Global Cancer in Women: Cancer Control Priorities

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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

The global burden of cancer in women has recently received much attention, but there are few comprehensive reviews of the burden and policy approaches to reduce it. This article, second in series of two, summarizes the most important cancer control priorities with specific examples of proven interventions, with a particular focus on primary prevention in low- and middle-income countries (LMIC). There are a number of effective cancer control measures available to countries of all resource levels. Many of these measures are extremely cost-effective, especially in the case of tobacco control and vaccination. Countries must prioritize efforts to reduce known cancer risk factors and make prevention accessible to all. Effective treatments and palliative care are also needed for those who develop cancer. Given scarce resources, this may seem infeasible in many LMICs, but past experience with other diseases like HIV, tuberculosis, and malaria have shown that it is possible to make affordable care accessible to all. Expansion of population-based cancer registries and research in LMICs are needed for setting cancer control priorities and for determining the most effective interventions. For LMICs, all of these activities require support and commitment from the global community. *Cancer Epidemiol Biomarkers Prev; 26(4); 458–70. ©2017 AACR.*

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

Introduction

This article is the second in a series of two articles on global cancer in women. The first describes the burden and trends of all cancers combined and for seven major cancer sites (breast, cervix, colorectum, liver, lung, ovary, and uterine corpus), which make up about 60% of cancer cases and deaths in women worldwide, as well as substantial disparities in the burden. This article outlines approaches for combating the growing global burden of these cancers and some other cancers.

Interventions to reduce the burden of cancer among women cover a wide spectrum of activities, including those to eliminate or reduce risk factors for cancer or increase access to care for early detection and treatment. In this article, we briefly discuss some of the most important and cost-effective interventions to curb the growing burden of cancer with emphasis in low- and middle-income countries (LMIC). When available, we present the World Health Organization's (WHO) recommendations, as they are likely to be more applicable to LMICs. It should be noted that these recommendations may be different from national recommendations in some countries.

Education and Cancer Awareness

Cancer awareness is a major contributing factor to cancer prevention and improvement in cancer outcomes (1, 2). Although there are variations across countries, cancer awareness in LMICs is generally low (1, 3). For example, only one-third of Chinese smokers know that smoking causes lung cancer (4), and less than 10% of female university students in many countries in sub-Saharan Africa know that excess body weight is a risk factor for postmenopausal breast cancer (3). Cancer awareness in Africa and West and South Asia is likely to be even lower in women, as adult literacy rates in women in these regions are approximately 15%–20% lower than in men (5). Individuals who are informed about cancers and their main risk factors, symptoms, and outcomes may be more likely to avoid unhealthy behaviors, notably smoking (6, 7), and participate in screening programs (when available), pay attention to early signs and symptoms of cancer, or seek care in a timely manner, when necessary, which can lead to improved cancer outcomes (2, 8–11). For example, although >97% of women in Thailand in 2009 were covered by health insurance schemes that provided free access to cervical cancer

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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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doi: 10.1158/1055-9965.EPI-16-0871

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screening, women with primary/secondary education and women with a bachelor or higher degree, respectively, were approximately 2 and 4 times more likely to participate in cervical cancer screening than those with no formal education (12). As another example, breast cancer awareness may increase proportion of early-stage breast cancers diagnosed (13, 14). Cancer education and awareness can also reduce the stigma that might be associated with cancer in many populations (15–21). This may be particularly important with regard to women's cancers, for which stigma may be associated with removal of female body parts (e.g., mastectomy and hysterectomy) or with sexually transmitted infections (e.g., human papillomavirus infection; refs. 15–20).

Tobacco Control

Tobacco use is the leading cause of preventable cancer deaths among women worldwide. In many high-income countries (HIC), smoking prevalence substantially increased first among men and 2–4 decades later in women (Supplementary Fig. S1). The smoking-related cancer mortality in each sex substantially rose 3–5 decades after the increase in smoking prevalence in the corresponding sex (22). This pattern is known as the smoking epidemic model. Smoking prevalence among men peaked much more recently in many LMICs than in HICs (e.g., the 1980s in Asia and the 1950s in the USA; ref. 23). Women have not yet begun smoking in large numbers in many LMICs, especially in Asia and Africa (23), with current smoking prevalence less than 5% in most of these countries. However, tobacco companies are increasingly targeting women in these regions and there is some evidence in some LMICs that smoking prevalence is increasing in young women (24, 25). Therefore, implementing effective tobacco control programs can have a substantial impact on keeping women in LMICs healthier, as there is a huge opportunity to avoid the replication of tobacco epidemic (as observed in HICs) and the future surge in the burden of lung cancer and other smoking-related diseases in this group.

The WHO Framework Convention on Tobacco Control (FCTC) is an international treaty outlining measures to control the global tobacco epidemic. It entered into force in 2005 after being approved by 40 states (26). To assist countries in the implementation of the FCTC, the WHO introduced the MPOWER policy 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 to be effective in reducing smoking in several regions of the world (27, 28).

