Global Cancer in Women: Burden and Trends

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This review is an abbreviated version of a report prepared for the American Cancer Society Global Health department and EMD Serono, Inc., a subsidiary of Merck KGaA, Darmstadt, Germany, which was released at the Union for International Cancer Control World Cancer Congress in Paris in November 2016. The original report can be found at https://www.cancer.org/health-care-professionals/our-global-health-work/global-cancer-burden/global-burden-of-cancer-in-women.html. Staff in the Intramural Research Department of the American Cancer Society designed and conducted the study, including analysis, interpretation, and presentation of the review. The funding sources had no involvement in the study design, data analysis and interpretation, or preparation of the review.

Abstract

There are striking disparities in the global cancer burden in women, yet few publications highlight cancer occurrence in this population, particularly for cancers that are not sex specific. This article, the first in a series of two, summarizes the current burden, trends, risk factors, prevention, early detection, and survivorship of all cancers combined and seven sites (breast, cervix, uterine corpus, ovary, colorectum, lung, and liver) that account for about 60% of the cancer burden among women worldwide, using data from the International Agency for Research on Cancer. Estimated 2012 overall cancer death rates in general are higher among women in low- and middle-income countries (LMICs) than high-income countries (HICs), despite their lower overall incidence rates, largely due to inadequate access to early detection and treatment. For example, the top mortality rates are in Zimbabwe (147 deaths per 100,000) and Malawi (138). Furthermore, incidence rates of cancers associated with economic development (e.g., lung, breast, colorectum) are rising in several LMICs. The burden of cancer among women could be substantially reduced in both HICs and LMICs through broad and equitable implementation of effective interventions, including tobacco control, HPV and HBV vaccination, and screening (breast, cervix, and colorectum). *Cancer Epidemiol Biomarkers Prev; 26(4); 444–57. ©2017 AACR.*

See related article by Islami et al. in this *CEBP Focus* section, "Global Cancer in Women."

Introduction

Cancer is a leading cause of death worldwide among women in both high-income countries (HICs) and middle-income countries. Moreover, the cancer burden is expanding in countries of all income levels due to the growth and aging of the population. Females make up 49.5% of the world population; however, they form a larger proportion of the population over 60 years, among whom cancer occurs most frequently, in both HICs and low- and middle-income countries (LMICs) due to differences in life expectancy and leading causes of mortality (1). The increasing cancer burden is expected to be particularly pronounced in LMICs, where the average life expectancy is increasing due to public health advances, such as the control of infectious diseases and reductions in maternal, infant, and childhood mortality (2). In addition to these increases due to population growth, the cancer burden is also growing among women in LMICs due to changes in the prevalence of cancer risk factors as countries experience economic transition. These risk factors include smoking, excess body weight, physical inactivity, and changes in reproductive patterns, such as a later age at first childbirth and fewer childbirths. As a result, cancers that were once common only in HICs are becoming more prevalent in LMICs.

Addressing the cancer burden in women is important not only for its health impact, but also to confront gender inequalities and recognize the role of women as societal and economic participants, as well as family caretakers (3). There is significant potential to reduce the suffering from cancer and to alleviate the economic burden to individuals, families, and societies. Numerous prevention and early detection interventions are proven to avert cancer cases and deaths in both high- and low-resource settings. Although LMICs may have limited resources for screening, a number of common cancers among females have known means of prevention and/or early detection that can be applied in resource-appropriate settings. This report is the first of two in a series on cancer in women. It summarizes the current burden, trends, risk factors, prevention, early detection, and survivorship of all cancers combined and for cancers of the breast, cervix, uterine corpus, ovary, colorectum, lung, and liver, which account for about 60% of cancer cases and deaths among women worldwide. The second report addresses policy approaches to the most important cancer control priorities, with specific examples of proven interventions focusing on primary prevention in LMICs.

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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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Materials and Methods

Estimates of the cancer burden in 2012, including incidence, mortality, and survivorship, are from the GLOBOCAN database produced by the International Agency for Research on Cancer (IARC; Lyon, France) of the World Health Organization (WHO; ref. 4). Additional cancer incidence data for trends come from the Cancer Incidence in Five Continents (CI5) database of the International Association of Cancer Registries and IARC. CI5 collects and publishes high-quality cancer incidence data from registries around the world; the most recent volume X (2003–2007) contains 290 population-based registries in 68 countries (5). Cancer incidence data for more recent years were accessed from the Surveillance, Epidemiology and End Results Program (6) for the United States and NORDCAN for Nordic countries (7). Mortality trend data through 2014 are from the WHO Cancer Mortality Database (8). Annual trend data are graphed using 5-year adjacent average smoothing. We present age-standardized rates adjusted to the 1960 Segi world standard population, modified by Doll and colleagues (9). Data on leading causes of death worldwide and several risk factors are from the WHO. Other risk factor information is drawn from the American Cancer Society/World Lung Federation's Tobacco Atlas (smoking data) and peer-reviewed literature.

Results and Discussion

Overall cancer burden

Among females, cancer is the second leading cause of death worldwide and in the Americas, Europe, and Western Pacific regions (Supplementary Tables S1 and S2). It is the third leading cause of death in the Eastern Mediterranean, fourth in South-East Asia, and sixth in Africa (Supplementary Table S2). There were an estimated 6.7 million new cancer cases and 3.5 million deaths among females worldwide in 2012 (Table 1; ref. 4). Of these, 56% of cases and 64% of deaths were in less developed countries. Worldwide numbers are expected to increase to 9.9 million cases and 5.5 million deaths annually by 2030 as a result of the growth and aging of the population alone (4).

By region, the greatest numbers of cancer cases and deaths among females are in Eastern Asia, with 1.7 million cancer cases and 1 million deaths estimated in 2012 (Supplementary Table S3; ref. 4). These figures reflect population size as well as cancer risk and are dominated by China, which constitutes about three quarters of female cancer cases and deaths in the region (4). Following Eastern Asia, the greatest numbers of cancer cases and deaths are in North America and South-Central Asia. In North America, cancer cases and deaths in the United States make up about 90% of the totals for the region, whereas cancer cases and deaths in India make up about 65% of the totals for South-Central Asia (4).

