Abstract. – Colorectal cancer (CRC) is a worldwide problem, with an annual incidence of 1 million cases and an annual mortality of more than 500,000 cases. CRC is the second most common cause of cancer mortality. CRC comprises 9% of the global cancer burden and is the most frequent in North America, Australia, New Zealand and parts of Europe, being considered as a disease of the Western lifestyle.

Despite a major decline in incidence and mortality, gastric cancer remains an important public health burden worldwide, especially in developing countries. Gastric cancer is still the fourth most common cancer and the second-third most common cause of cancer death. There is a 10-fold variation in incidence between populations at the highest and lowest risk. The incidence is particularly high in East Asia, Eastern Europe, and parts of Central and South America.

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of cancer-related death. Regional incidence rates are highest in areas of Southern and Eastern Africa and China. A striking increase in the rates of esophageal adenocarcinoma, in contrast, stable or even decreased trends in squamous cell cancer have been observed.

Pancratic cancer ranks the fourth and fifth most common cancer in man and women, respectively, and has the lowest 5-year survival rate of any gastrointestinal tumors.

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third most common cause of cancer mortality.

Key Words: Epidemiology, Colorectal cancer, Gastric cancer, Esophageal cancer, Pancreatic cancer, Hepatocellular carcinoma.

Introduction

Cancer is a major public health problem in the United States and many other parts of the world, including Europe. Currently, one in four deaths is due to cancer. Cancer accounts for about 25% of all death, ranking second only to ischemic heart disease. Cancer is one of the 5 leading causes of death in all age groups among both males and females. Cancer is the leading cause of death among women aged 40 to 79 years and among men aged 60 to 79 years. Cancer incidence rates in the US for all cancer sites combined increased from the mid-1970s through 1992 and decreased from 1992 through 1995. Observed incidence rates for all cancers combined were essentially stable from 1995 through 2000. A total of 1,500,000 new cancer cases and more than 500,000 deaths from cancer are projected to occur in the US in 2009. With an estimated 3.2 million new cases (53% occurring in men, 47% in women) and 1.7 million deaths (56% in men, 44% in women) each year, cancer remains an important public health problem in Europe and the ageing of the European population will cause these numbers to continue to increase even if age-specific rates remain constant.

Overall cancer incidence rates in the USA and Europe decreased in the most recent time period in both men and women, largely because of decreases in the three major cancer sites in men (lung, prostate, and colorectum) and in two major cancer sites in women (breast and colorectum). Although significant progress has been made in reducing incidence and mortality rates by improving survival, cancer still accounts for more death than heart disease in persons younger than 85 years of age.

In Hungary, mortality caused by malignant tumors represents the second cause of death. Statistics on disability has revealed that during the past 25 years the number of patients become invalid because of cancer has nearly doubled. In comparative international statistics cancer mortality and incidence of the Hungarian male population take the first and that of female population the second place. However, it is a promising sign that the first time over the past 25 years cancer mortality
decreased in year 2000 and during the last 10 years cancer mortality rates for all cancers combined in Hungary were essentially stable.11-14. Cancers of the lung, prostate and colorectum in man and cancers of the lung, breast and colorectum in women continue to be the most common fatal cancers in the US and Europe. These cancers account for half of the total cancer deaths among men and women. Gastrointestinal (GI) cancers account for 20% of estimated new cancer cases and 15% of estimated death worldwide.4-16.

We review the most important epidemiological data of major GI tumors and hepatocellular carcinoma.

**Colorectal Cancer**

Colorectal cancer (CRC) is the fourth commonest form of cancer occurring worldwide. CRC is an important public health problem: there are nearly one million new cases of CRC diagnosed worldwide each year and half a million deaths. CRC is the second most common cause of cancer mortality. CRC comprises 9% of the global cancer burden. CRC, however, is not equally common throughout the world. If the westernized countries (North America; those in northern, southern, western and central Europe; Australia and New Zealand) are combined, CRC represents 12.6% of all incident cancer in westernized countries in man and 14.1% in women. Elsewhere CRC represents 7.7% and 7.9% of all incident cases in men and women, respectively. Over one-third (36%) of new cases of CRC occur outside industrialised countries: therefore, the standard myth of CRC being a disease restricted to western countries needs to be dispelled.17,18. In Hungary, CRC represents a serious public health problem with an annual incidence of 9,000 new cases and an annual mortality of 5,000 cases.11,12.

