Review

Cancer Epidemiology, Biomarkers & Prevention

Global Cancer Incidence and Mortality Rates and Trends—An Update

Lindsey A. Torre[1], Rebecca L. Siegel[1], Elizabeth M. Ward[2], and Ahmedin Jemal[1]

Abstract

There are limited published data on recent cancer incidence and mortality trends worldwide. We used the International Agency for Research on Cancer's CANCER*Mondial* clearinghouse to present age-standardized cancer incidence and death rates for 2003–2007. We also present trends in incidence through 2007 and mortality through 2012 for select countries from five continents. High-income countries (HIC) continue to have the highest incidence rates for all sites, as well as for lung, colorectal, breast, and prostate cancer, although some low- and middle-income countries (LMIC) now count among those with the highest rates. Mortality rates from these cancers are declining in many HICs while they are increasing in LMICs. LMICs have the highest rates of stomach, liver, esophageal, and cervical cancer. Although rates remain high in HICs, they are plateauing or decreasing for the most common cancers due to decreases in known risk factors, screening and early detection, and improved treatment (mortality only). In contrast, rates in several LMICs are increasing for these cancers due to increases in smoking, excess body weight, and physical inactivity. LMICs also have a disproportionate burden of infection-related cancers. Applied cancer control measures are needed to reduce rates in HICs and arrest the growing burden in LMICs.*Cancer Epidemiol Biomarkers Prev; 25(1); 16–27. ©2015 AACR.*

See related commentary by Bray, p. 3

Introduction

Cancer is a leading cause of death worldwide in countries of all income levels. To add to the existing burden, the number of cancer cases and deaths is expected to grow rapidly as populations grow, age, and adopt lifestyle behaviors that increase cancer risk. This is especially important in low- and middle-income countries (LMIC) as they undergo economic transition, which includes greater mechanization of transport and labor, cultural shifts in the roles of women, and increased exposure and access to international markets. As a result, many of the lifestyle risk factors, such as tobacco use, physical inactivity, excess body weight, and reproductive patterns, which are already prevalent in high-income countries (HIC), are also becoming increasingly common in LMICs.

This article describes the burden and patterns in incidence and mortality for several common cancers worldwide using incidence and mortality data compiled by the International Agency for Research on Cancer (IARC) in Cancer*Mondial*.

Materials and Methods

Both cancer incidence and mortality data are provided by the IARC through the Cancer*Mondial* database (1). Cancer incidence data are drawn from *Cancer Incidence in Five Continents* (CI5). CI5 is a collaboration between the IARC and the International Association of Cancer Registries, which has compiled and published volumes of high-quality cancer registry data every 5 years since the 1960s (2). The most recent volume X of CI5 (2003–2007) includes 290 registries representing more than 400 populations. CI5 also produces CI5*plus*, which provides annual incidence data for select registries. For additional time periods beyond what is available in CI5, incidence data for the United States are drawn from the Surveillance, Epidemiology and End Results (SEER) Program (3), and data for Nordic countries are drawn from NORDCAN (4). Mortality data in the IARC Cancer*Mondial* database were extracted from the WHO Cancer Mortality Database and are available through 2012. Long-term annual data for visual assessment of trends are presented using 3-year moving averages for smoothing. Estimates for 2012 from the IARC's GLOBOCAN database are also used for more current cancer burden estimates (5). In this article, we primarily use incidence data from 50 registries and mortality data from 50 countries selected to represent the various regions of the world. Inconsistencies in sources for incidence and mortality data reflect differences in the structure for recording cancer versus vital statistics. Rates are age-standardized to the 1960 Segi world standard population, modified by Doll and colleagues (6).

Results and Discussion

All cancer sites

In 2012, an estimated 14.1 million new cancer cases and 8.2 million cancer deaths occurred worldwide (5). Incidence rates in the 50 selected registries range from over 400 per 100,000 males and 300 per 100,000 females to less than 100 per 100,000 in both males and females (Supplementary Fig. S1). Mortality rates in the 50 selected countries range from over 200 deaths per 100,000 males and over 100 deaths per 100,000 females to less than 50 deaths per 100,000 in both males and females (Supplementary

[1]American Cancer Society Surveillance and Health Services Research, Atlanta, Georgia. [2]American Cancer Society Intramural Research, Atlanta, Georgia.

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

Corresponding Author: Lindsey A. Torre, American Cancer Society, 250 Williams Street, Atlanta, GA 30303. Phone: 404-327-6591; Fax: 404-321-4669; E-mail: Lindsey.Torre@cancer.org

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Fig. S2). For both sexes, the highest rates are generally in North America, Oceania, and Europe.

All-sites cancer rates, however, mask the diversity in cancer profiles in individual countries. There is substantial variation in the most commonly diagnosed cancer in each country, especially among males (Fig. 1). According to GLOBOCAN 2012, prostate cancer is the most commonly diagnosed cancer among males in 87 countries, especially in North and South America; Northern, Western, and Southern Europe; and Oceania. Lung cancer is the most commonly diagnosed cancer among males in Eastern Europe. In contrast with the consistency in the leading cancer within most regions, there is considerable heterogeneity in leading cancers among males in Africa and Asia. In Africa, the leading cancers among men include prostate, lung, colorectum, liver, esophagus, Kaposi sarcoma, leukemia, stomach, and non-Hodgkin lymphoma, whereas in Asia they include lung, lip and oral

