Chapter 3

Breast Cancer

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INTRODUCTION

Disparities in Global Breast Cancer Outcomes[1]

Breast cancer is the world's most common cancer among women, and it is the most likely reason that a woman will die from cancer (maps 3.1 and 3.2). Breast cancer is becoming an increasingly urgent problem in low- and middle-income countries (LMICs), where incidence rates, historically low, have been rising by as much as 5 percent per year (Bray and others 2013). High-income countries (HICs) report the highest breast cancer incidence rates (figure 3.1), but these countries have also made the most progress in improving outcomes (Jemal and others 2002). In 2010, the majority of the 425,000 global breast cancer deaths occurred in LMICs, and that percentage is expected to grow (Parkin and Fernandez 2006).

Breast cancer fatality rates are inversely correlated with per capita gross domestic product (GDP) (Greenlee and others 2000). Historically, breast cancer incidence had been low in LMICs, but these rates are rising disproportionately at the same time that mortality rates are continuing to rise or remain high (figure 3.2). The aging of current global population means that nearly 50 percent more women will develop and die from breast cancer in 2020 than in 2002. This estimate does not take into account the likely increases in age-specific breast cancer incidence and mortality rates, especially among recent birth cohorts and among urban women in LMICs, because of changes in their childbearing patterns and their adoption of Western lifestyles (Parkin and Fernandez 2006; Porter 2008). The number of young lives lost is even more disproportionate than the total number; in 2010, breast cancer killed 68,000 women ages 15–49 years in LMICs, compared with 26,000 in this age range in HICs (Forouzanfar and others 2011).

HICs have made tremendous progress in improving outcomes (figure 3.2). Mortality rates, which had been essentially unchanged in the United States for the five decades between 1930 and 1980, have dropped nearly 2 percent each year since 1990 (Jemal and others 2009). Similar reductions have occurred in other HICs, such as Norway (Kalager and others 2010). The improvements are attributable to early detection by screening, combined with timely and effective treatment (Weir and others 2003). Randomized trials of screening mammography in the 1970s and 1980s demonstrated that early detection leads to stage shifting, improved survival, and reduced mortality (Chu, Smart, and Tarone 1988). Endocrine therapy for estrogen receptor (ER)–positive cancers and cytotoxic chemotherapy for ER-negative cancers improve survival among early and locally advanced breast cancers (Clarke 2006; Perloff and others 1988).

Low survival rates in LMICs are largely attributable to late-stage presentation and limited diagnostic and treatment capacities (Hisham and Yip 2003). In India, 50–70 percent of cases are diagnosed with locally

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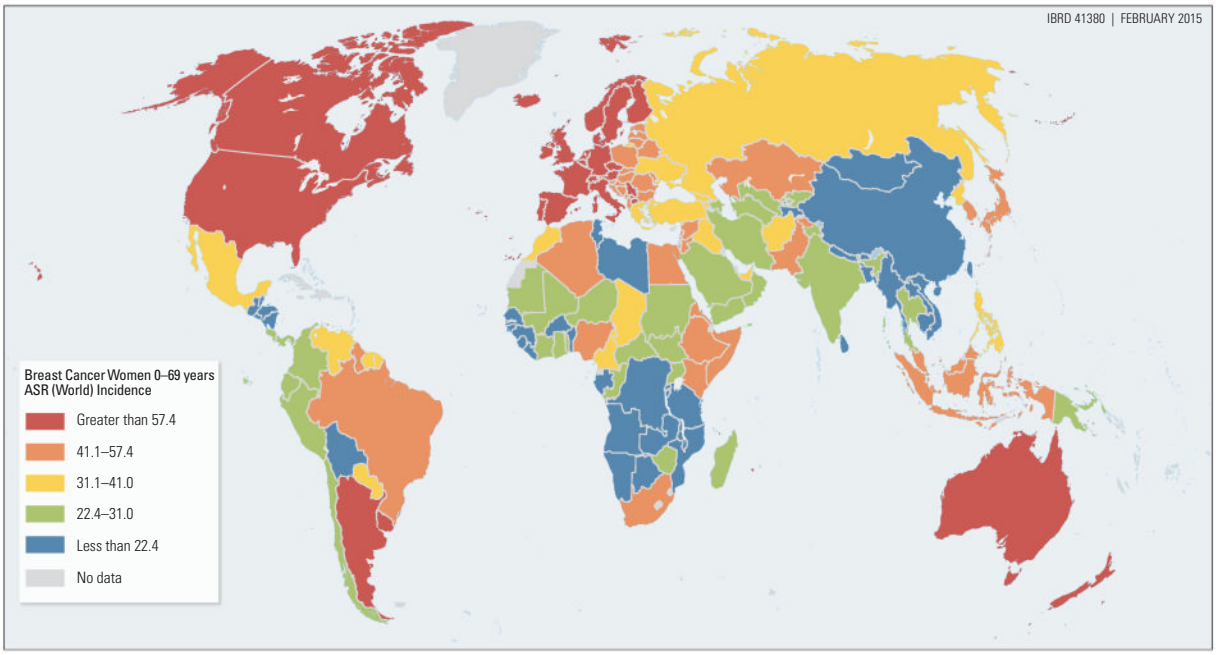
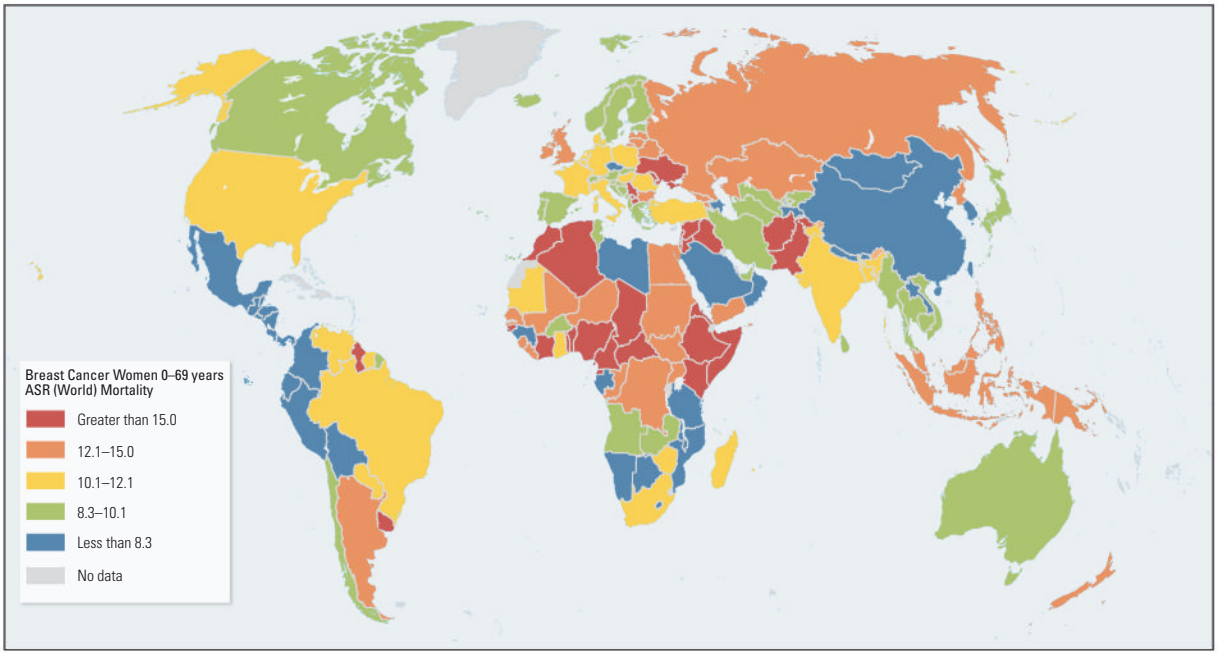
Map 3.1 Global Breast Cancer Incidence in Women in 2012