The incidence of CRC increases with increasing age, with the highest incidence among those aged 80 years and over. In the US, CRC is the most frequent form of cancer among persons aged 75 and older. Incidence rates are greater among men compared with women and among blacks compared with whites and other races.4,19,20. African-Americans have the highest rate of CRC incidence and mortality in the US. The recent increasing number of advanced and right-sided tumors has great importance in developing CRC prevention and treatment strategies for this population.21. It has been recently demonstrated that in sharp contrast to the overall declining rates of CRC in the US, incidence rates among adults younger than 50 years are increasing due to an increase in left-sided tumors, particularly in the rectum.22. Further studies are necessary to elucidate causes for this trend and identify potential prevention and early detection strategies.23.

Large differences exist in survival, according to the stage of disease. Approximately 50% of CRC cases are diagnosed at regional or distant stage. Substantial differences in the trends in CRC incidence and survival seem to exist between United Kingdom, Europe as a whole, and the US. In the United Kingdom, incidence has increased only slightly since 1971, whereas by the end of the 1990s, mortality had decreased by approximately 50% since 1950. This is consistent with 5-year survival rates improving from just over 20% in the early 1970s to almost 45% in the mid-1990s. Elsewhere in Europe, there have been generally greater declines in mortality in women than in men. Mortality has been falling recently in most EU countries, but is rising in Greece, Portugal and Spain.2,5,7,8. This variation in survival is not easily explained but could be related to stage of disease at presentation, or availability of more efficient treatment regimens and screening practices. The decrease in incidence of CRC and the improvement in mortality of CRC in the US have been largely attributed to an increase in CRC screening, particularly colonoscopy, among individuals ages 50 years and older. Screening for CRC can reduce incidence by preventing cancer occurrence through the detection and removal of precancerous polyps.24-28. It has been demonstrated that CRC screening is a cost-effective strategy not only in the US but also in Europe.29-33.

Despite widely published recommendations for screening programs compliance remains poor. As screening both average-risk and high-risk populations for CRC has its logistic and financial limitations, the addition of chemoprevention might be crucial in reducing the incidence of CRC.14. CRCs are thought to arise as the result of a series of molecular, biochemical and histopathologic changes that transform normal colonic epithelial cells into a neoplasm, with an adenomatous polyp as an intermediate step in this process.35,36. The main risk factors for CRC include diets low in vegetables and potentially, those high in processed meat and fat; excess body weight, lack of exercise, possibly drinking excess alcohol, smoking, and in-
herited factors such Familial Adenomatous Polyposis (FAP), Hereditary Non-Polyposis Colorectal Cancer (HNPCC), “cancer family” syndrome, and finally inflammatory bowel disease (IBD) (Table I). Primary prevention strategies seek to prevent the formation of CRC in an otherwise healthy population. These individuals may have not only predisposing genetic or environmental features, but also certain lifestyle risk factors may be present such as lack of physical exercise, smoking or alcohol intake. How individuals can reduce their risk of CRC is summarized in Table II. Secondary prevention involves the patient populations who have a known premalignant lesions and prevention of the progression of these precancerous lesions into CRC. Finally, tertiary prevention focuses on the prophylaxis of secondary primary tumors in patients cured of their initial CRC. Chemoprevention refers to use of synthetic or naturally occurring compounds to prevent the development of precancerous lesions (i.e., adenomatous polyps) or to reverse or delay their progression to invasive cancers. Chemoprevention includes dietary or pharmacologic interventions as well as the use of nutrients to suppress or reverse the carcinogenic process. The best candidates for chemoprevention include those individuals at high risk for development of CRC, such as those with previous history of colorectal adenomas or carcinomas, and those with familial adenomatous polyposis (FAP)27,38. The proposed mechanisms of action of most important potential chemopreventive agents are shown in Table III. It is important to note that chemoprevention cannot yet be accepted as standard medical practice. Use of chemopreventive agents cannot substitute for CRC screening and surveillance38.

