Guidelines for International Breast Health and Cancer Control–Implementation

Supplement to ***Cancer***

Guideline Implementation for Breast Healthcare in Low-Income and Middle-Income Countries

Overview of the Breast Health Global Initiative Global Summit 2007

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Breast cancer outcomes in low- and middle-income countries (LMCs) correlate with the degree to which 1) cancers are detected at early stages, 2) newly detected cancers can be diagnosed correctly, and 3) appropriately selected multimodality treatment can be provided properly in a timely fashion. The Breast Health Global Initiative (BHGI) invited international experts to review and revise previously developed BHGI resource-stratified guideline tables for early detection, diagnosis, treatment, and healthcare systems. Focus groups addressed specific issues in breast pathology, radiation therapy, and management of locally advanced disease. Process metrics were developed based on the priorities established in the guideline stratification. The groups indicated that cancer prevention through health behavior modification could influence breast cancer incidence in LMCs. Diagnosing breast cancer at earlier stages will reduce breast cancer mortality. Programs to promote breast self-awareness and clinical breast examination and resource-adapted mammographic screening are important early detection steps. Breast imaging, initially with ultrasound and, at higher resource levels with diagnostic mammography, improves preoperative diagnostic assessment and permits image-guided needle sampling. Multimodality therapy includes surgery, radiation, and systemic therapies. Government intervention is needed to address drug-delivery problems relating to high cost and poor access. Guideline dissemination and implementation research plays a crucial role in improving care. Adaptation of technology is needed in LMCs, especially for breast imaging, pathology, radiation therapy, and systemic treatment. Curricula for education and training

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in LMCs should be developed, applied, and studied in LMC-based learning laboratories to aid information transfer of evidence-based BHGI guidelines. ***Cancer* 2008;113(8 suppl):2221–43.** *Published 2008 by the American Cancer Society.**

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Cancer is the second most common cause of death in low-income and middle-income countries (LMCs), more than respiratory infections and diseases, human immunodeficiency virus/acquired immunodeficiency syndrome, diarrheal diseases, and tuberculosis.[1] Issued during the 58th World Health Assembly in 2005, the World Health Organization (WHO) Resolution on Cancer Prevention and Control (WHA58.22) urges member states to collaborate with WHO in the development of cancer control programs aimed at reducing cancer mortality and improving quality of life for cancer patients and their families.[2] This landmark WHO resolution calls on LMCs to integrate cancer control programs within existing health systems, to identify evidence-based, sustainable actions across the continuum of cancer care, and to make the best use of resources to benefit their populations afflicted with cancer. LMCs are urged to support research translating knowledge into effective public health measures for cancer prevention and treatment, to improve access to appropriate technologies for the early diagnosis and treatment of cancer, and to promote research evaluating low-cost interventions that are affordable and sustainable. In alignment with the WHO, the Institute of Medicine has called for the development and implementation of resource level-appropriate guidelines for the overall management of major cancers for which highly effective treatments are available, to provide a framework for systematic improvement in cancer control in LMCs.[3]

Among women, breast cancer is the most common cause of cancer-related death worldwide, and case fatality rates are highest in low-resource countries. Over 411,000 deaths result from breast cancer annually, accounting for >1.6% of female deaths from all causes. Projecting to 2010, the annual global burden of new breast cancer cases will be 1.5 million, and an ever-increasing majority will be from LMCs.[4] Globally, breast cancer is the most common cancer among women, comprising 23% of the 1.1 million female cancers that are newly diagnosed each year.[5,6] Approximately 4.4 million women who were diagnosed with breast cancer in the last 5 year currently are alive, making breast cancer the single most prevalent cancer in the world.[5] Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, the majority of breast cancer deaths in fact occur each year in developing rather than developed countries.[4]

Breast cancer is an urgent public health problem in high-resource regions and is becoming an increasingly urgent problem in low-resource regions, in which incidence rates have been increasing by up to 5% per year.[7,8] Although global breast cancer incidence rates have increased by approximately 0.5% annually since 1990, breast cancer rates in Japan, Singapore, and Korea have doubled or tripled in the past 40 years, and China's urban registries document 20% to 30% increases in the past decade alone.[9] In the urban areas of India, cervical cancer had the highest incidence among female cancers 15 years ago but now has been overtaken by breast cancer as the most commonly diagnosed cancer among women.[10] Despite the younger age structure of most developing countries, breast cancer already accounts for approximately 45% of the incident cases and 54% of the annual deaths.[4]

The breast cancer burden in LMCs predictably will continue to increase in coming years on the basis of 1) increasing life expectancy and 2) shifting reproductive and behavioral patterns associated with heightened breast cancer risk. Even assuming conservatively that there will be no change in underlying age-specific rates, there could be a nearly 50% increase in global incidence and mortality between 2002 and 2020 due to demographic changes alone. These increases will be disproportionately high in the developing world, with projected respective increases of 55% and 58% in incidence and mortality by the year 2020 in comparison to the known statistics from only 18 years prior.[4] These statistics most likely underestimate the actual rising breast cancer rates, because the few data available from LMCs reveal increases in breast cancer age-specific incidence and mortality rates, especially in recent birth cohorts. This is especially true among urban women and most likely is caused at least in part by the adoption of Western lifestyles, which tend to promote decreased parity, delayed childbirth, decreased physical exercise, and dietary habits associated with earlier

menarche, all of which have been associated with increasing rates of postmenopausal breast cancer.[6,9,11]

Despite significant scientific advances in breast cancer management, most of the world faces resource constraints that limit the capacity to improve early detection, diagnosis, and treatment of the disease. In LMCs, worsened cancer survival is largely because of late disease stage at presentation, which leads to particularly poor outcomes when coupled with limited diagnosis and treatment capacity.[12] It was reported in 2001 that, in India, between 50% and 70% of new patients present with locally advanced breast cancer (LABC) (stage III) or metastatic breast cancer (MBC) (stage IV) breast cancer at diagnosis.[13] By comparison, approximately 44% of European (EUROCARE) and 36% of American (Surveillance, Epidemiology, and End Results) breast cancer cases reportedly were locally advanced or metastatic at diagnosis between 1990 and 1992.[14] Compounding the problem of late diagnosis, breast cancer fatality rates are high, because LMCs typically lack the major components of healthcare infrastructure and resources necessary to implement improved methods for the early detection, diagnosis, and treatment of breast cancer.[15,16] Although most LMCs have not yet identified cancer as a priority healthcare issue, it will become an important health problem as the control of communicable diseases improves.[6]

In high-resource countries, evidence-based guidelines outlining optimal approaches to the early detection, diagnosis, and treatment of breast cancer have been defined and disseminated.[17-20] These guidelines are resource neutral, they fail to consider variable resource distributions where overall standards of living are high, and they fail to recognize ubiquitous deficits in infrastructure and resources in LMCs. Moreover, they do not consider implementation costs or provide guidance on how a suboptimal system can be improved incrementally toward an optimal system. Such guidelines defining optimal breast care and services, as pointed out by the WHO, have limited use in resource-constrained countries,[21] and there is a need for resource-based guidance related to strategies for reducing the burden of breast cancer for settings in which optimal care is not feasible.

The development and implementation of international, evidence-based breast healthcare guidelines oriented to countries or regions of the world with limited financial resources is a crucial step toward improving breast healthcare and breast cancer care in these regions. Current evidence regarding the value of earlier detection and cost-effective diagnosis and treatment can be applied to define 'best practices with limited resources' for breast healthcare. Although healthcare strategies may differ measurably, improvement in breast cancer outcomes can be achieved using the best standard of care that is practical in a given setting.