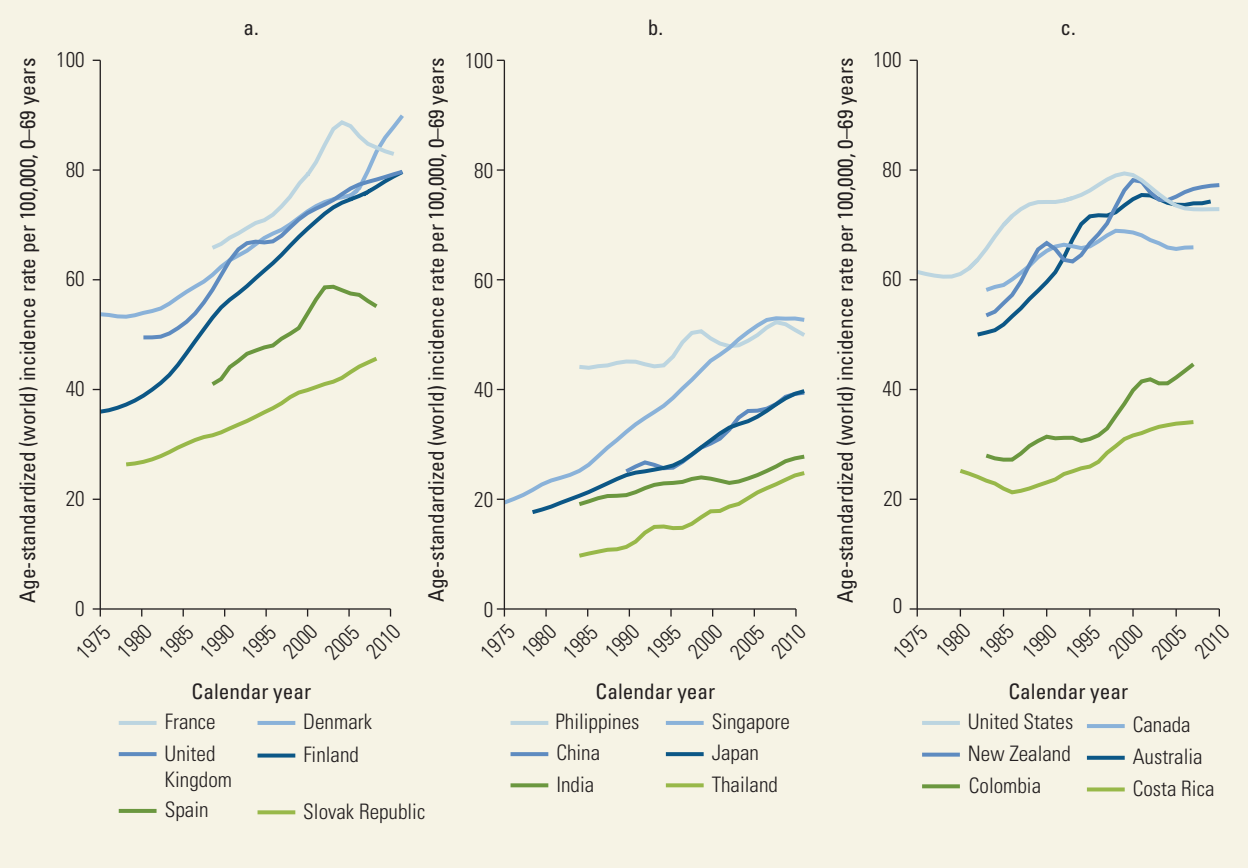
Source: Ferlay and others 2013.
Note: Values are estimated ASR per 100,000 women. ASR = age-standardized rate.

Map 3.2 Global Breast Cancer Mortality in Women in 2012



Source: Ferlay and others 2013.
Note: Values are estimated ASR per 100,000 women. ASR = age-standardized rate.

Figure 3.1 Trends in Age-Standardized Incidence Rates in Women, Selected Countries, 1975–2010



Sources: CI5 Plus (http://ci5.iarc.fr/CI5plus/Default.aspx); and Ferlay and others 2013.
Note: Values are age-standardized rates of breast cancer incidence per 100,000 women, for the world population structure.

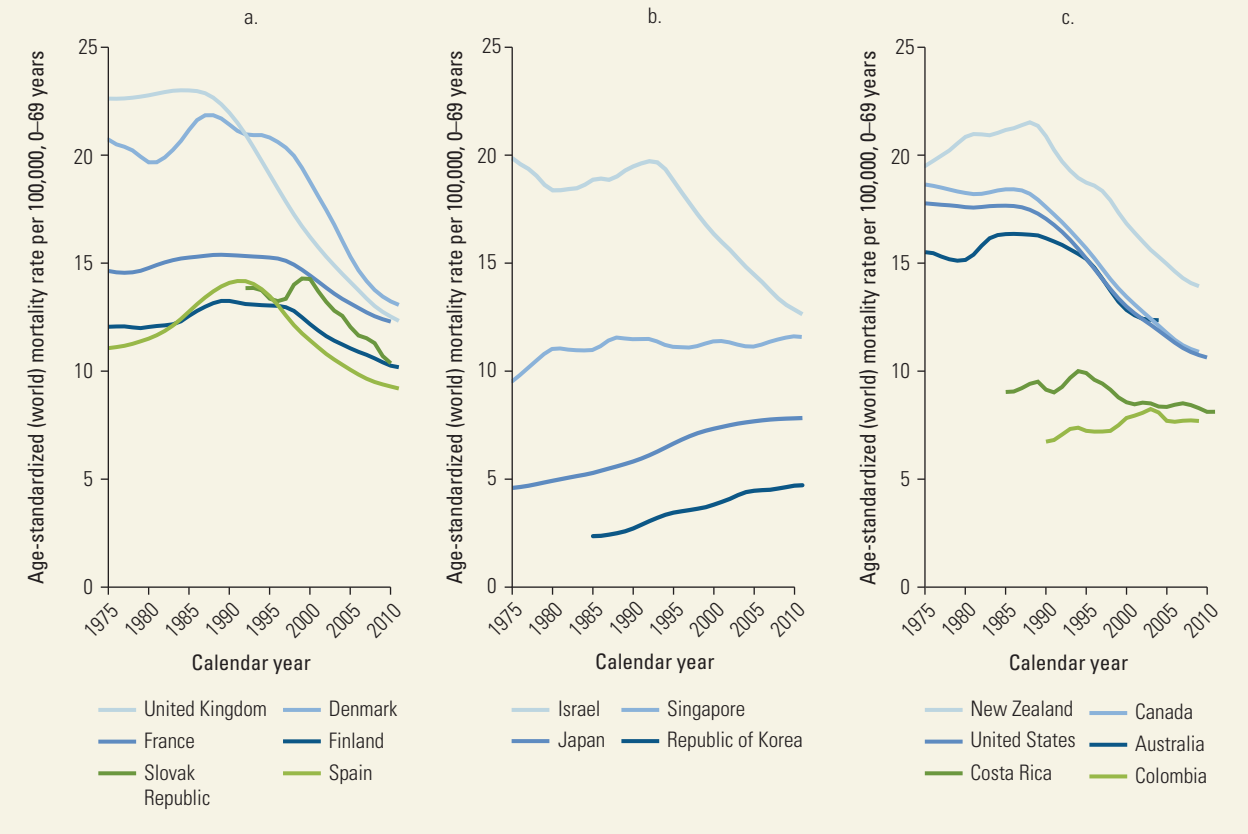
advanced or metastatic disease (Chopra 2001); the same was true of 38 percent of European and 30 percent of American cases in the early 1990s (Sant and others 2004). Accordingly, efforts to promote early detection followed by appropriate treatment are essential components of population-based breast cancer control strategies.

The two strategies of early detection and adjuvant systemic therapy are synergistic and mutually dependent for improving outcomes; early detection only works if it can be followed by prompt therapy. Mathematical modeling suggests that between 28 percent and 65 percent of breast cancer mortality reduction can be attributed to early detection; the balance is due to pharmacotherapy (Berry and others 2005). The interdependence of early detection and treatment underscores the essential role of guidelines for administering this comprehensive strategy in limited-resource settings to shift morbidity and mortality rates at the global level.

Risk Factors and Risk Reduction Strategies

Breast cancer risk increases with some factors that cannot be modified, such as age, genetic and familial risks, younger age at menarche, and older age at menopause; some factors that are somewhat modifiable, including delayed childbearing, avoidance of lactation, radiation exposure, and use of hormone replacement therapy; and some that are more modifiable, including body mass index, sedentary lifestyle, and moderate to high levels of alcohol use (McTiernan, Porter, and Potter 2008). Modifying these behaviors to the extent possible, although not proven in clinical trials to reduce risk, is likely to be beneficial, can be good for general health and noncommunicable disease prevention, and may be of interest to policy makers in LMICs. However, because most of these factors elevate risk only marginally, even successful reduction of them may only have a small effect on overall risk. Some risk factors are not amenable to change; others are associated with

Figure 3.2 Trends in Age-Standardized Breast Cancer Mortality Rates in Women, Selected Countries, 1975–2010



Sources: Ferlay and others 2013; WHO Mortality Database (http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html).
Note: Values are age-standardized rates of breast cancer mortality per 100,000 women, for the world population structure.

desirable outcomes, such as the education of women, which has major societal benefits even if it tends to delay childbearing.

RESOURCE-STRATIFIED GUIDELINES

Need for Cancer Care Guidelines Explicitly Addressing Resource Limitations

Early detection and comprehensive treatment together can improve outcomes. In HICs and upper-middle-income countries, the guidelines for achieving these goals are defined, updated, and disseminated (Morrow and others 2002; Smith 2000; Theriault and others 2013). The World Health Organization (WHO) has pointed out the limited utility of these guidelines in resource-constrained countries; they fail to include implementation costs and provide no guidance as to how treatment that is effective but less than optimal (and less expensive) could be provided affordably for poorer populations (WHO 2002).

Breast Health Global Initiative

Evidence-based, economically feasible, and culturally appropriate guidelines that can be used in settings with limited resources to improve outcomes have been developed by the Breast Health Global Initiative (BHGI), an international health alliance established in 2002. The BHGI has held five global summits addressing key aspects of care:

- Health care disparities, Seattle, Washington, 2002 (Anderson and others 2003)
- Evidence-based resource allocation, Bethesda, Maryland, 2005 (Anderson and others 2006)
- Guideline implementation, Budapest, 2007 (Anderson and others 2008)
- Optimizing outcomes, Chicago, Illinois, 2010 (Anderson and others 2011)
- Supportive care and quality of life, Vienna, 2012 (Cardoso and others 2013; Cleary and others 2013; Ganz and others 2013)

Modeled after the National Comprehensive Cancer Network in the United States (Winn and Botnick 1997), the BHGI applied an evidence-based consensus panel process to build a framework defining resource prioritization for early detection (Yip and others 2008), diagnosis (Shyyan and others 2008), treatment (Eniu and others 2008), and delivery systems (Eniu and others 2008) at four levels of available resources: basic, limited, enhanced, and maximal (box 3.1). The framework is designed to facilitate strategy development and decision making by policy makers and health care administrators initiating breast cancer control programs or reviewing existing services. Different resource levels may apply to different areas of a country, because health care access and resources vary with infrastructure and geography. The same methodology has been applied to the development of guidelines for the management of hepatocellular carcinoma in Asia (Poon and others 2009), non-small cell lung carcinoma (Soo and others 2009), endometrial cancer (Tangjitgamol and others 2009), head and neck cancer (Wee and others 2009), and HER2/neu-positive breast cancer (Wong and others 2009).