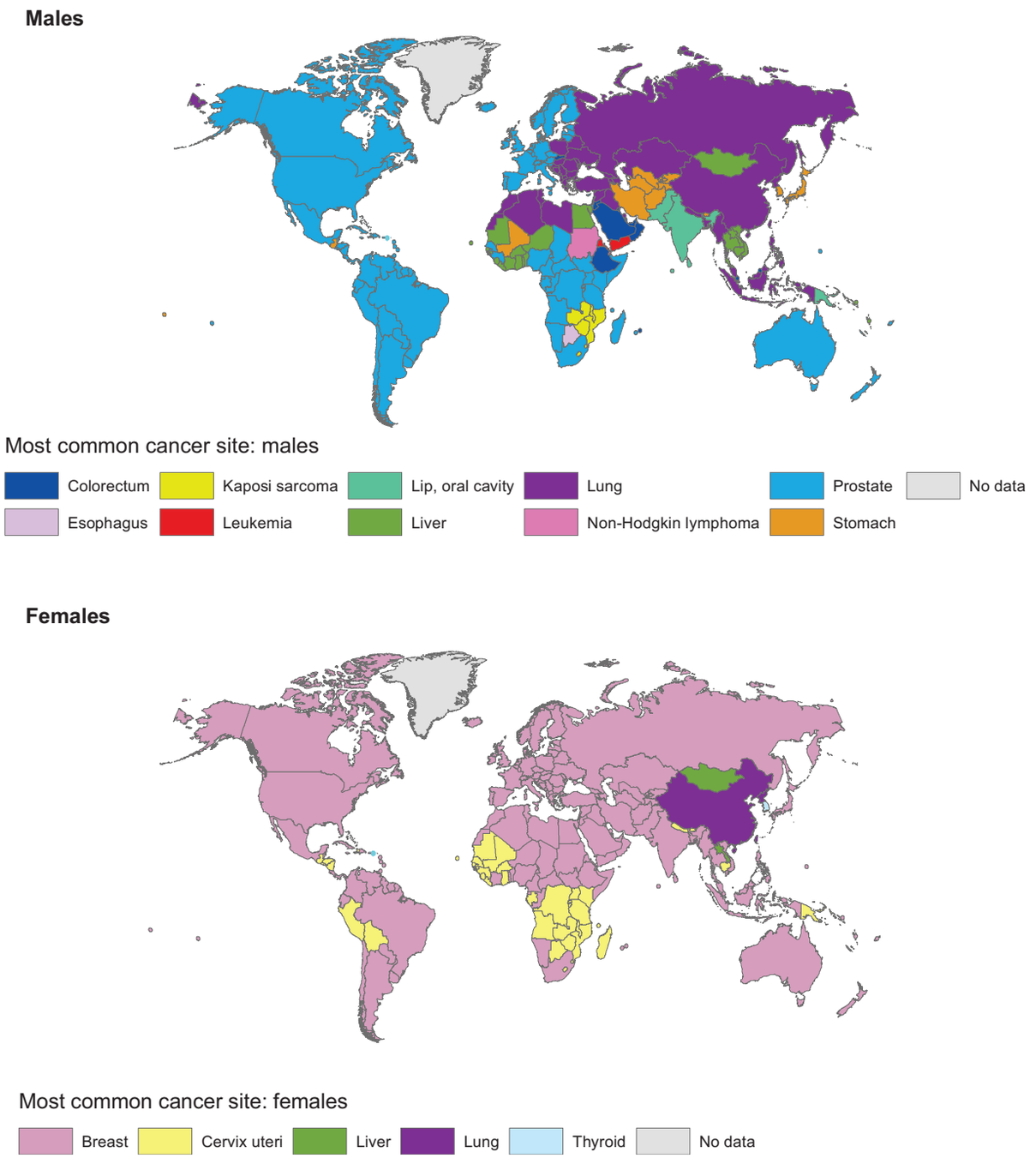

Figure 1.
Most commonly diagnosed cancers, 2012. (Compiled from GLOBOCAN 2012.)

cavity, liver, stomach, colorectal, and prostate cancers. Among females, breast is the most common cancer in North America, Europe, and Oceania. Breast and cervical cancers are the most frequently diagnosed cancers in Latin America and the Caribbean, Africa, and most of Asia. However, the most common female cancers in Asia also include lung (China, North Korea), liver (Lao People's Democratic Republic, Mongolia), and thyroid (South Korea). Below, we describe the incidence and mortality trends for eight major cancers worldwide. These cancers account for more than 60% of total global cases and deaths (5).

Lung and bronchus

An estimated 1.8 million new lung cancer cases were diagnosed in 2012 (5). Lung cancer incidence rates in selected registries are as high as 90 cases per 100,000 males (Turkey, Izmir) and 38 cases per 100,000 females (US, SEER 18 registries, Whites; Fig. 2). Aside from Turkey, the highest incidence rates among males are in the United States and Eastern Europe, whereas the highest rates among females are in North America and Northern Europe. Because of low survival even in more developed countries, lung cancer mortality rates are generally similar to incidence rates (Supplementary Fig. S3).

Lung cancer trends in a given country are primarily shaped by the tobacco epidemic. Lung cancer–related deaths appear in large numbers about two to three decades after the widespread uptake of smoking, with mortality trends approximating incidence trends due to the high fatality rate (7, 8). Among males, lung cancer mortality rates have peaked and are now decreasing in many HICs, reflecting the uptake and subsequent decline in male smoking prevalence (Supplementary Fig. S4). Lung cancer trends in women lag behind those in males because women began smoking later. In countries with the earliest uptake of smoking among women (e.g., US, UK, and Australia), lung cancer mortality rates have peaked, whereas they continue to climb in countries where women began smoking later (9). Although overall rates among women are increasing, rates among younger women are beginning to decrease in recent years in many countries, indicating early successes in tobacco control (9). In some LMICs where the tobacco epidemic is newer or has not yet taken hold, including Africa and parts of Asia, lung cancer mortality has not begun to rise, and could be arrested through swift application of tobacco control measures (9).

