

Exposure to radiation therapy results in significant long-term injury to the small intestine. Radiation may also increase the risk for small-bowel malignancies within the segments exposed. In a cohort study, Kleinerman and colleagues compared 49,828 women with cervical cancer treated with radiation therapy to 16,713 women with cervical cancer treated without radiation therapy. The relative risk for small-bowel cancer following radiation therapy was 1.8, and this risk remained high for up to 30 years following treatment.

**Celiac Disease**

Celiac disease has been associated with an increased risk for the development of cancer, including small bowel adenocarcinoma and lymphoma. In a British National Collaborative Study, 235 patients with both celiac disease and malignancy were studied. The most common tumor in these patients was small-bowel lymphoma, of which there were 67 cases. Nineteen patients had small-bowel adenocarcinoma, yet the expected incidence of this form of small-bowel cancer was only 0.23. The increased risk for small-bowel lymphoma and adenocarcinoma was not dependent on the clinical or histologic response to a gluten-free diet.

**Diet**

A limited number of studies have attempted to correlate the risk for small-bowel cancer with dietary habits. World Health Organization (WHO) data suggest a risk association with per capita intake of animal fat and protein. Regions where traditional diets are high in animal fat and protein were noted to have higher rates of small-bowel cancer. Using cases and controls to compare patients suffering from small-bowel adenocarcinomas, Chow and colleagues reported a statistically significant risk with higher intakes of meat and smoked foods. Other studies have suggested that sugar-sweetened nonalcoholic beverages may also pose a risk for the development of small-bowel tumors. While these studies suggest an association between certain dietary habits and the risk of small-bowel cancer, no causal relationship between any specific food and small-bowel cancer has been established.

**Smoking**

Data regarding the risk of cigarette smoking to the development of small-bowel tumors are not conclusive. Chen and colleagues found an increased risk for
small-bowel adenocarcinoma for smokers. Among their patients, the age- and sex-adjusted odds ratios for cigarette smokers were 4.6 for adenocarcinoma and 4.2 for carcinoid of the small bowel. Wu and colleagues also reported an increased risk, albeit non-significant, of adenocarcinoma for male smokers but not for female smokers. On the other hand, in two separate studies, Negri and colleagues and Chow and colleagues were unable to discern any tobacco-associated risk for small-bowel tumors.

Alcohol

Only a limited number of studies have investigated the risk of small-bowel cancer and the use of alcohol. The available data suggest that alcohol consumption increases the likelihood for small-bowel adenocarcinoma and possibly for small-bowel carcinoid tumors. Wu and colleagues reported a threefold increased risk for small-bowel adenocarcinomas among heavy drinkers (ie, > 80 g of alcohol a day). Chen and colleagues reported an alcohol-related risk for both small-bowel adenocarcinomas and small-bowel carcinoids, with an adjusted odds ratio for alcohol consumption of 4.0 for adenocarcinomas and 3.1 for carcinoids.

SUMMARY

Cancers of the small bowel are rare. Current data indicate an increasing incidence of these uncommon tumors, particularly small-bowel lymphomas. The risk for small-bowel cancer increases with age, and males are at slightly higher risk than females. Individuals suffering from FAP or long-standing Crohn’s disease are at much higher risk for small-bowel adenocarcinoma, compared to the general population.

REFERENCES