GLOBAL BURDEN OF CANCER IN WOMEN

Current status, trends, and interventions

Table of Contents

List of Abbreviations

CIN, cervical intraepithelial neoplasia

CTC, computed tomographic colonography

DAA, directly acting antiviral

DALY, disability-adjusted life-year

ELISA, enzyme-linked immunosorbent assay

FCTC, Framework Convention on Tobacco Control

GDP, gross domestic product

HBC, hepatitis B virus

HBsAg, hepatitis B virus surface antigen

HCV, hepatitis C virus

HIV, human immunodeficiency virus

HPV, human papilloma virus

IAEA, International Atomic Energy Agency

IARC, International Agency for Research on Cancer

LMICs, low- and middle-income countries

PACT, Programme of Action for Cancer Therapy

WHO, World Health Organization

YLL, years of life lost

YPLL, years of productive life lost

Introduction

Cancer is a leading cause of death worldwide among women in both high-income countries and middle-income countries. The cancer burden is also expanding in countries of all income levels due to the growth and aging of the population. This increasing burden is expected to be particularly pronounced in low- and middle-income countries (LMICs), where the average life expectancy is becoming longer due to public health advances such as the control of infectious diseases and reductions in maternal, infant, and childhood mortality. In addition to these increases stemming from population growth, the cancer burden is also growing 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, and physical inactivity. Changes in reproductive patterns which often accompany economic development, such as a later age at first childbirth and having fewer children, also affect the cancer burden in women. Due to these changes, cancers that were once common only in high-income countries are becoming more prevalent.

In addition to the burden of morbidity and mortality, cancer carries an economic burden. This includes direct costs, such as the costs of treatment, and indirect costs, such as the costs to family or society from loss of income or productivity due to illness or premature death. There are also other quantifiable costs of cancer, such as time spent by caregivers, transportation, and assistance in the home. The costs of cancer pose unique challenges in both high- and low-resource environments. In high-income countries, where the burden of cancer is already substantial, the costs of cancer and survivor care have skyrocketed. LMICs, on the other hand, are struggling to balance the growing demands on healthcare infrastructures with limited resources.

In addition to treatment, prevention and early detection interventions are needed in both high- and low-resource settings to avert cancer cases and deaths. Primary prevention is particularly

important; about one-third to one-half of cancer cases could be averted based on current knowledge of risk factors.[1] Screening can remove precancerous lesions or detect cancer at an early stage when there are more treatment options. While LMICs may have limited resources for screening, there are modalities available which can be suitable in a variety of settings. A number of common cancers among females have known means of prevention and/or early detection which can be applied in resource-appropriate settings. As such, while the global burden of cancer among women is substantial, there is also significant potential to reduce suffering and loss of life, as well as to alleviate the economic burden to individuals, families, and societies. Addressing this burden is particularly important not only for the potential for health impact, but also to confront gender inequalities and recognize the role of women as societal and economic participants as well as caretakers who influence the health of the whole family.[2]

In this report, we summarize the current burden of cancer among women worldwide, along with information on risk factors, economic burden, and cancer control measures. Many high-income countries have their own national recommendations or programs for cancer control. Throughout this report, we primarily present recommendations and guidelines from the World Health Organization (WHO), as they are more likely to be applicable to LMICs.

Chapter 1. Overall cancer burden

1.1. Number of cancer cases and deaths

Among females, cancer is the second leading cause of death worldwide, accounting for 14% of all deaths (Table 1.1), and in the Americas, Europe, and the Western Pacific regions. It is the third leading cause of death in the Eastern Mediterranean, fourth in South-East Asia, and sixth in Africa (Table 1.2).

Table 1.1. Leading causes of death among females worldwide (×1000), 2012

Rank	Top ten causes of death	Deaths	%
1	Cardiovascular diseases	8,820	34
2	Malignant neoplasms	3,544	14
3	Infectious and parasitic diseases	3,016	12
4	Respiratory diseases	1,756	7
5	Respiratory infections	1,461	6
6	Unintentional injuries	1,328	5
7	Neonatal conditions	1,097	4
8	Digestive diseases	929	4
9	Neurological conditions	821	3
10	Diabetes mellitus	813	3
	All causes	26,023	

According to estimates from the World Health Organization (WHO) International Agency for Research on Cancer (IARC), there were 6.7 million new cancer cases and 3.5 million deaths among females worldwide in 2012 (Table 1.3).[3] Of these, 56% of cases and 64% of deaths were in less developed countries. These numbers are expected to increase to 9.9 million cases and 5.5 million deaths among females annually by 2030 as a result of the growth and aging of the population.[3]

Table 1.2. Leading causes of death among females by world region (×1000), 2012

Rank	Top ten causes of death	Deaths	%	Top ten causes of death	Deaths	%
	Africa			**Americas**		
1	Infectious and parasitic diseases	1,568	35	Cardiovascular diseases	934	31
2	Cardiovascular diseases	513	12	Malignant neoplasms	615	20
3	Respiratory infections	479	11	Neurological conditions	259	9
4	Neonatal conditions	393	9	Respiratory diseases	200	7
5	Unintentional injuries	253	6	Diabetes mellitus	161	5
6	Malignant neoplasms	232	5	Digestive diseases	137	5
7	Nutritional deficiencies	174	4	Respiratory infections	132	4
8	Maternal conditions	171	4	Unintentional injuries	110	4
9	Digestive diseases	134	3	Infectious and parasitic diseases	110	4
10	Diabetes mellitus	99	2	Genitourinary diseases	91	3
	All causes	4,446		All causes	3,011	
	South-East Asia			**Europe**		
1	Cardiovascular diseases	1,685	27	Cardiovascular diseases	2,406	53
2	Infectious and parasitic diseases	889	14	Malignant neoplasms	886	20
3	Respiratory diseases	661	11	Neurological conditions	215	5
4	Malignant neoplasms	554	9	Digestive diseases	190	4
5	Unintentional injuries	436	7	Respiratory diseases	161	4
6	Neonatal conditions	402	6	Unintentional injuries	123	3
7	Respiratory infections	376	6	Respiratory infections	102	2
8	Digestive diseases	243	4	Diabetes mellitus	87	2
9	Diabetes mellitus	208	3	Infectious and parasitic diseases	86	2
10	Genitourinary diseases	181	3	Genitourinary diseases	75	2
	All causes	6,216		All causes	4,527	
	Eastern Mediterranean			**Western Pacific**		
1	Cardiovascular diseases	523	29	Cardiovascular diseases	2,730	71
2	Infectious and parasitic diseases	220	12	Malignant neoplasms	1,064	28
3	Malignant neoplasms	174	10	Respiratory diseases	602	16
4	Neonatal conditions	162	9	Unintentional injuries	299	8
5	Respiratory infections	139	8	Respiratory infections	228	6
6	Unintentional injuries	103	6	Diabetes mellitus	187	5
7	Digestive diseases	76	4	Digestive diseases	144	4
8	Diabetes mellitus	63	4	Infectious and parasitic diseases	142	4
9	Respiratory diseases	56	3	Neurological conditions	106	3
10	Genitourinary diseases	50	3	Genitourinary diseases	103	3
	All causes	1,792		All causes	3,870	

Table 1.3. 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

* Excluding non-melanoma skin cancers
Source: GLOBOCAN 2012

The number of cancer cases and deaths is a function not only of cancer risk but also population size. 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 (Table 1.4). This figure is dominated by China, which constitutes about three-quarters of female cancer cases and deaths in the region.[3] 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 US make up about 90% of the totals for the region, while cancer cases and deaths in India make up about 65% of the totals for South-Central Asia.[3]

Table 1.3. Estimated number of new cancer cases and deaths among females by world area (×1000), 2012*[3]

World area	Cases	Deaths
Eastern Africa	171	116
Middle Africa	44	31
Northern Africa	115	67
Southern Africa	43	26
Western Africa	113	74
Eastern Asia	1,714	1,002
South-central Asia	802	490
South-eastern Asia	404	238
Western Asia	149	79
Caribbean	43	24
Central America	110	57
Northern America	866	329
South America	410	209
Central and Eastern Europe	523	287
Northern Europe	254	116
Southern Europe	339	163
Western Europe	496	214
Australia/New Zealand	62	23
Melanesia	6	4
Micronesia	0.4	0.1
Polynesia	0.6	0.3

* Excludes nonmelanoma skin cancer.
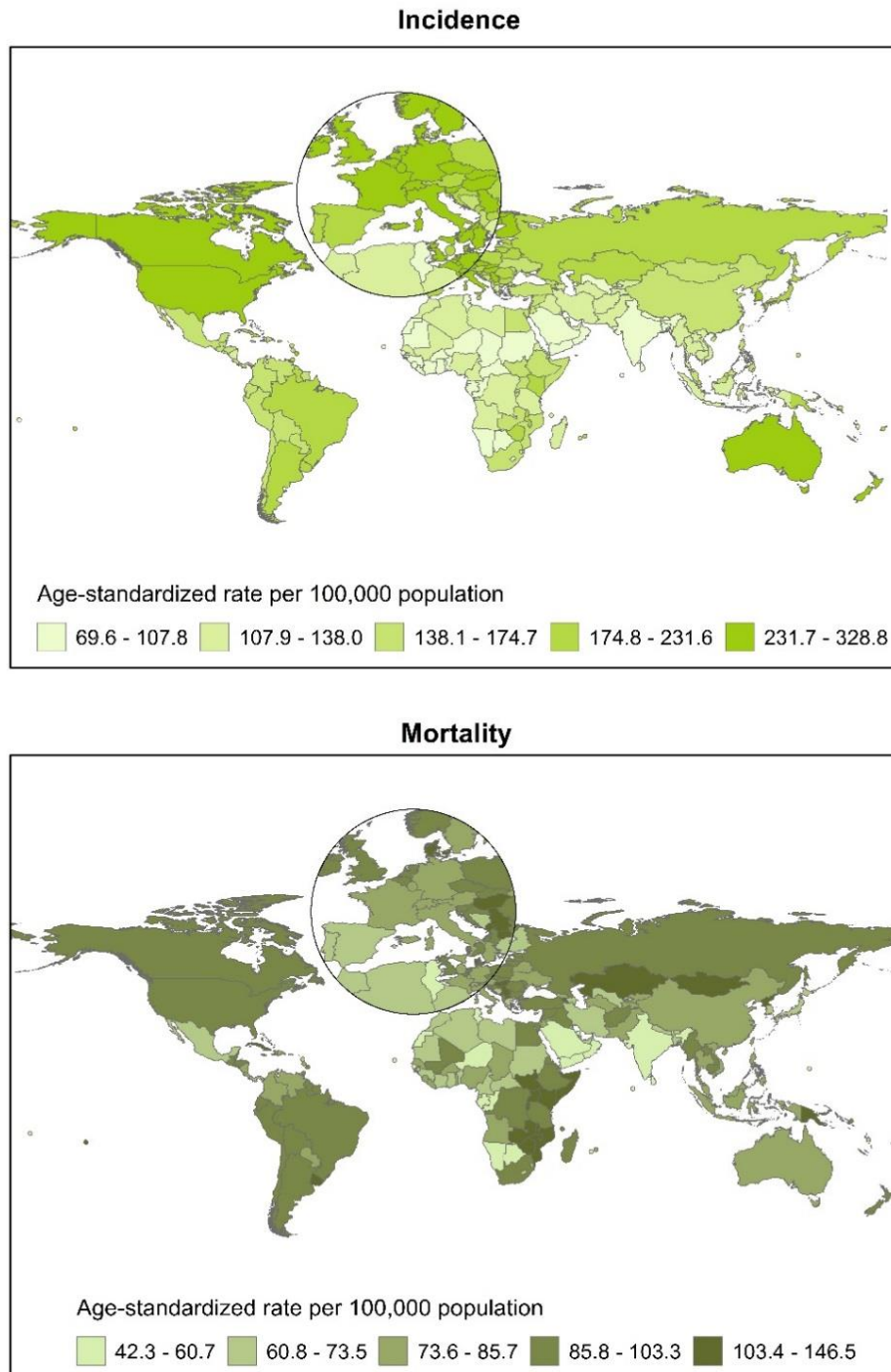
1.2. Incidence and mortality rates

In general, all-sites cancer rates among females are higher in high-income countries compared with LMICs (Figure 1.1). Overall estimated incidence rates in 2012 (per 100,000) are highest in the high-income countries of North America, Europe, and Australia/New Zealand, and Asia, with the top five rates in Denmark (329 cases per 100,000), the US (297), South Korea (294), the Netherlands (290), and Belgium (289).[3] Incidence rates are lowest in the LMICs of South-Central and South-Eastern Asia and Africa. All-sites cancer incidence rates reflect not only the cancer risk in a population, but also awareness, the prevalence of cancer screening, and detection practice.

In contrast to incidence, all-sites mortality rates among females are highest in select LMICs of Oceania, sub-Saharan Africa and Asia, followed by North America, Europe, and Australia/New Zealand. The top five estimated mortality rates worldwide in 2012 are in Zimbabwe (147 deaths per 100,000), Malawi (138), Kenya (133), Mongolia (127), and Papua New Guinea (125).[3] 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 access to early detection and appropriate treatment.

1.3. Most common cancers

Among females, breast, lung, and colorectal cancers are the three most frequently diagnosed cancers worldwide and in more economically developed countries (Table 1.2). In less developed countries, however, the top three most diagnosed cancers are breast, cervix, and lung. Breast, lung, and colorectal cancers are also the leading causes of cancer death among females worldwide, although their relative ranking differs in more and less developed countries. In more developed countries, the leading causes of cancer death are lung, breast, and colorectum, while the leading causes of death in less developed countries are breast, lung, and cervix.

Figure 1.1. Incidence and mortality rates for all cancers combined among females, 2012

Figure 1.2. Most commonly diagnosed cancers and leading causes of cancer death
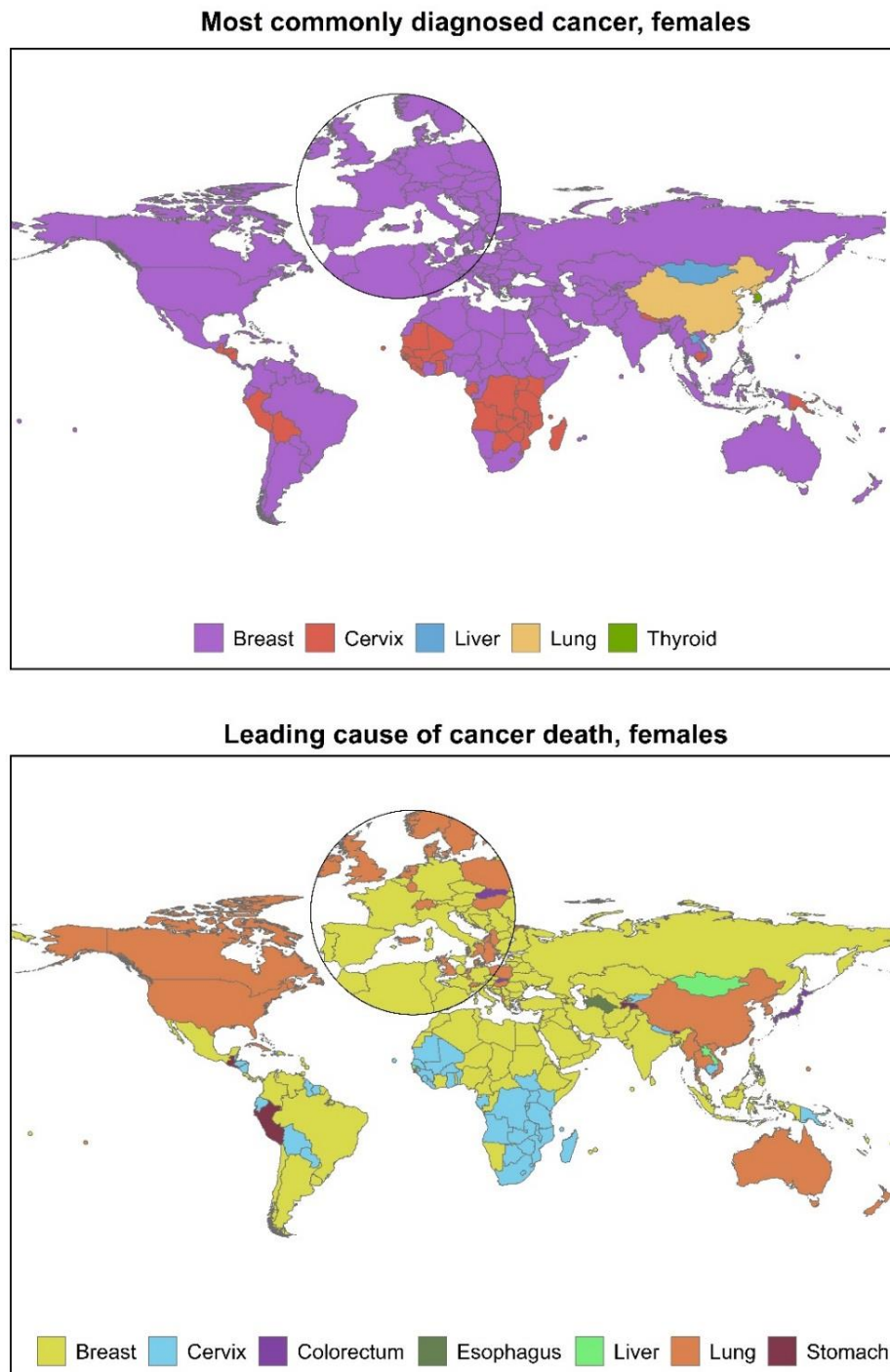
Breast cancer is the most commonly diagnosed cancer among women in 140 countries worldwide, and cervical cancer is the most common in 39 countries, all of which are LMICs (Figure 1.2). A few countries have other cancer types as the most commonly diagnosed in women, such as lung cancer in China and North Korea, liver cancer in Mongolia and Laos, and thyroid cancer in South Korea. There is more diversity in the most common cause of cancer death among women. Breast is the most common cause of cancer death in 103 countries, followed by cervix in 43 countries and lung in 27 countries. Other most-common causes of cancer 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.

Chapter 2. Select cancer sites

In this chapter, we briefly discuss the burden, trends, risk factors, prevention, early detection, and survivorship of five major female cancers worldwide, including cancers of the breast, cervix, lung, liver, and colorectum.

2.1. Cancer of the Breast
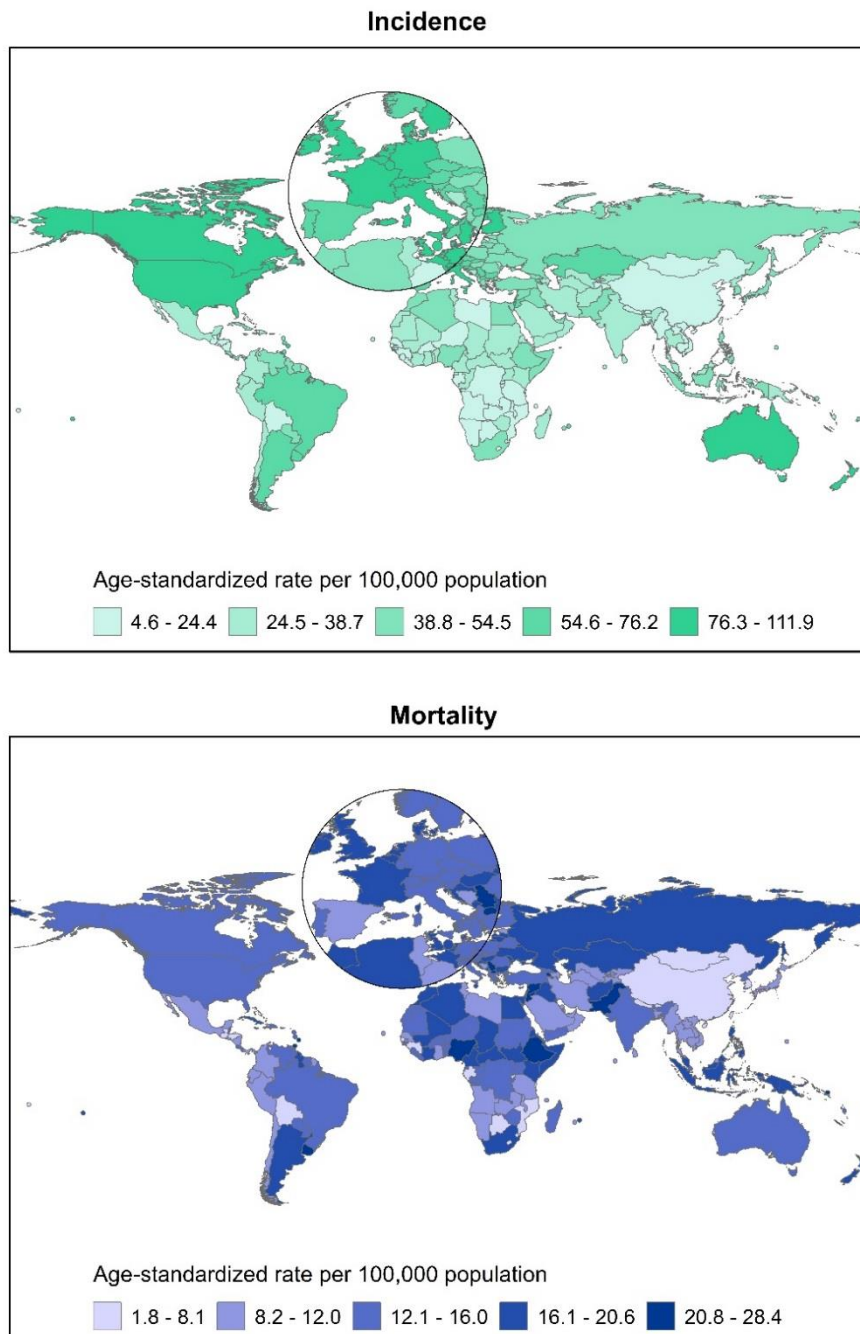
2.1.1. Burden, trends, and risk factors

2.1.1.1. Burden. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women worldwide, with an estimated 1.7 million cases and 521,900 deaths in 2012 (Table 1.2). It is also the most frequently diagnosed cancer in the majority (140 of 184) of countries (Figure 1.2) and accounts for 25% of cancer cases and 15% of cancer deaths among women worldwide. Global breast cancer incidence patterns reflect both risk factors and the availability of screening. The highest breast cancer incidence rates are in North America, Australia/New Zealand, and Northern and Western Europe, while the lowest are in Africa and Asia (Figure 2.1). 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, such as those in sub-Saharan Africa, despite their lower incidence because of late stage at diagnosis and limited access to treatment.

