
Benjamin O. Anderson, MD,* Roman Shyyan, MD,† Alexandru Eniu, MD,‡ Robert A. Smith, PhD,§ Cheng-Har Yip, MD,¶ Nuran Senel Bese, MD,# Louis W. C. Chow, MD,^ Shahla Masood, MD,® Scott D. Ramsey, MD, PhD,© and Robert W. Carlson, MD**

*University of Washington, Seattle, Washington; †Lviv Cancer Center, Lviv, Ukraine; ‡Cancer Institute I. Chiricuta, Cluj-Napoca, Romania; §American Cancer Society, Atlanta, Georgia; ¶University of Malaya Medical Center, Kuala Lumpur, Malaysia; #Cerrahpasa Medical School, Istanbul, Turkey; ^University of Hong Kong Medical Center, Pokfulam, Hong Kong; ®University of Florida, Jacksonville, Florida; ©Fred Hutchinson Cancer Research Center, Seattle, Washington; and **Stanford University, Stanford, California

Abstract: Breast cancer is the most common cause of cancer-related death among women worldwide, with case fatality rates highest in low-resource countries. Despite significant scientific advances in its management, most of the world faces resource constraints that limit the capacity to improve early detection, diagnosis, and treatment of the disease. 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 health care resources to improve breast cancer outcomes. Using an evidence-based consensus panel process, four BHGI expert panels addressed the areas of early detection and access to care, diagnosis and pathology, treatment and resource allocation, and health care systems and public policy as they relate to breast health care in limited-resource settings.

To update and expand on the BHGI Guidelines published in 2003, the 2005 BHGI panels outlined a stepwise, systematic approach to health care improvement using a tiered system of resource allotment into four levels—basic, limited, enhanced, and maximal—based on the contribution of each resource toward improving clinical outcomes. 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. Clinical breast examination combined with diagnostic breast imaging (ultrasound ± diagnostic mammography) can facilitate cost-effective tissue sampling techniques for cytologic or histologic diagnosis. Breast-conserving treatment with partial mastectomy and radiation therapy requires more health care resources and infrastructure than mastectomy, but can be provided in a thoughtfully designed limited-resource setting. The availability and administration of systemic therapies are critical to improving breast cancer survival. Estrogen receptor testing allows patient selection for hormonal treatments (tamoxifen, oophorectomy). Chemotherapy, which requires some allocation of resources and infrastructure, is needed to treat node-positive, locally advanced breast cancers, which represent the most common clinical presentation of disease in low-resource countries. When chemotherapy is not available, patients with locally advanced, hormone receptor-negative cancers can only receive palliative therapy. Future research is needed to better determine how these guidelines can best be implemented in limited-resource settings.

Key Words: breast cancer, diagnosis, early detection, guideline, health care systems, health planning, international health problems, low-resource countries, pathology, public policy, recommendations, resource allocation, screening, treatment

Breast cancer is the most common cause of cancer-related death among women around the globe (1). Each year, breast cancer is newly diagnosed in more than 1.1 million women, and these cases represent more than 10% of all new cancer cases. With more than 410,000 deaths each year, the disease accounts for more than 1.6% of all female deaths worldwide (2,3). Breast cancer is an urgent public health problem in high-resource regions and is becoming an increasingly urgent problem in low-resource regions, where incidence rates have been increasing by up to 5% per year (2,4).

Low-resource countries have generally not identified cancer as a priority health care issue because infectious diseases are the predominant public health threat in such settings. Nonetheless, resources are spent on cancer treatment when patients seek medical care for what is typically advanced-stage disease. Cancer becomes an increasing...
problem in such countries as the control of communicable
diseases improves and life expectancy increases (5). How-
ever, obstacles to improving cancer care arise from multi-
ple sources, including deficits in public knowledge and
awareness, social and cultural barriers, challenges in orga-
nizing health care, and insufficient resources.

In high-resource countries, evidence-based guidelines
outlining optimal approaches to early detection, diagno-
sis, and treatment of breast cancer have been defined and
published (6–9). These guidelines from wealthy coun-
tries are resource neutral and thus not only fail to consider
variable resource distributions where overall standards of
living are high, but also are unworkable in the presence of
ubiquitous infrastructure and resource deficits in limited-
resource countries. Moreover, they are not designed to
consider implementation costs or provide guidance as to
how a suboptimal system can be improved incrementally
toward an optimal system. As pointed out by the World
Health Organization (WHO), guidelines defining optimal
breast care and services have limited utility in resource-
constrained countries (10). Thus there presently is a lack
of resource-based guidance related to strategies to reduce
the burden of breast cancer in settings where optimal care
is not feasible.

The development of international evidence-based breast
health care guidelines oriented toward countries or regions
of the world with limited financial resources is a crucial
step toward improving breast health care and breast
cancer care in these regions. Although existing guidelines
generally assume a high level of resources and are therefore
of limited use in many areas of the world, current evidence
about the value of earlier diagnosis and cost-effective
diagnosis and treatment can nonetheless be applied to
define evidence-based “best practices with limited resources”
for breast health care for use in countries where access to
health care is marginal, breast cancer awareness is marginal,
and cultural barriers to effective care exist. To outline a
systematic, sequential approach to building a breast pro-
gram, guidelines for such countries may recommend the
use of health care strategies that differ from those used in
countries with a high level of resources, but still measur-
ably improve breast cancer outcomes by achieving the best
standard of care that is practical in that setting.

THE BREAST HEALTH GLOBAL INITIATIVE

Cosponsored by the Fred Hutchinson Cancer Research
Center and the Susan G. Komen Breast Cancer Founda-
tion, the Breast Health Global Initiative (BHGI) is a pro-
gram that strives to develop evidence-based, economically
feasible, and culturally appropriate guidelines that can be
used in nations with substantial resource constraints to
improve breast health outcomes. In October 2002, the BHGI
held the first Global Summit Consensus Conference on
International Breast Health Care (hereafter referred to as
the 2002 Global Summit) in Seattle, Washington. The aim
of the 2002 Global Summit was to establish breast health
guidelines that address how care may best be provided in
countries where health care resources are significantly
limited (11). The BHGI guidelines were developed using
a panel consensus approach with analysis of evidence-based
breast cancer research. Based on definitions created by the
WHO for national cancer programs (10), panels of
breast cancer experts representing 17 countries and 9
world regions created guidelines to address early detection,
diagnosis, and treatment of breast cancer in countries with
limited health care resources (i.e., those with either low-
or medium-level resources according to WHO criteria).

The resulting 2002 BHGI guidelines were published
and have been made available in an unrestricted fashion
on the Internet for worldwide access (12–15). To date,
they have been the only comprehensive consensus guidelines
that specifically address issues surrounding the implemen-
tation of breast care in limited-resource countries.

2002 BHGI GLOBAL SUMMIT: SUMMARY OF
RESULTS

To be applicable and effective, practice guidelines must
go beyond summarization of available evidence-based
research to consider and sometimes challenge the values
that are implicit in the way practice questions have been
framed and outcomes have been chosen (16). Gender
inequalities in health are a consequence of the basic
inequality between men and women in many societies.
Despite the importance of socioeconomic factors, women’s
health is also greatly affected by the extent and quality of
health services available to them (17). At the 2002 Global
Summit, two axioms were adopted as principles for
 guideline development:

• All women have the right to access to health care,
  although considerable challenges exist in implementing
  breast health care programs when resources are limited.
• All women have the right to education about breast can-
  cer, but it must be culturally appropriate and targeted
  and tailored to the specific population.

A review of the published and presented data confirmed
that in countries with limited resources, most women have
advanced or metastatic breast cancer at the time of diagnosis (5). Based on an evidence-based review and consensus discussion, four observations were made:

- Because advanced breast cancer has the poorest survival and is the most resource intensive to treat, efforts aimed at early detection can reduce the stage at diagnosis, potentially improving the odds of survival and cure, and enabling simpler and more cost-effective treatment. These efforts are likely to have the greatest overall benefit in terms of both survival and costs.
- There is a need to build programs that are specific to each country’s unique situation.
- The development of cancer centers can be a cost-effective way to deliver breast cancer care to some women when it is not yet possible to deliver such care to women nationwide.
- Collecting data on breast cancer is imperative for deciding how best to apply resources and for measuring progress.

These observations from the first Global Summit served as the basis of the 2005 BHGI Global Summit Consensus Conference on International Breast Health Care (hereafter referred to as the 2005 Global Summit), where specific recommendations were addressed.

**METHODS: 2005 BHGI GLOBAL SUMMIT**

With extended sponsorship of national and international collaborating organizations, the BHGI guidelines were reexamined, revised, and extended at the second Global Summit, held January 12–15, 2005, and hosted by the Office of International Affairs of the National Cancer Institute in Bethesda, Maryland. Twelve national and international groups joined the BHGI as collaborating organizations (Appendix A). In addition, to obtain input on international guideline development, the BHGI established affiliations with three WHO programs: the Cancer Control Programme, Health System Policies and Operations, and the Alliance for Health Policy and Systems Research. The 2005 Global Summit brought together more than 60 international experts from 33 countries of all resource levels. The experts had diverse specialties related to breast care and breast cancer: screening, pathology and cytology, surgery, oncology, radiation therapy, health economics, medical ethics, sociology, and advocacy. The experts were charged with reviewing, updating, and extending the previously published guidelines, and were organized into four panels: early detection and access to care, diagnosis and pathology, cancer treatment and allocation of resources, and health care systems and public policy. Each panel was asked to prepare a consensus statement summarizing the outcome of their work (18–21).

**PANEL SELECTION**

Drawing from the experts who participated in the 2002 Global Summit, the BHGI formed an international Scientific Advisory Committee (Appendix C). For each 2005 Global Summit panel, this committee selected two cochairs—one from a country with limited resources and the other from a country with adequate resources (Appendix D). In addition, the Scientific Advisory Committee developed a comprehensive list of more than 100 international experts from which the panel cochairs selected their panelists and speakers for the summit. The committee reviewed and approved the final panel and speaker selections.

**PANEL ORGANIZATION AND CONFERENCE PREPARATION**

Panel cochairs were asked to create a program whereby their expert panel could produce consensus guidelines. The cochairs were responsible for drafting the agenda for their panel’s conference day and for organizing and executing the writing of their panel’s consensus statement. Each panel held one full-day meeting, with a morning session consisting of plenary presentations on topics selected by the cochairs (Appendixes E–H) and an afternoon session consisting of discussion and debate among panelists regarding the content of their consensus statement. In addition, to reinforce the aim of the guidelines and to describe the diverse settings in which they might be used, each day began with a presentation by a breast cancer advocate from a limited-resource country to summarize the personal experience of women facing breast cancer in her country.

**RESOURCE STRATIFICATION DEFINITIONS**

To encourage a consistent approach to the discussion and the guidelines, each panel was asked to stratify health care resources relevant to their assigned areas into one of four levels, defined as follows:

- Basic level—Core resources or fundamental services absolutely necessary for any breast health care system to function. By definition, a health care system lacking any basic-level resource would be unable to provide breast
cancer care to its patient population. Basic-level services are typically applied in a single clinical interaction.

- **Limited level**—Second-tier resources or services that produce major improvements in outcome, such as increased survival, but which 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 may produce minor improvements in outcome but 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, but nonetheless should be considered lower priority than those in the basic, limited, or enhanced categories on the basis of cost or impracticality for limited-resource environments. In order to be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources.

This stratification scheme assumes incremental resource allocation and implementation. For example, the limited level assumes that a setting already has all of the resources recommended for the basic level. Using this scheme, the short-term goal is to move to the next level. Although the long-term goal may be to move to the maximal level in certain areas (e.g., the implementation of population-based mammographic screening), overall, most limited-resource countries must address more fundamental needs before these maximal-level resources or services can be realistically applied.

It should be noted that multiple resource levels often coexist within a country, region, or even an individual health care facility. A country may have community clinics that provide care at the basic level, regional hospitals that provide care at the limited level, and a national cancer center that provides care at the enhanced or maximal level. Because circumstances vary so widely around the world, decisions about how to plan the overall structure of a national breast program must be made on a country-by-country, region-by-region, or facility-by-facility basis.

The panels were also asked to develop checklists for the various interventions. For each intervention, these checklists would describe the strengths, limitations, and necessary resources needed to apply that intervention in the areas of early detection, diagnosis, treatment, or health care systems and public policies. Finally, the panels were asked to identify areas where evidence is lacking and research is needed to better inform future iterations of the guidelines.

**STATEMENT PREPARATION AND REVIEW PROCESS**

**Consensus Statement Preparation and Review**

Each panel’s discussion and debate were recorded and transcribed, and the transcripts were used as the basis for writing the four consensus statements. Panel discussion was directed at creating the stratification tables (Tables 1–7), which list how resources should be allocated based on the definitions of basic, limited, enhanced, and maximal. Panel cochairs coordinated the writing of statements, sections of which were coauthored by participating panelists. Consensus statement drafts were reviewed and edited by all coauthors of each statement. The final draft, including resolution of disagreements among coauthors, was the responsibility of the panel cochairs.

The consensus statements were then compared centrally for internal consistency in stratification by a subset of coauthors. Differences among panel recommendations were reviewed with panel cochairs and language was adopted to minimize the level of perceived inconsistencies.

**Table 1. Early Detection and Access to Care**

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Detection method(s)</th>
<th>Evaluation goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>Breast health awareness (education ± self-examination) Clinical breast examination (clinician education)</td>
<td>Baseline assessment and repeated survey</td>
</tr>
<tr>
<td>Limited</td>
<td>Targeted outreach/education encouraging CBE for at-risk groups Diagnostic ultrasound ± diagnostic mammography</td>
<td>Downstaging of symptomatic disease</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Diagnostic mammography Opportunistic mammographic screening</td>
<td>Opportunistic screening of asymptomatic patients</td>
</tr>
<tr>
<td>Maximal</td>
<td>Population-based mammographic screening Other imaging technologies as appropriate: high-risk groups, unique imaging challenges</td>
<td>Population-based screening of asymptomatic patients</td>
</tr>
</tbody>
</table>
In cases where resources were definitively stratified differently by the consensus panels, the panel recommendations were maintained in the tables, and instead, the nature of the differences are summarized, explained, and discussed in this overview.

### Individual Statement Preparation

Morning plenary speakers were invited to submit individual statements for publication on their topics along with the consensus statements. In many cases, individual statements were needed to develop and analyze specific topics that were too detailed and focused for inclusion in the consensus statements as a whole, but nonetheless were vital to an understanding of the overall guideline recommendations for limited-resource countries.

### Individual Statement Selection and Review

In lieu of the standard external peer-review process, submitted individual statements underwent a special internal review process, reflecting the unique structure

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**Table 2. Diagnosis and Pathology**

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Clinical</th>
<th>Pathology</th>
<th>Imaging and laboratory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>History</td>
<td>Interpretation of biopsies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical breast examination</td>
<td>Cytology or pathology report describing tumor size, lymph node status, histologic type, tumor grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fine-needle aspiration biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Core needle biopsy</td>
<td>Determination and reporting of ER and PR status</td>
<td>Diagnostic breast ultrasound ± diagnostic mammography, Plain chest radiography</td>
</tr>
<tr>
<td></td>
<td>Image-guided sampling (ultrasonographic ± mammographic)</td>
<td>Determination and reporting of margin status</td>
<td>Liver ultrasound, Blood chemistry profile/CBC</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Preoperative needle localization under mammographic or ultrasound guidance</td>
<td>On-site cytopathologist</td>
<td>Diagnostic mammography, Bone scan</td>
</tr>
<tr>
<td>Maximal</td>
<td>Stereotactic biopsy</td>
<td>HER-2/neu status</td>
<td>CT scanning, PET scan, MIBI scan, breast MRI</td>
</tr>
<tr>
<td></td>
<td>Sentinel node biopsy</td>
<td>IHC staining of sentinel nodes for cytokeratin to detect micrometastases</td>
<td></td>
</tr>
</tbody>
</table>

CBC, complete blood count; CT, computed tomography; ER, estrogen receptor; IHC, immunohistochemistry; MIBI, 99mTc-sestamibi; MRI, magnetic resonance imaging; PET, positron emission tomography; PR, progesterone receptor.

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**Table 3. Treatment and Allocation of Resources: Stage I Breast Cancer**

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment (adjuvant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Basic</td>
<td>Modified radical mastectomy</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Breast-conserving therapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Breast-conserving whole-breast irradiation as part of breast-conserving therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postmastectomy irradiation of the chest wall and regional nodes for high-risk cases</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Sentinel node biopsy</td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Sentinel node biopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reconstrucive surgery</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Breast-conserving therapy requires mammography and reporting of margin status.

<sup>b</sup>Requires blood chemistry profile and complete blood count (CBC) testing.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.
Table 4. Treatment and Allocation of Resources: Stage II Breast Cancer

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment (adjuvant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Basic</td>
<td>Modified radical mastectomy</td>
<td>—^4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Breast-conserving therapy^2</td>
<td>Breast-conserving whole-breast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>irradiation as part of breast-conserving therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postmastectomy irradiation of the chest wall and regional nodes for high-risk cases</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Sentinel node biopsy</td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Reconstructive surgery</td>
<td></td>
</tr>
</tbody>
</table>

^4Chest wall and regional lymph node irradiation substantially decrease the risk of postmastectomy local recurrence. If available, it should be used as a basic-level resource.

^2Requires blood chemistry profile and complete blood count (CBC) testing.

