

Editorial

The international health care burden of cancers of the gastrointestinal tract and liver

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Abstract

Cancers of the gastrointestinal tract and liver are a major worldwide health problem, accounting for three of the top five causes of cancer death in world. Gastrointestinal cancer rates are changing over time, and trends vary around the world: Gastric and liver cancer rates are much higher in developing countries; gastric and colorectal cancer mortality has decreased dramatically in some developed countries; pancreatic cancer appears to be slowly but steadily increasing in developed countries. Encouraging advances have been made, or are being made, in the prevention of some cancers of the digestive organs: reduction in rates of cigarette smoking (especially in esophageal squamous cancer and pancreatic cancer); control of *H. pylori* infection in gastric cancer; early detection and screening in colorectal cancer; and the prevention and early, more effective treatment of hepatitis B and C infections in liver cancer. Appreciation of the magnitude of gastrointestinal and liver cancers, the geographic variations in their incidence, and the advances in some prevention and treatment measures may help in the management of these malignancies.

Keywords: Gastrointestinal cancer, liver cancer, gastric cancer, colorectal cancer, esophageal squamous cancer, pancreatic cancer

Worldwide, cancer is a major cause of morbidity and mortality. It is estimated that in 2012 there were about 14 million new cancers cases and 8.2 million deaths from cancer in a world population of about 7 billion. The risk of getting cancer and dying of cancer by age 75 is about 18.5% and 10.5%, respectively. In this, the inaugural edition of *Cancer Research Frontiers*, we emphasize the compelling worldwide burden of cancers of the gastrointestinal tract and liver. Cancers of these organs pose huge

challenges, yet they have some instructive lessons regarding their cause, prevention and treatment.

Fig 1. illustrates the worldwide 2012 estimated age-standardized incidence and mortality rates of various cancers (both sexes), compiled by the International Agency for Research in Cancer (http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). The burden of digestive-organ cancers is evident, as five of the 15 cancers listed are cancers of the gastrointestinal tract (colorectum, stomach,

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esophagus, pancreas) or liver. These cancers account for three of the top five causes of cancer death in world (and five of the top nine).

The incidence and mortality from individual cancer sites varies substantially over time. With respect to cancers of the gastrointestinal organs and the liver/intrahepatic bile ducts, some remarkable and instructive trends are evident: for example, in the US the mortality rate for gastric cancer in both men and women has fallen dramatically in the last 50 years; in the 1950s gastric cancer was by far the most common cause of cancer death but now it is much less common

than lung, breast colorectal and several other cancers. Cancer of the colorectum, after rising gradually for about two decades, remained stable in men until about 1985, when it began a steady decline; in women, the decline started earlier and has been steady and gradual since about 1950. Mortality from pancreatic cancer has risen substantially, especially in men. Mortality from cancers of the liver and intrahepatic bile ducts, in men, declined for about three decades but has increased recently. Explanations for some of these trends are discussed in the following paragraphs.

