Chapter 16

Cancer in Low- and Middle-Income Countries: An Economic Overview

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INTRODUCTION

Health care is informed first and foremost by scientific and medical understanding of how to treat and prevent disease. Economics can, however, provide useful insights to inform policy in the design and implementation of the systems to provide health care, as well as in the process of prioritizing interventions to make the best use of scarce resources. Treating a single cancer patient may require the coordination of many inputs and may cost tens or even hundreds of thousands of dollars in high-income countries (HICs). Ongoing population cancer screening and early detection also require considerable coordination, including treatment for cases detected, and costs. Finally, although knowledge of cancer prevention is inadequate, prevention can be a costly endeavor—as demonstrated by the large sums spent on behavior change promotion (such as smoking cessation) or on vaccines to prevent cancer, such as against human papilloma virus to prevent cervical cancer and hepatitis B virus to prevent liver cancer—and economics can be informative.

The second section of this chapter reviews how the availability of resources for cancer care varies by economic status, using the World Bank's categories of low-income countries (LICs), middle-income countries (MICs) (comprising lower-middle-income countries and upper-middle-income countries), and HICs. At the same time, economy is not destiny. Countries at the same level of economic development differ because other factors intervene. Urbanization affects the patterns of cancer and the ability to access care. Local champions, governmental political leadership, and international partnerships can all loosen the constraints of local economic resources. Conversely, some countries are underachievers in cancer care despite their income level, perhaps because of leadership failures.

The third section reviews the cost-effectiveness of interventions for cancer care, where care is here defined to include prevention. The cost-effectiveness of interventions has been well studied in HICs, but much less so in low- and middle-income countries (LMICs). This section summarizes the literature on the economics of cancer care in LMICs; the section also draws on the literature from HICs, particularly for cancer treatment, in areas where reliable studies for LMICs are particularly scarce. It may be possible to make inferences for one country using results from another country; the validity of these inferences rises with the extent of the similarities in the two countries. Where possible, we separate out the findings for high-income economies in Asia, since they are likely to be more relevant for LMICs in this region than the results from North America or Western Europe.

We use the resource grouping suggested by Anderson and others (see chapter 3) for the Breast Health Global

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Initiative and apply this to other cancers. In this framework, facility resource environments fall into four categories of resource availability:

- Basic
- Limited
- Enhanced
- Maximal

These categories are correlated with the World Bank income groupings. LICs have a preponderance of Basic facilities, rural areas in MICs have more facilities with Limited capabilities, urban areas in MICs have more facilities with Enhanced capabilities, and much of the population in HICs has access to facilities with Maximal capabilities. The implications for the availability of resources specific to cancer care are described. This section requires some interpolation on the authors' part because of the paucity of previous work in the area and is subject to further validation by experts.

The fourth and final section contains conclusions, consisting of summary recommendations of packages of cancer care appropriate for each of the four resource environments, as well as priority areas where further research is required. The appropriateness of a package is defined by feasibility (those resources can be expected to exist or could exist with reasonable investments) and by likely cost-effectiveness (within the limits of available data). Although there are internationally validated resource-specific care guidelines for breast cancer (the Breast Health Global Initiative), no such guidelines are available as yet for other cancers. The packages presented here have been validated in consultation with the chapter authors of this volume (chapters 3 through 8), but need to be further refined by expert consultation.

AVAILABILITY OF CANCER CARE RESOURCES ACROSS COUNTRIES

Patterns of cancer vary across countries of different income levels (chapter 2 in this volume). Countries also have different capabilities for cancer care, depending on resource availability. Some of the resources for cancer care are specific to individual cancers, for example, the availability of a specific drug or test kit. Other resources are specific to cancer in general, for example, radiation therapy or the need for specialized medical personnel trained in oncology. Still others are not specific to cancer but affect many kinds of medical care, including imaging facilities, surgical facilities, pathology, and laboratory medicine services. Finally, there are broader factors that affect health care generally, such as the availability of health insurance (public, private, or mixed) and general administrative capability for the requisite health care systems.

LMICs generally have inadequate resources for health care, which conditions what is available specifically for cancer care and, hence, mortality rates. From a policy perspective, it is important to identify the priorities for investment to make maximum health gains with the available budgetary resources. We use cost-effectiveness analysis to provide some guidelines, for areas where additional recurrent expenditures would benefit care (such as buying additional drugs) and for areas where large investments in fixed costs are required (such as setting up a specialized cancer hospital).

Some resource constraints can be overcome. Even low-income Sub-Saharan African countries can acquire and maintain radiation facilities, although ensuring access for patients from remote rural areas may be difficult. It is more challenging, however, to advocate treatments that require sophisticated pathology and laboratory facilities. Such facilities are important for a wide range of medical conditions, for which cancer forms only a small percent, and they require a much larger effort and investment to set up and maintain, particularly the training of skilled personnel. It may be completely infeasible in such countries to consider certain types of organized screening if no insurance system is in place to finance the screening costs, much less the treatment of the cases diagnosed.

Table 16.1 provides examples of availability, by income grouping, of some specific resources relevant to cancer treatment; each resource is discussed in turn. Information about the availability of radiation therapy and cancer registries is available elsewhere (and not included in the table); quantitative data on the availability of skilled personnel and laboratories are not easily obtained.

Surgery

Surgery is the cornerstone of treatment for many solid tumors. The level of surgical skill and associated resources required varies by type of cancer. Surgery for earlier stage colon cancer or mastectomy for early-stage breast cancer can be undertaken at reasonably well-equipped first-level hospitals. More sophisticated facilities and skills are required for such procedures as breast-conserving surgery and rectal surgery. Surgery for certain precancerous conditions may be possible at lower-level facilities; cryotherapy for cervical cancer, for example, can be undertaken in clinics. Table 16.1 shows that HICs have more than 12 times as many operating

Table 16.1 Resource Availability Affecting Cancer Care by Country Income Groups

Resource	Low-income countries	Lower-middle-income countries	Upper-middle-income countries	High-income countries
Surgical facilities per 1,000 population,[a] 2007–08	1.3	4.7	9.9	16.4
Out-of-pocket health expenditure (% of health expenditures),[b] 2011	48.1	52.8	33.3	13.7
Availability of tamoxifen (% of countries where it is generally available, according to knowledgeable respondents),[c,d] 2010	34	53	80	85
Availability of oral morphine (% of countries where it is generally available, according to knowledgeable respondents),[c,d] 2010	27	28	57	81
Income range,[e] 2012 (US$)	1,036 and below	1,036–4,087	4,087–12,615	12,616 and above

a. Funk and others 2010.
b. World Bank 2013.
c. WHO 2012.
d. The question asked whether the medication was generally available in the public sector.
e. World Bank 2013.

theaters per capita as LICs (chapter 13 in this volume). Countries may face difficult choices as to how much surgical capacity to utilize for palliation for patients for whom there is no chance of cure, compared with those for whom there is the possibility of cure.