In general, overall cancer incidence rates among females are higher in HICs compared with LMICs (Fig. 1). Estimated incidence rates in 2012 (per 100,000) are highest in the HICs of North America, Europe, Australia, New Zealand, and Asia, with the top five rates in Denmark (329 cases per 100,000), the United States (297), South Korea (294), the Netherlands (290), and Belgium (289; ref. 4). High rates of lung, breast, and colorectal cancer are responsible for the high overall rates in Denmark and the United States, whereas thyroid cancer rates (largely attributed to overdiagnosis) drive the high rates in South Korea (4, 10). Incidence rates are lowest in the LMICs of South-Central Asia (<100; e.g., Maldives, Bhutan), South-Eastern Asia (<125; e.g., Laos, Vietnam), and Africa (<100; e.g., Niger, The Gambia). Cancer incidence rates reflect not only the cancer risk in a population, but also awareness, the prevalence of cancer screening, and detection practices.

In contrast to incidence, overall cancer mortality rates among females are highest in LMICs in Oceania, sub-Saharan Africa and Asia, followed by North America, Europe, Australia, and New Zealand. The top five estimated mortality rates worldwide in 2012 were in Zimbabwe (147 deaths per 100,000), Malawi (138), Kenya (133), Mongolia (127), and Papua New Guinea (125; ref. 4). Mortality rates are lowest in Northern and Western Africa, Central America, select islands of Oceania, and South-Central Asia. Mortality rates reflect underlying incidence as well as cancer mix and access to early detection and appropriate treatment.

Among females, breast, colorectal, and lung cancers are the three most frequently diagnosed cancers and the three leading

Table 1. Estimated new cancer cases and deaths worldwide for leading cancer sites among females, by level of development, 2012

Cases		Deaths	
Worldwide			
Breast	1,671,100	Breast	521,900
Colorectum	614,300	Lung, bronchus, & trachea	491,200
Lung, bronchus, & trachea	583,100	Colorectum	320,300
Cervix uteri	527,600	Cervix uteri	265,700
Stomach	320,300	Stomach	254,100
Corpus uteri	319,600	Liver	224,500
Ovary	238,700	Pancreas	156,600
Thyroid	229,900	Ovary	151,900
Liver	228,100	Esophagus	119,000
Non-Hodgkin lymphoma	168,100	Leukemia	114,200
All sites*	6,657,500	All sites*	3,548,200
More developed			
Breast	788,200	Lung, bronchus, & trachea	209,900
Colorectum	338,000	Breast	197,600
Lung, bronchus, & trachea	267,900	Colorectum	157,800
Corpus uteri	167,900	Pancreas	91,300
Ovary	99,800	Stomach	68,000
Stomach	99,400	Ovary	65,900
Thyroid	93,100	Liver	42,700
Pancreas	92,800	Leukemia	40,300
Melanoma of skin	91,700	Cervix uteri	35,500
Non-Hodgkin lymphoma	88,500	Corpus uteri	34,700
All sites*	2,826,900	All sites*	1,287,000
Less developed			
Breast	882,900	Breast	324,300
Cervix uteri	444,500	Lung, bronchus, & trachea	281,400
Lung, bronchus, & trachea	315,200	Cervix uteri	230,200
Colorectum	276,300	Stomach	186,100
Stomach	220,900	Liver	181,800
Liver	185,800	Colorectum	162,500
Corpus uteri	151,700	Esophagus	103,700
Ovary	139,000	Ovary	86,000
Thyroid	136,800	Leukemia	73,800
Esophagus	114,400	Pancreas	65,300
All sites*	3,830,600	All sites*	2,261,200

*Excludes nonmelanoma skin cancer.

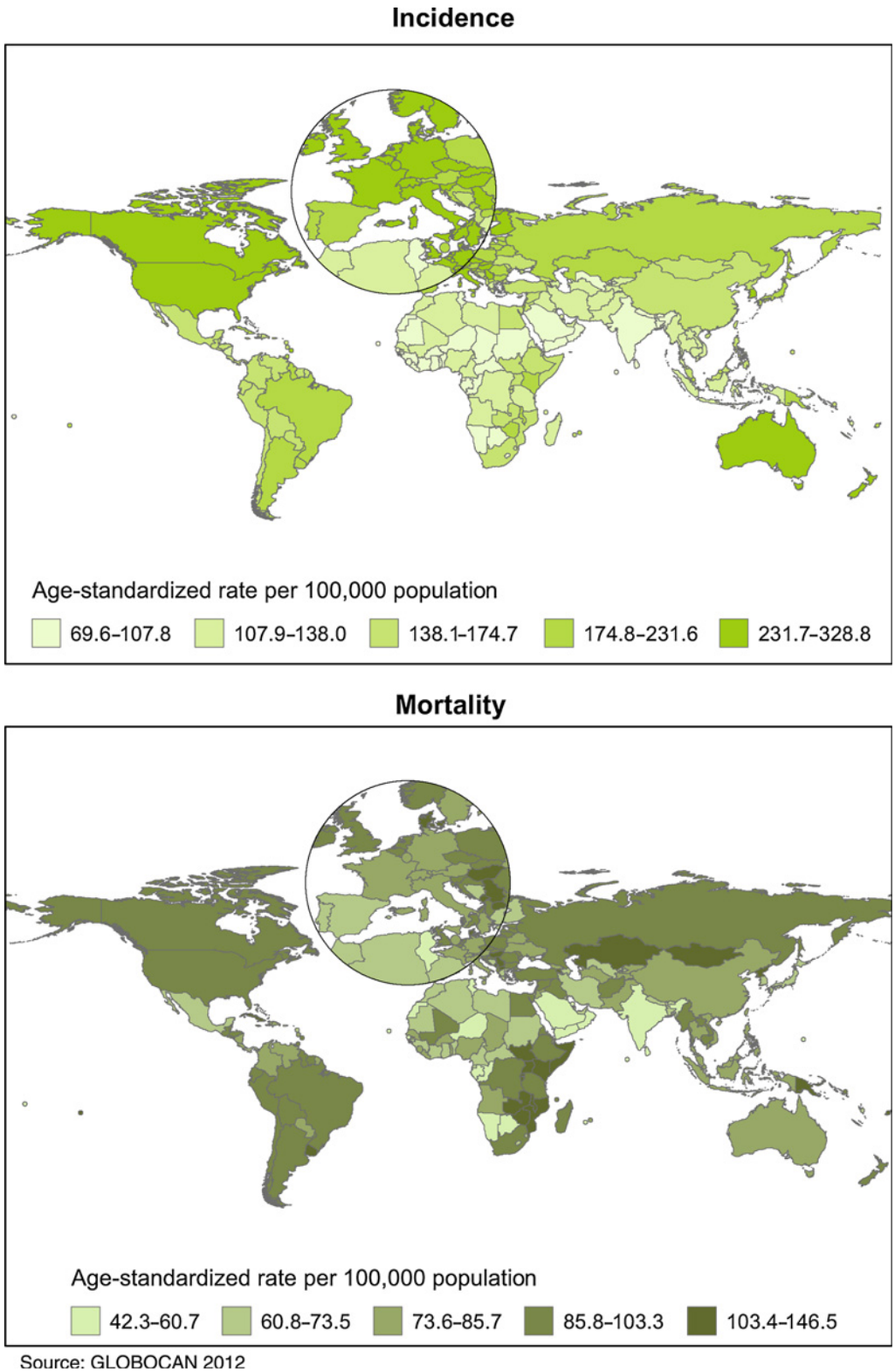

Figure 1.
Incidence and mortality rates for all cancers combined among females, age-standardized rate (world), 2012.