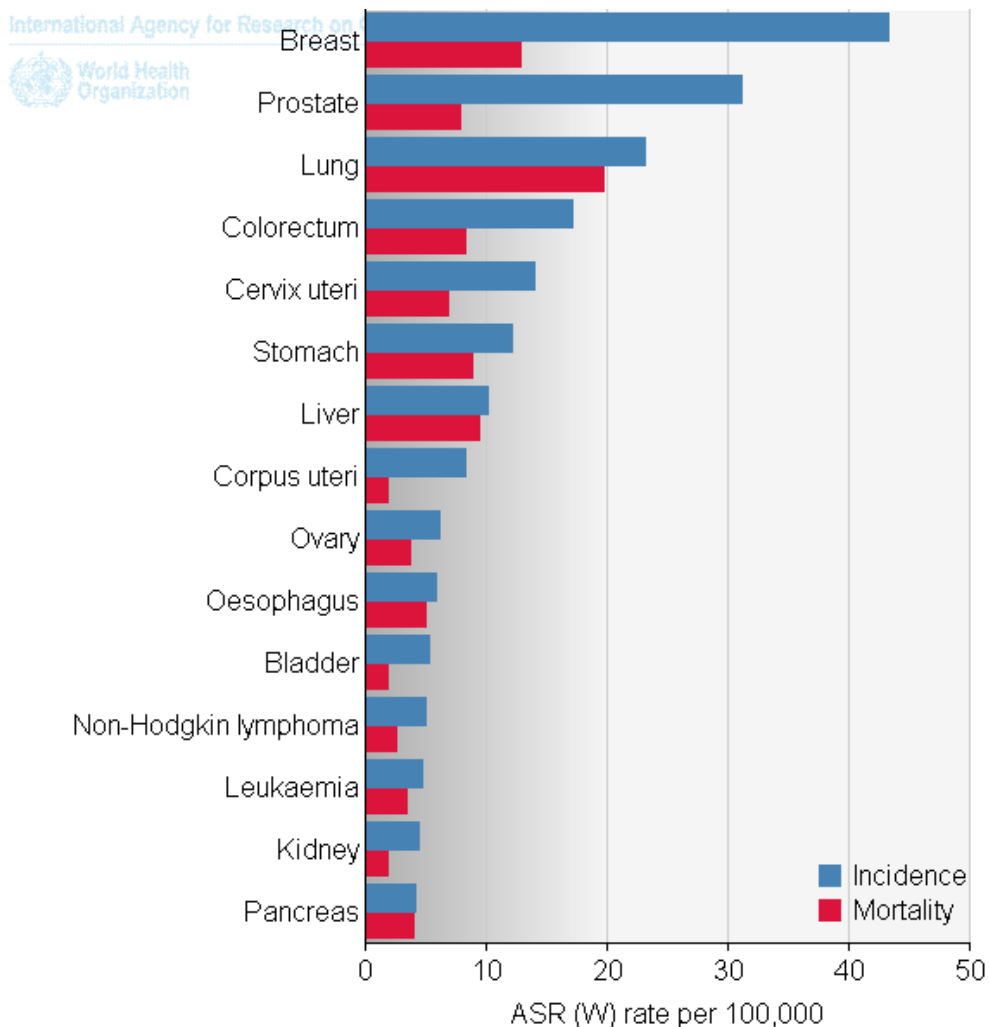


Fig. 1. Incidence and mortality rate of the 15 most common cancers in the world. Reproduced with permission from Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on June 10, 2014.

Esophageal cancers

Esophageal cancer is the 10th most common cancer and the 8th most common cause of cancer death in the world (Fig. 1). Worldwide, an estimated 482,000 people per year are diagnosed with esophageal cancer, and about 406,000 people die annually from the disease. The incidence and mortality of esophageal cancer varies greatly around the world (Fig. 2), with somewhat higher rates in less developed regions but substantial variability within countries of both more developed and less developed regions. The mortality rate of esophageal cancer is high, and the long-term survival rate low; only about 40% of patients survive for a year after the diagnosis is made, and only about 13% survive for five years.

A dramatic shift in the histologic spectrum of esophageal cancers has occurred in recent decades particularly in developed countries. Squamous cancer had been the dominant histologic type, but esophageal adenocarcinoma has been increasing rapidly in Western countries. The strongest risk factor for esophageal adenocarcinoma is underlying Barrett's esophagus, which is characterized by intestinal metaplasia of the esophageal epithelium and is related to chronic gastroesophageal reflux. Tobacco use is an additional risk factor for esophageal cancer, especially for squamous cell cancer; alcohol consumption increases the risk of squamous cell cancer; and overweight status or obesity increases the risk of adenocarcinoma. Regular use of non-steroidal anti-inflammatory drugs appears to be associated with a lower risk of esophageal cancer.