Radiotherapy

Radiotherapy is a key to improving survival for certain cancers. In Afghanistan, Iraq, and Sub-Saharan Africa, 25 countries lack any radiation unit; other countries have one unit per five million people (IAEA 2013). Clearly, the radiation unit alone is not the only constraint; sufficient trained staff members are also required. Not surprisingly, greater availability of radiotherapy is correlated with country income. Low-income countries can provide radiotherapy, but the main issue is that the capacity in many countries is completely insufficient to meet the need. Typically, facilities need, at a minimum, the Limited level of resources to be able to provide radiotherapy.

Medications

Pharmaceuticals of various kinds are vital to improve cancer survival rates, yet country income is associated with the availability of these agents. Access to tamoxifen for breast cancer is limited in LICs, as is access to pain control using oral morphine (table 16.1, using survey data from WHO 2012). The case is similar for chemotherapy agents, although no quantitative data were readily available. The budget constraints in LICs and rural areas of MICs often mean that these areas can only afford the lowest cost (usually older, off-patent) regimens. In addition to the cost of the agents, chemotherapy requires multiple visits to a health facility each month to obtain the supporting blood chemistry. Facilities need the Limited level of resources to support chemotherapy, effectively restricting its use to MICs and HICs.

Some effective but modest-cost cancer medications should be available, even from Basic level facilities. As long as a single laboratory test can be undertaken per patient to determine hormone receptor status, tamoxifen can be used, even in rural areas and LICs. Pain control medication, including morphine, should be available in all environments as long as access can be controlled.

Laboratories

Laboratories are an essential component of screening, diagnosis, and treatment options. They are required for rapid, accurate results from cytology or biopsies, or from the analysis of blood chemistry for chemotherapy. These services are typically not available in Basic, or even Limited, facilities. Although it is possible to send specimens collected from rural residents to a major city, the results are often not obtained in a sufficiently timely manner to provide optimal treatment. Hence, treatments involving extensive laboratory support are often not feasible in settings without facilities with Enhanced resources, as in urban areas of MICs (see Fleming in DCP3 volume 9, *Disease Control Priorities*).

Cancer Registries

Cancer registries, which form the basis for understanding and documenting patterns of cancer, are a basic tool in health care service provision. In LMICs, the percentage of the population covered by a high-quality registry, such as those in the International Agency for Research on Cancer's series on Cancer Incidence in Five Continents (Curado and others 2007), is in the single digits; this level rises to double digits in Europe; it is 80 percent or more only in Australia, New Zealand, and North America. Although it is not essential to have 100 percent population coverage, country planning and policy setting are much more difficult in the absence of a cancer registry of reasonable quality that covers at least one region.

Skilled Medical Personnel

The lack of adequate numbers of skilled medical personnel in LICs affects the ability to screen for, as well as to treat, cancer. LICs have few oncologists and oncology nurses, which limits treatment ability. Although some of the tests involved in cancer screening are often deceptively low-technology interventions (for example, Pap smears, clinical breast exams, and fecal occult blood tests), the organizational skills and infrastructure to conduct them successfully at scale and ensure appropriate referral make screening a high-technology intervention. Accordingly, organized screening programs become feasible in urban areas of MICs. Opportunistic screening, however, can occur in countries at all levels, provided that the screening test involved is not too demanding; clinical breast examination, visual inspection with acetic acid of the cervix, and the rapid DNA test for human papillomavirus (HPV) in low-resource environments are all possibilities. Campaign-style screening has been successfully used in LMICs, for example, in the Arab Republic of Egypt for breast cancer and in India for oral cancer; a rapid DNA test for cervical cancer is being piloted in low-resource provinces in China. In a campaign, the effort is made to screen a large number of the vulnerable groups in a short period of time, sometimes in local health facilities and sometimes using outreach, for example, using mobile facilities.

Health Insurance

Health insurance conditions access to all services, including treatment and screening. Individuals, who often underinvest in preventive health measures, may not see the value of paying for screening tests, particularly if they cannot afford treatment if they are subsequently diagnosed. The proportion of the population covered by health insurance typically increases with the level of development. In the poorer countries, only those people working in the formal sector or for the government may be covered; coverage in rural areas is minimal. Out-of-pocket spending on health constituted 48.1 percent of health expenditures in LICs, 52.8 percent in lower-middle income countries, 33.3 percent in upper-middle income countries, and only 13.7 percent in HICs (table 16.1, using data for the most recent years available from World Bank 2013). Expansion of insurance coverage in Mexico since 2003 through Seguro Popular—the scheme that covers those working outside the formal sector—was accompanied by an increase in coverage of cervical cancer screening and a reduction in the proportion of those abandoning breast cancer treatment (Knaul and others 2012). Chapter 17 elaborates further on the role of health financing in cancer care.

Although the importance of country resource levels for the inputs required for different aspects of cancer care has been documented, some countries underperform despite relatively high levels of income. The dislocation of public health systems in the Russian Federation following the economic system change, combined with adverse risk factors that include the relatively high consumption of fat, tobacco, and alcohol, is associated with high rates of incidence as well as overall cancer mortality. For example, 25 percent of the cases of colon cancer are diagnosed at stage 4 and 33 percent of newly diagnosed patients die within a year of diagnosis (Avksentyeva 2010). Many of those diagnosed are not eligible to receive reimbursement for drugs; of those who are eligible, drug supply problems inhibit the success of treatment. A cancer registry has existed since 1939 and, in theory, screening programs exist for at least five cancers. In practice, however, the lack of resourcing and lack of political will are associated with poor outcomes in cancer care (Avksentyeva 2010).