BHGI GUIDELINES

Guidelines on Early Detection

Shifting the stage distribution of disease to earlier stages is a necessary step to improving outcomes in LMICs, where many women typically present with locally advanced or metastatic tumors. Achieving stage shifting is likely to reduce mortality; even if this effect is small, the quality of life will be improved. Women would no longer present with large, sometimes ulcerated masses that are painful, odiferous, ostracizing, and amenable only to palliative treatment. Breast-preserving surgery will also be possible in more cases, further reducing morbidity and enhancing the quality of life.

Early detection approaches include screening for asymptomatic disease and early diagnosis of symptomatic disease (table 3.1). As a new screening program is implemented, more cancers will be detected initially, creating an apparent increase in disease incidence. As the screening program becomes established, the detection rate will decline to a steady state. Once diagnosed, more patients will require treatment, at a cost to the health care system. This increased cost may be partially offset by lower total treatment costs, because patients with earlier stage disease require less therapy, but this model assumes that the patients would have been treated in both cases. The cost and human resource requirements of increased demand for treatment must be factored into any decision to establish a screening program.

Mammographic Screening

The efficacy of mammographic screening was established in trials in HICs that included monitoring

Box 3.1

Definitions of Breast Health Global Initiative Resource Levels

- *Basic.* Core resources or fundamental services that are necessary for any breast health care system to function; basic-level services are typically applied in a single clinical interaction.
- *Limited.* Second-tier resources or services that are intended to produce major improvements in outcome and are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple clinical interactions.
- *Enhanced.* Third-tier resources or services that are optional but important; enhanced-level resources should produce further improvements in outcome and increase the number and quality of therapeutic options and patient choices.
- *Maximal.* High-level resources or services that may be used in some high-income countries and/or may be recommended by breast care guidelines that are not adapted to resource constraints. They should be considered lower priority than those resources or services listed in the basic, limited, or enhanced categories, on the basis of cost and/or impracticality for broad use in resource-limited environments. To be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources.

Source: Anderson and others 2008.
Note: The stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. Maximal-level resources should not be targeted for implementation in LMICs, even though they may be used in some higher-resource settings.

Table 3.1 Early Detection Resource Allocation

Early Detection	Level of available resources			
	Basic	Limited	Enhanced	Maximal
Public education and awareness	• Development of culturally sensitive, linguistically appropriate local education programs for target populations to teach value of early detection, breast cancer risk factors, and breast health awareness (education + self-examination)	• Culturally and linguistically appropriate targeted outreach/ education encouraging CBE for age groups at higher risk administered at district/provincial level using health care providers in the field	• Regional awareness programs regarding breast health linked to general health and women's health programs	• National awareness campaigns regarding breast health using media
Detection methods	• Clinical history and CBE	• Diagnostic breast US ± diagnostic mammography in women with positive CBE • Mammographic screening of target group[a]	• Mammographic screening every 2 years in women ages 50–69[a] • Consider mammographic screening every 12–18 months in women ages 40–49[a]	• Consider annual mammographic screening in women ages 40 and older • Other imaging technologies as appropriate for high-risk groups[b]
Evaluation goal	• Breast health awareness regarding value of early detection in improving breast cancer outcome	• Downsizing of symptomatic disease	• Downsizing and/or downstaging of asymptomatic disease in women in highest yield target groups	• Downsizing and/ or downstaging of asymptomatic disease in women in all risk groups

Source: Anderson and others 2008. Used with permission.
Note: CBE = clinical breast examination; US = ultrasound; ± = with or without.
a. Target group selection for mammographic screening should consider breast cancer demographics and resource constraints within the population.
b. Magnetic resonance imaging is more sensitive than mammography in detecting tumors in asymptomatic women who have an inherited susceptibility to breast cancer.

mammograms for image and interpretation quality. Mammography requires high-quality instrumentation and specially trained radiologists, whose performance varies substantially, depending on training and level of experience; screening efficacy is reduced if mammograms are of inferior quality, or if those who read mammograms are not adequately trained and assessed on an ongoing basis (Barlow and others 2004; Ichikawa and others 2010).

Ensuring the quality of imaging and interpretation is challenging in LMICs, due to the need to purchase machines, ensure ongoing quality control, and maintain screening registers.

Many organizations and investigators, including the International Agency for Research on Cancer (IARC) (IARC 2008) and the U.S. Preventive Services Task Force, have reviewed the evidence for the efficacy of screening with mammography (Nelson and others 2009). The evidence comes mainly from six trials, in which women were randomized to periodic mammographic screening or no screening. Based on these trials, IARC estimated a reduction in breast cancer of about 25 percent in women ages 50–69 years and about 19 percent in women ages 40–49 years. The results were consistent across studies in older women but were inconsistent for women in their forties.

Reviewing the same trials, the U.S. Preventive Services Task Force concluded that the mortality benefit is more consistent among younger women than previously described; 15 percent for ages 39–49; 14 percent for ages 50–59; and 32 percent for ages 60–69 (Nelson and others 2009). The U.S. Preventive Services Task Force withdrew a prior recommendation for routine screening for women ages 39–49 who are at average risk, based on the larger number of women who need to be screened to save a life (1,904 for ages 39–49; 1,339 for ages 50–59; and 377 for ages 60–69) (table 3.2) (U.S. Preventive Services Task Force 2009).

The positive predictive value of screening mammography increases with age. Premenopausal women tend to have denser breast tissue and a higher rate of benign lesions than postmenopausal women, resulting in greater difficulty in detecting lesions and lower sensitivity and specificity (that is, a higher rate of false-positives). Furthermore, the incidence of breast cancer increases with age in most populations.

Table 3.2 Pooled Relative Risk for Breast Cancer Mortality from Mammographic Screening Trials for Women Ages 39–74 Years

Age (years)	Trials included	Relative risk for breast cancer mortality (95% credible interval)	NNI to prevent one breast cancer death (95% credible interval)
39–49	8	0.85 (0.75–0.96)	1904 (929–6378)
50–59	6	0.86 (0.75–0.99)	1339 (322–7455)
60–69	2	0.68 (0.54–0.87)	377 (230–1050)
70–74	1	1.12 (0.73–1.72)	—

Source: Nelson and others 2009.
Note: NNI = number needed to invite to screening; — = not available.

Although it may be less cost effective to screen women in their forties than women ages 50 and older, a relatively high proportion of women with breast cancers in LMICs are ages 40–49, complicating the decision making about the parameters of a screening program. Without screening, the largest age cohort of breast cancer patients will be missed and many women will continue to present for treatment with more advanced stage disease.

Some groups question whether the demonstrated mortality benefit of mammographic screening might be outweighed by the risk of harm through false-positive studies or the potential for overtreatment of biologically favorable early-stage disease (Baum 2013; Gotzsche and others 2012). Informed consent should be provided to women so that they have an appropriate understanding of the potential risks as well as benefits of mammographic screening (Thornton 2014).

Standard practice in HICs is two-view mammography, in which the breast is imaged in two planes (MLO–medial/lateral oblique, CC–craniocaudal), which allows a more accurate reading. However, in older randomized trials, the quality of single-view mammograms was nearly equivalent to that of two-view mammograms. In LMICs with limited resources, consideration can be given to single-view mammography, if doing so will increase the coverage and the screening interval can be extended beyond one or two years. In women ages 50–69, screening every 33 months was as efficacious as screening every 18–24 months; in women ages 40–49, the reduction in mortality was inversely related to the screening interval (Breast Screening Frequency Trial Group 2002). When allocating limited resources for mammographic screening, it is more cost effective to screen a higher proportion of women less frequently than to screen a smaller proportion more frequently. The availability and cost of x-ray film may also limit the availability of screening in LMICs; digital mammography may provide an alternative, if costs are reduced to affordable levels.

Because mammographic screening is expensive and requires considerable infrastructure, consideration has been given in LMICs to screening with clinical breast examination (CBE) and breast self-examination (BSE).

Clinical Breast Examination

CBE is a basic tool in clinical management of breast cancer. However, no randomized trials to assess CBE alone as a screening tool have yet been completed, while the evidence from observational studies is inconsistent. A case-control study in Japan suggested that breast cancer deaths were reduced among asymptomatic women who underwent CBE screening (odds ratio = 0.56) (Kanemura and others 1999). A second Japanese study reported significantly greater reductions in the age-adjusted death rate from breast cancer in areas with high rates of screening coverage (principally by physical examination), compared with areas where coverage was not established (Kuroishi and others 2000). An early clinical trial conducted by the Health Insurance Plan of Greater New York demonstrated that a combination of mammography and CBE reduced the risk of breast cancer mortality; many of the tumors in the screened group were detected by CBE but not by mammography (Chu, Smart, and Tarone 1988). However, more recent randomized trials compared the combination of mammography and CBE with mammography alone, and the two approaches appeared to have equivalent outcomes (IARC 2008). As a result, IARC and the U.S. Preventive Services Task Force concluded that the evidence for the efficacy of CBE in reducing mortality from breast cancer is "inadequate" and "insufficient," respectively (U.S. Preventive Services Task Force 2009).

