Chapter 1

The Descriptive Epidemiology of Gastrointestinal Malignancies

Anthony Gamboa, Qi Lin, Peng Jin, Yifeng Zhou, Qiang Liu, Jinhua Hao, Qiang Cai and Roberd M. Bostick

What is New

- Esophageal adenocarcinoma and carcinoid tumor incidence rates continue to increase remarkably, while the rates for gastric cancer is declining worldwide, and that for colorectal cancer is declining in the United States.
- Liver cancer incidence continues to rise, though some predict that it will decline in the coming years as hepatitis B is addressed with vaccination and novel therapies for hepatitis C become available.
- Mortality trends for pancreatic cancer have shifted, with declining rates among African Americans and increasing rates among Caucasians, which is a reversal from a decade earlier.

Introduction

Examining the epidemiology of gastrointestinal malignancies reveals varying trends and evolving populations at risk. The most reliable data for
determining incidence rates, mortality, and trends for various malignancies of the gastrointestinal system include those from large public data sets. Worldwide, the GLOBOCAN project of the World Health Organization (WHO) provides incidence and mortality data for many types of cancer. In the United States, the American Cancer Society annually collates data from the tumor registries of all 50 states and publishes incidence and mortality estimates for the various cancers. Finally, the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) collects more in-depth data from selected regions of the United States; these data are readily accessed and frequently utilized by researchers who elucidate trends and updated data on cancer epidemiology. Epidemiological trends are key for investigators who address evolving threats in gastrointestinal malignancies, and awareness of these trends allows clinicians to maximize the application of current diagnostic and therapeutic tools for patient care.

The most common types of gastrointestinal cancers are colorectal, pancreatic, liver, gastric, and esophageal cancers, and many other gastrointestinal malignancies are responsible for high mortality rates as well.

**Esophageal Cancer**

The epidemiology of esophageal cancer continues to evolve rapidly. The incidence of adenocarcinoma of the esophagus has risen dramatically over the last four decades, and its incidence is surpassing that of squamous cell carcinoma of the esophagus in many Western countries, corresponding to increases in obesity and gastroesophageal reflux disease (GERD).

The most common histologic types of esophageal cancer are squamous cell carcinoma and adenocarcinoma. Typically, data are reported separately for the two types because their incidence rates and trends vary substantially.

Worldwide, the number of incident esophageal cancer cases was approximately 482,000 in 2008; there were 3–4 times more cases among males than among females; and the age-standardized esophageal cancer incidence rate is 7.0 per 100,000 population, making esophageal cancer the sixth most common malignancy among men and the ninth most common among women worldwide. The annual number of deaths from esophageal cancer is approximately 406,000, or 5.8 per 100,000
population worldwide. It is the fifth most common cause of cancer-related deaths among men, eighth most common among women, and the sixth most common overall worldwide. Approximately 83% of individuals diagnosed with esophageal cancer and 86% of those who die from the disease are in developing countries.\textsuperscript{2}

In the United States, the lifetime risk of an individual being diagnosed with esophageal cancer is less than 1%.\textsuperscript{3} The American Cancer Society estimates that 18,170 new cases of esophageal cancer will be diagnosed in 2014. Among these, 14,660 are expected to be in men and 3,510 in women. There will be an estimated 15,450 deaths from esophageal cancer in 2014, 12,450 in men and 3,000 in women. Among men in the United States, esophageal cancer will be the seventh leading cause of death from cancer. Using data from SEER, during 2003–2009, at diagnosis, approximately 22% of new cases had localized disease, 30% had regional spread, 36% had distant metastasis, and the remainder did not have staging information available. During the same time, the five-year relative survival rates for esophageal cancer were 39% for those with localized cancer at diagnosis, 21% for those with regional nodal spread, and 4% for those with distant metastasis. Over the last several decades, the esophageal cancer relative survival rates have improved. During 1975–1977, the overall five-year relative survival rate in the United States was 5%; during 1987–1989 it was 9%; and during 2003–2009, 19%. There is no difference in survival between adenocarcinoma and squamous cell carcinoma in this data.\textsuperscript{4}

There are important differences in the epidemiology of esophageal cancer by histologic type, geographic location, and race. Squamous cell carcinoma is more common worldwide than adenocarcinoma of the esophagus; however, the incidence of adenocarcinoma has surpassed that of squamous cell carcinoma in the United States, the United Kingdom, Australia, France, and some other Western European countries.\textsuperscript{5} In the United States, the incidence of esophageal adenocarcinoma increased from 0.4 to 2.58 per 100,000 between 1975 and 2009.\textsuperscript{6} The incidence increased 463% from 1975 to 2004 among white males and 335% among women, despite a declining rate of squamous cell carcinoma.\textsuperscript{7} Similar trends are reported in Western Europe. These rate changes correspond to changes in rates of obesity and GERD, which can cause Barrett’s esophagus. More than 90% of squamous cell carcinoma cases in the United States are attributed to alcohol and...
tobacco use. Declining rates of tobacco use may explain the decline in squamous cell carcinoma.8

The respective overall five-year relative survival rate among white and black patients in the United States diagnosed with esophageal cancer is 17% and 11%; for those with localized cancers, they are 41% and 20%; for those with regional spread, 21% and 15%; and for those with distant metastasis, 4% and 3%. The incidence of squamous cell carcinoma is higher among Blacks.4,9

Education has been inversely associated with esophageal cancer mortality rates. Among white males 25 to 64 years old, the mortality rate per 100,000 in 2007 was 7.92 among those with less than 12 years education compared to 2.93 among those with more than 16 years education. The mortality rates have also been increasing at a faster pace among those with less education; from 1993 to 2007, mortality annually increased 2.99% among those with less than 12 years education and 0.6% among those with more than 16 years education. In black males, mortality annually increased by 2.47% among those with less than 12 years education but decreased by 1.63% per year among those with more than 16 years education. These findings may be related to less or delayed access to medical care. They may also be related to different rates of smoking, alcohol consumption, and obesity between groups with different levels of education.10

In southern Africa, the incidence rate of esophageal cancer is more than 20 times higher than in northern, middle, and western Africa. A particularly high incidence is found in the “Asian belt” or “esophageal cancer belt,” which includes Turkey, northern Iran, central Asian republics, and northern and central China. The annual incidence in this region is more than 100/100,000, and of these cases, 90% are squamous cell carcinoma.1 Risk factors contributing to these high rates are poorly understood but may include drinking beverages at high temperatures, tobacco, and chewing Betel and Areca nut.11,12 There are wide variations in the incidence within these regions that remain unexplained. In China, the highest rates are found in the north-central provinces Shanxi and Henan. In central Asia, Turkmenistan and Kazakhstan have higher rates than their neighbors, and in within Iran, dry regions east of the Caspian Sea have a much higher incidence than the nearby humid regions to the west.9 In Taiwan,
the incidence rate of squamous cell carcinoma continues to rise while that for adenocarcinoma remains unchanged.13

Known risk factors for esophageal adenocarcinoma include higher body mass index, history of smoking, gastroesophageal reflux disease, and low fruit and vegetable consumption. Factors that contribute the development of esophageal squamous cell carcinoma include history of smoking, alcohol use, and low fruit and vegetable consumption.8

**Gastric Cancer**

Gastric cancer incidence continues to decline in most parts of the world, but cancers in the gastric cardia are increasing, as are noncardia gastric cancers among 25–39-year-olds in the United States.

Gastric adenocarcinoma is the most common form of cancer of the stomach, and herein it will be referred to as “gastric cancer.” Gastric cancer is the fourth most common type of malignancy in the world after lung, breast, and colorectal cancer, accounting for 8% of all new cases (989,600 diagnoses) and 9.7% of all cancer-related deaths (738,000 deaths). It is the third most common cause of cancer death among men and fifth among women. The incidence is twice as high among males than females, and over 70% of cases occur in developing countries.1,2,14

Across the world, gastric cancer incidence varies considerably. The incidence among Korean males is 62/100,000 and among Guatemalan women 26/100,000, compared to less than 1/100,000 in Botswana. Incidence is highest in Korea, Japan, China, Brazil, much of South America, Eastern Europe, and Portugal and lowest in North America, India, and much of Africa.