International Partnerships

Local champions can enable countries to outperform others at similar income levels. Local champions—key individuals willing to exert their influence in advocacy and/or leadership—can draw on substantial international resources that can make a difference, whether through partnership with a single other country or hospital or through membership in international networks. Partnerships have been used extensively for pediatric cancer in particular (Sloan and Gelband 2007, chapter 7). Although international financial resources can be important in saving lives, such as the radiation facilities provided by the International Atomic Energy Authority (IAEA) to selected Sub-Saharan African countries, the true value of these resources lies in access to

expertise and support for developing guidelines and systems.

Cancer care works best in the context of a national cancer plan, and political leadership and the will to provide the funding for the plan are keys. The World Health Organization reports that, although increasing numbers of countries surveyed have developed cancer plans over the past decade, many countries still have not dedicated resources to fund these plans (WHO 2012).

The role of partnerships with or membership in international networks matters at all levels, including the following examples:

- **For clinicians:** World Endoscopy Society, http://www.worldendo.org
- **For guideline-setting:** Breast Health Global Initiative, http://portal.bhgi.org/Pages/Default.aspx or Asia Pacific Working Group on Colorectal Cancer
- **For screening:** International Cancer Screening Network, http://appliedresearch.gov.icsn
- **For training:** IAEA's support of radiation personnel training in eight LICs and MICs through its Programme of Action for Cancer Therapy model demonstration sites project, http://cancer.iaea.org/pmds.asp

Partnerships between institutions, such as twinning arrangements between cancer hospitals, serve a similar function.

COST-EFFECTIVENESS

Cost-Effectiveness Methods

Cost-effectiveness methods are described in standard texts (such as Drummond and others 2005); these methods have been applied widely in LMICs for infectious disease, for example, where there are large flows of international assistance. These methods have been much less well used for cancer interventions in LMICs, with the exception of vaccines for hepatitis B (HBV) and HPV and new DNA tests for HPV.

For this volume, a systematic literature search was undertaken to identify studies from LMICs for all aspects of care for six cancers; the literature on tobacco control is addressed separately in chapter 10. The search covered English language articles contained in PubMed and EconLit from 2000 to 2013. The detailed search terms, inclusion criteria, and full table of results are available in annex 16A. The articles are also graded for quality using a checklist based on Drummond and others (2005).

Fewer than 15 articles were found for the cost-effectiveness of interventions for breast, colon, liver, oral, and pediatric cancers in LMICs—including four for HBV. In contrast, 16 articles were found that satisfied the inclusion criteria for the cost-effectiveness of vaccination and/or screening for cervical cancer. This result may reflect the fact that international funding has been available to investigate and promote the vaccines, principally through Gavi, the Vaccine Alliance. An additional six articles for breast and colon cancer were found for HICs in Asia. These six were included, since they may provide some guidance for MICs in this region.

Another reason that may explain the thin literature is that there are very few articles (whether for LMICs or HICs) on the cost-effectiveness of surgery, the cornerstone of cancer treatment. The effectiveness of basic surgery was established long before economic cost-effectiveness methods were developed and surgery became "usual care."

Given the lack of cost-effectiveness data for LMICs, the literature from other countries might prove helpful. The literature from HICs may provide guidance and the literature from HICs in Asia may be useful for other countries in the region. The cost-effectiveness literature has to be used cautiously, since the greater the difference in context (including disease patterns, prevalence, usual care alternatives, costs, and comorbidities), the less reliable the comparison is likely to be. We utilized cost-effectiveness findings from HICs from the web appendix of Greenberg and others (2010). Greenberg and colleagues undertook a systematic review of interventions for several cancers in HICs. Their approach yielded some useful studies, primarily for breast cancer, that have relevance for LMICs.

In tables 16.3 through 16.8, we indicate generally whether an intervention is "very cost-effective," "cost-effective," or "not cost-effective" in a given study. A few countries have set their own decision criteria, for example, the National Institute for Health and Care Excellence in the United Kingdom. In a comprehensive study of cost-effectiveness in Australia, Vos and others (2010) categorize interventions that cost less than US$10,000 per quality-adjusted life year (QALY) as very cost-effective; those interventions between US$10,000 and US$50,000 per QALY are cost-effective; and those over $50,000 per QALY are not cost-effective. A similar limit (US$50,000) is often used in the United States as the dividing line between what is and is not cost-effective. For countries that have not established their own threshold, the Commission on Macroeconomics and Health (2001) suggests that interventions costing less than one times the per capita gross national product per DALY averted are very cost-effective and those between one and three times per capita gross national product are cost-effective.

What is very cost-effective in HICs might merit consideration in LICs and what is cost-effective in HICs might be considered in MICs. This approach presupposes that the underlying model is similar, namely, the interventions are similar and the "no intervention" or "standard care" alternative scenarios are also similar, as are other key parameters. Country-specific data would be better in the future to guide policy.

The results summarized in the following section draw on the cost-effectiveness analyses in other chapters of this volume: Anderson and others (chapter 3), Denny and others (chapter 4), Sankaranarayanan and others (chapter 5), Rabeneck and others (chapter 6), Gupta and others (chapter 7), and Gelband and others (chapter 8). These analyses, in turn, utilize systematic literature surveys for the LMICs described in annex 16A.

Cost-Effectiveness Results

Table 16.2 summarizes the specific resources likely to be available at each of the four facility environments: Basic, Limited, Enhanced, and Maximal. Cancer care feasible in facilities with Basic resources is likely to be the norm in LICs, care feasible in facilities with Limited resources predominates for the rural population in MICs, care feasible in facilities with Enhanced resources is likely to be available for urban populations in MICs, and facilities with Maximal resources are broadly available only in some HICs. Almost all countries, irrespective of income, have some facilities with Maximal resources to which a minority of the population has access or can be referred.

These resource categories are used as an organizing framework for five of the six major cancers covered. The exception is pediatric cancer, which has a similar ranking of feasibility but is determined differently. Patients with pediatric cancers, which are relatively rare, are often referred to specialized facilities. Specialized facilities with the least expertise can successfully treat a limited range of pediatric cancers; the range increases as experience grows.