2.1.1.2. Trends. Breast cancer incidence rates increased in western countries between 1980 and the late 1990s (Figure 2.2). These increases are thought to be due to changes in reproductive factors, use of menopausal hormone therapy, and increased screening.[4] Since around 2000, however, rates in several of these countries have stabilized or decreased, which is thought to be due to decreased use of menopausal hormone therapy or plateaus in screening participation.[5] In

many LMICs, however, incidence rates have continued to increase, possibly due to changing

reproductive patterns, increased awareness, and/or screening.[4, 6]

Figure 2.1. Female breast cancer incidence and mortality rates

Incidence

Age-standardized rate per 100,000 population

| 4.6 - 24.4 | 24.5 - 38.7 | 38.8 - 54.5 | 54.6 - 76.2 | 76.3 - 111.9 |

Mortality

Age-standardized rate per 100,000 population

| 1.8 - 8.1 | 8.2 - 12.0 | 12.1 - 16.0 | 16.1 - 20.6 | 20.8 - 28.4 |

Source: GLOBOCAN 2012

Figure 2.2. Female breast cancer incidence trends, select countries
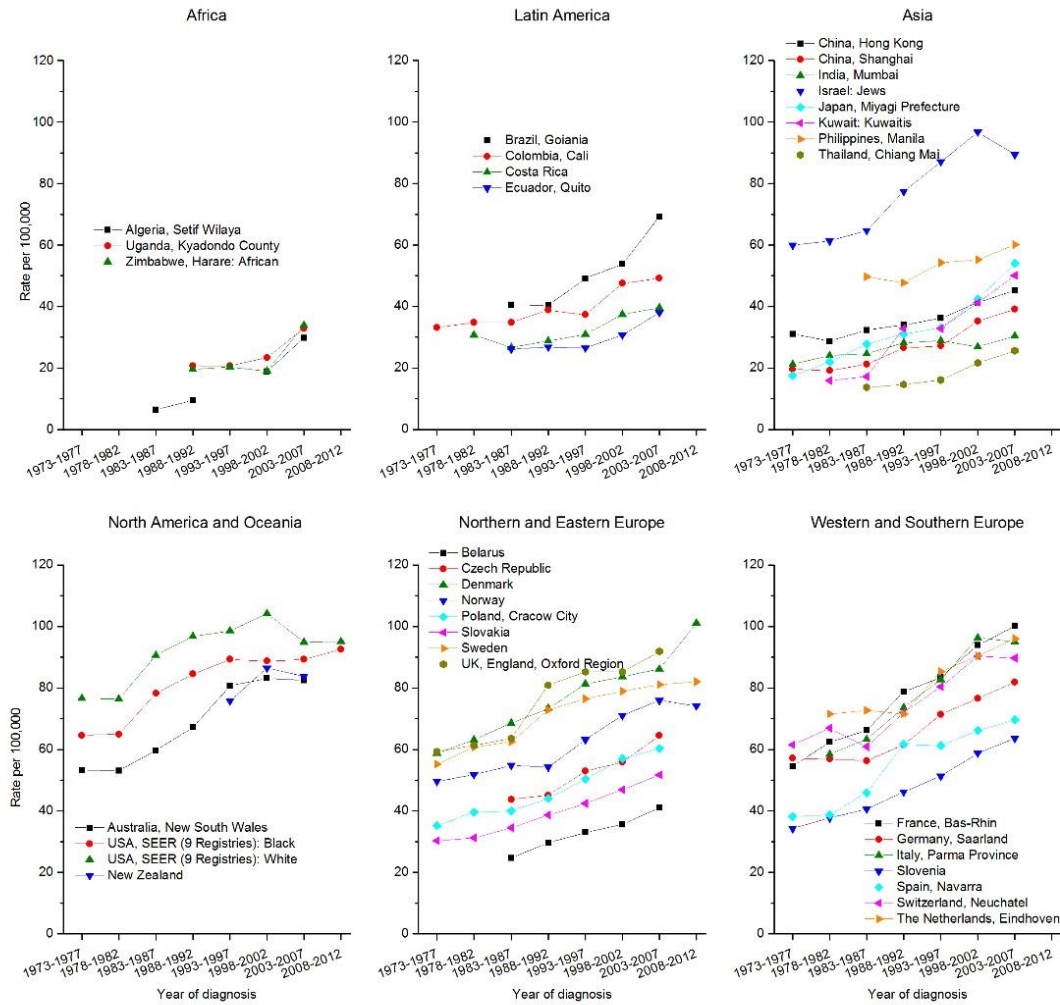
Sources: US- Surveillance, Epidemiology and End Results (SEER) Program, 9 registries, 1973-2012. Denmark, Norway, Sweden 2008-2012- NORDCAN. All others- Cancer Incidence in Five Cont

In contrast to the historically rising incidence rates, mortality rates in many high-income countries have been decreasing since around 1990 (Figure 2.3). These declines have been attributed to mammography screening and better treatments,[4] although the relative contribution of each is debated.[7-9] At the same time, however, mortality rates in countries with historically lower rates have increased. These increases are likely due to changes in risk factors in addition to limited access to early detection and treatment.[10-12]

Figure 2.3. Breast cancer mortality trends, select countries

Female breast cancer mortality trends, select countries, 1950-2013
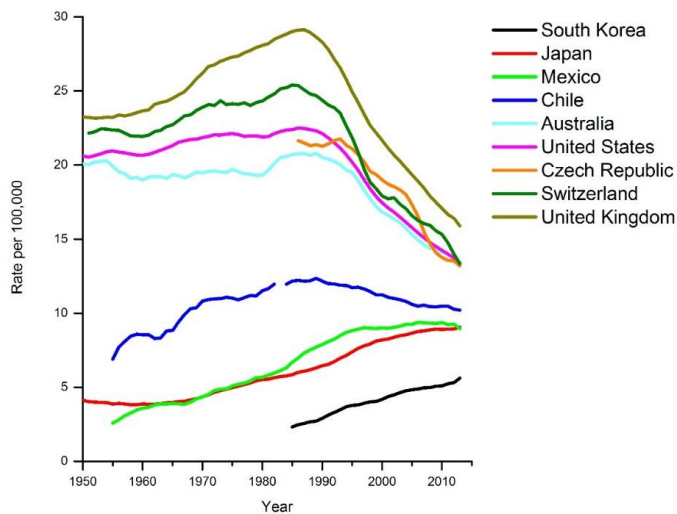
Source: WHO IARC Cancer Mortality Database

2.1.1.3. Risk factors. The established risk factors for breast cancer include family history of breast cancer, *BRCA1* or *2* mutations, some reproductive factors (nulliparity, early age at menarche, late 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 combined postmenopausal hormone replacement therapy), and radiation exposure.[13, 14] Also, recent prospective studies have shown an association between smoking and breast cancer.[15, 16] On the other hand, breastfeeding has been reported to reduce breast cancer risk,[17] in particular the risk of estrogen and progesterone receptor negative subtypes.[18]

2.1.2. Prevention and early detection

About 20% of breast cancers worldwide are due to modifiable risk factors including alcohol use, excess body weight, and physical inactivity,[19] and thus the adoption of a healthy lifestyle could substantially reduce the risk of breast cancer. Breast cancer mortality can also be reduced through screening.

2.1.2.1. Healthy lifestyle. Excess body weight increases the risk of postmenopausal breast cancer. Women with BMI>35 kg/m^2 are at a 1.6-fold higher risk of breast cancer and 2.1-fold higher risk of breast cancer death than those with normal BMI (<25 kg/m^2).[20] Women who have had a high BMI since they were younger and women who gain weight after menopause are at a higher risk,[20, 21] showing the importance of maintaining normal BMI throughout the life in order to reduce the risk of breast cancer.[22] Excess body weight is associated not only with breast cancer risk but also with indicators of poorer prognosis after development of breast cancer, such as larger tumor size and local and distant extension of cancer.[20]

The proportion of postmenopausal breast cancers attributable to excess body weight was 10.2% globally in 2012 and ranged from 4.1% in South-central Asia to 14.7% in the Middle-East and North Africa.[23] The corresponding proportions by country are shown in Figure 2.4. The highest proportions were in the United States, Bahamas, South Africa, Samoa, and a number of countries in the Middle East and Northern Africa.

Figure 2.4. Proportion of postmenopausal breast cancers attributable to excess body weight, 2012 [23]
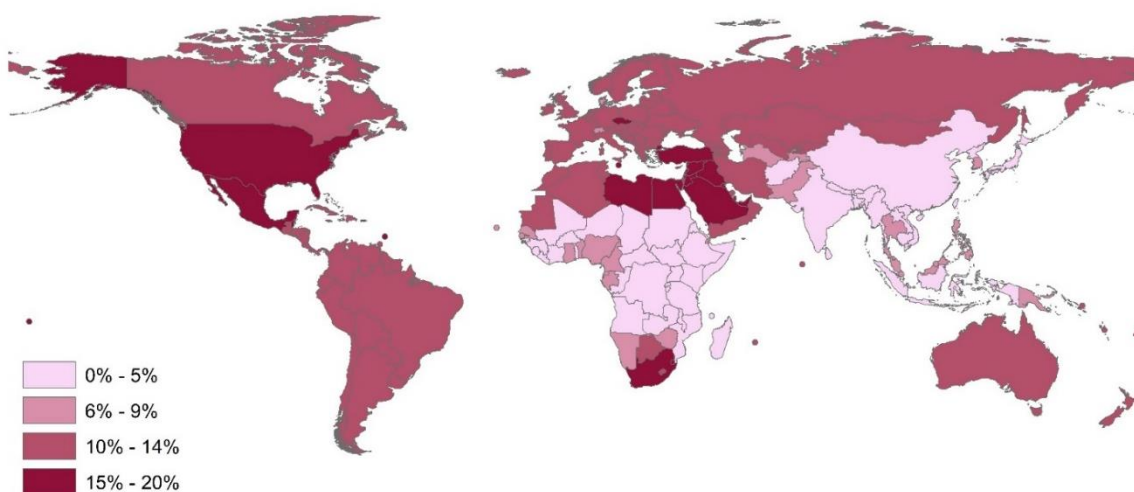
Physical inactivity and alcohol drinking are other potentially modifiable risk factors that contribute not only to breast cancer but also to many other cancers and chronic diseases. Women should be encouraged to limit or abstain from alcohol drinking and participate in physical activity regularly at the recommended level (see Section 4.4.2).

2.1.2.2. Screening. Mammography is an imaging method based on X-rays for the detection of breast cancer. By identifying tumors at earlier stages when treatment has a greater likelihood of success, screening with mammography reduces breast cancer mortality.[24-26] However, there are concerns about complications associated with over-diagnosis and over-treatment resulting from mammography detection of indolent cancer.[27, 28] A number of high-income countries have national programs for mammography screening (see Section 4.3.2), though the recommended age and frequency of screening varies across countries.

In high-income countries with organized or opportunistic mammography screening programs, other interventions such as clinical breast examination may not be recommended, because evidence for the effectiveness of those interventions is limited.[25, 29, 30] Mammography screening needs high-quality equipment, skilled radiologists, and efficient infrastructure to communicate positive results and follow up with patients until they receive appropriate treatment or further diagnostic procedures.[31] Due to limited resources, however, implementation of a mass screening program based on mammography will not be a feasible cancer control intervention in most LMICs.[32, 33]

Currently, WHO recommends mammography screening in high resource settings for women aged 50−69 years if the health-care system and shared decision-making strategies meet certain conditions; the suggested screening interval is two years.[34] In these settings, WHO suggests screening for women aged 40-49 or 70-75 only if the intervention is conducted in the context of

rigorous research, monitoring, and evaluation. In limited resource settings with relatively strong health systems, WHO suggests considering the same intervention for women aged 50−69 years only if the specified conditions are met by the health-care system and shared decision-making strategies. In limited resource settings with weak health systems, where mammography screening is not cost-effective and feasible, population-based mammography screening is not recommended. Instead, efforts should be made to provide universal access to prompt and effective diagnosis and treatment for women with symptomatic lesions. In both limited resource settings with weak or relatively strong health systems, WHO recommends against screening in women aged 40-49 or 70-75 years.[34]

Some studies have shown that clinical breast examination may reduce the stage of breast cancer at diagnosis in LMICs.[35, 36] Although more research is required before mass screening with clinical breast examination could be systematically recommended to all LMICs, clinical breast examination may be recommended as part of routine physical examination in those countries. Sessions for clinical breast examination can also provide an opportunity to increase women's awareness about breast cancer and its early detection.

2.1.3. Treatment

Breast cancer treatment usually involves breast-conserving surgery or mastectomy with removal of some of the axillary lymph nodes for disease staging. Radiation therapy, chemotherapy, hormone therapy, and/or targeted biologic therapy may also be used depending on the cancer stage and biologic characteristics and type of surgery. In LMICs, however, women are more likely to be diagnosed with later-stage disease, and all types of breast cancer treatment may not be available. Although many LMICs may have a few well-equipped hospitals in the capital or some larger cities, the majority of breast cancer patients usually do not have access to appropriate surgical therapy or

other kinds of breast cancer treatment.[37] Even for those who have access to the care, the follow-up for complications or recurrence of cancer may not be optimal.

In low-resource settings, mastectomy is the most common surgical treatment due to a greater proportion of advanced stage disease and the limited availability of radiotherapy. Pathology services may also be limited in these settings, making the use of systemic therapy difficult. Even in HICs, many breast cancer patients are unable to afford or access needed treatments.

2.1.4. Survival and survivorship

When breast cancer is detected at an early stage, treatment is more effective and a cure is more likely. In high-income countries, 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 after the disease has progressed, and survival is poorer. Five-year survival is 85% or higher in the US, Canada, Australia, Israel, Brazil, and many Northern and Western European countries, while it is 60% or lower in many LMICs, such as South Africa, Mongolia, Algeria, and India.[38]

In 2012, there were an estimated 6.2 million women worldwide who had survived breast cancer after being diagnosed within the preceding five years.[3] The highest prevalence of breast cancer survivors who were diagnosed within the past five years in the general population is in North America, Northern and Western Europe, and Australia/New Zealand (Figure 2.5), reflecting the availability of services for early stage at diagnosis in those countries. Denmark and Belgium had the highest prevalence of breast cancer survivors, with over 200 breast cancer survivors per 100,000 women.[3] 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.[39] Younger breast cancer patients may have impaired fertility or premature

menopause and are at increased risk of osteoporosis.[40] Other long-term effects of breast cancer treatment include cognitive impairment, chronic fatigue, hot flashes, and vaginal dryness.[41] Long-term survivor care for medical concerns, as well as psychosocial care addressing living with the risk of recurrence, body image changes, emotional distress, and social isolation, are needed; this type of care is less available in LMICs, where resources are limited and breast cancer survivorship issues are only recently being addressed.[39]

Figure 2.5. Breast cancer survivors diagnosed in last five years (through 2012 or latest available) [3]
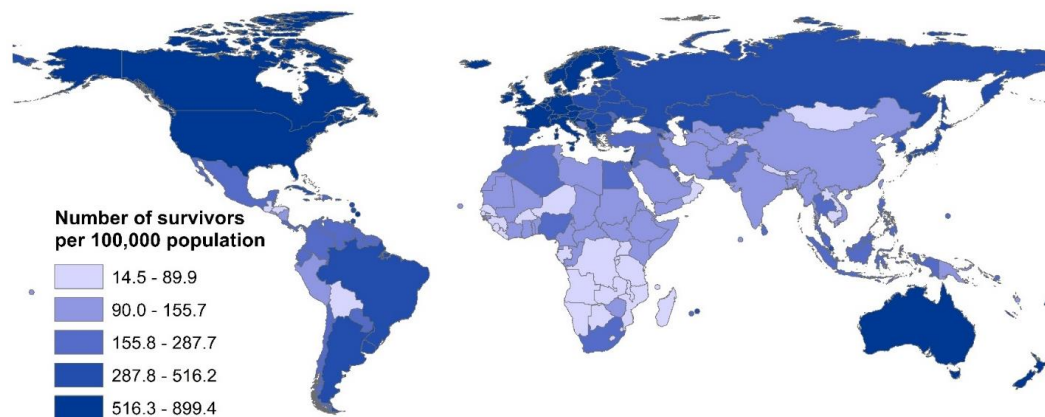
2.2. Cancer of the Cervix

2.2.1. Burden, trends, and risk factors

2.2.1.1. Burden. Cervical cancer was the fourth most frequently diagnosed cancer with an estimated 527,600 cases and the fourth leading cause of cancer death with 265,700 deaths among women worldwide in 2012. However, in developing countries, it is the second most commonly diagnosed cancer after breast cancer and the third leading cause of cancer death after breast and lung cancers.[3] In fact, almost 90% of cervical deaths in the world occur in developing countries, with India alone accounting for 25% of the total cases. Cervical cancer incidence and mortality

rates are highest in sub-Saharan Africa, Central and South America, South-eastern Asia, and

Central and Eastern Europe (Figure 2.6).

Figure 2.6. Cervical cancer incidence and mortality rates
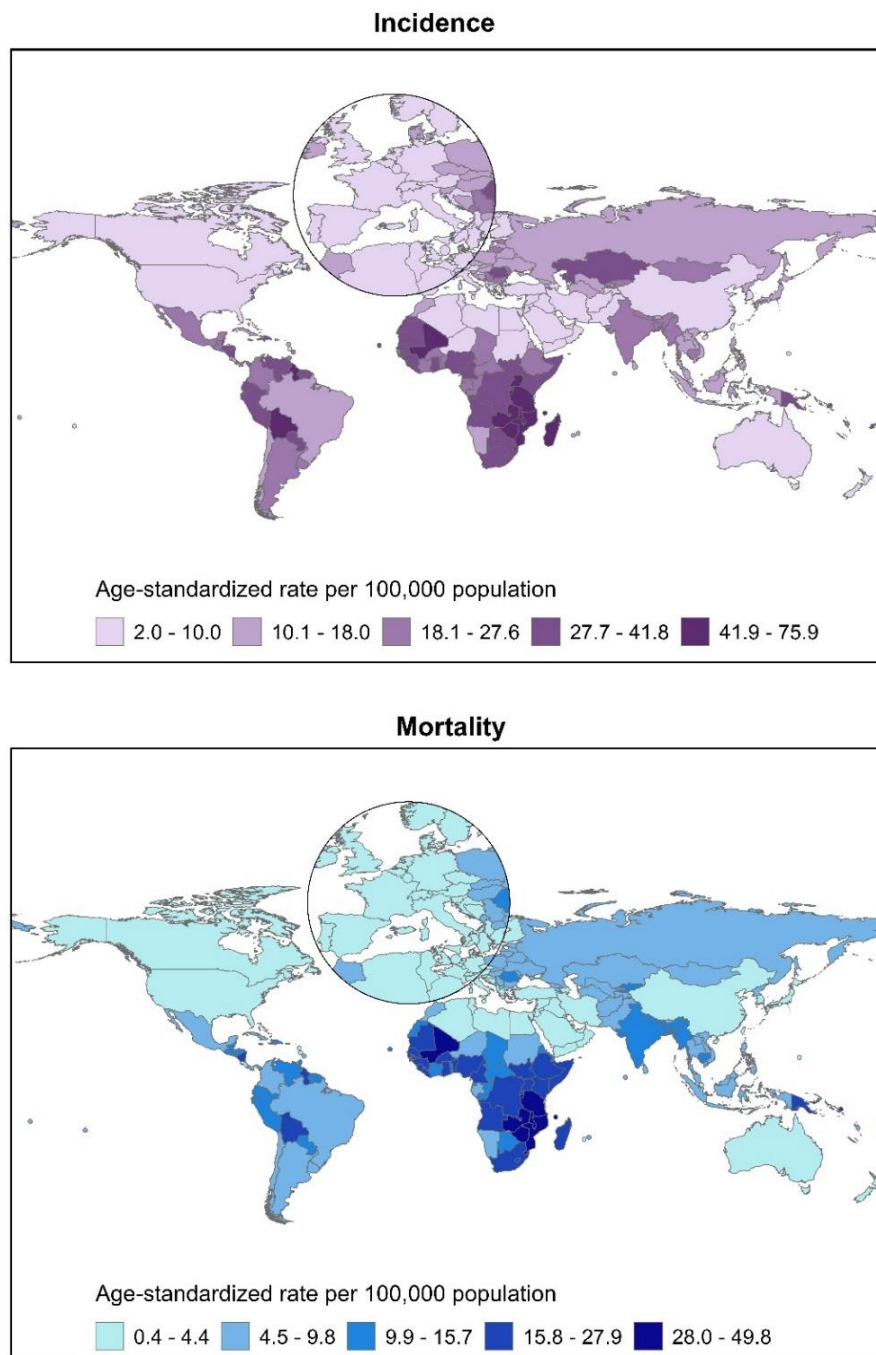
Source: GLOBOCAN 2012

Geographic variation in cervical cancer rates are due to differences in the availability of screening, which can prevent the development of cancer through the detection and removal of precancerous lesions, and the prevalence of human papillomavirus (HPV) infection (see Section 2.2.1.3).[42-44] Infection with human immunodeficiency virus (HIV) can promote progression of precancerous lesions, contributing to a higher burden of cervical cancer in regions with a greater prevalence of HIV infection, particularly in sub-Saharan Africa.[45]

2.2.1.2. Trends. In several high-income countries with available screening, cervical cancer incidence rates have decreased by as much as 80% over the past four decades (Figure 2.7).[33]

Figure 2.7. Cervical cancer incidence trends, select countries
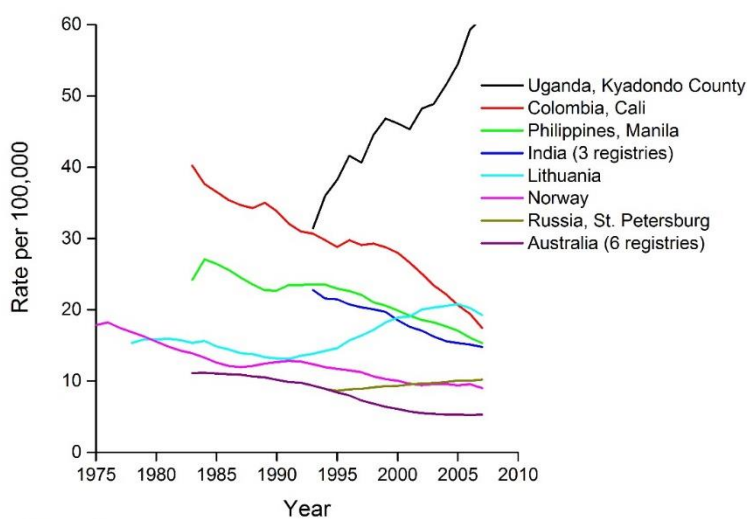
Rates have also decreased in some LMICs such as Colombia, the Philippines, and India, likely due to screening activities and improved socioeconomic conditions.[43] However, cervical cancer rates have increased in Uganda, Zimbabwe, and some countries of Central and Eastern Europe, as well as among younger 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.[44, 46-48]

2.2.1.3. Risk factors. The main risk factor of cervical cancer is infection with HPV, which is believed to have a causal role in all cases of cervical cancer.[49] Over a hundred types of HPV have been identified, but only some of HPV types have shown to cause cervical cancer. Based on available evidence, the International Agency for Research on Cancer has so far classified 12 types of HPV as definitively carcinogenic to humans, including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59.[50] HPV 16 and 18 are the most common subtypes identified in cervical cancer; together they are responsible for 70% of cervical cancers worldwide.[51]

Figure 2.8. Prevalence of cervical HPV infection

Estimated HPV prevalence (%) among women by region, all types combined, 1995-2009
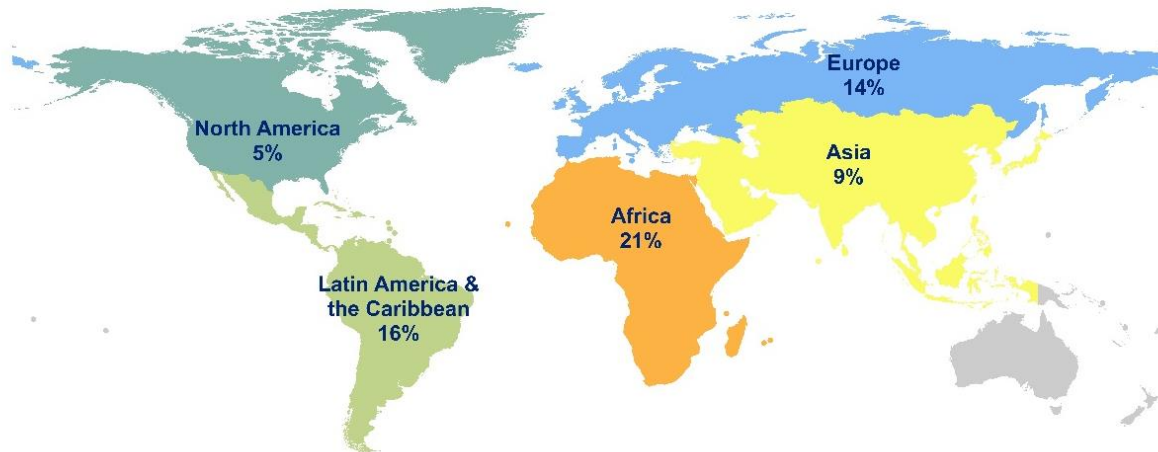
Source: Bruni L et al, J Infect Dis 2010

Sexual intercourse is the main route of acquiring cervical HPV infections. Nearly 80%-90% of the infections are cleared by the body within a few years; women with persistent infections will be at a higher risk of cervical cancer.[52, 53] It has been estimated that approximately 291 million

women (10.4%) worldwide at a given time have cervical HPV infection (Figure 2.8).[54] The

proportion of infected women is higher in younger, more sexually active age groups.[54] HPV

infection prevalence varies worldwide.

The estimated prevalence of cervical HPV 16 and/or 18 infection in women with normal

cervical cytology is approximately 3.9% globally, and although it varies across populations,[55] there

is little difference in overall prevalence between more and less developed regions (Table 2.1). The

prevalence of HPV in cervical tumors and precancerous lesions is substantially higher. For

example, prevalence of HPV 16 and/or 18 globally is 25.5% in low-grade cervical lesions, 51.5%

in high-grade lesions, and 70.0% in cervical cancer.[55]

Table 2.1. Estimated prevalence of HPV 16 and/or 18 infection in women with normal cervical cytology by geographical region [55]

Region	Prevalence (%)	No. tested ×1000	Region	Prevalence (%)	No. tested ×1000
World	3.9	453.2	**Asia**	3.4	142.7
More developed regions *	3.8	168.4	Central Asia	Unknown	–
Less developed regions **	3.8	282.2	Eastern Asia	3.4	111.5
Africa	3.8	19.7	Sothern Asia	4.4	8.8
Eastern Africa	4.7	4.1	South-eastern Asia	3.0	14.5
Middle Africa	Unknown	–	Western Asia	4.4	7.9
Northern Africa	3.0	2.2	**Europe**	3.8	180.1
Southern Africa	3.2	8.7	Eastern Europe	9.7	7.8
Western Africa	3.2	4.7	Northern Europe	4.2	86.8
Americas	4.5	105.0	Southern Europe	3.8	31.8
Caribbean	15.8	<1	Western Europe	2.6	56.1
Central America	4.1	16.8	**Oceania**	8.3	2.3
South America	5.8	78.0			
Northern America	4.4	10.2			

* Europe, Northern America, Australia/New Zealand and Japan.
** Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia and Polynesia

Factors that increase the risk of cervical HPV infection, including sexual intercourse at an early age and having multiple sexual partners, are associated with cervical cancer risk.[56] There are also other factors that increase cervical cancer risk in women infected with high-risk HPV subtypes, including higher parity, oral contraceptive use, HIV infection, and smoking.[56, 57]

2.2.2. Prevention and early detection

Because of the HPV vaccine and the potential of screening to detect and remove precancerous lesions, cervical cancer is considered nearly completely preventable. However, achieving optimal vaccination and screening remains a challenge in both high-income countries and LMICs.