In the United States, the American Cancer Society estimates that 22,220 new cases will be diagnosed in 2014, and that 13,730 will be males and 8,490 females. It is estimated that 10,990 deaths will occur in 2014, 6,720 among males and 4,270 among females. Over the last several decades in the United States, gastric cancer relative survival rates have improved. Between 1975–1977, the overall five-year relative survival rate in the United States was 15%; between 1987–1989 it was 20%, and between 2003–2009, 29%. Five-year survival rates are similar in Blacks (29%) and Whites (28%).4

In SEER, 25% of cases are localized, 30% have regional nodal spread, 34%
have distant metastasis at diagnosis, and 11% are unstaged. The five-year relative survival is 63.2% among those with localized tumors, 28.4% among those with regional nodal spread, and 3.9% among cases with distant metastasis.\textsuperscript{15,16}

Incidence rates among immigrants tend to be similar to those in the country to which they move rather than to those in their country of origin, especially as successive generations are born in their adopted country. Environmental factors are therefore thought to play a large role in the incidence rates. However, gastric cancer incidence among Japanese-born immigrants to the United States is three to six times higher than that among United States-born whites. Among Chinese male immigrants, the rate is the same as among United States-born white males, but among Chinese female immigrants, the rate is twice as high as among United States-born white females. These findings suggest that early environmental factors may play an important role in gastric carcinogenesis.\textsuperscript{17}

In most parts of the world, gastric cancer incidence has decreased. In 1975, it was the leading cause of cancer worldwide.\textsuperscript{1} The incidence rate has declined by more than 80% over the last 50 years in North America and many parts of Europe.\textsuperscript{14} The relative risk in the United Kingdom declined throughout the 20\textsuperscript{th} century.\textsuperscript{18} More recently, rates have declined in China, Japan, Korea, and in parts of South America.\textsuperscript{14}

The declining incidence worldwide is attributed to multiple factors. The introduction and widespread use of refrigerators may have corresponded to a decline in gastric cancer, presumably by reducing exposures to potentially harmful bacteria or fungi. Refrigerators also allow increasing amounts of fresh fruits and vegetables to be accessible to more people, and they reduce the need for highly salted or preserved foods. Other contributing factors include the identification and use of antibiotics for \textit{Helicobacter pylori} (\textit{H. pylori}) and the use of gastric cancer screening in Japan.\textsuperscript{14,19}

However, gastric cancer incidence has not decreased uniformly. Declining rates are noted for cancers of the fundus, body, and distal stomach, but cancers of the cardia have not decreased. Cardia cancers, which share many histologic and epidemiologic features with esophageal adenocarcinoma,\textsuperscript{20} are influenced by reflux disease and show less geographic variability.\textsuperscript{21}

Proximal gastric cancers are relatively more common among young white males in the United States, while distal gastric cancers are more
common in Asian, Black, and Hispanic populations. Different risk factors are thought to relate to cardia versus noncardia gastric cancers. *H. pylori* is strongly associated with noncardia gastric cancers, but it is inversely associated with gastric cardia cancer.²² In the United States between 1978 and 2005, the overall incidence of gastric cancer decreased by 34%, but the incidence of cardia cancers increased by 23%.²³

Trends in incidence also vary by histologic type of gastric cancer. There are two distinct histologic patterns for gastric cancers, which differ in epidemiology and behavior. The intestinal type, which is more common, is associated with *H. pylori*, male sex, and increasing age, and is frequently noncardia. The incidence of the intestinal type decreased by 44% between 1978 and 2005 in the United States. The diffuse type, which can be seen anywhere in the stomach and occurs approximately equally in males and females, is more common in younger groups and has a worse prognosis. Its incidence in the US increased by 62% through 2000 then slightly declined through to 2005. Among cardia cancers, the diffuse type increased by 377%.²³,²⁴

While the overall incidence rate of gastric cancer is declining, data suggest that it may be rising again among the youngest cohorts. From 1977 to 2006, noncardia gastric cancer incidence declined in all age and race groups except Whites, ages 25–39 years. In this demographic, the incidence increased from 0.27 to 0.45 per 100,000. The importance of this finding, despite the low absolute incidence, is that it may be foreshadowing changes in incidence as this cohort ages. It also suggests the possibility of new environmental risk factors for the disease.²⁵

Many risk factors, including smoking and first-degree relative with gastric cancer, have been associated with gastric cancer. Precursor lesions include adenomatous gastric polyps, chronic atrophic gastritis, dysplasia, intestinal metaplasia, and Menetrier disease.³ More information is needed to outline risk factors associated with cardia cancers and each histologic type.

### Biliary Cancers

Biliary cancers include gallbladder cancer, cholangiocarcinoma, and ampullary carcinoma. Taken together, biliary cancers comprise the sixth most common type of gastrointestinal malignancy in the United States after
colorectal, pancreatic, liver, gastric, and esophageal cancers. While the different forms of biliary cancers share some risk factors, they all have distinct behaviors. Data for incidence and trends for these tumors are less clear than those for other cancers because of the different methods of classifying these tumors used in the various large databases. In some cases there is conflicting evidence regarding trends, and much about the epidemiology of these cancers remains to be clarified.26

**Cholangiocarcinoma**

Cholangiocarcinomas are subcategorized as intrahepatic and extrahepatic because of differences in their anatomy, epidemiology, behavior, and therapy. Intrahepatic lesions arise from small bile ducts or large ducts proximal to the bifurcation of the left and right hepatic ducts. Extrahepatic lesions include hilar lesions, also known as Klatskin tumors, and include those involving the bifurcation of the left and right hepatic ducts, as well as the distal bile duct, which begin where the bile duct begins to traverse the duodenum. The epidemiology of cholangiocarcinoma differs between these two categories. However, various large databases have accounted for cholangiocarcinoma differently. For example, the SEER database includes most Klatskin tumors as intrahepatic cholangiocarcinomas, despite their usual classification as extrahepatic. Frequently, extrahepatic cholangiocarcinoma is grouped with gallbladder cancer, while intrahepatic cholangiocarcinoma is grouped with primary liver cancers, including hepatocellular carcinoma.27

Data on cholangiocarcinomas are limited and mostly based on a decades-old series of autopsies and a few studies from Japan.28 From these studies, cholangiocarcinomas were estimated to account for approximately 3% of all gastrointestinal malignancies, and among primary liver tumors, to be the second most common malignancy after hepatocellular carcinoma (HCC), accounting for approximately 10–20% of the total diagnoses.29 Data on the worldwide incidence of cholangiocarcinoma are not readily available. Estimated incidence rates for intrahepatic cholangiocarcinoma have ranged from 96/100,000 in men and 38/100,000 in women in parts of Thailand to as low as 0.2/100,000 in men and
The Descriptive Epidemiology of Gastrointestinal Malignancies

0.1/100,000 in women in Australia. Males are more frequently affected than women, at a ratio of 1:1.2–1.5.

In reports from the American Cancer Society, intrahepatic cholangiocarcinoma (ICC) is grouped with primary liver tumors and extrahepatic cholangiocarcinoma (ECC) is grouped with gallbladder cancer. Incidence rates for cholangiocarcinoma therefore are not well defined.

Some reports indicate that, in the United States, the incidence of ICC is increasing while that of ECC is decreasing. An analysis of SEER data revealed a 9.11% annual increase in ICC incidence and 9.44% annual increase in mortality from 1973 to 1997. In white persons, the age-adjusted mortality rate increased from 0.14 to 0.65/100,000, and in black persons 0.15 to 0.58/100,000 over the same time period. From 1975 to 1999, there was a 165% increase in ICC incidence. These studies were questioned because of misclassification of Klatskin tumors as ICC rather than as ECC. Correction for the misclassification yielded a more modest estimated 4% annual increase in ICC. Other reports from SEER indicate that from 2000 to 2005, the trends have changed, with ICC rates down slightly and those for ECC increasing. In summary, the true incidence and trends in ICC and ECC remain unclear and require further investigation.

Well-known risk factors for the development of cholangiocarcinoma include parasite infections, primary sclerosing cholangitis, choledochal cysts, gallstone disease, and toxins. Other risk factors include inflammatory bowel disease, hepatitis C or hepatitis B infection, cirrhosis, diabetes mellitus, obesity, alcohol use, and smoking.