^2Breast-conserving therapy requires mammography and reporting of margin status.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.

and goals of the BHGI program. All individual statement submissions were reviewed by panel cochairs and selected internal BHGI nonauthor reviewers. Individual statements that did not address issues specific to limited-resource countries were referred for journal submission outside of the BHGI guidelines. Some individual statements that developed individual topics of a more limited scope relevant to limited-resource countries were incorporated into guideline consensus articles. Individual statements that were accepted for publication were determined by the cochairs, internal BHGI reviewers, and the BHGI director to have specific merit in support of the consensus guidelines.

After final acceptance, all individual statements were coordinated with the consensus guideline statements for internal referencing as data in one or multiple consensus statements. As such, the combination of consensus and individual statements represents a complete BHGI guideline compendium, which is the final work product of the 2005 Global Summit and is published as a complete unit in this Breast Journal supplement.

2005 GLOBAL SUMMIT GUIDELINE OUTCOME SUMMARY

The four consensus panels each generated resource stratification tables (Tables 1–7). Detailed background material and organizing discussions are provided in individual consensus statements published together with this overview document (18–21). In most areas there was good agreement between consensus panels in the

Table 5. Treatment and Allocation of Resources: Locally Advanced Breast Cancer

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment (adjuvant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Basic</td>
<td>Modified radical mastectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Postmastectomy irradiation of the chest wall and regional nodes</td>
<td>Taxanes</td>
</tr>
<tr>
<td></td>
<td>Breast-conserving therapy^b</td>
<td>Breast-conserving whole-breast irradiation</td>
</tr>
<tr>
<td>Enhanced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Reconstructive surgery</td>
<td></td>
</tr>
</tbody>
</table>

^4Requires blood chemistry profile and complete blood count (CBC) testing.

^2Breast-conserving therapy requires mammography and reporting of margin status.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.
assigned stratification levels. However, review of the tables demonstrated certain points where some resources did not appear to have complete alignment. These points are described below.

Introduction of Breast Ultrasound and Diagnostic Mammography in Low-Resource Countries

In high-resource countries, diagnostic mammography is a fundamental resource for examination of lesions with any clinical presentation. Women age 30 years and older with a palpable lump undergo diagnostic mammography as the initial diagnostic study of choice (22). In high-resource countries, breast ultrasound is used to augment diagnostic mammography to specifically examine localized findings from the diagnostic mammogram or clinical breast examination (CBE). Screening breast ultrasound (general survey of the whole breast in clinically asymptomatic women) is generally discouraged because of the insufficient evidence base to determine if it is efficacious and cost-effective in the screening setting (23). A multicenter trial is now under way in the United States to evaluate the efficacy of screening whole breast ultrasound (24).

On the other hand, it was noted by multiple BHGI panelists that diagnostic breast ultrasound generally becomes available in low-resource countries before

Table 6. Treatment and Allocation of Resources: Metastatic (Stage IV) and Recurrent Breast Cancer

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment</th>
<th>Supportive and palliative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation therapy</td>
<td>Chemotherapy Endocrine therapy</td>
</tr>
<tr>
<td>Basic</td>
<td>Total mastectomy for ipsilateral breast tumor recurrence(^a)</td>
<td>Palliative radiation therapy</td>
<td>Classical CMF(^b) Anthacycline monotherapy or in combination(^b)</td>
</tr>
<tr>
<td>Limited</td>
<td></td>
<td></td>
<td>Ovarian ablation Tamoxifen</td>
</tr>
<tr>
<td>Enhanced</td>
<td></td>
<td></td>
<td>Aromatase inhibitors Bisphosphonates</td>
</tr>
<tr>
<td>Maximal</td>
<td>Growth factors Vinorelbine</td>
<td></td>
<td>Fulvestrant</td>
</tr>
</tbody>
</table>

\(^a\) Required resources are the same as those for modified radical mastectomy.

\(^b\) Requires blood chemistry profile and complete blood count (CBC) testing.

CMF, cyclophosphamide, methotrexate, and 5-fluorouracil.

Table 7. Health Care Systems and Public Policy

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Services</th>
<th>Facilities</th>
<th>Record keeping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>Primary care services Surgical services</td>
<td>Health facility</td>
<td>Individual medical records and service-based patient registration</td>
</tr>
<tr>
<td></td>
<td>Pathology services Oncology services Nursing services Palliative services</td>
<td>Operating facility Pathology laboratory Pharmacy Outpatient care facility</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Imaging services Radiation oncology services Peer support services Early detection programs</td>
<td>Imaging facility Radiation therapy Clinical information systems Health system network</td>
<td></td>
</tr>
<tr>
<td>Enhanced</td>
<td>Opportunistic screening programs Cancer follow-up Rehabilitation services Group support</td>
<td>Centralized referral cancer center(s) Population-based cancer registry Regional cancer registry</td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Population-based screening program Individual psychosocial care</td>
<td>Satellite (noncentralized or regional) cancer centers National cancer registry</td>
<td></td>
</tr>
</tbody>
</table>
diagnostic mammography is commonly used. Mammography is a highly specialized imaging tool that is considerably more expensive than ultrasound. Until the recent application of digital technology, which is itself quite expensive, mammographic imaging required the use of x-ray film, for which the cost and the quality control requirements can be an insurmountable barrier to widespread use in a low-resource country (25). Many health facilities will not purchase mammographic equipment because it is dedicated to the single use of breast imaging without any other radiographic applications. In contrast, ultrasound is commonly 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 which is desired for record keeping. Ultrasound equipment can use multiple different transducers, making it useful for many different applications. Thus there is an impetus for use of breast ultrasound in settings where mammography is unavailable, simply because the tool exists.

Breast ultrasound as an initial diagnostic test may have more utility in low-resource countries. Breast ultrasound is particularly useful for imaging masses in the breast, can be used to distinguish solid masses from fluid-filled cysts, and can characterize the shape and morphology of solid masses, all of which are very useful in determining which patients with palpable masses are more likely to have disease requiring a tissue biopsy (22). 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 evaluation of the extent of disease in the breast (26). Furthermore, premenopausal breast cancer appears to be relatively more common in low-resource 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 imaging (27).

Based on these findings, the BHGI Diagnosis and Pathology Panel advocates that both diagnostic mammography and breast ultrasound be implemented for breast imaging whenever possible. However, if forced to pick between these two breast imaging studies as the “next step,” the panel recommends that diagnostic ultrasound be implemented first (Table 2), despite the fact that this is the reverse order of implementation usually seen in high-resource countries.

Nonetheless, diagnostic mammography is a key component of breast imaging, and of particular importance for breast-conserving therapy. In preparation for breast-preserving radiation therapy, cancers should be removed with negative surgical margins (6). Although breast ultrasound is useful for assessing the extent of the invasive component of a breast cancer, ductal carcinoma in situ (DCIS) is not well imaged on breast ultrasound, but can be seen on mammography when the disease forms microcalcifications. Surgical margins should be clear of both invasive and noninvasive cancer, which is best predicted by the combined use of diagnostic mammography and breast ultrasound before surgery. Thus the BHGI Treatment and Allocation of Resources Panel members consider the availability of diagnostic mammography to be necessary in order to offer breast-conserving therapy (Tables 3–5).

**Hormone Therapy and Hormone Receptor Testing**

Hormone therapy is among the simplest methods of providing systemic therapy for estrogen receptor (ER)-positive breast cancers. As an oral medication, tamoxifen can be provided with minimal infrastructure other than an outpatient pharmacy. If tamoxifen is too expensive, surgical or radiation-induced oophorectomy has proven efficacy and can be performed in premenopausal women. For this reason, the Treatment and Allocation of Resources Panel categorized ovarian oblation and tamoxifen as basic-level resources for all stages of invasive cancer (Tables 3–6).

This recommendation for basic-level stratification by the Treatment and Allocation of Resources Panel contrasts with the recommendations of the Diagnosis and Pathology Panel that described ER and progesterone receptor (PR) testing as being a limited-level resource. Indeed, the use of ER and PR testing is of significant value because tamoxifen or oophorectomy is unlikely to be efficacious when the cancer fails to express ER and PR. Nonetheless, patients can be given these hormonal therapies, even if ER and PR testing is unavailable. However, if this algorithm is followed, a large fraction of patients will receive treatment that, were testing available, could be predicted not to have therapeutic utility.

The rate of ER-positive cancers may vary among different racial groups. In one study, the incidence of ER- and PR-positive cancers was found to be similar in Japanese and American women (28). By comparison, another study analyzing more than 1000 tumors of Chinese women found the ER positivity rate to be 54%, which is significantly lower than for Caucasian women, even when considering the potential confounding variable of menopausal status (29). Thus ER and PR testing, while considered to be a limited-level rather than basic-level resource, has
obvious importance for better guiding the use of therapy. Indeed, the savings in selective use of hormonal treatments should offset if not completely pay for the cost of hormone receptor testing.

Cytotoxic Chemotherapy and Related Infrastructure

With stage I breast cancer (≤2 cm tumor, node negative), chemotherapy can be used, and in high-level resource countries is generally recommended for those cancers between 1 and 2 cm in size (30). However, because the prognosis for stage I cancer is already good, chemotherapy only marginally increases survival in node-negative disease, particularly for smaller cancers (20). In contrast, as breast cancer becomes more advanced, and particularly with node-positive disease, chemotherapy becomes a mainstay of systemic therapy. To properly reflect this difference in the utility of chemotherapy between early stage and later stage disease, the Treatment and Allocation of Resources Panel determined that cytotoxic chemotherapy is a limited-level resource therapy for stage I cancer (Table 3) and for metastatic cancer (Table 6), but it is a basic-level resource for patients with stage II or locally advanced cancer (Tables 4 and 5).

Cytotoxic chemotherapy is a more resource intensive therapy to provide because of the need to give ongoing systemic therapy infusions, monitor blood counts, and treat potential complications. Because there are some breast cancers that do not absolutely require cytotoxic chemotherapy, such as stage I cancer, the infrastructure to support cytotoxic chemotherapy is not considered a basic-level resource at all levels. Thus there is a paradox that in a health care system that lacks the infrastructure for providing systemic chemotherapy, stage I, ER-positive cancers can be effectively treated and stage IV ER-positive cancer can be palliated, but stage II and locally advanced disease can only be palliated at best. Ironically these more advanced, but treatable cancers are the most common presentations in low-resource countries. The conclusion, then, for a hospital administrator or health care minister is that if they choose to seriously undertake breast cancer treatment in their environment, they need to establish the infrastructure early on for cytotoxic chemotherapy, even though this resource is considered higher than a basic-level resource for some stages of breast cancer.

CONCLUSION

As the most common cause of cancer-related death among women, breast cancer warrants attention within health care systems. Efforts toward the early detection, diagnosis, and treatment of breast cancer can be guided by evidence-based principles using a stratified approach to the introduction of needed resources. The BHGI guidelines provide a framework by which health care systems can adapt existing resources, or sequentially introduce new resources using cost-effective strategies, in ways that will optimize outcome. Future directions should include research to determine how these guidelines can best be implemented in order to help women around the globe stricken by this disease.

Acknowledgments

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- Fred Hutchinson Cancer Research Center
- Susan G. Komen Breast Cancer Foundation (grant SG04-0202-01)
- Agency for Healthcare Research and Quality (grant 1 R13 HS015756-01)
- National Cancer Institute, Office of International Affairs (NCI)
- Centers for Disease Control and Prevention (CDC)
- International Atomic Energy Agency (IAEA)
- American Society for Breast Disease (ASBD)
- World Society for Breast Health (WSBH)
- International Network for Cancer Treatment and Research (INCTR)

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- Amgen
- AstraZeneca
- Bristol-Myers Squibb
- Ethicon Endo-Surgery, Inc.
- Pfizer, Inc.

REFERENCES

Appendix A. Breast Health Global Initiative Collaborating Organizations

Alliance for Health Policy and Systems Research (AHPSR)
American Society for Breast Disease (ASBD)
Breast Surgery International (BSI)
Centers for Disease Control and Prevention (CDC)
International Atomic Energy Agency (IAEA)
International Network for Cancer Treatment and Research (INCTR)
International Society for Nurses in Cancer Care (ISNCC)
International Society of Breast Pathology (ISBP)
Middle East Cancer Consortium (MECC)
Pan American Health Organization (PAHO)
International Union Against Cancer (UICC)
World Society for Breast Health (WSBH)

Appendix B. Membership of the BHGI Steering Committee

Gabriel N. Hortobágyi, MD, FACP
Chairman, BHGI Steering Committee
Professor and Chairman of the Department of Breast Medical Oncology, Nellie B. Connally Chair in Breast Cancer, Director of the Breast Cancer Research Program, University of Texas MD Anderson Cancer Center, Houston, Texas

Diana Rowden
Director, International
The Susan G. Komen Breast Cancer Foundation, Dallas, Texas

Sherif Omar, MD, FACS
Past President, National Cancer Institute, Cairo University, International Network for Cancer Treatment & Research (INCTR), Breast Cancer Strategy Group, Cairo, Egypt

Hélène Sancho-Garnier, MD
International Union Against Cancer (UICC), Strategic Leader for Prevention and Early Diagnosis, Vald’Aurelle, France

László Vass, MD, PhD, FIAC
President, World Society for Breast Health (WSBH), Budapest, Hungary

Joseph D. Purvis, MD
Industry/Corporate Partner Representative
Executive Director, Clinical Research, Oncology, AstraZeneca Pharmaceuticals, Wilmington, Delaware

Bhadrasain Vikram, MD
Head, Radiotherapy & Applied Radiation, Biology Section, International Atomic Energy Agency (IAEA) of the United Nations (UN), Vienna, Austria

Benjamin O. Anderson, MD
Chair and Director, BHGI
Joint Associate Member, Public Health Sciences Division, Fred Hutchinson Cancer Research Center, and Professor and Director, Breast Health Center, Department of Surgery, University of Washington, Seattle, Washington

Joe Harford, PhD
Director, Office of International Affairs, NIH/National Cancer Institute (NCI), Bethesda, Maryland

Raimund Jakesz, MD
Professor and Head, Department of General Surgery, Vienna General Hospital, Clinical Department of General Surgery, Vienna University Surgical Clinic, President, Breast Surgery International, Vienna, Austria

Michael Silbermann, DMD, PhD
Executive Director, Middle East Cancer Consortium (MECC), Haifa, Israel

Shahla Masood, MD
Editor, The Breast Journal
Professor and Associate Chair, Department of Pathology, University of Florida, Jacksonville, Florida

Sylvia C. Robles, MD, MSc
Appendix C. Membership of the BHGI Scientific Advisory Committee

<table>
<thead>
<tr>
<th>Member</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ute-Susann Albert, MD, MIAC</td>
<td>Department of Gynecology, Endocrinology and Oncology, Philipps-University Marburg, Marburg, Germany</td>
</tr>
<tr>
<td>Benjamin O. Anderson, MD</td>
<td>Chair and Director, Breast Health Global Initiative; Joint Associate Member, Public Health Sciences Division, Fred Hutchinson Cancer Research Center, and Professor and Director, Breast Health Center, Department of Surgery, University of Washington, Seattle, Washington</td>
</tr>
<tr>
<td>Rakesh Chopra, MD</td>
<td>Senior Consultant, Indraprastha Apollo Hospital, New Delhi, India</td>
</tr>
<tr>
<td>Raimund Jakesz, MD</td>
<td>Professor and Head, Department of General Surgery, Vienna General Hospital; Clinical Department of General Surgery, Vienna University Surgical Clinic, Vienna, Austria</td>
</tr>
<tr>
<td>Susan Lim, MD, PhD</td>
<td>Consultant and General Surgeon, Susan Lim Surgery Pte. Ltd., Gleneagles Medical Centre, Singapore</td>
</tr>
<tr>
<td>Riccardo Masetti, MD</td>
<td>Director of the Breast Surgical Unit, Associate Professor of Surgery, Professor of Surgical Oncology, Department of Surgery, Catholic University of Rome, Italy</td>
</tr>
<tr>
<td>Gilberto Schwartsmann, MD</td>
<td>SA Office, Anti-Cancer Drug Development, Academic Hospital (HCPA), Federal University of Rio Grande do Sul, Porto Alegre, Brazil</td>
</tr>
<tr>
<td>Joseph Stines, MD</td>
<td>Chief, Department Radiology, Centre Alexis Vautrin, Vandoeuvre Les Nancy Cedex, France</td>
</tr>
<tr>
<td>László Vass, MD, PhD</td>
<td>Head, Department of Pathology/Cytopathology, University Teaching Hospital F. FLÓR of Pest County, Budapest, Hungary</td>
</tr>
<tr>
<td>Zhenzhou Shen, MD</td>
<td>Department of Surgery, Cancer Hospital, Fu Dan Medical University, Shanghai, People’s Republic of China</td>
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Appendix D. Panel Cochairs for the 2005 Global Summit