2.2.2.1. HPV vaccination. HPV vaccination can prevent several types of HPV that cause cervical precancerous lesions and cancer.[58] The first HPV vaccines were introduced in 2006 and are expected to substantially affect the burden of cervical cancer in the future as generations of vaccinated women age; however, the vaccine was introduced too recently to affect the current burden and trends. The most commonly used HPV vaccines globally are a bivalent and a quadrivalent vaccine. Both of these vaccines cover HPV 16 and 18, and consequently, can prevent the majority of cervical cancer cases.[59] The quadrivalent vaccine can also prevent infection with HPV 6 and 11, which cause anogenital warts. The WHO recommends targeting girls age 9-13 years for priority receipt of the HPV vaccine.[59] Older adolescent girls and young women can receive the vaccine as secondary target populations when it does not interfere with vaccination of the priority target population.[59] The schedule recommended by WHO for HPV vaccination is as follows: (1) two doses (0, 6 months) for females <15 years at the time of first dose; a third dose will be recommended if the interval between the 2 doses is shorter than 5 months; and (2) three doses (0, 1-2, 6 months) for females ≥15 years at the time of first dose.[59] Some newer types of vaccine, such as nonavalent vaccines, can prevent a higher number of HPV serotypes.[60] However,

as these vaccines are more expensive and further studies are required to indicate their cost-effectiveness, they are not commonly used at the moment, in particular in LMICs.

2.2.2.2. Other potentially preventable risk factors. Safer sexual behaviors, including condom use, can reduce the risk of HPV infection.[61] Approximately 3% of cervical cancers worldwide have been attributed to smoking.[62] Tobacco control measures are discussed in Section 4.1.

2.2.2.3. Screening. Although immunization against HPV can prevent cervical cancer, the vaccination coverage is not optimal in most populations worldwide. Moreover, even with a good coverage among adolescent girls, still there are 2-3 generations of women that have not received the vaccine or have already acquired the infection.[63] Screening will be the principal preventive measure to reduce the burden of cervical cancer in these women. The main target of cervical cancer screening is to identify early-stage invasive cancer, and more importantly, cervical intraepithelial neoplasia (CIN), a premalignant lesion that can progress to cervical cancer if left untreated. Based on the severity of dysplasia, CIN is categorized to CIN1 (low-grade), CIN2, and CIN3. In a pooled analysis of over 53,000 biopsy samples from 19 population-based studies in China, 2.0% of samples were CIN2+, and 2.1 % were CIN3+ [the study combined low grade lesions (CIN1) with normal biopsies and did not present data for CIN1 separately].[64] It has been estimated that every year approximately 1%–2% of women globally have CIN2+ lesions; this rate could be substantially higher in women with HIV infection.[65]

There are several strategies to screen for cervical cancer. Details of strategies recommended by WHO for women with and without HIV infection are available elsewhere.[65] A summary of the WHO recommendation is shown in Figure 2.9. WHO recommends cervical cancer screening for women 30 years of age and older, with the priority given to screening women aged 30–49 years.

Figure 2.9. Flowchart for identifying appropriate screening strategy for resource level (WHO guidelines) [65]
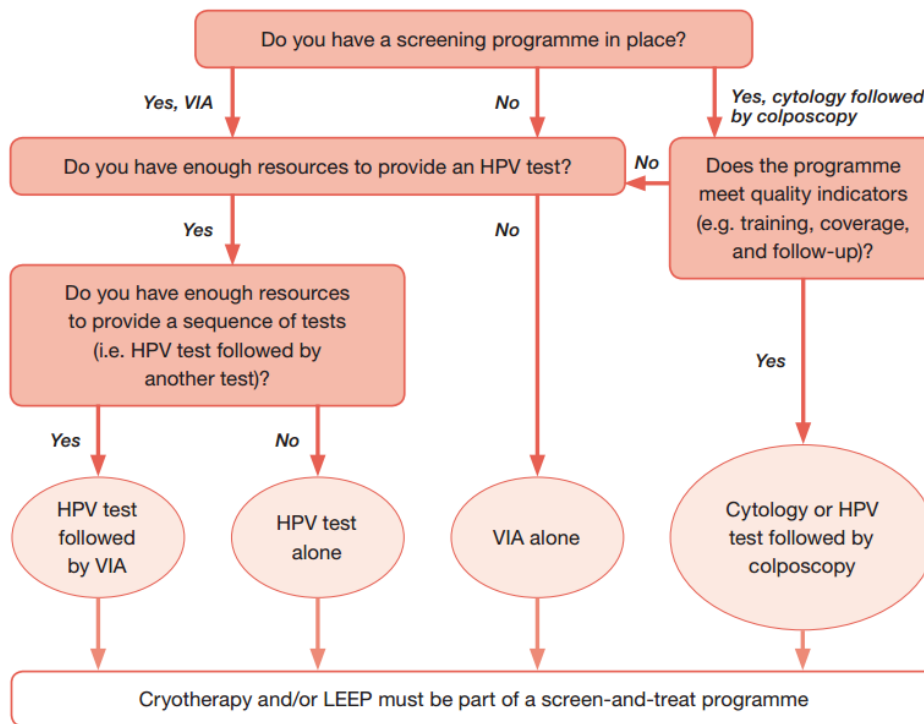
LEEP, loop electrosurgical excision procedure; VIA, visual inspection with acetic acid

Here, we briefly review more commonly practiced methods of screening.

Papanicolaou (Pap) test. Pap test is the conventional cervical cytology test. A positive Pap test is followed by colposcopy, a procedure to examine the cervix for signs of disease (with or without biopsy), and then treatment, if necessary. Using the Pap test in population-based screening programs has helped reduce the incidence and mortality of cervical cancer by up to 80% in several developed countries over the last five decades.[33] However, when implemented, screening programs based on Pap test in LMICs have not been as successful as programs in high-income countries.[33, 65, 66] Implementation of population-based screening based on cytology needs well-trained staff to obtain, prepare, and interpret specimens; a substantial amount of supplies and equipment; and efficient systems to link providers to cytology labs, communicate the results to

screened women in a timely manner, and do the follow-up when the test is positive. Also, because of more limited number of qualified providers, many women in LMICs may have to be referred to distant health care facilities to receive diagnostic and treatment services. For these reasons, when a high-quality screening program based on cytology and colposcopy is not available, more feasible methods with adequate sensitivity to detect cervical lesions can be more appropriate for cervical cancer screening in LMICs.

HPV DNA test. HPV DNA testing has been shown to be an effective test for primary cervical screening,[67] perhaps with a better long-term outcome than cytology and colposcopy.[68] In this method, a health provider takes a sample from the cervix using a swab or brush, and lab tests are used to detect high-risk types of HPV in the sample. The quality requirements for these samples are less strict than for Pap smear samples, and this method does not need an experienced cytologist to examine the samples. There are also self-collection kits that allow women to collect the samples by themselves. A few studies have shown some promising results from using self-collection methods in LMICs.[69-71] If further research shows the efficacy and cost-effectiveness of self-collection methods, they may help to increase the coverage of cervical screening programs, notably by targeting women who do not participate in standard programs.[72]

Visual inspection with acetic acid (VIA). The Pap test or HPV DNA testing may not be feasible in many countries with limited resources. In this situation, WHO recommends a strategy of screening with visual inspection with acetic acid (VIA). The VIA test is based on application of dilute acetic acid (vinegar) to the cervix during vaginal examination. Abnormal cervical tissue appears white after application of acetic acid, which is visible to the naked eye. VIA can be successfully performed by trained mid-level providers.[73]

WHO recommended tests. Overall, WHO recommends using HPV DNA testing as the first line of screening (Figure 2.9). However, when high-quality screening programs based on cytology and colposcopy are already in place, the screening could be done by either HPV DNA testing or cytology followed by colposcopy.[65] Otherwise, HPV DNA testing and/or VIA is recommended over screening with cytology and colposcopy (with or without biopsy).[65] The recommended method by WHO in order is (1) screening HPV DNA testing followed by VIA, (2) screening with HPV DNA test alone, and (3) screening with VIA alone when there are not enough resources to provide an HPV test.[65] Although screening with HPV DNA test alone can increase overtreatment, the difference between this test and VIA in overtreatment may be relatively small (157,000 cases with an HPV test versus 127,000 cases with VIA out of 1,000,000 women).[65] On the other hand, the sensitivity for detection of CIN2+ and the reduction in cervical cancer incidence and mortality with the HPV test may be higher compared to VIA.[65] As mentioned earlier, these recommendations may be different from screening guidelines in high-income countries.[25]

2.2.3. Treatment

Precancerous cervical lesions can be treated with a loop electrosurgical excision procedure (LEEP), which removes abnormal tissue with a wire loop heated by electric current; cryotherapy, the destruction of cells with extreme cold; laser ablation, the removal of tissue; or conization, the removal of a cone-shaped piece of tissue containing the abnormal tissue. According to WHO guidelines, cryotherapy is the treatment of choice when a lesion is identified through screening.[65] A lesion is not eligible for cryotherapy and LEEP should be considered as an alternative treatment when the entire lesion or the junction between the squamous epithelium and the columnar epithelium of cervix (squamocolumnar junction) is not visible; the lesion covers >75% of the

ectocervix (the visible part of cervix) or it extends into the endocervical canal; or the lesion extends beyond the reach of the probe used in cryotherapy.[65]

In LMICs, cryotherapy is generally used because of its ease of use and lower price. However, it does require a reliable supply of gas, which can be difficult, especially in rural areas. Alternative treatment modalities are being investigated to make the treatment of cervical lesions easier and less expensive for low-resource settings.[74] Invasive cervical cancers are generally treated with surgery or radiation, sometimes combined with chemotherapy. However, radiotherapy and chemotherapy may be limited or unavailable in many low-resource settings. In particular, radiotherapy is often needed for cervical cancer treatment, but many women in LMICs are unable to access this resource and go without treatment altogether.[75]

2.2.4. Survival and survivorship

Invasive cervical cancer can often be successfully treated if detected at an early stage. The estimated five-year net survival from cervical cancer is between 60% and 70% in many high-income countries with available data.[38] Among LMICs with available survival data, five-year survival is 46% in India, 56% in Thailand, and 62% in Ecuador.[38] In 2012, there were an estimated 1.5 million women worldwide who had survived since cervical cancer diagnosis during the preceding five years.[3] The highest prevalence of cervical cancer survivors is found in those LMICs that bear a disproportionately large cervical cancer burden, particularly in sub-Saharan Africa and South Asia (Figure 2.10). The highest prevalence of survivors is in Malawi, Guyana, and Bolivia, with over 200 cervical cancer survivors diagnosed within the past five years per 100,000 women. Cervical cancer survivors may suffer from impaired sexual function due to treatment, and quality of life may also be diminished.[76-78] They are also at higher risk of second cancers associated with

radiation therapy, HPV, or smoking.[79] Women in lower-resource settings may also experience

logistical and financial difficulties in receiving follow-on care.[80]

Figure 2.10. Cervical cancer survivors diagnosed in last five years (through 2012 or latest available) [3]
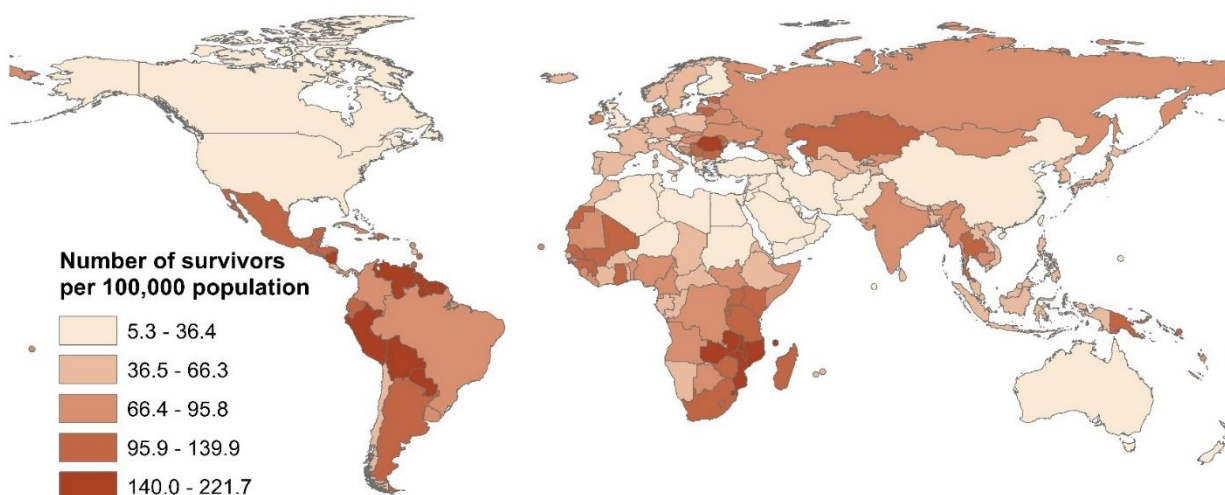
2.3. Cancer of the Lung

2.3.1. Burden, trends, and risk factors

2.3.1.1. Burden. Lung cancer is the third most frequently diagnosed cancer and the second leading

cause of cancer death among females worldwide, with an estimated 583,100 cases and 491,200

deaths in 2012 (Table 1.2). It is the leading cause of cancer death in more developed countries and

the second leading cause of cancer 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 (Figure 2.11). Because of the uniformly poor survival

from lung cancer, even in more developed countries, incidence and mortality rates within a given

country are similar.

Figure 2.11. Lung cancer incidence and mortality rates (females)

Incidence

Age-standardized rate per 100,000 population

| 0.0 - 3.8 | 3.9 - 8.3 | 8.4 - 14.4 | 14.5 - 23.9 | 24.0 - 37.6 |

Mortality

Age-standardized rate per 100,000 population

| 0.0 - 3.2 | 3.3 - 6.8 | 6.9 - 12.3 | 12.4 - 19.4 | 19.5 - 30.7 |
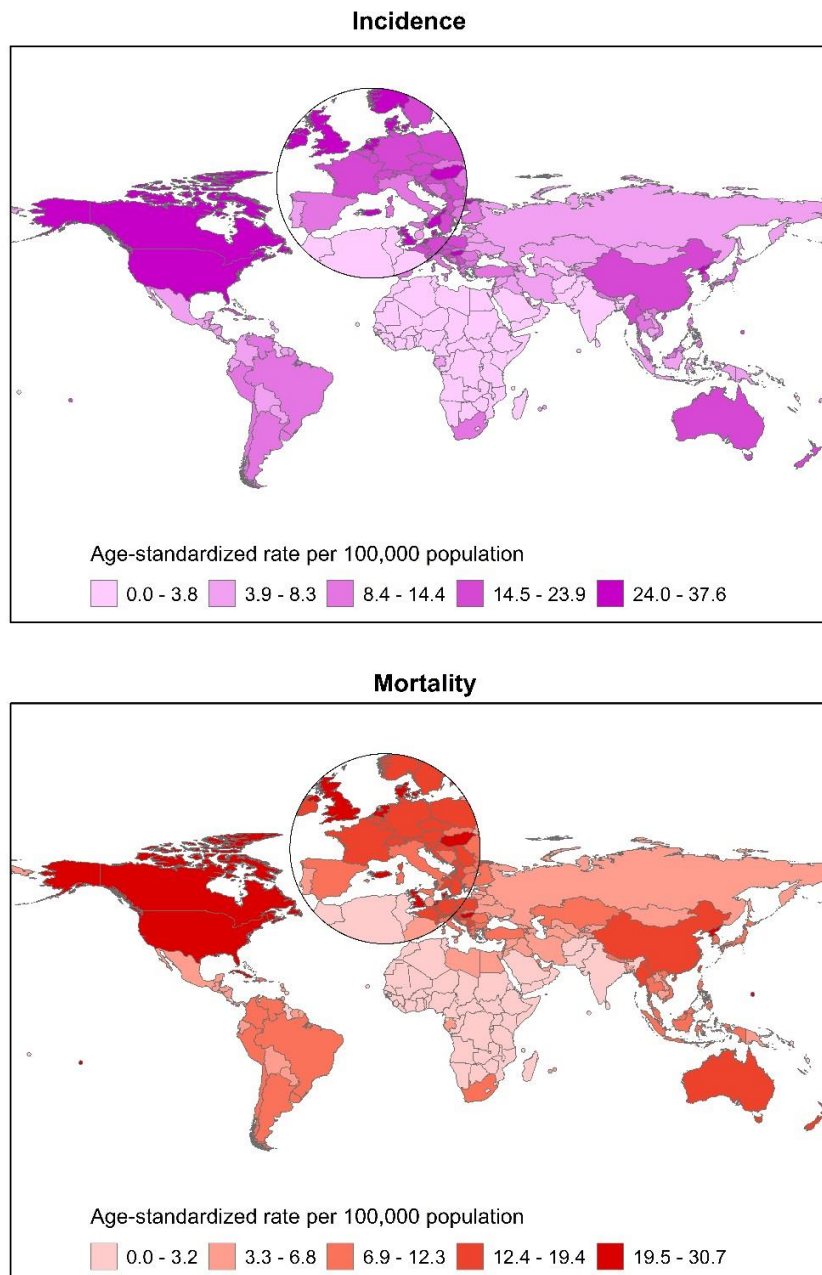
Source: GLOBOCAN 2012

2.3.1.2. Trends. Trends in lung cancer incidence and mortality rates reflect the tobacco epidemic.

Lung cancer mortality rates begin to increase about 20 to 30 years after widespread smoking begins

in a population, and they peak about 30 to 40 years following peak smoking prevalence.[81] In most

parts of the world, lung cancer trends in women have lagged behind those in men because women

began smoking later. Lung cancer mortality rates among women have peaked or are on the decline in places where women began smoking earliest, such as Hong Kong, the United Kingdom, Australia, and the United States (Figure 2.12). Meanwhile, rates continue to increase among women in regions where they began smoking later, including many countries of Europe and Latin America. Although overall lung cancer mortality rates among women are increasing in many countries, rates among younger women have begun to decrease in recent years in several of these countries as tobacco control measures take effect.[82] In LMICs in which tobacco use is not yet widespread among females, including Africa and parts of Asia, swift and effective tobacco control measures could prevent an increase in lung cancer deaths among women.

Figure 2.12. Lung cancer mortality trends (females), select countries
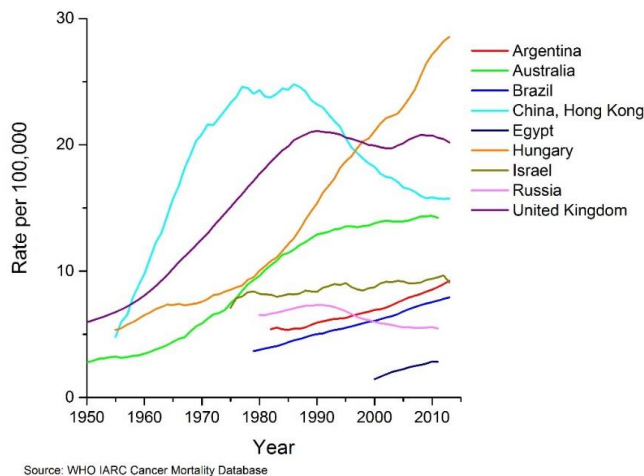
2.3.1.3. Risk factors. Lung cancer was the cause of death of an estimated 1.1 million men and 0.5 million women worldwide in 2012, corresponding to 24% and 14% of all cancer deaths in males and females, respectively.[83] Lung cancer was a rare disease before cigarettes became widely available in late 19th and early 20th century.[84, 85] Since then, tobacco smoking has been the most important cause of lung cancer. As a result, patterns in occurrence of lung cancer generally follows the patterns in prevalence of smoking and vary across populations. Currently, the proportion of

lung cancer attributable to smoking ranges from >80% in the United States and France to 40% in sub-Saharan Africa.[86-88]

Apart from smoking, there are several other risk factors for lung cancer, the prevalence of which substantially varies across the world. Exposure to secondhand smoke is estimated to cause 21,400 lung cancer deaths annually in non-smokers worldwide.[89] Another important risk factor for lung cancer among non-smoking women is indoor air pollution because of unventilated combustion of solid fuels (notably coal) in the household for heating and cooking.[90-92] Most lung cancer deaths due to secondhand smoke and indoor air pollution occur in LMICs, particularly China.[93, 94] In 2007, 29% of the population in China relied on coal for cooking and an additional 27% relied on wood, and generally women and children were the most exposed groups.[95] Female lung cancer rates are higher in China than in several European countries despite Chinese women having a lower smoking prevalence. Many of these deaths among non-smoking Chinese women have been attributed to exposure to secondhand smoking and indoor air pollution from solid fuels.[96, 97]

Other risk factors for lung cancer include outdoor air pollution,[98] occupational and non-occupational exposure to hazardous chemicals and elements,[99, 100] and exposure to radiation from indoor radon released from soil and building materials.[101] The estimated number of deaths in women worldwide in 2010 for the above risk factors other than smoking was as follows (in millions): household air pollution, 1.6; outdoor air pollution, 1.4; secondhand smoke, 0.35; occupational risk factors, 0.10; and residential radon, 0.03.[102]

2.3.2. Prevention and early detection

Because the majority of lung cancers worldwide are caused by smoking, lung cancer is highly preventable. There are several proven methods for reducing tobacco use, including excise tax on

tobacco, banning smoking in public places, and counter-advertising. Other causes of lung cancer, such as indoor air pollution, can also be reduced. For long-term heavy smokers, lung cancer screening has been shown to reduce mortality.

2.3.2.1. Avoidance of smoking/cessation. The typical tobacco epidemic model in high-income countries includes a surge in smoking among men, followed by a surge in smoking among women after a few decades.[103] The surge in smoking prevalence is followed by an increase in lung cancer incidence after a few decades in each gender. The epidemic model in many LMICs has differed from that in high income countries. After a surge in male smoking prevalence in many LMICs, female smoking prevalence had a more modest increase in most countries in South America and a few LMICs in Asia and Africa, but cigarette smoking in most other LMICs has remained a relatively uncommon habit among women (Figure 2.13).[104]

Figure 2.13. Female smoking prevalence, age 15+ years, 2013
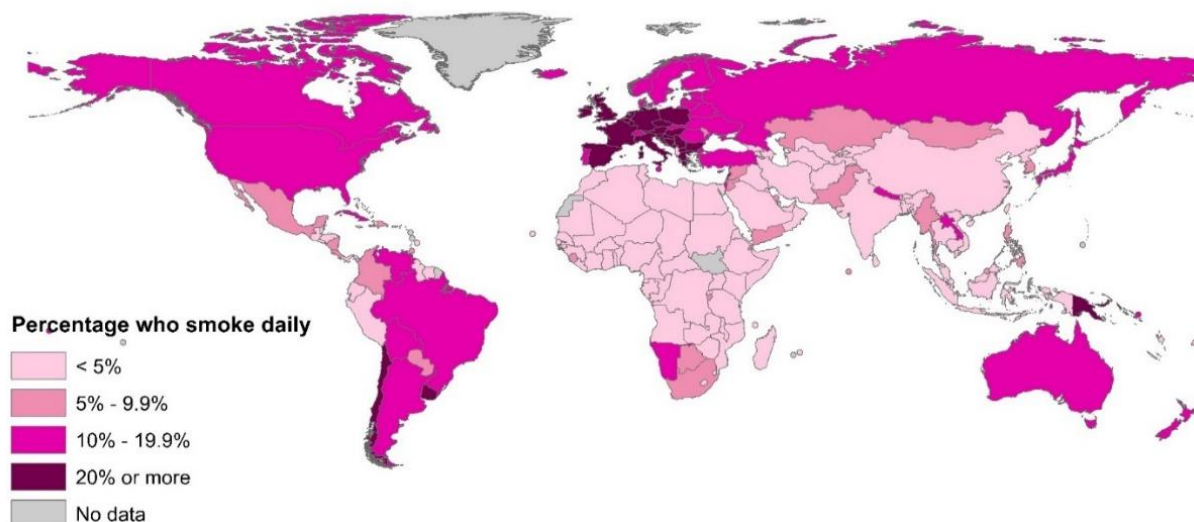
Source: Tobacco Atlas, fifth edition

Nevertheless, recent female youth (age 13-15 years) smoking prevalence in a number of LMICs, mainly in Africa, South America, and the Middle-East, is higher than in high income countries in Northern America and Oceania, raising concerns that smoking prevalence will be higher in the younger generation of women (Figure 2.14). Another concerning issue is that non-cigarette tobacco use has been common among women in certain LMICs. For example, water-pipe (hookah) smoking, which can have the same health effects as cigarette smoking, is a common habit among women in WHO Eastern Mediterranean region.[85] A major priority in LMICs should be to prevent an increase in female use of any tobacco product, and in particular initiation of smoking by young girls, to prevent an increase in morbidity and deaths related to smoking as seen in high-income countries.[105] Tobacco control policies are discussed in Section 4.1.