Tables 16.3 through 16.8 summarize by resource environment the feasibility of various interventions for the six cancers considered: breast, cervical, colorectal, liver, oral, and pediatric. The cost-effectiveness evidence is provided where it exists, along with the country context in which the data were obtained. For surgery, the cost-effectiveness data are virtually nonexistent, even for HICs, except for new techniques, such as laparoscopic surgery. Data are most abundant for pharmaceuticals,

Table 16.2 Cancer Care Tools in Four Resource Environments

Basic	• Resources for organized screening and treatment of precancer conditions do not exist; vertical programs, such as mobile services for screen-and-treat options in one or two visits, may be feasible. • Basic surgery is available but in limited supply; specialized surgery skills may be available only by referral to another facility. • Radiation therapy is very scarce or unavailable. • Chemotherapy is not feasible because of the lack of laboratory facilities for required blood work.
Limited	• Mobile screening units are an option; rapid DNA testing is possible, if cost is sufficiently low. • Availability of surgery is better but still limited. • Radiation therapy is scarce and patients may need to travel long distances for access. • Chemotherapy may be possible, using off-patent drugs and "classical" therapies; new techniques, such as metronomics, may be considered. Laboratory facilities are limited. • Limited treatment of precancer conditions occurs at lower-level health facilities and first-level hospitals.
Enhanced	• Organized screening can be considered, along with treatment of precancer conditions at facilities at different levels. • Radiotherapy and surgery are widely available. • Chemotherapy is possible and newer generations of drugs can be considered, although typically not those still on-patent. Laboratory facilities are available on site to support use of chemotherapy. • The most advanced hospitals can offer most of the care options available in high-income countries, but budgets are insufficient to make such care broadly available.
Maximal	• State-of-the-art treatment is available; however, even in high-income countries, health budgets still require hard choices, and private insurers or public systems may carefully ration access to the most costly therapies.

Note: Resource typology based on Breast Health Global Initiative (Anderson and others, chapter 3). Most facilities in low-income countries have Basic levels of resources, facilities in rural areas in middle-income countries generally have Limited resources, most facilities in urban areas of middle-income countries have Enhanced resources, and facilities with Maximal resources are widespread only in some industrial countries.

since these data are often required in HICs as part of the approval process for new drugs.

Interventions listed as options in the Basic environment are limited to those that the evidence suggests are very cost-effective in HICS or cost-effective in LMICs. The range of options is broadened a little in the Limited environment to include items that are "close to being very cost-effective" in HICs, or "possibly cost-effective in LMICs," and the greater feasibility of radiation and chemotherapy options broadens the range for consideration.

In the Enhanced environment, more interventions are feasible because of the greater availability of resources and because a larger percent of the population is located in urban areas and able to undertake treatments that require regular visits, for example, for preoperative radiotherapy, or require more intensive follow-up, for example, for organized screening. Options that are not recommended in this environment are those that are not cost-effective even in HICs.

Finally, in the Maximal environment, an even broader range of options is available, some of which are cost-effective in those environments. Those that are currently not cost-effective—for example, some new chemotherapy agents—may well eventually become cost-effective once they no longer have patent protection.

CONCLUSIONS

Feasibility and cost-effectiveness data suggest that cancer care can and should be expanded in LMICs. Table 16.9 summarizes the interventions, by cancer and by resource level, which are supported by feasibility and cost-effectiveness data, noting that virtually no

Table 16.3 Breast Cancer: Summary of Feasibility and Likely Cost-Effectiveness of Interventions, by Resource Level

Resource level	Intervention type	Intervention details	Cost-effectiveness (if available)
Basic	Detection	Clinical history and CBE	• CBE **cost-effective** in Ghana (Zelle and others 2012)
	Treatment, stages I and II	Modified radical mastectomy; ovarian ablation in premenopausal (stage I) or all (stage II)	—
		Test for ER and add tamoxifen if feasible; add chemotherapy (classical CMF or AC, EC, or FAC if blood chemistry and CBC available)	• Either tamoxifen or chemotherapy **very cost-effective** after surgery in United states for younger women (Hillner and Smith 1991; Malin and others 2002) • Tamoxifen **very cost-effective** in the Republic of Korea (Yang and others 2010)
	Treatment, locally advanced	Same options as for stages I and II; add preoperative chemotherapy if resources available	—
Limited	Detection	CBE with diagnostic ultrasound or mammography in target group	• Single lifetime CBE **very cost-effective** in India • Every three years or every five years **cost-effective** (Okonkwo and others 2008) • Annual CBE **very cost-effective** in Vietnam (Nguyen and others 2013)
	Treatment, stages I and II	Breast-conserving surgery; add irradiation of chest wall for high-risk stage II	• Breast-conserving surgery versus modified radical mastectomy **cost-effective** in United States (Norum and others 1997)
		Chemotherapy (classical CMF or AC, EC, or FAC if blood chemistry and CBC available)	• **Very cost-effective** after surgery in United States for younger women (Hillner and Smith 1991; Malin and others 2002) • **Cost-effective** in United States for older women (Desch and others 1993; Hillner, Smith, and Desch 1993; Malin and others 2002; Naeim and Keeler 2005)
	Treatment, locally advanced	Same options as for stages I and II; add irradiation of chest wall	—

table continues next page

Table 16.3 Breast Cancer: Summary of Feasibility and Likely Cost-Effectiveness of Interventions, by Resource Level (continued)

Resource level	Intervention type	Intervention details	Cost-effectiveness (if available)
Enhanced	Detection	Mammography every two years for women ages 55–69 years; every 12–18 months for women ages 40–54 years	• Mammography every year for women over age 50 years and every two years in high-risk women ages 40–49 years **cost-effective** in Mexico (Salomon and others 2012)
	Treatment, stages I and II	Breast-conserving surgery and whole-breast irradiation	—
		Aromatase inhibitors or LH-RH agonists (hormones) and taxanes (chemo) to replace tamoxifen and classical chemo, respectively	• Using raloxifene (taxane) instead of tamoxifen **cost-effective** for some women in United States (Armstrong and others 2001) • Using letrozole instead of tamoxifen **cost-effective** in United States (Delea and others 2007). Using anastrozole (aromatase) instead of tamoxifen **cost-effective** in Brazil (Fonseca, Araújo, and Saad 2009); **very cost-effective** in United States (Moeremans and others 2006); **not cost-effective** in Spain (Gil and others 2006)
	Treatment, locally advanced	Add trastuzumab for HER2/neu+ disease	• Short-course trastuzumab **very cost-effective** in United States compared with usual treatment for women with HER2+ disease (Malin and others 2002). Using letrozole (aromatase) instead of tamoxifen **very cost-effective** in United States for advanced disease (Dranitsaris, Verma, and Trudeau 2003; Karnon and others 2003)
Maximal	Detection	Mammography every year for women ages 40 years and older	• Mammography every three years in the Republic of Korea for women ages 45–65 years **not cost-effective** (Lee and others 2009) • Mammography every two years in Hong Kong SAR, China, for women ages 40–69 years **cost-effective** (Wong and others 2007)
	Treatment, stages I and II	Add trastuzumab for HER2/neu+ disease	• **Very cost-effective** in Singapore (de Lima Lopes 2011) • **Cost-effective** in Belgium (van Vlaenderen and others 2009), Canada (Hedden and others 2012), Italy and United States (Liberato and others 2007), Netherlands (Essers and others 2010)
	Treatment, stages I and II, locally advanced	Add growth factors and dose-dense chemotherapy	• Growth factors **cost-effective** in Japan for high-risk early cancer (Ishiguro and others 2010) • **Not cost-effective** in United States for early stage (Ramsey and others 2009)
	Metastatic	Use bevacizumab (chemo), fulvestrant (hormone), and growth factors (supportive)	• Bevacizumab **not cost-effective** in United Kingdom (Rodgers and others 2011), United States (Montero and others 2012) • Fulvestrant **cost-effective** in United Kingdom (Cameron and others 2008)