Gallbladder cancer

The incidence rate of gallbladder cancer is estimated to be 2.4/100,000 men in more developed areas, and 1.4/100,000 in less developed areas; in females, the corresponding rates are 2.1 and 2.2/100,000. The overall incidence is estimated to be 2.0/100,000 worldwide. The rates are generally higher in areas with a higher incidence of cholelithiasis. The overall mortality rates are greater than 90% at five years. The highest mortality rates for biliary tract cancers, which primarily consist of gallbladder cancer, have been observed in Chile, at up to 15.5/100,000.
The incidence of gallbladder cancer differs according to various demographic, geographic, and other factors. The female to male ratio has been estimated to be 3:1. In general, the incidence is highest in India (it has been reported to be as high as 21.5 per 100,000 females in Delhi), Asia, South and Central America, and parts of Eastern Europe, and lowest in North America and Northern Europe. The strongest risk factor is a history of cholelithiasis, with an estimated relative risk of 4.9. Gallstones that are present for 20 or more years may promote epithelial dysplasia and, ultimately, adenocarcinoma by causing trauma and promoting inflammation and infection in the gallbladder. Despite the increased risk, less than 1% of people with cholelithiasis develop gallbladder cancer. In Japan, gallstones were not found to be a risk factor.

Incidence rates in the United States are relatively low compared to worldwide rates and have been estimated at approximately 1.5/100,000. Rates vary widely by sex and ethnicity or race. The highest rates are among American Indians/Alaska Natives at 5.4 and 3.9/100,000 in women and men, respectively. In North America, among women, incidence rates per 100,000 are 3.7 in Hispanics, 1.6 in Asians/Pacific Islanders, 1.6 in Blacks, and 1.2 in Whites; among men, the rates per 100,000 are 1.3 in Hispanics, 1.3 in Asians/Pacific Islanders, 0.9 in Blacks, and 0.7 in Whites. From 1974 to 2009, the incidence declined among Whites and remained stable among Blacks. From 1992 to 2009, the incidence declined slightly among all groups except Blacks, in whom they were stable. There is speculation that rates may be declining due to the increased availability of cholecystectomy for patients with symptomatic gallstones, despite the increase in obesity, which is a risk factor for gallbladder cancer.

**Ampullary tumors**

Tumors of the Ampulla of Vater arise distal to the confluence of the pancreatic duct and common bile duct, proximal to the duodenum. These are relatively uncommon tumors, comprising 0.5% of all gastrointestinal cancers. Incidence rates vary from less than 0.1/100,000 in Finland to 1.2/100,000 in Colombia and 1.1/100,000 in Korea. In the United States, the incidence per 100,000 is approximately 0.3 in women and 0.4 in men. There is a male predominance, with a ratio of 1.48 men for every woman.
Among periampullary tumors, which may cause biliary obstruction and include ampullary tumors, pancreatic, duodenal, and distal bile ducts tumors, ampullary tumors account for approximately 8% of the total.37

In the United States the incidence is higher among Whites than Blacks, with incidence rates of 0.48 and 0.40/100,000 respectively. As estimated from SEER data, from 1973 to 2005, the incidence among all races increased 0.9% annually and was increasing faster in men than in women. Most persons diagnosed with these carcinomas had well- or moderately-differentiated tumors, and had better survival rates than those with advanced histologic grade tumors. Five-year survival rates vary by the extent of the disease. Patients with localized tumors have a 45% five-year survival rate; those with regional nodal spread, 31%; and those with distant metastasis, 4%. Among those with new diagnoses, 22.7% have localized disease, 67.1% have regional nodal spread, and 10.2% have distant metastasis. The overall survival rate tends to be better for papillary carcinomas than for other adenocarcinomas of the ampulla, possibly because of their exophytic growth pattern, which may cause earlier biliary obstruction precipitating earlier detection.38

Various risk factors for ampullary carcinomas have been identified. Ampullary carcinoma is the second most common site of malignancy after colorectal cancer in persons with Familial Adenomatous Polyposis (FAP). The mean age of development of ampullary carcinoma in FAP patients is 45 years, compared to that in non-FAP patients who develop sporadic ampullary carcinoma, on average, in their seventh or eighth decade. There is an association between ampullary tumors and Neurofibromatosis Type I and Muir-Torre syndrome. Smoking and chronic liver fluke infection are also risk factors. Most ampullary cancers develop from adenomas, which tend to develop approximately eight years before a cancer.37

Liver Cancer

Liver cancers primarily include hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Many large databases, including the National Cancer Institute’s SEER and the World Health Organization’s GLOBOCAN, group these malignancies together for epidemiological analysis. HCC accounts for 70–85% of primary liver cancers.1 For a
specific discussion of ICC, please see the section above on cholangiocarcinoma.

The worldwide incidence of liver cancer is 10.8/100,000 population, and accounts for 5.9% of all cancer diagnoses. Among males, the incidence per 100,000 population is 8.1 in more developed areas, 18.9 in less developed areas, and 16 overall, making primary liver cancers the fifth most common cancer site among men. Among women, the rate per 100,000 population is 2.7 in more developed areas, 7.6 in less developed areas, and 6 overall, making primary liver cancers the seventh most common cancer site among women. Liver cancer is the second leading cause of cancer death worldwide. In total in 2008, there were approximately 748,300 new diagnoses and 695,900 deaths from liver cancer, 50% of which were in China. The highest rates are in East Asia, Southeast Asia, and Africa.¹,²

In the United States, there will be an estimated 33,190 new diagnoses and 15,870 deaths from liver cancer in 2014. The male predominance is approximately 3:1 for diagnosis and 2:1 for death from liver cancer. Liver cancers are the tenth most common cancer diagnosis among men and the fifth leading cause of cancer death in the United States; in women, they are the ninth leading cause of cancer death. From 1992 to 2010, the annual increase in liver cancer diagnosis was 3.7% in men and 2.9% in women, with mortality increasing 2.3% per year in men and 1.4% per year in women. The five-year survival rate for localized cancers is 29%; for cancers with regional nodal spread, 10%; and for those with distant metastasis, 3%. A total of 22% of new diagnoses are localized, 30% have regional nodal spread, and 36% have distant metastasis. Overall five-year survival rates increased from 3% between 1975 and 1977 to 18% between 2003 and 2009. Survival among white patients from 2003 to 2009 was 17% at five years compared to 12% among black patients.⁴

**Hepatocellular carcinoma**

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. There is wide geographic and age-related variation in its incidence, which is largely related to the prevalence of the hepatitis B and C viruses. These viruses are strong risk factors for developing HCC.
In addition, incidence rates have been evolving as African and Asian populations migrate to North America and Europe. There is also variation across ethnic groups within a country. The broad epidemiological trends discussed above in regards to all primary liver cancers can be extrapolated to HCC, since HCC is the most common liver cancer in most countries.\textsuperscript{39}

HCC incidence rates are highest in Asia and sub-Saharan Africa, where more than 80% of all HCC cases occur. The incidence rate in parts of China is higher than 30/100,000, though recent decreases in incidence have been reported in China.\textsuperscript{40} In much of sub-Saharan Africa, where it is thought that HCC is under-diagnosed and reported, the published rates exceed 16/100,000. These rates reflect the high incidence of hepatitis B in these areas. In northern Europe and North America, incidence rates are less than 5/100,000. In southern Europe, where hepatitis C is more common than in northern Europe, rates are around 12/100,000.\textsuperscript{41} While HCC incidence tends to increase with age, the mean age at diagnosis in Africa and East Asia, excluding Japan, is lower than in Western countries, presumably because of the high rates of hepatitis B vertical transmission in these areas. The mean age of diagnosis in China is approximately 55–59 years, and in Europe and North America, 63–65 years.

In Japan, the rates per 100,000 in 2003 were 24 in men and 7.3 in women, and have declined steadily since the mid-1990s. The declining rates in Japan may be related to a decreasing prevalence of hepatitis C among younger generations. The highest incidence of hepatitis C may have been related to blood transfusions in the mid-20th century and to intravenous amphetamine use during and after World War II. There were stiffer penalties in place for amphetamine use starting in 1954, and there was a change from paid to voluntary blood donations in late 1960s. These changes may have led to the declining rates of hepatitis C infection and, therefore, HCC seen in Japan.