Figure 2.14. Female youth smoking prevalence, age 13-15 years, 2011 or latest available data
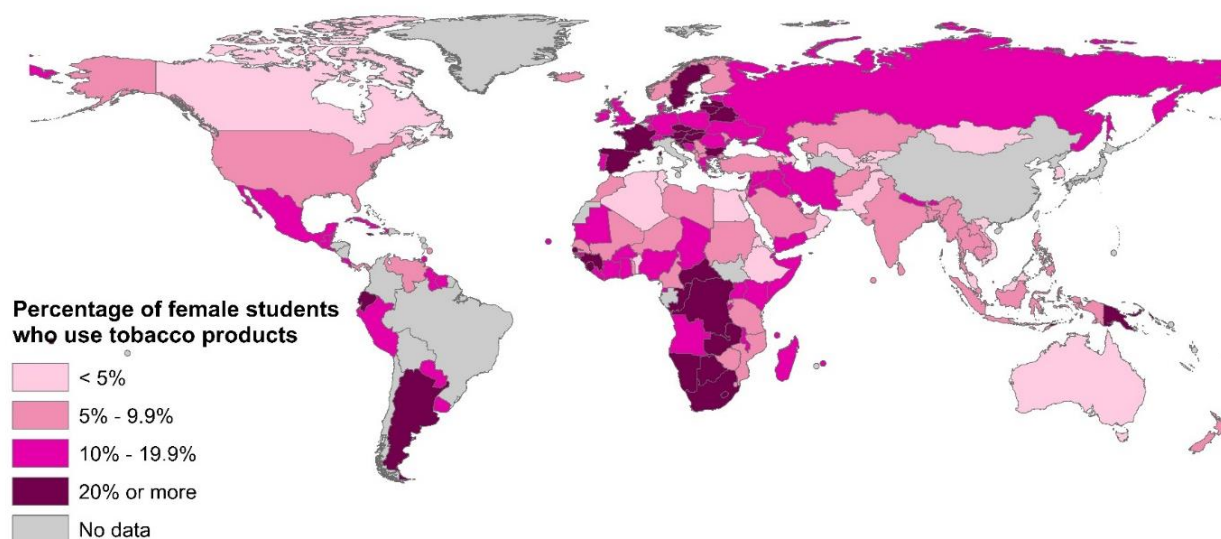
Source: Tobacco Atlas, fifth edition

Current smokers should receive appropriate help to quit tobacco use. Smoking cessation can prevent death from all major smoking-related diseases, including lung cancer.[106, 107] This reduction in lifetime excess risk will be much greater if smokers quit smoking in younger ages, in particular before age 40, although the risk of dying of lung cancer can be reduced by quitting at any age.[107]

2.3.2.2. Indoor air pollution mitigation. As discussed earlier, people in some LMICs are highly exposed to indoor air pollution from secondhand smoke or using solid fuels for cooking and heating. Women and children generally are more exposed, because they may traditionally spend more time at home than men. Also, women are more likely to prepare meals for the household, so they may be even more exposed to pollution related to using solid fuels for cooking.[108]

Exposure to secondhand smoke in the home can be reduced. Studies in high-income countries have shown that increasing awareness about health effects of secondhand smoking could lead to voluntary smoking ban in the household, and consequently, a reduction in the pollution related to secondhand smoke even in low-income households.[109, 110] Surveys in China have also shown an association of voluntary household smoking bans with education level and awareness about health effects of secondhand smoking.[111, 112] For example, the proportion of households with no smoking bans ranged from 81% among those with primary school or less education to 28% among those with a college or higher degree.[111]

Reducing exposure to air pollution from solid fuels is another important step to improve public health in many LMICs with more significant effects on women's and children's health. The countries with the highest proportion of using solid fuels for heating and/or cooking are LMICs located in WHO regions of Africa, South-East Asia, and Western Pacific (Figure 2.15).

Figure 2.15. Population using solid fuels for heating and/or cooking, 2013
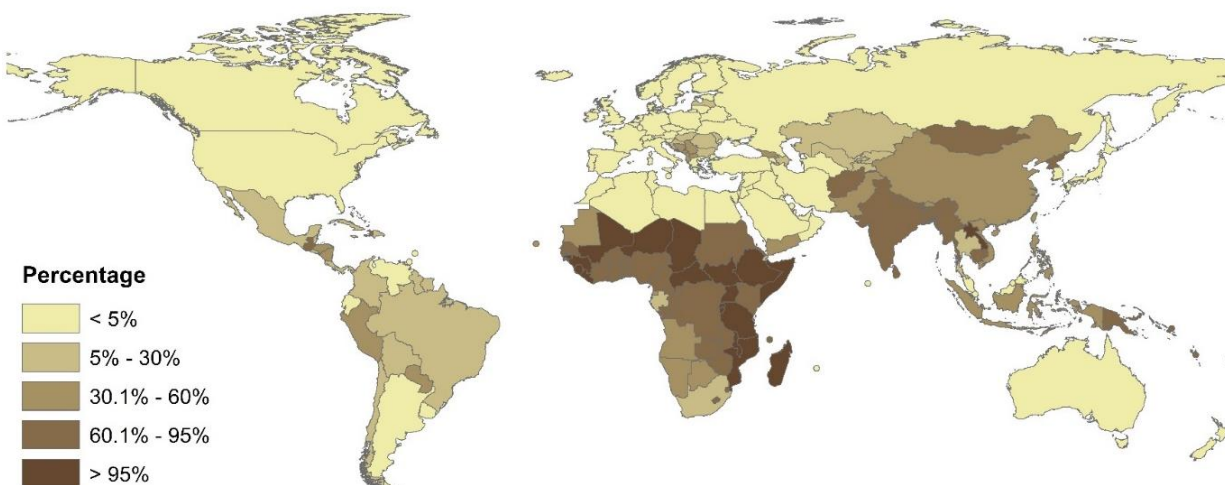
Source: WHO Global Health Observatory Data Repository

In 2012, 4.3 million deaths worldwide were attributable to household air pollution due to cooking and heating using solid fuels.[113] Only 19,000 of these deaths occurred in all high-income countries combined. The corresponding number (in millions) for LMICs by WHO region was 1.7 in South-East Asia, 1.6 in Western Pacific, 0.6 in Africa, 0.2 in the Eastern Mediterranean, 0.1 in Europe, and 0.1 in the Americas.[113] Two interventions to reduce indoor air pollution include providing access to clean fuel, notably liquefied petroleum gas (LPG), or improved solid fuel stoves.[114] Both of these strategies have shown to be cost-effective (able to produce satisfactory results in relation to cost) and cost-beneficial (resulting in economic benefits which outweigh the costs) in LMICs.[114, 115] Improved stoves could substantially reduce airborne particulates from solid fuels when they replace traditional stoves. However, few improved solid fuel stoves reduced airborne fine particulate levels below recommended limits for airborne particulates that can penetrate into the gas exchange regions of the lung (known as PM2.5 particulates).[116] Therefore, the impact of access to cleaner fuels on the health of the population is greater than using improved solid fuel stoves.[114, 115] Consequently, WHO recommends the use of LPG as the primary strategy

to improve indoor air quality.[116] However, providing secure and sustainable access to LPG is generally more costly than providing improved solid fuel stoves, and currently it may not be feasible in some low-resource populations.[114] In this case, providing access to improved solid fuel stoves can be an efficient intermediate step in reducing indoor air pollution until access to LPG is more widespread.[108, 116]

Actual prospective studies in LMICs have shown the positive impact of interventions to improve household air quality on reducing respiratory symptoms and the risk of respiratory disorders, including chronic obstructive pulmonary disease (COPD).[117-119] The interventions are expected to show a reduction in lung cancer risk in studies with longer follow-ups.

2.3.2.3. Screening. In a large-scale randomized trial in the United States, lung cancer mortality was reduced by approximately 20% among heavy smokers screened with three annual low-dose helical computerized tomography (CT) scans.[120] Currently, some high-income countries recommend lung cancer screening for heavy smokers (e.g. those with ≥30 pack-years smoking history) in certain age groups (e.g. 55-74 years).[25, 121] However, this screening is feasible only in high-resource settings, because it is based on advanced clinical settings with access to experienced radiologists and clinicians, high-quality CT scans, and appropriate equipment, space, and staff to manage suspicious lesions identified in CT scans. Because of false-positive results, the number of lesions to be addressed is generally more than the number of confirmed lung cancer cases in this screening.[120, 121] Currently, lung cancer screening does not seem feasible for LMICs, so the best strategy to reduce lung cancer deaths in these countries in the near term is to encourage smokers to quit. Smoking cessation programs can help smokers quit, but only 15% of the world's population lives in a country with a national smoking cessation program including a quit line and cost-covered nicotine replacement therapy and other cessation services.[122] Countries offering these services are

primarily high-income countries, although some LMICs of Latin America and the Middle East offer this complete cessation assistance. Although CT screening is feasible in high income countries, primary prevention through tobacco control is a better long term strategy than secondary prevention in both high and LMIC countries due to the morbidity and mortality burden even when lung cancer is diagnosed and treated at early stages.

2.3.3. Treatment

Because symptoms often do not appear until lung cancer is advanced, it is often diagnosed at later stages in both LMICs and HICs. Treatment is based on whether the tumor is small cell or non-small cell and other tumor characteristics, and generally includes surgery, radiation therapy, chemotherapy, and/or targeted therapies. Radiation therapy and chemotherapy may be limited in low-resource settings. Because targeted therapies require molecular testing of the tumor which is limited in low-resource settings, these therapies are less commonly used. In low-resource settings where lung cancer has been diagnosed at a late stage and appropriate treatment is unavailable, palliative care to relieve pain and reduce suffering is needed.[123]

2.3.4. Survival and survivorship

Prognosis of lung cancer is generally poor even in high-income countries. For lung cancer cases diagnosed from 2005 to 2009, five-year survival was less than 20% in almost all countries with available data.[38] In the United States, only 22% of women with lung cancer diagnosed in 2006-2012 survived for at least 5 years.[124, 125] In China, age-standardized 5-year relative survival for lung cancer diagnosed in 2003-2005 was 15% in men and 17% in women. The proportion in women ranged from 21% in urban areas to 12% in rural areas.[126] The prognosis is generally even poorer in many other LMICs. For example, an age-standardized 5-year relative survival of 3% in men and women combined has been reported from Libya.[127]

In 2012, there were an estimated 626,000 women worldwide who had survived lung cancer after being diagnosed within the preceding five years.[3] The highest prevalence of female lung cancer survivors was in Japan, North America, and Europe, reflecting the high rates of lung cancer cases among women in those countries. Lung cancer survivors may suffer from decreased quality of life, especially impaired respiratory function.[128] Lung cancer survivors are at risk for recurrence, especially among those who are current and former smokers. The risk is increased among survivors who continue to smoke, but some survivors may find it difficult to quit.[129]

2.4. Cancer of the liver

2.4.1. Burden, trends, and risk factors

2.4.1.1. Burden. Liver cancer is a leading cause of cancer death worldwide in both men and women. Liver cancer is the ninth most frequently diagnosed cancer and the sixth leading cause of cancer death among women worldwide, with an estimated 228,100 cases and 224,500 deaths in 2012 (Table 1.2). Liver cancer is a highly fatal cancer that is more common in less developed countries than in more developed countries and in males than females. Because of poor survival, liver cancer incidence and mortality rates are similar within a country. Global patterns in liver cancer reflect the prevalence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV), the primary risk factors for hepatocellular carcinoma, the dominant form of liver cancer worldwide. The geographic distribution of liver cancer in males and females is similar; however, liver cancer rates are generally two to three times higher among males than females. These differences are not well understood, but may be due to higher prevalence of liver cancer risk factors in males, such as alcohol use, as well as hormones, immune response, or epigenetics.[130]Rates are highest in Eastern and South-Eastern Asia, particularly in Mongolia and Laos, as well as Western and Northern

Africa and Central America. Rates are lowest in Oceania and Northern, Central, and Eastern Europe (Figure 2.16).

Figure 2.16. Liver cancer incidence and mortality rates (females)
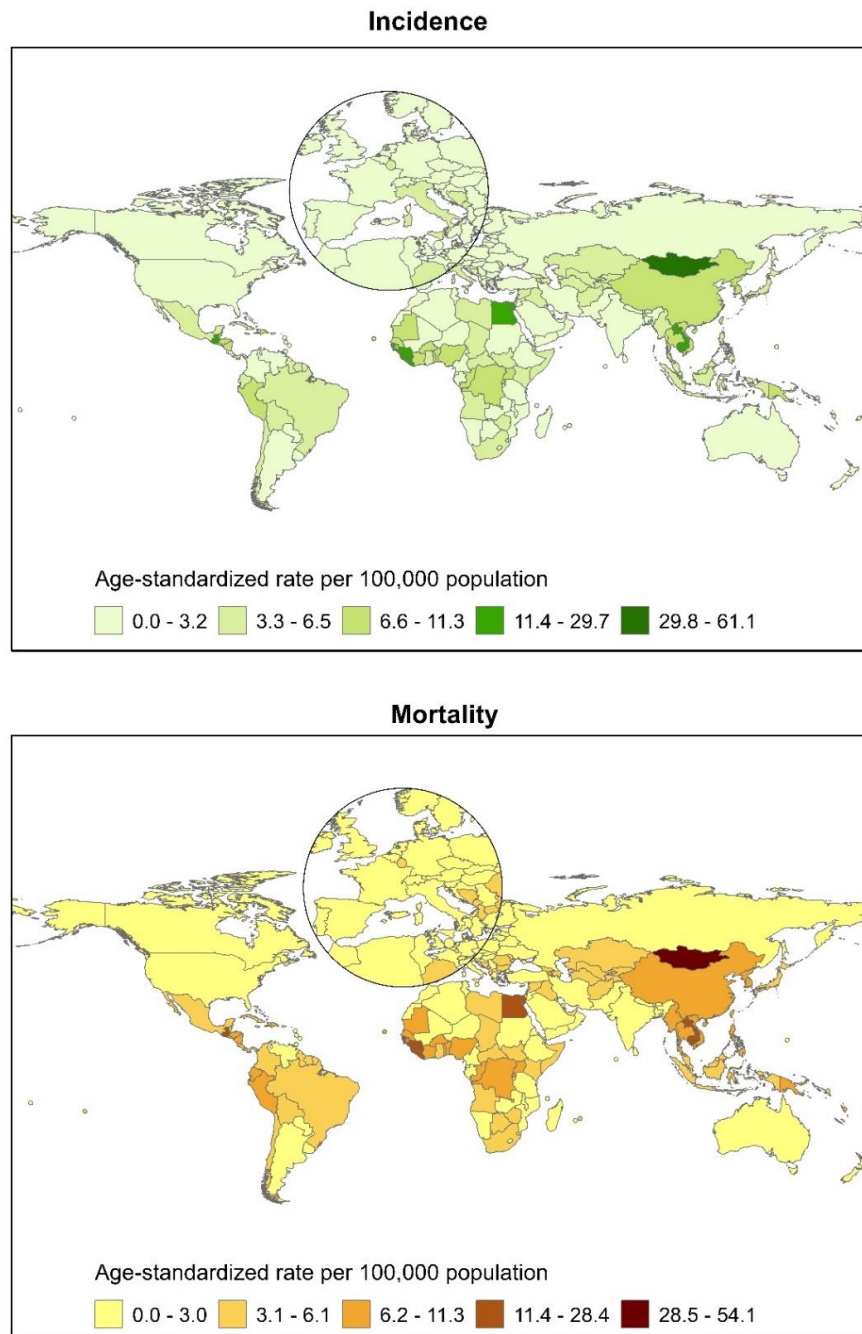
2.4.1.2. Trends. Liver cancer incidence rates are decreasing in historically high-risk countries, such as those in Eastern Asia (Figure 2.17). These declines have been attributed to public health policies and interventions, such as programs aimed at prevention of horizontal HBV transmission within families in China and reducing HCV infection through improved blood donation practices and policies discouraging intravenous drug abuse in Japan.[131, 132] In Taiwan, the introduction of the infant

Figure 2.17. Liver cancer mortality trends, select countries (females)

Liver cancer mortality rates, 1995-2013, age-standardized rate (world)
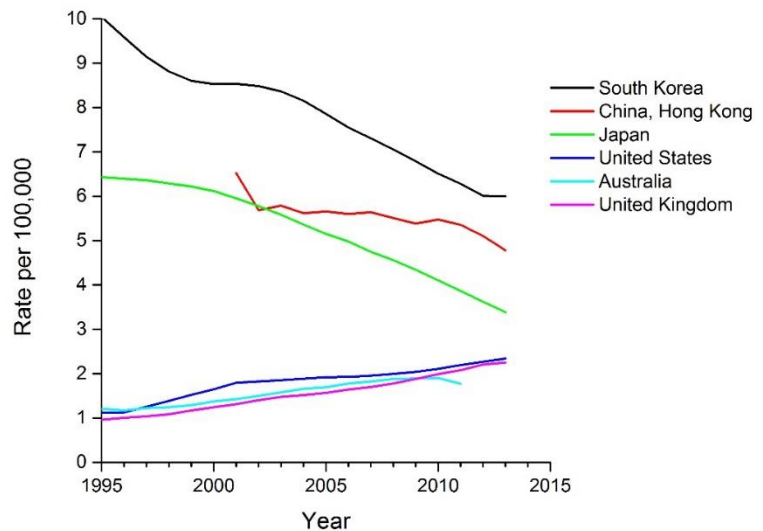
Source: WHO IARC Cancer Mortality Database

HBV vaccine in 1984 has resulted in more than an 80% decrease in liver cancer rates among vaccinated youth and young adults,[133] but it will be two to three decades before the incidence rates in these cohorts will affect the overall liver cancer 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.[134] The increases in the US are thought to be due to increased prevalence of chronic HCV infection due to exposure to contaminated blood or medical equipment and injection drug abuse during the 1960s and 1970s.[135] Obesity and type 2 diabetes may also have contributed to the recent increase in the incidence rates.[130, 136]

2.4.1.3. Risk factors. The risk of liver cancer is 23 times higher in individuals with a serological positive test for HBsAg (a marker of chronic HBV infection) and 17-times higher in individuals with a positive hepatitis C virus (HCV) ELISA test than those with a negative test.[137] The estimated

magnitude of risk can be even greater when more specific tests to identify hepatitis B virus (HBV) or HCV infections are used.[138] In some cases, HBV and HCV infections occur simultaneously; these people will be at a higher risk of liver cancer than those with single infections. Globally, infection with HBV and HCV are responsible for 30% of all infection-related cancer cases combined and for 77% of all primary liver cancers.[137] The burden is more prominent in less developed regions: of 228,100 liver cancer cases that occurred among women globally in 2012, 185,800 cases (82%) were in LMICs.[3]

Countries with a prevalence of ≥5% for HBV infection are generally located in Central Asia and WHO regions of Western Pacific and Africa (Figure 2.18), with many sub-Saharan African countries having prevalence rates of ≥8%.[139]

Figure 2.18. Hepatitis B virus prevalence, both sexes, from systematic review of studies 1957-2013
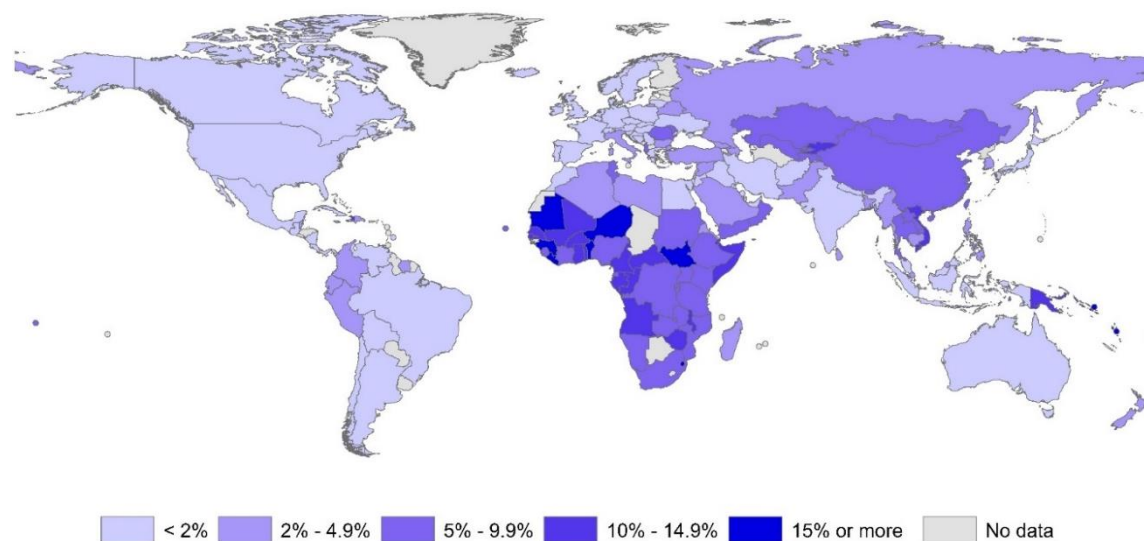
Source: Schweitzer A et al, Lancet 2015

The average prevalence of HBV infection by WHO region is as follows: Africa, 8.8%; Americas, 0.8%; Eastern Mediterranean, 3.0%; Europe, 2.1%; South-East Asia, 1.9%; and

Western Pacific, 5.3%.[139] In high-income countries, 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 healthcare setting or during intravenous drug use. In LMICs, on the other hand, HBV is generally acquired through mother to child transmission at birth or in early childhood.[140] When this occurs, HBV infection is more likely to progress to chronic HBV infection rather than being cleared by the body. Because of the frequency of mother-to-child transmission of HBV in LMICs, liver cancers associated with HBV in LMICs usually occur in earlier ages (approximately 10 years earlier) than in high-income countries.[141]

Countries with the highest prevalence of HCV infection (>3%) generally are located in WHO regions of Eastern Mediterranean, South-East Asia, and Western Pacific (Figure 2.19).[142] The prevalence in the Americas is generally lower than in the rest of the world.

Figure 2.19. Estimated hepatitis C virus prevalence, both sexes, 2005
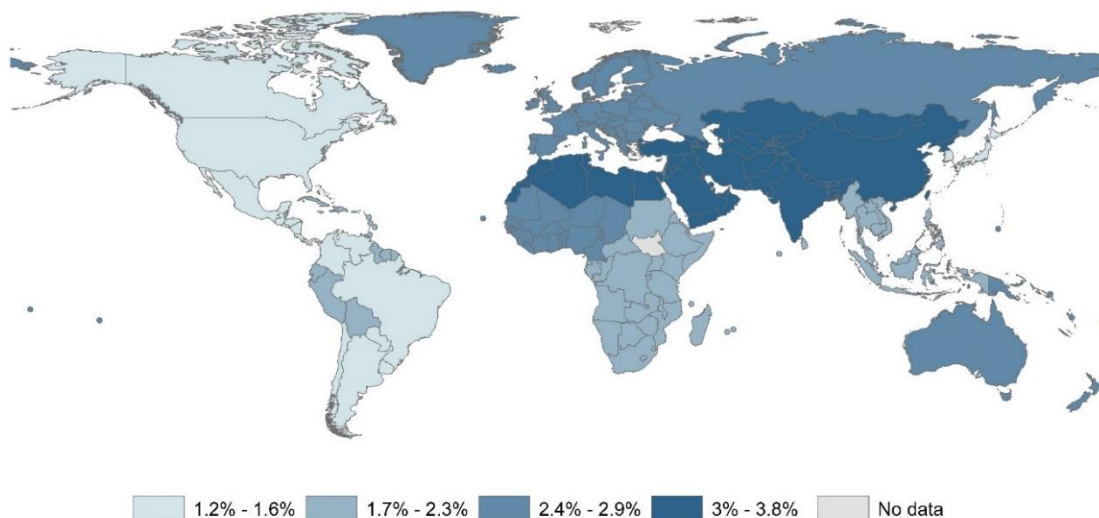
Source: Mohd Hanafiah K et al, Hepatology 2013

Although children born to mothers with HCV infection are at risk of acquiring the infection at birth,[143] most HCV infections occur at adolescence or later in both high income countries and LMICs,[142, 144] mainly following drug injections or receiving invasive procedures or blood products in settings with insufficient infection control standards.[143] For example, the high prevalence of HCV infection in Egypt occurred through the use of contaminated needles during mass campaigns to eradicate schistosomiasis.

In Northern Africa, South America, Japan, and industrialized countries in North America and Western Europe, HCV is more common than HBV infection.[141] On the other hand, HBV is much more common than HCV infection in the rest of the world.[141]

Other major risk factors of hepatocellular carcinoma include heavy alcohol drinking, excess body weight and/or diabetes type II, presence of nonalcoholic fatty liver disease, smoking, exposure to aflatoxins, and less common conditions such as hemochromatosis and alfa1-antitrypsin deficiency.[86, 145, 146] Of these risk factors, exposure to aflatoxin is substantial in certain LMICs, in particular in WHO regions of Western Pacific and Africa, followed by South-East Asia.[130, 134, 147] In China, where exposure to aflatoxin is more common than many other countries, approximately 25% of liver cancers have been attributed to aflatoxin.[148] Also, exposure to aflatoxin and hepatitis virus infection together may have a greater effect than either factor alone (a synergistic effect).[148] Apart from hepatocellular carcinoma, cholangiocarcinoma is common in Thailand and parts of Asia because of liver fluke infection.[149]

2.4.2. Prevention

The majority of liver cancer worldwide is caused by HBV and HCV infections, which can be prevented through public health measures (including vaccination for HBV and improvement in the use of sterile syringes and other medical instruments). Liver cancer can also be prevented through

antivirals in those with existing infection. However, there are barriers to prevention, including suboptimal HBV vaccination and the high cost of antiviral treatment for those with HBV and HCV infections.

