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Review: Cancer Surveillance Research

Cancer Epidemiology, Biomarkers & Prevention

Global Patterns of Cancer Incidence and Mortality Rates and Trends

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Abstract

While incidence and mortality rates for most cancers (including lung, colorectum, female breast, and prostate) are decreasing in the United States and many other western countries, they are increasing in several less developed and economically transitioning countries because of adoption of unhealthy western lifestyles such as smoking and physical inactivity and consumption of calorie-dense food. Indeed, the rates for lung and colon cancers in a few of these countries have already surpassed those in the United States and other western countries. Most developing countries also continue to be disproportionately affected by cancers related to infectious agents, such as cervix, liver, and stomach cancers. The proportion of new cancer cases diagnosed in less developed countries is projected to increase from about 56% of the world total in 2008 to more than 60% in 2030 because of the increasing trends in cancer rates and expected increases in life expectancy and growth of the population. In this review, we describe these changing global incidence and mortality patterns for select common cancers and the opportunities for cancer prevention in developing countries. *Cancer Epidemiol Biomarkers Prev; 19(8); 1893–907. ©2010 AACR.*

Introduction

Several migrant studies have documented that cancer rates in successive generations of migrants shift in the direction of the prevailing rates in the host country, suggesting that the international variations in cancer rates for most cancers largely reflect differences in environmental risk factors (including lifestyle and culture) rather than genetic differences (1, 2). In general, smoking, dietary patterns, and reproductive behaviors have been known to be the major risk factors for cancer in western (host) countries, and infectious agents in economically developing countries. However, these patterns are changing rapidly. While smoking prevalence is declining in economically developed countries, it is increasing in some developing countries in South America, Asia, and Africa (3). For example, current smoking prevalence among adult men in the West, including the United States, is about 20%, compared with more than 60% in China, Indonesia, Greece, and Jordan (3). Further, following earlier trends in several western countries, consumption of saturated fat and calorie-dense food and physical inactivity are increasing in less developed and economically transitioning countries, leading to increases in obesity among segments of the population in some countries where poverty and malnutrition are still major problems (4, 5).

Although the full impacts of these unhealthy lifestyle changes on the cancer burden in less developed or economically transitioning countries are likely to take decades to be realized, new alarming trends in cancer rates have already emerged in these countries (6-8). Cancers that once were rare and considered the diseases of western countries, such as colon, breast, and lung cancers, are now frequently diagnosed in less developed or economically transitioning countries and their rates are on the rise (9). In addition to the increasing trends, the future burden of cancer in the developing world is likely to be exasperated by the expected increases in life expectancy and aging and growth of the population (10). The proportion of cases diagnosed in less developed countries is projected to increase from about 56% in 2008 to more than 60% in 2030 (11). It is also projected that cancer will surpass ischemic heart disease as the leading cause of death worldwide in 2010 (12). In this review, we describe the changing global patterns of cancer incidence and mortality for select common cancer sites using incidence and mortality data compiled in Cancer*Mondial* by the IARC (13).

Data Source and Methods

High-quality population-based cancer incidence data have been collected throughout the world since the early 1960s and published periodically in *Cancer Incidence in Five Continents (CI5)*. IARC has made these data available

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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to the public in the Cancer*Mondial* database (13). This database also provides cancer mortality statistics for select countries, extracted from the WHO database. Only one sixth of the world population is covered by population-based cancer registries, and one third by death certification system (13). For this review, we mainly use incidence data for 45 select cancer registries with long-term data from CI5 and mortality data from WHO (13).

Incidence and mortality rates are age standardized to the 1960 world standard population to be consistent with the IARC and other international publications on cancer. Therefore, these rates cannot be compared with those standardized to the 2000 U.S. standard population, which gives more weight to rates occurring in the oldest age groups (14). Except for childhood cancers and cancers that commonly occur in young adults, rates standardized to the 2000 U.S. standard population are substantially higher than those standardized to the 1960 world population, by as much as 60% for colon, stomach, and lung cancers (15).

All cancer sites

It was estimated that there were about 12.7 million new cancer cases and 7.6 million cancer deaths in 2008 worldwide (11). Overall incidence rates (per 100,000) for 1998-2002 among the 45 select cancer registries worldwide vary by nearly 6-fold in men, from 86.3 in Algeria (Setif) to 453.3 in U.S. blacks, and by nearly 4-fold in women, from 80.3 in Algeria (Setif) to 302.3 in U.S. non-Hispanic whites (whites; Supplementary Fig. S1).

However, regional variations in overall cancer rates may mask important differences in composition of cancers. The most frequently diagnosed cancers by sex vary considerably across country (Supplementary Fig. S2). The most commonly diagnosed cancer among men is lung cancer in most parts of Eastern Europe and Asia; prostate cancer in North America, Australia, Western and Northern Europe, and South America; liver cancer in parts of West Africa; Kaposi sarcoma in central parts of Africa; esophagus in East Africa; and bladder cancer in Egypt. Among women, the most frequently diagnosed cancer is breast cancer in most parts of the world, including Australia, Western Asia, North Africa, North America, and parts of South America; cervical cancer in Central America, parts of South America, Sub-Saharan Africa, and India; liver cancer in Mongolia and Vietnam; and lung cancer in China and North Korea. We briefly describe the international incidence and mortality patterns for these common cancers, except for Kaposi sarcoma and bladder cancers, for brevity.

Lung and bronchus

Worldwide, lung cancer is the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women, with about 1.6 million new lung cancer cases and 1.4 million deaths expected to occur in 2008 (11). In men, the highest lung cancer incidence rates are reported in the United States (blacks) and in Eastern European countries and the lowest rates are found in Africa, Central and South America, and South Central Asia (Supplementary Fig. S3). In women, the highest lung cancer rates are reported in North America and parts of Europe, including the United Kingdom and Denmark and the lowest rates are found in Africa, South Central Asia, and Latin America. U.S. Hispanic men and women have higher rates than those of most registries or countries in Latin America (Supplementary Fig. S3). In contrast, several countries or registries in Asia have higher lung cancer rates than U.S. Asians for both men and women. Notably, the lung cancer rates in Chinese men and women, Filipino men, and Thai women exceed the rates among women in many European countries, including Germany and Finland.

International variations in lung cancer rates and trends largely reflect differences in the stage and degree of the tobacco epidemic (16, 17) because smoking accounts for about 80% of global lung cancer deaths in men and 50% of the deaths in women (18, 19). In several western countries where the tobacco epidemic was established and peaked by the middle of the last century, including the United States, the United Kingdom, Canada, and Australia, lung cancer rates have been decreasing in men and plateauing in women (20, 21). In contrast, in countries where the epidemic has been established more recently and smoking has just peaked or continues to increase, including China, Korea, and several countries in Africa, lung cancer rates are increasing (Fig. 1), and they are likely to continue to increase at least for the next few decades barring interventions to accelerate smoking cessation (16, 22).