Most of the evidence for the efficacy of CBE has come from studies in HICs, where women typically present with relatively small tumors. CBE has been advocated for LMICs for several reasons. CBE may be more efficacious in LMICs, where women tend to present with larger tumors; CBE is less expensive than mammography because it can be performed by trained health workers who are not physicians and requires less equipment than mammography. A recent study of 1,179 screened women in Jakarta, Indonesia, compared the use of mammography and CBE in a previously unscreened population and identified 14 breast cancers. Of the 14 cancers, 13 were detected by CBE (Kardinah and others 2014).

If CBE is used for screening breast cancer in LMICs, it should be done in such a way that its effectiveness can be evaluated. A randomized trial in the Philippines was unsuccessful because too few women with positive findings on CBE consented to further diagnostic tests to determine if the findings reflected a malignant or benign finding (Pisani and others 2006). A randomized trial of CBE and visual inspection of the cervix by specially trained women with a tenth-grade education is underway in Mumbai, India. Preliminary results show more breast cancers are being detected at early stages (stages 0, I, or II) in the screening group (62 percent) than in the control group (44 percent), but breast cancer mortality results are not yet available (Mittra and others 2010).

In addition to assessments of its efficacy—sensitivity, shifted stage distribution, and reduction in breast cancer mortality—all such efforts to evaluate the usefulness of CBE should include a measure of its specificity. If large numbers of lesions detected by CBE are found not to be cancerous on further evaluation, this puts a heavy burden on local diagnostic facilities. In addition, if many women undergo unnecessary breast biopsies, this may not be acceptable, either to the women targeted for screening or to policy makers who allocate scarce resources.

CBE accuracy depends on the skill of providers, the definition of proper techniques, and the type of training received. Strategies for providing routine feedback to health care providers about the accuracy of their examinations as determined on final diagnostic work-up are integral to successful CBE programs.

Breast Self-Examination

The aim of BSE is to detect *asymptomatic* breast conditions and should be distinguished from programs that promote early treatment of *symptomatic* breast cancer. BSE is the systematic search performed regularly by the women themselves for a lump or other change in the breast that is suggestive of cancer. In formal BSE training, a woman receives instruction in the four elements of the examination: visual inspection of the breasts in a mirror to look for asymmetry and dimpling; palpation in both the standing and lying positions with the arm above the head, using a circular motion with the pads of the three middle fingers, with systematic coverage of the entire breast and axilla; squeezing of the nipple to detect discharge; and monthly BSE practice.

Most evidence for the efficacy of BSE comes from two randomized trials from Saint Petersburg (Semiglazov and others 1999) and Shanghai (Thomas and others 2002). In both studies, women were randomized to either an intervention group that received instruction in BSE and periodic reminders to practice the procedure or to a control group that received no such education and no formal breast cancer screening. Mortality from breast cancer was unchanged by BSE instruction in these trials. Both the IARC working group and the U.S. Preventive Services Task Force concluded that the efficacy of BSE is unproven (U.S. Preventive Services Task Force 2009). However, it has been questioned if the negative findings of these BSE trials are relevant to LMICs, where women commonly present with large (> 4 cm) cancers at initial diagnosis. In the Shanghai trial, women in the control group were not taught BSE but nonetheless were largely successful in finding cancers when they were still small, that is, where 45 percent of the cancers were found as in situ or T1 invasive cancers measuring less than 2 cm (Thomas and others 2002). These favorable findings among the untrained control women from Shanghai stand in stark contrast to regions of India, where 76 percent of women present with locally advanced or metastatic (stage III or IV) disease at initial presentation (Chopra 2001). In this latter setting, the actual benefit of BSE training could potentially be much greater.

It remains unknown whether BSE could reduce mortality from breast cancer in populations in LMICs. It is not unreasonable to advocate that BSE be used as a screening tool in these settings, either alone or in combination with CBE. No new trials of BSE alone have been undertaken, but BSE instruction has been included in some of the studies of CBE. The IARC working group recommended randomized trials of BSE in conjunction with mammography. In LMICs where mammographic screening cannot be provided at least every two years, it may be particularly useful to teach BSE.

Any introduction of BSE should be accompanied by evaluation of its efficacy, including quantification of the benign lesions that must be evaluated. In both of the completed BSE trials, many more benign breast lesions were detected in the groups that received BSE instruction than in the control groups.

Breast Awareness Education

Programs to promote early diagnosis and treatment of symptomatic breast cancer are not screening programs, because they are not designed to detect asymptomatic lesions. Their purpose is to encourage women who have symptoms suggestive of breast cancer to seek medical care. Women can be educated to detect suspicious changes in their breasts and empowered to overcome social barriers that might prevent them from seeking care. Breast self-awareness programs should not be initiated unless adequate diagnostic and treatment facilities are available. And the programs should be established in such a way that they can be evaluated to determine their effectiveness.

Guidelines on Diagnosis

Diagnosis is a critical and often overlooked aspect of breast cancer management. Two key components of diagnosis are confirmation of a cancer diagnosis based on clinical evaluation and tissue sampling, and testing with the imaging and tumor markers needed for treatment planning (table 3.3).

Clinical Evaluation

A patient's history of general health and of factors specific to breast disease provides important information for clinical assessment of breast disease and comorbid conditions that might influence therapy choices. Complete physical examination performed in conjunction with CBE provides guidance on the extent of

Table 3.3 Diagnosis Resource Allocation

	Level of available resources			
Diagnosis	**Basic**	**Limited**	**Enhanced**	**Maximal**
Clinical	• History • Physical examination • CBE • Tissue sampling for cancer diagnosis (cytologic or histologic) prior to initiation of treatment	• US-guided FNAB of sonographically suspicious axillary nodes • SLN biopsy with blue dye[a]	• Image guided breast sampling • Preoperative needle localization under mammo and/or US guidance • SLN biopsy using radiotracer[a]	
Imaging and lab tests	See footnote b	• Diagnostic breast US • Plain chest and skeletal radiography • Liver US • Blood chemistry profile[b] • CBC[b]	• Diagnostic mammography • Specimen radiography • Bone scan, CT scan • Cardiac function monitoring	• PET scan, MIBI scan, breast MRI, BRCA 1/2 testing • Mammographic double reading
Pathology	• Pathology diagnosis obtained for every breast lesion by any available sampling procedure • Pathology report containing appropriate diagnostic and prognostic/predictive information to include tumor size, lymph node status, histologic type, and tumor grade • Process to establish hormone receptor status possibly including empiric assessment of response to therapy[c] • Determination and reporting of TNM stage	• Determination of ER status by IHC[c] • Determination of margin status, DCIS content, presence of LVI • Frozen section or touch prep SLN analysis[d]	• Measurement of HER2/neu overexpression or gene amplification[d] • Determination of PR status by IHC	• IHC staining of sentinel nodes for cytokeratin to detect micrometastases • Pathology double reading • Gene profiling tests

Source: Anderson and others 2008. Used with permission.

Note: BRCA1/2 = breast cancer genes 1 and 2; CBC = complete blood count; CBE = clinical breast examination; CT = computed tomography; DCIS = ductal carcinoma in situ; ER = estrogen receptor; FNAB = fine-needle aspiration biopsy; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; LVI = lymphovascular invasion; mammo = mammography; MIBI = methoxy-isobutyl-isonitrile; MRI = magnetic resonance imaging; PET = positron emission tomography; PR = progesterone receptor; SLN = sentinel lymph node; TNM = malignant tumor system; US = ultrasound.

a. The use of SLN biopsy requires clinical and laboratory validation of the SLN technique.

b. Systemic chemotherapy requires blood chemistry profile and CBC testing for safety. When chemotherapy is available at the basic level, these tests also should be provided.

c. ER testing by IHC is preferred for establishing hormone receptor status and is cost effective when tamoxifen is available. When tamoxifen is available at the basic level, IHC testing of ER status should be provided.

d. If the costs associated with trastuzumab were substantially lower, trastuzumab would be used as a limited-level therapy. In this case, measurement of HER2/neu overexpression and/or gene amplification would need to be available at the limited level to properly select patients for this highly effective but expensive HER2/neu-targeted biological therapy.

disease, the presence of metastatic disease, and the ability to tolerate more aggressive therapeutic regimens.

Diagnostic Imaging

Breast imaging, initially with ultrasound and at higher resource levels with diagnostic mammography, improves preoperative diagnostic assessment and permits image-guided needle sampling of suspicious lesions. Imaging also provides important information about the extent of disease, which helps determine whether breast conservation (lumpectomy followed by radiation therapy) is an option or mastectomy is required. Ultrasound is particularly valuable as an adjunct to CBE in providing detail on the size and extent of masses and thickenings, which helps to distinguish benign cysts from solid lesions and characterizes the shape and growth pattern of lesions. Diagnostic mammography, while helpful for breast conservation therapy, is not mandatory in LMICs when these resources are lacking. However, where screening mammography is common and where nonpalpable, noninvasive cancers are often diagnosed, diagnostic mammography is critical for determining the extent of disease and properly selecting patients for breast conservation surgery versus mastectomy (Theriault and others 2013).