Public health measures to reduce the rates of smoking, excessive alcohol drinking, and obesity should be promoted in efforts to reduce the frequency of esophageal cancer. Measures to reduce the frequency and cancer predilection of Barrett's esophagus are harder to define, but prevention and treatment of gastroesophageal reflux would be expected to reduce the frequency of this condition; surprisingly, though, strict correlation between these measures and prevention of esophageal adenocarcinoma associated with Barrett's esophagus

has not been established. Various endoscopic measures to eradicate esophageal intestinal metaplasia are being employed, but their cost and requirement for skilled endoscopists markedly restrict their widespread use.

Gastric cancer

Gastric cancer is the 6th most common cancer and the 4th most common cause of cancer death in the world. The incidence of gastric cancer varies widely throughout the world, with the highest rates being in eastern Asia, and the lowest rates in northern and southern Africa (Fig. 3). In most countries there is a marked male predominance of gastric cancer. Gastric cancer rates have fallen dramatically in most developed countries over the last 75 years; it was the most common cause of cancer death in the United States in 1930, with a rate of about 40/100,000 population, but it has fallen to 7th, with a rate of less than 5/100,000 by 2014. Worldwide, about 990,000 people were diagnosed with gastric cancer in 2008, and 737,000 deaths were attributed to the disease. Although survival rates from gastric cancer have improved, rates remain low (one in five persons for five years or more).

The declining incidence of gastric cancer in the United States and other developed countries is thought to be due to changes in environmental risk factors. Some suspected etiologic factors for gastric cancer (smoking and high dietary salt intake) have been identified, but the one predominant factor is that of gastric infection with the bacterium *Helicobacter pylori*. In the United Kingdom, almost one-third of gastric cancer cancers are linked to the presence of *H. pylori*. Thus gastric cancer is largely an infectious disease (or at least a consequence of an infectious disease). Eradication of the organism from the stomach has been documented to decrease the incidence of gastric cancer, and some investigators in Japan have suggested that eradication of the organism in that nation could virtually eliminate gastric cancer. Others, though, have warned of the risks of disrupting the gastrointestinal microbiome through the widespread use of antibiotics to treat *H. pylori* infection.