<table>
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<tr>
<th>Panel 2005</th>
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<tbody>
<tr>
<td>Early Detection and Access to Care</td>
<td>Maira Caleffi, MD, PhD, Surgeon and President, Breast Institute of Rio Grande do Sul, Porto Alegre, RS, Brazil</td>
<td>Robert A. Smith, PhD, Director of Cancer Screening, American Cancer Society, Atlanta, Georgia</td>
</tr>
<tr>
<td>Diagnosis and Pathology</td>
<td>Roman Shyyan, MD, MSc, Surgeon, Lviv Cancer Center, Lviv, Ukraine</td>
<td>Shahla Masood, MD, Professor and Associate Chair, Department of Pathology, University of Florida, Jacksonville, Florida</td>
</tr>
<tr>
<td>Treatment and Allocation of Resources</td>
<td>Alexandru Eniu, MD, Department of Breast Tumors, Cancer Institute I. Chiricuta, Cluj-Napoca, Romania</td>
<td>Robert W. Carlson, MD, Professor of Medicine, Division of Oncology, Stanford University, Stanford, California</td>
</tr>
<tr>
<td>Health Care Systems and Public Policy</td>
<td>Cheng-Har Yip, MD, Professor and Head of Surgery, Department of Surgery, University Malaya Medical Centre, Kuala Lumpur, Malaysia</td>
<td>Scott D. Ramsey, MD, PhD, Associate Member, Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, Washington</td>
</tr>
<tr>
<td></td>
<td>Benjamin O. Anderson, MD, Joint Associate Member, Epidemiology, Fred Hutchinson Cancer Research Center, Professor of Surgery, Director, Breast Health Center, University of Washington Medical Center, Seattle, Washington</td>
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</tr>
</tbody>
</table>

Appendix E. Plenary Session Agenda of the Early Detection and Access to Care Panel

Advocate Presentation
Augustine Quashigah, President, Breast Cancer Support Group of Ghana, West Africa
- “Impact of Accessibility on Effectiveness of Early Detection of Breast Cancer”
  Tony Hsu-His Chen, MSc, PhD (epidemiologist, preventative medicine, Taiwan)
- “Tumor Size and Breast Cancer Detection”
  Stephen W. Duffy, BSc, MSc (cancer screening, England)
- “Is Earlier Detection of Symptomatic Breast Cancers Still Early?”
  Dido Franceschi, MD (surgeon, Panama/Miami, Florida)
- “Breast Cancer Detection without Mammography: The Role of Breast Self-Awareness (BSA)”
  Robert M. Chamberlain, PhD (epidemiology, Houston, Texas)
- “Breast Cancer Detection in Romania”
  Gheorghe Peltecu, MD (gynecologist, Romania)
- “Outcome of Screening by Clinical Breast Examination in Manila, Philippines”
  Paola Pisani, PhD (epidemiology, International Agency on Research in Cancer/WHO, France)
Appendix F. Plenary Session Agenda of the Diagnosis and Pathology Panel

Advocate Presentation
Alicia Gimeno, Director, Educational Coordinator, Corporacion Yo Mujer (advocate group) Santiago, Chile

“Practice of Breast Pathology”
Helge Stalsberg, MD (pathologist, Norway)

“Overview of Tissue Sampling Techniques”
Riccardo Masetti, MD (surgeon, Italy)

“Breast Cancer Diagnostic Procedures in India: Consideration of Cost-Effectiveness and Availability of Resources”
Rajendra Badwe, MD (surgical oncologist, India)

“Fine Needle Aspiration Biopsy (FNAB) as a Diagnostic Procedure for Patient Triage”
László Vass, MD, PhD, FIAC (pathologist, Hungary)

“Optimal Pathology Report: Its Most Relevant Diagnostic and Prognostic Information”
Hernan Vargas, MD, FACS (surgeon, Peru/Torrance, California)

“Linkage of Epidemiological Studies and Clinical Practices in Diagnosis of Women’s Cancers”
Rengaswamy Sankaranarayanan, MBBS, MD (Screening Group, International Agency for Research on Cancer/WHO, France)

Appendix G. Plenary Session Agenda of the Treatment and Allocation of Resources Panel

Advocate Presentation
Tatiana Soldak, MD, Medical Director, CitiHope, International; Director, Belarusian Breast Cancer Screening and Early Diagnosis Project (New York, New York)

“Mastectomy vs. Breast Conservation: Influence of Limited Resources on Decision Making”
Raimund Jakesz, MD (surgeon, Austria)

“Situation Analysis in Ghana, West Africa”
Benjamin O. Anderson, MD (breast surgeon, BHGI Chair and Director, Seattle, Washington)

“Combined Modality Management of Locally Advanced Breast Cancer”
Gabriel N. Hortobagyi, MD, FACP (medical oncology, University of Texas MD Anderson Cancer Center, Houston, Texas)

“Metastatic Breast Cancer: Easier to Treat in a Country with Limited Resources?”
Jamie de la Garza-Salazar, MD (medical oncologist, Mexico)

“Ethical and Cultural Considerations for Breast Cancer Treatment in Developing Countries”
Gail Geller, ScD (ethicist, Johns Hopkins University School of Medicine, Bioethics Institute, Baltimore, Maryland)

“Inflammatory Breast Cancer: A Different Disease in the Middle East?”
Sherif Omar, MD (surgical oncologist, Cairo, Egypt)

Appendix H. Plenary Session Agenda of the Health Care Systems and Public Policy Panel

Advocate Presentation
Ranjit Kaur, MS, President, Reach for Recovery/International Union Against Cancer (UICC); President, Breast Cancer Welfare Association; Chairman, Malaysian Breast Cancer Council, Malaysia

“Global Breast Cancer Statistics: The 5 Continents Databases and GLOBOCAN”
D. Maxwell Parkin, PhD (formerly with International Agency on Research in Cancer, WHO, France; currently consultant, Clinical Trials Service Unit and Epidemiological Studies Unit, University of Oxford, United Kingdom)

“Health Care Systems in Developing versus Developed Countries”
Rafael Bengoa, MD (Director, Health System Policies and Operations, World Health Organization, Switzerland)

“Cost-Effectiveness as a Tool for Priority Setting in Developing Countries”
Scott Ramsey, MD, PhD (health economist, Translational and Outcomes Research Group, Fred Hutchinson Cancer Research Center, Seattle, Washington)

“Global and Regional Cost and Effects of Breast Cancer Control”
Rob Baultussen, PhD (health economist, The Netherlands)

“Tackling Early Detection of Breast Cancer in Multicultural Societies”
Larissa Remennick, PhD (medical sociologist, Israel)

“Public Education and Advocacy in Implementing Health Care Change”
Susan Braun, MA (President and CEO, Susan G. Komen Breast Cancer Foundation, Dallas, Texas)
Breast Cancer in Limited-Resource Countries: Early Detection and Access to Care

Robert A. Smith, PhD,* Maira Caleffi, MD, PhD,† Ute-Susann Albert, MD, MIAC,‡ Tony H. H. Chen, MSc, PhD,§ Stephen W. Duffy, MSc, Cstat,#, Dido Franceschi, MD,^ and Lennarth Nyström, PhD,© for the Global Summit Early Detection and Access to Care Panel

*American Cancer Society, Atlanta, Georgia, USA; †Hospital Moinhos de Vento Em Porto Alegre, and Breast Institute of Rio Grande do Sul, Porto Alegre, Brazil; ‡Philipps-University Marburg, Marburg, Germany; §College of Public Health National Taiwan University, Taipei, Taiwan; #Cancer Research UK Center for Epidemiology, Mathematics & Statistics, Wolfson Institute of Preventive Medicine, London, United Kingdom; ^University of Miami, Miami, Florida; and ©Umeå University, Umeå, Sweden

Abstract: Although incidence, mortality, and survival rates vary fourfold in the world’s regions, in the world as a whole, the incidence of breast cancer is increasing, and in regions without early detection programs, mortality is also increasing. The growing burden of breast cancer in low-resource countries demands adaptive strategies that can improve on the too common pattern of disease presentation at a stage when prognosis is very poor. In January 2005, the Breast Health Global Initiative (BHGI) held its second summit in Bethesda, MD. The Early Detection and Access to Care Panel reaffirmed the core principle that a requirement at all resource levels is that women should be supported in seeking care and should have access to appropriate, affordable diagnostic tests and treatment. In terms of earlier diagnosis, the panel recommended that breast health awareness should be promoted to all women. Enhancements to basic facilities might include the following, in order of resources: effective training of relevant staff in clinical breast examination (CBE) both for symptomatic and asymptomatic women; opportunistic screening with CBE; demonstration projects or trials of organized screening using CBE or breast self-examination; and finally, feasibility studies of mammographic screening. Ideally, for complete evaluation, such projects require notification of deaths among breast cancer cases and staging of diagnosed tumors.

Key Words: breast awareness, breast cancer, clinical breast examination, developing countries, diagnosis, imaging, mammography, screening

In the world, breast cancer is the most common cancer diagnosed in women and the most common cause of death from cancer. The most current estimates from the International Agency for Research on Cancer (IARC) for the global disease burden of breast cancer are for 2002, and in that year, the IARC estimates that there were approximately 1.15 million newly diagnosed cases and approximately 411,000 deaths (1). Incidence, mortality, and survival rates vary fourfold across the world’s regions because of underlying differences in known risk factors, access to effective treatment, and the influence of organized screening programs (2). Incidence and mortality rates tend to be higher in high-resource countries and lower in low-resource countries. Conversely, fatality rates tend to be higher in low-resource countries (1).

One feature common across the world’s regions is the observation that in many countries, breast cancer incidence rates are increasing. Based on current estimates of an average annual increase in incidence ranging from 0.5% to 3% per year, the number of new cases projected to be diagnosed in 2010, just 4 years from now, is 1.4–1.5 million (1). What is also clear is that there is an emerging disparity in long-term mortality trends, with mortality rising in parallel with incidence in some countries and declining in others despite rising incidence rates, a difference likely attributable to the combined effect of earlier detection and effective therapy.

The growing burden of breast cancer in low-resource countries demands adaptive strategies that can improve on the too common pattern of disease presentation at a stage when prognosis is very poor. Although it is commonly argued that interventions focused on adult chronic
conditions are a lower priority in low-resources settings, this reasoning may rest on the assumption that chronic disease interventions bear the same costs as common, high-tech interventions in higher-resource countries, and that they drain resources from other public health challenges, such as those focused on clean water, sanitation, and infectious diseases. However, it is possible that effective interventions focused on some cancers can be relatively low cost and that the implementation of simple interventions that could measurably reduce premature mortality in adults at productive ages should not be neglected until other health problems are solved (3,4). With breast cancer incidence rates now increasing more rapidly in some low-resource regions, as well as some developed regions that have not yet offered screening to the population, the inevitable outcome will be a continued increase in the mortality rate unless efforts are dedicated to diagnose breast cancer at a more favorable stage and ensure access to effective therapy.

**METHODS**

In October 2002, the Global Summit Consensus Conference was held in Seattle, Washington, to develop consensus recommendations for the early detection, diagnosis, and treatment of breast cancer in countries with limited resources (3,5). In the report from the first conference, the emphasis on early detection stressed the simple goal of diagnosing breast cancer at the earliest stage possible, depending on available local resources. Early detection could mean earlier diagnosis of symptomatic breast cancer, as well as the detection of occult breast cancer through mammographic screening in asymptomatic women. The report also emphasized necessary key social elements; that is, a supportive environment for women to seek care at the first indication of symptoms and access to appropriate, affordable diagnostic tests and treatment. In 2002, conference attendees recommended a stepwise process for building the foundation for achieving earlier detection, as follows: promote the empowerment of women to seek and obtain health care; create the infrastructure for the diagnosis and treatment of breast cancer; and promote early detection through breast cancer education and awareness. The report also recommended that if resources became available, early detection efforts should be expanded to include mammographic screening, since it offers considerably greater potential to reduce the incidence of advanced breast cancer than programs limited to earlier diagnosis of symptomatic breast cancer (6). This report, based on the biennial meeting held in Bethesda, MD, in January 2005, represents the continuation of the consensus process related to breast cancer detection and access to care in low-resource settings.

The methods and consensus process for the 2005 Global Summit are described elsewhere in this issue (7). Presentations in the early detection and access to care session at the summit focused on the value of detecting breast cancer at an earlier stage and the potential of various disease control strategies to achieve this goal. Conference attendees were told that the recommendations and conclusions from the 2002 meeting were open to revision. For this report, we relied on the literature review performed for the previous report and conducted a new MEDLINE search under the subject headings “breast awareness,” “clinical breast examination,” “breast self-examination,” and “mammography,” limited to the English language, from 2000 to 2005. We also performed an additional PubMed search under the subject headings “breast cancer,” “low-resource countries,” and “developing countries,” also limited to the English language, from 1990 to 2005.

As described in the overview article (7), each panel was asked to follow an incremental four-level health care resources stratification scheme, with levels defined as basic, limited, enhanced, and maximal, and to describe interventions and levels of service relevant to each level of resources. The panel’s recommendations acknowledge that different levels of resources may exist within a nation and, as well, that appropriate interventions may also vary within a nation. A position that has not changed since the 2002 summit was that women have a right to health care, and thus a core requirement at all resource levels is that women should be supported in seeking care and should have access to appropriate, affordable, diagnostic tests and treatment. This is a necessary condition before the initiation of any program focused on earlier breast cancer detection. Further, as additional resources become available, countries should strive to achieve the next level of resource-based service delivery. The Early Detection and Access to Care Panel based its recommendations (Table 1) on the published literature and on the consensus process (7) resulting from the presentations and deliberations during the 2005 summit.

**FINDINGS AND RECOMMENDATIONS**

The Importance of Early Diagnosis

The following discussion is framed by the consensus that there is solid evidence supporting the value of diagnosing breast cancer at an early stage (5,6,8–12). Individual randomized controlled trials (RCTs) (13,14)
and meta-analyses (15,16) have demonstrated the advantage of an invitation to screening, and detailed analysis of tumor characteristics and long-term survival have demonstrated the prognostic advantage of incrementally smaller tumors at the time of diagnosis (6). Although the technology of mammography offers the unique advantage of detecting occult breast cancer, the data on tumor size and survival also indicate there is an advantage to detecting palpable tumors at the earliest opportunity (14,17,18). The reduction in mortality in the RCTs of mammographic screening was predicted by reductions in the rates of lymph node-positive disease, and the magnitude of the reduction in the rate of advanced disease is a good surrogate of the eventual mortality reduction (16) (Table 2).

The importance of tumor size in improving survival is increasingly evident, and recent evidence by Elkin et al. (19) has shown that measuring the impact of an early detection program by stage alone would fail to observe tumor downsizing benefits within stage groups. These investigators recently showed that for breast cancers diagnosed in the United States between 1975 and 1999, within-stage migration of tumor size accounted for a significant proportion of the increased survival observed during that period (19). Although it is not possible to estimate the proportion of this improvement in U.S. survival attributable to mammography alone, insofar as a significant proportion of newly diagnosed breast cancers during this period were symptomatic, increased awareness and more rapid response to symptoms by women and doctors have likely played an important role.

One final point is worth noting. At any given level of service, ranging from simple improvements in breast health awareness and responsiveness to symptoms to the availability of advanced imaging technology, achieving higher rates of early detection is dependent on improving the sensitivity of the screening tool, and increasing the population coverage and adherence. The observations about the strong association between tumor size, advanced-stage disease, and prognosis, and the evidence about the value of behavioral interventions form the foundation for the following recommendations.

### Table 1. Resource Allocation for Early Detection and Access to Care

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Detection method(s)</th>
<th>Evaluation goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>Breast health awareness (education ± self-examination) Clinical breast examination (clinician education)</td>
<td>Baseline assessment and repeated survey</td>
</tr>
<tr>
<td>Limited</td>
<td>Targeted outreach/education encouraging CBE for at-risk groups Diagnostic ultrasound ± diagnostic mammography</td>
<td>Downstaging of symptomatic disease</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Diagnostic mammography Opportunistic mammographic screening</td>
<td>Opportunistic screening of asymptomatic patients</td>
</tr>
<tr>
<td>Maximal</td>
<td>Population-based mammographic screening Other imaging technologies as appropriate: high-risk groups, unique imaging challenges</td>
<td>Population-based screening of asymptomatic patients</td>
</tr>
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</table>

### Table 2. Relative Risks of Mortality and Diagnosis of a Node-Positive Breast Cancer in the Eight Randomized Controlled Trials (16)

<table>
<thead>
<tr>
<th>RCT</th>
<th>Mortality (95% CI)</th>
<th>Node-positive breast cancer</th>
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</thead>
<tbody>
<tr>
<td>HIP</td>
<td>0.78 (0.61–1.00)</td>
<td>0.85</td>
</tr>
<tr>
<td>Malmo</td>
<td>0.78 (0.65–0.95)</td>
<td>0.81*</td>
</tr>
<tr>
<td>Two-County</td>
<td>0.68 (0.59–0.80)</td>
<td>0.73</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>0.78 (0.62–0.97)</td>
<td>0.80</td>
</tr>
<tr>
<td>Stockholm</td>
<td>0.90 (0.63–1.28)</td>
<td>NK</td>
</tr>
<tr>
<td>NBSS-1</td>
<td>0.97 (0.74–1.27)</td>
<td>1.40</td>
</tr>
<tr>
<td>NBSS-2</td>
<td>1.02 (0.78–1.33)</td>
<td>1.17</td>
</tr>
<tr>
<td>Gothenburg</td>
<td>0.79 (0.58–1.08)</td>
<td>0.80</td>
</tr>
<tr>
<td>Overall</td>
<td>0.80 (0.73–0.86)</td>
<td>—</td>
</tr>
</tbody>
</table>

CI, confidence interval; HIP, Health Insurance Plan; NBSS-1, Canadian National Breast Screening Study-I; NBSS-2, Canadian National Breast Screening Study-II; NK, not known; RCT, randomized controlled trial.

*For the Malmo trial, we used stage II or worse because data for nodal status are not available.