In response to the globalization of the tobacco epidemic (23-26), WHO established the WHO Framework Convention on Tobacco Control to provide a framework for proven tobacco control measures (27), including raising the price of tobacco products, banning smoking in public places, restricting tobacco advertising and promotion, counteradvertising, and providing treatment and counseling for tobacco dependence (28). This framework has been ratified by 168 countries or parties as of March 2010. According to the 2009 summary progress report on implementation of the Framework Convention on Tobacco Control, 65 countries claimed to have developed and implemented comprehensive national tobacco control strategies, plans, and programs according to the Framework (29).

Environmental exposures other than smoking that may contribute to regional variations in lung cancer rates include radon and asbestos, certain metals (chromium, cadmium, arsenic), some organic chemicals, radiation, air pollution, coal smoke, and indoor emissions from burning other fuels (30). For example, Chinese women have higher lung cancer rates than women in several European countries, despite their low smoking prevalence (31). This is thought to reflect indoor air pollution from unventilated coal-fueled stoves and from cooking fumes (22, 32, 33).

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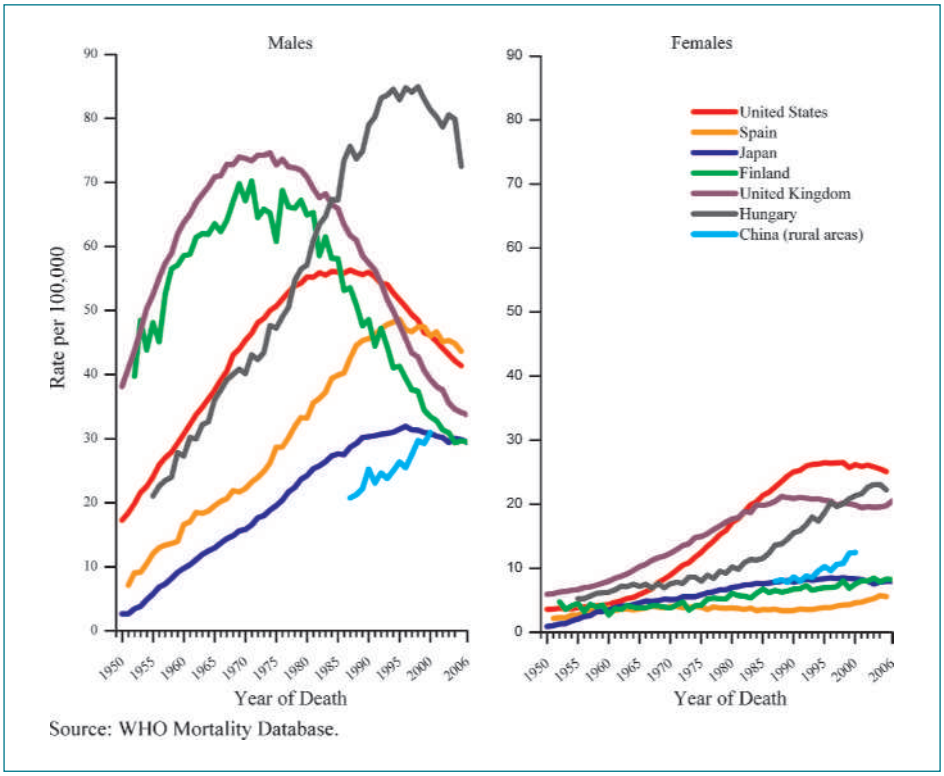

Figure 1. Trends in lung cancer mortality rates by sex in select countries, 1950-2006.

Colon and rectum

Colorectal cancer is the third most common cancer in men and the second in women. Worldwide, 1.2 million new colorectal cancer cases and 609,000 deaths were expected to occur in 2008 (11). There is a more than 10-fold difference in the regional incidence rates in both males and females (Supplementary Fig. S4). Generally, the highest incidence rates among both men and women are reported in Eastern European countries (Czech Republic and Slovakia), Japan (Miyagi), New Zealand, Australia, Germany, and U.S. blacks, whereas the lowest rates are found in Africa, Central and South America, and South Central Asia (India and Pakistan). U.S. Hispanic and Asian men and women have lower incidence rates than U.S. white or black men and women, but they have higher rates than their counterparts in Latin America and Asia; exceptions to these patterns are the substantially high rates in Japan (Miyagi) and Singapore (Supplementary Figs. S4 and S5).

While colorectal cancer incidence rates are stabilizing or declining in historically high-risk areas (United States, New Zealand, Canada), they are rapidly increasing in several historically low-risk countries, including Japan, Korea, China, and Eastern European countries (Slovakia, Slovenia, and Czech Republic; Supplementary Fig. S6; refs. 8, 34). Indeed, rates among males in the Czech Republic and Japan have already exceeded the peak rates observed in long-standing developed countries such as the United States, Canada, and Australia (8, 34). Notably, Japanese in California have substantially higher incidence rates (per 100,000) than Caucasians in California for both men (42.9 versus 36.6) and women (33.5 versus 26.9; Supplementary Fig. S5). Spain is the only Southern or Western European country with a large increase in the incidence rate (8, 34).

The increase in the incidence rates in several Asian and Eastern European countries and Spain is thought to reflect changes in dietary and lifestyle factors associated with westernization, including smoking and obesity (8, 34-37). For example, in some Eastern European countries such as the Czech Republic, nearly 60% of men are current cigarette smokers (3) and more than 25% of adults are obese (38). The decrease in the incidence rate in the United States in the most recent time period largely reflects detection and removal of precancerous lesions through colorectal cancer screening (39).

In contrast to the less favorable incidence trends, colorectal cancer death rates have been decreasing in several parts of the world (8). This may be attributed, in part, to improved treatment and increased awareness and early detection (39-42). Mortality rates, however, continue to increase in countries with limited resources and health infrastructure, including Mexico and Brazil in Central and South America and Romania in Eastern Europe (8). Five-year survival rates for colorectal cancer in developing countries range from 28% to 42% (43, 44), compared

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with more than 60% in the United States, Japan, and Switzerland (45, 46).

Preventive measures for reducing the burden of colorectal cancer in both low- and high-resource countries include being physically active, maintaining a healthy body weight, minimizing consumption of red meat and alcohol, maximizing consumption of fruit and vegetables, and cessation of smoking (6). High-resource countries could benefit from the implementation of colorectal screening that allows detection and removal of precancerous polyps and early-stage cancers (47-49). However, few countries (Czech Republic, Germany, Israel, Japan, and Poland) have national colorectal cancer screening programs; most have screening initiatives consisting of recommendations and/or guidelines with opportunistic screening or pilot studies (8, 50).