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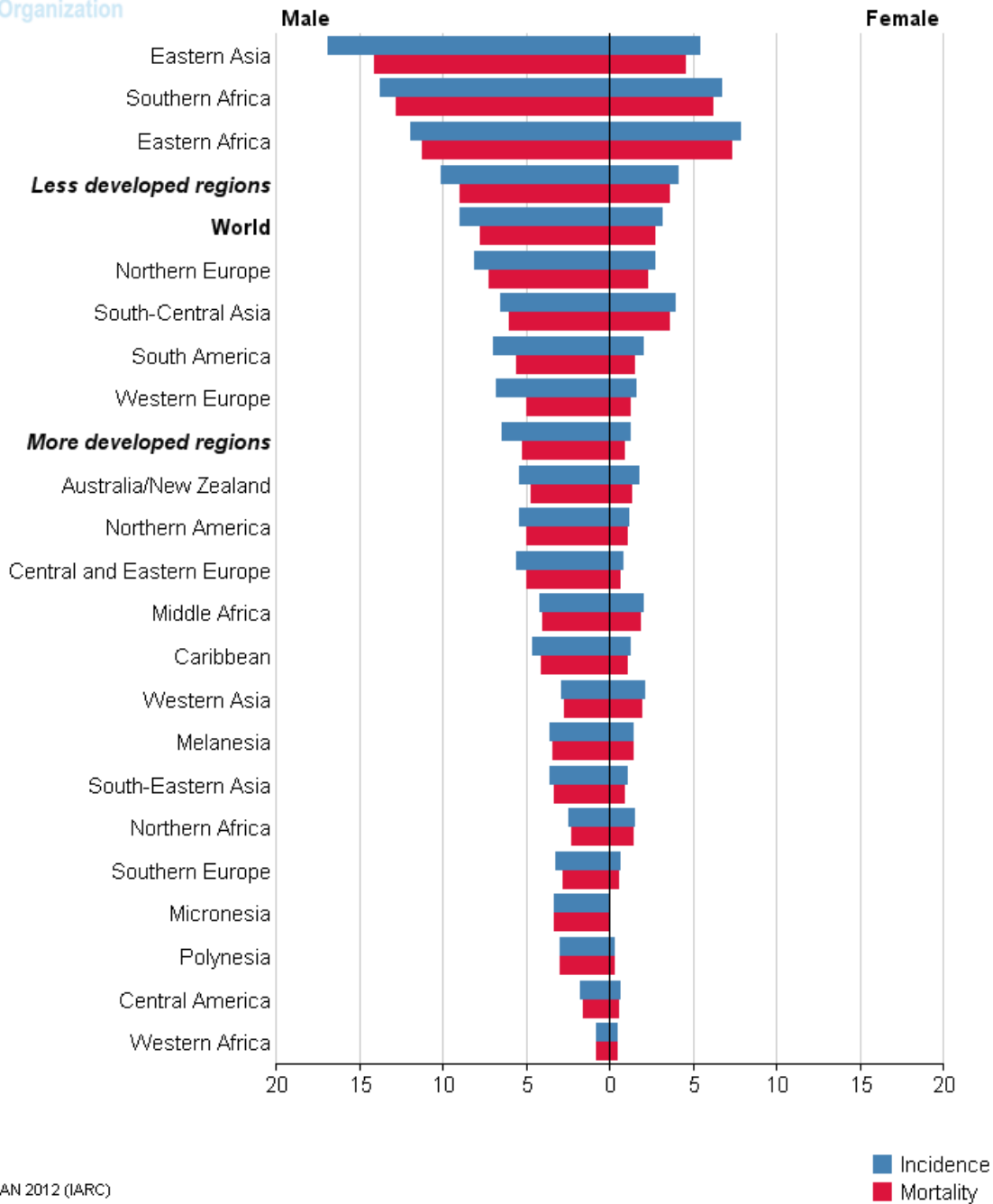
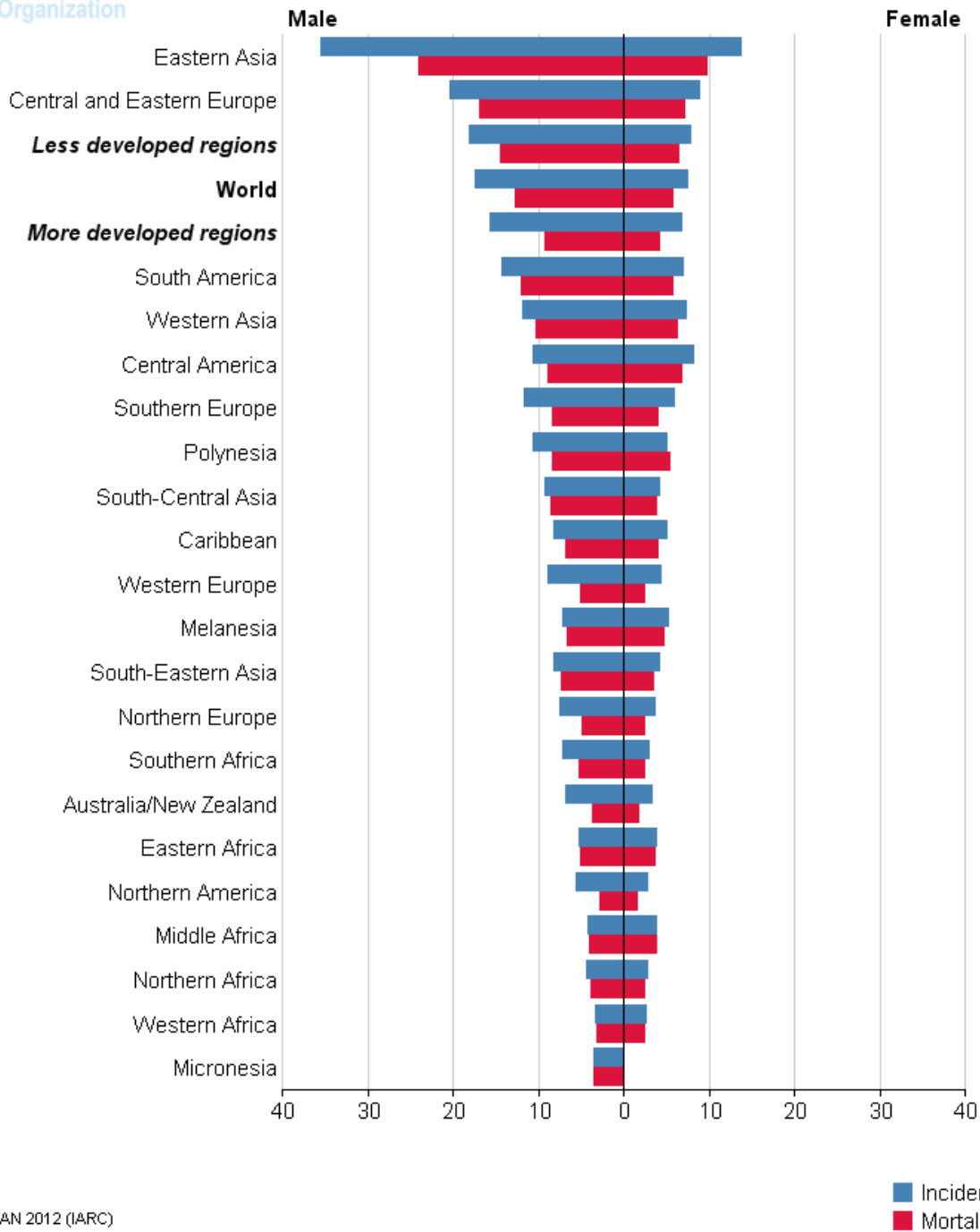