Preventing smoking initiation and promoting smoking cessation, even after years of smoking, can prevent lung cancer–related deaths. The WHO Framework Convention on Tobacco Control (FCTC), which entered into force in 2005, is an international treaty outlining measures to control the global tobacco epidemic (10). To assist countries in the implementation of the FCTC, the WHO introduced the MPOWER policy

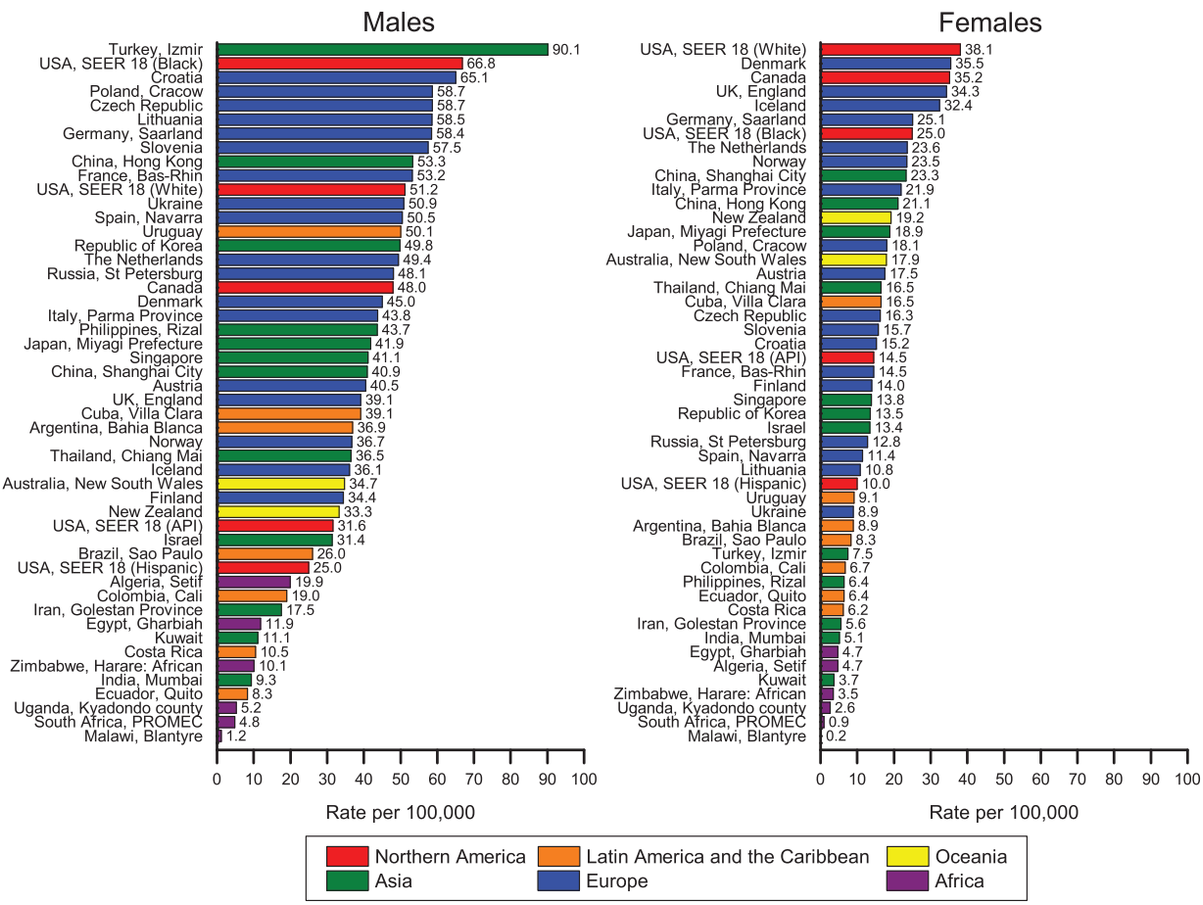

Figure 2.
Lung cancer incidence rates by sex, select registries, 2003–2007. (Compiled from *Cancer Incidence in Five Continents, Volume X.*)