In the United States, as estimated from SEER data, the incidence rates per 100,000 are approximately 7.9 in men and 2.3 in women; between 1975 and 2005 the overall age-adjusted incidence increased 4.9% annually, tripling from 1.6 to 4.9/100,000. The incidence increased in all birth cohorts between 1900 and 1959. Examining racial trends between 1992 and 2005 reveals that Asians/Pacific Islanders have the highest incidence of HCC. However, the incidence of HCC in this group increased only
1.0% annually, but increased faster in all other racial groups. The annual change was 5.0% in American Indians/Alaska Natives, 4.9% in Blacks, 4.6% in Whites, and 4.0% in Hispanics. The rates per 100,000 population were still highest among Asians/Pacific Islanders at 11.7, followed by Hispanics at 8.0, Blacks at 7.0, American Indians/Alaska Natives at 6.6, and Whites at 3.9. A total of 80% of the Asians/Pacific Islanders with HCC were born outside of the United States, as were 40% of Hispanics, 17% of Whites, 6% of Blacks, and 3% of American Indian/Native Alaskans.42

More recent incidence data from 2000 to 2005 revealed dramatic increases among black, white, and Hispanic men aged 50 to 59 years. In fact, Blacks aged 50 to 59 years had a higher overall incidence from 2003 to 2005 than did Asians/Pacific Islanders. The reasons for this shift in HCC incidence patterns among races is thought to relate to the high prevalence of hepatitis C among Blacks. Many of these individuals acquired hepatitis C in the 1960s, which led to increases in HCC incidence. Conversely, many Asians/Pacific Islanders with HCC were born outside of the United States in regions with a high hepatitis B prevalence. Asians/Pacific Islanders may not have been as affected by the hepatitis C epidemic as were other racial groups, as indicated by their relatively slower increase in HCC incidence among the 50 to 59 years age cohort. Hispanics born inside the United States tend to have higher incidence rates of HCC than do Hispanics born outside the United States, indicating that hepatitis B is less likely the principal risk factor in this group, and more likely that hepatitis C and other risk factors for cirrhosis in the United States, including hepatitis C, alcohol, and non-alcoholic fatty liver disease, may be contributing to HCC risk.42

The overall age-adjusted mortality rates from HCC are increasing 1.6% per year as incidence rates continue to rise. However, the cause-specific one-year survival rates in patients with HCC have almost doubled in the United States, from 25% in the early 1990s to 47% in the mid-2000s. Increased survival has been documented across all racial groups except American Indians/Alaska Natives, who had an annual 0.6% decrease in one-year survival. Five-year survival increased between 1992 and 1999 from 8% to 13%. These increased survival rates are correlated with diagnosing HCC at earlier stages. Between 1992 and 1993, at diagnosis, 28% of HCC cases had localized disease, 22% had regional spread, and 22% had distant metastasis; and between 2003 and 2004, 44% had localized disease, 29%
had regional spread, and 17% had distant metastasis. This trend may be related to increased screening efforts with imaging and alpha-fetoprotein levels. Increased survival may also be related to the more widespread utilization of surgery or liver transplant and to advances in medical and radiologic therapies for HCC. The cause-specific survival rates for patients with localized disease who received surgery were 91% at one-year.42

Certain populations are at increased risk for HCC, and identification of these groups is relevant because it allows for targeted screening and earlier identification of HCC. Patients with compensated cirrhosis have a HCC incidence rate of approximately 3% per year.43 HCC incidence is highest in patients with decompensated cirrhosis and those with hepatitis C cirrhosis.40 While the male-to-female ratio of HCC is around 3.7:1, the rates in men and women are almost equal in Western countries among those who do not have cirrhosis.9 An increased survival rate has been found in cirrhotic patients who have HCC diagnosed during screening.44

Hepatitis B, hepatitis C, non-alcoholic fatty liver disease, alcohol, and smoking are considered risk factors for HCC.45,46 Viral hepatitis, either hepatitis B or C, causes approximately 80% of HCC cases worldwide. Hepatitis B virus (HBV) is the leading cause of HCC worldwide, accounting for approximately half of all cases, and almost all cases in children.40 While HBV can lead to HCC in the absence of cirrhosis, approximately 85% of patients with HBV and HCC also have cirrhosis.57 Hepatitis B is transmitted by sexual contact, blood products, or vertically from mother to child. The risk for HCC among patients with HBV relative to those without is 10- to 100-fold higher. HBV accounts for a large proportion of HCC cases worldwide, including up to two-thirds in East Asia and Africa and one-fifth in Western countries. In patients with HBV, a family history of HCC confers a higher risk for HCC.48 Having a positive HBV surface antigen or e-antigen confers a higher risk for HCC. In Asia, the incidence of HCC per 100 person-years in inactive carriers of HBV is 0.2-100 person-years, 0.6 in patients with chronic infection but no cirrhosis, and 3.7 in those with compensated cirrhosis.40 In addition, a strong correlation was found between HBV serum viral load and HCC risk.49

Patients infected with the hepatitis C virus (HCV) are also at higher risk for HCC. In the United States, hepatitis C may account for 21% of
HCC cases, and the incidence appears to be increasing.\textsuperscript{50} In Taiwan, the lifetime incidence of HCC in patients with a positive hepatitis C serum antibody is 17\% in women and 24\% in men. In patients with both HBV surface antigen and HCV serum antibody, the HCC incidence rates are 27\% and 39\% for women and men, respectively. Risk increases with increasing HBV or HCV viral load.\textsuperscript{51} Typically, annual HCC incidence rates in patients with HCV cirrhosis range from 1–3\%. Not all studies have shown reduced risk of HCC in patients treated with interferon regimens,\textsuperscript{52} but patients who have sustained virologic responses seem to have low rates of HCC, especially if there is no prior evidence of cirrhosis.\textsuperscript{53} This finding may be relevant going forward as more effective treatments for HCV become widespread. Rates of HCC will likely begin to decline with widespread use of the HBV vaccine, and as the age cohorts affected by the hepatitis C epidemic become a smaller proportion of the population.

Education level has been associated with trends in liver cancer mortality. In the United States, among Whites with less than 12 years of education, liver cancer mortality is increasing 6.49\% annually, compared to only 0.41\% annually among those with more than 16 years of education. Among Black men, the annual increase in incidence among those with less than 12 years of education is 5.19\%, compared to an annual 0.47\% decrease among those with more than 16 years of education. These trends have been attributed to higher levels of alcohol use, obesity, and HBV and HCV among those who are less educated.\textsuperscript{10} Coffee drinking has been associated with not only lower levels of inflammation and fibrosis, but with a lower risk for developing HCC.\textsuperscript{40}

Pancreatic Cancer

Most (95\%) pancreatic cancers are ductal adenocarcinomas. The overall annual incidence of pancreatic cancer is 3.9/100,000 worldwide; among men and women the incidence is 4.4 and 3.3/100,000, respectively. Pancreatic cancer accounts for 2.2\% of all cancer diagnoses and for approximately 266,000 deaths annually, accounting for 3.5\% of all cancer-related mortality worldwide. The cumulative risk of developing pancreatic cancer until age 74 is 0.5\% in men and 0.3\% in women.\textsuperscript{2}
In more developed areas, the incidence per 100,000 population is 8.2 in men and 5.4 in women; in less developed areas, it is 2.7 in men and 2.1 in women. In the United States, the incidence rate exceeds that found in many other developed parts of the world. During 2005–2009, the age-adjusted incidence in the United States was 13.6 and 10.5/100,000 in men and women, respectively. The American Cancer Society estimates that there will be 46,420 new cases of pancreatic cancer and 39,590 deaths from the disease in 2014. Of the new cases, 23,530 will be males and 22,890 females. Despite being only the tenth leading incident cancer among men and ninth among women, because of its poor prognosis, pancreatic cancer is the fourth leading cause of cancer-related deaths among both males and females in the United States, accounting for approximately 7% of all cancer related deaths. The lifetime risk of developing pancreatic cancer is 1.48% in men and 1.45% in women in the United States.