Cosponsored by the Fred Hutchinson Cancer Research Center and by Susan G. Komen for the Cure, the Breast Health Global Initiative (BHGI) strives to develop evidence-based, economically feasible, and culturally appropriate guidelines that can be used in nations with limited healthcare resources to improve breast cancer outcomes. The BHGI held its first 2 Global Summits in Seattle, Washington in 2002 and Bethesda, Maryland in 2005 to address healthcare disparities[22] and evidence-based resource allocation[23] as they relate to breast cancer in LMCs. Modeled after the approach of the National Comprehensive Cancer Network,[24] the BHGI developed and applied an evidence-based consensus panel process (now formally endorsed by the Institute of Medicine[3]) to create resource-sensitive guidelines for breast cancer early detection,[25,26] diagnosis,[27,28] treatment,[29,30] and healthcare systems[31] as they relate to breast healthcare in LMCs. The BHGI guidelines are intended to assist ministers of health, policymakers, administrators, and institutions in prioritizing resource allocation as breast cancer treatment programs are implemented and developed in their resource-constrained countries.

The goal of the third BHGI Global Summit held in 2007 was to address the implementation of breast healthcare guidelines in LMCs. The BHGI resource-stratified guidelines that were formulated at the second Global Summit were broadened to identify effective implementation strategies and to measure the success of that implementation through the identification of key process metrics. The purpose of this article is to summarize the outcome of the 2007 BHGI Global Summit and to provide an outline for the next steps in systematic and comprehensive guideline implementation in LMCs with the goals of advancing breast healthcare delivery, improving quality of life for breast cancer patients and their families, alleviating or preventing breast cancer morbidity, and ultimately decreasing breast cancer mortality in these countries.

MATERIALS AND METHODS

The BHGI guidelines published in 2006[26,28,30,31] were reexamined, revised, and extended at the third Global Summit, which was held October 1 through 4, 2007 and was hosted by the American Society of Clinical Oncology (ASCO) in Budapest, Hungary. Nineteen national and international groups and agencies joined the BHGI as scientific organizational

partners, collaborating organizations, and participating organizations. The BHGI consensus conference methodology, which was used to organize both of the prior BHGI Global Summits, has been described previously.[23] The 2007 BHGI Scientific Advisory Committee nominated, reviewed, and ratified the selection of the 8 BHGI panel co-chairs for the 4 2007 Consensus Panels: Early Detection, Diagnosis, Treatment, and Health Care Systems. The 2007 panel co-chairs, in turn, worked with BHGI leadership to select panelists for each of the 4 consensus panels and to set assigned topics and speakers for plenary presentations.

Each panel held 1 full-day meeting that included a morning session of plenary presentations and an afternoon session of discussion and debate among panelists regarding the content of their consensus article. Each morning began with a presentation by a breast cancer advocate from a limited-resource country that summarized the personal experience of women facing breast cancer in that country. Each afternoon began with a summary of a current or future BHGI pilot project for implementation in a selected LMC.

Healthcare resources, as defined previously in the 2005 BHGI Global Summit, were stratified according to a 4-tiered system based on available resources relevant to program implementation:

- **Basic level**—Core resources or fundamental services that are absolutely necessary for any breast healthcare system to function; basic-level services typically are applied in a single clinical interaction.
- **Limited level**—Second-tier resources or services that are intended to produce major improvements in outcome such as increased survival, and are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple clinical interactions.
- **Enhanced level**—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 choice.
- **Maximal level**—High-level resources or services that may be used in some high-resource countries and/or may be recommended by breast care guidelines that do not adapt to resource constraints but that nonetheless should be considered a lower priority than those resources or services listed in the basic, limited, or enhanced categories on the basis of extreme cost and/or impracticality for broad use in a resource-limited environment; to be useful, maximal-level resources typically depend on the existence and functionality of all lower level resources.

On the basis of this stratification scheme, each of the 4 panels debated key issues related to guideline implementation for early detection,[32] diagnosis,[33] treatment[34] and healthcare systems.[35] Each panel's discussion was recorded and transcribed, and the transcripts were used as a starting point for writing the 4 consensus articles. Panel co-chairs coordinated the writing of those articles, sections of which were coauthored and/or edited by participating panelists. Consensus article drafts were reviewed and edited by all coauthors. Final drafting, including the resolution of disagreements among coauthors, as was overseen by the panel co-chairs as organized by BHGI staff.

In parallel with the afternoon Consensus Panel meetings, selected focus groups met to address discipline-specific topics related to LMC program implementation. Of these, 3 groups chose to prepare articles that would summarize their discussion and findings: the Radiation Therapy Focus Group,[36] the Systemic Therapy Focus Group,[37] and the Breast Pathology Focus Group.[38] Also, morning plenary speakers were invited to submit individual articles on their topics for publication together with the consensus articles. In lieu of the standard, external peer-review process, submitted articles underwent an internal, blinded peer-review process. All individual article submissions underwent blinded peer-review by panel co-chairs and selected internal BHGI nonauthor reviewers. Individual articles that did not address issues specific to LMCs or that did not directly complement issues related to guideline implementation were referred for journal submission outside of the BHGI guidelines. After final acceptance, all focus group and individual articles were coordinated with the consensus guideline articles for internal cross referencing. Thus, the combination of consensus, focus group, and individual articles represents a complete BHGI guideline compendium, which is the final work product of the 2007 Global Summit as published as a complete unit in this *Cancer* supplement.

RESULTS

Prevention Through Risk Factor Modification

A complete discussion of breast cancer prevention through risk factor modification in LMCs is provided by McTiernan et al separately in this BHGI supplement to *Cancer*.[39] In summary, health behaviors that may reduce the risk of breast cancer include prolonged lactation, regular physical activity, weight control, avoiding excess alcohol intake, avoiding prolonged use of exogenous hormone therapy, and avoiding excessive radiation exposure. These beha-

viors, although they have not been proven in clinical trials to reduce risk, are likely to be beneficial. Information on them can be provided as a prevention strategy in LMCs, although the methods of information delivery and follow-up will depend on financial and personnel resources. The magnitude of absolute risk reduction based on risk factor management is somewhat unclear. However, any of these health behaviors can reduce risk for other chronic diseases, so they may be of high interest for general public health in both LMCs and high-income countries.

Several strategies are available for reducing breast cancer risk in countries with lower resources, but few of them have completed rigorous testing in clinical trials.[39] Strategies to increase the prevalence and length of lactation may reduce risk for breast cancer in mothers in addition to providing nutritional benefits for infants and small children. Increased adiposity, a sedentary lifestyle, and moderate to high levels of alcohol use are associated with increased risk of breast cancer. The evidence of a role for specific dietary components is less clear. For individual women, counseling should include increasing physical activity and balancing energy such that weight remains stable over a lifetime and, preferably, with the body mass index remaining <25 kg/m^2. The provision of public transport and community-level and workplace facilities to enable these activities should be encouraged. Counseling should include limiting alcohol intake to no more than 1 drink per day on average. The use of combined estrogen/progesterone menopause hormone therapy should be limited to women with refractory menopausal symptoms and for as short a period as possible.

Early Detection

Strategies to reduce breast cancer risk cannot eliminate the majority of breast cancers that develop in LMCs, and breast cancer remains the most prominent cancer among women even in countries that lack the most common 'Westernized' breast cancer risk factors.[9] Early disease stage at detection, as discussed fully in the early detection consensus article provided separately in this BHGI supplement,[32] is a key determinant of breast cancer outcome, because earlier staged disease has lower breast cancer mortality and requires fewer resources to provide effective treatment (Fig. 1).

Public education is a key first step in implementing breast health programs (Fig. 1, column 1). The approach and scope of the public education program determine the success of early detection, as measured by stage at diagnosis, and also will drive the breadth of resource allocation needed for program implementation. Public education programs, as discussed fully by Kreps and Sivaram,[40] must include health education messages that convey the idea that breast cancer is curable in the majority of women when it is detected early, diagnosed accurately, and treated appropriately. To optimize success, communication methods need to be adapted to the cultural boundaries and taboos that invariably surround breast cancer diagnosis but that may differ among and within countries, depending on the social context and common healthcare belief systems.