causes of cancer-related death both worldwide, and in more economically developed countries (Table 1; ref. 4). This is also true in less developed countries, except that colorectal cancer is replaced by cervical cancer. Breast cancer is the most commonly diagnosed cancer among women in 140 of 184 countries worldwide, whereas cervical cancer is the most common in 39 countries, all of which are LMICs (Fig. 2). In a few countries, other cancer types are the most commonly diagnosed, such as lung cancer in China and North Korea, liver cancer in Mongolia and Laos, and thyroid cancer in South Korea. There is more diversity in the most common cause of cancer-related death among women. Breast is the most common cause of cancer-related death in 103 countries, followed by cervix in 43 countries and lung in 27 countries. Other most common causes of cancer-related death among women include stomach in Bhutan, Peru, El Salvador, Guatemala, and Tajikistan; liver in Laos, Mongolia, and The Gambia; colorectum in Japan and Slovakia; and esophagus in Turkmenistan.

In the following sections, we first provide an overview of leading female-specific cancers (breast, cervix, uterine corpus, and ovary) followed by selected non–sex-specific cancers (colorectum, lung, and liver), both groups in order of worldwide incidence.

Breast cancer

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death among women worldwide, with an estimated 1.7 million cases and 521,900 deaths in 2012 (Table 1), accounting for 25% of cancer cases and 15% of cancer-related deaths (4). Global breast cancer incidence patterns reflect both risk factors and the availability and use of mammography. The highest breast cancer incidence rates are in North America, Australia, New Zealand, and Northern and Western Europe (Supplementary Fig. S1). Mortality rates reflect the occurrence of the disease as well as the availability of early detection and treatment. Breast cancer mortality rates are higher in many LMICs than in HICs, such as those in sub-Saharan Africa, despite their lower incidence because of late stage at diagnosis and limited access to treatment.

Established factors that increase breast cancer risk include a family history of the disease, *BRCA1* or *2* mutations, reproductive factors that influence endogenous estrogen exposure (nulliparity, early age at menarche, later menopause, and later age at first full-term pregnancy), alcohol drinking, physical inactivity, excess body weight (postmenopausal breast cancer), the use of exogenous hormones (oral contraceptives and menopausal hormone replacement therapy), and high-dose radiation to the chest, particularly at a young age (11, 12). Recent prospective studies have also shown an association between smoking and breast cancer (13, 14). On the other hand, breastfeeding has been reported to slightly reduce breast cancer risk (15), particularly estrogen and progesterone receptor-negative subtypes (16).

The increase in breast cancer incidence rates in Western countries from 1980 to the late 1990s and currently in many LMICs (Supplementary Fig. S2) is likely due to changes in reproductive factors, use of menopausal hormone therapy (HICs), and increases in awareness and mammography screening (17, 18). Since around 2000, stabilized or decreased rates in Western countries coincide with decreased use of menopausal hormone therapy and plateaued screening participation (19). Breast cancer mortality rates in many HICs have been decreasing since around 1990 (Fig. 3) due to mammography screening and better treatments (17), although the relative contribution of each is debated (20–22). At the same time, however, mortality rates have increased in countries with historically lower rates. This trend is likely due to increased incidence rates accompanied by limited access to early detection and treatment (23–25).

It has been estimated that about 20% of breast cancers worldwide are due to modifiable risk factors, including alcohol use, excess body weight, and physical inactivity (26), offering the potential for a reduction in the disease burden by increasing healthy behaviors. In addition, screening with mammography reduces breast cancer mortality by identifying tumors at earlier stages when treatment has a greater likelihood of success (27, 28). However, effective mammography screening requires high-quality equipment, skilled radiologists, and efficient health care infrastructure to communicate positive results and follow up with patients until they receive appropriate treatment or further diagnostic procedures (29). There are also concerns about complications associated with overdiagnosis and overtreatment resulting from mammography detection of indolent cancer (30, 31). Because of limited resources, implementation of a mass screening program based on mammography will not be a feasible cancer control intervention in most LMICs (32, 33). Although clinical breast exam has not been found to reduce mortality in HICs with other available screening, the limited trials of clinical breast examination in LMICs have shown that it may reduce breast cancer stage at diagnosis (32, 34, 35). More research is needed before this method should be systematically recommended to all LMICs. However, clinical breast examination may be recommended as part of routine physical examination in these countries.

In HICs, breast cancer is often diagnosed at an early stage and the prognosis is good; in LMICs, however, breast cancer is more often diagnosed at a later stage, and survival is poorer. Five-year survival is 85% or higher in the United States, Canada, Australia, Israel, Brazil, and many Northern and Western European countries, whereas it is 60% or lower in many LMICs, such as South Africa, Mongolia, Algeria, and India (36). In 2012, there were an estimated 6.2 million women worldwide who had survived breast cancer after being diagnosed within the preceding 5 years (Supplementary Fig. S3; ref. 4). Many breast cancer survivors experience lasting physical effects from surgery and radiation treatment, including lymphedema of the arm and pain in the chest region; these effects are more common among breast cancer survivors in LMICs, where less invasive treatments may be unavailable (37). Younger breast cancer patients may have treatment-related side effects, such as impaired fertility or premature menopause (38). Long-term effects of breast cancer treatment include increased risk of osteoporosis, cognitive impairment, chronic fatigue, hot flashes, and vaginal dryness (39). Survivorship care for long-term medical and psychosocial needs is less available in LMICs, where resources are limited and these issues are only recently being addressed (37).