The five-year survival for pancreatic cancer varies by stage. For those with localized disease, the five-year survival is 24%; for those with regional spread it is 9%, and for those with distant metastasis, 2%. At diagnosis, only 9% of cases have localized disease, while 27% have regional spread and 58% have distant metastasis. Five-year overall survival has improved modestly but statistically significantly between 1975–1977 and 2003–2009, from 2% to 6%.

The incidence of pancreatic cancer increases with age. Between 2005 and 2009, among 35–39 year-olds, the incidence per 100,000 in men was 1.2 and in women, 1.0. Among persons older than 85 years, the incidence per 100,000 in men was 100.5 and in women, 87.7. The median age at diagnosis was 71 years.

Incidence and mortality rates also vary by race. During 2005 to 2009, the highest rates were in Blacks, with incidence and mortality rates of 15.2 and 13.8/100,000, respectively. The incidence and mortality rates per 100,000 among other groups were as follows: in Whites, the incidence was 11.7 and the mortality was 10.9; in Hispanics, they were 10.6 and 8.3; in American Indians/Alaska Natives, 9.9 and 8.8; and in Asians/Pacific Islanders, 8.8 and 7.5. Higher rates in African Americans have been associated with long-term diabetes, smoking, and family history of pancreatic cancer in men, and moderate-to-heavy alcohol consumption (more than seven drinks per week) and an elevated body mass index in women. In the
absence of these risk factors, it has been postulated that there would be no Black-White disparity.\textsuperscript{55}

While overall mortality rates from pancreatic cancer increased slightly during the 2000s, the trends were different for Whites and Blacks. From the early 1970s to the mid-1990s, mortality rates decreased in Whites but increased in Blacks. From the mid-1990s to 2009, those trends reversed, with mortality rates increasing in Whites and decreasing in Blacks. The reasons for the trends are unknown and not readily explained by any known risk factors.\textsuperscript{56} From 2000 to 2009, there was a 0.5\% annual increase in mortality in white men and women; in Asian/Pacific Islander men, there was an increase of 1.0\% per year, while among other race groups, there was no change in mortality. The incidence of pancreatic cancer increased 0.7\% annually in men and 1.1\% in women.\textsuperscript{54,57}

Education level has been associated with recent trends in pancreatic cancer, and increases in mortality rates have been limited to those with less education, while rates among persons with more than 16 years of education have not increased since the 1990s. An analysis of SEER data from 1993 to 2007 revealed that among white men aged 25 to 64 years, there was an average increase in mortality from pancreatic cancer of 1.43\% per year, compared to a decrease of 0.4\% among those with more than 16 years of education. Among white women, those with less than 12 years of education had a 1.57\% increase in mortality from pancreatic cancer per year, compared to an annual decrease of 0.69\% among those with more than 16 years of education. These trends may be related to differences in obesity, smoking and other risk factors.\textsuperscript{10}

Certain groups of patients are at higher risk of developing pancreatic cancer, including those with chronic pancreatitis. A large, multinational study involving five countries in Europe plus the United States found a standardized incidence ratio of developing pancreatic cancer (ratio of observed to expected cases) of 26.3 in patients with chronic pancreatitis. In patients who were followed for 10 years, the cumulative risk of pancreatic cancer was 1.8\%, and in those followed for 20 years, 4.0\%. The increased risk was found in both men and women, patients with non-alcoholic and alcoholic pancreatitis, and in all six countries in the study.\textsuperscript{58} However, the population attributable fraction from chronic pancreatitis was estimated at a modest 1.34\%, suggesting that curtailing chronic pancreatitis
prevalence would do little to reduce the overall incidence of pancreatic cancer.59

Hereditry appears to play a role in the risk of developing pancreatic cancer. Patients with autosomal dominant hereditary pancreatitis, which is associated with mutations in the \textit{HRSS1} gene, are at up to an 87-fold higher risk for pancreatic cancer. A French study found cumulative risks of pancreatic cancer in these patients at ages 50 and 75 years of 11% and 49% in men and 8% and 55% in women, respectively. Between 4 and 16% of patients with pancreatic cancer have a family member who was also afflicted with this disease.60 There is higher risk among relatives of an individual with pancreatic cancer, whether the pancreatic cancer case was considered sporadic or familial. Pancreatic cancer patients with a family history of the disease tend to develop the cancer at a younger age. Persons with a family history of pancreatic cancer have, on average, twice the risk of developing pancreatic cancer as those without a family history; in those with a first-degree relative with the disease, the risk is 7–9 times higher.54 There also appears to be an increased age-related risk in having a family member who was diagnosed before age 50 in cases of familial pancreatic cancer, but not in sporadic pancreatic cancer.61

Specific gene mutations have been recognized as conferring higher risk for pancreatic cancer. Overall, these mutations are rare and account for 5 to 10% of pancreatic cancer cases. \textit{BRCA2} mutations are thought to account for 6 to 19% of familial pancreatic cancer cases. It has been suggested that \textit{BRCA2} should be included in genetic testing of patients with more than one first-degree relative with pancreatic cancer. Having the \textit{BRCA2} mutation is associated with a 3- to 10-fold increase in pancreatic cancer risk.54,62,63 Patients with the Familial Atypical Multiple Mole-Melanoma syndrome are at a higher risk of pancreatic cancer. This syndrome is associated with the \textit{CDKN2A} gene, also called the \textit{multiple tumor suppressor-1} gene. These patients have a 13- to 22-fold higher pancreatic cancer risk.54 Patients with Peutz-Jeghers syndrome have up to a 132-fold relative risk of developing cancer and a cumulative risk of 36% of developing pancreatic cancer by the age of 64 years.64 Patients with hereditary nonpolyposis colorectal cancer (Lynch syndrome) have a cumulative risk of 3.68% of developing pancreatic cancer by the age of
70 years and an 8.6-fold higher risk relative to those without Lynch syndrome. Patients with familial adenomatous polyposis may also be at higher risk for pancreatic cancer, although this is not as well-defined.

**Colorectal Cancer**

Most colorectal cancers are adenocarcinomas. There were an estimated 1,233,000 new cases of colorectal cancer in 2008 worldwide, accounting for 9.7% of all cancer diagnoses. It is the third most common cancer in men and second in women. In 2008 the incidence per 100,000 population was 17.3 overall, 20.4 in men, and 14.6 in women. The cumulative risk of developing colorectal cancer to age 74 years is 2.0% overall, 2.3% in men, and 1.6% in women.

In 2008, there were approximately 608,000 deaths worldwide related to colorectal cancer, accounting for 8.0% of all cancer-related deaths. The mortality per 100,000 population in 2008 was 8.2 overall, 9.7 in men, and 7.0 in women. The cumulative risk of dying from colorectal cancer to age 74 years is 0.9% overall, 1.1% in men, and 0.7% in women.

Colorectal cancer is more common in developed countries: in more developed areas of the world, the incidence per 100,000 is 37.6 in men and 24.2 in women, and in less developed areas, it is 12.1 in men and 9.4 in women. The cumulative risk to age 74 years of developing colorectal cancer in developed areas is 4.4% in men and 2.7% in women, and in less developed areas, 1.4% in men and 1.1% in women. The highest incidence rates are in Australia, New Zealand, Europe and North America, and in Africa, South-central Asia, and Central America. There is less variation in rectal cancer across different regions of the world. Most of the differences in colorectal cancer incidence are due to colon cancer, excluding rectal cancers. Higher ratios of colon-to-rectal cancer are seen in areas with higher incidence rates of colorectal cancer, such as in the United States.