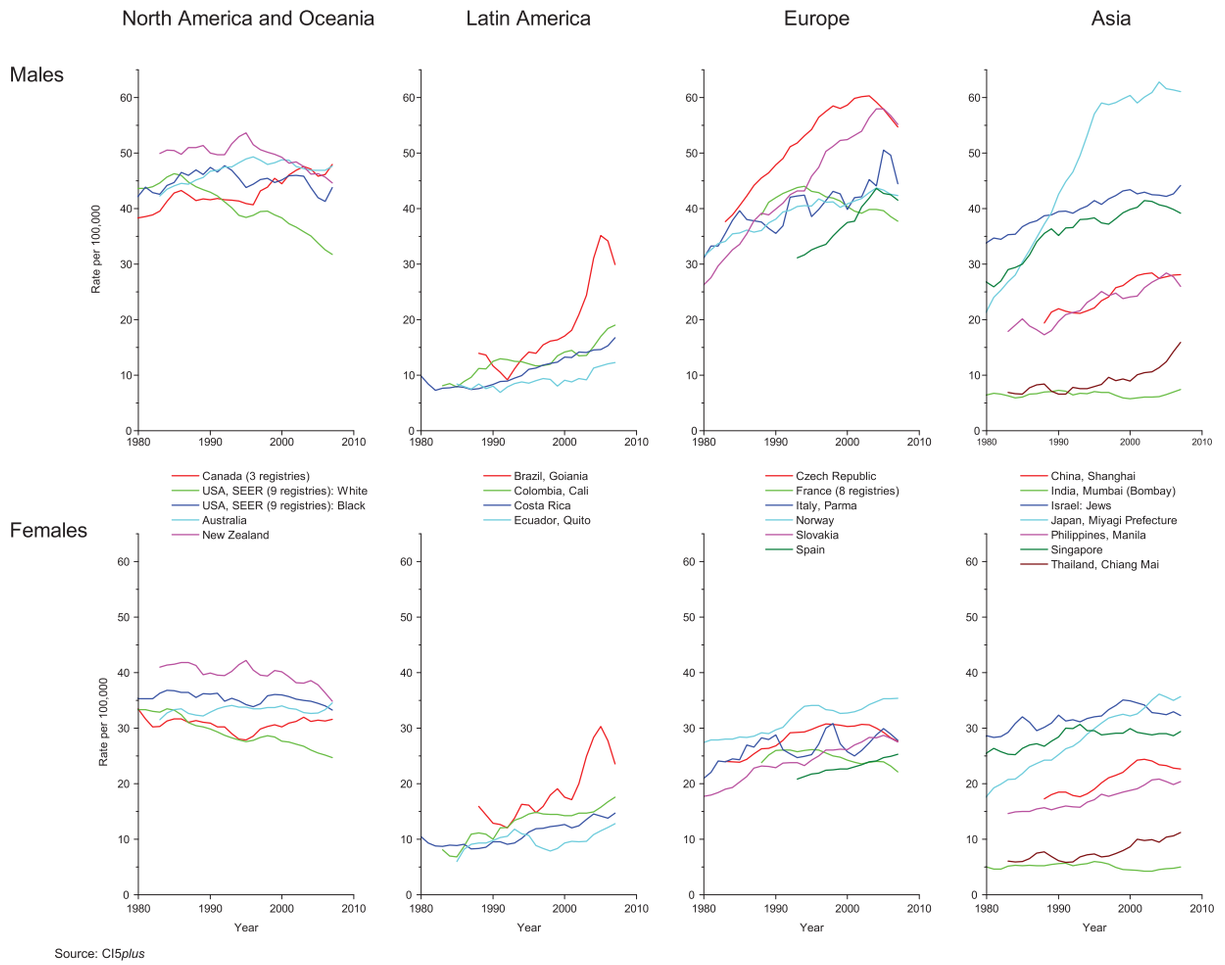

Figure 3.
Colorectal cancer incidence trends, select countries, 1980–2007. (Compiled from CI5*plus*.)

package, a set of evidence-based measures aimed at reducing demand for tobacco through taxation, smoke-free areas, monitoring, cessation assistance, education about the harms of tobacco, and bans on tobacco advertising. These measures have already proven effective in reducing smoking in several regions of the world. Screening with CT among former or current heavy smokers has also been shown to decrease lung cancer mortality by 20% in the United States (11); however, due to the infrastructure, technical expertise, and cost involved, it is unlikely that this screening method will benefit those in lower-resource countries in the near future.

Lung cancer can also be caused by certain occupational exposures, as well as air pollution, both indoor (from cooking and heating using coal or combustible materials) and outdoor (from particulate matter; refs. 12, 13). Exposure to indoor air pollution is thought to account for unexpectedly high rates of lung cancer among some populations with a low smoking prevalence, such as Chinese women (14).

Colon and rectum

In 2012, there were an estimated 1.4 million new colorectal cancer cases and 693,900 deaths (5). The highest colorectal cancer incidence rates among selected registries in both males and females are in Japan (Miyagi Prefecture; 62.4 cases/100,000 males and 37.2 cases/100,000 females). Other high rates are in Europe, Oceania, and North America (Supplementary Figs. S5 and S6). The lowest rates are found in Africa, some Asian countries, and Latin America and the Caribbean.

There is substantial variation in colorectal cancer incidence trends worldwide. Incidence rates are increasing in many countries where rates were historically low, such as those in Latin America and Asia (Fig. 3). Incidence rates have also been increasing in Eastern Europe, where they appear to have peaked at among the highest rates in the world. In the HICs of North America, Oceania, and Europe, rates are decreasing (United States, New Zealand, and France); relatively stable (Australia and Canada); or increasing (Norway, Spain, and Italy). The increases observed in Latin America, Asia, and Eastern Europe may be due to rapidly changing diet and activity patterns and increased smoking over the past several decades (15–17). The decreasing rates in the United States can be attributed largely to screening and removal of precancerous lesions, as well as reductions in risk factors (e.g., smoking), which have likely contributed to decreases in other countries as well (18, 19). However, incidence rates in the United States and Australia are increasing in adults younger than 50 years, for whom screening

is not recommended (18, 20). Reasons for this increase are unknown.

Despite rising incidence in several countries, colorectal cancer mortality rates are decreasing in many countries worldwide, likely due to screening and improved treatment (18, 19, 21). However, in some countries with rising incidence rates and fewer resources, such as Brazil, Chile, Romania, and Russia, mortality rates are increasing (16, 19).

Colorectal cancer risk can be reduced through a healthy lifestyle, including not smoking, maintaining a healthy body weight, staying physical active, consuming a diet low in red and processed meats and high in fiber, and minimizing alcohol consumption. Colorectal cancer cases and deaths can also be prevented through screening, which can remove precancerous lesions and detect cancer early. Several options for colorectal cancer screening are available, although they vary in cost and infrastructure requirements. Colonoscopy, which is a highly sensitive test, involves the highest cost and resources, whereas the fecal occult blood test (FOBT) is inexpensive, easy to perform, and thus the more practical option in many parts of the world. The fecal immunochemical test (FIT; also known as immunochemical FOBT or iFOBT) is often preferred to the guaiac-based FOBT (gFOBT) due to lack of dietary restriction requirements and its higher specificity, which may be especially relevant for some populations (22, 23). A noninvasive stool DNA test has also been developed and was recently approved by the US Food and Drug Administration (FDA) (24, 25). As of 2014, 36 countries, primarily those with high income and high incidence of colorectal cancer, had large-scale screening programs (26). Colorectal cancer screening programs may not be recommended in many LMICs, where colorectal cancer incidence is low (27). On the other hand, many LMICs with lower rates and rapidly westernizing lifestyles are now experiencing increasing colorectal cancer rates that may merit a screening program using FOBT or stool DNA test.

Female breast

Breast cancer is the leading cause of cancer-related death among females worldwide. In 2012, an estimated 1.7 million cases and 521,900 deaths occurred (5). Female breast cancer incidence rates vary by more than 10-fold among the selected registries, with the highest rates in Western Europe and the United States and the lowest rates in Africa and Asia (with the exception of Israel, which has among the highest rates; Supplementary Fig. S7). Mortality rates vary about 4-fold. The highest mortality rates are found in the United States among Black women, whereas the lowest are in Korean women.