Fig. 2. Incidence and mortality (per 100,000) of esophageal cancer in regions around the world. Reproduced with permission from Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on June 16, 2014.

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GLOBOCAN 2012 (IARC)

Fig. 3. Incidence and mortality (per 100,000) of gastric cancer in regions around the world. Reproduced with permission from Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on June 16, 2014.

Pancreatic cancer

Pancreatic cancer is the 15th most common and the 9th most common cause of cancer death in the world. Pancreatic cancer is increasing in prevalence worldwide, particularly in developed countries, and continues to be very difficult to diagnose early and treat effectively. Worldwide, about 178,000 people were diagnosed with pancreatic cancer in 2012. By the time the disease is diagnosed it often is far advanced. Although the survival rate from pancreatic cancer has more than doubled since the 1970s, the disease continues to have a high mortality rate, with an overall five-year survival rate of only about 4%. Factors associated with an increased risk for pancreatic cancer are cigarette smoking, smokeless tobacco chewing, type I or II diabetes, chronic pancreatitis, overweight status, and family history of the disease. Clearly, improved methods for earlier detection of pancreatic cancer are needed in order to reduce its high mortality rate. Thus far, attempts to screen for pancreatic cancer have been either unsuccessful (Ca19-9 blood test is insensitive for early pancreatic cancer) and/or too expensive and invasive for widespread use (endoscopic ultrasound and mutational analysis of pancreatic juice).

Colonic cancer

Colorectal cancer (CRC) is the 4th most common cancer and the 5th most common cause of cancer death in the world (Fig. 1). Worldwide, the incidence of CRC varies widely, with a less dramatic variability in mortality rates (Fig. 4); the highest rates of CRC are found in developed countries (Australia, Europe) and the lowest in western and middle Africa. In the field of colonic cancer there is both discouraging and encouraging news. The disease is becoming more widespread in many parts of the world, perhaps because of wide adoption of a so-called Western diet. In 2012, about 470,000 new cases of colonic carcinoma were reported worldwide, and about 694,000 persons died of the disease. In most countries, the incidence of colorectal cancer is increasing or stable; in the United States, however, the incidence has been steadily falling over the last 20 years. Survival rates also vary widely across the world, with stable to increasing rates in many developing countries but dramatically falling rates in some Western countries, particularly the

United States (Fig. 2) and Australia. Overall, the five-year survival rate of the disease has approximately doubled over the last five years; about one-half of patients survive for a least ten years, and 90% will survive for more than five years if the disease is diagnosed at the earliest stage.