Note: See individual studies for further details, such as age and hormone status, for which cost-effectiveness results were obtained. Screening and treatment typically become less cost-effective for women ages 60 years and older. Resource typology based on Breast Health Global Initiative (Anderson and others, chapter 3). Most facilities in low-income countries have Basic levels of resources, facilities in rural areas in middle-income countries generally have Limited resources, most facilities in urban areas of middle-income countries have Enhanced resources, and facilities with Maximal resources are widespread only in some industrial countries. The table is cumulative, for example, treatments that are feasible in facilities with Basic environments are also feasible in facilities with Limited, Enhanced, and Maximal resources. AC = doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan); CBC = complete blood count; CBE = clinical breast examination; CMF = cyclophosphamide, methotrexate, and fluorouracil; EC = epirubicin and cyclophosphamide; ER = estrogen receptor; FAC = fluorouracil, doxorubicin (Adriamycin), and cyclophosphamide (Cytoxan); LH-RH = luteinizing hormone–releasing hormone; — = not available.

cost-effectiveness data are available for surgery. The interventions provide suggestions to policy makers as to the sequence in which to add publicly funded interventions as country income increases, as part of a cancer plan.

Table 16.9 suggests that LMICs have cost-effective options in cancer control. More can be done in all countries in prevention, particularly tobacco control, and expansion of HPV vaccine and DNA testing for cervical cancer, provided that the costs can be reduced sufficiently. There are methods to reduce the risk of liver cancer. The large expansion of HBV vaccination is a success story in preventing cancer.

The cost-effectiveness results suggest that a sustained expansion of cancer treatment is appropriate in

Table 16.4 Cervical Cancer: Summary of Feasibility and Likely Cost-Effectiveness of Interventions, by Resource Level

Resource level	Intervention type	Intervention details	Cost-effectiveness (if available)
Basic	Prevention	HPV vaccination of adolescent girls	**Cost-effective** in LMICs if the following three conditions apply: 1. Cost per vaccinated girl is low enough (US$10–25): Gavi-eligible countries can likely achieve this 2. Incidence is high 3. Vaccine protection is long-lasting (chapter 4)
	Detection	VIA starting at age 35 years, one to three times per lifetime, or rapid DNA test starting at age 35 years, two or three times per lifetime, assuming cost per HPV test is less than US$10	• **Very cost-effective** (Praditsitthikorn and others 2011, Thailand) • Rapid DNA is **very cost-effective** in LMICs with screen-and-treat in single visit (Goldie and others 2005) but difficult to undertake in practice • **Cost-effective** in MICs with two visits required (Kim and others 2008; Levin and others 2010)
	Diagnosis	Colposcopy	—
	Treatment, precancer	Cryotherapy for suspicious precancerous lesions	—
	Treatment, early-stage cancer	LEEP, CKC, simple hysterectomy	—
Limited	Treatment, more advanced stage cancer	Surgery and/or radiation therapy	—
Enhanced	Screening	Cytology every two to three years, starting at time of initiation of sexual activity; DNA test 1–3 times per lifetime	• Cytology may be **cost-effective** if quality control is good (Kim and others 2008) • DNA testing **cost-effective** depending on test cost, frequency of testing (Campos and others 2012)
	Prevent and screen	HPV vaccination combined with screening	Can be **cost-effective** in all countries, depending on cost per vaccinated girl and cost of screening strategy chosen (Denny and others, chapter 4)
	Treatment options	Add chemotherapy (cisplatin) where warranted	—
Maximal	Treatment options	Trachelectomy (fertility-sparing surgery), brachytherapy, intensity-modulated radiotherapy	—

Note: Resource typology based on Breast Health Global Initiative (Anderson and others, chapter 3). Most facilities in low-income countries have Basic levels of resources, facilities in rural areas in middle-income countries generally have Limited resources, most facilities in urban areas of middle-income countries have Enhanced resources, and facilities with Maximal resources are widespread only in some industrial countries. The table is cumulative, for example, treatments that are feasible in facilities with Basic environments are also feasible in facilities with Limited, Enhanced, and Maximal resources. CKC = cold knife conization; HPV = human papillomavirus; LEEP = loop electrosurgical excision procedure; LMICs = low- and middle-income countries; MICs = middle-income countries; VIA = visual inspection with acetic acid; — = not available.

Table 16.5 Colorectal Cancer: Summary of Feasibility and Cost-Effectiveness of Interventions, by Resource Level