Cervical cancer

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related death, with an estimated 527,600 cases and 265,700 deaths worldwide in 2012 (Table 1; ref. 4). However, in developing countries, it is the second most commonly diagnosed cancer after

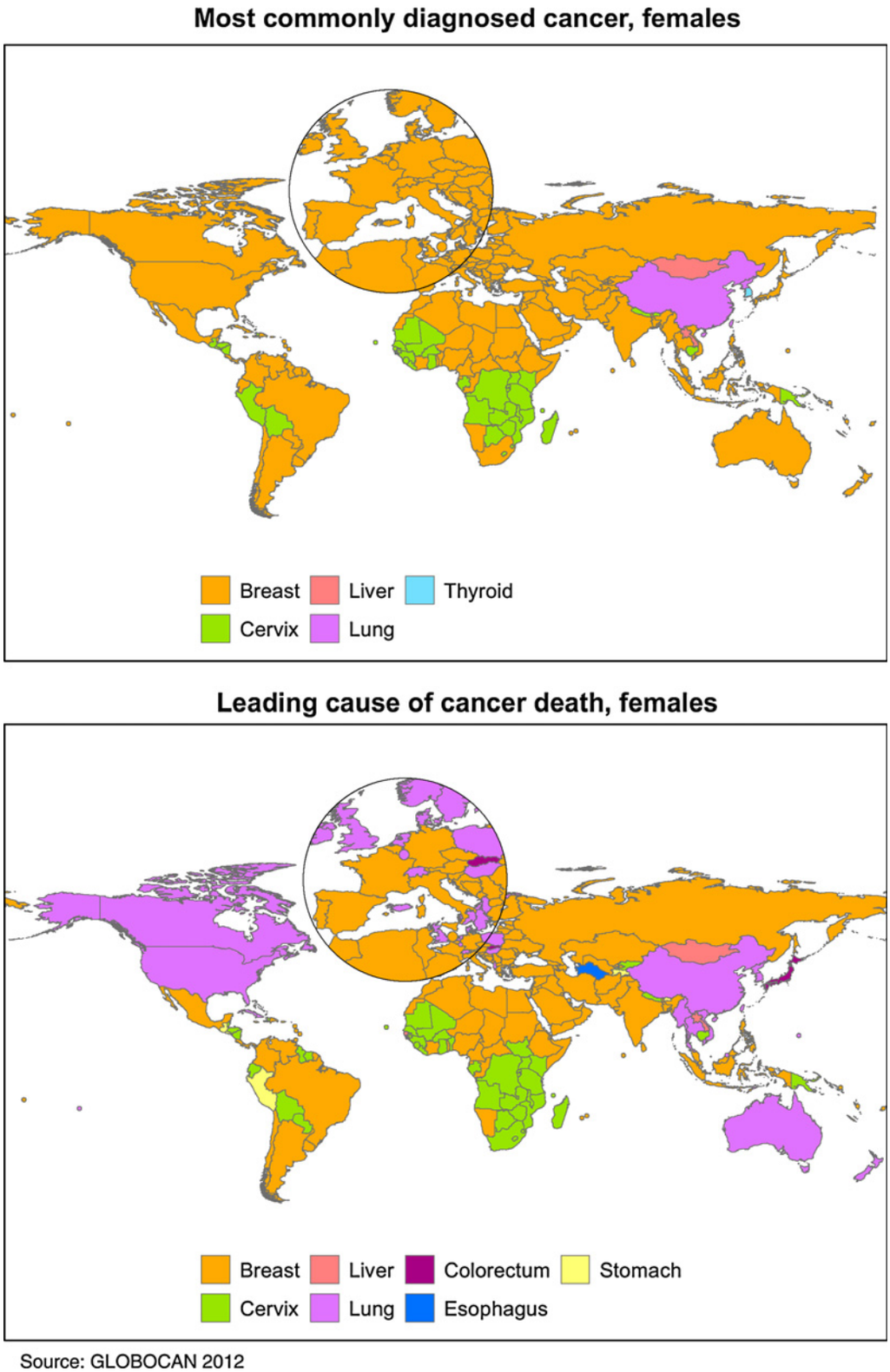

Figure 2.
Most commonly diagnosed cancers and leading causes of cancer death among females, 2012.

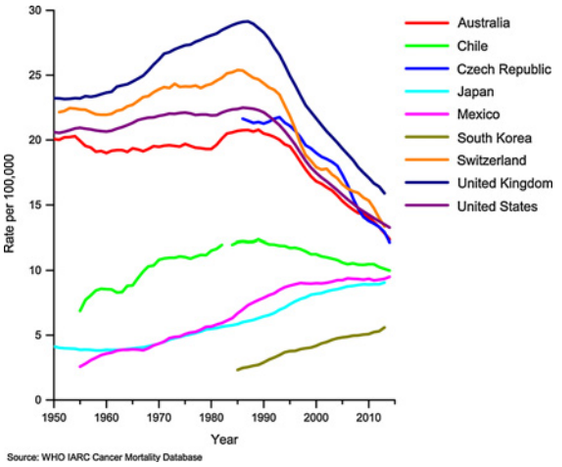

Figure 3.
Female breast cancer mortality trends, age-standardized rate (world), select countries, 1950 to 2014.

breast cancer and the third leading cause of cancer-related death after breast and lung cancers (4). In fact, almost 90% of cervical cancer deaths occur in developing countries, with India alone accounting for one quarter of the world's deaths. Cervical cancer incidence and mortality rates are highest in sub-Saharan Africa, Central and South America, and South-Eastern Asia (Supplementary Fig. S4).

The main risk factor for cervical cancer is chronic infection with human papillomavirus (HPV; ref. 40). Although more than a hundred types of HPV have been identified, the IARC has classified 12 types as definitively carcinogenic to humans (41). HPV 16 and 18 are the most common subtypes identified in cervical cancer; together, they are responsible for 70% of cervical cancers worldwide (42). It has been estimated that approximately 291 million women, or 10.4% of the population worldwide, have a cervical HPV infection at any given time (43). However, nearly 80% to 90% of these infections are cleared by the body within a few years; only women with persistent infections will be at risk of cervical cancer (44, 45). Factors that increase the risk of cervical HPV infection include sexual intercourse at an early age and having multiple sexual partners (46). Factors that increase cervical cancer risk in women infected with high-risk HPV subtypes include higher parity, oral contraceptive use, HIV infection, and smoking (46, 47). Regions with a greater prevalence of HIV infection, particularly in sub-Saharan Africa, have a higher cervical cancer burden (48).