Female breast

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide, with an estimated 1.4 million new breast cancer cases and 458,000 deaths in 2008 (11). Incidence and mortality rates vary internationally by more than 5-fold (Supplementary Fig. S7). Generally, the highest incidence rates are found in Switzerland, U.S. whites, Italy, and many other European countries, whereas low rates are found in Africa, Asia, and South America. The rates in U.S. Hispanics and Asians are substantially higher compared with the rates in most cancer registries in Asia and Latin America. Regional patterns in mortality rates are generally similar to the incidence patterns, although U.S. whites, Hispanics, and Asian-Pacific Islanders and Australia have relatively low rates, whereas U.S. blacks and Trinidad and Tobago have the highest rates (Supplementary Fig. S7).

The high breast cancer incidence rates in white women in the United States and in most European countries reflect the long-standing high prevalence of reproductive factors associated with increased risk of breast cancer, including early menarche, late child bearing, fewer pregnancies, use of menopausal hormone therapy, as well as increased detection through mammography (51, 52). In addition to these factors, the high breast cancer incidence rates in Israel may reflect the disproportionately high prevalence of *BRCA1* and *BRCA2* mutations in the Ashkenazi Jewish population (about 2%; ref. 53). The lifetime risk of being diagnosed with breast cancer in women with *BRCA1* or *BRCA2* mutation is about 50% (54), compared with 13% in all U.S. women (55). The relatively low mortality rates in the United States and many other western countries reflect the availability of early detection and improved treatments.

Breast cancer incidence rates in the United States have decreased since the early 2000s largely due to reduction in the use of menopausal hormone therapy (56-58); decreases in utilization of mammography (59) or decreases in the number of preclinical cases found by screening over the past 20 years may also have contributed to the decrease in the incidence rates (60, 61). Similar decreasing trends, in part due to reduction in the use of menopausal hormone therapy, have also been noted in many other western countries, including the United Kingdom, France, and Australia (62-64). In contrast to the incidence trends, breast cancer mortality rates in these and several other western countries have been stable or decreasing during the past 25 years (Supplementary Fig. S8) because of early detection through mammography and improved treatment (65-68). The favorable mortality trend in the most recent period in the United States, the United Kingdom, Australia, and France may also partly reflect reduction in the incidence rates.

Compared with the trends in the United States, Canada, the United Kingdom, and several other western European countries, breast cancer incidence and mortality rates among women have been increasing rapidly in many Eastern European, Asian, Latin American, and African countries (Fig. 2; refs. 65, 69-71). For example, incidence rates increased by 140% in Miyagi (Japan) from 1973-1977 to 1998-2002, by 40% in Chennai (India) from 1983-1987 to 1998-2002 (13), and by 4.5% per year in Kampala (Uganda) from 1991-2006 (72). Factors that contribute to these increasing trends are not fully understood, but thought to reflect lifestyle changes associated with westernization, including late child bearing, having fewer children, and consumption of calorie-dense food, physical inactivity, and obesity (5, 38, 73-75). The unfavorable mortality trend in several of these countries may have been exacerbated by poor survival because of lack of or limited access to early detection services and treatment. Only 40% of women in Campinas (Brazil) and Setif (Algeria) survive 5 years after a diagnosis of breast cancer (45), compared with 89% of women in the United States and more than 82% of women in Northern and Central Europe (46).

Implementation of population-based, organized mammography screening programs for early detection is cost prohibitive in many low- and middle-income countries (76). Increasing awareness of early signs and symptoms and screening by clinical breast examinations are the only viable options in these countries (77). Access to treatment for breast cancer and for all cancers in developing countries are limited by the small numbers of trained medical personnel, the availability and cost of cancer drugs, and the insufficiency or lack of modern equipment including radiotherapy machines (77). For example, a population of about 80 million people in Ethiopia is served by a single radiotherapy machine, compared with a European standard of one machine for every 250,000 people (78).

Prostate

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death among men worldwide, with 914,000 new cases and 258,000 deaths projected to occur in 2008 (11). More than half of these cases and deaths are expected to occur in more developed countries (11). Incidence rates (per

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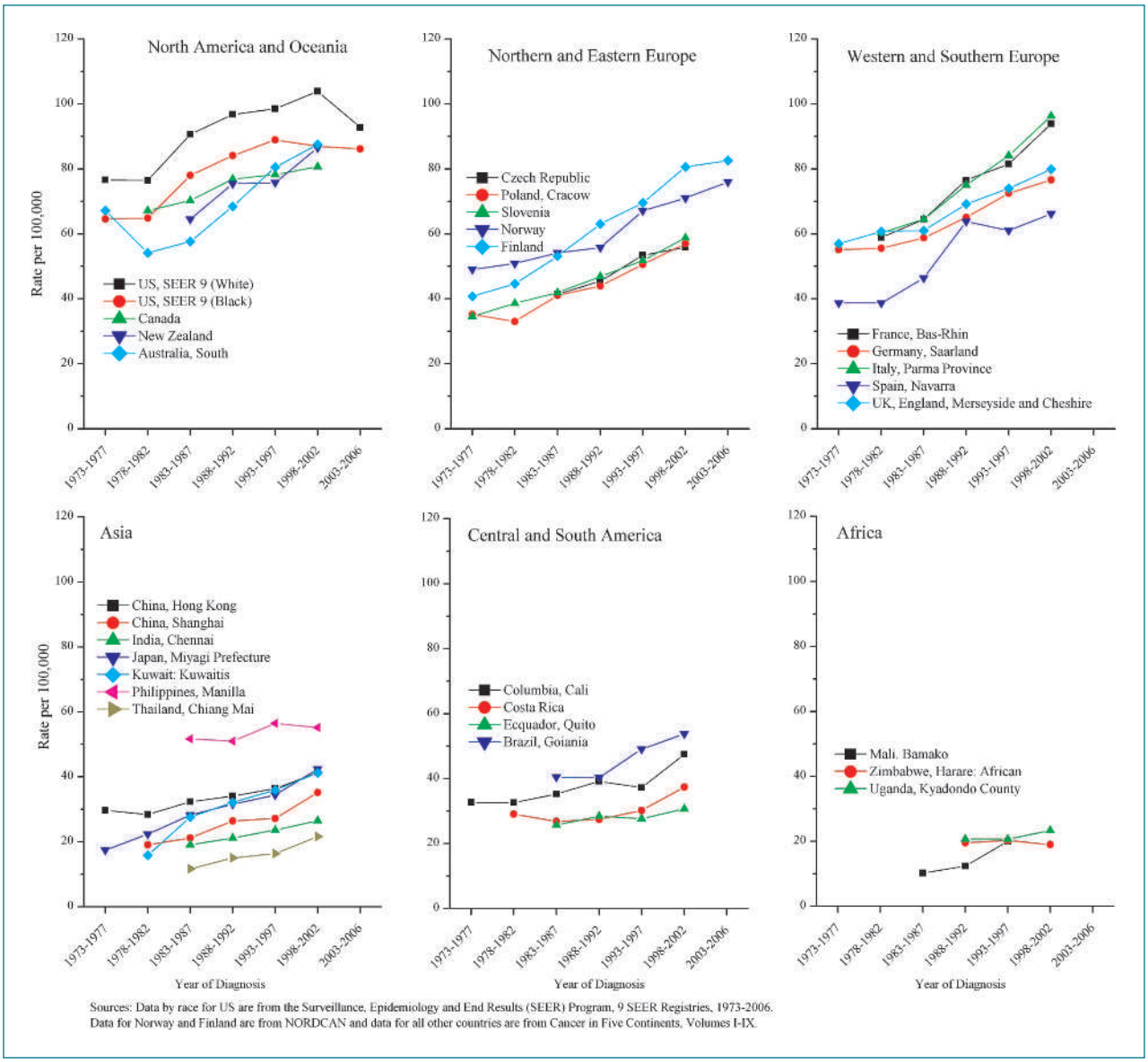