Breast cancer screening modalities include breast self-examination, clinical breast examination (CBE), and screening mammography (Fig. 1, column 2). The effectiveness and efficiency of each of these strategies must be considered in the context of resource availability and population-based need, which also determines the primary goal of a screening program (Fig. 1, column 3). Screening mammography is the only single modality with which prospective randomized trials have demonstrated an improvement breast cancer mortality, but its cost is prohibitive in many settings.[41] A survey of oncology experts reported by Cazap et al indicated that $>90\%$ of Latin American countries had no national law or guideline for mammography screening.[42] When screening mammography is used in LMCs, target populations and screening intervals need to consider what is optimal for the overall population and within the scope of available resources.[32]

In most developing countries, a larger proportion of women are younger. Breast cancer incidence rates are lower in younger women. This means that screening programs will have a lower yield in terms of cases detected per 1000 women screened. The resource implications of screening this type of population should be considered carefully on the basis of age distribution and likely incidence rates of the population in question. When introducing mammography screening, a strong case can be made for initiating screening in a limited age group of women in which age-specific incidence rates indicate that it is likely to be most productive; then, as the program gains experience, it may be expanded to additional age groups.[32] Those responsible for screening programs should consider the age-specific incidence rates of breast cancer in their country, the available resources, and the most recent information regarding the effectiveness of screening in various age groups to determine the appropriate targets for mammography screening.

Unlike screening mammography, it has not been demonstrated in randomized trials that CBE improves breast cancer mortality. Studies of CBE in

Early Detection Resource Allocation

Level of resources	Public Education and Awareness	Detection Methods	Evaluation Goal
Basic	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)	Clinical history and CBE	Breast health awareness regarding value of early detection in improving breast cancer outcome
Limited	Culturally and linguistically appropriate targeted outreach/education encouraging CBE for age groups at higher risk administered at district/provincial level using healthcare providers in the field	Diagnostic breast US +/- diagnostic mammography in women with positive CBE Mammographic screening of target group*	Downsizing of symptomatic disease
Enhanced	Regional awareness programs regarding breast health linked to general health and women's health programs	Mammographic screening every 2 years in women ages 50-69* Consider mammographic screening every 12-18 months in women ages 40-49*	Downsizing and/or downstaging of asymptomatic disease in women in highest yield target groups
Maximal	National awareness campaigns regarding breast health using media	Consider annual mammographic screening in women ages 40 and older Other imaging technologies as appropriate for high-risk groups†	Downsizing and/or downstaging of asymptomatic disease in women in all risk groups

FIGURE 1. Resource allocation for early detection for breast cancer. CBE indicates clinical breast examination; US, ultrasound; +/−, with or without. *Target group selection for mammographic screening should consider breast cancer demographics and resource constraints within the population. Please see text for complete discussion. †It has been demonstrated that breast magnetic resonance imaging is more sensitive than mammography in detecting tumors in asymptomatic women who have an inherited susceptibility to breast cancer. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in some higher income settings.

LMCs have been undertaken but have been problematic and inconclusive.[43] Inferential studies suggest that clinical down-sizing of palpable disease should improve outcome.[44] However, the establishment of clinical evaluation, which includes patient history as well as CBE, is a practical and necessary prerequisite for the operation of any early detection program, especially in an LMC in which patients typically present with advanced disease stage, and, at a minimum, provides a practical linkage between breast cancer early detection and diagnosis.

Diagnosis

Breast diagnosis consists of clinical evaluation, imaging and laboratory studies, and surgical pathology, each aspect of which is reviewed comprehensively separately in this BHGI supplement.[33] Obtaining a patient's history, specific both to her breasts and to her general health, provides important information for the clinical assessment of breast disease and comorbid disease that may influence breast cancer therapy choices (Fig. 2, column 1). Focused CBE and a complete physical examination provide guidance on the extent of disease, presence of metastatic disease, and ability to tolerate more aggressive therapeutic regimens.

Breast imaging, initially with ultrasound and, at higher resource levels, with diagnostic mammography improves preoperative diagnostic assessment, and also permits image-guided needle sampling of suspicious lesions (Fig. 2, column 2). Diagnostic mammography, although it is helpful for breast-conservation therapy, is not mandatory in LMCs when these resources are lacking.[45] Additional imaging studies facilitate metastatic workup and, thus, patient treatment selection. Selected laboratory studies are required for the safe administration of cytotoxic chemotherapy, which is a limited-level resource for treatment of stage I breast cancer (Fig. 3) and a

Diagnosis Resource Allocation

Level of resources	Clinical	Imaging and Lab Tests	Pathology
Basic	History Physical examination Clinical breast examination (CBE) Tissue sampling for cancer diagnosis (cytologic or histologic) prior to initiation of treatment	*	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† Determination and reporting of TNM stage
Limited	US-guided FNAB of sonographically suspicious axillary nodes Sentinel lymph node (SLN) biopsy with blue dye‡	Diagnostic breast ultrasound (US) Plain chest and skeletal radiography Liver US Blood chemistry profile* Complete blood count (CBC)*	Determination of ER status by IHC† Determination of margin status, DCIS content, presence of LVI Frozen section or touch prep SLN analysis §
Enhanced	Image guided breast sampling Preoperative needle localization under mammo and/or US guidance SLN biopsy using radiotracer‡	Diagnostic mammography Specimen radiography Bone scan, CT scan Cardiac function monitoring	Measurement of HER-2/neu overexpression or gene amplification§ Determination of PR status by IHC
Maximal		PET scan, MIBI scan, breast MRI, BRCA1/2 testing Mammographic double reading	IHC staining of sentinel nodes for cytokeratin to detect micrometastases Pathology double reading Gene profiling tests

FIGURE 2. Diagnosis resource table for breast cancer. CBE indicates clinical breast examination; TNM, classification of malignant tumor system; US, ultrasound; FNAB, fine-needle aspiration biopsy; SLN, sentinel lymph node; CBC, complete blood count; ER, estrogen receptor; IHC, immunohistochemistry; DCIS, ductal carcinoma in situ; LVI, lymphovascular invasion; mammo, mammography; CT, computed tomography; HER-2, human epidermal growth factor receptor 2; PR, progesterone receptor; PET, positron emission tomography; MIBI, methoxy-isobutyl-isonitrile; BRCA1/2, breast cancer genes 1 and 2. *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. †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 also should be provided. ‡The use of SLN biopsy requires clinical and laboratory validation of the SLN technique. §If the costs associated with trastuzumab were substantially lower, trastuzumab would be used as a limited-level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. Maximal resources level should not be targeted for implementation in LMCs, even though they may be used in some higher income settings.

basic-level resource for the treatment of lymph node-positive, estrogen receptor (ER)-negative, and locally advanced disease (Figs. 4 and 5).

Although surgical excision for diagnosis can be used when alternatives are unavailable, needle sampling is highly preferable for reasons fully delineated in prior BHGI publications.[27,28] Under no circumstances should mastectomy be considered an acceptable method for tissue 'sampling.'[27] Fine-needle aspiration biopsy (FNAB) is recognized as the most cost-effective procedure with the shortest turnaround time.[46] The choice of sampling procedures (FNAB, core-needle biopsy, or excisional biopsy) should be based on the availability and access to cytopathologists/pathologists in each medical community and on the training and experience of the available pathology specialists, as fully discussed by the BHGI Breast Pathology Focus Group.[38] Sentinel lymph node biopsy, although it is developed in the context of high-income countries, actually can be used by breast surgery teams in lower income settings at low cost when the technique is restricted to the use of blue dye without radiotracer.[47]

Quality surgical pathology is critical to breast program function (Fig. 2, column 3).[33,38] The availability of predictive tumor markers, especially ER

Treatment Resource Allocation: Stage I Breast Cancer

Level of resources	Local-Regional Treatment		Systemic Treatment (Adjuvant)		
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Biological Therapy
Basic	Modified radical mastectomy			Oophorectomy in premenopausal women Tamoxifen*	
Limited	Breast conserving surgery† Sentinel lymph node (SLN) biopsy with blue dye‡		Classical CMF§ AC, EC, or FAC§		‖
Enhanced	SLN biopsy using radiotracer‡ Breast reconstruction surgery	Breast-conserving whole-breast irradiation as part of breast-conserving therapy§	Taxanes	Aromatase inhibitors LH-RH agonists	Trastuzumab for treating HER-2/neu positive disease‖
Maximal			Growth factors Dose-dense chemotherapy		