Increasing awareness about the health hazard of smoking is an essential part of any tobacco control program. One way to increase the awareness is to use health warning labels on cigarette packaging. The FCTC recommends health warning labels on both the back and front, covering at least 50% of the pack. (23). Graphic warning labels are more effective than text-only warnings, and using them can even be more important in LMICs, because they can communicate health information directly to people with low literacy and in multilingual countries (29, 30). Many LMICs in the Americas and several in the Middle East and other regions have introduced warning labeling at the levels recommended by the FCTC (Supplementary Fig. S2, ref. 31). However, in a number of other LMICs, there are still no warning labels on cigarette packages or, where they exist, their size does not meet FCTC criteria. Recommended graphic labels can also help prevent the tobacco industry from using the packages as a marketing tool to attract users, especially youth. For example, in 2007, R.J. Reynolds Tobacco started a marketing campaign for Camel No. 9, targeting girls and young women by advertising in the media and using pink fuchsia or minty-green teal colors on a fashionable, trendy black package. This campaign was quite successful in reaching adolescent girls and increasing the desire to smoke among many of them (32). Among other FCTC provisions that can increase awareness about harms of smoking are mass media campaigns [which can reach many people at low costs, see Article 12 of FCTC (33)], especially when they are government-sponsored, and cessation programs (e.g., messaging through quitlines; ref. 34). Studies in HICs and LMICs have shown that increasing awareness about health effects of secondhand smoke could lead to voluntary smoking bans in households of all income levels (7, 35–37).

Taxation in particular has proven to be very effective in reducing smoking, in addition to being cost-effective (38, 39). The WHO recommends taxes amounting to at least 70% of the retail price, but few countries have reached this level (Fig. 1). HICs generally have higher levels of taxation, while many LMICs, particularly in Africa and the Middle East, have lower levels. Nevertheless, there are a few great success stories in LMICs. The "Sin Tax" Reform Law in the Philippines, for example, has greatly increased the total tobacco tax share (by 45% between 2012 and 2014), indexed the tax to inflation, simplified and improved the taxation system (from a four-tier to a one-tier system), and more importantly, was associated with a decrease in smoking prevalence from 30% in 2011 to 25% in 2015 (31, 40). Moreover, this reform has generated significant incremental revenues, a substantial part of which is used to helping finance the Philippines' universal health care program to provide coverage for low-income people (40).

Brazil is an example of the successful implementation of comprehensive tobacco control program which has had an effect on female smoking. Female smoking prevalence decreased from 25% in 1989 to 13% in 2008 following a series of tobacco control measures enacted starting in 1986 (41). By 2008, about 43% of once-daily female smokers in Brazil had quit smoking, and current smoking rate among young women aged 15–24 was only 6% (24). Should this progress be sustained, Brazil will have potentially avoided a huge future burden of tobacco-related cancers and other diseases among women. It should be noted, however, that Brazil has struggled in recent years to maintain the gains in tobacco control as a result of tobacco industry's aggressive actions, such as using the domestic legal system to challenge tobacco control measures (42, 43).

Household and Ambient Air Pollution

In many LMICs, reducing household air pollution can significantly improve public health, particularly women's and children's health, as they generally spend far more time than men at home. For example, a higher female lung cancer death rate in China than France (18.0 and 12.9 per 100,000, respectively) in 2012, despite much lower smoking prevalence among women in China (3%) than France (26%) has been attributed to higher exposure of Chinese women to secondhand smoke and household air pollution from using solid fuels (23, 44). In 2012, 4.3 million deaths worldwide (including 272,000 deaths from lung cancer) were attributable to household air pollution due to cooking and heating using solid fuels (45). Of these deaths, only

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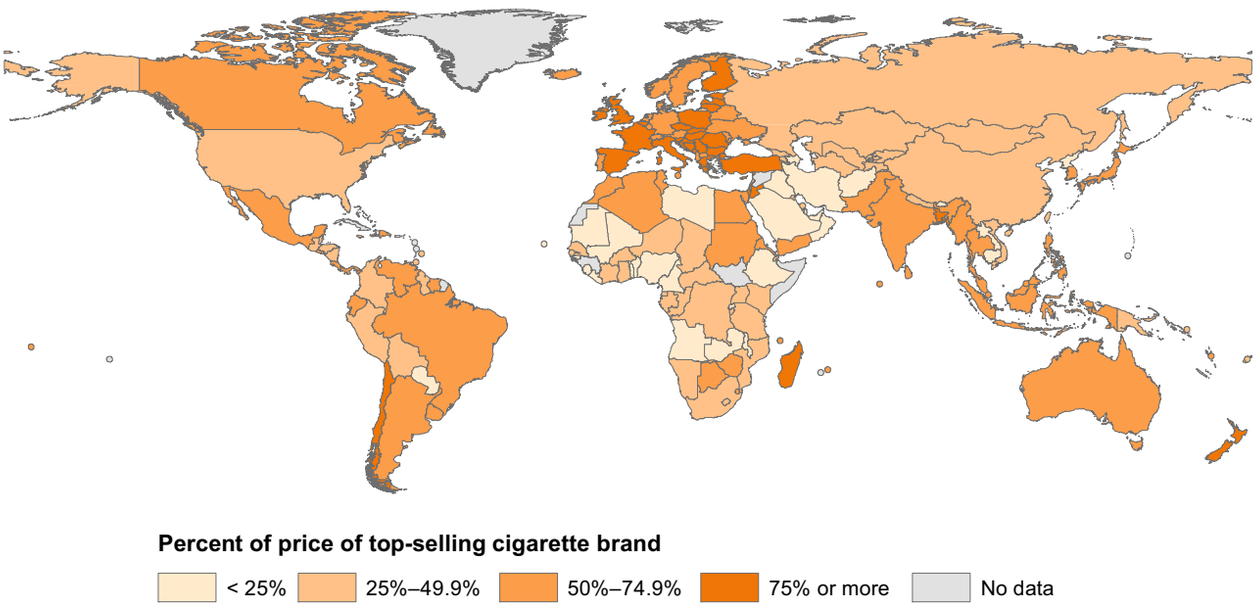

Figure 1.
Tobacco taxation, 2014.

about 19,000 (<1%) occurred in HICs, while 3.3 million (77%) occurred in LMICs in Western Pacific and Southeast Asia (45). The number of deaths was 1.8 million (41%) in women and 0.5 million (13%) in children (45). Two interventions to reduce household air pollution include providing access to clean fuel, notably liquefied petroleum gas (LPG), or improved solid fuel stoves (46). Although improved stoves could substantially reduce airborne particulate matter (PM) from solid fuels when they replace traditional stoves, few can reduce airborne fine particulate levels below suggested limits for PM with diameter $\leq$2.5 μm ($PM_{2.5}$) that can penetrate into the gas exchange regions of the lung (46–48). Consequently, WHO recommends the use of LPG as the primary strategy to improve household air quality (47). However, if providing secure and sustainable access to LPG is not currently feasible in some low-resource populations because of its higher costs (46), providing access to improved solid fuel stoves can be an efficient intermediate step in reducing household air pollution until access to LPG is more widespread (47, 49).