Figure 2. Trends in female breast cancer incidence rates for select registries, 1973-2006.

100,000) vary by nearly 50-fold worldwide, ranging from 3.9 in India to 178.8 in U.S. blacks (Fig. 3). Generally, the highest rates are recorded in North America, Oceania, and Northern and Western Europe, whereas the lowest rates are found in Asia and North Africa.

Much of the international variations in prostate cancer incidence rates reflect differences in the use of prostate-specific antigen (PSA) testing, which detects indolent prostate cancer cases that may not otherwise have been detected in one's lifetime (79-81). According to recent estimates, 23% to 42% of prostate cancer cases in Europe and the United States could be due to overdiagnosis through PSA testing (82, 83). The relatively low mortality rates in U.S. whites and in some European countries, where PSA testing is common, may also support the role of overdiagnosis to the high incidence rates in these countries. However, some of the international variations could be real. Two studies, conducted before the introduction of PSA testing, reported strong international ecologic correlation between per capita fat consumption and incidence or mortality rates, suggesting the role of animal fat in the occurrence of prostate cancer (84, 85). These findings were supported by subsequent analytic studies (86, 87). Further, the high prostate cancer incidence and mortality rates (Fig. 3) among black populations in the United States and other parts of the world [including Jamaica (88) and Trinidad and Tobago (89)] may reflect differences in genetic susceptibility (90, 91).

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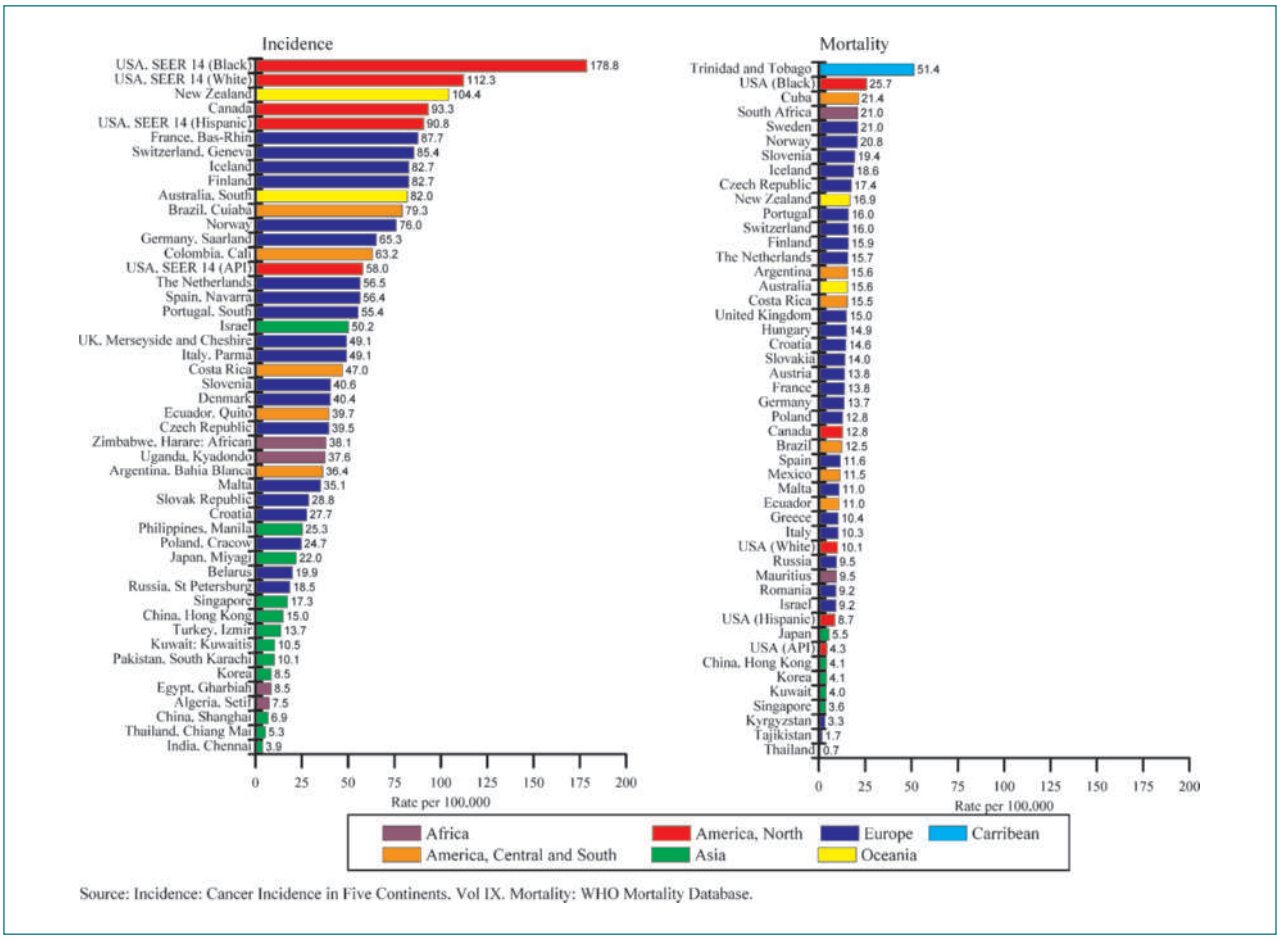

Figure 3. Prostate cancer incidence and mortality rates in select registries, 1998-2002.

Incidence rates in the United States, Canada, and Australia are generally decreasing after increasing dramatically between the late 1980s and early 1990s because of rapid dissemination of PSA testing, while rates in the United Kingdom and elsewhere in Europe continue to increase slightly because of increased awareness and gradual adoption of PSA testing (80). Prostate cancer mortality rates have been decreasing in most western countries, including the United States, Canada, Finland, France, Israel, Italy, the Netherlands, Norway, Portugal, Sweden, and Australia (80). The reason for this is not clear, but may reflect both improved treatment and early detection (92, 93). However, a recent randomized trial in the United States failed to show the benefit of PSA testing in reducing deaths from prostate cancer, although another trail in Europe showed a benefit (94, 95).