Tissue Sampling

Needle biopsy is preferred to surgical excision for initial diagnosis of the most suspicious breast lesions; if resource limitations preclude this option, then surgical excision is necessary. Mastectomy should never be used as a method of tissue diagnosis. Whether the tissue is obtained by needle sample or surgical excision, the sample must be processed and then evaluated by a pathologist to determine whether the disease is malignant or benign, and invasive or noninvasive (Shyyan and others 2008).

Tumor Markers

Once a cancer diagnosis is made, additional testing provides information on which to base pharmacotherapy choices. For example, tamoxifen and aromatase inhibitors are affordable generic oral medications that are quite effective in the management of ER-positive cancers with relatively manageable side effects, but these agents are relatively ineffective against ER-negative cancers (Howell and others 1998). The availability of ER testing is critical to proper selection of cancer therapy when endocrine therapies are available. Standard testing is based on immunohistochemical (IHC) methods, where quality assessment of testing methodology is important to avoid false-negative results (Hammond and others 2010; Masood and others 2008).

HER2/neu oncogene testing provides information on the relative aggressiveness of the cancer (HER2/neu-positive cancers are more aggressive), as well as on the likely drug sensitivity of the cancer (Yoo and others 2012). However, the most effective drug for HER2/neu-positive cancers is trastuzumab, which is unaffordable in most regions. Less expensive therapies are under investigation (Pinto and others 2013).

Guidelines on Treatment

Surgery

The modified radical mastectomy is the mainstay of treatment of local and regional (nodal) disease at the basic level of breast health care for early-stage (table 3.4) and late-stage (table 3.5) disease (Anderson and others 2008). The operation is not technically difficult, although surgeons must be trained to remove the breast and dissect axillary nodes properly (Thorat and others 2008).

Radiation Therapy

At increasing resource levels, the availability of radiation therapy allows for consideration of breast-conserving therapy, postmastectomy chest wall radiation, and palliation of painful or symptomatic metastases (see tables 3.4 and 3.5). Although radiation therapy requires significant infrastructure and can be cost limiting in improving treatment, the establishment of a radiation facility can be an important first step in creating an oncology center of excellence in an LMIC (Bese and others 2008).

Systemic Pharmacotherapy

Although surgery and radiation address local disease in the breast and regional disease in the lymph node beds, systemic therapy addresses microscopic disease elsewhere that can become metastases. When patients die from breast cancer, the cause is widespread metastatic disease. It is pharmacotherapy that ultimately improves breast cancer survival rates, since this is the only treatment directed at systemic disease. Pharmacotherapies for breast cancer consist of endocrine (hormonal) therapy, cytotoxic chemotherapy, and biological targeted (antibody) therapies (see tables 3.4 and 3.5).

- *Endocrine therapy* requires relatively few specialized resources, but it requires knowledge of hormone receptor status to identify the patients most likely to benefit. For ER-positive cancers, tamoxifen and aromatase inhibitors are oral drugs taken daily for five years or more that can be dispensed from

Table 3.4 Treatment Resource Allocation for Stage I and Stage II Disease

Treatment			Level of available resources			
			Basic	Limited	Enhanced	Maximal
Stage I	Local-regional treatment	Surgery	Modified radical mastectomy	Breast-conserving surgery[a] SLN biopsy with blue dye[b]	SLN biopsy using radiotracer[b] Breast reconstruction surgery	
		Radiation therapy			Breast-conserving whole-breast irradiation as part of breast-conserving therapy[a]	
	Systemic treatment	Chemotherapy		Classic CMF[c], AC, EC, or FAC[c]	Taxanes	Growth factors Dose-dense chemotherapy
		Endocrine therapy	Oophorectomy in premenopausal women Tamoxifen[d]		Aromatase inhibitors LH-RH agonists	
		Biological therapy		See footnote e	Trastuzumab for treating HER2/neu-positive disease[e]	
Stage II	Local-regional treatment	Surgery	Modified radical mastectomy	Breast-conserving surgery[a] SLN biopsy with blue dye[b]	SLN biopsy using radiotracer[b] Breast reconstruction surgery	
		Radiation therapy	See footnote f	Postmastectomy irradiation of chest wall and regional nodes for high-risk cases[f]	Breast-conserving whole-breast irradiation as part of breast-conserving therapy[a]	
	Systemic treatment	Chemotherapy	Classic CMF[c], AC, EC, or FAC[c]		Taxanes	Growth factors Dose-dense chemotherapy
		Endocrine therapy	Oophorectomy in premenopausal women Tamoxifen[d]		Aromatase inhibitors LH-RH agonists	
		Biological therapy		See footnote e	Trastuzumab for treating HER2/neu-positive disease[e]	

Source: Anderson and others 2008. Used with permission.

Note: AC = doxorubicin and cyclophosphamide; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; EC = epirubicin and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; HER2/neu = human epidermal growth factor receptor 2; LH-RH = luteinizing hormone-releasing hormone; SLN = sentinel lymph node.

a. Breast-conserving surgery can be provided as a limited-level resource but requires radiation therapy. If breast-conserving radiation is unavailable, then patients should be transferred to a higher-level facility for postlumpectomy radiation.

b. The use of SLN biopsy requires clinical and laboratory validation of the SLN technique.

c. Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests also should be provided.

d. ER testing by IHC is preferred for establishing hormone receptor status and is cost effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of ER status also should be provided.

e. If the costs associated with trastuzumab were substantially lower, trastuzumab would be used as a limited-level resource. In this case, measurement of HER2/neu overexpression and/or gene amplification would need to be available at the limited level to select patients properly for this highly effective but expensive HER2/neu-targeted biological therapy.

f. Chest wall and regional lymph node irradiation substantially decreases the risk of postmastectomy local recurrence. If available, it should be used as a basic-level resource.

pharmacies without special infrastructure and are considered very safe. Endocrine therapy could be given to all breast cancer patients, but it would be a waste of resources since it is only effective against ER-positive cancers. IHC methods involve special tissue-staining techniques with labeling antibodies, which requires pathology laboratory infrastructure; quality control is quite important to testing accuracy. Alternative simplified techniques for ER testing are of significant interest but remain experimental.

- *Systemic cytotoxic chemotherapy* is effective in most biologic subtypes of breast cancer. It is particularly important in the management of ER-negative cancers but is resource intensive. Chemotherapy has significant side effects that must be managed

Table 3.5 Treatment Resource Allocation for Locally Advanced and Metastatic Disease

Treatment			Level of available resources			
			Basic	Limited	Enhanced	Maximal
Locally advanced	Local-regional treatment	Surgery	Modified radical mastectomy		Breast-conserving surgery Breast reconstruction surgery	
		Radiation therapy	See footnote a	Postmastectomy irradiation of chest wall and regional nodes[a]	Breast-conserving whole-breast irradiation as part of breast-conserving therapy	
	Systemic treatment (Adjuvant and neoadjuvant)	Chemotherapy	Preoperative chemotherapy with AC, EC, FAC, or CMF[b]		Taxanes	Growth factors Dose-dense chemotherapy
		Endocrine therapy	Oophorectomy in premenopausal women Tamoxifen[c]		Aromatase inhibitors LH-RH agonists	
		Biological therapy		See footnote d	Trastuzumab for treating HER2/neu-positive disease[d]	
Metastasic and recurrent	Local-regional treatment	Surgery	Total mastectomy for ipsilateral breast tumor recurrence after breast-conserving surgery			
		Radiation therapy		Palliative radiation therapy		
	Systemic treatment	Chemotherapy		Classic CMF[b] Anthracycline monotherapy or in combination[b]	Sequential single agent or combination chemotherapy: Trastuzumab Lapatinib	Bevacizumab
		Endocrine therapy	Oophorectomy in premenopausal women Tamoxifen[c]		Aromatase inhibitors	Fulvestrant
		Biological therapy	Nonopioid and opioid analgesics and symptom management		Bisphosphonates	Growth factors

Source: Anderson and others 2008. Used with permission.

Note: Treatment resource allocation table for locally advanced, metastatic (stage IV), and recurrent breast cancer. AC = doxorubicin and cyclophosphamide; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; EC = epirubicin and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; HER2/neu = human epidermal growth factor receptor 2; LH-RH = luteinizing hormone-releasing hormone.

a. Chest wall and regional lymph node irradiation substantially decreases the risk of postmastectomy local recurrence. If available, it should be used as a basic-level resource.

b. Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests should be provided.

c. Estrogen receptor testing by immunohistochemistry (IHC) is preferred for establishing hormone receptor status and is cost effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of estrogen receptor status should be provided.

d. If the costs associated with trastuzumab were substantially lower, trastuzumab would be used at a limited level. In this case, measurement of HER2/neu overexpression and/or gene amplification would need to be available at the limited level to properly select patients for this highly effective but expensive HER2/neu-targeted biological therapy.

effectively. Correct drug selection is based on the extent or stage of the cancer and on tumor markers that can predict likely drug sensitivity. Proper drug dosing is important and must be individualized to the patient's body mass index; the dosage should be sufficiently high to provide optimal effects on the cancer but as low as possible to minimize adverse events. Proper management of these agents is critical; they must be handled under sterile conditions, they must be properly and safely administered, and

health care workers should not be directly exposed to these agents.

- *Biological targeted therapies* use monoclonal antibodies to control disease. HER2 neu-targeted therapy with trastuzumab is very effective in tumors that overexpress the HER2/neu oncogene, but cost largely prevents the use of this treatment in LMICs (Eniu and others 2008); a standard one-year course of treatment in the United States is approximately US$100,000. It remains unclear whether generic forms of trastuzumab will be available in the future.