**Table I.** Risk factors for colorectal cancer.

- Diets low in vegetables and potentially, those high in processed meat and fat
- Excess body weight
- Lack of exercise
- Smoking
- Drinking excess alcohol
- Inherited factors:
  - Familial Adenomatous Polyposis (FAP)
  - Hereditary Non-Polyposis Colorectal Cancer (HNPPC)
- “Cancer family” syndrome
- Inflammatory bowel disease

**Table II.** How individuals can reduce their risk of colorectal cancer.

- Increase intake of vegetables and fruits
- Reduce intake of calories (animal fats in particular)
- Increase physical activity
- Stop smoking
- Decrease alcohol consumption
- Consult a doctor as soon as possible if blood is present in the stool, a noticeable and unexplained change in bowel habits occurs, colicky pain occurs in the abdomen, or a sensation of incomplete evacuation after defecation recurs
- Participate in population-based screening programmes
- Strongly consider having a colonoscopy with polyp removal starting from 50 years of age

**Gastric Cancer**

Despite a major decline in incidence and mortality over several decades, gastric cancer (GC) with more than 750,000 new cases occurring annually, remains an important public health burden worldwide, especially in developing countries. GC is still the fourth most common cancer and the second-third most common cause of cancer death. In Japan, GC is a leading cause of cancer death. It accounts for 10% of new cancer cases in the world. There is a 10-fold variation in incidence between populations at the highest and lowest risk. The incidence is particularly high in East Asia, Eastern Europe, and parts of Central and South America. The incidence of GC has been declining in the USA, Europe and in the high-risk countries. GC rarely occurs before 40 years of age. From 40 onwards the incidence of GC increases with increasing age, to highest among those ages 80 years or older. Males are nearly twice as likely as females to develop GC4,39,40. Demographic trends differ by tumor location and histology. While there has been a marked decline in distal, intestinal type GCs, the incidence of proximal, diffuse-type adenocarcinomas of the gastric cardia has been increasing, particularly in the Western countries. Incidence by tumor sub-site also varies widely based on geographic location, race, and socio-economic status. Distal GC predominates in developing countries, among blacks, and in lower socio-economic groups, whereas proximal tumors are more common in developed countries, among whites, and in higher socio-economic classes. Diverging trends in the incidence of GC by tumor location suggest that they may represent two diseases with different etiologies39,41.
The main risk factors for distal GC include Helicobacter pylori (H. pylori) infection and dietary factors, whereas gastroesophageal reflux disease and obesity play important roles in the development of proximal GC (Table IV).42

Survival outcomes form GC is relatively poor with only 22% surviving 5 years after diagnosis.7

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### Table III. Proposed mechanisms of action of aspirin and nonsteroidal anti-inflammatory drugs and other chemopreventive agents.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Proposed mechanisms</th>
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<tbody>
<tr>
<td>ASA, NSAIDs</td>
<td>Alteration of prostaglandin production</td>
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<tr>
<td></td>
<td>Inhibition of cyclooxygenase-2 isozyme</td>
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<td></td>
<td>Induction of apoptosis</td>
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<tr>
<td></td>
<td>Antiangiogenic effect</td>
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<tr>
<td>UDCA</td>
<td>Reduction of secondary bile acids</td>
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<tr>
<td>HRT</td>
<td>Decreasing the production of secondary bile acids</td>
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<tr>
<td></td>
<td>Decreasing the production of IGF-1</td>
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<tr>
<td></td>
<td>Direct effects on the colorectal epithelium</td>
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<tr>
<td>Statins</td>
<td>Inhibition of HMG-CoA reductase</td>
</tr>
<tr>
<td></td>
<td>Induction of apoptosis</td>
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<tr>
<td></td>
<td>Proliferation inhibition in cancer cell lines</td>
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<td></td>
<td>Up-regulation of proapoptotic proteins</td>
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<tr>
<td></td>
<td>Inhibition of metastasis</td>
</tr>
<tr>
<td>Folate</td>
<td>Maintains the DNA methylation pattern</td>
</tr>
<tr>
<td>Calcium</td>
<td>Binding of fatty acids and bile acids in the colonic lumen</td>
</tr>
<tr>
<td></td>
<td>Inhibition of proliferation of the colonic mucosa</td>
</tr>
<tr>
<td></td>
<td>Reduction colonic epithelial hyperproliferation</td>
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<tr>
<td>Vitamin D</td>
<td>Inhibition DNA synthesis and cell proliferation</td>
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<tr>
<td></td>
<td>Induction of apoptosis</td>
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<td></td>
<td>Ability to modulate calcium absorption</td>
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<tr>
<td>Selenium</td>
<td>Activation of the p53 tumor suppressor protein</td>
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<td></td>
<td>Activation of DNA repair</td>
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<td>Increased glutathione peroxidase activity</td>
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<tr>
<td>Vitamins C, E, β-carotene</td>
<td>Antioxidant effect</td>
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<td></td>
<td>Neutralization of cell-damaging free radicals</td>
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<td>Stimulation of the immune system</td>
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</table>

Abbreviations: ASA: aspirin; NSAIDs: nonsteroidal anti-inflammatory drugs; UDCA: Ursodeoxycholic acid; HRT: Hormone-replacement therapy; IGF-I: insulin-like growth factor-I, HMG-CoA reductase: 3-hydroxy-3-methylglutaryl coenzyme-A reductase.