The number of deaths attributable to ambient (outdoor) air pollution is slightly higher in men than in women. Globally, 3.7 million deaths were attributed to this exposure in 2012 (including 402,000 lung cancer deaths), 44% of which (1.6 million) occurred in women, 53% in men, and 3% in children (50). Similar to household air pollution, most ambient air pollution–related deaths occur in LMICs (88%). Some of the major pollutants worldwide are PM, ozone (at ground level), nitrogen dioxide, and sulfur dioxide, but air quality usually is reported as mean concentrations of PM_{10} (PM with diameter $\leq$10 μm) and $PM_{2.5}$ (50). In 2016, the annual PM_{10} mean concentration (μg/m^3) was 25–31 in HICs in Europe and Americas, while it was >100 in LMICs in Asia and Africa and >150 in the Eastern Mediterranean region (51), much higher than the limits suggested by WHO (20 μg/m^3), although there is no safe level for PM (52). It should be noted that in rural areas, concentration of most ambient air pollutants may be lower, but the concentration of ozone at ground level may be higher than urban areas (53). Efforts to reduce ambient air pollution and its effects require collaboration between many sectors, including governments. Some activities may include investing in cleaner energy sources; improving traffic and increasing public transportation; improving technology in combustion process and filtration in vehicle engines, industries, residential places, and power production; and monitoring and reporting air pollution (53–55). Awareness should be increased to reduce behaviors contributing to air pollution at the individual level, put pressure on policymakers to act, and limit outdoor activities when air pollution level is high (53, 56).

Body Weight and Physical Activity

The prevalence of excess body weight (body mass index, BMI $\geq$ 25 kg/m^2; Fig. 2) and physical inactivity is rapidly increasing in many LMICs (57, 58). From 1975 to 2014, for example, the prevalence of excess body weight among women increased from 12% to 33% in China and from 39% to 64% in Iran (59). Both excess body weight and physical inactivity are more common in women than men (58, 60, 61). In particular, the participation of women in leisure activity and sports is much less than men in many LMICs (62). Overall, 5% of all new cancer cases in women worldwide are attributable to excess body weight (63). Also, 7% of breast cancer deaths worldwide are attributable to physical inactivity; this proportion in both sexes combined is 7% for colon cancer and 6% for all-cancer mortality (63).

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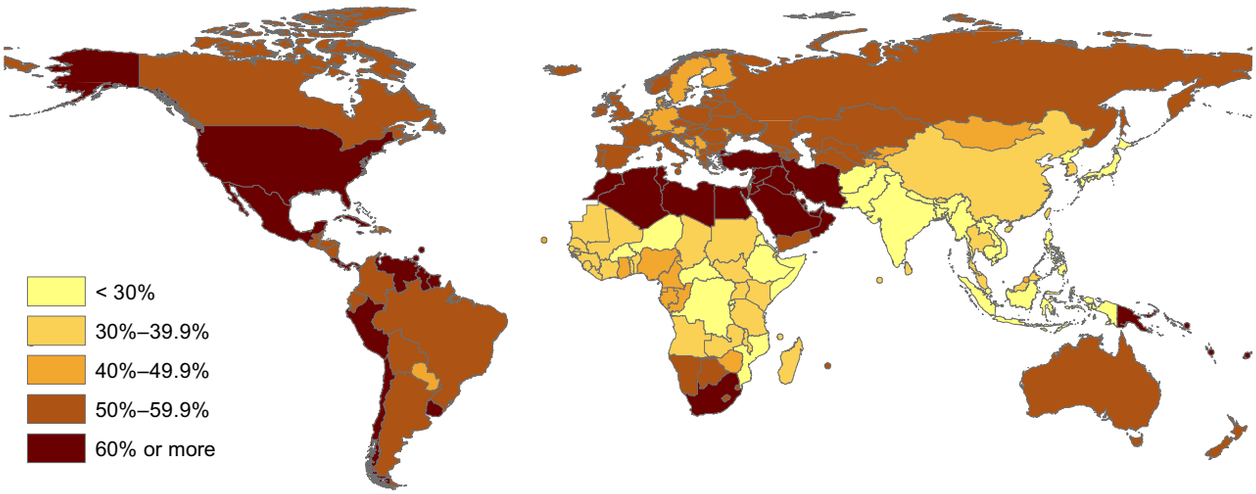

Source: WHO Global Health Observatory Data Repository

Figure 2.
Prevalence of excess body weight (BMI $\geq$ 25 kg/m^2) among women age 18+ years, 2014.

The shift in food supply appears to be the main contributor to excess body weight epidemic worldwide: economic development and increase in average income and availability of low-cost processed foods high in fats, refined starches, and sugar have increased the global consumption of foods high in calories (64, 65). Development and implementation of policies to counteract the influx and marketing of such unhealthy foods is often complicated by opposition from the food industry (66). Reduced physical activity due to urbanization is another contributing factor (64).