Higher breast cancer incidence in HICs reflects the use of breast cancer screening as well as higher prevalence of breast cancer risk factors (28). Breast cancer risk factors include weight gain after age 18 years, excess body weight (for postmenopausal breast cancer), use of menopausal hormone therapy (MHT), physical inactivity, alcohol consumption, and reproductive and hormonal factors, such as a long menstrual history, recent use of oral contraceptives, and nulliparity or later age at first birth (29, 30). Breastfeeding decreases the risk of breast cancer (30).

Incidence rates increased by about 30% in western countries between 1980 and the late 1990s, primarily due to increased screening, changes in reproductive patterns, and increased use of MHT (28). However, these rapid increases have slowed or plateaued since the early 2000s, when a major study reported an increased risk of breast cancer among users of MHT (Fig. 4). Declining or stable incidence rates may also be due to plateaus in screening participation (31). In contrast, breast cancer incidence rates in many other countries, especially LMICs, continue to increase. The causes of these increases are not completely understood, but are thought to include changing reproductive patterns as well as increased awareness and screening (28, 32).

In contrast with rising or stable incidence patterns, breast cancer mortality rates have been decreasing in many HICs since around 1990 (Supplementary Fig. S8). These declines are attributed to early detection and improved treatment (28), although the relative contribution of each varies according to statistical methods and approaches (33–35). Although mortality rates decline in the countries with historically higher rates, they continue to increase in lower-rate countries, such as those in Latin America and the Caribbean and parts of Asia. This is likely due to changes in risk factors, as well as limited access to early detection and treatment (16, 36, 37).

Although some breast cancer risk factors, such as reproductive patterns, are not modifiable, breast cancer risk can be decreased by maintaining a healthy weight, avoiding alcohol, and being physically active. Mammography screening can prevent breast cancer deaths by detecting the cancer at an early stage when treatment is more effective. Despite the limitations of mammography, including undetected cancers, false positives, and overdiagnosis (38, 39), numerous studies have shown that screening saves lives and increases treatment options (39, 40). However, not all countries have the resources to implement a population-based screening program. In these cases, awareness of early signs and symptoms and clinical breast examination are the recommended approaches (41).

Prostate

Prostate cancer is the second most frequently diagnosed cancer among males worldwide. Prostate cancer incidence varies by as much as 30-fold between selected registries, whereas mortality varies 18-fold (Supplementary Fig. S9). The highest incidence rates (cases/100,000) are in U.S. Blacks (SEER 18 registries, 168.3), followed by France (Bas-Rhin registry, 132.1) and Australia (New South Wales registry, 111.1). The highest mortality rates (deaths/100,000) are in Trinidad and Tobago (44.0), followed by U.S. Blacks (25.3), Cuba (23.5), and South Africa (22.4). The lowest incidence and mortality rates are in Asia. A large part of the variation in incidence rates reflects the use of PSA testing (42). However, differences in genetic susceptibility may also play a role in the disproportionately high rates in some populations of African descent (42, 43).

Incidence rates in countries where PSA testing was rapidly disseminated after its introduction in the late 1980s and early 1990s show similar trends—a rapid increase as more new cases of prostate cancer were detected, followed by a precipitous decline as the pool of prevalent cases available for detection diminished (42, 44). The gradual increase in incidence rates before the introduction of PSA testing in some of these countries is thought to reflect incidental diagnosis during transurethral resection of the prostate to treat benign prostatic hyperplasia (45). In other HICs where PSA testing was adopted more gradually, such as those in Western Europe, rates are increasing, but without a dramatic peak (42). However, incidence rates are also increasing in some countries where PSA testing did not begin until much later or is still uncommon, such as the United Kingdom, Japan, and Thailand (42).