### Table IV. Risk factors for gastric cancer.

**Distal gastric cancer**
- Helicobacter pylori infection
- Dietary factors:
  - high intake of salted, smoked, cured and/or pickled foods
  - high intake of heavily grilled or barbecued meat and fish
- Poor access to refrigeration
- Smoking
- Genetic factors:
  - “Cancer family” syndrome

**Proximal gastric cancer**
- Gastroesophageal reflux disease
- Excess body weight

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**Esophageal Cancer**

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of cancer-related death. Cancer of the esophagus accounts for 5.5% of all malignant tumors of the GI tract. During the past 30 years, there has been a dramatic shift in the epidemiology of esophageal cancer in North America and most Western countries, characterized by a very rapid rise in the incidence of this disease and a marked shift from squamous cell carcinomas occurring predominantly in the middle third and distal esophagus to adenocarcinoma arising in the distal esophagus and the gastro-esophageal junction (GEJ). Since the 1970s there have been substantial changes in the incidence of esophageal adenocarcinoma. Several studies have found that the incidence of esophageal adenocarcinoma has increased steadily since 1970s, and it now has one of the fastest growing rates among all types of cancers in Western countries43-48. Regional incidence rates are highest in areas of Southern and Eastern Africa, where the incidence rises to 32 cases per 100,000 population per year, and China where the incidence is 22 cases per 100,000 population per year. In contrast to a striking increase in the rates of adenocarcinoma of the esophagus in the last three decades, stable or even decreased trends in squamous cell cancer have been observed. Predisposing factors for squamous cell carcinomas include a high alcohol intake, and a heavy use of tobacco or nutritional deficiencies in vitamins and minerals. In contrast, Barrett’s esophagus (BE) is thought to be the precursor lesion in most cases of esophageal adenocarcinoma. A better understanding of this predisposing lesion could lead
the way reducing the incidence, morbidity and mortality associated with esophageal adenocarcinoma. Endoscopic surveillance and follow-up is advised in order to detect adenocarcinoma and its precursor precancerous lesions at an early and curable stage, although there has been much debate on this topic. The main risk factors for esophageal squamous cell carcinomas and for the development of Barrett’s adenocarcinomas are summarized in Table V.

The 5-year survival rates for esophageal cancer have doubled over the last 3 decades; however, survival is still characteristically poor for patients with this cancer. The 5-year survival for white patients has improved from 5% to 13%, while the 5-year survival for African-Americans has risen from 4% to 9%. For all races, the mean survival is only 12%.

**Pancreatic Cancer**

Pancreatic cancer ranks the fourth and fifth most common cancer in man and women, respectively, and has the lowest 5-year survival rate of any GI cancers. Worldwide, over 250,000 people die annually of pancreatic cancer. The highest incidence and mortality rates of pancreatic cancer are found in developed countries. The incidence of pancreatic cancer has increased over the past four decades in western countries, but plateaued since 1970 at a frequency of 8 and 13 per 100,000 person-years in women and men, respectively. The incidence is highest in North America and New Zealand, intermediate in Europe and Japan. There is an approximate five fold variation in incidence around the world, with the lowest incidence being noted in developing countries in Africa and the India subcontinent. Due to the poor 5-year survival of less than 5%, incidence and mortality rates are virtually identical. Pancreatic cancer is rare before the age of 40 years. The risk of malignancy increases markedly after the age of 50 with most patients diagnosed between 65 and 80 years of age. Outcomes from pancreatic cancer are very poor with only 4% of cases surviving 5 years from diagnosis. Outcomes are poor even when the disease appears to be localised at diagnosis. Therefore, identification of patients at higher risk is a major goal in the management of pancreatic cancer (Table VI). Consistent evidence of a positive association was found for family history, and cigarette smoking. Overweight or obesity during early adulthood was associated with a greater risk of pancreatic cancer and a younger age of disease onset. Obesity at an older age was associated with a lower overall survival in patients with pancreatic cancer. Many studies documented a positive association with diabetes mellitus and chronic pancreatitis, although the etiologic mechanisms are unclear. Other associations were detected, but the results were inconsistent. These included positive associations with red meat, sugar, fat, alcohol or coffee consumption, and protective effects of dietary folate, aspirin, and statins.