Breast Awareness

Timely diagnosis of symptomatic disease relies on breast health awareness in the potential patient population and in primary health care professionals, and thus increased breast health awareness is a key element of interventions at all resource levels. Although awareness is an elusive concept, it clearly has great potential for improving the outcome of breast cancer patients. It is important to be mindful that the great majority of women in the world in whom breast cancer is diagnosed each year are symptomatic at the time of diagnosis, and that the majority of women in the world do not have access to screening mammography. Thus, based on the observation of the association between tumor size and prognosis, it should be clear that the goal of earlier detection is not simply the
goal of detecting a greater proportion of breast cancers when they are asymptomatic, but also downsizing symptomatic breast cancers as well.

In the United Kingdom, Stockton et al. (20) found that in the 1980s before the National Breast Screening Program began, the rate of advanced breast cancer fell dramatically, and it is believed that this downstaging was due to increased awareness that resulted from the greater presence of public education messages about early detection. A similar pattern was observed in Yorkshire, where a generalized shift toward a more favorable stage at diagnosis that could not be attributed to screening was observed before a reduction in mortality (21). The introduction of systemic therapy was determined to have no impact on short-term survival, leaving little explanation other than a generalized trend toward earlier detection of palpable masses by women or their doctors or both. Therefore awareness is worth pursuing, despite difficulties of definition and uncertainties in how awareness should be promoted. Even in discussions of recent data questioning the value of teaching and conducting breast self-examination (BSE), the importance of awareness is still stressed (22,23).

An important aspect of awareness is dissemination of the knowledge that breast cancer is not rapidly fatal if diagnosed early and in many cases is “curable.” In the 1970s and 1980s, the majority of women who developed breast cancer died from the disease (24). With earlier stages at presentation and better treatment, this is no longer the case (14). It is clear from the very advanced stage at presentation in some low-resource countries that diagnosis is often delayed in patients who must have been aware of symptoms for some time (25). Fear of diagnosis, among other factors, is a major contributor to the very advanced stage of disease in many countries, and in fact, this is a global phenomenon not restricted to only limited-resource areas (26–28). However, avoidance of diagnosis is mitigated in developed countries by the fact that public education about the importance of early detection has been prevalent for decades, access to care is greater, and most women are acquainted with long-term survivors of breast cancer and are less deterred from seeking consultation when symptoms occur. Insofar as this greater responsiveness has evolved over many years, it seems reasonable to speculate that a public education strategy that emphasizes the survivability of breast cancer and uses surviving breast cancer patients will be productive in this effort.

The association between knowledge of surviving patients and greater acceptability of diagnosis may have a synergistic, cumulative effect. Knowledge of long-term survivors may stimulate early consultation for symptoms, which may lead to an earlier average stage at presentation, resulting in turn in more long-term survivors. We conclude that enhanced awareness has considerable potential for improving the stage at presentation and therefore survival. How to engender that awareness among health care workers as well as the general public and on which particular facets of breast disease to focus are priorities for evaluation, both globally and in local settings.

Clinical Breast Examination

An important feature of health care provider education is training in the clinical breast examination (CBE) procedure. CBE training is necessary as a key contributor to prompt diagnosis of symptomatic disease. In addition, it is likely to be of use in the early diagnosis of disease that is asymptomatic (i.e., unknown to the patient) in areas where mammographic screening is unavailable. Although this examination may not be able to detect the very small tumors that can be seen only on mammography, it has the potential to improve the situation wherein the majority of tumors diagnosed are at stage III or IV (25,29,30).

Despite the compelling logic for the value of CBE, evidence on its efficacy is remarkably limited. In fact, the lack of data on CBE was cited by the 2002 Global Summit as a factor in not directly recommending the implementation of CBE programs in limited-resource countries (5). Further, most of the evidence is from higher-resource settings, and quite often in the context of the added value of CBE in the context of mammography (11,29–31). The Canadian National Breast Screening Study II (NBSS-2) found no significant difference in breast cancer mortality between the group offered mammography and the group offered CBE (32,33). Although this finding has been cited as evidence that mammography confers no additional advantage to well-done CBE (33), the weight of the evidence is to the contrary, both from the RCTs (34) and case series (31). Further, the NBSS-2 was not an equivalence trial, and the 95% confidence interval around the result was too wide to suggest equivalence.

Recently Pisani et al. (35) published the first results of an ambitious RCT in the Philippines designed to evaluate the efficacy of annual CBE performed by trained nurses and midwives. The target population was women 35–64 years of age residing in 12 municipalities in Manila \( n = 340,000 \), and the units of randomization were 202 health centers in the municipalities. The first round of screening took place in 1996–1997, and of 151,168 women offered CBE, 92% agreed to participate in the study. However, the study was closed after the first round
because of the unwillingness of the majority of women who screened positive to participate in follow-up examinations. Among 3479 women with positive findings on screening, only 1220 (35%) completed a diagnostic follow-up examination. Forty-two percent of women actively refused any further investigation, including a home visit, and 23% were not traceable. Although follow-up was very poor, the results of this study are not entirely dissuasive of the potential to screen with CBE. Test sensitivity for annual examination was 53.2%, and for biennial examination was 39.8%. Further, the investigators documented an improvement in stage at diagnosis in examined women. Pisani et al. (35) concluded that the aborted study offered some valuable lessons for introducing CBE screening, including having realistic expectations about the necessity of ongoing training and monitoring of examiners, and for newly trained personnel to acquire greater levels of experience. No less important is identifying and overcoming culturally related health beliefs that could be a major barrier to the success of a screening program.

Even though there is still no direct randomized trial evidence that regular, high-quality screening CBE confers an advantage over no CBE, or even the more common, cursory, low-quality CBE received by most women today, such an advantage cannot be ruled out. However, the evidence to date indicates that for a program of CBE to be successful, barriers at every step of the continuum of the screening process will need to be identified, understood, monitored, and overcome.

At the most basic level, competent CBE should be available to women with breast symptoms. Once access is in place, there also may be a role for opportunistic screening; that is, screening that takes place on the occasion of health care encounters for other reasons (36). This does not mean that at every visit to a primary care provider CBE should take place or be offered. Rather it means that the provider chooses appropriate occasions for CBE based on the nature of the consultation, the state of the health and mind of the patient, and the time since the last CBE. This is similar to the opportunistic CBE and mammographic screening currently taking place in parts of North America and Europe. The occasion of CBE also provides an opportunity for a care provider to discuss early signs and symptoms of breast cancer, and to stress the importance of immediately reporting breast changes to their provider. If the patient is interested in conducting periodic BSE, during CBE, information and instruction about BSE can be provided and the patient’s technique can be reviewed.

Once CBE is readily available as a clinical resource, a limited-resource area may consider formal programs of screening for as yet undetected symptomatic breast cancer using CBE. One national trial of CBE was completed in the Philippines (35), but this provides only indirect results, suggesting that further investigation should be pursued. Another is under way in India (Badwe RA, unpublished observation, 2005), although results will not be available for some years. Thus the efficacy of CBE as a stand-alone screening tool is not yet established. The current state of knowledge about the efficacy of CBE programs implies that the introduction of any program of CBE needs to be subjected to thorough evaluation, and this in turn implies that regions with such programs should have systems in place to enable the identification of deaths in patients with breast cancer. In addition, to facilitate evaluation early in the program, before large numbers of deaths have been observed, information on disease stage should be available.

The randomized trials of mammographic screening showed that a mortality reduction is achieved by early detection only if there is first a reduction in the rate of advanced-stage disease, and indeed, a reduction in the incidence of advanced disease is a fairly consistent predictor of an eventual reduction in mortality (16). It cannot be too strongly emphasized that a fundamental part of any strategy to reduce mortality and morbidity from breast cancer in limited-resource areas, whether it includes CBE screening or not, is the means to monitor that strategy and to identify and correct failures. Thus a basic component of any formal program of CBE should include identification of deaths in breast cancer cases as well as routine staging of breast tumors.

**Formal BSE**

Training in BSE has not been shown to reduce mortality from breast cancer, and the most frequently cited studies for that conclusion are the BSE trials in the former Soviet Union and in Shanghai, China (37,38). This does not mean that there is definitive evidence that BSE or BSE instruction is ineffective or would not be effective in any setting (38), despite overinterpretation of this evidence by some commentators (22,39). The absence of evidence of a benefit is not the same as evidence of no benefit (40). In the case of the Shanghai trial, several points are worth noting. First, it was a trial of BSE instruction, not BSE. Second, approximately half of the tumors among women in the control group were stage T1 or better, suggesting there already was a heightened sense of awareness about breast symptoms in this population and the BSE instruction might have had more limited potential for improvement in downstaging in Shanghai compared with other populations. Finally, the Shanghai trial shows an 8% reduction
in node-positive disease and an 11% reduction in stage T2 or worse disease in the group offered BSE training. This suggests that in the future, if follow-up was continued, a reduction in mortality of similar size would be evident.

Although BSE cannot be positively recommended on the basis of current evidence, we would not actively discourage its use either. BSE instruction may have the greatest value not so much in stimulating regular self-examinations, but rather simply in promoting greater awareness of breast symptoms. We would, however, make the same recommendations as for CBE screening: because there is not yet an evidence base for its efficiency, any BSE program should be rigorously evaluated, both in terms of deaths in patients with breast cancer and in terms of stage of disease. The program must be able to identify deaths in patients and to ascertain the stage of disease at diagnosis.

**Mammography**

At the present time, mammographic screening is the gold standard for early detection of breast cancer, and regions with enhanced resources should aspire to provide access. Figure 1 shows the effect of an invitation to mammographic screening on mortality from breast cancer in the randomized trials of breast cancer screening (16). The figure indicates a 20% reduction in breast cancer screening with an invitation to mammography. The IARC concluded that the effect of actually being screened would be considerably larger (8), and much larger effects, that is, 40% or more in women who actually participate in screening, have been observed in recent evaluations of service screening (41).

The panel advises against new RCTs of breast cancer screening with an emphasis on efficacy as part of a strategy for introducing mammography in populations in which mammography currently is not available. There is little reason to question the value of early detection with mammography in population settings where it has not yet been introduced, and considerations about the implementation of mammographic screening should be limited to whether a mammographic screening program would be cost effective and whether high quality would be sustained. In the United States, Europe, and elsewhere, strong quality assurance programs have been developed to ensure that the technical quality of mammography is high (42,43). The implementation of mammographic screening must be accompanied by strong quality assurance programs that include regular assessments of quality control, and medical audits and feedback to interpreting physicians and radiologic technologists.

**Social and Cultural Considerations**

A common response to the disproportionate incidence of advanced-stage breast cancer and high fatality rates is to stress the importance of educating women to recognize the early signs of breast cancer and to promptly report these to a health care provider. Although education is a critical element in any early detection program, it is a mistake to neglect other potential barriers to earlier diagnosis. The experience of two recent, large RCTs, one of BSE (38) and the other focused on CBE (35), are examples of situations in which greater awareness of social and cultural factors influencing the potential of earlier detection programs might have changed the course or conduct of the study.

![Figure 1. Relative risk of mortality associated with an invitation to screening in the randomized trials of breast cancer screening, all ages (16).](image-url)
In the Shanghai BSE trial, investigators evaluated the efficacy of BSE instruction in a population in which more than half of the newly diagnosed breast cancers in the control group were small, stage I tumors, suggesting that the population already had a high degree of awareness and that there might have been little opportunity to improve the stage of diagnosis further. In the first year of the Philippines CBE trial, the investigators observed that the large majority of women accepted an invitation to undergo CBE, and subsequently the large majority of women who screened positive refused to be examined further (35). In both cases, consideration of factors outside the clinical realm, that is, factors that could have been explored and understood using the tools of medical anthropology and sociology, might have revealed important social and cultural factors that would have led to modifications in the study design and the intervention. There is, of course, no certainty that this would have been the case, but each study provides valuable lessons about the critical importance of understanding current patterns of disease presentation, and social and behavioral factors that may influence those patterns.

A variety of barriers to awareness, seeking and obtaining care, and responsiveness to screening are evident in the literature (26,35,44,45) and were identified during the 2002 Global Summit: fatalism, inability to act without husband’s permission, fear of casting stigma on one’s daughters, fear of being ostracized, fear of contagion, reticence, language barriers (e.g., the absence of a word for cancer in some languages), preference for traditional healers, and others. These barriers fall into two general groups: those that can be addressed with education and those that need to be addressed with tailored approaches that take into account culture, religion, and other factors. In both instances, and likely in every setting, tailored approaches will need to be directed toward women, health care workers, and others in the community. Some tailored approaches other than those directed toward women may include soliciting the help of respected leaders (e.g., rabbis for ultraorthodox Jewish women, or sheiks for Muslim women, etc.) and outreach to men in strong, patriarchal societies, or traditional healers.

Although we present only a limited number of examples here, the discussion during the 2005 Global Summit led to the conclusion that a narrow education/clinical response approach to breast cancer that neglects an understanding of potentially powerful barriers is a strategy that increases the likelihood of program failure. It may also lead to the mistaken impression that the key elements of an intervention were unsuccessful, when in fact, the intervention would have worked quite well, but was not sufficient alone to overcome neglected or unforeseen social and cultural barriers to earlier detection and care.

As noted above, a key barrier to address is the perception that breast cancer is universally fatal. In countries with a lower incidence of the disease, predominately late stage at presentation, and demographic or geographic barriers, most women may not know of any breast cancer survivors. Yet patients with breast cancer can play a vital role in awareness and screening programs. By sharing their experiences, they can provide information about barriers and help remove taboos surrounding the disease. Advocacy groups can greatly influence the knowledge, attitudes, and behavior of the public, as well as the political process and resources available for breast cancer.

When planning awareness programs, guidelines should address who will be the target for the awareness messages. Targeting messages to a specific population is essential to avoid overloading the system. For example, failing to target a breast awareness message might result in many adolescent women presenting with breast pain, which would drain the resources available to identify older women with breast cancer.

The panel strongly encourages the contribution and perspective of medical anthropology and medical sociology, and the application of these perspectives and methodologies to the understanding of the local situation will be helpful in clarifying barriers. In all regions, it is likely that there are factors other than, or in addition to, lack of awareness that explain why women typically present with late-stage breast cancer.

**Implementing Evaluation Programs**

The objective of any of the intervention programs described here is to reduce morbidity and mortality from breast cancer, and to do so without adversely affecting the health status of those who participate. Different programs have been suggested, depending on the resources of the country, and in each instance, introducing a program creates a responsibility to evaluate and monitor its effectiveness. Evaluation is a process that attempts to determine as systematically and objectively as possible the relevance, effectiveness, and impact of activities in light of their objectives (46). Effectiveness is a measure of the extent to which a specific intervention procedure, regimen, or service does what it is intended to do for a specified population; it is a measure of the extent to which a health care intervention fulfills its objectives.

The effectiveness of a program is a function of the quality of the individual components. The success of the program is judged not only by its impact on breast cancer...
morbidity and mortality, but also by the organization, implementation, execution, and acceptability of the program; for example, a program with a low acceptability in the population will never reach its objectives. There are several handbooks on the evaluation and monitoring of health interventions (47), and in particular, screening programs (48). Planning for the evaluation and monitoring of an intervention should take place at the same time as planning the intervention.

A prerequisite for evaluation of a program is usually the availability of a control group to allow for comparison, either geographically or temporally. Thus, various disease-specific or behavioral endpoints of interest may be evaluated by comparing data from a region in which the intervention is taking place with data from a region without the intervention, or alternatively, before and after comparisons in the same region. Other approaches are also available. Finland designed the introduction of their screening program for evaluation by delaying invitation to the program by 2–4 years for some birth-year cohorts to facilitate comparison of the program between birth cohorts that were invited earlier and later (49). A similar approach became possible in Sweden because of a lack of resources and radiologists in some areas that forced some counties to delay the start of their screening program (50) or limit the age span for women invited (51,52). Thus, in Sweden, evaluation of the effectiveness of the service screening program with mammography was possible for the 50- to 69-year age group by comparing counties that initiated the program early and counties that had to wait until resources were available, and for the 40- to 49-year and 70- to 74-year age groups by comparing counties that invited women age 40–74 years to screening with counties that invited only women age 50–69 years.

Another prerequisite for being able to evaluate screening with mammography or CBE is the availability of population-based registries for cancer and cause of death (48). If there is a lack of these registries, other outcome measures, so-called surrogate measures or performance parameters, have to be defined, for example, the interval cancer rate or the proportion of screen-detected cases that are node negative, and the evaluation must be based on screening history data collected within the program (42).

**CONCLUSION**

If resources are adequate, mammography is the screening modality of choice for the early detection of breast cancer. It is the only evidence-based early detection method, and both evidence from RCTs and data showing a survival advantage at 20 years or longer associated with incrementally smaller tumor size demonstrate the advantage of detecting occult breast cancer over symptomatic breast cancer. Insofar as increasing tumor size is associated with poorer outcomes, there is also an advantage for detecting symptomatic breast cancer at a smaller size. However, it must be appreciated that in some regions of the world, mammographic screening programs simply are not feasible due to a lack of resources, and yet, in many of these areas, the majority of cases present at stage III or IV, implying that there is considerable opportunity for earlier diagnosis without expensive imaging technology. In these circumstances, the first priority is to have in place facilities for prompt diagnosis and surgical treatment. Once that capacity is established, improvements focused on earlier diagnosis can be considered. It should be kept in mind that in some low-resource areas, treatment in addition to surgery is unavailable to the majority, and thus, in these circumstances, enhancing the potential for diagnosis at a stage when the disease is still within surgical control becomes even more urgent.