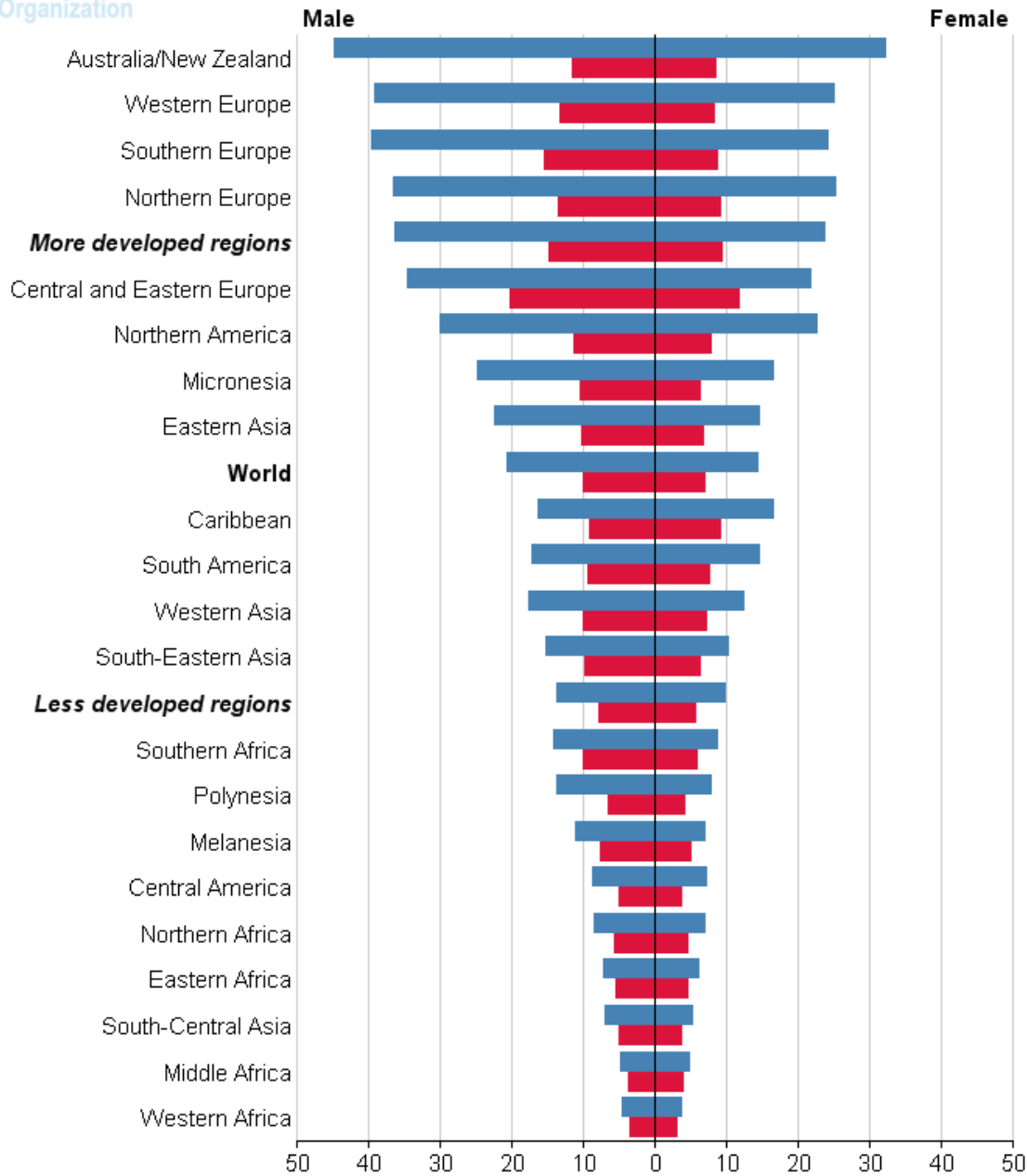
The causes of colonic cancer are becoming better understood but remain incompletely defined. High intake of red meat and processed meat is a risk factor, whereas a diet rich in fiber seems to reduce the risk. Overweight status or obesity, lack of physical activity, smoking, diabetes, chronic ulcerative colitis, Crohn's disease, and a family history of the disease are associated with an increased risk; people with a first-degree relative have twice the average risk of developing colonic cancer. The importance of hereditary factors in the cause of colonic cancer is becoming increasingly appreciated. About 5% of all CRCs are thought to be due to hereditary syndromes due to identified genes, with Lynch syndrome being the most common followed by the adenomatous polyposis syndromes (familial adenomatous polyposis and MUTYH-associated polyposis) and the hamartomatous polyposis syndromes (juvenile polyposis, Peutz-Jeghers syndrome, and PTEN hamartomatous syndromes).