FIGURE 3. Treatment resource allocation table for stage I breast cancer. SLN indicates sentinel lymph node; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone-releasing hormone; HER-2/neu, human epidermal growth factor receptor 2. *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. †Breast-conserving surgery can be provided as a limited-level resource but requires breast-conserving radiation therapy. If breast-conserving radiation is unavailable, then patients should be transferred to a higher level facility for postlumpectomy radiation. ‡The use of SLN biopsy requires clinical and laboratory validation of the SLN technique. §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. ‖If the costs associated with trastuzumab were substantially lower, trastuzumab would be used as a limited-level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in some higher income settings.

testing, is critical to the proper selection of cancer therapy when endocrine therapies are available, recognizing that quality assessment of immunohistochemical testing is important to avoid false-negative results. Interdisciplinary communication underlies the basis of success for breast diagnostic programs at all economic levels. Furthermore, the interaction of the pathologist with the radiologist and the surgeon (interdisciplinary team collaboration) is critical in the examination and reporting of the pathology specimen, because the clinical situation in which the specimen was obtained can have a marked influence on the significance of certain pathologic findings and, in the case of cancer, can be critical in determining accurate tumor staging.

Treatment

Breast cancer treatment consists of surgery, radiation therapy, and systemic therapy, each aspect of which is reviewed comprehensively separately in this BHGI supplement[34] and is summarized below (Figs. 3-6).

Treatment Resource Allocation: Stage II Breast Cancer

Level of resources	Local-Regional Treatment		Systemic Treatment (Adjuvant)		
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Biological Therapy
Basic	Modified radical mastectomy	*	Classical CMF† AC, EC, or FAC†	Oophorectomy in premenopausal women Tamoxifen‡	
Limited	Breast conserving surgery§ Sentinel lymph node (SLN) biopsy with blue dye‖	Postmastectomy irradiation of chest wall and regional nodes for high-risk cases*			¶
Enhanced	SLN biopsy using radiotracer‖ Breast reconstruction surgery	Breast-conserving whole-breast irradiation as part of breast-conserving therapy§	Taxanes	Aromatase inhibitors LH-RH agonists	Trastuzumab for treating HER-2/neu positive disease¶
Maximal			Growth factors Dose-dense chemotherapy		

FIGURE 4. Treatment resource allocation table for stage II breast cancer. CMF indicates cyclophosphamide, methotrexate, and 5-fluorouracil; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; SLN, sentinel lymph node; LH-RH, luteinizing hormone-releasing hormone; HER-2/neu, human epidermal growth factor receptor 2. *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. †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. ‡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. §Breast-conserving surgery can be provided as a limited-level resource but requires breast-conserving radiation therapy. If breast-conserving radiation is unavailable, then patients should be transferred to a higher level facility for postlumpectomy radiation. ‖The use of SLN biopsy requires clinical and laboratory validation of the SLN technique. ¶If the costs associated with trastuzumab were substantially lower, trastuzumab would be used at a limited level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in some higher income settings.

Surgical therapy

The ability to perform modified radical mastectomy (MRM) is the mainstay of locoregional treatment at the basic level of breast healthcare (Figs. 3-5, column 1). Although MRM (total mastectomy plus level I/II axillary lymph node dissection) is considered fundamental surgical training in high-income countries, surgeons from LMCs may have had less exposure to the procedure and may not be knowledgeable regarding the operation's proper technical execution. A retrospective review of patients referred from outside institutions to Tata Memorial Hospital in Mumbai, India indicated that, of 424 women who underwent 'therapeutic' surgical interventions, 191 women (45%) were judged to have had incomplete surgery. Of these, 153 patients underwent completion revision surgery, and 123 had residual axillary lymph nodes, including 64 patients (52%) with metastatic lymph nodes that had been left behind in the axillary bed.[48]

Treatment Resource Allocation: Locally Advanced Breast Cancer

Level of resources	Local-Regional Treatment		Systemic Treatment (Adjuvant or Neoadjuvant)		
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Biological Therapy
Basic	Modified radical mastectomy	*	Preoperative chemotherapy with AC, EC, FAC or CMF†	Oophorectomy in premenopausal women Tamoxifen‡	
Limited		Postmastectomy irradiation of chest wall and regional nodes*			§
Enhanced	Breast-conserving surgery Breast reconstruction surgery	Breast-conserving whole-breast irradiation as part of breast-conserving therapy	Taxanes	Aromatase inhibitors LH-RH agonists	Trastuzumab for treating HER-2/neu positive disease§
Maximal			Growth factors Dose-dense chemotherapy		

FIGURE 5. Treatment resource allocation table for locally advanced breast cancer. AC indicates doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; LH-RH, luteinizing hormone-releasing hormone; HER-2/neu, human epidermal growth factor receptor 2. *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. †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. ‡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. §If the costs associated with trastuzumab were substantially lower, trastuzumab would be used at a limited level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in some higher income settings.

Radiation therapy

The availability of radiation therapy allows for consideration of breast-conserving therapy, postmastectomy chest wall radiation, and palliation of painful or symptomatic metastases (Figs. 3-6, column 2). Radiation therapy, as detailed by the BHGI Radiation Treatment Focus Group,[36] has a major impact on local tumor control for early and locally advanced disease, and effective and safe radiation therapy also can improve overall survival rates.[49,50]

The use of evidence-based doses and techniques is crucial for achieving the best possible clinical outcomes and reduced complications. The cost of developing and maintaining a radiation therapy program should be balanced against the cost of managing complications of treatment, both of which contribute to the overall management costs of breast cancer patients.[36] For patients with distant metastases, radiation therapy is an effective tool for palliation, especially for bone, brain, and soft tissue metastases (Fig. 6, column 2).

There is a huge insufficiency of radiation therapy resources in LMCs. Thus, there is a need to provide the necessary equipment and also to improve the quality, technique, and utilization of resources in an optimal and sustainable fashion. Radiation therapy

Treatment Resource Allocation:
Metastatic (Stage IV) and Recurrent Breast Cancer

Level of resources	Local-Regional Treatment		Systemic Treatment (Palliative)		
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Supportive Therapy
Basic	Total mastectomy for ipsilateral breast tumor recurrence after breast conserving surgery			Oophorectomy in premenopausal women Tamoxifen*	Nonopioid and opioid analgesics and symptom management
Limited		Palliative radiation therapy	Classical CMF† Anthracycline monotherapy or in combination†		
Enhanced			Sequential single agent or combination chemotherapy Trastuzumab Lapatinib	Aromatase inhibitors	Bisphosphonates
Maximal			Bevacizumab	Fulvestrant	Growth factors

FIGURE 6. Treatment resource allocation table for metastatic (stage IV) and recurrent breast cancer. CMF indicates cyclophosphamide, methotrexate, and 5-fluorouracil. *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. †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. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in some higher income settings.

can be delivered with a cobalt-60 unit or a linear accelerator (LINAC) along with other quality-assurance tools.[36] Although LINAC is considered the preferred therapy in most settings, telecobalt machines are a reasonable alternative in LMCs. It is noteworthy that LINAC requires consistent electricity for powering and water for cooling the equipment. Thus, in some low-income settings, it may be more practical to provide telecobalt technology. In either circumstance, applying safe and effective treatment requires well trained staff, support systems, geographic accessibility, and the initiation and completion of treatment without undue delay.[51] To specifically address these issues in LMCs, in 2004, the International Atomic Energy Agency established the 'Programme of Action for Cancer Therapy' to seek and direct funds from individuals, charitable trusts, foundations, and the public and private sectors to help patients in poor countries receive appropriate cancer treatment, an initiative that has been welcomed by the WHO.