A number of studies and interventions in LMICs to promote physical activity, healthy diet, and reduce excess body weight, particularly among children in schools, have shown positive results (67–69), and limited evidence indicates that they are cost-effective ways to prevent chronic diseases, including cancer (70, 71), but most of the interventions have been small-scale. The Academia da Cidade in Brazil, an example of a large-scale community intervention, provides free daily physical activity training and equipment in public parks or plazas since the 1990s and has been used as a model to increase physical activity in some other countries (72). Surveys suggest that not only participation in this program but also even knowing about the program or seeing the trainings are associated with higher physical activity (73), indicating the effect of increasing awareness. Improving the design of urban environments, such as more parks and public transportation density, may also help to increase physical activity at the community level (74).

The same types of policies that have been successful in tobacco control have the potential to substantially reduce unhealthy diet (75). A simulation study in several highly populated LMICs has shown cost-effectiveness of several interventions that are used for tobacco control, including mass media campaigns, [food] labeling, advertising regulations, and taxation, as well as worksite interventions, physician counselling, and school-based interventions, in reducing excess body weight, especially with a multiple-intervention strategy (76). Similar to tobacco products, lower-income populations are more sensitive to changes in the price of foods (77). Therefore, a major strategy to improve diet in LMICs can include increasing the price of high-calorie foods through taxation, and perhaps decreasing the price of healthier food items, at least for low-income groups. Mexico was one of the first countries to implement taxation on nonessential high-calorie foods and sugary beverages at the national level in 2014. Although more research is required on the effects of this intervention, short-term results show an average of 5% reduction in the purchase of taxed foods beyond the expected change in one year, while this reduction was 10% in low-income households (78). A greater decrease was observed in purchases of taxed beverages (up to 17%; ref. 79). Food labels provide information about the content of the food and can increase consumer awareness. There are a number of LMICs, mostly in Latin America and Asia, which have mandatory or voluntary labeling legislation (80). Some countries may modify popular labeling systems to make it more appropriate for the needs of the country. For example, Mexico implemented its own mandatory front-of-pack nutrition label, which was announced in 2014 and came into effect in July 2015, and its effects are yet to be evaluated (81, 82).

Vaccination

The human papillomavirus (HPV) and hepatitis B virus (HBV) vaccines are the only two vaccines that prevent cancer. The HPV vaccine can prevent cervical cancer (83) and probably several other HPV-related cancers, including anal cancer (84). HBV vaccination can prevent HBV-related chronic liver disease and liver cancer (85). Several factors have made vaccination one of the most feasible and cost-effective methods to prevent HPV- and HBV-associated cancers, in particular in LMICs. In just a few visits, the vaccines can be delivered to newborns/infants (HBV) or adolescents (HPV). Also, vaccination is much less costly than

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Table 1. The estimated net cost of HPV vaccination and number of cervical cancer deaths prevented by vaccination of one birth cohort of 12-year-old girls (87)

Area	Net cost (million US$)	No. of girls to be vaccinated (millions)	Cervical cancer deaths prevented (×1000)	% Spending (of all countries' spending)	% Prevented deaths (of all countries)
Country income level					
Low	130	9.7	110	3.2	26.2
Lower-middle	670	24.8	200	16.3	47.6
Upper-middle	830	17.6	90	20.2	21.4
High	2,500	6.1	16	61.0	3.8
WHO region					
Africa	200	10.8	130	4.9	31.0
Americas	1,200	7.5	56	29.3	13.3
Europe	1,100	4.9	17	26.8	4.0
Eastern Mediterranean	360	6.2	18	8.8	4.3
South-East Asia	390	17.0	150	9.5	35.7
Western Pacific	930	11.6	42	22.7	10.0
All countries	4,100	58.1	420	100	100

diagnostic procedures and treatment of chronic diseases and cancers related to these infections.

HPV vaccination

It is believed that HPV infection is involved in all cervical cancers (86); for the burden of disease, see part I of this series. HPV vaccination is generally recommended for adolescent girls, before they become sexually active. This vaccination can prevent many cervical cancer cases globally (Table 1; Supplementary Fig. S3). A WHO analysis suggests that, out of 179 countries included, HPV vaccination will be very cost-effective in 156 countries (87%), cost-effective in 17 other countries, and not cost-effective in only 6 countries (87); the latter countries are mostly located in the Middle East and have low incidence of cervical cancer (Supplementary Fig. S4). According to this analysis, spending approximately US$ 200 million and 390 million per one birth cohort of 12-year-old girls in Africa and Southeast Asia could prevent 130,000 and 150,000 deaths, respectively, which represents 31% and 36% of 420,000 cervical cancer deaths preventable by HPV vaccination in the same age cohort worldwide (87).

From 2013 to 2015, the number of countries that had introduced HPV vaccination in their national immunization program increased from 45 (Supplementary Fig. S2) to 81 (Supplementary Fig. S5; ref. 88, 89), in large part due to an increase in international monetary and technical assistance to LMICs by the Global Alliance for Vaccines and Immunization (GAVI; ref. 90). However, inclusion of HPV vaccination in a national program does not necessarily indicate a high vaccination coverage in that country. For example, in 2014, only 50% of girls aged 13–17 in the United States had received 2 doses of HPV vaccine (91). Nevertheless, available data strongly indicate that high coverage for HPV vaccination is potentially achievable worldwide, including in LMICs, through political commitment, securing financial resources, increasing awareness about cervical cancer and its prevention, and when the program is appropriately designed according to the needs of the community (92, 93). For instance, Bhutan (94), Rwanda (95), and Uganda (96) achieved vaccination coverages of approximately 90% or more in girls. Inclusion of HPV vaccine delivery through schools in HPV vaccination programs, as shown in the above three and some other countries, have been associated with a better vaccination adherence in LMICs (93). Initial guidelines recommended 3 doses of HPV vaccines, but current WHO guidelines have reduced it 2 doses of bivalent or quadrivalent vaccines for girls <15 years (except those who are immunocompromised and/or HIV infected), which reduces the cost and can increase the adherence (97). However, there may be variations in vaccination guidelines across countries. For example, the US Centers for Disease Control and Prevention (CDC) recommends a 2-dose schedule only for the nonavalent HPV vaccine (98).