In terms of earlier diagnosis, breast health awareness should be promoted to all women. Enhancements to basic facilities might include, in order of resource availability, effective training of relevant staff in CBE for both symptomatic and asymptomatic women; opportunistic screening with CBE; demonstration projects or trials of organized screening using CBE or BSE; and finally, feasibility studies of mammographic screening. Ideally, for complete evaluation, such projects require notification of deaths among breast cancer cases and staging of diagnosed tumors.

Although there is a rich body of literature related to breast cancer interventions in higher-resource countries, in particular the United States and Europe, the published literature related to interventions focused on early detection in lower-incidence/low-resource areas is quite limited. However, the goal of earlier breast cancer detection and prompt, appropriate therapy is clear enough, and there is little need to entirely reinvent the wheel. Over the past several decades there has been an accumulation of both cross-cultural and locally specific experience in low-resource countries, both among health workers and as documented in the published literature, in programs focused on family planning (53), oral rehydration therapy (54), breast-feeding (55), cervical cancer (56,57), oral cancer (58), infectious disease (59,60), HIV and AIDS (61), and others. Many of these programs are ongoing and may be appropriate vehicles for introducing breast health awareness. Further, many of the behavioral interventions
focused on disparate targets have been built on a set of common denominators that have meaning to the target population and have also benefited from prior experience within and across populations. Here, in many respects, well-documented failures may be as informative as successes. Although not addressed in detail here, the implementation of more complex, higher-resource interventions can initially be risk based, with higher-risk women identified through questionnaires or interviews during opportunistic encounters for health care. This strategy also requires careful evaluation, because risk-based strategies in the West have not successfully identified a significant proportion of incident breast cancer cases through careful targeting of women with known risk factors (62).

The global health community faces a growing challenge with breast cancer, and there is an increasing consensus that it is past time to apply the lessons learned over the last several decades, in whatever ways are feasible, to reduce the incidence rate of advanced breast cancer throughout the world. Although additional research is necessary, investigations should strive to be short-term demonstrations with potential for rapid application of strategies that have been shown to be effective. Beyond this, what also is needed is an international consortium of public health organizations to commit to a mission-oriented, long-term agenda focused on global breast cancer. The consortium could establish the core leadership to support demonstration projects, technology transfer, evaluation, surveillance, and regular opportunities for information exchange among scientists, clinicians, health workers, and advocates. Such an organization could not only support a more systematic, evidence-based approach to reducing premature mortality from breast cancer in various resource settings, but also could stimulate public health initiatives sooner than they otherwise might begin. Ultimately the beneficiaries of such leadership would be the women of the world, most of whom are still at risk for a late diagnosis of breast cancer. We hope that the evidence reviewed and the guidelines presented in this report will help inform and advance efforts to improve breast health outcomes in limited-resource settings. In the words of naturalist David Starr Jordan (1851–1931), “Wisdom is knowing what to do next; virtue is doing it.”

PANELISTS

Robert A. Smith, PhD (panel cochair), American Cancer Society, Atlanta, Georgia, USA; Maira Caleffi, MD, PhD (panel cochair), Hospital Moinhos de Vento Em Porto Alegre, and Breast Institute of Rio Grande do Sul, Porto Alegre, Brazil; Ute-Susann Albert, MD, MIAC, Philipps-University Marburg, Marburg, Germany; Ana Jovicevic Bekic, MD, MSc, Institute of Oncology and Radiology of Serbia, Belgrade, Serbia and Montenegro; Robert M. Chamberlain, PhD, University of Texas MD Anderson Cancer Center, and University of Texas School of Public Health, Houston, Texas; Tony H. H. Chen, MSc, PhD, Department of Public Health, Institute of Preventative Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; Stephen Duffy, MSc, CStat, Cancer Research UK Center for Epidemiology, Mathematics & Statistics, Wolfson Institute of Preventive Medicine, London, United Kingdom; Dido Franceschi, MD, Sylvester Comprehensive Cancer Center, University of Miami School of Medicine, Panama/Miami, Florida; Kardinahe, MD, Dharmais Hospital, National Cancer Center, Jakarta, Indonesia; A. Nandakumar, MD, MPH, National Cancer Registry Programme of India, Bangalore, India; Lennarth Nyström, PhD, Umeå University, Umeå, Sweden; Gheorge C. Peltecu, MD, PhD, Carol Daila University of Medicine and Filantropia Hospital, Bucharest, Romania; Paola Pisani, PhD, International Agency for Research on Cancer, World Health Organization, Lyon, France; Larissa Remennick, PhD, Bar-Ilan University, Ramat-Gan, Israel; Cecilia Sepulveda, MD, MPH, Program on Cancer Control, World Health Organization, Geneva, Switzerland.

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REFERENCES


Breast Cancer in Limited-Resource Countries: Diagnosis and Pathology

Roman Shyyan, MD, MSc,* Shahla Masood, MD,† Rajendra A. Badwe, MD, MBBS,‡ Kathleen M. Errico, PhD, ARNP,§ Laura Liberman, MD,¶ Vahit Ozmen, MD,#, Helge Stalsberg, MD,^ Hernan Vargas, MD,© and László Vass, MD, PhD,¢ for the Global Summit Diagnosis and Pathology Panel

*Lviv Cancer Center, Lviv, Ukraine; †University of Florida, Jacksonville, Florida; ‡Tata Memorial Hospital, Mumbai, India; §University of Washington and Seattle University, Seattle, Washington; ¶Memorial Sloan-Kettering Cancer Center, New York, New York; #Istanbul University, Istanbul, Turkey; ^University Hospital of North-Norway, Tromso, Norway; ©Harbor-UCLA Medical Center, Torrance, California; and ¢University Teaching Hospital F. FLÓR of Pest County, Budapest, Hungary

Abstract: In 2002 the Breast Health Global Initiative (BHGI) convened a panel of breast cancer experts and patient advocates to develop consensus recommendations for diagnosing breast cancer in countries with limited resources. The panel agreed on the need for a pathologic diagnosis, based on microscopic evaluation of tissue specimens, before initiating breast cancer treatment. The panel discussed options for pathologic diagnosis (fine-needle aspiration biopsy, core needle biopsy, and surgical biopsy) and concluded that the choice among these methods should be based on available tools and expertise. Correlation of pathology, clinical, and imaging findings was emphasized. A 2005 BHGI panel reaffirmed these recommendations and additionally stratified diagnostic and pathology methods into four levels—basic, limited, enhanced, and maximal—from lowest to highest resources. The minimal requirements (basic level) include a history, clinical breast examination, tissue diagnosis, and medical record keeping. Fine-needle aspiration biopsy was recognized as the least expensive reliable method of tissue sampling, and the need for comparing its clinical usefulness with that of core needle biopsy in the limited-resource setting was emphasized. Increasing resources (limited level) may enable diagnostic breast imaging (ultrasound ± mammography), use of tests to evaluate for metastases, limited image-guided sampling, and hormone receptor testing. With more resources (enhanced level), diagnostic mammography, bone scanning, and an onsite cytologist may be possible. Mass screening mammography is introduced at the maximal-resource level. At all levels, increasing breast cancer awareness, diagnosing breast cancer at an early stage, training individuals to perform and interpret breast biopsies, and collecting statistics about breast cancer, resources, and competing priorities may improve breast cancer outcomes in countries with limited resources. Expertise in pathology was reaffirmed to be a key requirement for ensuring reliable diagnostic findings. Several approaches were again proposed for improving breast pathology, including training pathologists, establishing pathology services in centralized facilities, and organizing international pathology services.

Key Words: breast cancer, core needle biopsy, developing countries, diagnosis, fine-needle aspiration biopsy, imaging, mammography, surgical biopsy, triple test, ultrasound

Correct diagnosis is a prerequisite for successful cancer treatment. The diagnosis of breast cancer relies on a combination of clinical examinations, pathology tests, and imaging studies that provide the clinician with relevant prognostic and predictive information to counsel patients and initiate cancer treatment. In these guidelines, we focus on the central aspects of breast cancer diagnosis and pathology that should form the core of the breast cancer program in countries with limited resources. In addition, we expand on the previous guidelines formulated in 2003 by stratifying the recommendations explicitly into resource levels.

METHODS

An international group of breast cancer experts and advocates met at a summit in Bethesda, Maryland, on January 12–15, 2005, to reexamine consensus recommendations for breast cancer diagnosis and pathology in countries with limited resources. In the morning, summit participants gave presentations on topics related to the
diagnosis and pathology of the disease, and current approaches and barriers to delivery of these services in parts of the world where resources are markedly constrained. In the afternoon, the Diagnosis and Pathology Panel, a subgroup of conference participants, reviewed the available evidence, the Breast Health Global Initiative (BHGI) 2003 guidelines on diagnosis (1), and current international guidelines on breast cancer diagnosis; debated approaches to diagnosis and pathology under the constraints of limited resources; and drafted preliminary recommendations. The panel, representing 12 countries with resource levels spanning the spectrum, followed a process similar to that followed in the first BHGI summit (2), based on methods initiated by the World Health Organization (WHO) (3), to address cancer care in countries with low- or medium-level resources.

One of the panel’s aims was to take the 2003 guidelines to the next level by making specific recommendations about resource stratification for diagnosis and pathology. The stratification scheme specifies four levels: basic, limited, enhanced, and maximal. These levels refer to the method or the set of methods (e.g., surgical biopsy, imaging) used in a health unit (e.g., a community, city, or region) and not necessarily to a country overall; the different levels were conceptualized as coexisting within the same country.

In this stratification scheme, basic-level methods are those that are absolutely required to have a breast program. Limited-level methods provide a large improvement in outcome relative to the basic level. Enhanced-level methods provide a small improvement in outcome relative to the limited level. And maximal-level methods are those recommended by existing guidelines that assume unlimited resources. These levels were conceptualized as incremental. Therefore, every successive level assumes that the health care unit already has all the methods needed for the lower level(s) and now has sufficient resources to add more methods. In this way, the scheme provides a logical, systematic framework for building diagnostic and pathology capacity.

The methods used are described in greater detail in the accompanying overview (4). The final work product of the Diagnosis and Pathology Panel is the substance of this report.

FINDINGS AND RECOMMENDATIONS

Issues Related to Diagnosis and Pathology

Goal of Diagnosis The primary goal of diagnosis in countries with limited resources, just as in countries with abundant resources, is to accurately distinguish benign from malignant breast lesions and invasive from non-invasive breast lesions, thereby permitting delivery of timely and appropriate care. The panel reaffirmed three main themes of the first summit: 1) that improving breast cancer awareness and education facilitates diagnosis of the disease at an early stage; 2) that early diagnosis is advantageous because it is lifesaving and cost effective, and requires less aggressive therapy; and 3) that collecting accurate national statistics about breast cancer (type, tumor size, stage, treatment, and outcome), available resources (personnel, equipment, and facilities), and competing priorities (health or other issues) will help to tailor these guidelines for breast cancer diagnosis and pathology to the needs of an individual country.

Definitions The panel also reaffirmed the key distinction between a clinical diagnosis and a pathology diagnosis. Clinical diagnosis refers to a diagnosis based on a combination of the history, findings on a clinical breast examination (CBE), and results of breast imaging studies (mammography and ultrasound). These findings may suggest a benign or malignant diagnosis.

Pathology diagnosis, also called tissue diagnosis, refers to a diagnosis based on the microscopic features of cells or tissues, which allow a lesion to be properly categorized pathologically. The interpretation of these microscopic findings is the definitive diagnosis (i.e., the final word).

Simplicity of the Process Simplicity in the diagnostic process is critical in limited-resource settings because patients may face numerous barriers that prevent repeated visits. To address such barriers and increase compliance, diagnostic tests and tissue sampling techniques should be used in a combination that allows establishing the pathology diagnosis and assessing the extent of the disease in one visit.

Quality of the Process Panelists emphasized that it is important not only that a diagnostic test is available but also that it is done competently so that a correct diagnosis is made and the treatment providers can be confident about the results. Specific recommendations on quality assurance and standardization of practices are provided in a later section.

Correlation of Findings Regardless of the type of tissue sampling that is performed for diagnosis, the pathology results must be correlated with all other information, including clinical findings and the findings of imaging
studies (if available), to assess for concordance. The panel reaffirmed that this so-called triple test is key for ensuring accurate diagnosis. If the clinical findings, imaging findings, or both are highly suggestive of breast cancer, but the biopsy yields benign findings, the biopsy result is considered discordant; it may be necessary to repeat the biopsy to ensure an accurate diagnosis.

**Importance of the System** Implementation of a breast pathology program requires more than the resources needed to perform and interpret the biopsy. This program must be integrated in a comprehensive system that addresses other facets of care. For example, there must be mechanisms in place for specimen labeling and transportation, documentation of pathology results in the patient’s medical record, and communication of the results to other health care providers and the patient. Follow-up is also essential after biopsy and enables evaluation of diagnostic performance; this practice is discussed in greater detail in the section on record keeping.

**Diagnostic Process**

The diagnostic process entails both initial diagnosis (to establish the presence or absence of breast cancer) and, when cancer is present, staging (to determine the extent of disease) (5); the latter may include an examination to ascertain whether a patient has metastases. Knowledge of the stage of the disease is important for estimating prognosis and making choices between curative and palliative therapy. The panel again noted the importance of using the triple test for accurate initial diagnosis and agreed on the need for a judicious approach for the use of tests after diagnosis for staging.

**Clinical Assessment** The methods used in clinical assessment for breast cancer include a history, CBE, physical examination, and when appropriate, assessment for metastatic disease.

**History** Taking a medical history is the initial step in evaluating a breast complaint. Providers should obtain baseline information regarding symptoms, menopausal status, and breast cancer risk factors, and should document the findings in the patient’s record. In addition to obtaining the history relevant to breast health, the panel endorsed obtaining an overall medical history to appropriately document the presence or absence of other illnesses that might affect treatment decisions.

**Clinical Breast Examination** CBE is a procedure whereby a health care provider examines a woman’s breasts, chest wall, and axillae; it can be used as either a screening test or a diagnostic test (6). When used as a diagnostic test (i.e., in a patient with signs or symptoms of a breast problem), CBE plays a fundamental role in providing information about breast changes that may signal the presence of cancer. A breast mass, nipple discharge, or other changes in the skin, nipple, or both are frequent initial symptoms of breast cancer that require prompt attention (6,7). The panel agreed that CBE is important for confirming the presence of a dominant mass and other breast abnormalities, for documenting tumor size, and for determining the local extent of disease.

**Physical Examination** In patients with findings suggestive of early breast cancer, physical examination is unlikely to provide diagnostic information beyond that provided by history and CBE, although it may reveal evidence of other illnesses that may have potential implications for treatment decisions, such as malnutrition or AIDS. In patients with findings suggestive of advanced breast cancer, physical examination may provide information about the presence of metastases in the lymph nodes and distant sites, as discussed below.

**Assessment of Metastatic Disease** Assessment of metastatic disease in patients with primary breast cancer is a component of cancer staging. Patients with metastatic breast cancer uniformly succumb to their disease; however, survival may range from a few months to several years (8). In countries with limited resources, patients often present with disease that has already metastasized, and proper staging is valuable in planning cancer treatment.

Obtaining a medical history is the first step in the assessment of metastatic disease. Pulmonary, musculoskeletal, and abdominal symptoms may raise clinical suspicion for metastatic disease and prompt a diagnostic examination. Physical examination may reveal lymphadenopathy, hepatomegaly, or bone tenderness that likewise suggests metastatic disease.

Laboratory measurement of the serum alkaline phosphatase level as a method of screening for bone and liver metastases has been suggested. However, elevated alkaline phosphatase levels have high false-positive and false-negative rates. Thus, this test is not a good predictor of bone or liver metastases in patients with breast cancer (9) and cannot be recommended.

A number of studies have evaluated the role of bone scanning, chest radiography, and liver ultrasonography in breast cancer staging at the time of diagnosis. Overall the yield for these imaging studies is low and stage dependent. The prevalence of metastases detected by imaging techniques is near zero in patients with stage I or II breast cancer (0.5%), but dramatically increases in patients with...
stage III disease (8–40%) (10). In a study of patients with stage III disease, the findings of bone scan, chest radiograph, and liver ultrasound were positive for metastases in 14%, 7%, and 6% of cases, respectively (11). An additional important consideration is the occurrence of false-positive results in tests with a low yield. Such results cause additional testing at a significantly increased cost and unnecessarily subject patients to anxiety, discomfort, and less frequently, morbidity.

Therefore, the panel recommends a judicious approach to laboratory and imaging studies to assess metastatic disease, regardless of the level of resources available. Extensive, routine laboratory and imaging studies are not justifiable in patients with early breast cancer in the absence of symptoms or physical findings. In contrast, in patients with T4 or N1–2 breast cancer, bone scanning, chest radiography, and liver ultrasonography have a higher yield and are indicated when resources permit. The panel recommends their introduction at the limited-resource level (chest radiograph and liver ultrasound) and enhanced-resource level (bone scan).

**Breast Imaging** The breast imaging modalities used in diagnosing breast lesions include diagnostic mammography and diagnostic ultrasound.

**Diagnostic Mammography** Diagnostic mammography is complementary to physical examination in evaluating women with signs and symptoms of breast cancer, and provides a more accurate assessment of the extent of disease in women known to have cancer (12). It also provides additional information about the contralateral breast because a small but significant percentage (3–5%) of women with breast cancer will have synchronous or metachronous cancer in the other breast (13).