In contrast to the prostate cancer incidence and mortality trends in western countries, rates are increasing in some Asian and Eastern European countries, such as Japan, Singapore, and Poland, where PSA testing is not commonly used (Supplementary Fig. S9). The increase in these countries is thought to reflect westernization, including increased consumption of animal fat, obesity, and physical inactivity (80).

Stomach

Stomach cancer is the fourth most commonly diagnosed cancer and the second leading cause of cancer death worldwide, with an estimated 990,000 new cases and 738,000 cancer deaths in 2008 (11). Incidence rates (per 100,000) vary from 3.3 in men and 2.0 in women in Egypt to 65.9 in men and 25.9 in women in Korea (Fig. 4). These large regional variations mainly reflect differences in prevalence of *H. pylori* infection, which accounts for more than 60% of gastric cancer worldwide (96). Differences in smoking prevalence may also, in part, contribute to this variation because it accounts for about 10% of all stomach cancer cases worldwide (18, 97). The regional variations in gastric cancer mortality rates have also been linked with differences in dietary sodium and nitrate intake in an ecologic study (98), although the contribution of salt intake to the worldwide stomach cancer burden has not been quantified.

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Incidence rates for stomach cancer have declined steadily in several western countries (99), with rates decreasing by more than 80% since 1950 in the United States (100). Similar decreasing trends, albeit at much lower magnitudes, have been noted in more recent years in countries with historically high stomach cancer incidence rates including Japan, China, Korea, Columbia, Ecuador, Ukraine, and Russia (99). Reasons for this remarkable worldwide decrease in incidence and mortality rates are not fully understood, but are thought to include decreased reliance on salted and preserved foods and increased availability of fresh fruits and vegetables due to the invention of refrigeration, reduction in chronic *H. pylori* infection due to improved hygiene and use of antibiotics (96), and increased screening activities (in Japan; ref. 99). Reduction in smoking may have also contributed to the decrease in stomach cancer rates in the United States, the United Kingdom, and other western countries, where the tobacco epidemic has long been established.

In contrast to the decreasing overall stomach cancer incidence rates, which are largely determined by the trends in the fundus and distal stomach (pylorus), incidence rates have increased for cancer of the gastric cardia (the proximal part of the stomach) in the United States and many European countries, including Denmark and the United Kingdom (101, 102). This increase is thought to reflect a rise in the gastroesophageal reflux disease associated with the obesity epidemic (103). Improvements in histologic diagnosis and verification of tumors of the esophagus and stomach are also thought to contribute to the increase in gastric cardia adenocarcinoma of the esophagus (101, 104).

Preventive measures for stomach cancer include avoidance of foods preserved by salting and pickling, decreasing initiation and increasing cessation of smoking, increasing consumption of fresh fruits and vegetables, and reduction of *H. pylori* infection through improved hygiene (105). Early detection programs are available in Japan and Korea (106, 107). There is also considerable

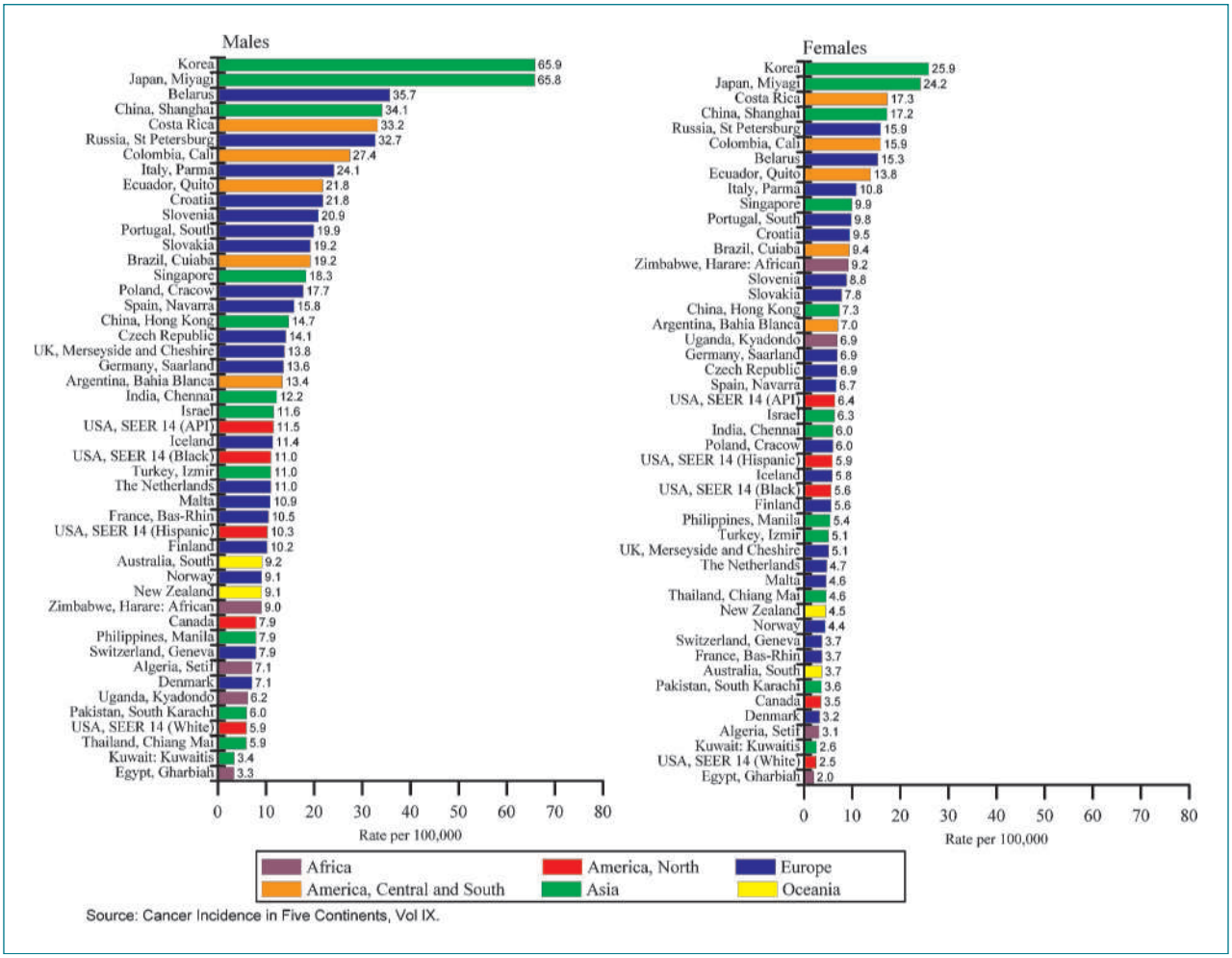

Figure 4. Stomach cancer incidence rates by sex in select registries, 1998-2002.