HBV vaccination

Chronic HBV infection (i.e., persistence of HBsAg for at least 6 months) affects 240 million people, and between 20% and 30% of people with chronic infection will eventually develop cirrhosis and/or liver cancer (99). This infection is associated with about 686,000 deaths (300,000 of which liver cancer; ref. 100), and most of these deaths occur in LMICs (99). HBV vaccination is the most cost-effective measure to prevent HBV infection and its complications (99, 101). In 1992, WHO recommended the inclusion of HBV vaccination in all national infant immunization programs. Since then, almost all countries have followed this recommendation. However, although prevalence of HBV infection is high (>8%) in 28 countries in the WHO African region and 10 countries in the Western Pacific (102), the coverage in many countries in these two regions is not optimal and needs to be improved as a priority (Supplementary Fig. S6). In addition to the importance of securing adequate long-term local or international funding (e.g., through Gavi; ref. 103), improvements in effectiveness of vaccine delivery may increase the coverage. Some of the improvements include increasing the coverage of the vaccine supply chain, increasing awareness about benefits of the vaccination among providers and the general population, and finding ways to increase the number of infants born in facilities that can provide HBV vaccine, as well as the number of infants who are born elsewhere and receive the vaccine soon after birth (104).

There are also some LMICs in Asia and South America that have relatively low HBV infection rates and suboptimal vaccination coverage. These countries will also benefit from an increase in the coverage. For example, despite a moderate HBV infection rate of 2%–4%, it has been estimated that every year 17,000 people in India die because of HBV-related liver cancer (105). This number does not include deaths from more common acute and chronic complications of HBV infection, including acute and chronic hepatitis or liver failure and cirrhosis of the liver. HBV vaccination coverage is less than optimal in several HICs. In 6 European countries (Denmark, Finland, Iceland, Norway, Sweden, and the United Kingdom), where the prevalence of chronic HBV infection

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is <1% (102), universal HBV vaccination is considered unnecessary, and only high-risk groups and infants born to pregnant women who test positive for HBV infection receive vaccination (106). In those countries, however, many eligible infants (born to mothers with HBV) and infants born to mothers with unknown HBV status (especially among immigrants) may not receive some or any doses of HBV vaccine (106, 107).

Access to Screening

The majority of cancers, including breast and cervical cancers, are diagnosed at a later stage in sub-Saharan Africa and other parts of the developing world (108–111). Major contributing factors include lack of knowledge about cancer signs and symptoms, low literacy rates, seeking traditional medicine, delays in referral and diagnosis, absence of local health care facilities (distance), lack of transportation, and unaffordability of care (10, 110, 112–116), which highlight the importance of both increasing cancer awareness in the general public and health care providers and improving access to early detection.

There is strong evidence for the effectiveness of screening for cervical, breast, and colorectal cancers. Generally, cervical and breast cancers are more likely to be diagnosed in younger women, and their incidence rates among women in LMICs are higher than colorectal cancer. For example, the estimated incidence rate per 100,000 among women in Eastern Africa in 2012 was 42.7 for cervical cancer, 30.4 for breast cancer, and 6.1 for colorectal cancer (117). On the basis of the burden and needed infrastructure, cervical cancer screening definitely has a much higher priority in LMICs than breast and colorectal cancer screening; between the latter two, breast cancer screening may have a higher priority (118). However, setting priorities for screening in a given country will depend on the availability of resources and infrastructure and cost-effectiveness of the intervention.

Cervical cancer screening

Cervical cancer screening can reduce cervical cancer incidence and mortality (119, 120). As mentioned in part I of this series, the standard screening method in HICs (based on cytology, or Pap test) has not been as successful in most LMICs due to the lack of appropriate infrastructure and logistics (Fig. 3A). In these countries, screening based on HPV DNA testing or visual inspection with acetic acid, (VIA; screen and treat) could be alternative approaches (121). Currently, WHO recommends screening of women $\geq$30 years, with priority given to women aged 30–49 years (121). The age range and screening intervals will depend on resources. Although the recommended interval is 5 years after a negative HPV DNA test and 3–5 years after a negative VIA or cytology (121), even screening once in a lifetime could be beneficial (121, 122). Several studies have shown cost-effectiveness of either HPV DNA testing or VIA for preventing cervical cancer cases in LMICs (Table 2; refs. 122–124).

A number of LMICs had started a national or pilot cervical cancer screening program (Fig. 3B). However, many LMICs have not done so, including several countries in sub-Saharan Africa, especially in Central Africa, where the burden of cervical cancer is the highest. This is probably because of a mixture of having limited resources and infrastructure and lack of sufficient political support. Malawi, a country in Southern Africa in which cervical cancer accounts for 45% of all female cancers (125), has become one of the few African countries with a national cancer screening program due to strong support from the government. Despite an increase in participation of women in cancer screening in Malawi (9% in 2011 to 27% in 2015), however, the participation in this country or other LMICs with a national program is still far below the optimal levels, and many screened women may not receive the required treatment (which is generally cryotherapy) or may be lost to follow-up for a repeat cryotherapy, or when necessary, other treatments (125, 126). In a feasibility study coordinated by WHO in 6 African countries, 39% of the screened women eligible for treatment did not receive cryotherapy for several reasons, including equipment being nonfunctional on the day of screening (126). In addition to governments' commitment to establishing and scaling up cervical cancer screening programs, the following actions could increase the efficiency of the programs: increasing awareness about the screening, providing standardized counselling, active follow-up, ensuring reliable equipment, reducing the lag between screening and treatment, and integrating the screening into routine primary health care to women (20, 126). Implementation research is also needed to increase participation rates and decrease loss to follow-up.