Incidence trends vary as well. Rates have declined in the United States, while in Eastern Europe, Spain, Italy, and parts of the United Kingdom, as well as China, Japan, India, rates increased from the early 1990s to the early 2000s. These differences are thought to be related to economic development and “Westernization” in Asia and parts of Europe, which have led to changes in diet and, possibly, smoking and physical activity.
Colorectal cancer screening in countries such as the United States, Canada, and New Zealand may also contribute to these differences, since screening practices can reduce colorectal cancer incidence rates by removing precancerous polyps.66

Colorectal cancer claims many more lives in developed countries than in less developed countries: the mortality per 100,000 population in more developed areas is 15.1 in men and 9.7 in women, and in less developed areas, it is 6.9 in men and 5.4 in women. The cumulative risk to age 74 years of dying from colorectal cancer in developed areas is 1.7% in men and 1.0% in women, and in less developed areas, 0.8% in men and 0.6% in women.1

In the United States, colorectal cancer is the second most common type of cancer overall, third among women and third among men.59 The American Cancer Society estimates there will be 96,830 new cases of colon cancer and 40,000 of rectal cancer diagnosed in 2014. Almost equal numbers of incident colon cancer cases are predicted for men and women, but for rectal cancers, 23,380 are predicted in men and 16,620 in women. Colorectal cancer will account for 8% of the total cancer diagnoses in men and women. There will be an estimated 50,310 deaths from colorectal cancer in 2014, 26,270 in men and 24,040 in women, accounting for 8% of total cancer related deaths in men and 9% in women. Among men ages 40–59 and 60–79, colorectal cancer is the second most common type of cancer in the United States after lung cancer.4

Geographically, there is some variation within the United States. In general, the highest incidence is seen in southeastern states. The highest incidence of colorectal cancer is in Kentucky, where the incidence per 100,000 population is 63.9 in men and 46.0 in women, and the lowest is in Utah, where it is 39.4 in men and 31.2 in women. Among men, the mortality rate per 100,000 population is highest in Mississippi at 24.8 and lowest in Utah at 14.3. Among women, the highest mortality is in the District of Columbia at 18.9/100,000, and the lowest is in Utah at 10.7/100,000.4

The cumulative lifetime risk of developing colorectal cancer in the United States is 1 in 20 in men and 1 in 22 in women. The cumulative risk prior to age 50 years, when screening for cancer and precancerous polyps typically begins in average risk individuals, is 1 in 305 in men and 1 in 334 in women.4
There are racial disparities in the incidence and mortality of colorectal cancer within the United States. The highest incidence and mortality rates are among African Americans and the lowest is among Asian Americans. Per 100,000 population, the respective incidence rates for male and female Whites are 50.9 and 38.6; for Blacks, 62.5 and 46.7; for Asians/Pacific Islanders, 40.8 and 31.0; for American Indians/Alaska Natives, 51.7 and 42.7; and for Hispanics, 47.3 and 32.6. Mortality rates also reflect these disparities. Per 100,000, the respective mortality rates for male and female Whites are 19.2 and 13.6; for Blacks, 28.7 and 19.0; for Asians/Pacific Islanders, 13.1 and 9.7; for American Indians/Alaska Natives, 18.7 and 15.4; and for Hispanics, 16.1 and 10.2. Some of the racial disparities are thought to be related to access to colonoscopy for screening.

Colorectal cancer survival rates in the United States vary widely by the stage at diagnosis. The five-year survival rate is 90% for those diagnosed with localized cancers, 70% for those with regional nodal spread, and 13% for those with distant metastasis. Fortunately, a minority of cases of colorectal cancer has distant metastasis at diagnosis. From 2003 to 2009, 40% of cases had localized disease, 38% had regional nodal spread, and 23% had distant metastasis at diagnosis. Overall, there has been an increase in five-year survival since the 1970s. In SEER data from 1975 to 1977, the five-year survival rate was 51%; from 1987 to 1989, it was 60%; and from 2003 to 2009, 65%. The most recent five-year survival rates were 67% in Caucasians and 56% in African Americans.

In the United States, colorectal cancer incidence rates increased from the 1950s to the 1980s but have been declining over the last several decades. Between 2001 and 2010, the incidence decreased annually by an average of 3.0% in men and 2.6% in women, between 2006 and 2010, it decreased by an average of 3.6% in men and 3.3% women, and from 2008 to 2010, 4.7% in both men and women.

Although colorectal cancer incidence is decreasing among all races and ethnicities, there are racial disparities in this trend. From 2001 to 2010, among White men the average decline in incidence was 4.0% per year; among Black men, 2.0%; among Asians/Pacific Islander men, 2.0%; among American Indian/Alaska Native men, 1.4%; and among Hispanic men, 2.9%. Trends in women were similar, although the disparity between Whites and Blacks was not as pronounced. The average
annual decrease in incidence among women was 3.3% in Whites, 2.9% in Blacks, 2.2% in Asians/Pacific Islanders, 1.3% in American Indians/Alaska Natives, and 2.8% in Hispanics.\textsuperscript{57}

Colorectal cancer mortality rates have also continued to decline. In men, from 1990 to 2002, the mortality rate declined by an average of 2.0% per year. From 2001 to 2010, the mortality rate declined even more rapidly at an average of 2.9% per year. Between 1984 and 2001, mortality rates in women declined by an average of 1.8% per year, and from 2001 to 2010, 2.9% per year. Mortality rates have declined in all races and ethnicities except among American Indian/Alaska Native women, in whom the mortality rates increased by an average of 0.4% per year from 2001 to 2010.\textsuperscript{57} Declines in mortality and incidence have been attributed in part to colorectal cancer screening efforts, leading to both earlier diagnosis of cancers and removal of precancerous polyps. Polypectomy has been shown to reduce the development of colon cancer. Advances in treatment have also led to increases in mortality.\textsuperscript{67}

Education and socioeconomic status are inversely associated with colorectal cancer incidence in the United States. In a large prospective cohort study of over 500,000 persons from various parts of the country, there was a significantly higher proportion of cancers of the right colon among study participants with postgraduate education than in those with less than 12 years of education. This relatively higher rate of cancers of the proximal colon was also seen in persons who live in neighborhoods in the top quintile of socioeconomic status relative to those in the bottom quintile. This study also found a 42% higher risk of colorectal cancer in those with less than 12 years of education compared to those with postgraduate education. Those in the bottom quintile in socioeconomic status had a 31% higher risk of colorectal cancer compared to those in the top quintile.\textsuperscript{68} Much of the higher risk among people with less education and lower socioeconomic status was estimated to be related to lifestyle factors. Eating a poor diet, which was defined as a diet least similar to a Mediterranean diet, was associated with a 91% higher risk of colorectal cancer. Physical inactivity, compared to daily activity, was associated with a 44% higher risk. Body mass index (BMI) of 34 kg/m\textsuperscript{2} relative to less than 20 kg/m\textsuperscript{2} was associated with a 55% higher risk. Together, diet, physical activity level, smoking status, and BMI accounted for 43.9% of the estimated higher incidence
of colorectal cancer in those with less education and 36.2% of the disparity based on socioeconomic status. Right-sided cancers were more frequently related to these lifestyle factors than were left-sided and rectal cancers. Some of the socioeconomic differences in incidence may also be related to access to colorectal cancer screening.\(^69,70\)

There has been a relative increase in the number of right-sided colorectal cancers compared to the numbers of left colon and rectal cancers over the second half of the 20\(^{th}\) century, both in the United States and internationally.\(^71,72\) However, an analysis of SEER data from 1992 to 2008 revealed a slight increase in right-sided colon cancer rates in men until 1999, and then a decline in the incidence by an average of 2.6% per year. In women, the incidence of right-sided cancers was increasing slightly until 2000, and since then, it has annually decreased by an average of 2.3%. For late-stage right-sided tumors, the incidence rates from 2000–2008 annually declined 3.9% in men and 3.3% in women. Over this time period left-sided tumors also annually declined, 3.5% in men and 2.9% in women.\(^73\)

There is some thought that this reversal in the trend of right-sided tumor incidence may be related to colonoscopy utilization. Colonoscopy use increased very gradually through the 1990s, and by 2000 the utilization rate was 20%. By 2008, largely due to Medicare coverage for screening colonoscopy, the utilization rate was 48%.\(^73\)

Right-sided tumors are more common in women than in men; in an analysis of SEER data, they accounted for 47% of colorectal tumors in women and for 37% in men.\(^73\)

**Small Bowel Tumors**

Most tumors of the small intestine are adenocarcinomas, carcinoids, lymphomas, and sarcomas, the latter of which are typically gastrointestinal stromal tumors (GISTs). In contrast to that for colon cancer, the incidence of small bowel cancer may be increasing. Despite accounting for 75% of the length of the gastrointestinal tract, small bowel tumors account for only 5% of gastrointestinal tract tumors.\(^74\)

Worldwide incidence rates vary by region and are most common in the United States and Western Europe and least common in Asia. The incidence per 100,000 is typically reported to be near 2 in North America,
The Descriptive Epidemiology of Gastrointestinal Malignancies

where the highest incidence rates are seen, and less than 1 in China and India. Small bowel cancers tend to be more common in areas where colon cancer incidence is higher, but there is no correlation between small bowel and stomach cancer rates. In France, small bowel cancer incidence per 100,000 was estimated to be 1.2 in men and 0.8 in women.  