Diagnostic mammography requires trained personnel, equipment, facilities, reporting, and follow-up systems, and establishing and maintaining a high-quality diagnostic mammography program is relatively costly (14). Moreover, this imaging cannot replace the need for a pathology diagnosis in women with signs or symptoms of breast cancer. The panel identified the following factors influencing the decision to introduce diagnostic mammography: 1) the availability of the equipment and skilled personnel, 2) the cost of film for mammography, 3) the predominant size of lesions at presentation (e.g., palpable versus non-palpable disease), 4) the patient population being assessed (e.g., younger women, who have dense breasts and who may be more likely to have cysts, versus older women), and 5) alternatives for establishing the diagnosis (e.g., aspiration to establish that a mass is a cyst). In addition, in countries with limited resources, few women are able to undergo breast-conserving therapy because of the typically advanced stage of cancer at presentation and because this therapy is resource intensive (15). In this context, the benefit of determining the extent of cancer within the breast seems low when compared with the cost of a diagnostic mammography program.

The panel concluded that the introduction of diagnostic mammography can be recommended at the limited level of resources. If mastectomy is the only available surgical treatment for breast cancer, diagnostic mammography is not essential; however, if breast conservation is offered, diagnostic mammography is necessary to determine if there is cancer elsewhere in the same quadrant (multifocal disease) or in different quadrants (multicentric disease).

Approaches to treating breast cancer hinge on the stage at the time of diagnosis because treatment for locally advanced breast cancer differs from that for early stage breast cancer (15). Mammography can help distinguish early stage from late-stage cancer, although this benefit varies depending on the patient and the cancer.

**Diagnostic Ultrasound** Breast ultrasound can be used as a screening test (when performed in asymptomatic women, with the goal of identifying otherwise occult breast cancer) or as a diagnostic test (when performed in women with abnormalities on physical examination, mammography, or both). For women who have a palpable breast lump or a focal symptom, ultrasound can play an important role in further evaluation of the clinical findings. In this group of women, ultrasound has three important contributions: distinguishing simple cysts from solid masses (16), providing an estimation of the likelihood of malignancy in a solid mass (17), and guiding tissue sampling for a pathology diagnosis (18,19).

Ultrasound, like mammography, can help determine the extent of cancer within the breast, which again is important when breast-conserving therapy can be offered to women. Ultrasound is more widely available than mammography in countries with limited resources and is particularly useful in women with palpable lesions, as noted above. In addition, this modality can also help assess the status of the axilla, can guide a minimally invasive (needle) biopsy in the axilla, and can allow examination of the liver to detect metastatic disease. The panel therefore recommends introduction of diagnostic ultrasound at the limited-resource level.

**Pathology Diagnosis** The diagnosis of breast cancer carries prognostic and therapeutic implications that are life changing for a woman. The panel strongly and uniformly recommends that all women suspected of having breast cancer have an accurate pathology diagnosis that confirms
the presence of the disease before beginning definitive treatment. This includes women who have clinical findings strongly suggestive of cancer. A pathology diagnosis should not be bypassed, even when health care resources are very limited, because a misdiagnosis of breast cancer can lead to erroneous treatment of women without breast cancer, which is harmful to the woman and wasteful of treatment resources.

The most basic function of pathology in breast care is the formulation of timely and accurate diagnosis. It can be achieved by the use of appropriate biopsy (tissue sampling) techniques, optimal tissue processing, and competent interpretation of gross and microscopic pathology findings. A successful pathology service requires timely and accurate comprehensive reporting, as well as archiving of slides, tissue blocks, and reports with accurate patient and specimen identification.

A variety of methods are available for sampling a breast lesion to determine if it is cancer, and they have comparable accuracy if properly performed. Two general groups of methods are reliable for obtaining a pathology diagnosis: minimally invasive biopsy, also called percutaneous or needle biopsy (i.e., fine-needle aspiration biopsy [FNAB] and core needle biopsy), and surgical biopsy (i.e., incisional biopsy and excisional biopsy).

The panel reaffirmed that the choice among these methods in the limited-resource setting will be influenced by factors such as availability of the necessary equipment and expertise (1). Regardless of the method used, procedures should be performed by appropriately trained staff and with sterile technique to minimize the risk of infectious complications. In addition, single-use equipment should be disposed of after use, and multiuse equipment should be properly sterilized between uses.

Minimally Invasive Biopsy Minimally invasive biopsy has advantages over surgical breast biopsy. The former is less invasive, less expensive, does not cause scarring or deformity, and can be performed in a clinic, obviating the need for an operating room (20). For women with early stage breast cancer, minimally invasive biopsy can convert what would otherwise have been two operations (surgical biopsy for diagnosis, followed by definitive surgery for treatment) into one operation (a single definitive surgery after needle biopsy); for women with locally advanced or metastatic breast cancer, it can provide a pathology diagnosis, enabling initiation of treatment (21).

Minimally invasive biopsy techniques differ with respect to two parameters: the needle used (fine needle versus core needle) and the method used to guide needle placement (palpation versus imaging). For most palpable lumps, the needle can be placed under the guidance of palpation; for other lesions, the needle may be placed with image guidance (discussed below).

Fine-needle aspiration biopsy involves removal of cellular specimens with a small (22-or 25-gauge) needle (22). Advantages of FNAB include that it is the least invasive and least expensive breast biopsy method. Disadvantages include the need for personnel trained in obtaining and interpreting breast cytology specimens; small sample size, and difficulty in interpreting atypical and indeterminate lesions, as well as a moderately high frequency of insufficient samples. The frequency of insufficient samples, reported in as many as one-third of palpable (23) and nonpalpable (24) lesions, can be minimized by obtaining multiple (e.g., five or more) specimens and by having a cytologist onsite to review them, when feasible (22).

Fine-needle aspiration biopsy is the most cost-effective approach to biopsy if properly performed (25–27) and if a quality cytopathology service is available. Provisions can be made to refer the pathology interpretation of the FNAB samples to other regional consultants in specialized centers. In countries with limited resources, the panel recommends introduction of FNAB at the basic level, provided the accompanying requirement for a quality cytopathology service is also met.

Core needle biopsy is also commonly used to obtain tissue samples from breast lesions, particularly nonpalpable and image-detected abnormalities (28). In this procedure, tissue specimens are removed with a cutting needle (usually 14-gauge) and automated gun. Obtaining multiple (e.g., three to five) specimens maximizes the chance of definitive diagnosis. However, as for FNAB, the success of this procedure depends on appropriate patient selection, the availability of experienced pathologists, and correlation of the pathology findings with the clinical and imaging information. Core needle biopsy has limitations similar to those of FNAB with respect to small sample size and difficulty in interpreting atypical and indeterminate lesions (29). Given this modality’s higher cost and limited availability in many countries, the panel recommends its introduction at the limited-resource level.

Of note, the value and cost-effectiveness of FNAB versus core needle biopsy has never been formally studied in a limited-resource setting, and panelists therefore cited the need for a well-designed study to compare the utility of the two methods. Such a study would evaluate the feasibility of using minimally invasive procedures to provide tissue diagnosis in limited-resource settings and measure the effectiveness of local health care providers’ training in the performance of these procedures.
Surgical Biopsy  Surgical biopsy is the traditional method for obtaining a pathology diagnosis of breast lesions, and it is considered the gold standard. Surgical biopsy provides tissue for histologic diagnosis and takes advantage of techniques and pathology expertise currently available in most countries. The disadvantages of this method include its invasive nature and substantial cost when performed in an operating room. However, costs are reduced if it is performed in the outpatient setting (30).

In countries with limited resources, a majority of women with breast cancer have large primary tumors at the time they seek medical care (17). A surgical biopsy under local anesthesia is more expensive, time-consuming, and traumatic than minimally invasive biopsy, but provides the greatest amount of histologic information. The panel concluded that this procedure should be introduced at the basic-resource level, provided a country also meets the pathology requirements for that level.

Record Keeping*

All Global Summit panels identified the need for a system of record keeping in countries with limited resources to document the clinical stage of the breast cancer and clinical outcomes, among other information.

Medical Records  Permanent, quality medical records are essential for documenting diagnostic findings, treatments given, and patient outcomes, and for communicating this information to other health care providers. In addition, well-kept medical records are useful for generally assessing the prevailing patterns of breast cancer presentation and care, which can be helpful for planning resource allocation and monitoring changes as additional resources are applied. The panel agreed that medical records should be available at the basic-resource level.

In terms of diagnosis and pathology, the medical record should document the patient’s name and unique medical record number, dates, clinical findings, imaging findings, types of biopsies performed (including needle used, whether guidance was used, and number of samples obtained), pathologic findings reported according to the pathologic TNM (pTNM) system, whether a cytologist was onsite during the procedure (for FNAB), and the patient’s outcome (clinical, imaging, and surgical pathology information, when available). The panel endorsed the use of the clinical TNM (cTNM) staging system (31) and, because tumor size substantially affects prognosis (32) and a given T stage applies to a wide range of sizes, the panel also encourages documentation of tumor size. Quality pathology reports, discussed below, should become part of the medical record.

Follow-Up  In addition to its obvious benefits in terms of continuity of care and support for patients, follow-up is essential for assessing and improving diagnostic performance, as previously noted. The frequency of insufficient samples with a diagnostic method should be documented at the time of the procedure and the outcome data collected during follow-up should be analyzed to assess a given method’s true-negative, false-negative, true-positive, and false-positive rates. This follow-up information should help to optimize biopsy procedures based on outcome data. The panel recommends that some form of follow-up be in place at the basic-resource level, recognizing that the method and frequency of follow-up will vary by setting.

Pathology Report  Elaboration of the pathology or cytology report is the responsibility of the pathologist, but requires close collaboration with surgeons and radiologists. Accurate pathologic diagnosis starts with the clinician, who provides relevant historical and physical examination information. The need for the triple test to minimize errors in diagnosis is particularly important when minimally invasive biopsy (FNAB or core needle biopsy) is used (33).

Prognostic and predictive parameters are useful to guide treatment because there is significant variability in the natural history of breast cancer (34). Predictive factors, in contrast, are clinical, pathologic, and biologic characteristics that are used to estimate the likelihood of response to a particular type of therapy (35). Features such as tumor size, lymph node status, histopathologic type, and tumor grade should be universally documented because of their limited cost and important prognostic significance (36–41). Conceptually, these features are useful in providing patients an estimate of prognosis, which facilitates their education, involvement in their therapy, and respect for their autonomy.

In the limited-resource setting, assessment of the expression of estrogen receptors, progesterone receptors, or both is recommended only if hormonal therapy such as tamoxifen, aromatase inhibitors, or surgical or medical ovarian ablation is possible. The panel recommends introduction of this assessment at the limited level, although some panelists favored introducing it at the basic level instead.

*The recommendations of this panel were integrated with those of the Health Care Systems and Public Policy panel and are presented in the matrix guideline Table 1 from that panel’s consensus statement (49).
Measurement of HER-2/neu is problematic because the cost of immunohistochemical analysis, fluorescence in situ hybridization, and trastuzumab therapy is prohibitively expensive in the limited-resource setting; therefore the panel recommends introducing this test only at the maximal-resource level. Such important pathologic pieces of information as the status of the microscopic margin of resection and the status of the sentinel node are recommended at the limited level and maximal level, respectively, where resources also allow breast conservation and sentinel lymph node biopsy.

**Registries** Whereas medical records provide critical information about breast health and breast care for individual patients, registries provide such information for the populations they cover. Depending on their coverage, registries may be resource intensive. The panel therefore recommends introduction of local, regional, and national registries at the limited, enhanced, and maximal levels, respectively.

**Quality Assurance and Standardization**

Because treatment decisions and estimations of prognosis are based on the results of diagnostic and pathology tests, these tests must be done at a level that ensures that the information they provide is reliable and useful. Therefore the panel recommends consideration of formal quality assurance procedures whereby diagnostic findings are recorded and the accuracy of these findings is monitored over time. Such procedures help identify areas for improvement. Standardization of pathology procedures and reports is important for better characterizing breast lesions and improving communication among health care providers. A pathology service should provide not only diagnostic information, but also prognostic and predictive information, whenever possible.

Diagnostic capacity is critical to the success of a comprehensive breast health care program in countries with limited resources. This central role of diagnosis highlights the importance of training health care providers in pathology and its subspecialties (e.g., cytopathology) (42). The availability of pathologists with expertise in breast pathology differs around the globe. Approaches for improving breast pathology include training pathologists, establishing pathology services in centralized facilities, and organizing international pathology services. Panelists expressed opposing viewpoints about the advisability of training nonpathologist health care providers (such as nurses) to perform preliminary steps in diagnostic procedures, such as obtaining aspirates for FNAB.

**Stratification of Diagnostic and Pathology Methods**

The panel’s consensus guidelines for stratification of diagnostic and pathology methods by level of resources are summarized in Table 1, and the requirements for competent performance of each of these methods are shown in Table 2.

**Table 1. Resource Allocation for Diagnosis and Pathology**

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Clinical</th>
<th>Pathology</th>
<th>Imaging and laboratory tests</th>
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<tbody>
<tr>
<td>Basic</td>
<td>History</td>
<td>Interpretation of biopsies</td>
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<tr>
<td></td>
<td>Physical examination</td>
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<td></td>
<td>Clinical breast examination</td>
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<td></td>
<td>Surgical biopsy</td>
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<tr>
<td></td>
<td>Fine-needle aspiration biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Core needle biopsy</td>
<td>Determination and reporting of ER and PR status</td>
<td>Diagnostic breast ultrasound ± diagnostic mammography</td>
</tr>
<tr>
<td></td>
<td>Image-guided sampling (ultrasonographic ± mammographic)</td>
<td></td>
<td>Plain chest radiography</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Liver ultrasound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Blood chemistry profile/CBC</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Preoperative needle localization under mammographic or ultrasound guidance</td>
<td>Onsite cytopathologist</td>
<td>Diagnostic mammography</td>
</tr>
<tr>
<td>Maximal</td>
<td>Stereotactic biopsy</td>
<td>HER-2/neu status</td>
<td>CT scanning, PET scan, MIBI scan, breast MRI</td>
</tr>
<tr>
<td></td>
<td>Sentinel node biopsy</td>
<td>IHC staining of sentinel nodes for cytokeratin to detect micrometastases</td>
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</table>

CBC, complete blood count; CT, computed tomography; ER, estrogen receptor; IHC, immunohistochemistry; MIBI, 99mTc-sestamibi; MRI, magnetic resonance imaging; PET, positron emission tomography; PR, progesterone receptor.
in a checklist format. The personnel suggested in the latter table refer to those generally used in countries with a maximal-resource level; the panel agreed that creative use of existing personnel, cross-training individuals to perform different tasks, and development of incentives to attract and maintain trained personnel may be useful for meeting personnel requirements in the limited-resource setting.
Although there was generally agreement as to the diagnostic and pathology methods that were feasible in countries with limited resources, there was some debate within and between panels regarding the level at which specific methods should be introduced. The panel noted that the resource level applied in a given health unit will depend on factors such as available personnel, equipment, and facilities; the needs of the population served; and competing health care priorities. Such health system considerations are discussed in an accompanying guideline (43).

**Basic Level** Minimal diagnostic and pathology requirements include the ability to take a history, perform CBE and physical examination, make a pathology diagnosis of breast cancer by interpreting the specimens obtained by surgical biopsy or FNAB, determine clinical and pathologic stage, and record this information in the medical record. The panel emphasized that even at the basic level, the availability of accurate information regarding breast cancer size and stage at presentation, and breast cancer treatment and outcome is invaluable to determine the next steps required to decrease breast cancer mortality.

**Limited Level** At the limited level, characterized by increasing but still constrained resources, the panel recommends that diagnostic breast imaging with ultrasound or mammography be available. Core needle biopsy, as a minimally invasive method for obtaining histological diagnosis, can be performed on palpable masses at low cost, and can provide tissue for immunohistochemical staining to determine hormone receptor status prior to surgical intervention. At the high end of limited resources, the panel also suggests introducing image-guided needle sampling. Panelists agreed that ultrasound guidance for needle biopsy has the advantages of lower cost and multipurpose use of the equipment; in contrast, stereotactic guidance was considered to require a higher (maximal) level of resources. The accompanying guidelines addressing treatment recommend breast-conserving surgery at the limited-resource level (44); if breast conservation is offered, diagnostic breast imaging is essential. Although the panel uniformly agreed about the importance of assessing hormone receptor status, which in the context of limited resources is practical only if hormonal therapy is available, it disagreed as to whether such assessments should be introduced at the basic or limited level. Also at the limited level, the health unit may have the capability for determining and reporting the margin status and better assessment for metastatic disease with plain chest radiography, liver ultrasound, and blood chemistry profile/complete blood count.

**Enhanced Level** At the enhanced level, the level at which breast conservation is available (44), the panel recommends introduction of core needle biopsy with mammographic or ultrasound guidance and preoperative needle localization under mammographic or ultrasound guidance. Improved pathology services may involve the presence of an onsite cytopathologist. Higher-level resources should also allow the use of more sophisticated methods of metastatic examination, such as bone scanning.