Breast cancer screening

Several HICs have organized opportunistic breast cancer screening programs using mammography. Although a few upper middle-income countries in Eastern Europe and Americas have a breast cancer screening program based on mammography (Fig. 3A), many other LMICs are unlikely to afford such a program with a high coverage/participation rate in the near future (127, 128). There is also limited evidence on cost-effectiveness of mammographic screening in LMICs (129), although there is variation across countries. In its latest position paper, WHO recommends mammography screening for women ages 50–69 years in LMICs only when there is a relatively strong health system and shared decision-making strategies for patients and health care providers meet certain conditions (130). However, in a more recent evaluation, the International Agency for Research on Cancer (IARC) states that mammography is also beneficial for women ages 70–74 years (129). Clinical breast examination may have the potential to be beneficial in LMICs, pending the results of further studies. According to IARC, there is sufficient evidence that clinical breast examination can shift the stage distribution of breast tumors to a lower stage based on three clinical trials and a few observational studies, but the results on its effects on breast cancer mortality in clinical trials are not available yet (129).

Colorectal cancer screening

The various screening modalities (e.g., fecal/blood tests, endoscopies) for colorectal cancer have been discussed in part I of this series. Unlike screening for breast and cervical cancers, there are few countries (all HICs) with organized or opportunistic colorectal cancer screening programs. However, considering the increase in incidence rates of colorectal cancer in countries without screening (131), more countries may consider establishing a colorectal cancer screening program. The implementation of screening programs based on laboratory tests may be more feasible in some middle-income countries, as it reduces the number of people that will need endoscopy (132, 133). For example, a pilot program based on fecal immunochemical test

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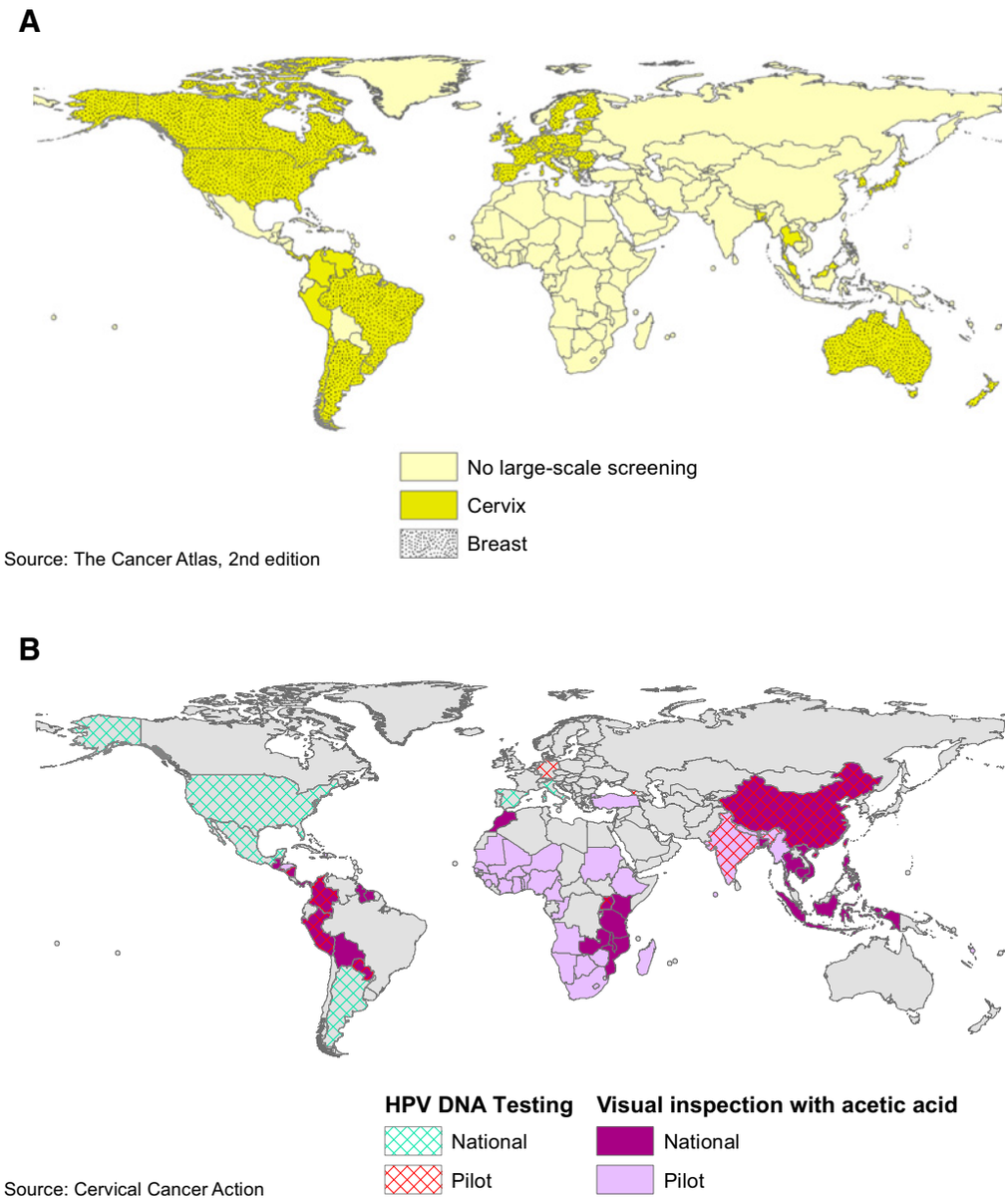

Figure 3.