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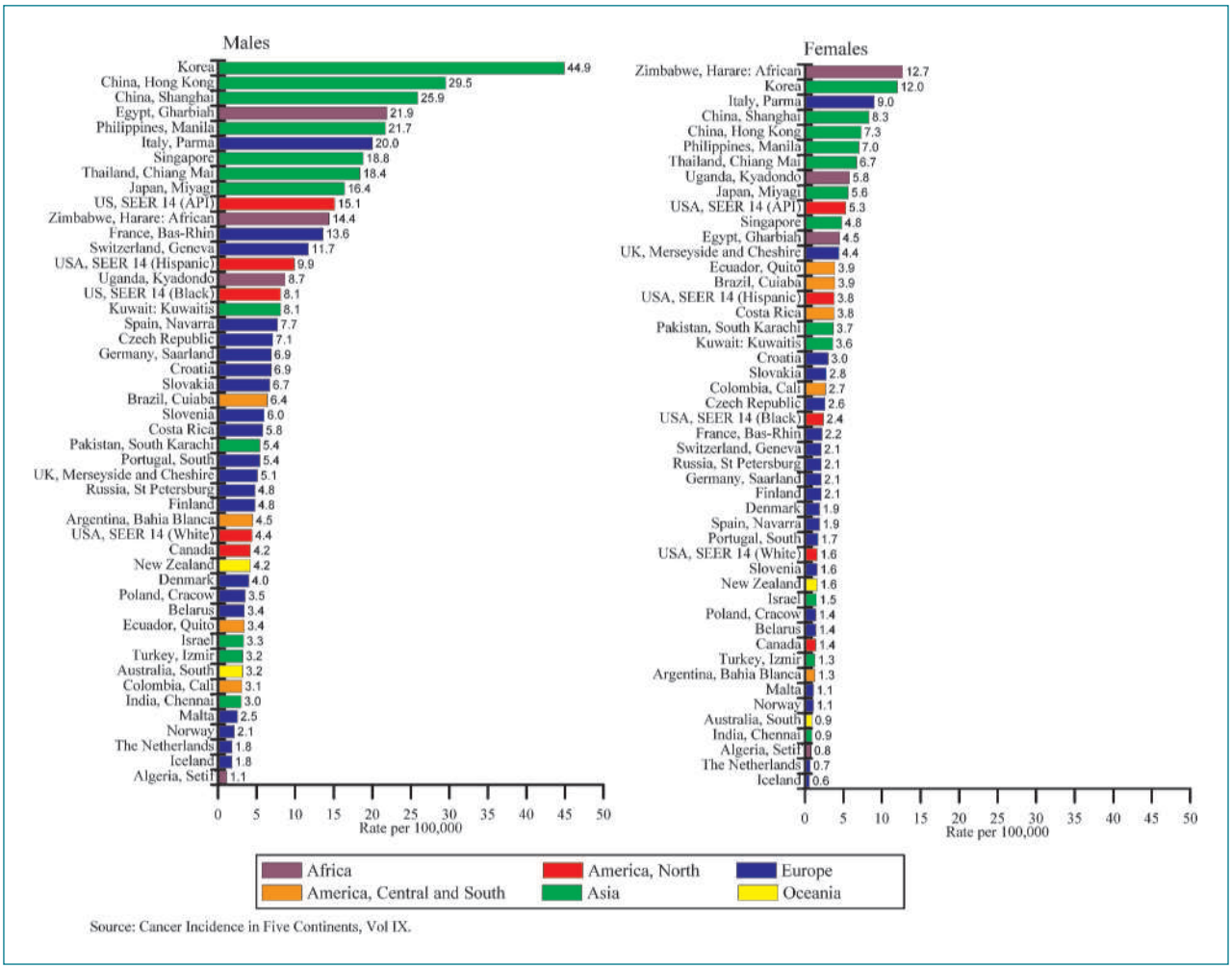

Figure 5. Liver cancer incidence rates by sex in select registries, 1998-2002.

interest in *H. pylori* screening and treatment in high-risk populations, such as China, Japan, and Korea, where the prevalence of *H. pylori* infection in the general population reaches as high as 50% (108), although there is a concern that extensive use of antibiotics could lead to development of antibiotic-resistant strains of *H. pylori* (109).

Liver

Liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide, with an estimated 748,000 new liver cancer cases and 696,000 deaths during 2008 (11). Nearly 85% of these cases occur in less developed countries, with China alone accounting for more than 50% of the total (11). There is a 20- to 40-fold difference in international variations in liver cancer rates (Fig. 5). Generally, the highest rates are found in Asia and West and Central Africa, and the lowest in Europe, Oceania, and North America. U.S. Hispanics and Asians have higher rates than U.S. whites, but they have lower rates than their counterparts in Asia and Latin America (Fig. 5; Supplementary Fig. S10). Among primary liver cancers occurring worldwide, hepatocellular carcinoma accounts for 70% to 85% of the total cases (110).

International variation in liver cancer rates is largely explained by the distribution of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections (111), with HBV infection generally dominating in high-risk areas, including Asia and Sub-Saharan Africa, and HCV infection dominating in low-risk areas, including most parts of Europe and North America (96, 110, 112, 113). Exceptions to these patterns are the much higher prevalence of HCV than HBV in Japan, Pakistan, and Egypt, and the converse in Greece (110, 113). These two viruses account for 78% (HBV, 53%; HCV, 25%) of the total liver cancer deaths globally, with the estimates by region varying from about 64% in the Americas to about 90% in Japan and Singapore (110). Other known risk factors that contribute to the international variations in liver cancer rates include dietary exposure to aflatoxins in low-resource

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tropical countries and alcohol-related cirrhosis, smoking, and nonalcoholic fatty liver disease (obesity) in most western countries (111, 113, 114). Most of these factors, however, are thought to act as cofactors in the presence of coexisting chronic viral infections (6, 111). Substantial variations in liver cancer rates also occur within country by region or subpopulation due, in part, to differences in the historical prevalence of HBV and HCV chronic infections (39, 115-117). In New Zealand, for example, liver cancer rates and prevalence of hepatitis B surface antigen are 3 to 10 times higher in the Maori population than in whites (116).