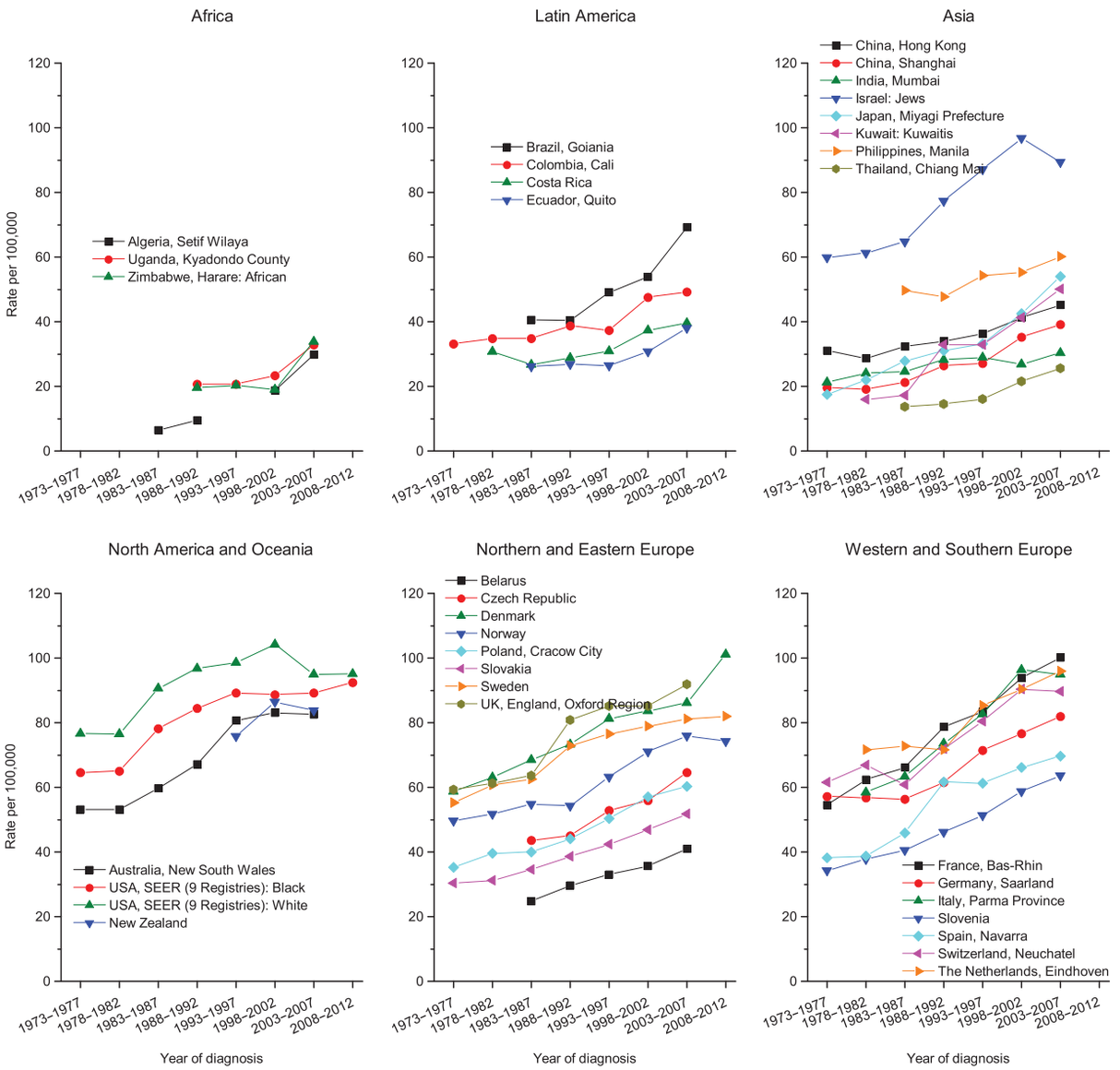

Figure 4.
Female breast incidence trends, select countries, 1973–2012. (Compiled from: US, Surveillance, Epidemiology, and End Results [SEER] Program, 9 registries, 1973–2012; Denmark, Norway, Sweden, 2008–2012 NORDCAN; all others, *Cancer Incidence in Five Continents, Volumes I–X.*)

Mortality rates have generally been declining in the HICs of North America, Oceania, Western Europe, and parts of Northern Europe since the 1990s (Supplementary Fig. S10). These decreases are thought to be due to improved treatment and/or early detection, although the contribution of PSA testing is debated (42); a large randomized trial in Europe found a significant reduction in mortality associated with PSA testing, whereas a U.S. trial with a different study design did not (46, 47). Rates peaked only recently or continue to increase along with incidence in Asia, Latin America and the Caribbean, Southern and Eastern Europe, and the Baltic states. Although the causes of prostate cancer are not well understood, possible reasons for these increases include increased prevalence of risk factors associated with economic development, such as greater consumption of animal fats, excess body weight, and physical inactivity (15, 42).

There are few known risk factors that can be modified to avoid prostate cancer, but research is being conducted on early detection and medical means of prevention. Routine screening using PSA testing is no longer recommended for men at average risk, as overdiagnosis is estimated to account for 23% to 42% of screen-detected cancers (48), and the side effects of treatment are often serious. However, studies are being conducted to more effectively test for prostate cancer, distinguish more aggressive forms of the disease, and identify men at higher risk of developing prostate cancer (49). The chemoprevention of prostate cancer is also being investigated (50).

Stomach

In 2012, an estimated 951,600 stomach cancer cases and 723,100 deaths occurred (5). The highest stomach cancer

Figure 5.
Stomach cancer incidence rates by sex, select registries, 2003–2007. (Compiled from *Cancer Incidence in Five Continents, Volume X*.)

incidence and mortality rates among both males and females are found in Eastern and Western Asia, Latin America, and some former Soviet European countries (Fig. 5 and Supplementary Fig. S11). Among males, incidence rates (cases/100,000) in Japan (Miyagi Prefecture, 66.7) and Korea (64.6) are twice as high as the next highest rates in Iran (Golestan Province, 30.4). Among females, incidence rates in Japan and Korea are 60% higher than the next highest rates in Ecuador and Costa Rica. Chronic infection with *Helicobacter pylori* (*H. pylori*) accounts for about 90% of cases of noncardia gastric cancer worldwide (51), and thus plays a large role in shaping regional variations in stomach cancer. Other risk factors are thought to include availability of fresh fruits and vegetables, dietary patterns, and methods of food preservation (52).

Stomach cancer incidence and mortality rates have been steadily declining since the middle of the 20th century in many HICs of North America and Europe, and more recently in many other countries, including those in Asia and Latin America (Supplementary Fig. S12). These decreasing trends are thought to be attributable to declining prevalence of *H. pylori* infection due to sanitation and antibiotics, in addition to better availability of fresh produce and less reliance on salt-preserved foods (53). Reductions in smoking in countries where it was common may have also contributed to the declines (54). Overall stomach cancer trends are dominated by the declining occurrence of non-cardia gastric cancer, which is linked to *H. pylori* (55); however, it is noteworthy that rates of gastric cardia cancer are increasing in the United States and many European countries (56–58). This is thought to reflect increasing obesity, although the possible influence of improvements in classification of gastric cancers cannot be ruled out (57, 59, 60).

Until recently, the best known strategies for preventing stomach cancer, aside from reduced prevalence of chronic *H. pylori* infection, included limiting consumption of preserved foods, eating more fruits and vegetables, and not smoking. However, a more active approach to treatment of *H. pylori* for the prevention of stomach cancer is currently being evaluated. In recent randomized trials, screening for and eradication of *H. pylori* using antibiotics was shown to reduce the risk of stomach cancer (61). Although this approach requires further research, it may represent a promising new way to further decrease stomach cancer rates in countries where chronic *H. pylori* infection is common.