Geographic variation in the burden and trends in cervical cancer incidence reflect differences in availability of screening, which can prevent the development of cancer through the identification and removal of precancerous lesions, and the prevalence of cervical HPV infection (Supplementary Fig. S5; refs. 49–51). In several HICs, cervical cancer incidence rates have decreased by as much as 80% over the past four decades since the advent of the Pap test (Supplementary Fig. S6; ref. 32). Rates have also decreased in some LMICs, such as Colombia, the Philippines, and India, probably because of screening activities and improved socioeconomic conditions (50). However, cervical cancer rates have increased in Uganda, Zimbabwe, and some countries of Central and Eastern Europe, as well as among younger women in many countries of Europe, Japan, and China, likely due to increased HPV prevalence associated with changing sexual practices in combination with inadequate screening; trends in factors contributing to progression of high-risk HPV infections, such as smoking, HIV, and oral contraceptive use, may have also played a role (51–54).

Cervical cancer is considered nearly completely preventable because of the generally slow progression of disease and the availability of screening and the HPV vaccine (55). The commonly used bivalent and quadrivalent vaccines help protect against infection with HPV 16 and 18 and thus, in theory, could prevent about 70% of cervical cancer cases (56); the newer nonavalent vaccine can potentially prevent up to 90% of cervical cancer cases (57). The WHO recommends targeting girls ages 9 to 13 years for priority receipt of the HPV vaccine (56). Although immunization against HPV can prevent the majority of cervical cancer cases, vaccination coverage is not optimal in most populations worldwide. Moreover, even with improvements in coverage among adolescent girls, there are still 2 to 3 generations of women whose age precludes vaccination, including those who have already acquired the infection (58). Screening is the principal preventive measure to reduce the burden of cervical cancer in these women. Although the Pap test has helped reduce the incidence and mortality of cervical cancer in developed countries (32), its implementation has not been as successful in LMICs because of logistical obstacles in health systems and infrastructure (32, 59, 60). Other more feasible methods include HPV DNA testing and visual inspection with acetic acid (VIA). HPV DNA testing has been shown to be an effective test for primary cervical screening (61), and a few studies have even shown promising results from using self-collection methods in LMICs (62–64). VIA can be successfully performed by trained mid-level providers (65).

Invasive cervical cancer can often be successfully treated if detected at an early stage. The estimated 5-year net survival for cervical cancer is between 60% and 70% in many HICs (36). Among LMICs with available survival data, 5-year survival is 46% in India, 56% in Thailand, and 62% in Ecuador (36). In 2012, there were an estimated 1.5 million women worldwide with a cervical cancer diagnosis in the preceding 5 years (Supplementary Fig. S7; ref. 4). Cervical cancer survivors may suffer from treatment-related impaired sexual function and diminished quality of life (66–68). They are also at higher risk of second cancers associated with radiotherapy, HPV, or smoking (69). Women in lower-resource settings may also experience logistical and financial difficulties in receiving follow-up care (70).

Uterine corpus cancer

Cancer of the uterine corpus accounts for about 5% and 2% of worldwide cancer incidence and mortality among women (4). In 2012, uterine corpus cancer was the 6th most common cancer among women worldwide and the 14th leading cause of cancer-related death with an estimated 319,600 cases and 76,200 deaths (Table 1; ref. 4). The highest incidence rates for uterine corpus cancer are in North America and Eastern Europe, whereas the highest mortality rates are in Melanesia, Eastern Europe, and the Caribbean (Supplementary Fig. S8). Incidence rates are generally higher in HICs than in LMICs.

Most of the risk factors for uterine corpus cancer, the vast majority of which are endometrial cancers, are related to hormones (71). These include excess body weight, abdominal

fatness, menopausal estrogen therapy, early age at menarche and late menopause, nulliparity, polycystic ovary syndrome, and tamoxifen use (72). Excess body weight alone is estimated to account for about 34% of uterine corpus cancer cases worldwide (73). Other risk factors include Lynch syndrome and diabetes (74). Factors that decrease risk include pregnancy, oral contraceptive and intrauterine device use, physical activity, and, unlike other cancers, current smoking (in postmenopausal women; refs. 71, 75–77).

Uterine corpus cancer incidence trends are affected primarily by changes in the prevalence of excess body weight, hysterectomy, and reproductive/hormonal factors, such as parity and menopausal hormone therapy use (78). Incidence rates have been increasing since around 2000 in the United States, Central and Eastern Europe, and several other European countries (Norway, United Kingdom, Spain), likely due to the strong association between endometrial cancer and excess body weight and the increasing prevalence of overweight in these regions, as well as decreasing parity in some countries (78, 79). Incidence rates are also increasing in some historically lower risk regions, such as Asia, likely for the same reasons (80). Mortality rates are increasing in line with incidence (Supplementary Fig. S9; refs. 79, 81).

A substantial proportion of uterine corpus cancers could be avoided through maintenance of a healthy weight (73). Although there is no screening method for uterine corpus cancer, many cases manifest with postmenopausal bleeding at early stages, and women should seek prompt medical care. Because of early symptoms of uterine corpus cancer, early diagnosis and treatment is common in HICs, where 5-year survival is around 80% (82, 83). Survival is lower in LMICs with less available health services and treatment; 5-year survival in Benghazi, Libya, is only 17% (84). In 2012, there were an estimated 1.2 million women worldwide who had received a diagnosis of uterine corpus cancer in the previous 5 years (4). Uterine corpus cancer survivors may experience treatment-related issues, including infertility, early onset of menopause, sexual problems, and lymphedema of the lower extremities.

Ovarian cancer

Ovarian cancer accounts for about 4% of worldwide cancer incidence and mortality among women (4). Ovarian cancer was the 7th most common cancer and the 8th leading cause of cancer-related death in 2012 with 238,700 cases and 151,900 deaths (Table 1). The highest incidence rates are in Northern and Eastern Europe, and the same regions plus Melanesia have the highest mortality rates (Supplementary Fig. S10).

Family history of breast or ovarian cancer is an important ovarian cancer risk factor, with known genetic predisposition (predominantly germline mutations in *BRCA1* or *BRCA2*) accounting for 10% to 15% of cases (85). Women who have had breast cancer and those with Lynch syndrome are also at increased risk (86). Ovarian cancer shares some hormone-related risk factors with uterine corpus cancer, such as menopausal hormone therapy (combined as well as estrogen only) and excess body weight, as well as protective factors such as pregnancy and oral contraceptive use (72, 87, 88). Use of oral contraceptives is estimated to reduce ovarian cancer risk by as much as 30% in ever users, with greater risk reduction in long-term users (89). Risk is also reduced with tubal ligation (86). Smoking is a risk factor for relatively rare mucinous tumors (90).