A, Countries with large-scale cervical (based on Pap smear) and breast cancer screening programs, 2014. **B,** HPV screening programs using HPV DNA testing and visual inspection with acetic acid, 2015.

(FIT) every five years and colonoscopy for people with a positive test has been successfully implemented in Lampang province, Thailand; 63% of 127,000 target population were screened and 72% of those with a positive test underwent colonoscopy (133).

Access to Cancer Treatment

About 80% of people with advanced cancer experience moderate to severe pain. Although opioid analgesics such as morphine are a safe, effective, easy to use, and inexpensive means of treating moderate to severe pain in cancer patients (134), LMICs consume <5% of the medicinal opioids despite containing 85% of the world's population (Supplementary Fig. S7), resulting in a large number of cancer patients in LMICs dying with untreated pain (135). This underutilization has a number of causes, including difficulty in obtaining the drugs due to inadequate training of health care providers, legal and regulatory restrictions and supply chain issues, and concerns about diversion, addiction, and abuse. However, with implementing mechanisms for appropriate prescription and delivery of opioids by governments and health care providers and proper training, these barriers can be overcome (134, 136, 137). In Uganda, for instance, the government now

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Table 2. Estimated mean reduction in lifetime risk of cervical cancer (%) following screening, HPV vaccination, or both, versus no interventions, in select LMICs

Country	Screening only (Pap test)[a]	Screening only (HPV DNA test)[b]	Vaccination only[c]	Vaccination + screening (HPV DNA test)
Argentina (176)	18.2		52.2	68.6
Chile (176)	14.2		45.6	60.0
Colombia (176)	20.8		49.4	67.1
Peru (176)	19.1		43.0	55.0
Mexico (176)	16.7		40.3	56.4
South Africa (123)	14.7	24.8	46.4	59.7
Uganda (123)	15.1	25.0	51.5	63.7

[a]Cytology-based screening for 3 times at ages 35, 40, and 45 years, assuming 70% population coverage for 3-visit testing (first visit: Pap test; if necessary, second: colposcopy and biopsy, third: treatment).

[b]Screening based on HPV DNA testing 3 times per lifetime at ages 35, 40, and 45, assuming 70% population coverage with 2-visit HPV DNA testing each time (one day for testing, the other for results, and if necessary, treatment).

[c]Vaccination at ages 9–12 years, assuming 70% coverage of the female population with three doses given by age 12.

makes oral morphine available to patients with cancer at no cost, and nurses with special training in palliative medicine can prescribe morphine; this has improved pain control, especially in rural areas (138, 139).

About 80% of cancer patients may need surgery at least once during their treatment (140) and about 50% may benefit from radiotherapy (141). In LMICs, moreover, surgery is often the only available curative or palliative treatment in the absence of radiotherapy or chemotherapy due to resource constraints (142). However, less than 25% of patients globally will receive safe, affordable, and timely surgery (140), and access to radiotherapy is limited in many LMICs, particularly in Africa and Southeast Asia, where about 30 countries have no radiotherapy services available (Supplementary Fig. S8; refs. 138, 143). Even when radiotherapy equipment is available, it may not be functioning properly (144). Many LMICs may need international assistance to establish sustainable access to radiotherapy equipment. Currently, the main source of assistance is the International Atomic Energy Agency (IAEA), which in collaboration with WHO and some international cancer organizations, works with ministries of health in capacity building, such as training of radiotherapy workforce and the procurement of equipment (145).

The cost of cancer drugs has skyrocketed with the development of new and more effective targeted treatments and immunotherapy (146). The WHO List of Essential Medicines, whose selections are based on public health impact as well as relative cost-effectiveness compared with similar drugs, contains 46 cancer medicines as of May 2015 (146, 147). There are a number of cancer drugs on the list which can be obtained at a relatively low cost; for example, the total cost of generic drugs per patient for treating Burkitt lymphoma in Cameroon, Ghana, and Malawi, with a 50% cure rate, is <US$50 (148). However, there are also others that may be cost-prohibitive in lower-income settings and even for equitable access in HICs. Some approaches to make cancer drugs more affordable in LMICs include providing generic drugs, negotiation with pharmaceuticals for lower prices, expansion of health coverage, and increase in involvement in clinical trials (149).

Many LMICs lack a sufficient number of trained specialists to diagnose and treat cancer due to scarcity of local educational opportunities and/or "brain drain", when highly-skilled professionals emigrate (150). For instance, many countries in sub-Saharan Africa have fewer than one pathologist per million inhabitants (Supplementary Fig. S9; ref. 151). When a country lacks sufficient number of oncologists, surgeons and some other health professionals may be responsible for providing cancer care beyond their specialty (142). This indicates that while there is a need for oncologic specialists in places where there are none, some cancer treatments can still be successfully delivered in these settings. Collaborations between local leadership and cancer specialists in other countries have started in several LMICs to deliver cancer care through local physicians and nurses (152, 153). For example, Rwanda is one of the first countries in sub-Saharan Africa that has established a cancer center in a rural area to provide basic imaging, pathology services, surgery, chemotherapy, and palliative care (153). In its first two years of action (2012–2014), the center provided care to 2,326 patients, 71% of whom were women (154). Individuals living outside larger cities in LMICs may need to travel long distances to have access to cancer care, with additional costs of travel, accommodation, and absence from work for patients and people accompanying them (1).