2.4.2.1. HBV vaccine. HBV vaccine has been shown to prevent HBV-related chronic liver diseases and liver cancer in vaccinated people.[150] For vaccination of infants and neonates, WHO recommends "*All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three doses.*"[151] In most LMICs, transmission of HBV occurs at birth from mother to child (vertical transmission) or in early childhood from child to child.[140] HBV acquired at this time is more likely to progress to chronic HBV infection. Therefore, administration of the first dose right after the birth is very important. Omitting the birth dose and administrating the first dose when infants receive their other routine vaccines for the first time (4–8 weeks of age) can lead to chronic HBV infection in up to 90% of infants born to HBsAg and HBeAg-positive mothers.[151]

According to WHO, either of the following options are appropriate: (1) a three-dose schedule, one dose delivered at birth, then two doses at the same time as the first and third doses of diphtheria–tetanus–pertussis (or DTP) vaccine are given; or (2) a four-dose schedule, one delivered at birth, then three doses usually given with other routine vaccines. For the dose at birth, only monovalent HBV vaccine must be used. For other doses, either monovalent vaccine or a combined vaccine including HBV may be used.[151]

In addition to HBV vaccination, administration of hepatitis B immune globulin (HBIG) as a prophylactic measure may provide additional benefit when mothers are HBsAg-positive (an indicator of 'chronic' infection), in particular when they are also HBeAg-positive (an indicator of 'active' infection).[151] When mothers are HBsAg-positive but HBeAg-negative, administration of

HBIG to full-term newborns may not add much additional protection against perinatal infection if HBV vaccination can be administered within 24 hours after birth. Nevertheless, when mothers show indication of a very active infection (very high HBV DNA concentrations in blood), a proportion of newborns (10% or more) may acquire the infection despite HBV vaccination and/or HBIG prophylaxis. WHO has not made a recommendation with regard to antiviral therapy of these group of women during pregnancy to reduce the risk of HBV transmission, because information on the safety or efficiency of this treatment is limited.[151]

Catch-up HBV vaccination may be considered for adolescents or individuals at a higher risk of acquiring HBV infection, such as health workers, travelers to endemic areas, and injection drug users.

2.4.2.2. Antiviral treatments. 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. For HCV, antiviral treatments have been improving in recent years. The newest directly acting antivirals do not need to be administered in combination with other drugs (interferons or ribavirin), and have shown to have a high response rate (>85%) in a shorter period with fewer adverse effects then earlier treatments; therefore, they are included in the first line of treatment of HCV in high-income countries.[146, 152-154] With this treatment, most patients could be cured in 8-24 weeks; the duration of treatment depends on several factors, including the liver status, genotype of HCV, and previous treatments.[152] As the genotype of HCV is one of the main factors that determine the medications and duration of HCV treatment, WHO recommends genotyping before selecting the appropriate treatment.[143]

The available treatment for HBV infection generally halts the progression of liver disease by suppressing HBV replication and does not cure the infection. Therefore, it is generally used for

a group of patients with indicators of chronic active hepatitis B disease,[155, 156] who usually need long durations of treatment for a prolonged suppression of the virus.[155] Currently, either pegylated alpha interferon or nucleos(t)ide analogues are used for this purpose, depending on liver disease status.[155] However, WHO does not recommend interferons for use in LMICs because of their high cost and the need for careful monitoring to prevent potentially significant adverse effects.[151] WHO also does not recommend certain HBV nucleos(t)ide analogues to which HBV could become resistant more quickly than to other ones.[151]

A major issue with antiviral treatments for chronic HBV and HCV infections is their high cost.[156, 157] For example, the cost of a 48-week course of pegylated interferon and ribavirin for treatment of HCV is approximately US$ 12,000 in Vietnam and US$ 18,500 in Indonesia,[158] which is multiple times higher than the GDP per capita in those countries (US$ 2,100 in Vietnam and US$ 3,500 in Indonesia in 2011-2016).[159] Newer drugs are even much more costly: a 12-week treatment of HCV genotype 1 with second generation DDAs in Europe may cost US$ 150,000.[160] Therefore, antiviral treatments are often beyond the reach of the majority of patients in LMICs,[152, 161, 162] and even of a substantial proportion of the population in high-income countries.[160, 163] Health authorities in LMICs should try to facilitate the access of the patients in need to antiviral treatments, for example, by negotiating with pharmaceutical companies for reduced prices and generic forms of the medicines, extending insurance coverage, and obtaining international aid, when possible.[151, 152, 158] Due to the major cost barriers, the most cost-effective approach and a major priority in LMICs must be prevention of HBV and HCV infections.

2.4.2.3. Other preventive measures. Although many HBV and HCV infections in LMICs occur at birth or early childhood, these infections may occur later in life as a result of exposure to contaminated blood products or injections or sexual intercourse.[140] Prevention of transfusion- and

injection-related infections is crucial in reducing the burden of these infections. This is even more important for prevention of HCV infection, for which no vaccines are currently available. Furthermore, blood transfusions are the major source of HCV in some countries such as India.[138, 144] Increasing awareness about routes of transmission of HBV and HCV, as well as other risk factors of liver cancer is also important. People should be encouraged to limit alcohol intake, not smoke, and maintain a healthy weight. In regions with a high exposure to aflatoxins, reducing or eliminating the exposure should be one of the priorities of the communities and health authorities. Public health campaigns for the control of liver fluke infection in areas where they are common have also been successful.[164, 165]

2.4.3. Treatment

In countries with developed health care systems, early stage liver cancer can sometimes be treated successfully with surgery to remove part of the liver (partial hepatectomy) if the patient has sufficient healthy liver tissue. In low-resource settings, however, this is usually not an option due to the later stage at diagnosis and limited health facilities available. Likewise, liver transplantation is also an option for patients with small tumors who cannot undergo partial hepatectomy, but this is only available in highly developed health care systems. Other treatment options include ablation (tumor destruction) or embolization (blocking blood flow to the tumor). There are fewer treatment options for patients diagnosed at an advanced stage. The palliative procedures that may increase the survival of liver cancer patients, such as chemoembolization (a percutaneous procedure to deliver a relatively large dose of chemotherapeutic agents directly to the tumor and embolization) or administration of sorafenib (a biological medication that inhibits protein tyrosine kinase and is used for treatment of advanced cases of kidney and liver cancers and some cases of thyroid cancer),[166, 167] also need a highly advanced health care infrastructure and/or are very costly.

2.4.4. Survival and survivorship

Liver cancer is one of the most fatal cancers, with low survival in countries of all resource levels.[38] Among countries with available data, five-year survival ranges from less than 10% (India, Mongolia, Thailand, Chile, Colombia, Czech Republic, Denmark, Finland, Slovenia, UK) to about 20% (Jakarta, Indonesia; South Korea; Belgium).[38]

In 2012, there were 180,000 women worldwide who had survived liver cancer after diagnosis within the previous 5 years.[3] The highest prevalence was in several countries in Asia including Japan, Mongolia, and South Korea, reflecting the high liver cancer rates in those countries. Liver cancer survivors live with the risk of spread or recurrence. For those in high-income countries 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.

2.5. Cancer of the colorectum

2.5.1. Burden, trends, and risk factors

2.5.1.1. Burden. Colorectal cancer is the second most frequently diagnosed cancer and the third most common cause of cancer death among women worldwide, with an estimated 614,300 cases and 320,300 deaths in 2012 (Table 1.2). Colorectal cancer is a leading cancer among both males and females. Rates and trends are similar for both sexes. The highest incidence and mortality rates among women are generally in Australia, New Zealand, Europe, North America, with high rates also in South Korea, Israel, and Singapore (Figure 2.20). The lowest rates are in Africa and South-Central Asia.

Figure 2.20. Colorectal cancer incidence and mortality rates (females)

Incidence

Age-standardized rate per 100,000 population

| 1.0 - 5.6 | 5.7 - 10.8 | 10.9 - 17.4 | 17.5 - 25.4 | 25.5 - 35.8 |

Mortality

Age-standardized rate per 100,000 population

| 0.7 - 3.8 | 3.9 - 6.0 | 6.1 - 8.1 | 8.2 - 10.8 | 10.9 - 14.5 |
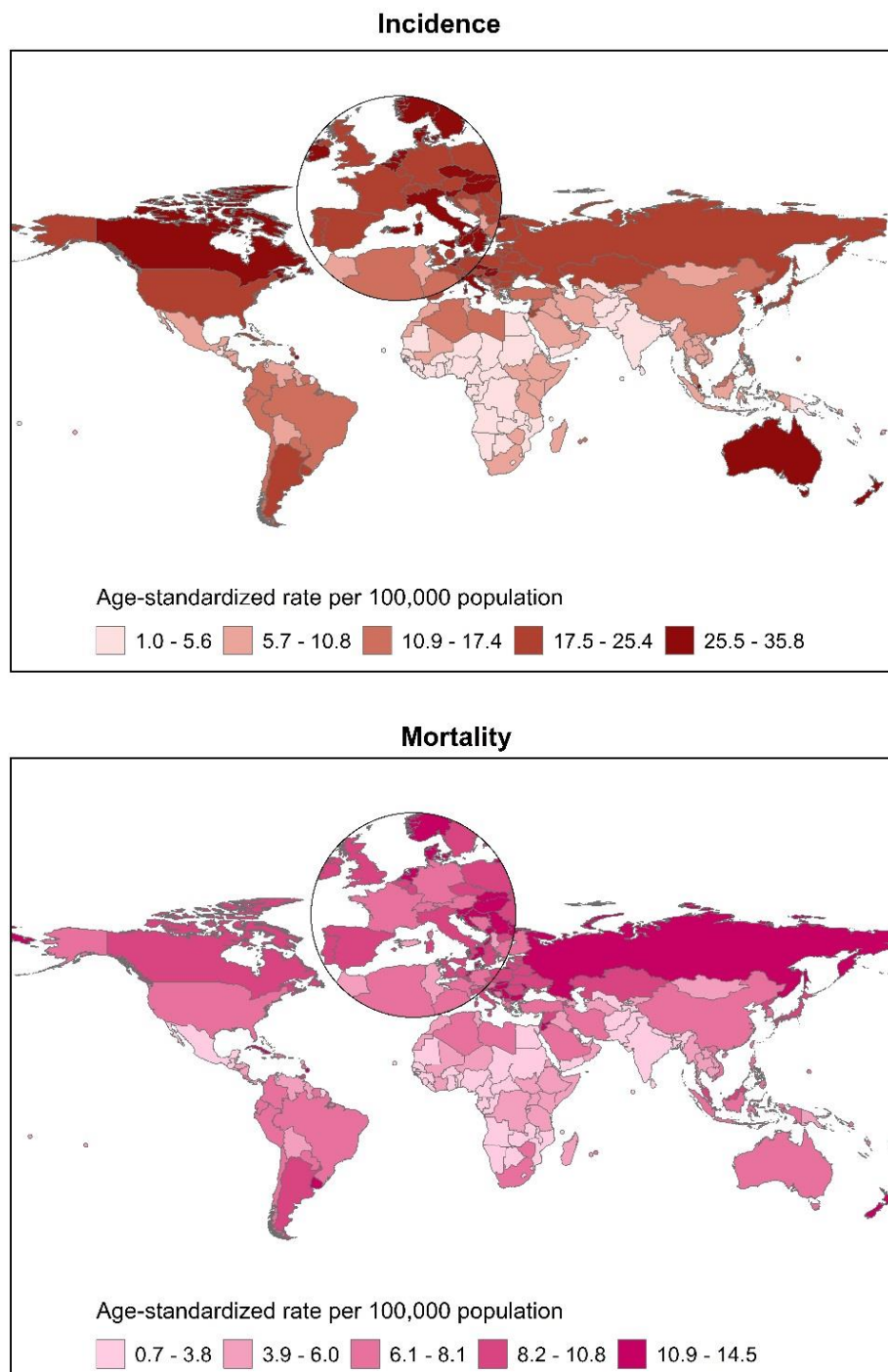
Source: GLOBOCAN 2012

2.5.1.2. Trends. Trends in colorectal cancer incidence rates vary widely worldwide. In high-income countries, rates are either increasing (Norway, Spain), decreasing (US, New Zealand), or stable (Australia; Figure 2.21). Decreases in incidence in the US have been attributed to reductions in the prevalence of risk factors like smoking as well as screening, which can detect and remove precancerous lesions; these factors have likely contributed to decreases in other countries as well.[168] At the same time, incidence rates are increasing in many LMICs where rates have been historically low, such as those in Latin America and Asia. Colorectal cancer has a number of risk factors associated with western lifestyles, including consumption of red and processed meats, excess body weight, alcohol consumption, smoking, and physical inactivity; as such, it is considered a marker of the "cancer transition," in which developing LMICs experience increases in cancers typical in high-income countries.[169]

Figure 2.21. Colorectal cancer incidence trends (females), select countries, 1980-2013
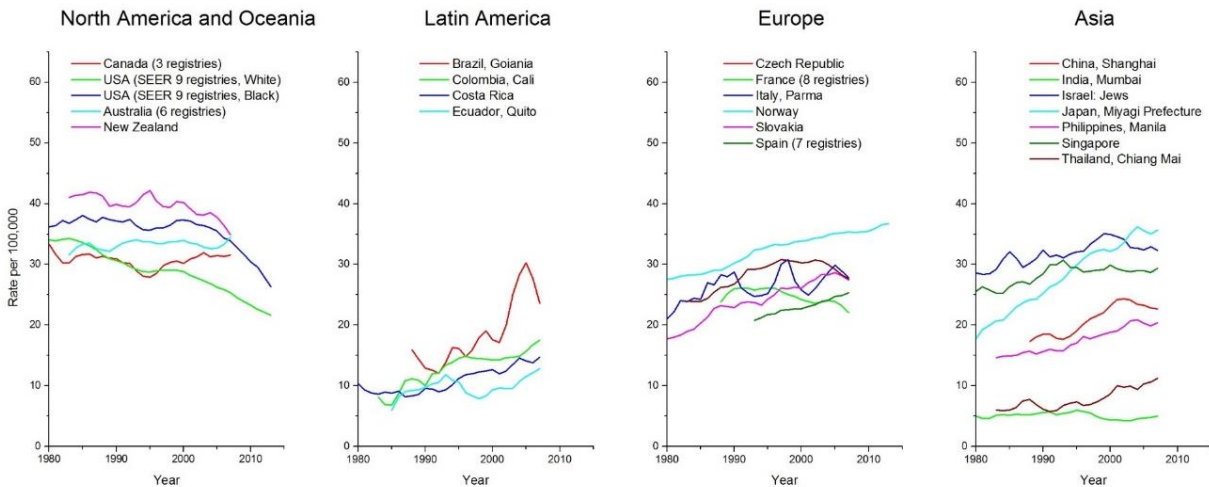
Source: CI5*plus*; US SEER registries; NORDCAN (Norway)

In contrast to the varying incidence trends, colorectal cancer mortality rates have been decreasing in a number of countries worldwide, particularly in high-income countries (Figure 2.22). These decreases have been attributed to improvements in treatment and early detection (such as in the US), in addition to the factors contributing to the decreases in incidence.[169] However, mortality continues to increase in several LMICs with rising incidence, such as Romania, Brazil, and Mexico because of increases in the underlying risk factors.

Figure 2.22. Colorectal cancer mortality trends (females)

Colorectal cancer mortality rates, 1975-2013, age-standardized rate (world)

Source: WHO IARC Cancer Mortality Database
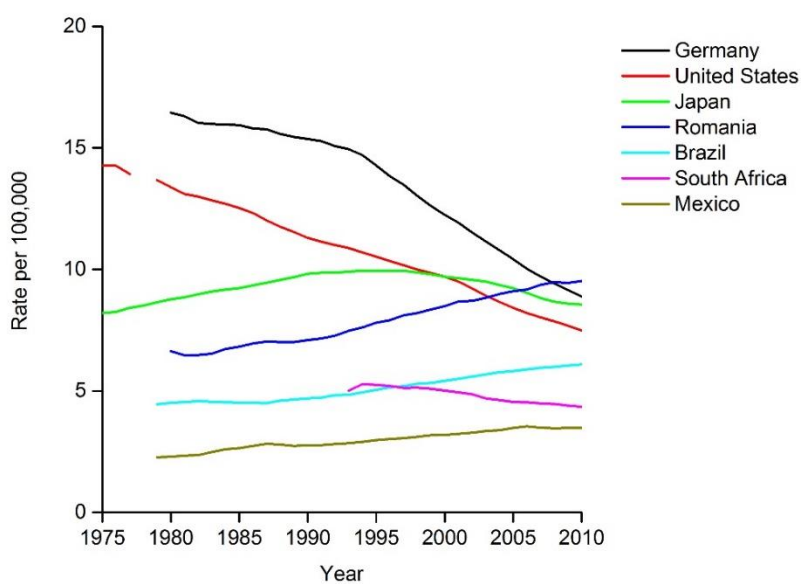
2.5.1.3. Risk factors. Risk factors for colorectal cancer include family history of colorectal cancer, smoking, excess body weight, alcohol drinking, and consumption of processed meat.[170-172] Also, red meat consumption is likely to increase the risk of colorectal cancer.[172] On the other hand, physical activity, diets high in dietary fiber, hormone replacement therapy, and the use of nonsteroidal anti-inflammatory drugs reduce the risk.[170, 171, 173] The recent increase in the incidence of colorectal cancer in LMICs largely reflects an increase in unhealthy diet (e.g. high in excess

energy and red and processed meat, low in fruits and vegetables), excess body weight, and sedentary lifestyles in those countries, while there is limited access to early detection and treatment of colorectal cancer in many LMICs.

Female current smokers are at a 20%−60% higher risk of colorectal cancer than never smokers.[15, 16, 174] One unit increase in BMI (kg/m^2) is associated with 2% increase in the risk of colorectal cancer, and the magnitude of this increase is greater for colon cancer (3% per unit of BMI) than rectal cancer.[173] Compared to never alcohol drinkers, the risk of colorectal cancer is 17% higher with moderate drinking (>12.5−≤50 grams ethanol or >1−≤4 drinks per day) and 44% higher with heavy drinking (>50 grams per day).[175] People who consume the highest levels of red meat are at a 10%−20% higher risk of colorectal cancer than those who consume the lowest levels.[176] The risk of colon cancer is 14% lower in women with the highest level of physical activity than in women with the lowest levels.[173, 177] It should be noted that although the magnitude of the associations between most of the potentially modifiable risk factors and colorectal cancer risk is relatively modest, due to their high prevalence the impact of these risk factors at the population level can be substantial.

Both overall excess body weight and weight gain in adulthood are associated with colorectal cancer risk.[178, 179] The proportion of colon cancers attributable to excess body weight in 2012 was 5.0% in sub-Saharan Africa, 16.1% in the Middle-East and North Africa, 15.4% in Latin America and Caribbean, 21.0% in North America, 6.9% in East Asia, 4.2% in South-eastern Asia, 4.2% in South-central Asia, 16.0% in Eastern Europe, 18.4% in Northern Europe, 18.1% in Southern Europe, 18.7% in Western Europe, 19.1% in Oceania, and 13.0% globally.[23] Excess body weight is a rapidly increasing risk factor in many LMICs.[180] Currently, prevalence of excess body weight among women in a number of LMICs is as high as the prevalence in the United States (at

least 60%) (see Section 4.4.2). Although the contemporary incidence rates for female colorectal cancer in many LMICs is relatively lower than in high-income countries, with current patterns in prevalence of excess body weight the rates are likely to increase in LMICs in the future. Assuming that excess body weight is also an indicator of unhealthy diet and physical inactivity, all these factors would contribute to the expected increase in colorectal cancer rates in LMICs.

2.5.2. Prevention and early detection

Worldwide, more than 10% of colorectal cancers are attributable to a combination of excess body weight, physical inactivity, and unhealthy diet.[19] Colorectal cancer can also be caused by smoking, which accounts for a notable proportion of colorectal cancers in countries where smoking is common. In the US, about 8% of colorectal cancers among women are estimated to be caused by smoking.[181] While it remains that a large proportion of colorectal cancers are caused by unknown or non-modifiable risk factors, many colorectal cancers can be prevented through healthy lifestyle behaviors.

2.5.2.1. Healthy lifestyle. Women should be encouraged to not smoke, be physically active, maintain/achieve healthy body weight, limit alcohol and red and processed meat consumption, and eat more fruits and vegetables. Prevalence of exposures and prevention measures are discussed in sections 2.3.2 and 4.1 for smoking and 4.4.2 for excess body weight and physical activity. Currently, WHO has no specific recommendation with regard to red or processed meat intake other than the one made in 2002, recommending moderation in the intake of processed meat.[182] Some institutions recommend limiting red meat consumption (no more than 300–500 grams per week) and avoiding processed meat.[183] Red meat refers to beef, pork, lamb, and goat. With regard to fruit and vegetable intake, WHO suggests consuming more than 400 grams of fruits and vegetables per day.[184] Low-dose aspirin may prevent colorectal cancer incidence and mortality, but available

evidence is not strong enough to recommend chemoprevention with aspirin to reduce the burden of colorectal cancer.[185]

2.5.2.2. *Prevention through screening endoscopy.* In addition to early detection, screening for colorectal cancer using endoscopic and radiologic methods has the potential to prevent colorectal cancer. Most cases of colorectal cancer develop from progression of colorectal adenomas.[186] Several large-scale studies have shown that removing adenomas is beneficial.[187-190] In endoscopic screening, endoscopists can identify and remove adenomas during the screening procedure, which can reduce colorectal cancer incidence.[187-190]

2.5.2.3. *Screening.* There are two groups of tests for colorectal cancer screening. One group primarily detects cancer and generally includes lab tests that detect blood or other biological markers in stool samples. The other group can detect both cancer and precursor lesions and includes radiologic and endoscopic examinations. The methods in the first group may reduce cancer mortality, whereas those in the second group have the potential to reduce both cancer incidence (by removing precancerous lesions) and mortality. The methods that detect both colorectal cancer and precursor lesions (the second group) generally have a higher sensitivity and specificity than stool-based tests.[191, 192] Another advantage of endoscopic methods is that biopsy samples can be taken from suspicious lesions or the lesion can be removed during the screening; a positive stool-based test must be followed by endoscopy. However, methods based on imaging are costlier and may not be easily accessible to everybody, in particular in LMICs. Moreover, unlike the first group, the second group methods generally need bowel preparation, and in the case of endoscopy, sedation. Many patients may feel less comfortable with undergoing endoscopic or imaging examinations, so adherence to screening may be higher with stool-based tests.[193]

The method of screening for each individual can be chosen according to personal preference, clinical implications, and access to the tests.[25] The recommended starting and stopping age and screening intervals may vary across guidelines and by individual risk. For example, screening in those with a family history of colorectal cancer may start earlier than others. Nevertheless, the implementation of screening programs based on lab tests (the first group above) are generally more feasible in LMICs than those based on colonoscopy or imaging, because the latter requires a more advanced clinical infrastructure.[192, 194]

Guaiac fecal occult blood test (gFOBT). gFOBT indirectly detects blood in the stool. Colorectal cancer is one of the reasons for the presence of blood in the stool, but it is not the only cause, and even blood from animal meats can result in a positive test. Therefore, a positive gFOBT test does not necessarily confirm a diagnosis of cancer, and it must be followed-up by colonoscopy.[193] Randomized clinical trials have shown that regular gFOBT tests (every 1-2 years) can reduce colorectal cancer death.[193]

Fecal immunochemical test (FIT). In FIT, an antibody against human globin is used to detect hemoglobin in stool. As this test detects human hemoglobin from the lower intestines, blood from other causes (e.g., gastric bleeding, because globin from upper gastrointestinal bleeding degrades during intestinal transit) or ingested animal meats does not cause a false positive test.[193] However, although in preliminary analyses of randomized clinical trials this test has been shown to reduce colorectal cancer mortality and is recommended by some screening guidelines,[25, 195] its effects needs to be confirmed in clinical trials with longer follow-ups.[193] A positive FIT test must be followed-up by colonoscopy.

Exfoliated fecal DNA. This stool test can find certain changes in DNA that could indicate cancer or polyps (such as KRAS mutations among others).[196] The commercial tests also measure

hemoglobin using immunoassay. In a large-scale, cross-sectional study the sensitivity of fecal DNA test was 92% for the detection of colorectal cancer and 42% for the detection of advanced adenomas,[196] indicating the potential of this test to detect precursor lesions. Similar to other stool-based tests, those with a positive DNA test need to be followed-up by colonoscopy.

Computed Tomographic Colonography (CTC). This method provides images of the organs in the abdomen and pelvis, including colon and rectum.[197] Although CTC needs bowel preparation, an advantage of CTC over endoscopic procedure is that it does not need sedation.[198] However, when a suspicious lesion is seen in CTC, colonoscopy will be required to take biopsies or remove adenomas. Unlike stool-based tests, CTC may detect adenomas. Currently, however, only detection of larger adenomas (≥1 cm) are comparable between colonoscopy and CTC. Colonoscopy is still a much better method for the detection of smaller adenomas.[197]

Flexible Sigmoidoscopy. In this method, a flexible fiberoptic instrument is used to examine the rectum and lower colon. During this procedure, endoscopists can remove or take biopsies from suspicious lesions. This method has been shown to reduce both colorectal cancer incidence and mortality.[199] A major drawback of this method is that it does not allow to examine upper colon, in which many cases of colorectal cancer occur.[193]

Colonoscopy. In this method, a flexible fiberoptic instrument is used to examine the entire colon and rectum, and suspicious lesions can be removed or biopsied. Results of cohort studies have shown that colonoscopy can reduce both colorectal incidence and mortality.[193] As this method allows the examination of the entire colon, it is likely that colonoscopy is associated with a greater reduction in colorectal cancer incidence and mortality than flexible sigmoidoscopy. Clinical trials are underway to compare the role of colonoscopy and sigmoidoscopy in the outcome of screening.[193]

2.5.4. Treatment

Surgery is the treatment of choice for non-metastatic colorectal cancer. Surgery for colon cancer generally can be done by a general surgeon; but surgery for rectal cancer is usually much more complicated and surgeries done by a specialized surgeon and in specialized hospitals are associated with better outcomes.[200] Surgery may be accompanied by chemotherapy and/or radiation therapy. Radiation therapy is most more important for rectal cancer and may improve local control of stage two and three rectal cancer. Adjuvant chemotherapy following surgery has been recommended for stage three colon cancer and stage two and three rectal cancer (four months for rectal cancer if chemoradiation is administered).[200]

Surgery is also an important treatment for many metastatic colorectal cancers. It has been shown that although metastatic colorectal cancer is generally incurable, surgical resection of the colorectal cancer and liver and lung metastases, when possible, may improve the survival and even result in cure in a small group of patients.[200] Nevertheless, this treatment needs highly specialized surgeons and hospitals. Other treatments for metastatic colorectal cancer include radiofrequency ablation and stereotactic body radiotherapy (which use advanced radiologic methods for a targeted radiation dose to the tumor) can improve the outcome, but they generally need advanced hospitals. In fact, for the majority of cases of metastatic colorectal cancer treatment is palliative.