Interpretation of temporal trends in liver cancer rates could be affected by changes in classification of diseases and/or by difficulties in distinguishing primary liver cancer from secondary liver cancer (118-120). Nevertheless, liver cancer rates have decreased during the past decade in select European (especially southern Europe) and Asian countries (111, 119, 121). The decrease in southern European countries is thought to reflect screening of blood products for HCV and HBV markers, reductions in alcohol consumption and smoking prevalence, and/or improved treatment for liver cancer as well as for cirrhosis (mortality rates only; refs. 111, 119, 121). The decrease in select Asian countries, including China and Korea, is thought to reflect reduction in transmission of HBV during childhood and adulthood through improved hygienic and sanitary conditions and reduction in contamination of food with aflatoxins through better food storage system (111, 121, 122). Infant hepatitis immunization programs implemented over the past two decades in these and other countries have been shown to substantially decrease the trend in children and adolescents (123, 124), but are too recent to affect the trends in adults or at all ages (125).

In contrast to the decreasing trends in high-risk countries, especially in Asia, liver cancer rates are increasing in several parts of the world, including the United States, Egypt (126), Japan (127), Oceania, and Europe, in part due to widespread HCV infection through injected drug use and contaminated blood transfusion and/or needles used for medical purposes (111, 119, 128-133). The obesity epidemic and associated diabetes are also thought to contribute to the growing burden of liver cancer in the United States and several other countries (119, 132). According to the American Cancer Society Cancer Prevention Study II, liver cancer death rates were four times higher in obese people than in those with normal body weight (134).

Preventive strategies for liver cancer include prevention of HBV and HCV infections and avoidance of excessive alcohol consumption, as well as implementation of policies to reduce aflatoxin contamination of food supply in low-resource tropical countries (6). A vaccine that protects against HBV has been available on the market since 1982, and in 1992, WHO recommended that all countries include HBV vaccine as part of the routine infant immunization program (135). As of 2008, a total of 177 countries (91%) had introduced HBV vaccine into their national infant immunization schedules (136). However, countries that have yet to implement the program include many Sub-Saharan Africa and Asian countries, where the viral infection rate and the disease burden are among the highest (135). In contrast to HBV, no vaccine is available against HCV. Therefore, HCV prevention strategies include screening of blood, organ, tissue, and semen donors for antibodies to HCV and instituting adequate infection control practices during all medical, surgical, and dental procedures.

Esophageal cancer

Esophageal cancer is the eighth most frequently diagnosed cancer and the sixth leading cause of cancer deaths worldwide, with an estimated 482,000 new cases and 407,000 deaths in 2008 (11). The highest incidence rates are found in Asia and Sub-Saharan Africa and the lowest rates are found in Europe and North America (Supplementary Fig. S11). Generally, rates are much higher in men than in women.

Cancer of the esophagus occurs in two major histologic forms, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC; ref. 137), each with distinct geographic patterns (138-140). ESCC dominates in most parts of the world, especially in high-risk areas such as China and Iran, where it accounts for about 90% of the total esophageal cases (141-143). Smoking and alcohol consumption are the major risk factors for ESCC, whereas smoking and obesity are major risk factors for EAC (144, 145). Smoking and alcohol consumption account for more than 90% of ESCC in the United States and several other western countries (144, 145), but these risk factors play a less significant role for the cancer burden in high-risk areas such as Linxian (China) and Golestan (Iran; refs. 143, 146). In these regions, both smoking prevalence and alcohol consumption are low (147) and the incidence of ESCC in women is as high as in men, despite the low prevalence of smoking in women compared with men (141). Suggested risk factors for ESCC in these high-risk areas include poor nutrition, lack of fruit and vegetables, drinking hot beverages, and opium (143, 146, 148-151).

In addition to differences in geographic patterns and major risk factors, ESCC and EAC show markedly different temporal trends. ESCC incidence rates continue to decrease in most western countries and in some high-risk countries due, in part, to the decrease in smoking prevalence (men only) and alcohol consumption, improved socioeconomic status, and the availability of more fruit and vegetables in high-risk areas (102, 138, 152). However, incidence rates for ESCC have continued to increase in some countries such as Taiwan due, in part, to increased consumption of cigarettes, alcohol, and betel nuts (153).

In stark contrast to the trends for ESCC in most countries, incidence rates for EAC are increasing in several economically developed countries, including the United States, the United Kingdom, and Denmark (138,

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152, 154). This increase is thought to primarily reflect increases in gastroesophageal reflux disease and Barrett's esophagus, a precursor of esophageal cancer, related to the obesity epidemic in these countries (103, 155). Other suggested contributing factors for this pattern include the declining prevalence of *H. pylori* infection due to improved sanitation and widespread utilization of antibiotics (156-158) and increased tendency to classify cancers located in gastroesophageal junction as EAC, rather than as gastric cardia (159). *H. pylori* is hypothesized to be protective against EAC because it reduces the acidity of stomach contents and thereby reduces esophageal damage from reflux (145).

Cervix uteri

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide, with an estimated 529,000 new cases and 275,000 deaths expected to occur in 2008 (11). The incidence rates (per 100,000) among select cancer registries worldwide range from less than 5 in Egypt, China (Shanghai), and many European countries to more than 45 in Sub-Saharan Africa countries (Fig. 6). In most parts of Sub-Saharan Africa, South America, the Caribbean, and Southern Asia, cervical cancer is the leading cause of cancer death and premature death among women (160). U.S. Hispanics and Asians have higher cervical cancer incidence and mortality rates than U.S. whites, but lower rates than their counterparts in Latin America and Asia (Fig. 6; Supplementary Fig. S12).

Persistent infection with about 15 high-risk human papillomavirus (HPV) types is the major risk factor for cervical cancer, with HPV-16 and HPV-18 infections accounting for about 70% of the total cases (161); multiple sexual partners, younger age at first sexual intercourse, immunosuppression, and cigarette smoking serve as cofactors to the HPV persistent infection and progression to cancer (162, 163). The large regional variation in cervical cancer rates reflects geographic differences in HPV prevalence (164) and/or the availability of Pap test screening