**Maximal Level** The panel’s main focus was on developing guidelines for diagnosis and pathology in countries with less than maximal resources. However, maximal resources make available additional diagnostic and related methods that can further improve outcomes in patients with breast cancer, including (but not limited to) stereotactic biopsy, sentinel node biopsy, determination of HER-2/neu status, use of immunohistochemical staining to detect micrometastases, and advanced imaging studies. Panelists agreed that although resource constraints may limit the methods that can be applied in the short term, the maximal level should be the goal for the long term.

**PANELISTS**

Roman Shyyan, MD (panel cochair), Lviv Cancer Center, Lviv, Ukraine; Shahla Masood, MD (panel cochair), University of Florida, Jacksonville, Florida; Justus Apffelstaedt, MD, FCC(S), MBA, University of Stellenbosch, Tygerberg, South Africa; Rajendra Badwe, MD, MBBS, Tata Memorial Hospital, Mumbai, India; Arturo Beltran-Ortega, MD, National Cancer Institute-Mexico, Mexico City, Mexico; Louis Chow, MD, University of Hong Kong Medical Center, Hong Kong; Kathleen Errico, PhD, ARNP, University of Washington, and Seattle University, Seattle, Washington; Laura Liberman, MD, Memorial Sloan-Kettering Cancer Center, New York, New York; Riccardo Masetti, MD, Catholic University of Rome, Rome, Italy; Vahit Özmen, MD, Istanbul University, Istanbul, Turkey; Paola Pisani, PhD, International Agency for Research on Cancer, Lyon, France; Rengaswamy Sankaranarayanan, MBBS, MD, International Agency for Research on Cancer, Lyon, France; Helge Stalsberg, MD, University Hospital of North-Norway, Tromsø, Norway; Hernan Vargas, MD, Harbor-UCLA Medical Center, Torrance, California; László Vass, MD, PhD, University Teaching Hospital F. FLÓR of Pest County, Budapest, Hungary.
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Breast Cancer in Limited-Resource Countries: Treatment and Allocation of Resources

Alexandru Eniu, MD,* Robert W. Carlson, MD,† Zeba Aziz, MD,‡ José Bines, MD,§ Gabriel N. Hortobágyi, MD, ¶ Nuran Senel Bese, MD, # Richard R. Love, MD, † Bhadrasain Vikram, MD, € Arun Kurkure, MD, ‡ and Benjamin O. Anderson, MD,** for the Global Summit Treatment and Allocation of Resources Panel

* Cancer Institute I. Chiricuta, Cluj-Napoca, Romania; † Stanford University, Stanford, California; ‡ Allama Iqbal Medical College, Lahore, Pakistan; ¶ Instituto Nacional de Cáncer, Rio de Janeiro, Brazil; § University of Texas MD Anderson Cancer Center, Houston, Texas; # Tüüncü Mehmet Efendi Cad. Dr. Rıfat Paşa Sok, Istanbul, Turkey; † Ohio State University Comprehensive Cancer Center, Columbus, Ohio; € International Atomic Energy Agency of the United Nations, Vienna, Austria; § Indian Cancer Society, Cooperage, Mumbai, India; and ** University of Washington, Seattle, Washington

Abstract: Treating breast cancer under the constraints of significantly limited health care resources poses unique challenges that are not well addressed by existing guidelines. We present evidence-based guidelines for systematically prioritizing cancer therapies across the entire spectrum of resource levels. After consideration of factors affecting the value of a given breast cancer therapy (contribution to overall survival, disease-free survival, quality of life, and cost), we assigned each therapy to one of four incremental levels—basic, limited, enhanced, or maximal—that together map out a sequential and flexible approach for planning, establishing, and expanding breast cancer treatment services. For stage I disease, basic-level therapies are modified radical mastectomy and endocrine therapy with ovarian ablation or tamoxifen; therapies added at the limited level are breast-conserving therapy, radiation therapy, and standard-efﬁcacy chemotherapy (cyclophosphamide, methotrexate, and 5-ﬂuorouracil [CMF], or doxorubicin and cyclophosphamide [AC], epirubicin and cyclophosphamide [EC], or 5-ﬂuorouracil, doxorubicin, and cyclophosphamide [FAC]); at the enhanced level, taxane chemotherapy and endocrine therapy with aromatase inhibitors or luteinizing hormone–releasing hormone (LH-RH) agonists; and at the maximal level, reconstructive surgery, dose-dense chemotherapy, and growth factors. For stage II disease, the therapy allocation is the same, with the exception that standard-efﬁcacy chemotherapy is a basic-level therapy. For locally advanced breast cancer, basic-level therapies are modiﬁed radical mastectomy, neoadjuvant chemotherapy (CMF, AC, or FAC), and endocrine therapy with ovarian ablation or tamoxifen; the therapy added at the limited level is postmastectomy radiation therapy; at the enhanced level, breast-conserving therapy, breast-conserving whole-breast radiation therapy, taxane chemotherapy, and endocrine therapy with aromatase inhibitors or LH-RH agonists; and at the maximal level, reconstructive surgery and dose-dense chemotherapy and growth factors. For metastatic or recurrent disease, basic-level therapies are total mastectomy for ipsilateral in-breast recurrence, endocrine therapy with ovarian ablation or tamoxifen, and analgesics; therapies added at the limited level are radiation therapy and CMF or anthracycline chemotherapy; at the enhanced level, chemotherapy with taxanes, cetuximab, or trastuzumab, endocrine therapy with aromatase inhibitors, and bisphosphonates; and at the maximal level, chemotherapy with vinorelbine, gemcitabine, or carboplatin, growth factors, and endocrine therapy with fulvestrant. Compared with the treatment of early breast cancer, the treatment of advanced breast cancer is more resource intensive and generally has poorer outcomes, highlighting the potential beneﬁt of earlier detection and diagnosis, both in terms of conserving scarce resources and in terms of reducing morbidity and mortality. Use of the scheme outlined here should help ministers of health, policymakers, administrators, and institutions in limited-resource settings plan, establish, and gradually expand breast cancer treatment services for their populations.

Key Words: breast cancer, chemotherapy, developing countries, endocrine therapy, hormonal therapy, lumpectomy, mastectomy, surgery, treatment

Guidelines for breast cancer treatment have been developed for countries with a high level of health care resources (1–3). In the guidelines presented here, we focus on the central aspects of breast cancer treatment and resource allocation that should form the core of breast cancer treatment programs across the spectrum of settings from basic to maximal levels of medical resources. These guidelines should assist ministers of health, policymakers, administrators, and institutions in
prioritizing resources when the available resources are limited.

**METHODS**

As part of the Breast Health Global Initiative (BHGI), a panel of breast cancer experts and patient advocates met in 2002 to develop evidence-based consensus recommendations for the treatment of breast cancer in countries with limited resources. The multinational panel followed a process recommended by the World Health Organization (WHO) to address international breast cancer care in countries with low-level or medium-level resources (4). After reviewing available evidence and consensus-defined breast care guidelines, the panel debated approaches for breast cancer treatment and specifically considered how this treatment may best be provided under the constraints of significantly limited resources. The results of this consensus have been previously published (5,6).

As a continuation of this effort, a multinational panel of breast cancer experts and patient advocates was convened in Bethesda, Maryland, on January 14, 2005, to update and extend the earlier evidence-based consensus guidelines. Specifically, the panel was charged with developing recommendations for systematically prioritizing medical therapies across the entire spectrum of resource levels.

The cumulative work product of the 2002 and 2005 panels is the substance of this report. A detailed description of the methodology used is given elsewhere in this supplement (7). Because the treatment of breast cancer is a rapidly evolving area of medical care, these guidelines should be viewed as a work in progress and not as recommendations to be applied indefinitely.

**FINDINGS AND RECOMMENDATIONS**

**Treatment-Related Issues**

**Principles of Breast Cancer Treatment** The treatment of localized invasive breast cancer involves an assessment of the clinical and pathologic features of the tumor and of the health status of the patient; the application of therapy aimed at eradicating local disease in the breast, the chest wall, and the regional lymph nodes; the potential application of systemic therapy aimed at eradicating subclinical, micrometastatic disease; and the follow-up of women after treatment for evidence of recurrent disease. Relapsed or metastatic disease is, with few exceptions, incurable; treatment is aimed at controlling symptoms, with the aim of preserving quality of life and prolonging survival.

**Analytic End Points** The assessment of the value of treatment for breast cancer may be based on a number of different endpoints or outcomes, including survival, disease-free survival, quality of life, and cost. The recommendations of the panel are made considering all of these end points and outcomes.

**Early and Accurate Diagnosis** The early and accurate diagnosis of breast cancer is important for optimizing treatment. Compared with the treatment of more advanced breast cancer, the treatment of early breast cancer is less resource-intensive and generally has superior outcomes. Accurate histologic diagnosis is necessary to ensure that women with breast cancer may be given optimal treatment and that healthy women are not erroneously treated. The availability of resources to provide accurate histologic diagnosis and accurate assessment of prognostic and predictive factors, such as the presence or absence of estrogen receptors (ERs) and progesterone receptors (PRs) in a tumor, is crucial for making decisions regarding systemic therapy and for providing cost-effective breast cancer care. The following guidelines offer approaches for the early detection of breast cancer (8) and the diagnosis of breast cancer (9) when health care resources are limited.

**Education** Education of health care professionals, traditional healers, women, governmental agencies, and the public about breast health and about breast cancer detection, diagnosis, and treatment is central to the provision of high-quality breast cancer care (10).

**Access to Breast Cancer Data** The availability of cancer registries is highly desirable. Such registries assist in assessing the effectiveness of breast cancer care in the region of the registry and in identifying areas to which limited resources should be applied to optimize breast cancer care. In the absence of cancer registries, cancer incidence can be approximated using GLOBOCAN data provided by WHO (11). However, these estimated statistics cannot be used for monitoring the outcomes of interventions.

**Cultural, Religious, and Social Factors** Breast cancer, its diagnosis, and its treatment impact the patient, the patient’s family, and society in many ways (12). Consequently, treatment considerations must respect local cultural, religious, and social factors.

**Staging Systems** The use of consistent, reproducible criteria for the staging of breast cancer allows for the comparison of treatments across treatment facilities, the selection of appropriate treatment for the individual patient, and the estimation of overall prognosis. The American Joint Committee on Cancer (AJCC) and the TNM
Committee of the International Union Against Cancer (UICC) have both developed TNM-based tumor staging systems that are similar and compatible (13,14). In this guideline, we use the clinical staging system for breast cancer developed by the AJCC and updated in 2002 (13,15).

**Research** Although progress has been made in the management of breast cancer, in no clinical situation has the treatment of the disease been optimized. In countries with limited resources, large numbers of patients with breast cancer are treated each year. Limited-resource populations differ from resource-rich populations in having disease that is more advanced at diagnosis and fewer available therapeutic options. Therefore, scientifically robust clinical trials need to be performed specifically in limited-resource countries to address questions special to these populations. In addition, the assumption that the results of studies from wealthy countries universally apply in limited-resource settings requires validation in selected key areas. Whenever possible, participation in well-designed clinical trials appropriate for the resource level of the setting and for the special clinical problems of patients with breast cancer and the regional health care system should be encouraged. These research efforts benefit both the patient and society.

**Stage I and II Breast Cancer**

**Local Treatment.** Local treatment of stage I or II disease entails modified radical mastectomy (with postmastectomy radiation therapy in some cases) or breast-conserving therapy.

**Modified Radical Mastectomy** Local treatment of stage I and II breast cancer normally requires treatment of the entire breast and the axillary lymph nodes with surgery, radiation therapy, or a combination of these. Modified radical mastectomy (mastectomy plus a level I and level 2 axillary dissection) is effective local treatment for breast cancer and uses surgical techniques that are widely available (16). This procedure is a rapid treatment and is usually associated with a short posttreatment convalescence and limited long-term complications.

Modified radical mastectomy may be performed alone or in association with reconstruction. A number of breast reconstruction techniques are available that differ greatly in the extent of surgery, complication rates, technical difficulty for the surgical team, and recovery (17). Reconstruction of the breast enhances body image, self-esteem, and psychosocial adjustment for many women, but does not impact the probability of disease recurrence or survival. Unfortunately the cost of breast reconstruction can be prohibitive in countries with limited resources, with costs depending on whether the procedure is performed using implants, myocutaneous flap reconstruction, or a combination of these.

After treatment by mastectomy and adjuvant systemic therapy, there is a substantial risk of local-regional recurrence within the first 1–2 years, particularly in the chest wall, when the ipsilateral axillary lymph nodes are involved by cancer. Postoperative radiation therapy substantially decreases the risk of local-regional recurrence and has also been shown to improve survival among patients with positive lymph nodes (16,18–20).

**Breast-Conserving Therapy** An alternative treatment to mastectomy is breast-conserving therapy, that is, breast-conserving surgery (a lumpectomy or a “quadrantectomy”) followed by radiation therapy (16,21,22). More specifically, breast-conserving therapy entails complete excision of the tumor in the breast, surgical axillary staging, and radiation therapy to the whole breast and potentially to the regional lymph node-bearing areas. Under appropriate conditions, breast-conserving therapy allows preservation of the breast and provides survival equivalent to that of a modified radical mastectomy. The main benefit of breast-conserving surgery for many women is the preservation of body image, which greatly improves their quality of life.

Breast-conserving therapy requires high-quality breast imaging (mammography and, if available, ultrasound) to ensure that complete excision of the tumor is possible and is achieved, and surgical pathology services to ensure tumor-free margins of excision. If it is not feasible to perform detailed margin assessment because pathology services are unavailable, it may still be reasonable to provide local control with surgery and radiation, if it is possible to create wide (greater than 1.0 cm) margins, using the “quadrantectomy” skin-resecting approach.

Other requirements for breast-conserving therapy include surgical services experienced in achieving a good cosmetic result while achieving negative pathologic margins of excision, support systems to allow for the delivery of radiation therapy over a period of weeks, and the availability of radiation therapy facilities. The radiation therapy facilities should have radiation oncologists and support staff (including technologists and medical physicists), megavoltage radiation teletherapy equipment, a simulator, immobilization devices, and a planning computer. In addition, the facilities should be geographically accessible to patients and should allow treatment without long delay.

Studies evaluating the use of wide excision of the tumor alone (i.e., without radiation therapy) have demonstrated higher rates of recurrence in the local-regional area, but
major differences in survival have not been observed (21–25). However, the panel consensus is that patients who can undergo breast-conserving surgery without radiation therapy are the exceptions rather than the rule. In other words, a health care system must be able to provide radiation therapy in order to offer surgery less than modified radical mastectomy for invasive cancer.

Postmastectomy Irradiation of the Chest Wall and Regional Lymph Nodes The chest wall and regional lymph nodes represent a common site of recurrent disease after modified radical mastectomy. Risk factors for local-regional recurrences include involved axillary lymph nodes, large tumor size, positive margins of resection, and involvement of the skin or chest wall (26). In North American breast cancer treatment guidelines, postmastectomy radiation therapy is generally recommended for tumors larger than 5 cm in maximum diameter and those with four or more involved axillary lymph nodes, those with positive surgical margins on resection, and those with involvement of the skin or underlying chest wall (1,27). The use of postmastectomy chest wall radiation therapy decreases the relative risk of local-regional recurrences in all groups of patients, with the largest absolute risk reduction occurring in those with the highest risk for recurrent chest wall disease. Postmastectomy chest wall and regional lymph node irradiation with a proper technique may also improve overall survival in women with axillary lymph node-positive breast cancer (1,18–20,25,27).

There is general agreement that patients with four or more positive axillary nodes should receive radiation therapy after mastectomy, but its role among patients with one to three positive nodes remains controversial (27,28). As for breast-conserving therapy, necessary resources include the availability of radiation therapy facilities (equipment and staff), geographic accessibility, access to treatment without long delay, and support systems to allow delivery of radiation therapy over a period of weeks. Recommended doses and schedules for radiation therapy are outlined in an accompanying article (29).

Systemic Treatment After primary treatment, a large number of women with initial stage I or II breast cancer will ultimately experience a relapse of their disease and die from it. A number of factors are independently prognostic for recurrence, including the number of involved axillary lymph nodes, tumor size, tumor histologic grade, and tumor hormone receptor status (30). These factors may be used to estimate a woman’s individual risk for recurrence of disease and of death from disease when given local treatment alone. These same factors may also be used to predict the relative and absolute reduction in risk of recurrence and of death from breast cancer that is achieved with the use of systemic chemotherapy or endocrine therapy (31–33). The decision-making process regarding the use of systemic therapy thus is strongly influenced by the pathologic characteristics of the tumor, especially tumor size, number of involved axillary lymph nodes, and tumor hormone receptor status. Computer-based models have been developed for estimating the risks of breast cancer relapse and death, and the benefits from adjuvant therapy in North American populations of women (34,35). The applicability of these models to other populations has not been assessed.

The availability of careful pathologic assessment, including the determination of tumor ER and PR content, is central to making decisions about systemic adjuvant therapy (36,37). The best current technology for assessing hormone receptor status is with immunohistochemical reactions performed on histologic sections prepared from paraffin-embedded breast tumor tissues that have been fixed in 10% buffered formalin. Across different populations, approximately 55% of breast tumors will stain positive for both ER and PR, 8% will stain positive for ER only, 8% will stain for PR only, and 29–39% of tumors will not stain positive for either receptor (37).