Overall, successful surgery may be possible even in low-income countries, although radiation therapy, chemotherapy, and other treatment methods may be limited.[193] In the case of metastatic disease where other therapies are unavailable, palliation is essential.

2.5.4. Survival and survivorship

Survival for colorectal cancer varies worldwide and depends on availability of early detection and treatment. In North America, Australia/New Zealand, and many high-income countries of Europe,

colon and rectum five-year relative survival is 60% to 65%.[38] Five-year colon and rectum cancer survival of more than 65% has been reported in Israel and South Korea, while elsewhere in Asia survival ranges from 16% (rectum) and 31% (colon) in Mongolia to about 55% in Chinese registries.[38] Survival from colorectal cancer is much higher when it is detected early; however, fewer than half of colorectal cancers are diagnosed early, even in high-resource countries, due to suboptimal screening. For example, about 40% of colorectal cancers are diagnosed at an early stage in Canada, Denmark, and the UK.[201] Among colorectal cancer survivors, bowel dysfunction is common. Cancer recurrence is also common, and survivors are also at higher risk of second primary cancers of the colon and rectum, as well as other sites, especially in the digestive system.[202]

Chapter 3. Economic burden

Most studies on the economic burden of cancer have been conducted in high-income countries.[203] In this chapter, we present estimated economic burden of cancer worldwide, and when available, provide examples for the economic burden in LMICs.

3.1. Treatment costs

The estimated global economic burden of cancer in 2009 was US$ 286 billion, which included medical costs (US$ 151 billion, 53%), non-medical costs (costs of transportation, caregiving, and so on; US$ 66 billion, 23%), and productivity loses (US$ 69 billion, 24%).[204] Also, an additional sum of US$ 19 billion was spent on cancer research.

The three cancer sites with the highest economic burden worldwide in 2009 in both sexes combined were lung (US$ billion 53), colorectal (US$ billion 33), and breast (US$ billion 24).[204] The cost was US$ 5 billion each for endometrial and ovarian cancer and US$ 3 billion for cervical cancer. Approximately US$ 268 billion (or 94% of the total estimated global costs) was spent in high-income countries. The cost in other country income groups was US$ 1 billion in low-income, US$ 8 billion in lower middle-income, and US$ 9 billion in upper middle-income countries.[204]

High-income countries spend more on early detection of cancer and cancer treatment and care. As a result, the cost of treatment per cancer in these countries is higher than in LMICs. For example, the average cost per treatment of breast cancer in 2009 was highest in the United States (approximately US$ 67,000) and lowest in Ethiopia (around US$ 110; Figure 3.1). Of 172 countries included in the analysis, the average cost of treatment per cancer was US$ 5,000 or less in 125 countries.[204] The variation in the cost of cancer treatment generally follows the country income level.

Figure 3.1. Cost of breast cancer treatment per cancer in select countries
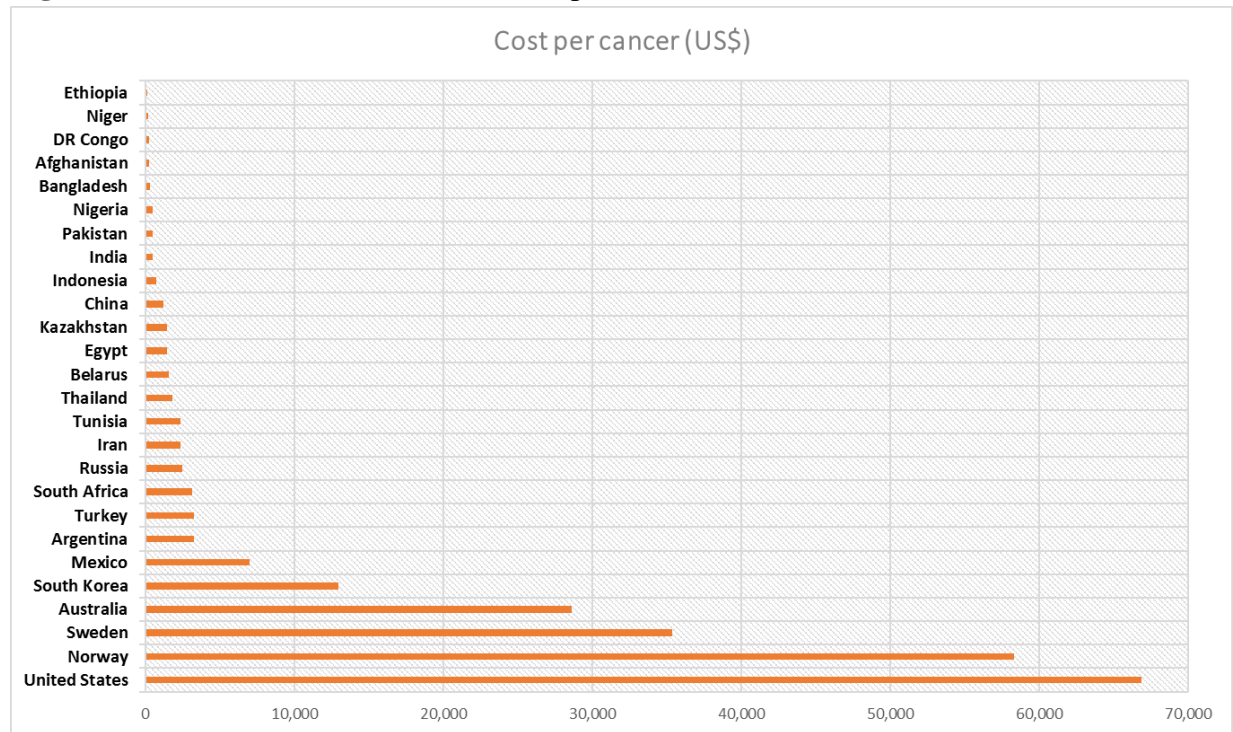
The high cost of treatment is a main reason for inadequate delivery of cancer treatment. In a study in Nigeria, 81% of cervical cancer cases referred for radiotherapy to the study center did not receive the treatment because of financial issues.[205] Usually, there is also inequality in affordability and access to care within a given country. Larger cities are more likely to have more advanced infrastructure for cancer care, as well as a higher proportion of people who could afford the care.[206] Therefore, lower-income individuals in rural areas or smaller towns are less likely to afford or have access to cancer care in LMICs. Due to lack of widespread health facilities capable of providing cancer care in many LMICs, cancer patients may need to travel long distances to have access to cancer care. This can further increase non-medical costs of cancer treatment and be a major barrier for access to care,[205] especially if we take into account the arrangements for travel and accommodation for people accompanying the patients, who may also have to be absent from their work for a long time. Inequality in access to cancer care is not confined to LMICs only, and

many low-income cancer patients in high-income countries may not receive the treatments that they need for similar reasons.[207]

Due to their high cost, many chemotherapeutic agents are not included in national essential medicines lists in many low-resource countries.[208-210] There is variation in the number of included agents across countries, and the number is lower in countries with lower resources. For example, the median number of oncology essential medicines in a recent study ranged from 11 in low-income countries to 18 in lower middle-income and 26 in upper middle-income countries.[209]

High costs of cancer treatment indicate the importance of cancer prevention measures in LMICs. It has been estimated that a US$ 11.4 billion investment in certain preventive interventions in LMICs can potentially save up to US$ 100 billion in cancer treatment costs.[211]

3.2. Costs to society

A major part of the economic costs of cancer to society results from loss of productivity. One way to estimate this loss is to calculate years of productive life lost (YPLL) due to premature death.[212] Traditionally, premature death is defined as death before age 75 years, but other ages (e.g. 70 years) may also be used by some researchers.

The estimated economic burden of cancer due to loss of productivity in 30 European countries in 2008 was €75 billion (€49 billion in men; €26 billion in women).[212] In the United States, YPLL from all cancers in 2006 was 4.5 million in men (15.4 per death) and 4.7 million in women (17.5 per death), corresponding to a productivity loss of US$ 94 billion in men and US$ 82 billion in women.[213] The estimated productivity loss due to premature death from female breast cancer alone in 2008 was US$ 5.5 billion worldwide.[214] In South Korea, the YPLL per death for

both sexes combined in 2009 was 17.3, with an estimated total productivity loss of US$ 5.3 billion.[215]

Similar to other issues related to the economic burden of cancer, few studies from LMICs are available on societal costs of cancer.[216] A study in Iran reported that although the number of cancer deaths in 2012 was higher in men (30,000) than in women (23,000), because of longer life-expectancy and lower age at death with some female cancers, the estimated total YPLL for men (563,000) was only slightly higher than women (549,000), and YPLL per death was higher in women (24 years) than in men (19 years).[217] On the other hand, due to a higher rate of employment and wages for males, the estimated cost of productivity loss was substantially higher in men (US$ 1.2 billion) than in women (US$ 722 million).

Cancer can also lead to economic loss to society by reducing productivity of family members of cancer patients and informal caregivers. This issue is discussed in the next section.

3.3. Economic burden on survivors and their families; lifetime care needs

Even in high-income countries, financial hardship after diagnosis of a cancer is common. For example, in a study in the United States, 32% of cancer survivors reported cancer-related financial problems.[218] These people were at a higher risk of forgoing or delaying medical care than others.[218] Financial hardship was more common in people younger than 65 years of age than older people.[219] People aged 65 or more in the United States are generally covered by Medicare health insurance and Social Security and may receive some other benefits.

In many cases, a family member or another close person provides hands-on care for cancer patients. The support provided by these informal caregivers varies, but it mainly includes personal care, coordination of medical care (including transportation), shopping and housework, emotional

support, and managing finances.[220] Caregivers may spend significant time providing care and support to patients, especially during active treatment and end-of-life, and this usually has financial consequences for them and their families, in addition to the impact on their health (including a higher risk of anxiety and depression), lifestyles, and social relations.

It is most likely that cancer survivors and their families in LMICs face a greater financial hardship than those in high-income countries. The available evidence, although limited, indicates that many cancer patients in LMICs who manage to receive treatments will have problems with some of their basic needs, such as purchasing food or paying for their utility bills (Table 3.3).[221] Many survivors may also need financial assistance from their relatives or friends.[205] This is despite the fact that many of those who afford cancer treatments in LMICs are of higher socioeconomic status.

Table 3.3. Summary of select studies on economic burden on survivors and their families

Country (year of study); sex; cancer site	Costs related to cancer	Other indicators of economic burden
Argentina (2002-2004);[221] only women; cervix	At least one member of the patients' household in 45% of cases reduced working hours and in 28% stopped working. 39% of households partially or totally lost family income. Due to loss of income, the number of household below the poverty level increased by 8%.	In household of patients, payments were delayed for essential services such as telephone or electricity in 43% of cases (leading to the service cut in 12% of all cases); 38% had to sell the property or use savings and 37% had to reduce daily food consumption. Problems in paying for education occurred in 23% of the patients' households.
India (1995-1996 and 2004);[222] both men and women; all cancers	The comparison group in this study was those with communicable diseases. Within the major non-communicable diseases, out of pocket expenses per hospital stay and per outpatient visit were the highest for cancer (e.g. the outpatient visit cost in the public sector was ~1150 Indian Rupees for cancer and ~350 for heart disease).	Compared to the comparison group, the cost for treatment of cancer was 2.7 time more likely to exceed 40 % of household income; the risk of impoverishment because of cost of care was 2.3 times higher for cancer patients.
Nigeria (1995-2004);[205] only women; cervix	Patients were referred for radiotherapy. 81% of patients could not afford and receive the treatment.	The 29% that afforded the treatment were of upper social class groups. However, 83% of them still needed additional funds from relatives and friends.
Pakistan (2009-2010);[223] both men and women; breast (60%) and head and neck (40%)	Monthly income: Mean, US$ 996 Median, US$ 562 Monthly cancer care: Mean, US$ 1093 Median, US$ 946	Perception of financial burden of cancer care: Significant for 42%, Unmanageable for 27%

Chapter 4. Overarching policy approaches

There are a number of policy approaches to reduce the burden of cancer. These policies cover a wide spectrum of activities, including those to eliminate or reduce risk factors of cancer or increase access to care for early detection and treatment of cancer. They also include monitoring risk factors or cancer outcomes in order to assess the success of the existing policies or the need for new ones. In this chapter, we briefly discuss some of the most important approaches and provide some specific examples. When available, we primarily present WHO's recommendations, as they are likely to be more applicable to LMICs. It should be noted that these recommendations may be different from national recommendation in some countries.

4.1. Tobacco control

Tobacco is one of the leading causes of preventable cancer deaths among women worldwide. There are a number of proven steps which can be taken at the policy level to curb smoking.

The WHO Framework Convention on Tobacco Control (FCTC), which entered into force in 2005, is an international treaty outlining measures to control the global tobacco epidemic. 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. Taxation in particular has proven to be very effective in reducing smoking, in addition to being cost-effective.[224, 225] Most countries now have taxes amounting to at least 25% of the purchase price of the leading cigarette brand (Figure 4.1). However, the WHO recommends taxes amounting to at least 75% of the retail price, and few countries have reached

this level. High-income countries generally have higher levels of taxation, while many LMICs, particularly in Africa and the Middle East, have lower levels.

Figure 4.1. Tobacco taxation, 2014

Percent of price of top-selling cigarette brand

| | < 25% | | 25% - 49.9% | | 50% - 74.9% | | 75% or more | | No data |

Source: WHO Report on the Global Tobacco Epidemic, 2015

Brazil is an example of the successful implementation of tobacco control 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 consistent with MPOWER enacted starting in 1986.[226] By 2008, about 43% of once-daily female smokers in Brazil had quit (compared to 45% in the UK and the US), and current smoking among young women 15-24 was only 6% (compared to 20% in Uruguay).[227] Although it will take decades for resulting reductions in mortality to appear, should this progress be sustained, Brazil will have potentially avoided a huge future burden of disease among women.

Women have not begun smoking in large numbers in many parts of the world, especially in LMICs in Asia and Africa.[228] While this presents an opportunity for tobacco companies in the form of a vast untapped market, it is also an opportunity to avoid a growing burden of lung cancer in countries where smoking among women remains rare.[85] Female smoking in Africa and the Middle East remains at or below 10% in all countries and less than 5% in most (Figure 2.13). Apart from more developed urban populations (Singapore, Hong Kong, Japan), Nepal, and Laos, smoking prevalence has remained less than 10% among women in Eastern, Southern, and Southeastern Asia. Though smoking prevalence among women 15 years and older in China is low at 2% in 2013, it has one of the largest populations of female smokers in the world (estimated at 12.6 million) [227] and limited evidence suggests that it may be increasing among young women.[227, 229] With effective tobacco control measures, a large burden of lung cancer among women could be averted in these countries.

4.2. Vaccination

HPV and HBV vaccines are the two major vaccines that prevent cancer. HPV can prevent precancerous lesions and cancer of the cervix [58] and probably several other HPV-related cancers, including anal cancer.[230] HBV vaccination can prevent HBV-related chronic liver disease and liver cancer.[141] Several factors have made vaccination against these carcinogenic infections one of the most feasible and cost-effective methods to prevent HBV- and HPV-associated cancers, in particular in LMICs. In just a few visits the vaccines can be delivered to newborns/infants (HBV) or adolescents (HPV), which generally provides a lifelong protection against these infections. Also, vaccination is much less costly than diagnostic procedures and treatment of chronic diseases and cancers related to these infections.

4.2.1. HPV vaccination

4.2.1.1. Health impact. There are several studies examining the health impact of the HPV vaccine on cervical cancer. The HPV vaccine also protects against other HPV-related cancers including anogenital and possibly oropharyngeal cancers, so the health impact of the vaccine is even greater when considering other cancers affected. A recent analysis funded by WHO has estimated the number of cervical cancer cases or deaths that could be prevented by HPV vaccination and cost-effectiveness of this intervention in all countries worldwide.[231] The countries with the highest numbers of preventable cervical cancers per 100,000 vaccinated girls are generally located in sub-Saharan Africa, South America, Eastern Europe, and Central Asia (Figure 4.2). Most high-income countries that had introduced HPV vaccination into their national immunization programs earlier are among the countries with the lowest number of preventable cervical cancer cases per vaccinated girls because their baseline incidence is lower due to cervical cancer screening.

Figure 4.2. Estimated number of cervical cancer cases prevented per 100,000 girls who receive HPV vaccine [231]
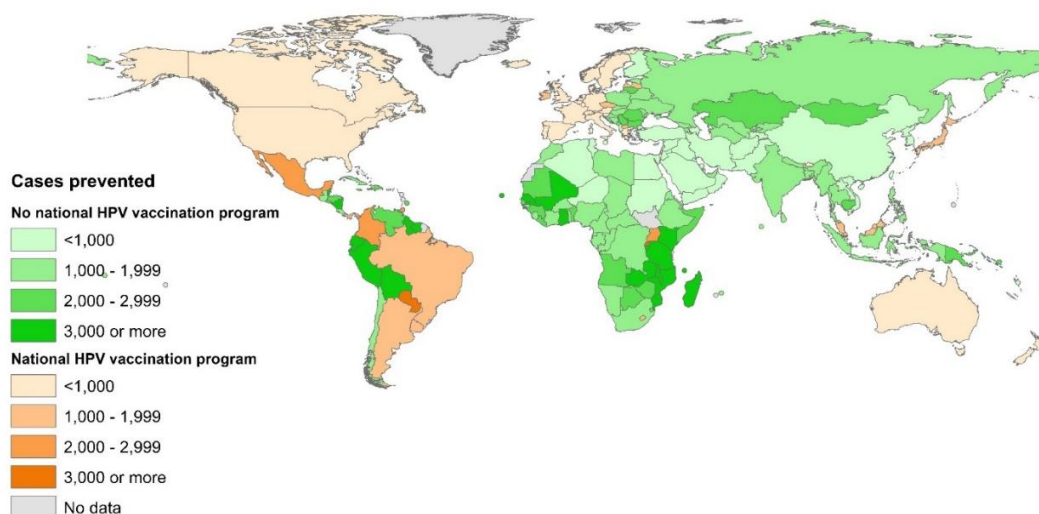
The number of cervical cancer deaths prevented through vaccination of one birth cohort of 12-year-old girls from the same analysis [231] by country income and WHO region is shown in Table

4.1. As cervical cancer occurs in relatively younger ages than many other adult cancers, prevention of the cancer can potentially avert a greater number of years of life lost (YLLs) than some other cancers. The disability-adjusted life-year (DALY) is another metric for quantifying the burden of disease: it sums up YLLs and the lost years of healthy life due to disability. Therefore, the DALY considers the burden from both mortality and morbidity (unhealthy life). In 2008, the age-standardized DALYs per 100,000 for cervical cancer were lower in Australia and New Zealand (58); North America (74); the Middle-East and North Africa (82); Western, Southern, and Northern Europe (79 to 105); and East Asia excluding China (112). It was much higher in China (141); Eastern Europe (231); Southeastern Asia (243); Latin America and the Caribbean (355); South-Central Asia excluding India (363); India (466); Oceania excluding Australia and New Zealand (507); and sub-Saharan Africa (641).[232] These numbers indicate a great disparity in terms of DALYs related to cervical cancer between high-income countries (mostly in the group with a lower DALY) and LMICs (mostly in the group with higher DALYs).

Table 4.1. Net cost of HPV vaccination and the number of cervical cancer deaths prevented by vaccination of one birth cohort of 12-year-old girls

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

4.2.1.2. Cost effectiveness. Researchers have assessed the cost-effectiveness of HPV vaccination of all 12-year-old girls worldwide (58 million girls).[231] They compared the cost per DALY averted against gross domestic product (GDP) per capita in each country. When the cost per DALY averted was below GDP per capita, the intervention was defined as very cost-effective, and when it was between one to three times GDP per capita, the intervention was defined as cost-effective. Of 179 countries included in the analysis, HPV vaccination was suggested to be very cost-effective in 156 countries (87%) and cost-effective in 17 other countries (Figure 4.3). In only 6 countries was the vaccination estimated not to be cost-effective; most of these countries were located in the Middle-East and had low incidence of cervical cancer.

Figure 4.3. Cost-effectiveness of HPV vaccination [231]
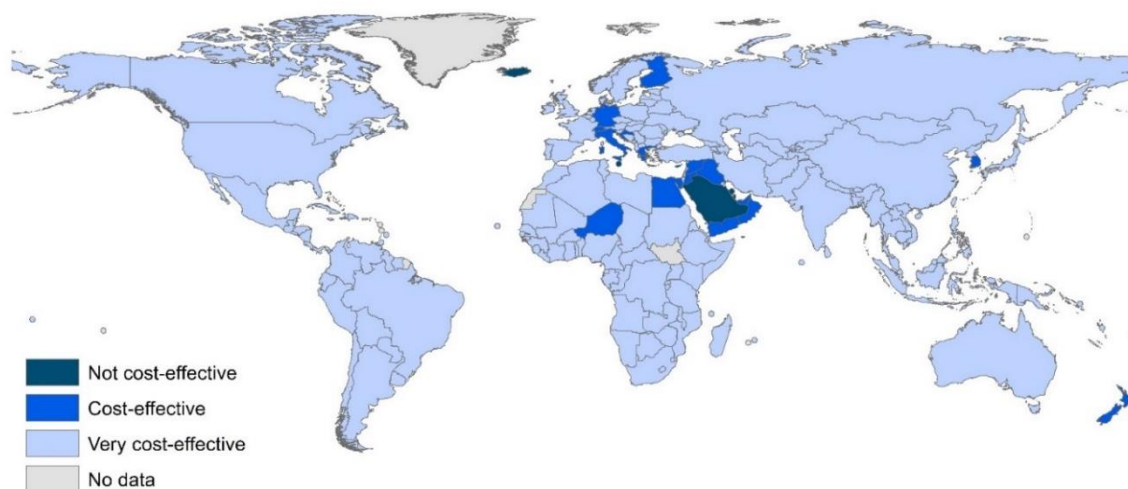
According to this analysis, the WHO regions that would have the highest return from investment in HPV vaccination programs are Africa and South-East Asia. While the net spending in Africa (approximately US$ 200 million) would be 5% of global spending if all 12-year-old girls worldwide in a given year were to be vaccinated, the prevented cervical cancer deaths in this region would be 31% of all prevented deaths in the vaccinated individuals globally (Table 4.1). The

corresponding proportions for spending and prevented cervical cancer deaths in South-East Asia are estimated to be 10% and 36%, respectively, with a net spending of approximately US$ 390 million.

The results of this analysis [231] were consistent with the results previously published from 24 out of 26 LMICs included in a systematic review [233] and with results from all 72 countries included in another analysis.[234] Another analysis of cost-effectiveness of HPV vaccination in sub-Saharan Africa showed that the vaccination was very cost-effective in all countries when the cost of vaccination was <25–50 international dollars per vaccinated girl, or the price of HPV vaccine offered to eligible countries by Gavi, the Vaccine Alliance (for more information about Gavi, see Section 4.2.1.3).

4.2.1.3. Availability and coverage. According to WHO, by 2013, 45 countries had introduced HPV vaccination in their national immunization program and four additional countries planned to do so, whereas 145 countries had no plans in this regard (these countries shown in Figure 4.2). Although there were several LMICs in the WHO Americas and Western Pacific regions that had implemented the vaccination program, only three countries in Africa (Lesotho, Rwanda, Uganda) and one in South-East Asia (Bhutan) had done so. None of the countries in the Eastern Mediterranean region had introduced HPV vaccination in their national immunization program. However, the number of countries with HPV vaccination in their national immunization program was substantially increased to 81 countries by August 2015 (Figure 4.4).[235] A major contributor to this progress is an increase in international monetary and technical assistance to LMICs, and notably, the role of Gavi, the Vaccine Alliance.