Liver

In 2012, liver cancer was estimated to be the second leading cause of cancer-related death among males (5). Liver cancer incidence rates (cases/100,000) range from 1.9 (Algeria, Setif) to 41.3 (Korea) among males and from 0.8 (Netherlands) to 13.9

(Zimbabwe, Harare: Africans) among females (Supplementary Fig. S13). In general, the highest incidence and mortality rates among both sexes are in Eastern and Southeastern Asia and parts of Africa (Supplementary Fig. S14). Notably, it is estimated that 50% of liver cancer cases and deaths worldwide occur in China (5). About 70% to 90% of liver cancers globally are hepatocellular carcinoma (HCC), which is most often caused by chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV; ref. 62). Chronic infection with HBV or HCV is more common in LMICs, where 92% of all liver cancers are attributed to these viruses (53). Other risk factors for HCC that are more common in HICs include obesity, type 2 diabetes, cirrhosis related to heavy alcohol consumption, nonalcoholic fatty liver disease (associated with obesity), and smoking (63, 64). Aflatoxin, a toxin produced by a fungus that can infest stored grains, peanuts, soybeans, and corn, is also a risk factor primarily in LMICs. Another type of liver cancer, cholangiocarcinoma, is rare in most parts of the world, but has high rates in Thailand and other parts of Asia due to liver fluke infection (65).

Liver cancer mortality rates are increasing in areas that have until now experienced relatively low rates, such as North America, Oceania, and Central and Northern Europe (66). In the United States, these increases are thought to be attributable to increased prevalence of chronic infection with HCV as a result of exposure to contaminated blood or medical equipment and injection drug abuse during the 1960s and 1970s, and possibly contributed to by increases in obesity and type 2 diabetes in recent years (64, 66, 67). Liver cancer incidence rates are decreasing in areas that have historically had high rates of liver cancer, such as China and Japan. In China, this is thought to be due to reduced aflatoxin exposure and HBV infection through public health programs (68, 69). In Japan, reduced chronic schistosomiasis infection and HCV infection through improved blood donation practices and policies that deterred intravenous drug abuse are thought to have contributed to declining liver cancer rates (68, 70). The HBV vaccine has resulted in a more than 80% decline in liver cancer incidence rates among youth and young adults in Taiwan, where universal childhood HBV vaccination was introduced in 1984 (71); however, HBV vaccination cannot have caused the decreases witnessed in adults in other Asian countries because it was introduced too recently.

Liver cancer can be prevented through a variety of public health measures. HBV vaccination has been available since 1982 and has now been introduced in 181 countries, with most achieving more than 80% coverage of the full recommended dose for infants (26). HCV can be prevented through medical practices, including screening of donated blood and tissue products and infection control procedures. Needle exchange programs for injection drug users can also prevent the spread of HCV. Although no vaccine is available for HCV, new antiviral therapies may prevent chronic infection from developing in those with acute HCV infection (72). Antiviral therapies have also been shown to reduce the risk of developing liver cancer among those who have already progressed to chronic HBV or HCV (73). However, these treatments may be too costly to implement in resource-constrained settings. In the United States, the Centers for Disease Control and Prevention recommends a one-time test for HCV infection for all adults born between 1945 and 1965, as this group accounts for three-quarters of chronic HCV infections and HCV-related deaths (74). Additional preventive strategies include behavioral changes (limiting alcohol consumption and not smoking); increasing societal awareness (public health education campaigns about how to prevent liver flukes in water sources); environmental modifications (crop substitution and improved grain storage to prevent aflatoxin contamination); and medical interventions (mass drug administration to treat liver fluke infections; refs. 66, 75, 76).

Esophagus

In 2012, an estimated 455,800 esophageal cancer cases and 400,200 deaths occurred (5). The highest esophageal cancer incidence rates among the selected registries in both males and females are in Malawi, South Africa, and Iran (Supplementary Fig. S15). Mortality data are unavailable for most of the countries with the highest esophageal cancer risk. The highest mortality rates among countries with available data are in Kazakhstan and South Africa (Supplementary Fig. S16). Esophageal cancer is usually about three to four times more common in males than in females, and has two main types: squamous cell carcinoma (SCC) and adenocarcinoma. Regional variations in both the magnitude of rates and in the more common type of esophageal cancer are driven by differences in risk factors. SCC is the more common type in the highest-risk area, often referred to as the "esophageal cancer belt," which stretches from northern Iran through the Central Asian republics to north-central China. SCC can be caused by tobacco smoking and alcohol, but these behaviors are not common in this region, where the risk factors driving the high rates are not well understood. They are thought to include poor nutritional status, low intake of fruits and vegetables, and drinking beverages at very high temperatures (77–80). In Africa, which has some of the highest incidence rates, the causes are also poorly understood, but may include alcohol, dietary factors, and fungal contamination of maize (81). In Western countries, where SCC is less common than in other countries, alcohol and tobacco use account for almost 90% of cases (82). Adenocarcinoma is more common in areas with lower overall esophageal cancer rates (83). The main known risk factors for adenocarcinoma are obesity, chronic gastroesophageal reflux disease (GERD), and smoking (84). GERD, which is most common in overweight adults, can cause Barrett esophagus, which predisposes a person to develop esophageal cancer. Low fruit and vegetable consumption are also risk factors for adenocarcinoma (84).

Trends in esophageal cancer differ by histologic type. SCC incidence rates are decreasing in North America and Europe due to reductions in alcohol and tobacco use (85–87). At the same time, adenocarcinoma rates have been increasing in Western countries, including the United States, Australia, France, and England, likely due to increasing obesity, which increases the risk for GERD, Barrett esophagus, and subsequent development of esophageal adenocarcinoma (88). Increasing adenocarcinoma rates might also be related to the declining prevalence of *H. pylori* infection, which may protect against this type of esophageal cancer (89–91).