Ovarian cancer incidence and mortality rates have been decreasing in HICs over the past two decades, likely due to use of oral contraceptives and decreased use of menopausal hormone therapy (Supplementary Fig. S11; ref. 91). Some of the declines in mortality may also be attributable to improvements in treatment (92). Increases in incidence and mortality, such as in Southern, Central, and Eastern Europe through the 1980s and 1990s and up to the present in some LMICs (Brazil, Colombia, Venezuela), are likely due to decreasing parity (91, 92).

Salpingo-oophorectomy in women who test positive for inherited ovarian cancer susceptibility genes can reduce risk, and some ovarian cancers could be avoided through the maintenance of healthy weight (73). Although oral contraceptives reduce risk of ovarian cancer, their use is not recommended solely for primary prevention (93). Because ovarian cancer is a highly fatal disease, screening remains an area of active research. Two large randomized controlled trials of transvaginal ultrasound plus biomarker testing in the United States and the United Kingdom (also including a risk algorithm study arm) found no mortality benefit in average-risk women after about 15 years, although results indicated improvements with longer follow-up; future analyses are planned (94, 95).

Ovarian cancer has nonspecific symptoms, causing more than 60% of cases to be diagnosed at the distant stage even in HICs (96). Thus, 5-year survival is about 30% to 40% in most countries (36). In 2012, there were an estimated 586,600 women worldwide who had received a diagnosis of ovarian cancer in the previous 5 years (4). Ovarian cancer survivors may experience similar treatment-related issues as uterine corpus cancer survivors.

Colorectal cancer

Colorectal cancer is the second most frequently diagnosed cancer and the third most common cause of cancer-related death among women worldwide, with an estimated 614,300 cases and 320,300 deaths in 2012 (Table 1; ref. 4). The highest incidence and mortality rates among women are generally in Australia, New Zealand, Europe, and North America, with high rates also in South Korea, Israel, and Singapore (Supplementary Fig. S12).

Factors that increase risk for colorectal cancer include family history of colorectal cancer, excess body weight, physical inactivity, alcohol drinking, smoking, and consumption of red and processed meat (97–99). Factors that reduce risk include a diet sufficient in dietary fiber and high in dairy/calcium, hormone replacement therapy, and the use of NSAIDs (98–100). In Europe, an estimated 11% of colorectal cancers are attributable to not having a combination of healthy lifestyle features, including healthy body weight, physical activity, not smoking, limited alcohol consumption, and healthy diet (26). Risk is generally higher in men than women for reasons that are not well understood, but may include differences in risk factor exposures, sex hormones, and interactions between the two (101). For example, risk ratios for developing colorectal cancer (and particularly colon cancer) per 5 kg/m^2 increase in body mass index are higher among men than women, possibly because of differences in sex hormones (102). Furthermore, several studies have shown that excess body weight increases risk of colorectal cancer more among premenopausal than postmenopausal women, reinforcing this hypothesis; however, further research is required to elucidate this potential relationship (103).

Trends in colorectal cancer incidence rates vary widely worldwide, even within income groups. For example, among HICs, rates are increasing in Norway and Spain, decreasing in the United States and New Zealand, and stable in Australia (Supplementary Fig. S13). Increases in incidence in HICs are likely due to changes in modifiable risk factors (104). Decreases in incidence in the United States have been attributed to changing patterns in risk factors and the uptake of endoscopy screening, which can detect and remove precancerous lesions (105–109), whereas decreases or plateaus in other countries without established screening programs (Australia, New Zealand) are probably due to risk factor changes, including Western lifestyle factors as well as NSAIDs or menopausal hormone therapy use (104). Incidence rates are increasing in many regions where rates have been historically low, such as Latin America and Asia. Colorectal cancer is considered a marker of the "cancer transition," in which developing LMICs experience increases in cancers typically more common in HICs due to increases in known risk factors associated with a Western lifestyle (104). In contrast to the variations in incidence trends, colorectal cancer mortality rates have been decreasing in many countries worldwide, particularly HICs (Supplementary Fig. S14). These decreases have been attributed to improvements in treatment and early detection, as well as decreases in incidence (104). However, mortality rates are increasing in several LMICs with rising incidence, such as Romania, Brazil, and Mexico.

There are several proven measures for prevention and early detection of colorectal cancer. Many colorectal cancers can be prevented by not smoking, exercising, and maintaining a healthy weight. In addition, all recommended screening tests for colorectal cancer can potentially detect malignancy early, and some also allow for the removal of adenomas, from which the majority of colorectal cancers arise (109). Stool-based tests include the guaiac fecal occult blood test (gFOBT), fecal immunochemical test (iFOBT or FIT), and fecal DNA tests. The gFOBT and FIT tests primarily detect cancer, whereas the fecal DNA test can also detect precursor lesions (110). Radiologic and endoscopic examinations can also detect precursor lesions and generally have a higher sensitivity and specificity than stool-based tests (111, 112). However, these imaging methods are costlier and may not be easily accessible to everybody, especially in LMICs. The implementation of stool-based screening programs is also generally more feasible in LMICs because they require less clinical infrastructure (112, 113). However, all positive tests must be followed up with colonoscopy, making the availability of these services a prerequisite for any screening program.

Survival for colorectal cancer varies worldwide and depends on availability of early detection and treatment. In North America, Australia, New Zealand, and many HICs of Europe, 5-year relative survival is 60% to 65% (36). In Asia, 5-year survival ranges from more than 65% in Israel and South Korea to 16% (rectum) and 31% (colon) in Mongolia (36). Several studies have documented higher survival from colorectal cancer in women than men when adjusting for other patient and cancer characteristics (114, 115), although the reasons are not well understood; they may include sex differences in inflammatory response and sex steroid effects (116). Despite proven low-cost options for early detection, fewer than half of colorectal cancers are diagnosed at a localized stage, even in high-resource countries. For example, only about 40% of colorectal cancers are diagnosed at an early stage in Canada, Denmark, and the United Kingdom (117). In 2012, there were 1.6 million women alive worldwide with a colorectal cancer diagnosis in the previous 5 years (4). Colorectal cancer survivors are at risk for treatment-related bowel dysfunction and are also at higher risk of second primary cancers of the colon and rectum, as well as other sites, especially in the digestive system (118).