In early-stage breast cancer, radiation therapy is an essential part of breast-conservation treatment (Figs. 3 and 4; column 2). Standard treatment includes the irradiation of the entire breast with an additional boost to the tumor site and should be delivered after treatment planning with at least 2-dimensional imaging. Among patients with lymph node-positive disease, postmastectomy radiation therapy has demonstrated local control and overall survival advantages. However, if access to radiation could be limited more specifically, then preference for postmastectomy radiation might be given to patients with $\geq$4 positive lymph nodes. Chest wall

and supraclavicular lymphatic irradiation is considered standard treatment for locally advanced disease. However, routine axilla irradiation is not recommended because of the heightened risk of lymphedema. When indicated, internal mammary chain irradiation may be considered when used with cardiac-safe radiation techniques and appropriate planning. The long-term risks of cardiac morbidity and mortality require special attention to the volume of heart and lungs exposed, and attempts should be made to reduce exposure to these tissues. Alternative treatment schedules such as hypofractionated radiation and partial breast irradiation currently are investigational and should not be considered as standard care in LMCs.

Systemic therapy

The use of systemic cytotoxic chemotherapy is effective in the treatment of all biologic subtypes of breast cancer but is more resource intensive to provide (Figs. 3-6, column 3).[34] The provision of endocrine therapy requires relatively few specialized resources but, optimally, requires knowledge of hormone receptor status to assure the treatment of those patients who are most likely to benefit (Figs. 3-6, column 4). HER-2-targeted therapy is very effective in tumors that overexpress the HER-2/*neu* oncogene, but cost largely prevents the use of this treatment in LMCs (Figs. 3-5, column 5).

Tamoxifen remains useful and is recommended for patients with ER-positive tumors in LMCs (Figs. 3-5, column 4). Aromatase inhibitors (AIs) produce better results than tamoxifen and are recommended for countries with enhanced and maximal resources, but cost constraints make tamoxifen a very reasonable alternative to AIs. No overall survival benefit has been attributed to AIs over tamoxifen. Hormone therapy should be used after surgery for at least 5 years.

Trastuzumab combined with taxanes yields high pathologic response rates in patients with HER-2/*neu*-overexpressing tumors, is recommended in countries with enhanced and maximal resources, and should be made available in countries with lower levels of resources at lower costs because of its high efficacy. In patients who are candidates for trastuzumab, it should be continued for a total of 1 year. Clinical trials to evaluate the role of shorter durations of trastuzumab are appropriate for LMCs and should be encouraged.

Management of locally advanced disease

Recent data indicate that LABC and MBC are the most common stages at presentation and include 60% to 80% of cases in most LMCs.[6,52,53] Although the incidence of LABC has decreased significantly in developed countries with enhanced and maximal resources because of widespread education and increasing use of screening mammography, as fully discussed in a separate article of this BHGI supplement,[37] LABC remains a daily challenge for oncologists in LMCs in which limitations to proper management also include a lack of local data, cultural circumstances, and weak, inefficient healthcare systems.

Preoperative chemotherapy is the preferred primary therapy for LABC, because it allows an early assessment of sensitivity to treatment as well as breast conservation (Fig. 5).[37] Clinical assessment of chemosensitivity may be particularly helpful, because emerging data suggest that there could be differences in host metabolism of systemic treatment agents—tamoxifen, alkylating agents, taxanes—on genetic bases, with associated differences in efficacy and toxicity among genetically different populations.[54,55] Research specifically directed at differences among groups in response to systemic therapy may be warranted.[56] Although the preferred initial treatment of LABC is systemic therapy, if optimal chemotherapy and evaluation are not available, then primary MRM is acceptable. However, it should be recognized that, without systemic therapy, surgery alone for LABC is unlikely to improve outcome given the high likelihood of systemic recurrence; thus, the role of MRM without adjuvant treatment for LABC should be viewed primarily as palliative therapy.

After responding to systemic therapy, most patients with LABC will require a MRM followed by radiation therapy.[36] Locoregional therapy decisions should be based on both the pretreatment clinical extent of disease and the pathologic extent of the disease after chemotherapy (Fig. 5, columns 1 and 2). Accordingly, physical examination and imaging studies that accurately define the initial extent of disease are required before treatment.[57] The success of breast conservation after preoperative chemotherapy depends on careful patient selection and achieving negative surgical margins. Adjuvant breast radiation is indicated for all patients who are treated with breast conservation. For patients who undergo mastectomy, chest-wall and regional lymph node radiation should be considered for those who present with clinical stage III disease or who have histologically positive lymph nodes after preoperative chemotherapy.[57]

Metastatic and inflammatory breast cancer should be managed initially with preoperative therapy irrespective of resource level. Standard preoperative therapy includes anthracycline-based chemotherapy (Figs. 5 and 6; column 3). The addition of sequential taxane after anthracycline-based chemotherapy improves pathologic responses and breast-conservation rates, although it may not improve survival. The combination is considered appropriate treatment at the

Breast Care Programs:
Human Resource Allocation

Level of resources	Patient and Family Education	Human Resource Capacity Building	Patient Navigation
Basic	General education regarding primary prevention of cancer, early detection and self examination Development of culturally adapted patient and family education services	Primary care provider education re breast cancer detection, diagnosis and treatment Nursing education re cancer patient management and emotional support Pathology technician education re tissue handling and specimen preparation Trained community worker	Field nurse, midwife or healthcare provider triages patients to central facility for diagnosis and treatment
Limited	Group or one-on-one counseling involving family and peer support Education regarding nutrition and complementary therapies	Nursing education re breast cancer diagnosis, treatment and patient management Imaging technician education re imaging technique and quality control Volunteer recruitment corp to support care	On site patient navigator (staff member or nurse) facilitates patient triage through diagnosis and treatment
Enhanced	Education regarding survivorship Lymphedema education Education regarding home care	Organization of national volunteer network Specialized nursing oncology training Home care nursing Physiotherapist & lymphedema therapist On-site cytopathologist	Patient navigation team from each discipline supports patient "handoff" during key transitions from specialist to specialist to ensure completion of therapy
Maximal		Organization of national medical breast health groups	

FIGURE 7. Breast care programs: human resource allocation table. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in some higher income settings.

enhanced and maximal levels; however, costs and lack of a clear survival benefit do not justify its use at limited-resource levels. Combined cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy is less potent than anthracycline and taxanes, but it may be used in its classic schedule in LMCs because of the lower costs and fewer complications. It remains to define the role for preoperative endocrine therapy better, but such therapy appears to be feasible and acceptable in elderly women.[37]

Healthcare Systems

Poorer outcomes in LMCs may relate to their healthcare systems, which have limited capability for successful early detection, diagnosis, and treatment of breast cancer (Figs. 7 and 8). Impediments to better outcomes include deficits in public education and awareness, insufficient numbers of appropriately trained healthcare workers, limited access to screening/treatment facilities, inadequate supplies of necessary drugs, and timeliness of treatment after diagnosis. These points are reviewed comprehensively in the Health Care Systems Consensus Panel article[35] and are summarized here.

Public education

Obstacles to improving cancer care arise from multiple sources, including deficits in public knowledge and awareness, social and cultural barriers, challenges in organizing healthcare, and insufficient resources (Fig. 7, column 1). Early breast cancer detection improves outcome in a cost-effective fashion, assuming treatment is available, but requires public education to foster active patient participation in diagnosis and treatment.

Professional education and training

Education of healthcare professionals, trusted traditional healers, governmental agencies, women, and the public regarding breast health and about breast cancer detec-

Breast Care Programs:
Support Systems Resource Allocation

Level of resources	Services	Record Keeping	Cancer Care Facility	Breast Care Center
Basic	Diagnostic/Pathology services Nursing services Oncology services Palliative services Psychosocial services Primary care services Surgical services	Individual medical records and service-based patient registration	Health facility Operating facility Outpatient care facility Pharmacy Home hospice support External consultation pathology laboratory	Breast healthcare access integrated into existing healthcare infrastructure
Limited	Imaging services Peer support services Radiation oncology services	Facility-based medical records and centralized patient registration Hospital level cancer registry	Clinical information systems Health system network Imaging facility Internal pathology laboratory Radiation therapy	"Breast Center" with clinician, staff and breast imaging access Breast prostheses for mastectomy pts
Enhanced	Cancer follow-up Group support Screening programs Rehabilitation services Survivorship services	Resource Room(s) for education/outreach Facility based follow-up Regional cancer registry	Centralized referral cancer center(s) Radiation therapy: low energy linear accelerator, electrons, brachytherapy, treatment planning system	Multidisciplinary breast programs Oncology nurse specialists Physician assistants
Maximal	Universal access to screening Individual psychosocial care	Representative national cancer registry	Satellite (non-centralized or regional) cancer centers	

FIGURE 8. Breast care programs: support systems resource allocation table. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in same higher income settings.

tion, diagnosis, and treatment is central to the provision of high-quality breast cancer care (Fig. 7, column 2).