Esophageal cancer can be prevented through a healthy lifestyle, including maintaining a healthy weight, not smoking, and avoiding alcohol. Consuming a diet with sufficient fruits and vegetables may also lower risk (92). Further study is needed to determine prevention measures in highest-risk areas, such as the esophageal cancer belt, as the major risk factors in those areas are not clear. Studies are ongoing to determine how to prevent GERD and Barrett esophagus from progressing to esophageal cancer. Treating GERD with proton pump inhibitor drugs or surgery may prevent Barrett

esophagus and cancer (88), and surveillance of those with Barrett esophagus may reduce esophageal cancer mortality (93, 94).

Cervix uteri

An estimated 527,600 cervical cancer cases and 265,700 deaths occurred in 2012 worldwide (5). Cervical cancer is the third leading cause of cancer-related death in females in LMICs, but is rare in HICs. Cervical cancer incidence and mortality rates are highest in sub-Saharan Africa, Southeast Asia, Latin America and the Caribbean, and Central and Eastern Europe (Supplementary Fig. S17). In Zimbabwe (Harare: Africans, 86.7 cases/100,000 women), Malawi (Blantyre, 76.3), and Uganda (Kyadondo County, 54.3), rates are more than twice as high as those in all other registries. Some of the lowest incidence rates are in Western Asia. Geographic variation is due to differences in the availability of screening, which allows for the detection and removal of precancerous lesions, and human papillomavirus (HPV) prevalence (95–97). HPV infection prevalence ranges from 5% in North America to 21% in Africa (95). Cervical cancer incidence in sub-Saharan Africa is also influenced by the high prevalence of HIV infection, which has been found to promote progression of cancerous lesions (98).

In HICs where screening programs were introduced several decades ago, cervical cancer incidence rates have decreased by as much as 4% annually, and 70% overall (99, 100). Rates have also decreased in some high-incidence areas, including India and Brazil, possibly due to improved socioeconomic conditions or screening (97). In contrast with these trends, rates are rising in Zimbabwe, Uganda, and some countries of Central and Eastern Europe (101–103). Increasing trends in younger generations of European women are thought to be due to increasing prevalence of high-risk HPV infection due to changing sexual practices and inadequate cervical screening (101, 104).

Vaccines that protect against the two types of HPV that cause the majority (70%) of cervical cancer have been available since 2006, and a new vaccine that protects against nine types of HPV and can prevent about 90% of cervical cancer cases was licensed by the FDA in 2014 (105). The high cost of HPV vaccines has been a barrier to widespread vaccination in resource-limited countries; however, GAVI, the Vaccine Alliance has negotiated lower prices for eligible countries and began demonstration projects starting in 2013 (106). Fewer doses than the three currently recommended would also make vaccination more affordable and feasible. Some evidence is already available to support fewer doses (107). In 2014, the WHO changed its previous recommendation of a 3-dose schedule to a 2-dose schedule, concluding that it is non-inferior to the 3-dose schedule in terms of immunogenicity in girls age 9 to 14 years and will facilitate vaccine uptake (108). Further research is encouraged to investigate the possibility of using one dose (109). Screening remains important even for women who have been vaccinated because the vaccines do not protect against all types of HPV that cause cervical cancer, or against already-established infections. As such, both vaccination and screening play an essential role in reducing the burden of cervical cancer. The Papanicolaou test is commonly used in HICs, but LMICs may not have the infrastructure and resources to implement it. In these countries, visual inspection using acetic acid and HPV tests may be more cost-effective and feasible (110).

Limitations

The strength of our study is the compilation of the most current incidence data from *Cancer Incidence in Five Continents* from registries meeting high-quality standards and WHO mortality data collected from a variety of countries around the world. However, these data are limited by their coverage. Only a small proportion of countries in the world have cancer registration, and of those, many have only partial coverage within the country, often of an urban area. LMICs are less likely to have high-quality cancer registration; for instance, 95% of the North American population is covered by high-quality cancer registration, compared with 8% in Latin America and the Caribbean, 6% in Asia, and 2% in Africa (26). Also, high-quality cancer incidence data from *Cancer Incidence in Five Continents* are currently available only through 2007, although additional years are available from select countries or registries. *Cancer Incidence in Five Continents* has recently issued a call for 2008 to 2012 data for its forthcoming volume XI, which will enhance future studies of the global cancer burden (111). To address the need for high-quality cancer registration in LMICs, IARC's Global Initiative for Cancer Registry Development has been established to support and strengthen cancer registries (112). A similarly small percentage of countries are covered by vital registration, for example, 25% in Latin America and the Caribbean, and 18%, 3%, and 0% in Europe, Asia, and Africa, respectively (26). Mortality data also range in quality and completeness (113). Therefore, reported cancer rates in some countries may reflect the accuracy and coverage of data rather than true occurrence of disease or death, affecting the interpretation of comparisons across countries. Differences in screening practices may also bias cancer incidence comparisons between countries. Finally, due to practical constraints and the desire to present data from a variety of countries worldwide, data do not completely represent cancer patterns worldwide.

Conclusions

The burden of cancer is substantial in countries of all income levels. The rates of many cancers are being brought under control in Western countries through decreasing prevalence of known risk factors, early detection, and improved treatment. In contrast, rates for cancers commonly found in HICs, such as lung, breast, and colorectum, are now rising in many LMICs due to increases in risk factors typical of western countries, such as smoking, excess body weight, physical inactivity, and changing reproductive patterns. Moreover, these countries continue to bear a disproportionate burden of infection-related cancers, including stomach, liver, and cervix.

A large proportion of cancers can be prevented through measures including tobacco control, vaccination, early detection, and promotion of healthy lifestyles. In addition, the burden of suffering can be reduced through appropriate treatment and palliative care. To apply these cancer control measures equitably around the world, a concerted effort will be required not only from individual country governments but also from international agencies, donors, civil society, and the private sector.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Lindsey A. Torre, Rebecca L. Siegel, Elizabeth M. Ward, et al.

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