Lung cancer

Lung cancer is the third most frequently diagnosed cancer and the second leading cause of cancer-related death among females worldwide, with an estimated 583,100 cases and 491,200 deaths in 2012 (Table 1; ref. 4). It is the leading cause of cancer-related death in more developed countries and the second leading cause of cancer-related death in less developed countries, following breast cancer. Geographic variation in lung cancer is primarily related to tobacco use, the major cause of the disease. Incidence and mortality rates are highest in North America, Northern and Western Europe, Australia, New Zealand, and Eastern Asia (Supplementary Fig. S15). Country-specific lung cancer incidence and mortality rates are similar because of generally limited successful treatment options and poor survival, even in more developed countries.

Smoking accounts for about half of lung cancer deaths in women worldwide (119). Other risk factors for lung cancer include exposure to secondhand smoke, which is estimated to cause 21,400 lung cancer deaths annually in nonsmokers (120), and indoor air pollution from unventilated combustion of solid fuels (notably coal) for heating and cooking (90, 121, 122), which is most common in LMICs in Africa and Asia (Supplementary Fig. S16). Most lung cancer deaths due to secondhand smoke and indoor air pollution occur in LMICs, particularly China (123, 124). Female lung cancer rates are higher in China than in several European countries, despite Chinese women having a lower smoking prevalence (125, 126). Additional risk factors for lung cancer include outdoor air pollution (127), occupational and nonoccupational exposure to hazardous chemicals and elements (128, 129), and exposure to radiation from indoor radon released from soil and building materials (130). Sex differences in susceptibility to lung carcinogens have been proposed, especially for an increased risk of lung cancer among female nonsmokers; this remains a topic of active research (116, 131).

Trends in lung cancer incidence and mortality rates tend to reflect the stage and degree of the tobacco epidemic in the country. The typical tobacco epidemic in HICs includes a surge in smoking first among men, then a few decades later among women, which is why lung cancer trends in women have lagged behind those in men in these countries (132). Lung cancer incidence rates peak about 30 to 40 years following peak smoking prevalence (133). Lung cancer mortality rates among women have stabilized or are declining in places where smoking uptake in women began early and has been declining for some time, such as Hong Kong, the United Kingdom, Australia, and the United States (Fig. 4). Meanwhile, rates continue to increase in regions where smoking in women began later, including many countries of Europe and Latin America. In many of the countries where lung cancer mortality rates in women are increasing, rates in young women have begun to decrease in recent years as tobacco control measures take effect (134). Rates are flat in many LMICs of Africa and Asia, where smoking prevalence in women remains low (Supplementary Fig. S17; refs. 135, 136).

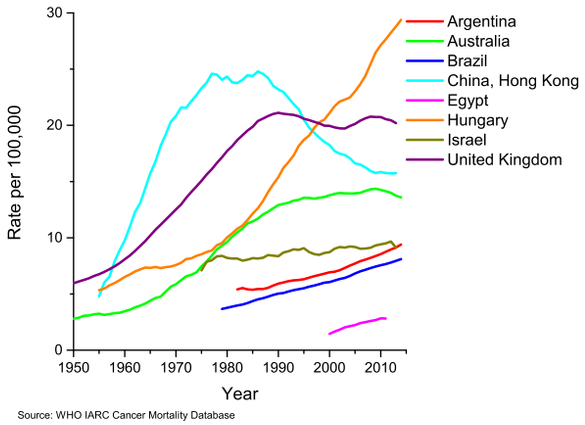

Figure 4.
Female lung cancer mortality trends, age-standardized rate (world), select countries, 1950 to 2014.

Lung cancers caused by smoking are preventable. There are several proven strategies for reducing tobacco use, including excise taxes on tobacco, banning smoking in public places, and counteradvertising, which are discussed in detail in the second article in this series. Tobacco control efforts implemented in the United States, along with increased awareness of the health hazards of smoking, have resulted in large reductions in smoking and 8 million fewer premature smoking-related deaths in the past several decades as a result (137). However, smoking trends in some LMICs are troubling. Current smoking prevalence in adolescent girls in a number of LMICs in Africa, South America, and the Middle East is higher than in many HICs, raising concerns that smoking prevalence will be higher in the younger generation of women (Supplementary Fig. S18; ref. 138). A major priority in LMICs should be to lower smoking initiation in young girls to avoid repeating the high smoking-attributable morbidity and mortality experienced in HICs (139). In addition, smoking cessation at any age can reduce the likelihood of smoking-related disease, including lung cancer (140, 141), with the greatest benefit before age 40 (141). The majority of lung cancers are diagnosed at a later stage, even in HICs. Many deaths could be averted through screening for early detection. In a large-scale randomized trial in the United States, lung cancer mortality was reduced by approximately 20% among heavy current or former smokers screened with helical CT scans (142). Currently, some HICs recommend lung cancer screening for high-risk individuals (143, 144). However, this screening is feasible only in high-resource settings, because it requires extensive health systems resources. Currently, lung cancer screening is limited by these practical requirements even in HICs and is not feasible for LMICs. Thus, tobacco control remains the best strategy to reduce lung cancer and other smoking-related premature deaths.

Because of the generally later stage at diagnosis, 5-year relative survival for lung cancer cases diagnosed from 2005 to 2009 was less than 20% in almost all countries with available data (36). In the United States, only 22% of women diagnosed during 2006 to 2012 survived their lung cancer for 5 years (79, 145). In China, age-standardized 5-year relative survival for lung cancer diagnosed in 2003 to 2005 was 17% in women, ranging from 21% in urban areas to 12% in rural areas (146). The prognosis is generally even poorer in many other LMICs. For example, 5-year survival of 3% in men and women combined has been reported from Libya (84). In 2012, there were an estimated 626,000 women alive worldwide who had a lung cancer diagnosis within the previous 5 years (4). Lung cancer survivors may suffer from decreased quality of life, especially impaired respiratory function (147), and those who are current or former smokers are at particularly increased risk for additional smoking-related diseases.

Liver cancer

Liver cancer is the ninth most frequently diagnosed cancer and the sixth leading cause of cancer-related death among women worldwide, with an estimated 228,100 cases and 224,500 deaths in 2012 (Table 1; ref. 4). Among the liver cancer cases that occurred in women globally in 2012, 81% were in less developed countries (4). Like lung cancer, liver cancer mortality rates approximate incidence because of poor survival. Liver cancer rates are generally two to three times higher among males than females for reasons that are not well understood, but probably include a higher prevalence of disease risk factors in males, as well as endogenous influences. In general, the highest rates are in Eastern and South-Eastern Asia, particularly in Mongolia and Laos, as well as Africa (The Gambia, Guinea, Egypt) and Central America (Guatemala; Supplementary Fig. S19).