Figure 4.4. HPV vaccination programs, 2015 [235]
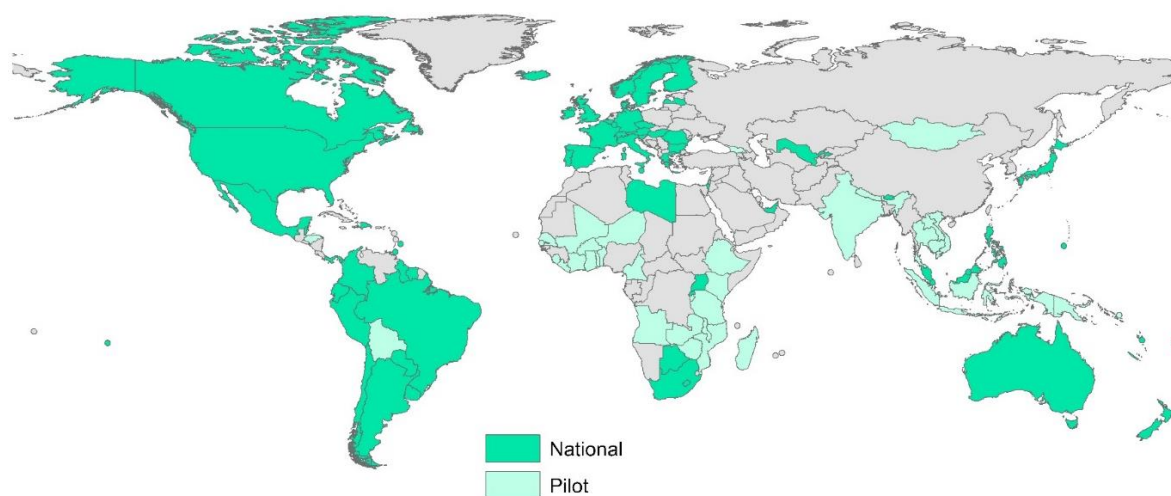
Source: Cervical Cancer Action

Gavi was established in 2000 as an international organization in order to increase access to vaccines for children in LMICs. Since then, Gavi has seen an annualized growth rate of 18.8% in its funding. In 2014, Gavi provided US$ 1.7 billion for vaccination in LMICs, accounting for 46% of all development assistance for vaccination worldwide.[236] Currently, 77% of Gavi's funding comes from governments, 22% from foundations, corporations and organizations, and 1% from private individuals.[237] HPV vaccination of girls is one of the immunization programs supported by Gavi. Countries with an average Gross National Income (GNI) per capita of ≤1,580 US$ during the preceding three years are eligible to apply for Gavi support.[238]

Currently, however, there are still a number of countries in Latin America and the Caribbean, Africa, Asia, and Eastern Europe which have no national HPV vaccination program. It should also be noted that inclusion of HPV vaccination in a national program does not necessarily indicate a high vaccination coverage in that country. For example, in 2014, only 50.3% and 39.7% of girls aged 13–17 in the United States had received 2 and 3 doses of HPV vaccine, respectively.[239] Nevertheless, through political commitment and appropriately-designed programs,

high coverage rates can be attained. For instance, Bhutan was one of the first LMICs that included HPV vaccination in their national immunization program.[240] They planned to routinely administer quadrivalent vaccines to 12 year-old girls, as well as a one-time catch-up doses to 13–18 year-old girls, in 2010. The vaccination took place mainly at schools, while out-of-school girls were immunized at health facilities. The estimated 3-dose vaccination coverage was approximately 99% among 12 year-old girls. From 2011, HPV vaccination became part of routine immunization at health facilities, which was followed with a decline in the 3-dose coverage to 67–69%. This coverage increased to over 90% in 2014 after the vaccination was begun in schools again.[240] High coverage has also been reported from other LMICs with national HPV vaccination programs, including Rwanda [241] and Uganda.[242] Some analyses suggest that a combination of HPV vaccine delivery through schools and health facilities may be associated with a better vaccination adherence in LMICs.[243] In any case, available data strongly indicate that high coverage for HPV vaccination is potentially achievable worldwide, including in LMICs, when the program is appropriately designed according to the needs of the community.[244]

4.2.2. HBV vaccination

The global burden of HBV infection is substantial. Chronic HBV infection (i.e., persistence of HBsAg for at least six months) affects 240 million people and kills 650,000 people every year.[151] Most of these people live in LMICs. Between 20% and 30% of people with chronic HBV infection will eventually develop cirrhosis and/or liver cancer.[151] HBV vaccination is the most cost-effective measure to prevent HBV infection and its complications.[151, 245] In 1992, WHO recommended the inclusion of HBV vaccination in all national immunization programs. Since then, almost all countries have followed the recommendation (Figure 4.5). WHO recommended that all infants should receive HBV vaccine.

Figure 4.5. Infant hepatitis B vaccine coverage, 2014

Percent of one-year-olds who have received three doses of hepatitis B vaccine

[ ] < 50%   [ ] 50% - 74.9%   [ ] 75% - 89.9%   [ ] 90% or more   [ ] No data
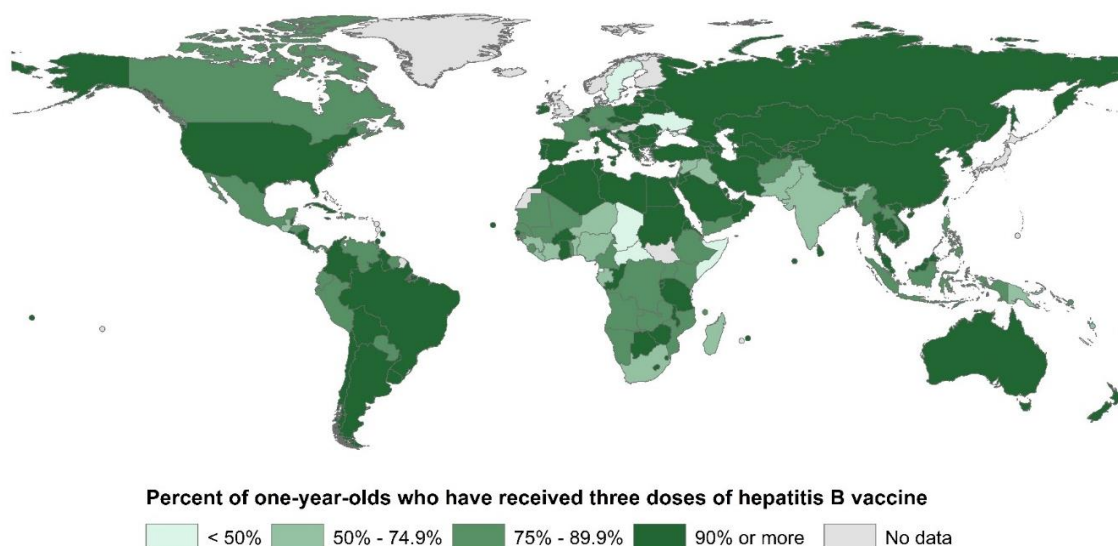
Source: WHO Global Health Observatory Data Repository

Countries with no data may represent countries where hepatitis B is not endemic (e.g., Scandinavian countries) and national hepatitis B vaccination programs have not been introduced.

HBV vaccination coverage in several high-income countries is less than optimal (Figure 4.5). This is mainly because the prevalence of HBV infection in those countries is very low, so the vaccination of all infants may not be considered as a priority and only high-risk groups may be targeted for vaccination.[246] However, in a number of countries in the WHO African region and a few countries in the Western Pacific with a high prevalence of HBV infection (see Section 2.4.1.3, Figure 2.18), the coverage is not optimal and needs to be improved as a priority. There are also some LMICs in Asia and South America that have relatively low HBV infection rates and sub-optimal vaccination coverage. These countries will also benefit from an increase in the coverage. For example, despite a relatively low HBV infection rate, it has been estimated that every year 17,000 people in India die because of HBV-related liver cancer.[138] 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.

4.3. Access to healthcare

In this section, we provide two examples illustrating issues surrounding access of women to healthcare in LMICs. These examples relate to access to screening for cervical and breast cancers.

4.3.1. Cervical cancer screening

4.3.1.1. Health impact. Cervical cancer screening can reduce cervical cancer incidence and mortality. A screening program based on HPV DNA testing for three times during the lifetime (at ages 35, 40, and 45), with a 70% coverage, can prevent approximately one-fourth of cervical cancer cases by identifying precursor lesions (Table 4.2). The mean cancer reduction with a 3-year interval for cytology-based screening from age 25 to 65 years was between 41.6% and 46.7% in Algeria, Lebanon, and Turkey.[247] The assumption for the latter estimates was 70% coverage for cytology at first visit, with 15% loss-to-follow-up at each subsequent visit (if necessary, 2 more visits for colposcopy/biopsy and treatment). The effect of screening on reducing cervical cancer mortality can be even greater, as it can result in a more favorable prognosis by identifying cervical cancers at earlier stages. A combination of vaccination of adolescent girls and screening of adult females has been shown to be more effective in reducing cervical cancer incidence than either of these measures alone.

As mentioned in section 2.2.2 on cervical cancer screening methods and WHO guidelines, the standard screening method in high-income countries is based on cytology (Pap test). However, this method has not been as successful when implemented in LMICs compared with HICs due to the lack of appropriate infrastructure. Therefore, unless a well-functioning screening program based on cytology is already in place, such a program is not recommended for LMICs. Studies have shown that cervical cancer screening based on HPV DNA testing or VIA can be better alternatives in LMICs.

Table 4.2. 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 [234]	18.2		52.2	68.6
Chile [234]	14.2		45.6	60.0
Colombia [234]	20.8		49.4	67.1
Peru [234]	19.1		43.0	55.0
Mexico [234]	16.7		40.3	56.4
South Africa [248]	14.7	24.8	46.4	59.7
Uganda [248]	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: Pat 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).
[c] Vaccination at ages 9–12, assuming 70% coverage of the female population with three doses given by age 12.

4.3.1.2. Cost effectiveness. It has been estimated that delivering either HPV DNA testing or VIA once or twice in a lifetime to women 35–45 years old will be a very cost-effective intervention.[249]

According to the cost of labor and material used, the cost of Pap test, HPV DNA testing, VIA, and consequently, life-time screening vary across countries.[249] When available, HPV DNA testing generally has a higher sensitivity/specificity and greater effect on reducing cervical cancer incidence than VIA.[63] On the other hand, usually VIA needs one visit (treatment can be provided for those with abnormal lesions in VIA on the same day), whereas HPV DNA testing needs two (one visit for test and one visit to treat, if necessary, according to the result of the test), and the HPV test is generally more costly.[63] Based on available resources and infrastructure, LMICs can choose one of the screening methods recommended by WHO (Section 2.2.2, Figure 2.9). A number of studies have indicated that HPV vaccination and cervical screening will generally be much more

cost-effective than a cancer screening program alone in LMICs (Table 4.2), and the difference is greater when the cost of vaccination is lower.[63, 234, 247-249]

4.3.1.3. Availability and coverage. Few LMICs have a national screening program based on cytology and colposcopy (Figure 4.6).

Figure 4.6. Map of countries with large-scale breast and cervical cancer screening programs, 2014 *

Source: The Cancer Atlas, 2nd edition

* Cervical cancer screening based on pap smear.
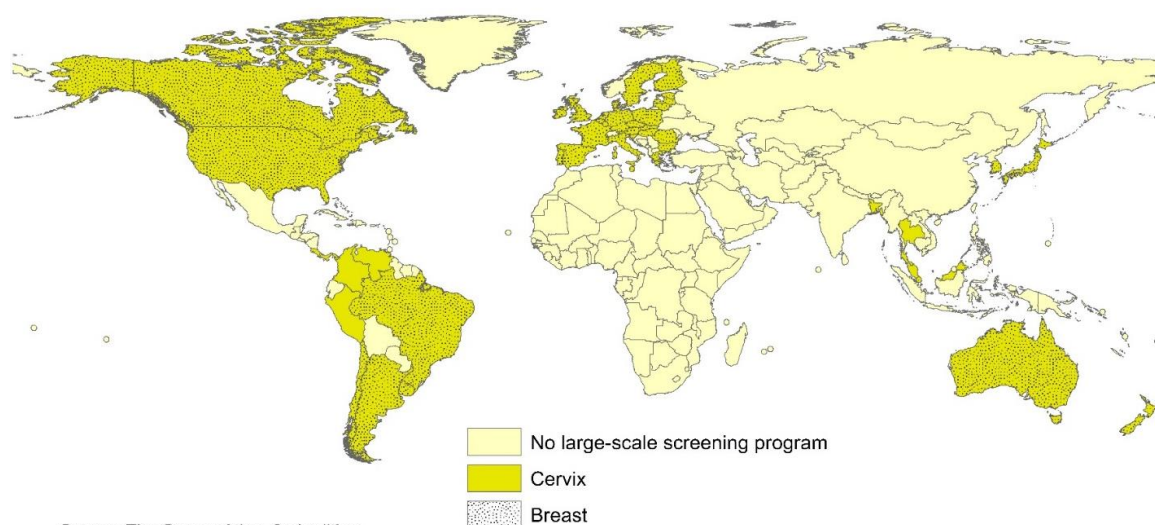
HPV DNA testing needs validated platforms and appropriate quality assurance programs.[250] As of August 2015, only 6 countries had implemented HPV DNA testing in their national screening programs, but several LMICs had started pilot programs (Figure 4.7). Also, a number of LMICs had started a national program based on VIA, and many others had started pilot programs (Figure 4.7). However, although many sub-Saharan African countries have started a national or a pilot cervical cancer screening program, several countries in Central Africa have not done so.

Figure 4.7. HPV screening programs using HPV DNA testing and visual inspection with acetic acid, 2015 [235]

Source: Cervical Cancer Action
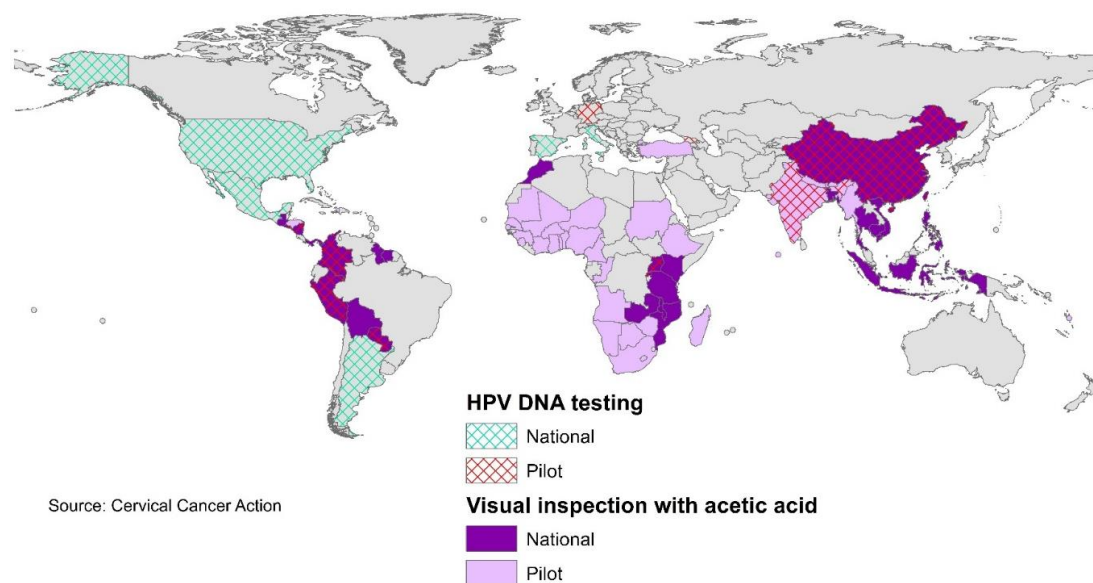
4.3.2. Breast cancer screening

4.3.2.1. Cost effectiveness. Evidence on cost-effectiveness of breast cancer in LMICs is limited. As discussed in Section 2.1.2, however, in many LMICs mammography screening is not cost-effective and feasible[33, 251] because implementation of a national mammography screening is costly and needs advanced health care infrastructure.[31] Currently, WHO recommends mammography screening for women aged 50−69 years in LMICs only when there is a relatively strong health system and the shared decision-making strategies for patients and healthcare providers meet certain conditions.[34] In all limited resource countries (either with weak or relatively strong health systems), WHO recommends against screening in women in other age groups.[34] Although clinical breast examination has been suggested as a promising method for breast cancer screening in low-resource settings, more research is needed before it or other potential screening methods can be recommended as a routine method for breast cancer screening at the population level in all LMICs.

4.3.2.2. Availability and coverage. Few LMICs have a breast cancer screening program based on mammography (Figure 4.6), and many are unlikely to afford such a program in the near future.

4.4. Education and health promotion

Increasing cancer awareness and health promotion programs are essential to the success of cancer control interventions. In this section, we briefly review the overall role of increasing cancer awareness in LMICs and provide examples of a few educational programs with regard to nutrition and physical activity, as well as the cost-effectiveness of selected educational and health promotion programs.

Figure 4.8. Cigarette warning labels, 2014

No warnings or small warnings
Medium size warnings missing some appropriate characteristics OR large warnings missing many appropriate characteristics
Medium size warnings with all appropriate characteristics OR large warnings missing some appropriate characteristics
Large warnings with all appropriate characteristics
Data not reported

Source: WHO Report on the Global Tobacco Epidemic, 2015

More information about increasing awareness about the health effects of smoking is provided in Section 4.1. As an example, Figure 4.8 shows the status of cigarette warning labels worldwide. The labels are recommended by the FCTC and have been shown to be effective in reducing smoking. Larger warnings are more efficient than smaller ones in this regard.[104] Many LMICs in the Americas and several ones in the Middle East and other regions have introduced

warning labelling at the levels recommended by the FCTC. However, in a number of other LMICs, there are still no warning labels on cigarette packages or, where they exist, they are still too small based on FCTC criteria.

4.4.1. Cancer awareness/education

In addition to access to health care, a major contributing factor to cancer prevention and improvement in cancer outcomes is cancer awareness.[206, 252] Overall, cancer awareness in LMICs is low, although there are variations across countries.[206, 253] For example, only one-third of Chinese smokers know that smoking causes lung cancer,[254] and less than 10% of female university students in many countries in sub-Saharan Africa know that alcohol drinking and excess body weight are risk factors of breast cancer.[253] Individuals who are informed about cancers and their main risk factors, symptoms, and outcomes may be more likely to avoid unhealthy behaviors, notably smoking,[109, 255] 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,[252, 256-259] although the effect of awareness may vary across populations or by cancer site and risk factor. Cancer awareness can also reduce the stigma that might be associated with cancer in many populations.[260-266] This may be particularly important with regard to women's cancers, for which stigma may be associated with cancers of the female body parts and those associated with sexually transmitted infections (e.g., cervical cancer, which is related to HPV infection).[260-265] However, programs to increase cancer awareness should not be confined to these cancers only, because the stigma can also be associated with other cancers.[266]

Heightened cancer awareness can produce a positive impact on cancer outcomes. The majority of breast cancers are diagnosed at a later stage in sub-Saharan Africa, where usually there is a relatively long delay between the onset of symptoms and seeking medical care.[267-270] Among

the most important factors contributing to late care-seeking in sub-Saharan Africa, in addition to distance to healthcare facilities and low income, are low literacy rates, lack of knowledge about breast cancer and self-examination of the breast, and waiting until experiencing pain.[269] Comparable situations exist in many other LMICs. Several studies in LMICs have shown that an increase in public awareness is followed by a reduction in stage of breast cancer at diagnosis.[33, 35, 258]

As a result, increasing public cancer awareness must be among the highest priorities in any strategies for cancer control in LMICs. It should be noted that even among some health care professionals in LMICs cancer awareness may not be optimal.[206, 271-273] Appropriate material about cancer control and prevention and multidisciplinary cancer care should be incorporated in the curriculum for health care professionals in universities, and continuous training should be provided to practicing professionals.

4.4.2. Diet and nutrition, physical activity

A healthy lifestyle is necessary for normal growth and function of the body and to prevent many diseases, including several types of cancer. The importance of some dietary factors is briefly discussed in section 2.5.2.1.

Excess body weight is a rapidly growing risk factor in many LMICs.[180] Currently, prevalence of excess body weight among women in almost all LMICs in Oceania and the WHO regions of the Americas and Eastern Mediterranean is 50% or more (Figure 4.9). Many of these countries, as well as Canada, South Africa, and the United States, have among the highest prevalence of excess body weight among women worldwide. The corresponding prevalence is also high in many other African and Asian countries, with 30% or more. Maintaining normal weight (defined as BMI $18.5 - 24.9$ kg/m^2) can prevent a number of cancers or other chronic diseases.

Overall, people with a normal weight, including those who have lost excess weight, have a higher quality of life on average than those with excess body weight.[274]

Figure 4.9. Prevalence of excess body weight (BMI>25) among women age 18+ years, 2014
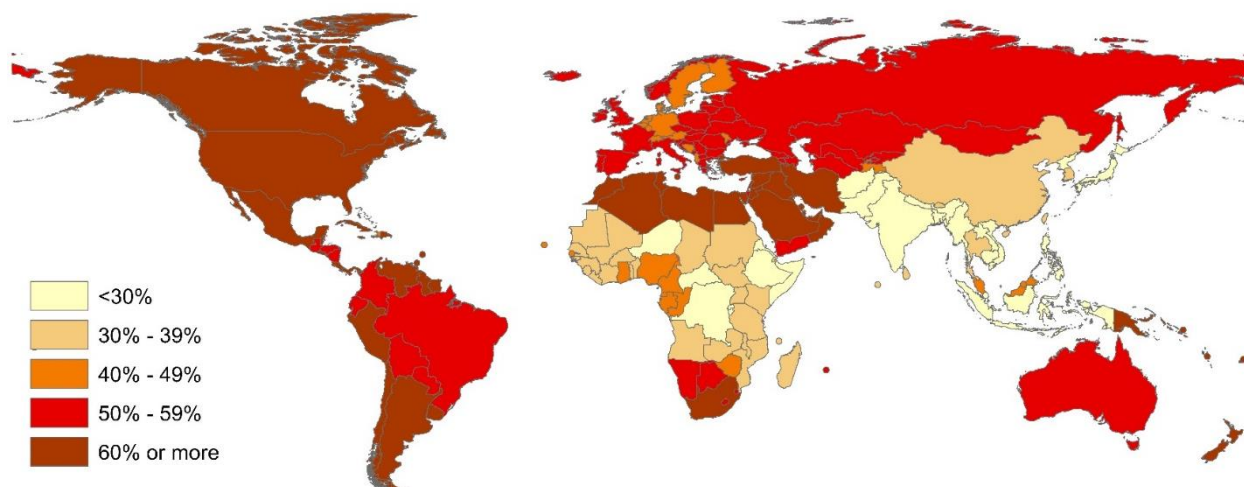
Source: WHO Global Health Observatory Data Repository

For adults aged ≥18 years, WHO recommends "*at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity*".[275] The activity can be recreational, occupational, household chores, or for transportation (e.g. walking or cycling), and it should be done for at least 10 minutes in each session. Increasing the duration of moderate-intensity activity to 300 minutes per week, or performing 150 minutes of vigorous-intensity activity per week, or equivalent combinations of both will increase the health benefits. Muscle-strengthening activities should be practiced at least 2 days a week. In the age group ≥65 years, people with poor mobility should perform physical activity at least 3 days per week to increase balance and prevent falls. Also, when people aged ≥65 years are not able to practice physical activity at the recommended levels because of health issues, they should be as physically active as they can.[275]

4.4.3. Cost-effectiveness evidence

Studies in high-income countries have shown that many interventions for increasing awareness and promoting healthy diet, physical activity, and weight loss are cost-effective.[276-278] For example, a study simulating a cohort of US adults found that community based physical activity interventions were cost-effective with cost-effectiveness ratios ranging from $14,000 to $69,000 per quality adjusted life year gained in comparison to no physical activity intervention.[279] Research on preventive measures in LMICs is limited, but available evidence indicates that interventions to promote healthier lifestyles are a cost-effective way to prevent chronic diseases, including cancer, in those countries.[280, 281]

It should be noted that successful interventions in high-income countries may not be feasible or cost-effective in LMICs, due to substantial differences in resources and health care infrastructure.[282] This is even true for lower-resource communities in high-income countries, which may not receive or benefit equally from some interventions as higher income groups.[283] Many interventions in high-income countries are in a clinical setting; however, due to more limited resources, the priority for promoting healthy lifestyles in LMICs should be given to efficient non-clinical interventions, when possible.[282]

As an example, we briefly discuss the cost-effectiveness of interventions to reduce excess body weight, physical inactivity, and unhealthy diet in LMICs. The main strategies for this purpose include increasing general awareness using appropriate health information and communication methods, implementing measures to increase the price of unhealthy foods while reducing the price of healthy foods, improving food labelling, and limiting the marketing of unhealthy food, in particular to children.[284] A simulation study estimated the effect of these interventions on health outcomes and expenditures and cost-effectiveness of these measures in Brazil, China, India,

Mexico, Russia, and South Africa, as well as a high-income state, England.[284] This analysis included seven interventions, including mass media campaigns, worksite interventions, physician counselling, school-based interventions, food labelling, measures for changing the price of foods, and food advertising regulations. All of these measures were shown to save lives. Specifically, the total estimated number of annual life-years (all causes) saved in these seven countries combined varied from 240,000 for mass media campaigns to 740,000 for food advertising regulations relative to a situation with no preventive policies; these two interventions also had the lowest (240,000) and highest (920,000) numbers of averted DALYs, respectively.[284]

The cost of delivering all above seven measures in LMICs is substantially lower than in high-income countries, although there is variation in the cost across LMICs. In terms of effects on lowering health expenditure, measures to change the price of food were the strongest in the above analysis.[284] This measure showed to be cost-saving (saving money in the long run by creating future reductions in health expenditures) in all countries included in the analysis. Food labelling was also cost-saving in many countries. Cost-effectiveness ratios considering cost per year of healthy life gained were very favorable for food advertising regulation and mass media campaigns and favorable for physician counselling. The effects of physician counselling were much greater in countries in which people had a higher access to primary health care. School-based interventions were not cost-effective in the short-term, but they approached the cost-effectiveness of measures targeting adults during longer periods of time. The analysis also found that a multiple-intervention strategy was associated with greater health gains and cost-effectiveness.[284] This study indicates the importance of primary interventions in reducing the burden of diseases (including cancer) related to excess body weight, physical inactivity, and unhealthy diet and the cost-effectiveness of individual and multiple-strategy interventions.