Cancer center organization

The use of multidisciplinary teams for the management of breast cancer in general, and LABC in particular, is strongly recommended and should be available wherever patients with breast cancer are treated (Fig. 8, columns 3 and 4).[35,37,58] Even if some members of a full team (oncologist, radiologist, radiotherapist, pathologist, gynecologist, nurse, psychoanalyst, and physiotherapist) are unavailable, whoever is available should meet and discuss patient management together. In LMCs, in which some specialists are unavailable, the team approach should be adapted to include only 2 to 4 members (eg, surgeon, radiologist, pathologist, and medical and/or radiation oncologist). Every effort should be made to have local pathologists available. Patient advocates may play an important role in encouraging the setup of multidisciplinary teams and can serve a special role in strengthening patient navigation through a given healthcare system (Fig. 7, column 3).

Radiation facilities

The delivery of radiation therapy requires a healthcare system that can provide the basic equipment, the human resources, and the patient access to scheduled care to ensure safe and effective radiation therapy (Fig. 8, column 1). The current supply of megavoltage radiotherapy machines (cobalt-60 or LINAC) is only 18% of the estimated need in some parts of the developing world.[59] Cobalt machines are less expensive and have lower quality assurance, maintenance, and staffing needs.[60] Because treatment interruptions from machine breakdown or machine servicing adversely affect patients' outcomes,[61] the ability to provide preventive maintenance is an important consideration. The colbalt-60

units have greater simplicity with regard to mechanical and electrical components and operations and, hence, are an attractive option for a low-resource setting. LINACs have a higher technical sophistication and, hence, higher maintenance requirements. Cobalt-60 units have a constancy of beam output and predictability of decay; however, compared with LINACs, cobalt-60 units have poor field flatness, lower percentage depth dose, greater penumbra, lower dose rate, and less favorable beam profile. Colbalt-60 is limited in its ability to deliver more complex treatments. Compared with LINAC, it may result in an increased dose to the contralateral breast, a higher skin dose, or some dose inhomogeneities in the treated breast, especially during breast-conservation irradiation. However, these disadvantages can be mitigated by a proper treatment plan and the use of simple accessories, such as wedges.[36]

Drug delivery

The implementation of scientific evidence-driven recommendations is limited by resources and by the availability of manpower, modern equipment, and costs of drugs. The prices are notably affordable for CMF; doxorubicin and cyclophosphamide; and cyclophosphamide, doxorubicin, and 5-fluorouracil combinations, and those drugs are on the WHO list of essential chemotherapeutic drugs.[62] Nonetheless, patients in many LMCs do not have access to the standard drugs used to treat breast cancer in the higher income settings (Fig. 8, column 1). Remedying drug distribution problems and reducing the cost of prohibitively expensive drugs is difficult to do at the facility level, but it may be possible to create partnerships with drug companies to receive medicines for free or at reduced cost.

Options for reducing drug use could include decreasing treatment time or using intermittent rather than continuous therapy.[63] Another approach could be to use strategies that increase bioavailability of the drug, such as taking food in conjunction with medicines that increase drug absorption.[64] Older drugs that previously were discarded or were considered minimally active in breast cancer are being re-evaluated from a targeted therapy perspective. The platinum drugs, such as cisplatin, have resurfaced as active treatment for breast cancer after preclinical models suggested their synergism with trastuzumab as HER-2-targeted treatment.[65]

It is more likely, however, that government intervention is needed to address the drug delivery problem in LMCs. Government officials can and should work to improve drug donation programs, get better prices from pharmaceutical companies, and obtain licenses to produce generic medicines. In particular, opiates for pain control, which are the mainstay of palliative care, often are unavailable. Preliminary estimates indicate that 4.8 million individuals per year do not receive treatment for moderate to severe pain caused by cancer.[66] Developing countries consume only approximately 6% of the world's morphine, despite housing >80% of the world's population.[67] Increasing the availability of opioids for pain control will require reducing attitudinal, access, and legal barriers as well as realistic pricing of generic agents.

There also is broader concern that research and development of cancer drugs is driven mainly by commercial considerations rather than public health priorities, leading to the creation of drugs that are unlikely to reach populations in less developed countries. Although many breast cancer drugs are relatively standardized at this point, in the future, more targeted, genetically based drugs will be developed that may exclude large portions of populations in LMCs because of cost.

Process Metrics

Appropriate quality-assurance and quality-control measures should be integrated into cancer care programs at all levels of early detection, diagnosis, and treatment. Focusing efforts on improving performance in problem areas can assure the efficient use of resources and the maximization of their positive impact. Nonpunitive reporting of errors is a critical step in improving patient safety and processes. Proper methodology for defining quality-improvement initiatives must be considered and adapted to existing resources.[68]

Process metrics are useful tools that health ministers and facility managers can use to track progress and inform future decisions. Carefully selected process metrics can be collected without excessive effort or cost and can be used to measure the effectiveness of a facility's or country's ability to detect, diagnose, and treat cancer. Without metrics, it is difficult to determine the success of a breast cancer program. The suggested metrics in this article are very basic and are intended only to provide a general orientation to metrics and models (Fig. 9). Specific measurements will need to be designed at the local level, in which an intricate understanding of the available resources and program goals can inform their creation and use.

Generally, the sophistication of metrics will increase with the level of resources. However, it is possible that certain metrics can be used at many levels of resources and that the outcome expectations change as resources levels increase. In many LMCs, the collection of even rudimentary measurements will be

Process Metrics for LMC Breast Healthcare Programs

Level of resources	Early Detection	Diagnosis	Treatment	Programmatic
Basic	# Pts with documented H&P / # Pts evaluated *Description: The ratio of the number of patients who have a recorded history and physical examination within the target group to the number of patients who were clinically evaluated within the target group for a center or program providing organized breast healthcare.*	# Pts with tissue dx / # Pts with suspic. mass *Description: The ratio of the number of patients who receive a tissue diagnosis (benign or malignant) to the number of patients who had a "suspicious mass" (finding on CBE that the clinical examiner considers abnormal and therefore warranting further evaluation).*	# Pts treated for ca / # Pts with tissue dx ca *Description: The ratio of the number of patients who receive cancer treatment of some fashion (surgery beyond surgical biopsy, radiation tx and/or systemic tx) to the number of patients who had a tissue diagnosis of cancer.*	Median pathologic tumor size *Description: The median pathologically determined size of invasive breast primary tumors within the target group for a center or program providing organized breast healthcare.*
Limited	% Pts with CBE-detected abnormalities who undergo breast imaging for work-up	% Pts with biopsy-proven cancer diagnosis who have documented TNM stage	% Pts with ca diagnosis who start treatment within 120d of tissue diagnosis	% cancer Pts who have TNM stage I or II disease at initial biopsy-proven diagnosis
Enhanced	% Pts age 50-69 who had screening mammogram within past 24 months	% Pts with biopsy-proven cancer diagnosis who have documented HER-2/neu status	% Pts treated by lumpectomy starting XRT within 120d of last surgical procedure	% cancer Pts who have TNM stage I or II disease who at 5 yrs have no evidence of disease recurrence
Maximal	Maximal category process metrics determined based upon standards of care in high-income countries	Maximal category process metrics determined based upon standards of care in high-income countries	Maximal category process metrics determined based upon standards of care in high-income countries	Maximal category process metrics determined based upon standards of care in high-income countries

FIGURE 9. Table of process metrics for breast healthcare programs in low-and middle-income countries. Pts indicates patients; H&P, history and physical; dx, diagnosis; suspic., suspicious; CBE, clinical breast examination; ca, cancer; tx, treatment; TNM, tumor classification system; HER-2/neu, human epidermal growth factor receptor 2; d, day; XRT, external beam radiotherapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in same higher income settings.

difficult. Despite these difficulties, LMCs should actively engage in creating and using metrics that can be integrated easily into existing practices.