The early detection of colonic cancer or its precursor lesions has become recognized as very important in reducing the occurrence of advanced neoplastic disease or death. Screening for colorectal is one of the most effective cancer screening modalities. Fecal occult blood testing is relatively inexpensive but requires regular testing, whereas endoscopic screening is more invasive and expensive and not applicable to many resource-limited countries.

Liver cancer

Like gastric cancer, liver cancer is thought to be caused in part by infectious agents; in this case, viruses that cause hepatitis and cirrhosis, although other causes of cirrhosis, such as steatohepatitis and hemochromatosis, contribute also. Liver cancer remains a very serious international health problem; it is the 7th most common cancer but the 3rd most common cause of cancer death in the world (Fig. 1.).

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GLOBOCAN 2012 (IARC)

■ Incidence
■ Mortality

Fig. 4. Incidence and mortality (per 100,000) of colorectal cancer in regions around the world. Reproduced with permission from Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on June 16, 2014.

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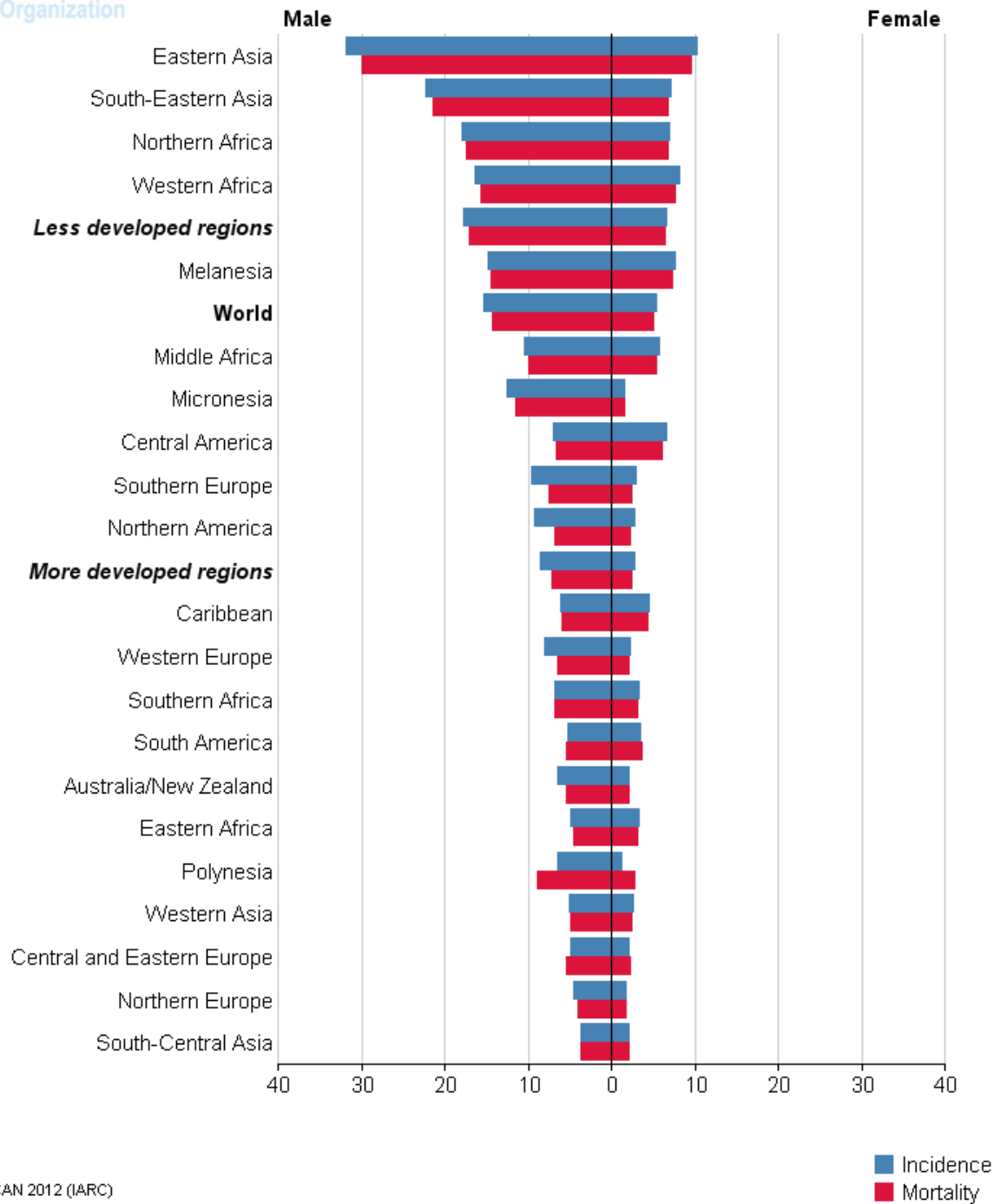