Resource level	Intervention type	Intervention details	Cost-effectiveness (if available)
Basic	Prevention	Tax cigarettes	**Very cost-effective** for various cancers
	Detect/diagnose	Use barium enema where colonoscopy not available	—
	Treatment, stages I, II, III colon	Hemicolectomy and regional lymph node dissection	—
	Treatment, stages I, II, III rectal	Abdominal perineal resection with lymph node dissection	—
	Treatment, stage IV colorectal	Consider palliative surgery	—
Limited	Treatment, stages I and II colon	Hemicolectomy and regional lymph node dissection	—
	Treatment, stage I rectal	Abdominal perineal resection with lymph node dissection	—
	Treatment, stage III colon	Hemicolectomy and regional lymph node dissection plus adjuvant 5-fluorouracil	• Adjuvant chemotherapy **close to being very cost-effective** in United States versus no adjuvant after surgery for colorectal cancer (Nostrum and others 1997) • Adjuvant chemotherapy **close to being very cost-effective** in United States versus no adjuvant after surgery for colorectal cancer, colon cancer (Smith and others 1993)
	Treatment, stages II and III rectal	Abdominal perineal resection with lymph node dissection plus preoperative short course radiotherapy; add 5-fluorouracil	• Adjuvant chemotherapy **close to being very cost-effective** in United States versus no adjuvant after surgery for colorectal cancer (Nostrum and others 1997) • Preoperative radiotherapy **very cost-effective** in United States versus no preoperative radiotherapy (van den Brink and others 2004)
	Treatment, stage IV colorectal	Consider palliative surgery; consider palliative 5-fluorouracil-based chemotherapy	—
Enhanced	Detection	Organized screening (beginning with pilot)	• **Very cost-effective** in United States (gFOBT) (Pignone, Russell, and Wagner 2005) • **Cost-effective** in United States (colonoscopy) (Pignone, Russell, and Wagner 2005) • **Very cost-effective** in high-income Asia (gFOBT, sigmoidoscopy, colonoscopy) (Park, Yun, and Kwon 2005; Tsoi and others 2008; Wong, Leong, and Leong 2004; Wu and others 2006)
	Treatment, stages I and II colon	Hemicolectomy with en bloc removal of at least 12 lymph nodes	—
	Treatment, stage I rectal	Total mesorectal excision	—
	Treatment, stage III colon	Hemicolectomy plus removal of at least 12 lymph nodes plus adjuvant FOLFOX	FOLFOX **very cost-effective** in United Kingdom versus 5-fluorouracil plus leucovorin (Aballéa and others 2007)

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Table 16.5 Colorectal Cancer: Summary of Feasibility and Cost-Effectiveness of Interventions, by Resource Level (continued)

Resource level	Intervention type	Intervention details	Cost-effectiveness (if available)
	Treatment, stages II and III rectal	Total mesorectal excision; preoperative chemo-radiotherapy; capecitabine or infusional 5-fluorouracil; adjuvant FOLFOX	—
	Treatment, stage IV colorectal	Consider palliative surgery; palliative radiation; FOLFOX/FOLFIRI; possibly aggressive surgery for cure	—
Maximal	Treatment, stages I and II colon	Surgery: can use polypectomy for selected stage I cancers; consider adjuvant 5-fluorouracil or capecitabine in high-risk stage II; can consider LAC	• LAC **not cost-effective** in United States (Hayes and Hansen 2007) • **Not cost-effective** in United States for colorectal cancer (de Verteuil, Hernández, and Vale 2007)
	Treatment, stage I rectal	Total mesorectal excision	—
	Treatment, stage III colon	Hemicolectomy plus removal of at least 12 lymph nodes plus adjuvant FOLFOX	FOLFOX **very cost-effective** in United Kingdom versus 5-fluorouracil plus leucovorin (Aballéa and others 2007)
	Treatment, stages II and III rectal	Total mesorectal excision; preoperative chemo-radiotherapy; capecitabine or infusional 5-fluorouracil; adjuvant FOLFOX	—
	Treatment, stage IV colorectal	As for stage IV (Enhanced); plus biological options (bevucizumab, aflibercept; if K-Ras wild-type cetuximab, panitumumab; regorafenib)	• Cetuximab plus irinotecan versus active or best support care **not cost-effective** in United States (Starling and others 2007) • Bevucizumab plus irrotecan and 5-fluorouracil plus leucovorin versus irrotecan and 5-fluorouracil plus leucovorin **not cost-effective** in United States (Tappenden and others 2007)

Note: Resource typology based on Breast Health Global Initiative (Anderson and others 2014). Most facilities in low-income countries have Basic levels of resources, facilities in rural areas in middle-income countries generally have Limited resources, most facilities in urban areas of middle-income countries have Enhanced resources, and facilities with Maximal resources are widespread only in some industrialized countries. The table is cumulative, for example, treatments that are feasible in facilities with Basic environments are also feasible in facilities with Limited, Enhanced, and Maximal resources. FOLFIRI = folinic acid, fluorouracil, and irinotecan; FOLFOX = folinic acid, fluorouracil, and oxalipatin; gFOBT = guaiac fecal occult blood test; K-Ras = Kirsten rat sarcoma viral oncogene homolog; LAC = laparoscopically-assisted colectomy; — = not available.

Table 16.6 Liver Cancer: Summary of Feasibility and Likely Cost-Effectiveness of Interventions, by Resource Level

Resource level	Intervention type	Intervention details	Cost-effectiveness (if available)
Basic	Prevention	Hepatitis B vaccination of neonates (East and Southeast Asia); infants (Sub-Saharan Africa)	**Cost-effective/very cost-effective** in intermediate- and high-prevalence countries (Beutels 2001; Ozawa and others 2012)
		Aflatoxin reduction through better post-harvest handling and storage	**Cost-effective** in Guinea (Khlangwiset and Wu, 2010)
Limited	Prevention	Hepatitis B vaccination of infants or adolescents	**Cost-effective/very cost-effective** in intermediate- and high-prevalence countries (Beutels 2001; Ozawa and others 2012)
		Aflatoxin reduction through biocontrol (different seed strains)	**Very cost-effective** in Nigeria (Wu and Khlangwiset 2010), but validation needed; however, analysis did not take account of cost of diffusion of technology

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Table 16.6 Liver Cancer: Summary of Feasibility and Likely Cost-Effectiveness of Interventions, by Resource Level (continued)

Resource level	Intervention type	Intervention details	Cost-effectiveness (if available)
		Prevention programs for hepatitis C through reducing unsafe injections (for example, auto-disposable syringes) and screening blood donors	Using auto-disposable syringes is **very cost-effective** in India (Reid 2012)
		Prevention programs for liver flukes through education regarding food habits and hygiene	—
Enhanced	Prevention	Hepatitis B vaccination of infants, children, and adolescents	**Cost-effective** in intermediate and high-prevalence countries (Beutels 2001; Ozawa and others 2012)
	Treatment	Screening for and treatment with praziquantel for liver flukes in high-prevalence regions	—
Maximal	Prevention	Hepatitis B vaccination of adolescents	**Possibly cost-effective or not cost-effective** in low-prevalence countries (Beutels 2001)
	Treatment	Hepatitis B virus treatment with antivirals or immune system modulators	**Possibly cost-effective** in HICs (chapter 8)
	Treatment	Hepatitis C: pegylated interferon treatment plus ribavirin	**Cost-effective only in select patients** in HICs (chapter 8)
	Treatment	Various treatments of hepatocellular carcinoma or cholangiocarcinoma	**Not cost-effective** even in HICs because of poor survival even with treatment (chapter 8)

Note: Resource typology based on Breast Health Global Initiative (Anderson and others, chapter 3). Most facilities in low-income countries have Basic levels of resources, facilities in rural areas in middle-income countries generally have Limited resources, most facilities in urban areas of middle-income countries have Enhanced resources, and facilities with Maximal resources are widespread only in some industrial countries. The table is cumulative, for example, treatments that are feasible in facilities with Basic environments are also feasible in facilities with Limited, Enhanced, and Maximal resources. HICs = high-income countries; — = not available.