DISCUSSION

The improvements in survival in the industrial world observed in recent decades have been attributed to early detection by screening and to timely and effective treatment guided by extensive and rigorous clinical trials in screening and treatment.[69,70] Consequently, breast cancer mortality, which had been relatively unchanged from the 1930s through the 1980s, has dropped by 1.4% to 3.1% per year between 1990 and 2003 in the US.[71] Notably, minority women in the US are more likely to present with advanced-stage disease and have higher mortality rates than white women, although white women and black women who present with similar stage disease and receive similar treatment have similar outcomes. These findings suggest that differences in stage at presentation and treatment should represent primary targets of research and interventions designed to reduce disparities in cancer outcomes among women.[72]

An approach for evidence-based breast health improvement in LMCs is defined in the BHGI guidelines. Breast health interventions for early detection, diagnosis, and treatment in LMCs are delineated and explained in the published BHGI *Guidelines for International Breast Health and Cancer Control*. The guidelines outline programmatic approaches to support key breast health interventions that can be replicated in communities in which resources are limited to support comprehensive and functional breast healthcare programs using sustainable applications for breast healthcare implementation. The BHGI guidelines provide a resource-sensitive, stratified framework for guidance on how to overcome obstacles

to implementation of breast health interventions when resources are limited, including underserved communities in high-income countries.

Organizational collaboration among regional, national, and international groups to improve healthcare delivery in LMCs can facilitate effective guideline implementation. The adoption of evidence-based breast healthcare guidelines for implementation oriented to LMCs is a crucial step toward improving breast healthcare and breast cancer care in these regions. Improving a healthcare system so that it can deliver better breast healthcare can be accomplished best if multiple sectors act in collaboration. Improvements are most likely to be achieved when healthcare ministries and governmental agencies, nongovernmental organizations, national cancer institutes, and public and patient groups work together.

To successfully implement the BHGI guidelines in LMCs, 3 goals must be addressed. First, dissemination and implementation (D&I) strategies need to be developed so that guideline adoption takes place. Rather than assuming that we know the optimal approaches to information transfer in LMCs, varied strategies need to be explored and studied in different LMC environments. Second, education of the public, of healthcare providers, and of health system administrators is necessary for guideline adoption to be successful and sustained. Third, effective and affordable technology for detection, diagnosis, and treatment must be achieved in target LMCs so that cancer diagnosis and treatment is performed correctly.

Guideline Dissemination and Implementation Research

The dominant paradigm even now in the medical community is that good research and publication should be sufficient to ensure the translation of scientific findings into general practice.[73] Unfortunately, a landmark Institute of Medicine (IOM) report from 2001 clearly identified the failure to translate much scientific innovation into practice.[74,75] More recently, Rubenstein and Pugh separated the IOM's second translational block—clinical research to practice—into 2 parts: 1) clinical research to guidelines and 2) guidelines to practice.[76] D&I researchers maintain that the process is complex, and they have begun to identify factors and processes that are critical to the adoption of new technologies and practices.[77] Although there already has been some D&I work on assessing readiness for change, it usually has focused on just 1 component, such as providers or health units, or it has focused on intention without considering self-efficacy or environment. In the conclusion of their extensive review of the implementation literature, Greenhalgh et al note the need for more research on system readiness for innovation and for more studies evaluating the implementation of specific interventions.[78]

A review of available information strongly suggests that there is a crucial role for research in applying the experience and knowledge of high-income societies to the challenges of women and breast cancer throughout the world.[56] A recent survey of oncology experts from Latin American countries indicated that 94% of the surveyed experts considered clinical-epidemiologic research development on breast cancer insufficient in their country.[42] The main reasons identified were insufficient economic retribution and lack of available time. To our knowledge, very little research on guideline implementation has been done in LMCs. It is necessary to determine whether the basic frameworks and instruments that have been described in high-income countries apply in these very different environments and what adaptation is needed to make them both valid and feasible. A systematic program of research to develop appropriate readiness assessment instruments and to identify effective implementation strategies is needed now in a variety of LMCs. Thus, as we move forward to support the adoption, implementation, and maintenance of the new evidence-based principles embodied in the BHGI guidelines, it will be critical to incorporate careful evaluation into the efforts to ensure that lessons concerning effectiveness and efficiency are captured. It is precisely because resources are scarce in these countries that it is even more imperative for LMCs to adopt effective practices as quickly as possible and to design implementation approaches with limited resources in mind.[73]

Education and training programs

Public education is mandatory to improve breast health outcome in LMCs. The mediating effects of psychosocial and cultural variables on the impact of breast cancer interventions in LMCs are understudied. The personal representations of illness that guide health behavior vary across cultures. These representations underlie and influence women's response to prevention and screening campaigns as well as the likelihood of initiating and complying with treatment and follow-up.[56] Regardless of resource availability, breast health outcomes cannot improve unless women understand the benefits of early detection and are willing to undergo timely diagnosis and treatment. Practical evidence-based strategies are needed for effective communication to the public to promote early detection of breast cancer, enhance breast cancer diagnosis, improve the quality of breast cancer treatment, support the information

needs of breast cancer survivors, improve palliative care, and increase the sensitivity of end-of-life care for breast cancer.[40]

Professional education and training programs for breast healthcare exist in many international settings. However, these efforts primarily target the education of healthcare providers in high-income countries about novel (and usually expensive) technologies and drugs used in the delivery of cutting-edge care. These professional educational efforts typically do not address the specific needs of healthcare providers in LMCs in which infrastructure is lacking or dysfunctional. Healthcare organizations and agencies need to collaborate on improving breast healthcare to develop curricula that are selected appropriately for healthcare providers in target LMCs. These educational curricula need to be tailored to the specific resource constraints that drive medical decision-making and therapy.

One example of targeted education and training is in breast pathology. The development of optimal breast pathology services has been recognized as a fundamental requirement for the delivery of quality breast healthcare with emphasis on patient's safety. The financial burden of establishing and maintain breast pathology services is counterbalanced by the cost savings from decreased adverse effects and excessive use of treatment resources resulting from incomplete or incorrect pathologic diagnoses. Proper training in breast pathology, for both pathologists and laboratory technicians, is critical to programmatic success and provides the underpinnings of programmatic success for any country at any level of economic wealth.[38]

BHGI collaborators have now established a model breast pathology laboratory at the Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana.[79] This program, which is supported by BHGI collaborator Helge Stalsberg from Norway, has created a training program and laboratory infrastructure that has proven to be sustainable with existing resources at KATH. At the University Hospital of North Norway (UNN), a plan to re-establish surgical pathology at KATH was developed through discussions with the Ghanaian hospital. This program development is a model for pathology infrastructure development in a low-income environment. Two KATH technicians came to UNN and trained in the histopathology laboratory for 3 months. On their return, they started producing slides at KATH. Since April 2006, weekly shipments of hematoxylin and eosin-stained slides have been sent to UNN by courier service. When needed, paraffin blocks are sent on request. From March 2006, 2 young Ghanaian physicians have been received as trainees at the UNN, doing full resident work and training with the aim of being approved as specialists in pathology in Ghana by 2010. This type of training approach could be mirrored in other countries and also serves as an educational model for specialties outside of pathology.

Technology application and development

Even in low-income settings, some basic-level technology is necessary to provide cancer care. Existing technologies in imaging (ultrasound, mammography, x-ray), tissue sampling (minimally invasive needle biopsy), and pathology (histopathology and/or cytology, immunohistochemistry) are necessary resources for effective cancer care. BHGI guidelines can be used in LMC settings to identify needed standard technology infrastructure.