Fig. 5. Incidence and mortality (per 100,000) of liver cancer in regions around the world. Reproduced with permission from Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on June 16, 2014.

About 0.5 million persons were diagnosed with liver cancer in 2012, and about an equal number died of the disease. Liver cancer is often diagnosed late, thus contributing to a poor survival rate; worldwide, only about 5% of patients survive their disease. Liver cancer is much more common in men than in women and is generally more common in less developed regions of the world with the highest rates in Eastern Asia and the lowest in Northern Europe and South Central Asia (Fig. 5). This pattern is changing as the rate of steatohepatitis-related liver cancer is increasing in some developed countries.

Because liver cancer often is due to infection with hepatitis B or C viruses, there is promise that preventing the infections (through immunization and public health measures) or treating them effectively will dramatically reduce the frequency of these cancers. High cost of the therapeutic agents, however, limits their widespread use. Less common or less severe risk factors for liver cancer are cigarette smoking, diabetes, occupational exposure to vinyl chloride, and exposure to aflatoxin produced by fungi, which can contaminate foodstuffs stored in hot, humid conditions. Heavy alcohol consumption increases the risk of liver cancer about five fold, largely by increasing the incidence of cirrhosis in patients infected with hepatitis B or C viruses.

Summary

Cancers of the gastrointestinal tract and liver are a major worldwide health problem. These cancers account for three of the top five causes of cancer death in the world (and five of the top twelve). Gastrointestinal cancer rates are also changing over time, and trends vary around the world: Gastric and liver cancer rates are much higher in developing countries; gastric and colorectal cancer mortality has decreased dramatically in some developed countries; pancreatic cancer appears to be slowly but steadily increasing in developed countries. Encouraging advances have been made, or are being made, in the prevention of some cancers of the digestive organs: reduction in rates of cigarette smoking (especially in esophageal squamous cancer and pancreatic cancer); control of *H. pylori* infection in gastric cancer; early detection and screening in colorectal cancer; and the prevention and early, more effective treatment of hepatitis B and C infections in liver cancer. For further progress in the prevention, early detection, and treatment of these diseases, research at both the basic molecular level and the epidemiologic and clinical levels are badly needed and deserve intense international attention and adequate funding.