Table 16.7 Oral Cancer: Summary of Feasibility and Likely Cost-Effectiveness of Interventions, by Resource Level

Resource level	Intervention type	Intervention details	Cost-effectiveness (if available)
Basic	Prevention	Tobacco and alcohol taxes	**Cost-saving** (cannot be separated from impact on other cancers) (chapter 10)
	Screening	Visual screening by trained personnel (for example, dentist or nurse) of high-risk groups (known or self-declared tobacco and alcohol users) or by all at risk (for example, over 35 years of age) in high-prevalence regions; screening is sporadic rather than organized	• **Cost-effective** where prevalence is reasonably high; **very cost-effective** for screening high-risk groups (India: Subramanian and others 2009) • Cost-effective in three HICs with prevalence of 30 or more per 100,000 in men, age-adjusted population (Netherlands: van der Meij, Bezemer, and van der Waal 2002; United Kingdom: Speight and others 2006; United States: Dedhia and others 2011)
	Diagnosis	Visual inspection; biopsy; X-ray to diagnose spread	—
	Treatment	Surgery, no adjuvant treatment, for stages I, II, III; availability of surgery for oral reconstruction very limited	—
		Pain control, stage IV	

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Table 16.7 Oral Cancer: Summary of Feasibility and Likely Cost-Effectiveness of Interventions, by Resource Level (continued)

Resource level	Intervention type	Intervention details	Cost-effectiveness (if available)
Limited	Treatment	Add postoperative radiotherapy if indicated (stage II or III, depending on type and location of tumor) or radical radiotherapy instead of surgery (stage II or II, depending on type/location of tumor)	—
		Palliative radiotherapy, stage IV	
Enhanced	Screening	Organized screening is possible	**Cost-effective** (Dedhia and others 2011; Speight and others 2006; Subramanian and others 2009; van der Meij, Bezemer, and van der Waal 2002)
	Diagnosis	CT scan to confirm spread	—
	Treatment	Surgery and/or radiotherapy or brachytherapy and/or off-patent chemotherapy, stages II, III and IV, depending on type/location of tumor; reconstructive surgery possible	—
		Palliative chemotherapy, stage IV	
Maximal	Diagnosis	PET, MRI to determine spread if bone/soft tissue potentially involved; can consider chemotherapy with patent drugs	—

Note: Resource typology based on Breast Health Global Initiative (Anderson and others, chapter 3). Most facilities in low-income countries have Basic levels of resources, facilities in rural areas in middle-income countries generally have Limited resources, most facilities in urban areas of middle-income countries have Enhanced resources, and facilities with Maximal resources are widespread only in some industrialized countries. The table is cumulative, for example, treatments that are feasible in facilities with Basic environments are also feasible in facilities with Limited, Enhanced, and Maximal resources. CT = computerized tomography; HICs = high-income countries; MRI = magnetic resonance imaging; PET = positron emission tomography; — = not available.

Table 16.8 Pediatric Cancer: Summary of Likely Cost-Effectiveness of Interventions, by Experience Level

Experience level	Cancer treated	Cost-effectiveness (if available)
Center with least expertise	Burkitt lymphoma	**Very cost-effective** (Malawi: Bhakta and others 2013)
	Hodgkin lymphoma (adolescents and adults)	**Very cost-effective** (Norway: Norum and others 1996)
Center with more expertise	Wilms tumor	**Cost-effective** (Brazil: Bhakta and others 2013)
	Acute lymphoblastic leukemia	**Very cost-effective** (Netherlands: van Litsenburg and others 2011); **cost-effective** (China: Luo and others 2009)
	Intraocular retinoblastoma	—
Center with most expertise	Sarcomas, brain tumors, acute myeloid leukemia, high-risk neuroblastoma, other retinoblastomas	—

Note: Sequencing of cancer is illustrative rather than exhaustive. Feasibility of treatment of pediatric cancer does not follow the same pattern as adult cancers. Pediatric cancers are rare and many low-income countries have used the approach of treatment in specialized centers. Prevention is not an important issue (other than via hepatitis B vaccination); because incidence is very low, population-level screening is not an option. — = not available.

all LMICs. The expansion of capacity for surgery and radiation is a priority throughout. The use of tamoxifen is feasible and cost-effective for breast cancer in LICs, and newer hormone treatments can be cost-effective in MICs. In MICs, the use of classical chemotherapy regimens for breast and cervical cancer is cost-effective; in areas where Enhanced facilities predominate. Chemotherapy can be expanded to include newer regimens for breast and cervical cancers and chemotherapy regimens for colon and oral cancers.