Globally, about 70% of all hepatocellular carcinomas, the dominant form of liver cancer worldwide, is caused by chronic infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV; ref. 148). Countries with a prevalence of $\geq$5% for HBV infection are generally located in Asia and Africa, with many African countries having a prevalence of 8% or higher (Supplementary Fig. S20; ref. 149). In these regions and other LMICs, HBV is generally acquired through mother-to-child transmission at birth or in early childhood (150). HBV acquired at this time is more likely to progress to chronic HBV infection. In HICs, in contrast, HBV infection mainly occurs later in life as a result of sexual contact or exposure to the blood of an infected person, often in a health care setting or during intravenous drug use. Countries with the highest prevalence of HCV infection (>3%) generally are located in North Africa and Asia (Supplementary Fig. S21; ref. 151). Although children born to mothers with HCV infection are at risk of acquiring the infection at birth (152), most HCV infections occur at adolescence or later in both HICs and LMICs (151, 153), mainly following drug injections or receiving invasive procedures or blood products in settings with insufficient infection control standards (152). In some regions where infections are the primary cause of liver cancer, such as Eastern and South-Eastern Asia, there is no sex difference in the prevalence of HBV and HCV to explain differences in incidence (116). Reasons why these viruses affect women differently than men are not well understood, but are thought to include hormonal exposures, immune response, or epigenetics (116, 154, 155).

Other major risk factors for hepatocellular carcinoma include heavy alcohol drinking, excess body weight, type II diabetes, nonalcoholic fatty liver disease, smoking, and exposure to aflatoxins (77, 156, 157). In many regions, higher prevalence of alcohol consumption and smoking likely contribute to higher liver cancer rates among males than females (116). Aflatoxin exposure is substantial in certain LMICs, particularly in parts of Asia and Africa (154, 158, 159). For example, approximately 25% of liver cancers in China are attributed to aflatoxin, which may act

synergistically with HBV/HCV infection to promote carcinogenesis (160). In addition, liver fluke infection is a common cause of cholangiocarcinoma in Thailand and other parts of Asia (161).

Liver cancer trends are primarily related to changes in the prevalence of chronic HBV and HCV infections in older generations. Liver cancer incidence rates are decreasing in historically high-risk countries, such as those in Eastern Asia (Supplementary Fig. S22). These declines have been attributed to public health policies and interventions, such as programs aimed at prevention of horizontal HBV transmission within families (e.g., in China), reducing HCV infection through improved blood donation practices and policies discouraging intravenous drug abuse (e.g., in Japan), and reducing aflatoxin exposure (e.g., in China; refs. 162, 163). In Taiwan, the introduction of the infant HBV vaccine in 1984 has resulted in more than an 80% decrease in liver cancer rates among vaccinated youth and young adults (164), but it will be two to three decades before the lower risk in these cohorts will be reflected in overall incidence trends. In contrast, rates in historically low-risk countries, such as those in North America, Oceania, and Central and Northern Europe, have been increasing (158). The increases in the United States are thought to be due to increased prevalence of chronic HCV infection due to exposure to contaminated blood products or medical devices and injection drug abuse during the 1960s and 1970s (165). Obesity and type II diabetes may also have contributed to the recent increase in the incidence rates in the United States and other parts of the world (154, 166).

Liver cancer can be prevented through medical and public health measures aimed at reducing the prevalence of risk factors, including HBV and HCV viruses, aflatoxins, and liver flukes. The HBV vaccine has been shown to prevent HBV-related chronic liver diseases and liver cancer (167), and the WHO recommends immunization of infants as soon as possible after birth (168) because of the high frequency of early-life transmission in LMICs (150). Prevention of transfusion- and injection-related infections is also crucial in reducing HBV and HCV infections. Blood transfusions are a major source of HCV in some countries such as India (153, 169). Among those who are already infected with HBV or HCV, a reduction in risk of liver cancer has been shown with the use of antiviral treatments; however, antiviral treatments for chronic HBV and HCV infections have a high cost (170, 171) and are often beyond the reach of the majority of patients in LMICs (172–174), and even a substantial proportion of the population in HICs (175, 176). Because of these cost barriers, the most cost-effective approach in most parts of the world remains prevention of HBV and HCV infections. In regions with a high exposure to aflatoxins, reducing or eliminating the exposure should be a public health priority. Public health campaigns for the control of liver fluke infection in areas where they are common are also effective (177, 178).

Liver cancer is one of the most fatal cancers, with low survival in countries of all resource levels (36). Among countries with available data, 5-year survival ranges from less than 10% (India, Mongolia, Thailand, Chile, Colombia, Czech Republic, Denmark, Finland, Slovenia, the United Kingdom) to about 20% (Jakarta, Indonesia; South Korea; Belgium; ref. 36). In 2012, there were 180,000 women living with a liver cancer diagnosis in the previous 5 years (4). Liver cancer survivors live with the risk of spread or recurrence. For those in HICs where organ transplantation is available, treatment with liver transplantation involves adherence to intense lifelong follow-up, including medicines to inhibit rejection of the organ, which come with a number of side effects including immune suppression.

Strengths and limitations

A strength of this study is the compilation of the most recent global cancer data sources, including GLOBOCAN 2012, cancer registries, and vital registration, to describe the worldwide cancer landscape for women as completely as possible. We also include the most up-to-date information available on risk factors. However, coverage and quality of cancer data in LMICs is not optimal, with many lacking registration entirely. For instance, only 6% and 2%, respectively, of the populations in Asia and Africa are covered by high-quality cancer registration, whereas vital registration coverage in these regions is 3% and 0% (179). The GLOBOCAN data are estimates, and this may affect their ability to accurately portray the cancer burden in a given country.

Conclusions

The cancer burden among women is high in both HICs and LMICs, and it is expected to increase as populations grow and age and as risk factors associated with urbanization increase in prevalence. Moreover, health disparities within countries may worsen in the absence of targeted intervention because poverty, which is associated with higher cancer risk, is increasing in some countries (180). However, there are many known strategies to reduce cancer morbidity and mortality, particularly for lung cancer and cervical cancers, two of the top four cancers in women worldwide. These two cancers combined represent about 20% of all cancer-related deaths among women, many of which could be prevented through effective tobacco control, HPV vaccination, and the implementation of screening activities.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L.A. Torre, F. Islami, E.M. Ward, A. Jemal
Development of methodology: L.A. Torre, F. Islami
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.A. Torre, F. Islami
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.A. Torre, F. Islami, A. Jemal
Writing, review, and/or revision of the manuscript: L.A. Torre, F. Islami, R.L. Siegel, E.M. Ward, A. Jemal
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