**Hepatocellular Carcinoma**

Primary liver cancer is the sixth most common cancer in the world and the third most common cause of cancer mortality. More than 600,000 new cases are diagnosed each year and more than 550,000 deaths due to liver cancer occur. In most countries, 75-90% of liver cancer...
Tumors are hepatocellular carcinoma (HCC), thus trends in liver cancer incidence and mortality tend to reflect trends in HCC incidence and mortality. The incidence of HCC is high in all low-resource regions of the world, with the exception of Northern Africa and Western Asia. There is a wide geographic variability in HCC incidence. The great majority of HCC (>80%) occurs in either sub-Saharan Africa or in Eastern Asia, with one country alone, China, accounting for over 50% of cases. With some exceptions, countries in North America, South America, Northern Europe and Australia tend to have low incidence rates, while countries in Central and Southern Europe tend to have intermediate rates. The highest incidence rates (40/100,000 in men and 10/100,000 in women) are recorded in Thailand, Japan, Korea, and certain parts of China. In most high-resource countries, age-standardized rates are below 5/100,000 in men and 2.5/100,000 in women. Intermediate rates (5-10/100,000 in men) are observed in areas of Southern and Central Europe.

Survival rates of HCC are uniformly poor in both high-rate and low-rate areas. The 5-year survival rate was 8% in the US during 1988-2001, 9% in Europe during 1995-1999, and 5% in developing countries in 2002.71-74.

The majority of HCC arise in a background of chronic liver disease due to viral hepatitis (B or C) or ethanol abuse. Cirrhosis from any cause may dominate the clinical picture and determine the prognosis. With the exception of some area of the world where hepatitis B virus (HBV) infection is endemic and the role of other oncogenic agents (i.e., aflatoxin) may be important, it is uncommon to find HCC in the absence of cirrhosis. Recent epidemiologic data indicate that in the US and in some European countries, the mortality rate from HCC is increasing, conversely, cirrhosis-related mortality not due to HCC declined in the early 1990s in the same areas. A similar trend was noted also in Italy, between 1969 and 2000, where the mortality rates of cirrhosis showed a clear decline while the mortality rates for HCC slowly increased.75-79. Hepatitis C virus (HCV) infection is associated with the highest HCC incidence in persons with cirrhosis, occurring twice as commonly in Japan than in the West (5-year cumulative incidence, 30% and 17%, respectively), followed by haemochromatosis (5-year cumulative incidence, 21%). In HBV-related cirrhosis, the 5-year cumulative HCC risk is 15% in high endemic areas and 10% in the West. In the absence of HCV and HBV infection, the HCC incidence is lower in alcoholic cirrhosis (5-year cumulative risk, 8%) and subjects with advanced biliary cirrhosis (5-year cumulative risk, 4%)76.

Older age, male sex, obesity, the presence of diabetes mellitus, iron overload, severity of compensated cirrhosis at presentation, and sustained activity of liver disease are important predictors of HCC, independent of etiology of cirrhosis (76, 80-85). The main factors affecting progression to HCC in HCV and HBV-related cirrhosis are shown in Table VII. In viral-related cirrhosis, HBV/HCV and HBV/HDV co-infections increase the HCC risk (2- to 6-fold relative to each infection alone), as does alcohol abuse (2- to 4-fold relative to alcohol abstinence). Sustained re-

<table>
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<tr>
<th>Hepatitis C-virus (HCV) related cirrhosis</th>
<th>Hepatitis B-virus (HBV) related cirrhosis</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>Male sex</td>
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<tr>
<td>Age at infection and diagnosis</td>
<td>Age at infection and diagnosis</td>
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<tr>
<td>Alcohol intake</td>
<td>Alcohol intake</td>
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<td>Severity of liver disease</td>
<td>Severity of liver disease</td>
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<td>HBV genotype</td>
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<tr>
<td>HBV co-infection</td>
<td>HCV or HDV co-infection</td>
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<tr>
<td>Co-morbidity:</td>
<td>Environmental contamination:</td>
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<tr>
<td>– Porphyria cutanea tarda</td>
<td>– Aflatoxins</td>
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<td>– Steatosis</td>
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<td>– Obesity</td>
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<td>– Diabetes mellitus</td>
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<td>– Iron overload</td>
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duction of HBV replication lowers the risk of HCC in HBV-related cirrhosis. Better knowledge of individual risk factors for HCC in patients with cirrhosis is the key for designing effective preventive strategies and for disease management.

References