4.5. Monitoring for policy guidance: cancer registries and vital registration

An important factor to determine priorities and develop and assess the success of cancer control programs is the availability of reliable cancer surveillance data. This information comes from cancer registries and vital registration.

All cancer registries collect basic information on cancer incidence, such as patient age and cancer type. Some cancer registries also collect more detailed data, including data on stage at diagnosis, type of treatment received, and survival. There are variations in the quality of collected information and coverage of population-based cancer registries (nationwide versus regional coverage) across countries. No established cancer registries exist in several countries in sub-Saharan Africa and Central Asia (Figure 4.10).

Figure 4.10. Status of population-based cancer registries and percent of regional population covered by high-quality registration, 2013
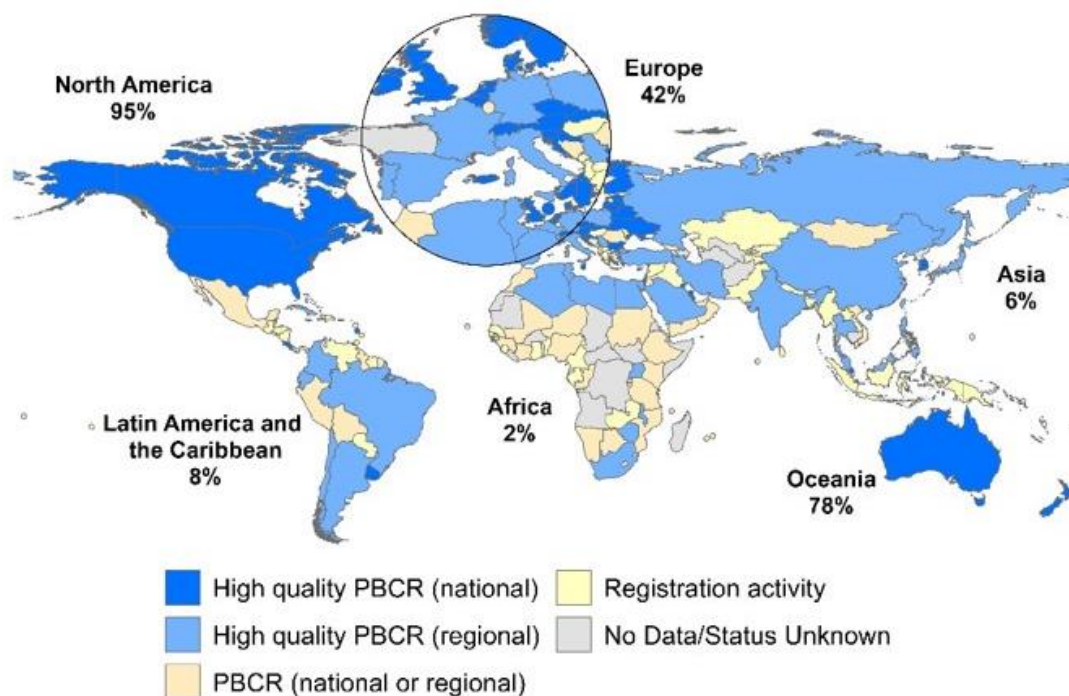
Source: The Cancer Atlas, second edition

Cancer death data come from a country's vital registration system. Like cancer registries, there is wide variation globally in the quality and completeness of death certification. Many countries in the world, especially in Africa, the Middle East, and South-Central and South-Eastern Asia, lack vital registration (Figure 4.11). Few countries in the world have high quality complete death registration. Others have low or middle quality registration, or registration may only cover a select part of the country, often an urban area. Vital registration systems could also collect some other pieces of valuable information. Since 1998, for example, questioning about smoking history is part of the routine death notification process in South Africa.[285] This has helped researchers conduct nationwide analyses of smoking related deaths.[285]

Figure 4.11. Quality of death certification from vital registration systems and percent of population covered by high-quality complete vital registration, 2013
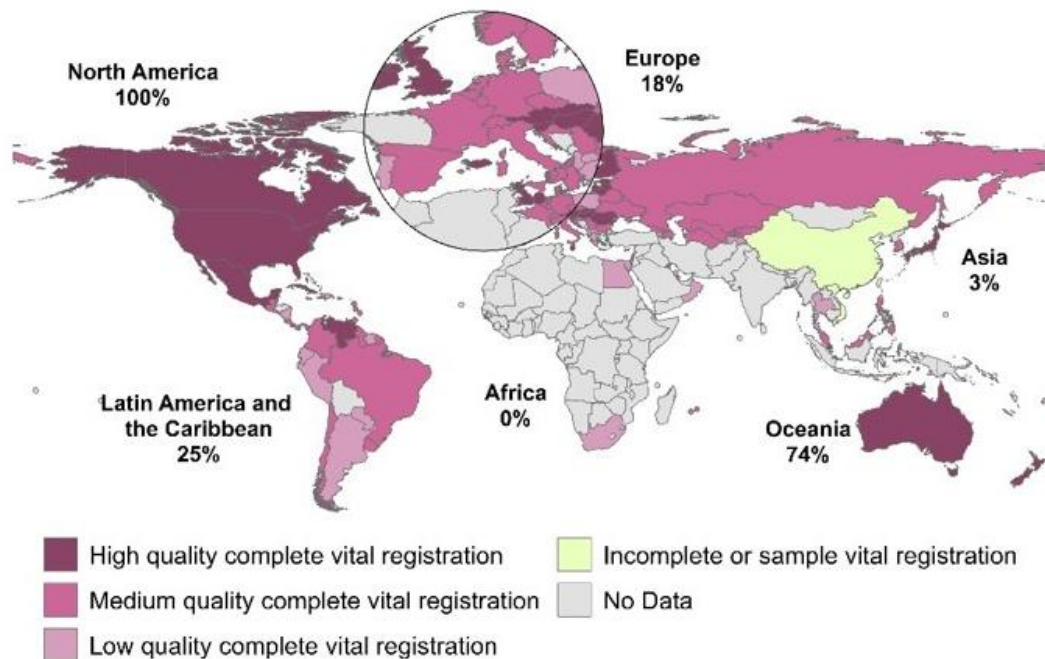
Source: The Cancer Atlas, second edition

Due to the limitations in quality and coverage of cancer registries described above, reported cancer rates in some countries may reflect the accuracy and the coverage of data collection rather than the true cancer incidence or mortality. This can affect the ability to draw comparisons between countries, as well as a country's ability to rely on their data for priority-setting. These issues are particularly challenging for LMICs, which often lack high quality cancer and death registration to accurately assess changes in disease and death as the burden shifts from infectious to non-communicable diseases. To address these issues in LMICs, IARC's Global Initiative for Cancer Registry Development has been established to support and strengthen cancer registries.

Chapter 5. Oncology infrastructure and resources

Surgery, chemotherapy, and radiotherapy are the primary means of cancer treatment. These treatment modalities are generally highly specialized and available in high-income countries, although they may also come at a high cost which can create disparities in access. In LMICs, on the other hand, these modalities may be limited or unavailable to cancer patients, or too expensive for most to afford. Investment and development is needed for a trained healthcare workforce, as well as improved access to cancer treatment and diagnostic technologies, medicines, and infrastructure.

5.1. Healthcare workers

A trained group of specialists including oncologists, oncologic surgeons, and pathologists is needed to diagnose and treat cancer, but many LMICs lack a sufficient workforce due to scarcity of local educational opportunities and/or "brain drain".[286] For instance, many countries in sub-Saharan Africa have fewer than one pathologist per million inhabitants (Figure 5.1).

Figure 5.1. Availability of pathologists in sub-Saharan Africa [287]
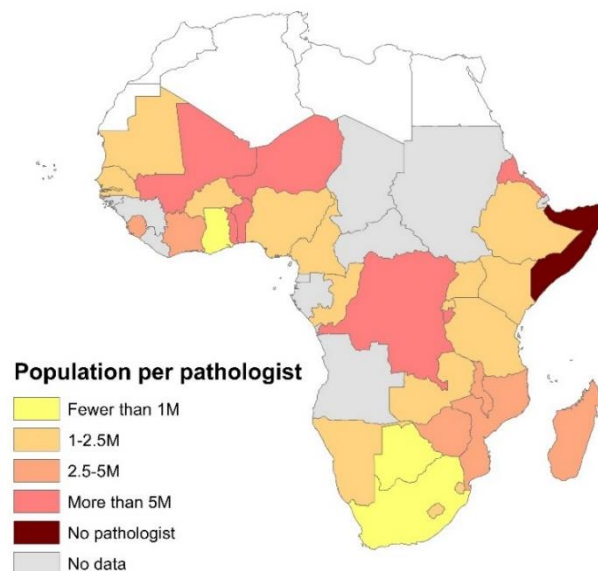
Source: Adesina A et al, Lancet Oncol 2013

Surgery plays a central role in cancer treatment in LMICs. About 80% of cancer patients are estimated to need surgery at least once during their treatment; however, less than 25% of patients will receive safe, affordable, and timely surgery.[288] In addition, while cancer is often treated with surgery for curative or palliative purposes in the absence of radiotherapy or chemotherapy due to resource constraints, many LMICs lack sufficient numbers of oncologic surgeons, and surgery is often performed by a general surgeon without special training in cancer surgery.[289] When a country lacks oncologists, surgeons are also responsible for providing cancer care beyond surgery and must dispense chemotherapy.[289]

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. Through partnerships with cancer specialists in other countries, demonstration projects in several LMICs have begun to deliver cancer care for treatable cancers such as breast, cervix, and Kaposi's sarcoma through local physicians and nurses.[123] Local leadership paired with international collaboration has also led to the establishment of a cancer treatment center in Uganda as well as a pediatric cancer research network in Central America which has achieved improved survival for pediatric cancer patients.[290]

5.2 Cancer medicines

The cost of cancer medicines has skyrocketed as increasingly targeted and effective anticancer agents have been developed. The WHO List of Essential Medicines, whose selections are based on public health impact as well as relative cost-effectiveness compared to similar drugs, contains 46 cancer medicines as of 2015. While there are a number of cancer drugs on the list which can be obtained at a relatively low cost, there are also others that may be cost-prohibitive in lower-income settings. While placing a drug on the WHO List of Essential Medicines is the first step in ensuring access to these important drugs for those who need them, the Expert Committee which developed

the list acknowledged that some drugs are too expensive for equitable access, even in high-income countries, but that access should remain a top priority.[291]

5.3. Radiation therapy

In addition to a scarcity of human resources, LMICs may also lack the physical infrastructure and equipment needed to provide cancer care. For instance, radiotherapy is an important part of many cancer treatments, with about 50% of cancer patients with potential to benefit from radiotherapy during the course of their treatment;[292] however, radiotherapy is accessible to only a fraction of the patients who need it in LMICs (Figure 5.2).

Figure 5.2. Estimated radiotherapy coverage, 2014

Percent of patients needing radiotherapy that can access this treatment

< 25%   25% - 49.9%   50% - 74.9%   75% - 99.9%   100% or more   No data
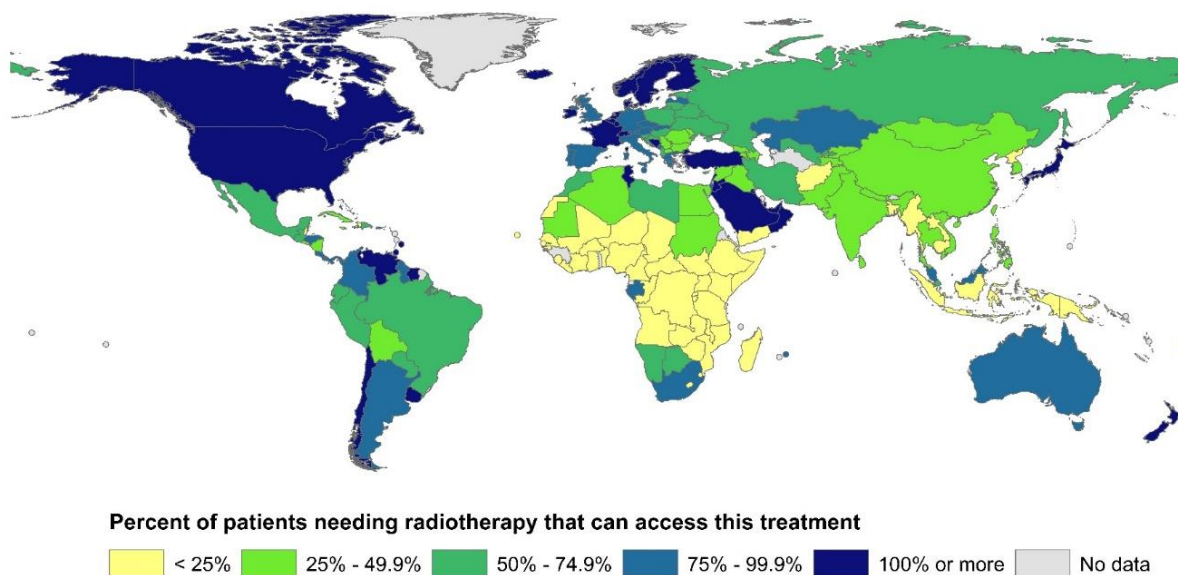
Source: The Cancer Atlas, second edition, with data from the International Atomic Energy Agency

*Countries with 100% or more coverage include some where supply exceeds need.

The situation is particularly grave for cervical cancer, which often requires radiotherapy, especially for more advanced cancers; many women in LMICs with limited or no access to radiotherapy receive no treatment at all.[75] While LMICs account for 60% of cancer cases

worldwide, they possess only 32% of available radiotherapy machines.[293] The gravest shortages of radiotherapy equipment are in Africa and South-Eastern Asia, where about 30 countries have no radiotherapy services available.[293] Furthermore, in many LMICs where radiotherapy equipment is available, it may be outdated, compromising its function and reliability.[75]

To address the insufficient availability of radiotherapy in many LMICs, the Programme of Action for Cancer Therapy (PACT) was established by the International Atomic Energy Agency (IAEA). In collaboration with the WHO, IARC, and other international cancer organizations, this program works with Ministries of Health to provide overall cancer control capacity building, including the training of the radiotherapy workforce.[294] The IAEA also established the Advisory Group on increasing access to Radiotherapy Technology in LMICs (AGaRT). This advisory group acts as a facilitator between suppliers and users of radiotherapy equipment to promote accessible and appropriate radiotherapy technologies to meet the needs of LMICs.[295]

5.4. Pain control and palliative care

About 80% of people with advanced cancer experience moderate to severe pain. Opioid analgesics such as morphine are a safe and effective means of treating moderate to severe pain in cancer patients and are included on the WHO's List of Essential Medicines.[293] However, in spite of being effective, inexpensive, and easy to use, these drugs are underutilized in LMICs, which contain 85% of the world's population but consume less than 5% of the medicinal opioids.[296] This results in a large number of cancer patients in LMICs dying with untreated pain (Figure 5.3).

Indeed, the global use of medicinal opioids increased from approximately 3 billion daily doses per year in 2001-2003 to 7.4 billion doses in 2011-2013.[296] However, this increase only happened in North America, Western and Central Europe, and Oceania, the regions in which 95.7% of global opioid use in 2011-2013 occurred.[296]

The underutilization of opioid analgesics to relieve pain in LMICs has a number of causes, including difficulty in obtaining the drugs due to legal and regulatory restrictions and supply chain issues, as well as other barriers including inadequate training of healthcare providers and concerns about diversion, addiction, and abuse.[293] However, these barriers can be overcome. In collaboration with the American Cancer Society Treat the Pain program, which works to improve access to safe use of opioid analgesics to treat cancer pain around the world, governments have taken steps to improve provision of needed pain relief. For instance, the government of Uganda now makes oral morphine available to patients at no cost.[293]

Figure 5.3. Untreated deaths in pain, 2013

Number of untreated deaths in pain due to HIV or cancer

< 1,000   1,000- 4,999   5,000 - 9,999   10,000 - 14,999   15,000 or more   No data
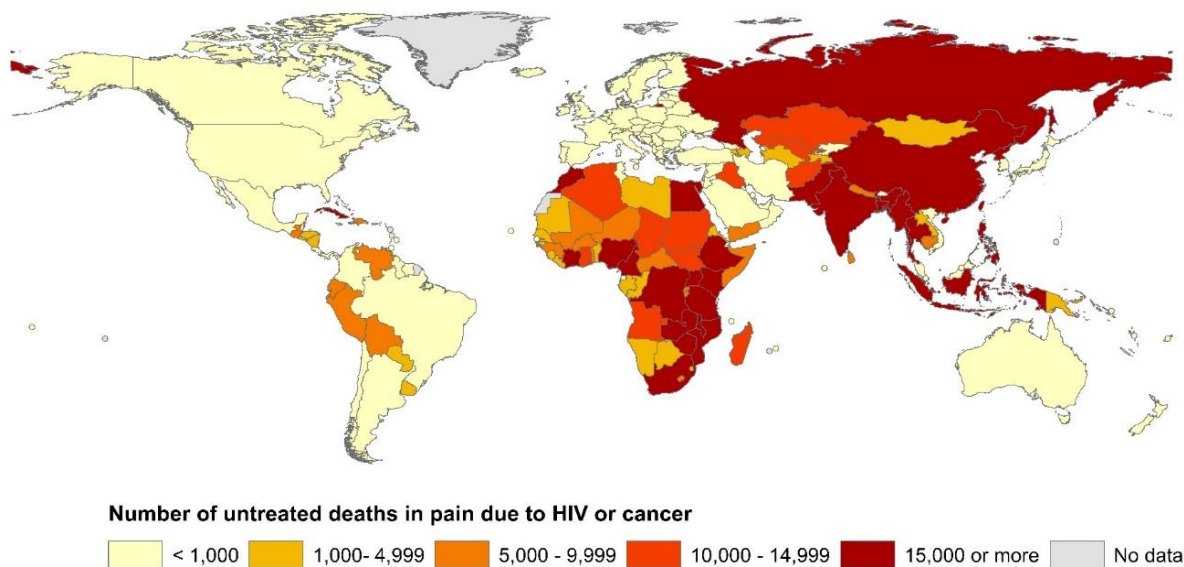
Source: Treat the Pain

5.5 Survivor care

Even after treatment has ended, cancer survivors continue to have ongoing needs for medical and psychosocial care. Cancer survivors often experience a lower quality of life than those who have not had cancer.[297] In high-income countries, the transition from active treatment to

lifetime continuation of care for cancer survivors is an area receiving active attention and development; in LMICs, however, this remains an area for increased support and improvement as the survivor population grows.[297]

5.6. Investment and support

Cancer care is an urgent need in many LMICs with a growing burden and few resources. In general, a country must possess a healthcare system with sufficiently trained staff and a necessary level of infrastructure for a cancer control plan including diagnosis and treatment to be implemented successfully.[294] For countries with few resources, prioritization of numerous cancer treatment needs as well as prevention and early detection is difficult. However, experience has shown that initial investment in select high-yield areas can be leveraged into development of complementary areas in the future; for instance, investment in radiotherapy services leads to a general strengthening of health systems and the workforce which can then be applied to other areas, such as diagnostics.[294] Treatment may seem the most pressing priority to address the needs of today's cancer patients, but prevention and early detection must also be addressed.

While the cancer control needs of LMICs may seem daunting, past experience with other diseases like HIV, tuberculosis, and malaria have shown that it is possible to harness resources and make a substantial impact, even in the face of a multifaceted disease requiring significant investment and complex interventions.[123] Partnerships between global investments in cancer treatment in LMICs will accomplish several goals simultaneously: address the immediate need for treatment; strength health systems; and ameliorate the global inequity in cancer treatment.[123] With a global commitment to action and investment, cancer treatment and control is possible.

Chapter 6. Research

While enormous progress in cancer control has been brought about by discoveries in cancer research, much work remains. The areas of prevention and cancer control in LMICs are particularly understudied.

Many experts agree that the solution to cancer lies in prevention rather than cure;[298] however, prevention has not been a global research priority. Prevention research makes up less than 5% of total cancer research funding while research is primarily focused on cancer biology and treatment, especially medicines (Figure 6.1).[299] While this work has yielded huge gains in terms of cancer treatment, prevention and other cancer research topics have been left behind. In addition, all types of research from prevention to treatment are hindered by a lack of sufficient implementation research, which applies new scientific findings in a real-world setting to assess impact. This research gap between scientific discoveries and their application to improve outcomes must be addressed to accelerate progress worldwide.

Figure 6.1. Percent of cancer research funding allocated by Common Scientific Outline category in Europe, 2002-2003 [300]
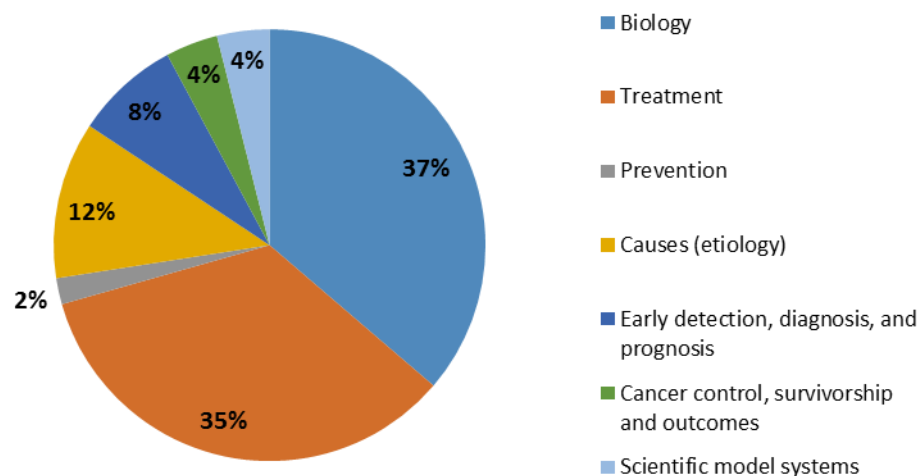
Currently, prevention and implementation research on cervical cancer screening is taking place worldwide. It is known that screening and removal of precancerous lesions of the cervix can prevent cervical cancer. However, cervical screening using the earliest established method, the Pap test, has been difficult to conduct in LMICs due to the infrastructure required. New screening tests have been developed which may make cervical cancer screening more accessible in LMICs, such as visual inspection with acetic acid (VIA) and HPV testing (see Section 2.2.2.3).[74] Studies assessing the feasibility and impact of these methods in LMICs are ongoing.

As cancer research has been primarily conducted in and focused on high-income countries, there are many unmet needs for cancer research in LMICs. Research in LMICs also remains underfunded, with about 3% of global cancer research funding going towards projects relevant to LMICs.[301] As mentioned previously, prevention research receives a small fraction of that funding. In addition to prevention, more research is needed on ways to apply effective cancer treatments that meet the needs of LMICs. The use of the newest cancer technologies or drugs may not be feasible in these countries due to cost and infrastructure requirements, but there are already available drugs and technologies which could be adapted in a cost-effective manner to provide effective treatment options in LMICs.

Scientists are investigating ways to develop and apply existing technologies and treatments to improve outcomes for women with breast cancer in LMICs. There are affordable treatments available for breast cancer, even in LMICs, through basic surgery, radiation therapy, and low-cost generic drugs. However, there are barriers to the use of these treatments in LMICs which must first be overcome. For example, the estrogen receptor (ER) status of the tumor must be ascertained in order for the appropriate treatment to be applied. In many countries, however, the cost of tissue

biopsy supplies and diagnostic tests is prohibitive. Research is ongoing to develop cost-effective

methods to sample tissue and determine ER status in LMICs and limited-resource settings.[74]

Conclusion

The burden of cancer among women is high in both HICs and LMICs, although the distribution of most common cancers differs. This burden is expected to increase as populations grow and age and as the prevalence of cancer risk factors increases in some countries, especially in LMICs. The costs of cancer are considerable and even catastrophic in HICs and LMICs alike. However, this burden of disease, loss of life, and economic hardship is not inevitable. All of the most common cancers among women worldwide, including lung, breast, cervix, liver, and colorectum, have known means of prevention and/or early detection which can be applied to reduce incidence and mortality. Furthermore, lung cancer and cervical cancer, two of the top four cancers in women worldwide, have several proven prevention measures. These two cancers combined represent about 20% of all cancer deaths among women. Many of these deaths could be prevented through effective tobacco control, vaccination, and screening activities.

There are a number of effective cancer control measures available to countries of all resource levels. Many of these measures are extremely cost-effective given the lives saved for the cost of the intervention, especially in the case of vaccination. To prevent cancer in the future, countries must prioritize policies to reduce known cancer risk factors and make prevention accessible to all. For those who have cancer today, effective treatments and palliative care are also needed. In addition to these needs, cancer surveillance and research for prevention and treatment are indispensable for the setting of cancer control priorities and for determining the most effective interventions and treatments in a given context. For LMICs, all of these activities may require support and commitment from the global community.

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