In the United States, the American Cancer estimates there will be 9,160 new cases of small intestinal cancer in 2014, with 4,880 in men and 4,280 in women. The estimated number of deaths from small bowel cancers in 2014 is 1,210, 640 of which are in men and 570 in women. The SEER program of the National Cancer Institute estimates that there were 2.1 cases per 100,000 individuals in the US in 2013, and 0.4 deaths from small bowel cancer per 100,000 individuals from 2006–2010. The incidence per 100,000 population is 2.5 in men and 1.7 in women. The estimated cumulative lifetime risk of developing small bowel cancer in the United States is 0.2%. Small bowel tumors are the 24th most common cancer in the United States, accounting for 0.5% of all cancers and 0.2% of all cancer related deaths. The median age at diagnosis is 66 years. The overall five-year survival rate with malignancies of the small intestine was 64.5% from 2003–2009.  

Incidence varies by race in the United States, with the highest rates in African Americans and the lowest in Asians/Pacific Islanders, Hispanics, and American Indians/Alaska Natives. From 2006 to 2010, the incidence per 100,000 among African Americans was 3.9 in men and 2.8 in women, compared to 2.5 and 1.7 among male and female Whites, respectively. Rates among other populations were lower. Among men, the rates per 100,000 population were 1.6 in American Indians/Alaska Natives, 1.5 in Hispanics, and 1.2 in Asians/Pacific Islanders. Among women, the incidence per 100,000 was not reported for American Indians/Pacific Islanders because there were so few cases. In Hispanic women, the rate was 1.4, and in Asian/Pacific Islander women, it was 0.9 per 100,000. The higher incidence among African Americans reflects higher rates of carcinomas and carcinoids, while Caucasians have a higher rate of small bowel lymphomas than do African Americans. The incidence of sarcomas is approximately the same in the two racial groups. The incidence differences are likely related to both environmental and genetic factors.  

The incidence of small bowel cancer is increasing in the United States. According to one estimate, in 1975 the incidence per 100,000 population
was 1.1, whereas in 2010 it was 2.4. On average, the incidence rate has increased by 2.4% per year over the last ten years. Most of the increase has been in carcinomas, carcinoids, and lymphomas, whereas the increases in sarcomas have been more modest. The fastest rate of increases has been among African American men. Despite the increasing incidence, the number of deaths from small bowel cancer declined by 1.0% per year over the same time period. The five-year relative survival for those diagnosed with small bowel cancer increased from 32.8% in 1975 to 66.2% in 2005. Other analyses have indicated that while small bowel carcinoids may have increased four-fold over the last several decades, increases in rates of other small bowel tumors were less pronounced.

Survival with small bowel cancer varies by stage. The five-year relative survival of those with localized cases is 81.2% compared to 69.5% of those with regional nodal spread and 42.1% in those with distant metastasis. There are relatively similar numbers of localized, regional and distant cancers diagnosed. SEER estimates that 31% of cases have localized cancers, 36% have regional nodal spread, and 27% have distant metastasis, with the remainder being unstaged.

The incidence of subtypes of small bowel tumors per 100,000 population were 0.59 for carcinomas, 0.55 for carcinoids, 0.3 for lymphomas, and 0.17 for sarcomas.

Adenocarcinomas, carcinoids, lymphomas, and sarcomas each have a proclivity to certain parts of the small bowel. In general, adenocarcinomas occur most frequently in the duodenum and become less common moving distally through the small bowel. The opposite pattern is seen for carcinoids and lymphomas, which are much more common in the ileum than in the jejunum or duodenum. A Canadian study reported that 54.7% of small bowel adenocarcinomas occurred in the duodenum, 29.9% in the jejunum, and 18% in the ileum; 3.9% of small bowel carcinoids occurred in the duodenum, 9.2% in the jejunum, and 86.7% in the ileum; 49.5% of lymphomas were in the ileum, 29.4% in the jejunum, and 21% in the ileum; and the highest frequency (46.7%) of small bowel sarcomas occurred in the jejunum. In the United States, an analysis of SEER data revealed similar findings: 49% of carcinomas were found in the duodenum; 52% of carcinoids were in the ileum; lymphoma incidence increased moving distally, with approximately three times as many cases in the ileum than in the duodenum; and the incidence of sarcomas was similar throughout the small bowel.
Patients with small bowel cancer are at higher risk for cancers of the colon, rectum, pancreas, ampulla, and genitourinary system. This risk is most marked among patients with carcinoma of the small bowel, which is associated with an additional 68% higher risk for a second primary malignancy. Patients with Familial Adenomatous Polyposis, Hereditary Nonpolyposis Colorectal Cancer, and Peutz-Jeghers syndrome are at higher risk for both small and large bowel cancers. In general, patients with colon cancer are also at higher risk of small bowel cancer. It is speculated that this overlap in risk may be related to common genetic factors, including those related to DNA mismatch repair deficiencies, and environmental factors including diet.

Gastrointestinal Lymphomas

The gastrointestinal (GI) tract is the most common extranodal site for Non-Hodgkin’s lymphoma (NHL), while Hodgkin’s lymphoma (HL) is extremely rare in the gastrointestinal tract. The GI tract is a common secondary location for lymphoma. From GLOBOCAN data, it was estimated that there were 355,000 new cases of NHL worldwide in 2008 with an incidence of 5.1/100,000. The American Cancer Society estimates that in the US, there will be 70,800 cases of NHL in 2014.

Typically, lymphomas of the GI tract arise from the mucosa-associated lymphoid tissue of the GI tract (MALT) and are referred to as MALT lymphomas. Most are B-cell lymphomas, and most of these arise from the marginal zone B cells and therefore are classified as extranodal marginal zone B-cell lymphomas. T-cell lymphomas are rare but are seen in patients with celiac disease. Most GI lymphomas in developed countries arise from the stomach, whereas in the Middle East the small intestine is the predominant site.

A population-based study from a cancer registry in France revealed an age-standardized incidence rate of GI lymphomas per 100,000 population of 0.94 in men and 0.54 in women (a 1.74 male:female incidence ratio). The mean age of diagnosis was 63 years. Gastrointestinal lymphomas accounted for 15.7% of all NHL diagnoses and 59% of extranodal NHL cases. Lymphomas accounted for 1.7% of all digestive tract malignancies overall, and for 6.5% of those in patients younger than 45 years.
In the same study, the stomach was the most common site for gastrointestinal lymphomas, accounting for 54% of all cases, followed by the small bowel (17%), colon (15%), rectum (12%), and mesentery (3%). Many studies, however, estimate the incidence of gastric lymphomas to be relatively higher and the incidence of colon lymphomas to be relatively lower, closer to 3% of GI lymphomas. Lymphomas accounted for 3.7% of all gastric, 18.8% of small bowel, 0.6% of colon, 0.7% of rectal, and 9.5% of mesenteric or peritoneal malignancies. Approximately half of the cases were low-grade and half were high-grade lymphomas. Overall five-year survival was 34%, and was higher for gastric and rectal lymphomas than for small bowel and colon lymphomas.

Studies from Germany and Greece found relatively similar epidemiologic patterns. Approximately 16% of NHL cases were gastrointestinal. In these studies, 68 to 75% of gastrointestinal lymphomas occurred in the stomach. Up to 20% involved multiple sites in the gastrointestinal tract. Most cases, up to 90%, were stage I or II. Small intestinal lymphoma cases and cases with multiple gastrointestinal sites had the poorest survival rates.

Gastric lymphoma is the most common primary GI lymphoma in developed countries. There is a strong direct association between H. pylori prevalence and gastric lymphoma incidence. The incidence of GI lymphoma in H. pylori infected individuals ranges from 1/30,000 to 1/80,000. Some evidence suggests that H. pylori may be associated with higher risk for small bowel lymphomas. Other than those with H. pylori, populations potentially at risk for GI lymphomas include patients with celiac or inflammatory bowel disease (IBD), although the data are not entirely consistent. Although initial studies suggested that there may be higher risk for GI lymphomas among patients with IBD, most subsequent large population studies suggested that they may not be at higher risk. The initial findings may have been due to referral bias.