Introduction of breast imaging in LMCs. In high-resource countries, diagnostic mammography is a core resource for workup for lesions of all clinical presentations, Women aged $\geq$30 years with a palpable lump generally undergo diagnostic mammography as the initial diagnostic study of choice.[80] In high-resource countries, breast ultrasound is used to augment diagnostic mammography and specifically to examine localized findings from the diagnostic mammogram and/or CBE. Screening breast ultrasound (a survey of the whole breast in clinically asymptomatic women) generally is discouraged because of insufficient evidence to determine whether ultrasound is efficacious and cost-effective as a screening tool.[81] Currently, a multicenter trial is underway in the US to evaluate the efficacy of screening whole-breast ultrasound.[82]

By contrast, diagnostic breast ultrasound generally becomes available in low-resource countries before diagnostic mammography becomes common. Mammography is a highly specialized imaging tool that is considerably more expensive than ultrasound. Until the recent application of digital technology (which, itself, is quite expensive), mammographic imaging required the use of x-ray film, for which the costs and quality-control requirements can be an insurmountable barriers to widespread use in a low-resource a country.[16] Many health facilities will not purchase mammographic equipment, because it is dedicated to the single use of breast imaging without any other radiographic applications. By comparison, ultrasound commonly is available in all resource settings, because it can be used for imaging many parts of the body, and it requires no film other than that for record keeping. Ultrasound equipment can use multiple different transducers, making it useful for many different diagnostic applications other than

evaluation of the breast. Thus, there is a strong impetus for the use of breast ultrasound in settings in which mammography is unavailable.

Although a comparative study has not been performed in a resource-constrained setting, diagnostic breast ultrasound may have more utility than diagnostic mammography as an initial diagnostic test in LMCs. Breast ultrasound is particularly useful for imaging masses in the breast, it can be used to distinguish solid masses from fluid-filled cysts, and it can characterize the shape and morphology of solid masses, all of which are very useful in determining which palpable masses are more likely to be disease requiring a tissue biopsy.[80] Because patients in low-resource settings most commonly present with locally advanced, palpable, invasive cancers, ultrasound can provide considerable supplemental information after a positive CBE for the evaluation of the extent of breast disease.[83] Furthermore, premenopausal breast cancer appears to be relatively more common in low-income countries based on the younger average age at diagnosis. Younger, premenopausal women more commonly have dense breasts that are less amenable to mammographic imaging and more amenable to ultrasound.[84]

Breast pathology in LMCs. The quality of breast healthcare and the ultimate clinical outcome of patients with breast cancer are related directly to the quality of breast pathology practice. In regions of the world with few or no on-site pathologists, attempts should be made to find another pathology laboratory to assist them with processing of the specimen and interpretation of the pathology samples. Adequate tissue sampling and processing and the appropriate use of ancillary studies, such as biomarker studies for prognostic/predictive factors, require sufficient healthcare and financial resources. False-positive and false-negative diagnoses result in under and over treatment. False-positive diagnoses of cancer commonly are attributable to interpretation errors. False-negative diagnoses of cancer are attributed most often to a nonrepresentative specimen or to severe artifactual changes in the tissue material. However, specimen quality also plays an important role in false-positive diagnostic errors, because over interpretation is more likely to occur in a poor-quality specimen because of either limited material on which to base the diagnosis or because of significant artifactual changes from poor fixation or slide preparation, making interpretation more difficult. These shortcomings can be minimized if steps are taken to ensure adequate specimen quality and if pathologists acquire and maintain high-level diagnostic skills in breast pathology.[38]

Hormone therapy is among the simplest methods of providing systemic therapy for ER-positive breast cancers. Tamoxifen, as an oral medication, can be provided with minimal infrastructure other than an outpatient pharmacy. If tamoxifen is too expensive, then surgical or radiation-induced oophorectomy has proven efficacy and can be performed in premenopausal women. Thus, the use of hormone receptor testing is of significant value, because tamoxifen and/or oophorectomy are unlikely to be efficacious when the cancer fails to express ER and PR. Patients can be given these hormone therapies even if ER and PR testing is unavailable. However, if this algorithm is followed, then a large proportion of patients will receive therapy that, if testing had been available, would have been predicted to have no therapeutic utility. In regions that have no accessibility to performance on-site ancillary testing such as ER immunohistochemistry, locating a laboratory in the region that has the capacity to perform the needed test is strongly recommended.[38]

The rate of ER-positive cancers may vary among different racial groups. In 1 study, the incidence of ER- and PR-positive cancers was similar in Japanese women and American women.[85] By contrast, another study analyzing >1000 tumors in Chinese women indicated that the ER-positive rate was 54%, which is significantly lower than the rate for Caucasian women, even when considering the potential confounding variable of menopausal status.[86] Thus, ER and PR testing, although it is considered a limited-level resource rather than a basic-level resource, has obvious importance for guiding the use of therapy. Indeed, savings from the selective use of hormone treatments should offset (if not completely pay for) the cost of the hormone receptor testing.

Informatics in breast healthcare delivery. International partnership addressing health issues in LMCs requires the development and application of low-cost communication tools to facilitate information transfer between partner organizations and to make key information generally available to the public.[38] For example, telepathology has the potential to enhance training in some settings and can be used for consultation on challenging cases on an ongoing basis using expertise at a distance. The availability of broad-band connections capable of handling the large amount of information that needs to be transferred remains an issue in many low- and medium-resource settings, as has demonstrated at Tata Memorial in Mumbai, India.[87]

In 2005, the BHGI developed an Internet website on the Fred Hutchinson Cancer Research Center server (www.bhgi.info) to facilitate outside communi-

cation regarding BHGI activities. The BHGI website serves as an information portal, providing access for downloading BHGI publications and materials. Because the website is written in HTML, modifying information on the website is cumbersome and expensive. It also lacks flexibility and does not permit interactive dialogue. In 2007, BHGI developed a customized Internet portal using the Microsoft program Sharepoint 2003 to facilitate dialogue, information exchange, and article preparation for the 2007 Global Summit participants. This BHGI Sharepoint portal has become a hub of the international communication for the Global Summit, facilitating organization of the meeting and ensuing collaborative writing this BHGI supplement. This application, although it is a significant improvement on the BHGI website for communication and dialogue, still has limitations. Future applications for open access informatics could prove to be invaluable tools for improving information dissemination and for providing linkages among healthcare organizations and facilities in LMCs.

Use of novel technology. Although some tools that are used commonly in high-income countries are unaffordable in LMCs, other simpler tools are available and can be applied. Special collaborations with technology companies can be formed for the development of modular diagnostic clinics that integrate clinical evaluation, basic imaging, tissue sampling, and histopathologic assessment to make accurate cancer diagnoses and to prepare for treatment. Innovative technology development could improve healthcare delivery when that technology is targeted toward low-cost applications in LMCs.

Development of learning laboratories

The implementation of D&I research, education, and training and technology application could be vetted through the development of international learning laboratories to create unique environments for information transfer, collaborative learning, study, and analysis. Through collaboration between the BHGI and in-country sponsoring organizations, specialized curricula and methodology could be developed based on the BHGI guidelines. BHGI learning laboratories established in collaboration with sponsoring institutions in LMCs could become a venue for education and training. A key principle in the success of these learning centers would be the recognition that experts from high-, middle-, and low-income countries all have information, experience, and skills to share. Although experts from high-income countries may have expertise in the application of cutting-edge diagnostic tools or therapies, experts from LMCs have expertise in the reality of healthcare delivery in limited-resource settings. Real-world problem solving will require a collaborative approach using mutual knowledge transfer from all participants.

By applying D&I research methodology, the outcome of training opportunities and educational exchanges in Learning Laboratories could be assessed and measured. Participants from LMCs who come for breast health education could be tracked after their training to determine which aspects of the Learning Laboratory curriculum proved useful and which aspects warrant more improvement and study. By obtaining organized feedback from Learning Laboratory participants, the effectiveness of the BHGI guidelines could be tested and improved. Thus, the BHGI Learning Laboratory could become the operational model for BHGI guidelines application and testing in a practical, real-world LMC environment as a key step toward improving breast healthcare delivery in LMCs around the globe.

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