As treatment is scaled up, screening is more important to stage-shift treatment. LICs with largely Basic

Table 16.9 Summary Recommendations Based on Feasibility and Cost-Effectiveness, by Resource Level

Cancer	Intervention by resource level
Primary prevention	
Tobacco-related	Taxation of cigarettes, legislation, regulation (ALL)
Cervical	HPV vaccine (ALL: cost-effectiveness depends on price)
Liver	• HBV vaccination integrated with expanded program for immunization (B)
	• Neonatal (L, E); adolescent (E, M)
	• Screening blood donors (E, M); reducing unsafe injections (L, E, M)
	• Education to prevent liver fluke infection (L, E, M)
	• Aflatoxin reduction: post-harvest storage (B); biocontrol (L)
Screening and detection (to stage-shift treatment)	
Breast	• Clinical breast exam (B, L)
	• Mammography (E, M)
Cervical	• Visual inspection with acetic acid (B, L)
	• Rapid DNA test and treat in two visits (L)
	• DNA test, cytology (E, M)
Colorectal	Fecal immunochemical test (E); fecal immunochemical or endoscopy (M)
Liver cancer	Screen and treat for liver flukes in high-prevalence regions (E, M)
Oral cancer	Visual inspection (L, high-prevalence countries only)
Treatment with curative intent	
Breast	• Surgery (ALL); radiation (L, E, M)
	• Hormones: tamoxifen (B, L); aromatase inhibitors, LH-RH agonists (E); fulvestrant (M)
	• Chemotherapy: CMF or AC (B); EC or FAC (L); taxanes (E); trastuzumab (E, M)
	• Growth factors (M); bevacizumab (M)
Cervical	• Surgery (ALL); trachelectomy (M)
	• Cryotherapy (B, L); radiotherapy (L, E, M); brachytherapy, intensity modulated brachytherapy (M)
	• Chemotherapy (cisplatin) (E, M)
Colorectal	• Surgery: colon (ALL); rectal (L, E, M)
	• Radiation: preoperative, rectal (L); chemo-radiotherapy preoperative, rectal (E, M)
	• Chemotherapy: classical 5-fluorouracil (L); FOLFOX (E, M)
Liver	• Antivirals or immune system modulators for hepatitis B (M)
	• Hepatitis C (M, cost-effective only in select patients)
	• Treatment of liver cancer (M, although not generally cost-effective)
Oral	Surgery (ALL); radiotherapy (L, E, M); brachytherapy (E, M); chemotherapy (E, M)
Pediatric	• Burkitt lymphoma, Hodgkin lymphoma (specialized center, least expertise)
	• Wilms tumor (specialized center, more expertise)
	• Sarcomas, brain tumors, acute myeloid leukemia, high-risk neuroblastoma (specialized center, most expertise)

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Table 16.9 Summary Recommendations Based on Feasibility and Cost-Effectiveness, by Resource Level (continued)

Cancer	Intervention by resource level
Advanced disease	
All	• Pain control (ALL) • Home or hospice care (ALL) • Palliative radiotherapy (L, E, M, as resources allow) • Palliative surgery (as resources allow) • Palliative chemotherapy (L, classical; E, next generations; M, on-patent, as resources allow) • Aggressive treatment with curative intent (M)

Note: Resource typology based on Breast Health Global Initiative (Anderson and others, chapter 3). Most facilities in low-income countries have Basic levels of resources, facilities in rural areas in middle-income countries generally have Limited resources, most facilities in urban areas of middle-income countries have Enhanced resources, and facilities with Maximal resources are widespread only in some industrial countries. Higher resource–level countries can consider any of the options from lower resource levels. The table is cumulative, for example, treatments that are feasible in facilities with Basic environments are also feasible in facilities with Limited, Enhanced, and Maximal resources. AC = doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan); ALL = all resource levels; B = Basic resource level; CMF = cyclophosphamide, methotrexate, and fluorouracil; E = Enhanced resource level; EC = epirubicin and cyclophosphamide; FAC = fluorouracil, doxorubicin (Adriamycin), and cyclophosphamide (Cytoxan); FOLFOX = folinic acid, fluorouracil, and oxalipatin; HBV = hepatitis B virus; HPV = human papillomavirus; L = Limited resource level; LH–RH = luteinizing hormone–releasing hormone; M = Maximal resource level. Recommendations are based on existing cost-effectiveness data and expected availability of resources. Recommendations for basic surgery, radiation therapy, hormone therapy, and classical chemotherapy are based on expert opinion, where cost-effectiveness studies are not available, and are subject to development of infrastructure where it does not yet exist.

facilities are not readily able to undertake organized screening. Opportunistic screening in LICs and organized screening in MICs can help to identify cancer earlier to increase the chance of a cure. In LICs, cost-effective screening choices include clinical breast examination, visual inspection of the cervix with acetic acid, and visual inspection for oral cancer in high-prevalence countries, with rapid DNA test-and-treat for cervical cancer potentially feasible as country income increases or the cost of the test falls. Urban areas in MICs can consider mammography and fecal immunochemical testing for colon cancer, where prevalence patterns dictate. MICs can screen in rural areas for liver flukes, if prevalent.

For the common pediatric cancers, a case can be made for centralizing treatment, either in-country or in-region. Evidence suggests that many pediatric cancers can be treated cost-effectively, even in LMICs, and scale-up is feasible.

To support countries as they develop cancer plans, more work on costing is needed. Experience with other global health concerns facing LMICs (for example, HIV-AIDS and nutrition) suggests that credible estimates of total costs are important. These estimates can help to convince the international community that action is possible and may motivate the substantial mobilization of resources required. Estimating resource requirements will be a key next step for the global fight against cancer.

Further research is needed to validate the recommendations for cervical, colorectal, liver, oral, and pediatric cancer made in table 16.9, including expert consultations and updating of the systematic literature reviews. The literature search was conducted only in English, but groups are undertaking cost-effectiveness studies in Brazil and China, and some literature is not yet categorized in PubMed. Table 16.9 also does not include studies after 2007 for HICs, except for breast cancer.

It is clear that the literature on cost-effectiveness in LMICs is thin. More studies need to be done using best practice methodology, such that findings can be compared across countries. Multi-country studies with common assumptions are valuable to help identify the types of situations where a particular intervention is cost-effective. For screening, there are good multi-country studies for cervical cancer using a common model, but almost none for the other cancers. Although the WHO's Choosing Interventions That Are Cost-Effective multi-country work has been done for cervical, breast, and colon cancer screening (for example, Ginsberg and others 2012), this needs to be updated using state-of-the-art models similar to the large ones used in HICs. Future economics work on cancer is to cost out the ingredients required for the priority interventions, such that costs of resource-appropriate care can be estimated in individual countries. This approach can help countries to plan for and mobilize the resources needed to implement a cancer plan.

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ANNEX 16A

The annex to this chapter is as follows. It is available at http://www.dcp-3.org/cancer.

- Annex 16A. Search terms, Inclusion Criteria, and Results

NOTE

World Bank income classifications as of July 2014 are as follows, based on estimates of gross national income per capita for 2013:

- Low-income countries: US$1,045 or less
- Middle-income countries:
  - Lower-middle-income: US$1,046–US$4,125
  - Upper-middle-income: US$4,126–US$12,745
- High-income countries: US$12,746 or more

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