IMPLEMENTATION OF BHGI GUIDELINES: AN EARLY DETECTION MODEL

Before an LMIC initiates a breast cancer control program or evaluates existing programs, careful assessment of the local situation is needed. This assessment consists of three parts:

- Breast cancer problem in the population
- Existing infrastructure that will be utilized for the program
- Social and cultural barriers to women's participation in the program

Assessing the Breast Cancer Problem

A realistic estimate of the number of women with breast cancer in the population in which screening is proposed is an essential part of the planning process; the lower the prevalence, the higher the number of women who have to be screened to detect cases and prevent deaths.

Estimating the frequency of breast cancer in LMICs can be a challenge and may require using less than ideal methods. The ideal situation is where the number of women in the target screening population is known and a reliable population-based cancer registry covers a substantial portion of the population. These elements, in conjunction with information from countries with well-developed breast cancer screening programs, would support a reasonable estimate of expected impact. In countries with poorer enumeration of the target population or cancer registration, more extrapolation is involved; estimates of breast cancer burden and expected benefit become less reliable but still useful. For example, incidence rates for populations that may be similar to populations without registries are found in *Cancer Incidence in Five Continents* (Curado and others 2007).

Accurate mortality rates can serve as good measures of the extent of the breast cancer problem. However, mortality rates can be misleading if the population size is not accurately enumerated, if many deaths are unreported, or if certification of the cause of death is not accurately recorded. In the absence of adequate information on the population to be screened, reviews of death certificates can be useful. The number of deaths certified as due to breast cancer during specific years can be obtained to provide a rough estimate of the number of annual breast cancer deaths in the population. In addition, the proportion of all deaths due to breast cancer can be calculated and compared with the proportion of deaths from other causes. If breast cancer is a small problem relative to other preventable causes of death, then a screening program may not be warranted, but if breast cancer deaths constitute a relatively high proportion of preventable deaths, this information can help to justify the costs of screening.

A review of hospital records can be useful in assessing the magnitude of the problem. If a single hospital serves all cancer patients in a defined population, then the hospital records can be reviewed to estimate the number of cases to be expected annually. A record review can provide an indication of the importance of breast cancer relative to other cancers in the population and relative to other reasons for hospitalization. If admissions for breast cancer constitute a relatively high proportion of all preventable causes of admission, or a high proportion of all admissions for cancer, then a screening program may be justifiable; if breast cancer is a rare cause of hospitalization, then it may not warrant high prioritization.

The presence of social or financial barriers that keep women from accessing services will limit the effectiveness of a screening program; it will be important to consider initiatives to overcome such barriers.

Assessing the magnitude of the problem before implementing a screening program also includes determining the disease stage distribution at diagnosis. This information would be found in population-based cancer registries or hospital-based registries. In the absence of cancer registries, the records in clinics, hospitals, and pathology laboratories can be reviewed. If a high proportion of breast cancers are diagnosed at advanced stages, then a screening program, or an educational program to encourage earlier diagnosis of symptomatic breast cancers, could have a substantial impact on the burden. Conversely, if a high proportion of breast cancers are already being diagnosed at early stages, then screening programs based on BSE, and probably also on CBE, are unlikely to have a large impact on mortality or morbidity.

Assessing the Infrastructure for Screening, Diagnosis, and Treatment

Mammography, the only screening method of proven efficacy, serves as an example for assessing infrastructure.

For a mammographic screening program to result in earlier detection of breast cancers in the population in LMICs and elsewhere, six elements need to function adequately:

- Means to recruit enough women in the target population to have a meaningful impact on the breast cancer burden
- Facilities to ensure high-quality mammograms
- Sufficient number of radiologists who can properly interpret mammograms in a timely manner
- Means to recontact women with suspicious findings and ensure that they come to facilities for further evaluation in a timely fashion
- Adequate diagnostic facilities and trained pathologists to provide timely and accurate tissue diagnoses
- Sufficient facilities and personnel to provide timely and appropriate treatment

Regardless of the screening modality used—BSE, CBE, or screening mammography—gaps in this system at any level must be identified and addressed before a program of early detection is established.

Assessing Social and Cultural Barriers

Women in LMICs may be unaware of breast cancer, or they may have misconceptions about its nature or curability or have fatalistic attitudes toward diseases in general (Yip and others 2008). Under such circumstances, programs to enhance public awareness of breast cancer and to teach that breast cancer outcomes are improved through early detection are critical to improving participation in early detection programs, regardless of the selected methods for early detection.

Cultural barriers to participation need to be identified and strategies developed to overcome them. These barriers may include the attitudes of women as well as their husbands; in some cultures, women must obtain their husbands' permission to seek medical services. Efforts to empower women and educate men may be required for programs to succeed. Cultural and social barriers are highly specific to different countries, religions, and ethnic groups and cannot be comprehensively reviewed here. However, an example illustrates how they may be addressed. In a survey in the Palestinian Authority (Azaiza and others 2010), women were more likely to undergo screening mammography if they were less religious, if they described fewer personal barriers to examinations, and if they indicated a lower degree of cancer fatalism.

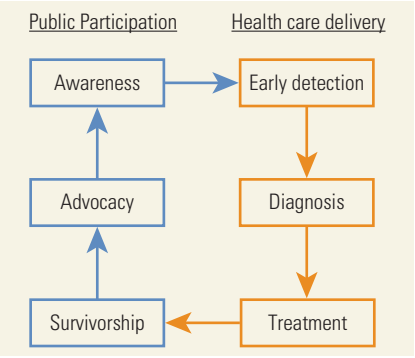
Women who consented to CBE had a higher perceived effectiveness of CBE and described lower levels of cancer fatalism. Muslim women were half as likely as Christian women to participate in CBE screening. Women were more likely to perform BSE if they were more highly educated, resided in cities, were Christian, were less religious, and had a first-degree relative with breast cancer. These results suggest that participation in screening might be improved by recruiting religious leaders as spokespersons for early detection and by staffing screening clinics with women physicians and nurses sensitive to the needs of conservative Muslim women who must remain covered in public.

Women who are correctly diagnosed and properly treated for early-stage breast cancer can survive the disease and can organize breast cancer survivor groups, such as Reach for Recovery (figure 3.3). Such groups can play a vital role in educating the public about the value of early detection and in providing newly diagnosed women with practical and emotional support (Ashbury and others 1998). Survivor groups can organize into political advocacy groups that have a real and positive impact on health care policy or national cancer research agendas (Schmidt 2009; Visco 2007).

Identifying Target Groups

Identifying a target group for screening in LMICs should be based on the burden of disease in the population, the potential benefit from screening, and available resources (Humphrey and others 2002). Other than the small subset of women at very high risk of developing breast cancer due to genetic predisposition, it is very difficult to predict which women are destined to develop breast cancer. Although women with BRCA (breast cancer gene) mutations generally have a strong family history of breast and/or ovarian cancer, family history

Figure 3.3 Synergistic Relationship between Public Participation and Health Care Delivery in Downstaging Breast Cancer and Improving Outcomes



Source: Harford and others 2011. Used with permission.

is not a particularly good tool for selecting women for screening, since approximately 80 percent of breast cancers occur in women who lack a known family history of breast cancer. As a result, the only two risk factors used for determining candidacy for screening are gender and age.

In Western countries, breast cancer incidence increases sharply with age until the usual age at menopause and then increases more slowly. In LMICs, incidence increases with age until menopause but then either continues to increase less steeply with age than in Western countries, levels off, or decreases with age (Freedman and others 2006). This phenomenon is the result of an aging and growing population (Chia and others 2005; Wong, Cowling, and others 2007); over time, the age-specific incidence curves for LMICs are expected to more closely approximate those of Western countries (Yip and others 2008).

In LMICs where incidence rates in women ages 50 years and older are beginning to increase with age, the prevalence of the disease in the population may have approached a level at which establishing screening programs will be cost effective.

Considering Coverage and Impact

Coverage of the target population is also important. If screening is efficacious in reducing mortality from breast cancer, but only a small proportion of the women in the target population receives the service, then the impact of the screening program on mortality in the population will be minimal. The following simple formula illustrates the impact (Thomas and others 2013):

$$\text{Impact} = \text{Efficacy} \times \text{Coverage}$$

If we assume that mammograms reduce mortality from breast cancer by 25 percent, and if 40 percent of the women in a target population are screened, then the screening program would be expected to reduce mortality in the target population by 10 percent ($0.25 \times 0.40 = 0.10$). Mammographic screening programs in LMICs should be designed in such a way that the proportion of women in the target population who are screened can be maximized.

COST-EFFECTIVE INTERVENTIONS IN LMICs

The BHGI resource-adapted guidelines provide a sound foundation for creating intervention packages for early detection (table 3.1), diagnosis (table 3.3), and treatment by disease stage (tables 3.4 and 3.5) at each of BHGI's four defined resource levels: Basic, Limited, Enhanced, and Maximal. By contrast, WHO's Choosing Interventions That Are Cost-Effective (WHO-CHOICE) framework provides a somewhat different and not entirely comparable set of breast cancer guidelines (Murray and Lopez 1996; Tan-Torres Edejer and others 2003). WHO-CHOICE was established as an initiative to provide evidence to policy makers who must decide on the interventions and programs that maximize health outcomes for given available resources, reporting on the costs and effects of a wide range of health interventions but without direct alignment with current stage-based treatment strategies for specific diseases.