Affordability of cancer care, even when available, is a major issue in LMICs. For example, 81% of cervical cancer cases referred for radiotherapy to a treatment center in Nigeria and 70% of patients who required chemotherapy in a center in Tanzania did not receive the treatment mostly because of financial issues (143, 155). Health insurance plans in many LMICs may cover a relatively small proportion of the population and have high copayments, and they may not cover some cancer care services because of their high cost (134). Establishing publicly funded universal health coverage (UHC) in LMICs is likely to increase access to care even for low-income people (156, 157). WHO recommends taking into account the three dimensions of coverage: proportion of the service cost covered, the number of covered services, and the proportion of covered people (157). There should also be a balance among cancer treatment and preventive and early detection measures. Nevertheless, due to limited resources, providing UHC will be a challenging task in LMICs, especially in lower income countries (154, 158, 159). Discussing these challenges and possible means to overcome them are beyond the scope of this article, but making strong political commitments is the first step to provide UHC. Despite these challenges, a number of LMICs, notably in the Americas and Southeast Asia, are transitioning to provide UHC, and several countries, such as Bangladesh, Brazil, Colombia, Mexico, Peru, the Philippines, and Thailand, have made substantial progress in expanding UHC, although still more improvements are required (40, 156, 157, 160–162).

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Population-based Cancer Registries

Cancer registries and vital registrations are an integral part of any evidence-based cancer control programs as they set priorities and assess the effectiveness of such programs. There are variations in the quality of data and coverage (nationwide versus regional) of population-based cancer registries across countries. The IARC and the International Association of Cancer Registries compile high quality population-based incidence data from around the globe and publish these data periodically as the Cancer Incidence in Five Continents (CI5) series. However, only 14% of the world population was covered by the registries included in the latest edition (Volume X, registration period 2003–2007), with a great disparity in coverage between LMICs and HICs: Africa (2%), Asia (6%), Central and South America (8%), Europe (42%), Oceania (78%), and North America (95%; ref. 163). No population-based cancer registries exist in several countries in sub-Saharan Africa and Central Asia (Supplementary Fig. S10; ref. 138). IARC's GLOBOCAN is another valuable source of information, which provides estimates for cancer incidence and mortality by cancer site and sex for all countries (164). However, national estimates for most LMICs are based on information from nonrepresentative regional registries or neighboring countries (164). To improve the coverage and quality of cancer registries in these countries, IARC has recently established the Global Initiative for Cancer Registry Development (165, 166).

Similar to cancer registries, there is wide variation globally in the availability, quality and completeness of death certification. Almost all countries in Africa and many countries in the Middle East and South-Central and Southeast Asia lack vital registration (Supplementary Fig. S11, ref. 138). Of those countries with vital registration most are of low or medium quality and regional (often urban areas) rather than national. Vital registration systems could also collect some other pieces of valuable information. Since 1998, for example, ascertaining smoking history of decedents has been part of routine death notification process in South Africa, which allowed the estimation of tobacco-attributable deaths in the country (167). Another example is the Navrongo health and demographic surveillance system in Ghana, which collects information on smoking and alcohol drinking at the subnational level (168, 169).

Research

Cancer research has been primarily focused on cancer problems of HICs, and only about 3% of global cancer research funding goes toward projects relevant to LMICs (170). Although many findings from studies conducted in HICs are applicable to LMICs, there are several other unanswered research questions that are specific to LMICs (171, 172). For example, approximately 90% of cases of esophageal cancers in high-risk populations in Asia and Africa are squamous cell carcinomas (SCC), whereas most esophageal cancers in the United States and other western countries are adenocarcinomas (117). While smoking and excess alcohol consumption are responsible for the majority of esophageal SCC in the United States and other western countries, reasons for the high rates of esophageal SCC in parts of Asia and sub-Saharan Africa are unknown (173). The incidence rate of esophageal SCC is 2–3 times lower in women than men in western countries, but in high-risk populations, this cancer almost equally affects men and women (173). There are also opportunities to identify novel risk factors for cancers in LMICs, which may have significant public health implications for cancer control not only in LMICs but also in HICs. For example, Epstein–Barr virus (EBV) was the first virus that was shown to cause human cancer based on evidence from studies of EBV and Burkitt lymphoma in endemic areas of Africa (174, 175). This discovery was made when the causal association between viruses and human cancers was controversial (175), and it has served as a catalyst for identification of other carcinogenic human viruses. LMICs will need more international collaborations and assistance to conduct cancer research and build the required infrastructure.

Conclusions

Cancer is a major public health problem among women in both HICs and LMICs, and there are a number of effective cancer control measures available to countries of all resource levels to combat the growing burden of the disease. Most primary prevention measures are extremely cost-effective, especially tobacco control and vaccination, and they can also substantially reduce the burden of some other common noncommunicable diseases such as diabetes and cardiovascular diseases. Effective treatments and palliative care are also needed for those who develop cancer. However, the use of the newest cancer drugs and technologies may not be feasible in most LMICS due to cost and infrastructure requirements, but there are drugs and technologies that could be adapted in a cost-effective manner to provide effective treatment options. In addition to these needs, the availability of high-quality population-based cancer registries and etiologic, health services, and implementation research are essential for cancer control priority setting and for determining the most effective interventions in a given context. For LMICs, all of these activities may require support and commitment from the global community.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received October 31, 2016; accepted November 8, 2016; published OnlineFirst February 9, 2017.

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