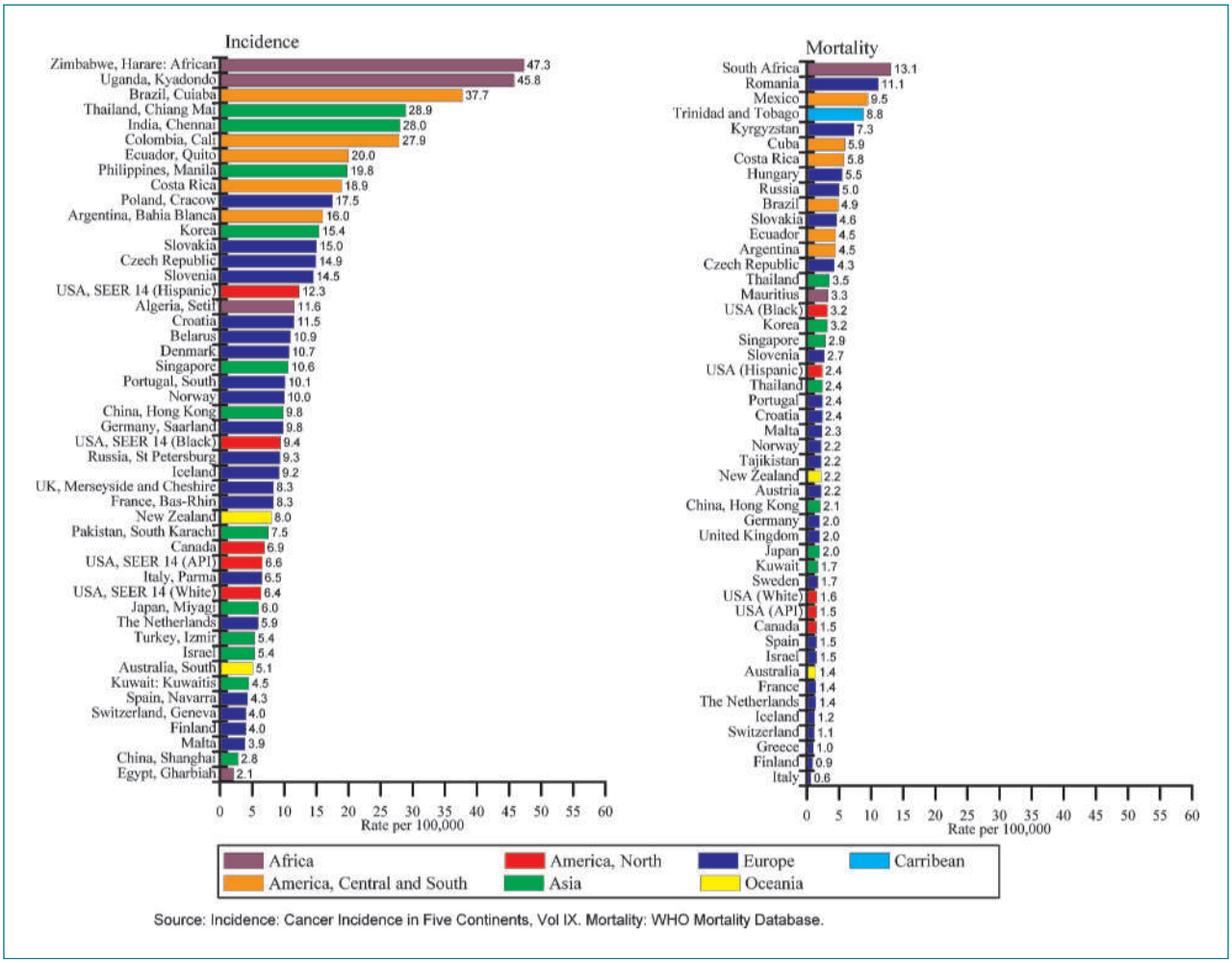

Figure 6. Cervical cancer incidence and mortality rates in select registries, 1998-2002.

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(organized or opportunistic) that allows the detection and removal of precancerous lesions (165-168). In several western countries, where screening programs have long been established, cervical cancer rates have decreased by as much as 65% over the past four decades. For example, in Finland, cervical cancer incidence rates decreased from 21.1 in 1966 to 7.3 in 2007 (13). Rates have also decreased in high-risk areas, including China, Taiwan, Korea, and India, in part due to improved screening activities and socioeconomic conditions (70, 167, 169-171), although the decreases in proportionate terms were much smaller compared with those in western countries.

In contrast to the favorable trends at all ages combined, cervical cancer rates have been increasing among younger generations in several countries, including Finland, the United Kingdom, Denmark, and China (165, 170, 172). This unfavorable trend is thought to reflect increases in HPV prevalence from changing sexual behaviors (165, 170, 172). The exceptionally low overall cervical cancer rates in the Middle East and other parts of the developing world are thought to reflect low prevalence of HPV infections due to societal disapproval of extramarital sexual activity (173).

The implementation of conventional cytology-based screening, a Pap test followed by colposcopy/biopsy and treatment, is not feasible in most low- and middle-income countries because of cost and less developed healthcare infrastructure. However, many low-tech, affordable, and effective screening techniques have been developed for use in these countries, including visual inspection of cervix for lesions using either acetic acid or Lugol's iodine and DNA testing for HPV in cervical cell samples (174-176). Vaccination of adolescents against HPV-16 and HPV-18 infections, which cause about 70% of all cervical cancer worldwide, is another new opportunity for substantially reducing the future burden of cervical cancer in both low- and high-resource countries. However, the current high cost of the vaccine (more than US$300 for all three doses) will be the major impediment in the introduction and wide application of these vaccines in poor-resource countries, at least in the short term (177).

Issues in Data Interpretation

The interpretations of international incidence and mortality patterns presented here could be affected by several factors. First, we describe the international variations in cancer rates largely based on 45 select cancer registries, and the variations for some cancer sites could be much larger than given here. Second, the high incidence rates in western countries for some cancers may, in part, reflect detection practices through screening and imaging techniques, rather than true disease occurrence. Third, compared with developed countries, information on routine medical records and death certificates is more likely to be incomplete and population estimates are less likely to be accurate in less developed countries, affecting the accuracy of the rates (13). Finally, most population-based cancer registries worldwide are regional rather than national, and regional data may not be representative of national data because of substantial regional differences in risk factors, socioeconomic status, and access to early detection services. Further, most cancer registries in the developing world are located in metropolitan areas, where unhealthy lifestyle factors and western behaviors that increase cancer risk are far more prevalent than in the general population (178, 179).

Summary

While cancer rates in general are decreasing in the United States and many western countries, they are increasing in less developed and economically transitioning countries, including Eastern European countries, because of adoption of unhealthy western lifestyles such as smoking and physical inactivity and consumption of calorie-dense food. Cancers that were once known as diseases of industrialized countries, such as lung, colon, and breast cancers, are now commonly occurring in economically transitioning and less developed countries. Most of these countries also continue to be disproportionately affected by cancers related to infectious agents, such as cervix, liver, and stomach cancers, which are potentially preventable.

WHO has developed guidelines and policies for establishing an effective national cancer control program to accelerate the translation of cancer control knowledge into action according to capacity and economic development (180-182). In economically developing countries, this includes raising awareness on the increasing burden of cancer, reducing the prevalence of major risk factors (obesity, tobacco, and infectious agents), the application of low-technology and cost-effective approaches to prevention/early detection of cervical cancer, and improving the availability of palliative care. A number of developing countries, including Vietnam and Tanzania, have developed national cancer control programs, although these programs are funded inadequately because of limited resources and other competing public health programs (183). International public health agencies and private and government donors can play significant roles in strengthening existing cancer control programs and/or implementing new programs to arrest the growing burden of cancer in economically developing countries (184). Development of a cancer control program should include the establishment of a cancer registry to asses the cancer burden and identify priorities and to evaluate the effectiveness of the program.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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