Whether grounded in the BHGI or WHO-CHOICE framework, the development of analytical models to identify clinically effective and cost-effective approaches for improving breast health requires linking resources to interventions and patient outcomes (Brown and others 2006; Gold and others 1996). The value-for-money question can be summarized as follows: given the assumed level of resources available within a given geopolitical area, what administratively and financially feasible set of interventions has the greatest favorable impact on health outcomes? This section reviews and assesses progress to date in identifying cost-effective interventions for breast cancer in LMICs.

Appraisal of the Literature

As the recent review by Zelle and Baltussen (2013) well illustrates, substantial variations exist in the precise purpose, scope, methodology, assumptions, and technical quality of published cost-effectiveness analyses on breast cancer interventions in LMICs. The following section focuses on a selected set of studies that yields findings relevant to components of the BHGI guidelines while paying close attention to important cost-effectiveness analysis data and methods issues. Nine of the studies were among 23 selected for detailed manuscript-quality evaluation by Zelle and Baltussen and were generally among the highest rated, according to the authors' scoring scheme. The studies illustrate how cost-effectiveness analyses can be carried out in limited-resource settings.

Salient features and recommendations of these key studies are summarized in the online annex 3A to this chapter, tables 3A.1 through 3A.3. We have further mapped the study contexts to BHGI resource levels and highlighted features following methodological best-practice guidelines. Here, we focus on the cost-effectiveness results. Our conclusions about whether an

intervention is cost effective were guided throughout by the following WHO recommendations (WHO 2001):

- If the intervention's applicable incremental cost-effectiveness ratio (ICER) is less than or equal to the nation's or region's GDP per capita, the intervention is "very cost effective."
- If the ICER is between one and three times the GDP per capita, it is "cost effective."
- If the ICER exceeds three times the GDP per capita, the intervention is "not cost effective."

Early Detection

Annual CBEs are very cost effective in Vietnam (Nguyen and others 2013); biennial mammography screening is cost effective in Hong Kong SAR, China (Wong, Kuntz, and others 2007). An analysis examining combinations of both screening modalities applied to different age groups in India concluded that several alternative CBE detection strategies were very cost effective, while the most efficient among various mammography screening strategies analyzed (biennial screening for women ages 40–60) was not cost effective (Okonkwo and others 2008). An analysis in the Republic of Korea determined that the most cost-efficient mammography strategy (given a prior decision to adopt this modality) is screening every three years for women ages 45–65 (Lee, Jeong, and others 2009).

Treatment

In analyses of hormonal adjuvant therapies post-surgery, Fonseca and others (2009) found that the aromatase inhibitor anastrozole was cost effective compared with tamoxifen in a Brazil-based cost-effectiveness analysis. In Korea, Yang and others (2010) calculated that tamoxifen was very cost effective compared with no hormonal therapy for hormone receptor-positive patients under a variety of assumptions; it was very cost effective or cost effective for hormone receptor-negative patients in only a subset of cases (for example, when the patient was stage III and under age 50). A self-described preliminary cost-effectiveness analysis that excluded certain cost categories found that a combination of oophorectomy and tamoxifen was very cost effective compared with "observation" in a Vietnam-based analysis (Love and others 2002).

The cost-effectiveness of alternative combination chemotherapy regimens post-surgery was investigated for China (Liubao and others 2009) and Korea (Lee, Jee, and others 2009). Liubao and others found that substituting docetaxel for doxorubicin in a treatment package that otherwise included cyclophosphamide was cost effective; Lee and others concluded that substituting docetaxel for fluorouracil in another, more complex regimen was very cost effective. A China-based analysis (Bai and others 2012) concluded that radiation therapy following breast-conserving surgery, compared with no radiation, was very cost effective under a wide range of assumptions.

Combination Screening-Treatment Interventions

The four cost-effectiveness analyses summarized in annex table 3A.3 are all based on the WHO-CHOICE framework (Tan-Torres Edejer and others 2003); each examines alternative intervention packages involving screening and treatment for breast cancer from the perspective of a particular nation or world region. Three of the papers (Ginsberg and others 2012; Groot and others 2006; Salomon and others 2012) investigate roughly the same six options: treat only stage I, only stage II, only stage III, or only stage IV disease; treat all stages; or treat all stages, plus some variant of a breast screening and/or educational program (the "extensive program" option). Zelle and others (2012) evaluated a total of 17 options, including these six and others that differed largely on whether screening was by CBE or mammography and by the age range for screening.

Some modeling assumptions of WHO-CHOICE are not in alignment with standard stage-based treatment protocols. For example, two model options assume that early-stage breast cancer is not treated with chemotherapy when, in practice, most stage II and some stage I breast cancers do warrant chemotherapy on the basis of high-level, prospective randomized clinical trials (Theriault and others 2013). This modeling assumption could lead to incorrect cost-effectiveness conclusions, since chemotherapy is among the most expensive of the required multimodality treatments. WHO-CHOICE also assumes that lumpectomy and sentinel lymph node biopsy is the surgery for Stage I and II when, in practice, breast cancers in LMICs are often too large for breast-conserving surgery, and sentinel lymph node biopsy is often an unavailable technique in these settings such that complete axillary node dissection is routinely performed for all invasive cancers.

There is a general convergence in the recommendations, notwithstanding the diversity in geopolitical setting for these cost-effectiveness analyses. In the Asian and Sub-Saharan African regions analyzed, Groot and others (2006) concluded that the extensive program was very cost effective. For Southeast Asia and Sub-Saharan Africa, Ginsberg and others (2012) found that variants of the extensive program (differing by the assumed fraction of the female population covered) were all cost effective. Focusing on Brazil, Salomon and

others (2012) calculated that the option of treating all four stages of breast cancer was very cost effective, while the extensive program that considered various screening options was cost effective. For Ghana, Zelle and others (2012) found that a variant of the extensive program defined to include biennial CBE screening for women ages 40–69 was cost effective.

Implications for Choosing Cost-Effective Breast Cancer Interventions

Although we agree with Zelle and Baltussen (2013) that many published analyses of breast cancer interventions in LMICs suffer from serious data or methods limitations, noteworthy exceptions exist, including, for the most part, the studies included in annex 3A, tables 3A.1 through 3A.3.

Yet even these conceptually strong studies reveal another important limitation: the range of intervention topics examined represents only a fraction of the important questions in prevention and control. This issue becomes evident by comparing the interventions evaluated in annex 3A, tables 3A.1 through 3A.3, with the range of BHGI-recommended interventions across the cancer continuum (tables 3.1, 3.3, 3.4, and 3.5). Although there are several well-executed cost-effectiveness analyses on early detection and screening (annex 3A, table 3A.1), we found no analyses of comparable scope and quality investigating alternative breast cancer diagnostic techniques and procedures in LMICs. In the treatment domain, we included a handful of excellent cost-effectiveness analyses examining alternative chemotherapy regimens, hormonal therapy strategies, or radiation following breast cancer surgery (annex 3A, table 3A.2); there are no cost-effectiveness analyses examining alternative multimodal adjuvant treatment *strategies* in LMICs.

The cost-effective analyses focused on combination screening-treatment interventions (annex 3A, table 3A.3), while limited, do suggest that *breast cancer intervention packages consistent with the BHGI guidelines* could be evaluated through these analyses and tailored to the resource level that best characterizes the region, nation, or subnational arena for application.

FIELD STUDIES

The summarized evidence for the efficacy of mammography, CBE, and BSE is based largely on studies in HICs and upper-middle-income countries, and the results may not be directly applicable to LMICs. We recommend strongly that early detection programs in LMICs be designed in advance in such a way that they can be evaluated during their early years (McCannon, Berwick, and Massoud 2007). Methods that have been employed for program evaluation include observational studies and randomized trials. Two types of observational studies are comparisons of screening modalities and assessments of temporal trends in stage of disease. Randomized trials may be clinic- or population-based.

Comparison of Modalities

A recent study in Indonesia that compared the use of screening mammography and CBE in a previously unscreened population found similar efficacy for breast cancer detection (Kardinah and others 2014). Midwives and trained lay health workers were trained to perform CBE; volunteers recruited women to come to the clinics for screening. Among the 1,179 previously unscreened women, 289 had a suspicious finding on CBE and/or mammogram (24.5 percent) and required further work-up: 167 had an abnormal CBE and 191 had an abnormal mammogram. After work-up and tissue sampling, 14 breast cancers (1.2 percent) were diagnosed in this unscreened population. Of the 14 cancers, 13 were detected by CBE. Mammography only identified one additional cancer not found by CBE.

These findings suggest that when starting a screening program in a previously unscreened population, most of the prevalent cancers will be found by CBE; mammography adds few additional cancer cases in the initial screening phase. The study also demonstrates that a large fraction of women (14 percent in this study) will require diagnostic evaluation beyond CBE. Screening programs based on CBE will require significant diagnostic infrastructure based on additional imaging and tissue sampling.