Gastrointestinal Stromal Tumors (GISTs)

Gastrointestinal Stromal Tumors (GISTs) arise from submucosal tissue in the GI tract. The incidence of GISTs has been poorly elucidated because
these tumors were not well-defined molecularly until around 2000, so the incidence rates derived from large data sets prior to 2000 are problematic. One study that used SEER data from 1992 to 2000 indicated that the incidence per 100,000 population was 0.74 overall, 0.86 in men, 0.66 in women, 1.24 in Blacks, and 0.64 in Whites. At diagnosis, 53% of cases had localized disease, 19% had regional nodal spread, and 23% had distant metastasis. The five-year survival rates were 64% for patients with localized tumors and 13% for those with distant metastasis.86

Other, newer studies with more reliable data on GISTs estimated higher incidences for the tumors. The incidence in Sweden was estimated to be 1.45/100,000 from 1983 to 2000,87 in Iceland it was estimated to be 1.1/100,000,88 and in Taiwan, 1.37/100,000.89 The incidence of small GISTs in autopsy studies and analyses of whole stomachs was over 22%, primarily in the proximal stomach. The clinical significance of this is unknown.90 The mean age at diagnosis for GISTs is around 60–65 years, and only 1% of cases are in persons less than 21 years of age.91

GISTs may be seen throughout the GI tract. Most, typically 60–70%, are found in the stomach, followed by 20–30% in the small intestine, 5% in the colon and rectum, and less than 5% in the esophagus.92 From SEER data, the most common site for a GIST was found to be the stomach (51% of cases), followed by the small intestine (36%), the colon (7%), the rectum (5%), and the esophagus (1%).86

Neuroendocrine Tumors

Neuroendocrine tumors, which arise from cells of the neuroendocrine system, include those of the gastrointestinal tract, or carcinoid tumors, and the pancreas.

Gastrointestinal tract neuroendocrine tumors (carcinoid tumors)

Carcinoid tumors may arise anywhere within the gastrointestinal (GI) tract. They were originally termed carcinoid because they were noted to behave differently from gastrointestinal tract adenocarcinomas. It is thought that the incidence of these tumors may be increasing.93
A recent analysis of SEER data on GI carcinoid tumors found the average incidence of GI carcinoid in the United States from 2000 to 2009 to be 2.6/100,000, with the highest incidence among Blacks at 4.6/100,000. The incidence in men and women was found to be approximately equal, the mean age at diagnosis was 60 years, and 38% of tumors were in the small bowel and 34% in the rectum. The incidence from 1973 to 2009 increased 4.4% annually, faster than any other tumor type examined except esophageal adenocarcinoma. The increases in incidence were similar in men and women and among different races and ethnicities. Carcinoid tumors of the stomach increased 7.0% per year, those of the rectum increased 7.8% per year, and those of the appendix decreased 3.6% per year. GI carcinoid accounts for 0.52% of all cancers diagnosed and 71% of all carcinoids, with most of the remainder being diagnosed in the lungs. Patients with carcinoid have substantially higher risk for developing a second primary malignancy, especially in the stomach or small bowel.

Patients with GI carcinoid tumors have better survival rates than those with most other GI tumors. Using SEER data, the 5-, 10-, and 20-year disease specific survival rates for those with carcinoid were found to be 91%, 86%, and 77%, respectively. Most patients with GI carcinoid died from causes not related to their carcinoid, mainly cardiovascular causes. Those with tumors in the small bowel had a lower survival rates than did those with tumors located in other parts of the GI tract. Survival rates for localized carcinoids were 95.6%; for regional tumors, 86.5%; and for tumors with distant metastasis, 52.4%.

The reasons that GI carcinoids are increasing rapidly are debated. Some suggest that the increasing use of endoscopy, especially colonoscopy, may lead to more of these tumors being identified. However, this does not explain the rise in incidence in the small bowel.

Although the incidence is increasing, the survival rates have not improved. Given the increasing incidence and lack of improvement in treatment, the National Institutes of Health placed neuroendocrine tumors and carcinoids as the second priority for funding after autism.

**Neuroendocrine tumors of the pancreas**

Pancreatic neuroendocrine tumors (NETs), also referred to as islet cell tumors, include insulinomas, gastrinomas, glucagonomas, VIPomas,
somatostatinomas, and others. According to SEER, they account for 1.3–3% of pancreatic tumors and have a better prognosis than do adenocarcinomas of the pancreas (median survival of 27 months vs. 4 months).96,97 The most common types of pancreatic NETs are insulinomas and glucagonomas, which occur at similar rates of around 0.05–0.3 cases per 100,000, followed by VIPomas which are eight times less common, and glucagonomas, which are 17 times less common. Somatostatinomas and other pancreatic NETs are even less common.9

An analysis of SEER data from 1973 to 2003 revealed that the incidence of pancreatic endocrine tumors decreased from 0.16–0.12/100,000. Many cases are diagnosed at an advanced stage. Among the staged cases in SEER, 14% had localized disease, 23% had regional nodal spread, and 54% had distant metastasis. The median survival was 124 months for those with localized disease, 70 months for those with regional spread, and 23 months for those with distant metastasis. The incidence was similar in Whites and Blacks and in women and men. Those with NETs of the pancreatic head were less likely to have distant metastasis (48%) compared to those with tumors of the pancreatic body (57%) or tail (58%), but this was not associated with longer survival. Increasing age is associated with a worse prognosis. Over time, the overall survival from pancreatic NETs has improved.97

**Anal Cancer**

Cancers of the anus are rare but increasing in frequency. From SEER data, it was estimated that in the United States there were 7,060 new cases in 2013, accounting for 0.4% of all new malignancies. The American Cancer Society estimates there will be 7,210 new cases in 2014 with 2,660 being men and 4,550 women. The estimated number of deaths from anal cancer in 2013 was 880. The incidence rate from 2006 to 2010 was estimated to be 1.7/100,000 with 0.2 deaths per 100,000 population per year. The lifetime cumulative risk of developing anal cancer is 0.2%.4,15 Among anal cancers, 80% are squamous cell carcinomas, 16% are adenocarcinomas, and 4% are other types.9

An analysis of SEER data indicates that the incidence of squamous cell carcinoma of the anus is increasing. The incidence per 100,000 from 1973 to 1996 was 1.0 in men and 1.4 in women, compared to 3.0 in men and
2.4 in women between 1997 and 2009. From 1997 to 2009, the annual average increase in incidence was 9.3% in men and 4.8% in women. Increases were seen in Whites and Blacks and across all age groups.98

Anal squamous cell carcinoma is linked to the human papilloma virus (HPV), and populations with a higher HPV prevalence are at higher risk for developing anal cancer.99 HPV prevalence estimates range from 10 to 55% and varies by the population studied.98

Men who have sex with men (MSM) have higher risk for anal cancer.100 AIDS is associated with higher risk for anal cancer, and it is estimated that the risk may be twice as high in MSM with AIDS as in MSM without AIDS.101 In one study, other risk factors for anal cancer included receptive intercourse, especially among men for whom there was an estimated 33-fold higher risk (in women, it was estimated to be 1.8-fold higher, a finding that was also statistically insignificant). Among heterosexual men, a history of gonorrhea was associated with a 17-fold higher risk of anal cancer, being seropositive for Herpes simplex virus type 2 with a 4.1-fold higher risk, and Chlamydia with a 2.3-fold higher risk. Cigarette smoking was also found to be statistically significantly directly associated with risk.102

**Take Home Messages**

- Gastrointestinal malignancies account for approximately one-third of all cancers and almost 40% of cancer-related mortality worldwide.
- The most common malignancies of the gastrointestinal system include colorectal, gastric, liver, esophageal, and pancreatic cancers.
- Incidence and mortality rates are constantly evolving as risk factors change, populations move, and prevention efforts expand.

**References**


The Descriptive Epidemiology of Gastrointestinal Malignancies

The Descriptive Epidemiology of Gastrointestinal Malignancies


The Descriptive Epidemiology of Gastrointestinal Malignancies