Temporal Trends in Stage of Disease

In Malaysia, almost all diagnosed cancers are treated in a single referral hospital in the State of Sarawak, with a population of approximately two million. By reviewing the medical records of all women with breast cancer at that hospital before and after an early detection initiative, it was possible to assess the impact of the program on breast cancer in the population (Devi, Tang, and Corbex 2007). The intervention consisted of the following elements:

- Training community nurses who worked in rural clinics to perform CBE and teach BSE
- Circulating pamphlets and posters to motivate women to go to their nearest clinic at the earliest signs of a breast problem

- Instructing community nurses to hold health education talks and discussion groups on early diagnosis during monthly visits to villages, to teach BSE and perform CBE
- Strengthening the system for referring women with signs and symptoms of breast cancer to first-level hospitals for diagnosis

The proportion of breast cancers that were diagnosed at late stages (stage III or IV) was 77 percent in 1993 before the program began and 37 percent in 1998 after the program began. Since these statistics are for nearly all women in the population who were treated for breast cancer, regardless of whether they participated in the program, they reflect the impact of the program on the population and suggest that the program had a positive impact.

Population-Based Randomized Trial

In a cluster randomized trial of CBE and cervical cancer screening by visual inspection of the cervix after acetic acid application (VIA) by lay women in Mumbai (Mittra and others 2010), 20 informal settlements (slums) were randomly allocated to screening or control groups (10 slums in each group) and women ages 35–64 years in each slum were considered eligible for the trial; more than 75,000 women were eligible for each arm of the study. Women with a tenth-grade education were trained to perform CBE and VIA; these trained workers then invited women in the screening arm of the trial for screening; women in the control arm received no screening. Three of four rounds of screening at two-year intervals were completed between 1998 and 2005.

The preliminary results showed that more breast cancers were detected in the screening arm than in the control arm (125 versus 87 cases). The proportion of cancers detected at early stages was higher in the screened arm than the control arm (62 percent versus 44 percent, stage 0, I, or II disease); this is a difference that achieved statistical difference by the third cycle of screening ($p = 0.004$). These results indicate that CBE performed by specially trained women may be efficacious in reducing mortality from breast cancer in the slums of India; the results clearly indicate that continuation of the trial is warranted to provide direct evidence for a reduction in breast cancer mortality by CBE. The analyses of the data from this trial include all women and all breast cancers in the screening group, whether or not the women were actually screened. The results indicate the impact of screening as it was actually implemented in the target population.

Clinic-Based Cluster Randomized Trial

The National Cancer Institute of Colombia (Instituto Nacional de Cancerología, or INC; 2006) adapted the BHGI guidelines for MICs to develop a pilot screening program in Bogotá. The INC guidelines recommend screening with annual clinical CBE and mammography every two years for women ages 50–69. Based on these guidelines, the INC designed a pilot study to evaluate opportunistic screening as a programmatic approach to improve early detection in the country (Murillo and others 2008). *Opportunistic screening* is defined as the systematic offer of CBE and mammography for all women ages 50–69 who visit health centers on their own, regardless of motivation. It implies that screening is clinic-based with no outreach outside the health centers. The primary objectives of the study are to evaluate the effect of opportunistic screening on population coverage, to determine the impact of opportunistic screening on clinical stage at diagnosis, and to identify the basic requirements for implementing opportunistic screening within the Colombian health system.

A cluster randomized trial was undertaken with health centers as the units of randomization. The screening consisted of recruitment in the clinics and follow-up by health care assistants (auxiliary nurses, backed up by registered nurses), CBE performed by general practitioners, and mammography by radiologists and radiology technicians. Mammography quality control comprises examination and adjustment of mammography machines before starting screening, quality control of mammography films, and evaluation of mammography reading according to international standards. CBE quality control was done by breast surgeons who periodically visit health centers to evaluate general practitioners' practice of CBE and differences between the diagnoses of the surgeons and general practitioners are recorded. In the control group, women who would be eligible for screening if they had been in the intervention group are given general information about breast cancer but are not offered screening.

Women attending the health centers regularly were assigned to opportunistic screening or no intervention, according to the random allocation of their clinic. Because the Colombian health system is insurance-oriented, randomization was stratified by health insurance company to control for the effect of administrative factors on access to screening and diagnosis. After the enrollment of approximately 12,000 women (about 6,000 per arm), 88.9 percent and 99.8 percent, respectively, in the opportunistic screening branch who were offered screening had a

mammogram and a CBE, compared with 11.7 percent and 5 percent, respectively, of the control women. The preliminary results show a threefold greater rate of breast cancer detection in the screened group than in the control group (15 and 5 cases, respectively) and a higher proportion of cases at an early stage at diagnosis (13/15 = 86.6 percent versus 3/5 = 60 percent). Furthermore, the enrollment rate (2.9 patients per center per day) does not overburden the general practitioners or other clinic staff. At completion of follow-up, it should be possible to compare the stage of disease at diagnosis in the women screened compared with the control arm. It will also be possible to compare the stage distribution at diagnosis between the two groups, providing a measure of the impact of the screening program in the population of women served by the clinics participating in the trial.

CONCLUSIONS

Population-Based Screening Mammography

Breast cancer screening remains a major area of controversy. In HICs, the debate persists about whether mammographic screening leads to increased detection of cancers that would not become significant threats to a woman's life in her natural lifetime. Treatment of these cancers would, by definition, constitute overtreatment. Arguing against this premise is the fact that in nearly all countries where age-adjusted breast cancer mortality is decreasing, screening mammography has been established, for example, Australia, Denmark, Italy, Spain, and the United States. In contrast, Japan has not implemented screening mammography; despite adequate treatment standards, breast cancer mortality has plateaued and stabilized, but it has not yet decreased. These observations are consistent with Cancer Intervention and Surveillance Modeling Network (CISNET) modeling, which demonstrates synergy between screening and adjuvant treatment in reducing breast cancer mortality at the population level (Berry and others 2005); the modeling suggests that screening mammography will continue to be important in breast cancer control for the foreseeable future.

The effectiveness of screening mammography could be improved if it were possible to identify patients who did not need immediate treatment, even though a lesion is found. Although the debate continues regarding the age at which screening mammography should begin—age 40 years or age 50 years—new biological research on cancer progression may identify a patient subgroup warranting a wait-and-watch strategy.

Clinical Breast Examination as an Early Detection Tool

Screening mammography is unfeasible in most of the world, but CBE is a practical option in many LMICs to provide at least basic breast cancer treatment. Evidence suggests that in LMICs with rising breast cancer incidence rates, CBE will help curb the rise in mortality. What remains unknown is whether CBE, combined with highly effective treatment, can further curb breast cancer mortality and lower breast cancer mortality at the population level. The increasing use of CBE provides opportunities for research on health care delivery in limited resource settings.

Diagnosis, Treatment, and Patient Triage

Fine-needle aspiration and core needle biopsy tissue sampling techniques are necessary for diagnosing palpable lumps and distinguishing between benign and malignant lesions. However, the key systems questions go beyond selection of a tissue sampling technology. The cost of needles, availability of pathology services, and patient selection to determine which patients should be brought to second-level or third-level care centers require systematic assessment of existing resources in a health care delivery system. Before an early detection strategy is implemented, an assessment must be made of available resources, missing tools, and geographic distribution of the patient population, as well as social and cultural issues that could affect patient participation.

Once a situation-appropriate early detection, diagnosis, and patient triage strategy is devised, economic evaluation becomes relevant and important. The evolution of breast health systems will require pilot projects to determine what systems can work and, in parallel, it will require new analyses to assess economic impact. It will be important to proceed in a stepwise, systematic fashion, documenting outcomes, so that successful models can be adapted and adopted in other settings.

Economic Analyses and the Future of Breast Health Care in LMICs

The BHGI resource-stratified guideline approach can be used in priority-setting analyses in LMICs. Cost-effectiveness analyses can identify interventions yielding the greatest gain in health (for example, life years gained and disability-adjusted life years averted) per dollar spent, from which practical strategies can be built. We recognize, however, the limitations in comparing and extrapolating results from one country to another and

among groups within the same population, depending on the methodology, input data, and assumptions in the studies. A core principle in developing BHGI guidelines has been to recognize that one size does not fit all.

The WHO-CHOICE framework has brought consistency, but these models are highly simplified compared with the breast cancer models used in HICs. In each case, decisions must be made:

- Determining which analytical models to use (WHO-CHOICE, CISNET, other micro-simulation models)
- Finding appropriate data that are as faithful as possible to the place of application
- Sorting out at the policy level how to work in concert with national and local health agencies so the modeling is not only academically sound but practical for local decision making

The resource-stratified approach, although enormously challenging, identifies key building blocks for cost-effectiveness analysis models that will translate resource-conditional breast health guidelines into prioritized intervention strategies.

NOTES

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

- Annex 3A: Summary of Salient Features and Recommendations of the Cost-effectiveness Studies Relevant to Breast Cancer Screening, Treatment, and Control in Low- and Middle-Income Countries.

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

- Low-income countries (LICs): US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  - Lower-middle-income: US$1,046–US$4,125
  - Upper-middle-income (UMICs): US$4,126–US$12,745
- High-income countries (HICs): US$12,746 or more

1. Maps and figures in this chapter are based on incidence and mortality estimates for ages 0 to 69, consistent with reporting in all *DCP3* volumes. Global cancer statistics are estimates for the year 2012 and have been provided by the International Agency for Research on Cancer from its GLOBOCAN 2012 database. Observable population-based data were derived from *Cancer Incidence in Five Continents, 10th edition*, and for trends over time from *CI5 Plus* (http://ci5.iarc.fr/CI5plus/Default.aspx). The discussion of burden (including risk factors), however, includes all ages unless otherwise noted. Interventions also apply to all age groups, except where age ranges or cutoffs are specified.

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