Endocrine Therapy Many breast cancers are responsive to a wide variety of endocrine therapies. Benefit from such therapies may be predicted by the presence of ER or PR in the breast cancer. The use of adjuvant endocrine therapy in women with hormone receptor-positive breast cancer substantially reduces the risk of disease recurrence and death (32). The benefit from endocrine therapy is considerable enough that in the absence of hormone receptor determination (i.e., unknown receptor status), a breast cancer should be considered receptor positive. The most widely used endocrine therapy is the selective estrogen receptor modulator (SERM) tamoxifen. The SERM toremifene is similarly efficacious (38). Evidence suggests that 5 years of tamoxifen therapy is superior to shorter durations of therapy (32). Ten years of tamoxifen therapy provided no advantage over 5 years of therapy in two studies of women with lymph node-negative breast cancer (39,40).

The benefit of chemotherapy is additive to that achieved with the use of tamoxifen (32). Therefore the use of both cytotoxic chemotherapy and tamoxifen provides benefits greater than those from either therapy alone. Tamoxifen is associated with toxicity, including hot flashes and a low risk of thromboembolic disease, endometrial carcinoma, and cataracts. In postmenopausal
women, tamoxifen appears to maintain bone mineral density. In women with hormone receptor-positive tumors, tamoxifen decreases the risk of second, contralateral breast cancers.

In postmenopausal women, the major source of estrogen is the conversion of adrenally synthesized androgen to estrogens by the aromatase enzyme. This conversion is inhibited by the use of selective aromatase inhibitors. These agents do not adequately suppress estrogen levels in women with functioning ovaries. Selective aromatase inhibitors have been evaluated in postmenopausal women in direct comparison with tamoxifen or in sequence with tamoxifen (41,42). Recent evidence from six randomized phase III trials suggests a benefit from the use of aromatase inhibitors in postmenopausal women either alone or sequentially with tamoxifen (43–47). All trials have shown improvement in disease-free-survival in favor of the incorporation of an aromatase inhibitor in the treatment of hormone receptor-positive breast cancer in postmenopausal women.

These gains achieved with aromatase inhibitors must be balanced with the substantial costs associated with these agents as well as their different toxicity profiles (48). Tamoxifen and the aromatase inhibitors are usually very well tolerated, with few patients stopping treatment due to toxicity. However, tamoxifen causes more uterine bleeding, endometrial cancer, and thromboembolism. Substantial numbers of patients who take aromatase inhibitors experience musculoskeletal symptoms, osteoporosis, and fractures.

The aromatase inhibitors should only be used in postmenopausal women with breast cancers that express ER or PR. Many related questions remain unanswered, including the optimal duration of adjuvant endocrine therapy, the ideal sequence of tamoxifen and aromatase inhibitors, and the long-term toxicity and risks of the aromatase inhibitors (49). The aromatase inhibitors should not be used in the treatment of invasive breast cancer in women with functioning ovaries.

Ovarian ablation (e.g., surgical oophorectomy or radiation ablation) or suppression (e.g., use of gonadotropin-releasing hormone or luteinizing hormone–releasing hormone [LH-RH] analogs) with or without tamoxifen is an effective endocrine therapy in the treatment of breast cancer in premenopausal women (33,50,51). Early studies of ovarian ablation or suppression in premenopausal women unselected for the hormone receptor status of their breast cancer demonstrated disease-free and overall survival equivalent to those achieved with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy (33,52). Recent studies have demonstrated that ovarian ablation plus tamoxifen may be superior to CMF chemotherapy in premenopausal women with hormone receptor-positive breast cancer (51).

**Cytotoxic Chemotherapy** Cytotoxic chemotherapy has an established role in the treatment of invasive breast cancer (31). It is important that this therapy not be unnecessarily delayed, nor should suboptimal doses or schedules of treatment be given (53–55). Policymakers, administrators, providers, and patients must understand that reducing the standard dosage administered or the number of courses given can compromise the benefits of this therapy and that doing so simply to reduce costs is unacceptable.

In women who have undergone local treatment for stage I or II breast cancer, cytotoxic chemotherapy reduces the annual odds of recurrence by approximately 24% (31). This therapy is beneficial to patients regardless of hormone receptor or axillary lymph node status. The magnitude of risk reduction for recurrence or death achieved with combination chemotherapy decreases with increasing age. The efficacy of cytotoxic chemotherapy in women more than 70 years of age remains uncertain. Both physicians offering this treatment and their patients should understand the degree of risk reduction it may provide (31). In general, combination chemotherapy is superior to single-agent chemotherapy. As previously noted, the benefits achieved with cytotoxic chemotherapy are additive to those achieved with tamoxifen (32).

**Node-Negative Breast Cancer** Many patients with node-negative breast cancer experience recurrence of their disease (13). Independent prognostic factors may be used to distinguish women who are more likely to have a recurrence; these factors include age, tumor grade, histology, and hormone receptor status (56). HER-2/neu status and angiolympathic invasion have also been proposed as independent prognostic factors. Thus women with axillary node-negative disease who have a moderate risk of recurrence can experience benefit from chemotherapy. A variety of chemotherapy regimens can be used; four cycles of doxorubicin and cyclophosphamide (AC) or six cycles of CMF are widely used and appropriate regimens in this context. Women who have small, hormone receptor-positive stage I tumors or comorbid conditions and women who are elderly may derive little benefit from the addition of chemotherapy to endocrine therapy.

**Node-Positive Breast Cancer** The benefits of adjuvant chemotherapy in patients with node-positive breast cancer have been well established. A number of cytotoxic chemotherapy regimens are effective for treating such disease.
In unselected women, anthracycline-containing chemotherapy appears overall to be superior in efficacy to CMF chemotherapy (31). Classical (oral cyclophosphamide) CMF has proved to be equivalent to anthracycline-based chemotherapy in several clinical trials, and represents an effective and less expensive adjuvant chemotherapy regimen (57). Although the chemotherapy agents in CMF are less expensive than those in AC, CMF requires more frequent visits and intravenous administrations. Furthermore, patient compliance with the oral cyclophosphamide used in the most effective CMF regimen is not assured.

In the adjuvant setting, the addition of taxanes to anthracycline-based chemotherapy may be superior to anthracycline-based chemotherapy alone (58–60). Interpretation of the results of studies of this combined approach is confounded by the potential interaction between endocrine therapy and taxanes. At present, the routine use of taxanes for the treatment of breast cancer in the adjuvant setting is still controversial in women with hormone receptor-positive breast cancer.

Cytotoxic chemotherapy often requires intravenous administration and may be associated with serious and sometimes life-threatening complications. Such therapy must be delivered by an experienced health care team that is familiar with the management of immediate and delayed toxicities of the chemotherapy regimen. In addition, the use of cytotoxic chemotherapy requires the availability of laboratory facilities to monitor white blood cell, red blood cell, and platelet counts; the ability to monitor cardiac function (echocardiography, electrocardiography); pharmacy services to compound the drugs; antiemetics; infusion facilities to administer intravenous chemotherapy; and the availability of medical services to monitor and manage the toxicities of treatment (laboratory facilities, transfusion services for red blood cells and platelets, growth factors, hydration facilities, microbiology laboratories, broad-spectrum antibiotics, and pulmonary and cardiac support systems).

**Trastuzumab** Four large, multicenter, randomized trials are testing trastuzumab as an addition to the adjuvant treatment of breast cancer patients with overexpression or amplification of HER-2/neu. Since the panel meeting in January 2005, the initial results of three of the trials (61–63) have been presented. The first interim analysis of the fourth trial (BCIRG 006) was completed and will be presented at the European Conference on Clinical Oncology meeting in November 2005. These data were not available for analysis during the panel meeting, and in view of the high costs required for testing and treatment, recommendations concerning the use of trastuzumab will be discussed and included in a future version of this article.

**Locally Advanced Breast Cancer**

Locally advanced breast cancer (LABC) encompasses breast cancer with a wide range of biological behaviors. It includes cancer with the following features:

- T3 tumors: those larger than 5 cm in greatest diameter.
- T4 tumors: those with chest wall involvement, edema, or ulceration of the skin; those with satellite nodules; or inflammatory carcinoma.
- N2 nodal status: metastasis in ipsilateral axillary lymph node(s) fixed to surrounding structures or to each other, or metastasis in clinically apparent ipsilateral internal mammary lymph node(s) without axillary lymph node involvement.
- N3 nodal status: metastasis in ipsilateral internal mammary lymph node(s) with ipsilateral axillary lymph node involvement, or metastasis in ipsilateral infraclavicular or supraclavicular lymph node(s).

Locally advanced breast cancer represents 50–80% of all breast cancer cases in countries with limited resources (64,65). Approximately half of the women die of their disease within 5 years of diagnosis. The treatment of LABC is multidisciplinary, necessitates extensive staging, and requires a combined-modality treatment approach involving surgery, radiation therapy, and systemic therapy. LABC is thus an important health problem that uses substantial resources. Such resources could be used in a more effective way if these cancers were detected at an earlier stage.

The initial management of LABC requires histologic sampling (e.g., core biopsy, incisional biopsy, or skin biopsy) for confirmation of the diagnosis and for determination of hormone receptor status prior to the initiation of neoadjuvant chemotherapy.

**Neoadjuvant Chemotherapy** The standard approach to LABC requires initial treatment with anthracycline-based neoadjuvant (primary) chemotherapy for four to eight cycles (66,67). Anthracycline-based chemotherapy is preferred over CMF chemotherapy based on indirect evidence from studies of women with axillary node-positive breast cancer or metastatic disease. An adequate dose intensity and total dose of anthracycline should be used (54,55) and treatment should be given without long delay. CMF chemotherapy is appropriate in women who cannot receive anthracycline-containing chemotherapy because of underlying heart disease.
Patients who are treated with neoadjuvant chemotherapy need to be monitored carefully for evidence of response. Patients with LABC whose tumors respond to primary chemotherapy fare better than those with breast cancers that do not respond to primary chemotherapy. A pathologic complete response to primary chemotherapy predicts better survival (68). Patients with responding tumors should receive neoadjuvant treatment for up to eight cycles, depending upon the response of the disease and the chemotherapy regimen utilized; the threshold for anthracycline-associated cardiac toxicity should not be exceeded. Patients who do not respond after four cycles of optimally dosed anthracyclines generally receive local treatment.

In the neoadjuvant setting, the addition of a sequential taxane after anthracycline-based chemotherapy has been demonstrated to increase the rate of pathologic complete response compared with anthracycline-based chemotherapy alone (67,69,70). However, this improvement did not translate into a survival benefit in the largest of these trials (71). Therefore the role of the taxanes in primary chemotherapy for inoperable LABC remains to be defined.

Recent evidence suggests that neoadjuvant endocrine therapy may be beneficial in postmenopausal patients with hormone receptor-positive disease. Patients who are not candidates for any chemotherapy can be initially managed with endocrine therapy (an aromatase inhibitor or tamoxifen in postmenopausal women, or tamoxifen in premenopausal women) and then receive local treatment. Although all of the trials suggest a benefit in favor of aromatase inhibitors over tamoxifen, there are no long-term follow-up or survival data available. Therefore the neoadjuvant use of aromatase inhibitors in LABC remains investigational.

**Local Treatment** Optimal control of LABC requires, when feasible, local treatment with both surgery and radiation therapy.

**Surgery** After an initial course of neoadjuvant chemotherapy, the use of surgery is appropriate (1,66). Most patients with LABC will require a modified radical mastectomy, a procedure that remains the standard surgical treatment for operable locally advanced disease. The role of breast-conserving surgery in LABC is unclear and the subject of research. Selected patients may be treated with wide local excision followed by whole-breast and regional lymph node irradiation. Because the majority of patients in developing countries present with locally advanced disease, including positive lymph nodes, treatment with mastectomy without postoperative irradiation of the chest wall and regional lymph nodes would generally be insufficient in this setting.

**Radiation Therapy** The results of randomized trials and data extrapolated from trials involving women with node-positive disease support the use of local-regional radiation therapy in patients with LABC who are treated with mastectomy (18–20,76,77). This therapy should be delivered to the chest wall and to the supraclavicular and axillary nodes. The recommended dose of radiation is 50 Gy in 25 fractions or equivalent (29). The role of internal mammary lymph node irradiation is unclear.

In patients in whom mastectomy is not possible after neoadjuvant chemotherapy, the use of whole-breast and regional lymph node irradiation alone is appropriate. Patients who are treated with radiation therapy without surgery should be given tumoricidal doses to areas of bulk disease (60–66 Gy in 30–33 fractions or equivalent) (29,78).

**Systemic Treatment after Local Treatment** After local treatment, systemic treatment may entail chemotherapy and endocrine therapy.

**Chemotherapy** After local treatment, most patients should be treated with additional chemotherapy. A recently reported study showed a trend toward improved relapse-free and overall survival even in those patients with LABC who had a poor response to anthracycline-based neoadjuvant chemotherapy when given a non-cross-resistant regimen after surgery (79).

**Endocrine Therapy** The panel’s recommendations for adjuvant endocrine therapy of LABC are the same as those for stage I and II breast cancer. After completion of chemotherapy, patients with LABC and hormone receptor-positive tumors should receive adjuvant endocrine therapy. The role of aromatase inhibitors in postmenopausal women with hormone receptor-positive LABC continues to be defined, although their activity should be substantial based on the results achieved with the use of adjuvant or sequential aromatase inhibitors in early stage breast cancer.

**Metastatic (Stage IV) or Recurrent Breast Cancer**

Patients with detectable metastatic or recurrent breast cancer have, with rare exceptions, incurable disease. The treatment of their breast cancer is based on prognostic and predictive factors and how the available therapies are expected to impact both quality of life and overall survival.

**Local-Regional Treatment** For patients with metastasis confined to a single site, local treatment with surgery, radiation therapy, or both is appropriate. In women who have undergone breast-conserving therapy and who experience an ipsilateral in-breast recurrence of their
Systemic Treatment  Despite advances in primary and adjuvant therapy, metastatic breast cancer is essentially incurable with standard treatment, and the median survival of patients with metastatic breast cancer is approximately 2 years (81). Systemic treatment in most patients extends survival, but only modestly. The focus of treatment is therefore mainly palliation and improvement of quality of life. The goal is to reduce disease-related symptoms, with minimum treatment-related toxicity.

If the patient has indolent disease, no impending visceral crises, and hormone receptor-positive disease, a trial of endocrine therapy should be given (1). In patients with an impending visceral crisis or with receptor-negative disease, cytotoxic chemotherapy is preferred, as it is more likely to produce a response. Trials comparing combination chemotherapy with single-agent therapy have shown higher rates of response and longer times to first disease progression with the combination, but with greater overall toxicity and with survival that is not different from that with the use of sequential single-agent therapy. A number of active cytotoxic agents can be used, including anthracyclines, taxanes, capecitabine, vinorelbine, cyclophosphamide, methotrexate, and gemcitabine. The choice of drugs depends on financial considerations, preferences regarding the route and schedule of administration, and toxicity.

Surveillance after Treatment of Stage I, II, or III Breast Cancer

After the treatment of stage I, II, or III breast cancer, women remain at risk for the development of recurrent disease for many years. The post-treatment surveillance of women for a recurrence includes history and physical examinations at increasing time intervals in conjunction with yearly mammography evaluation and, in women taking tamoxifen, pelvic examination. The use of surveillance chest radiographs, ultrasound, computed tomography, and blood chemistries has not been demonstrated to substantially aid the diagnosis of recurrent disease, nor has it been demonstrated to enhance overall survival (82–84).

Allocation of Resources

The WHO has stated that “an initial priority, especially in developing countries, should be the development of national diagnostic and treatment guidelines to establish a minimum standard of care, and promote the rational use of existing resources and greater equity in access to treatment services” (4). Some of the therapies used in the treatment of breast cancer require sophisticated technology that is available only in settings with substantial resources, and the cost of establishing and maintaining medical facilities is high. Thus WHO has recommended that medical facilities should initially be concentrated in relatively few places in a country to optimize the use of resources. Medical facilities can be made more widely available when additional resources are available.

Countries with limited resources constitute a heterogeneous group. Important differences often exist with regard to social, economic, and health system development, not only between countries, but also between different regions of the same country. Furthermore, limited-resource countries often have large social and economic inequalities that give rise to a sharp contrast between the poor majority of the population and the wealthy minority, which enjoys a standard of living and a level of health comparable or nearly so to those in affluent countries.

To develop guidelines for breast cancer treatment, and based on WHO recommendations (4), the panel used the following scheme to stratify breast cancer therapies:

- Basic level: Core resources necessary for any breast health care system to function. Core resources can be applied in a single clinic interaction.
- Limited level: Second-tier resources to provide breast health care that improve outcome in a major way. Limited resources may involve single or multiple clinical interactions.
- Enhanced level: Third-tier resources that make some optional treatments available.
- Maximal level: Resources applied in a modern breast health care practice, typical of a country with high-level resources, that improve outcome in a minor way compared with the enhanced level.

This incremental, step-by-step allocation scheme accounts for the aforementioned disparities in a population and provides a means for better ensuring equity in access to care. It is a pragmatic approach that takes into consideration...
the fact that although the ultimate goal of every health care system is to offer optimal care to all patients, resource constraints may necessitate intermediate steps toward this goal.

According to the incremental nature of this scheme, each successive level assumes that all of the resources for the preceding levels are already available to all patients in the health unit (a community, a city, a region, or a country). For example, in order for the health system to be able to offer enhanced-level treatments, it should first be able to provide to all patients in the health unit with basic- and limited-level treatments. This sequential strategy should prevent substantial inequity in the use of limited resources, and it prioritizes resource utilization for the greatest benefit of the largest number of people possible.

In applying this scheme, the short-term goal is to advance to the next higher level, and the long-term goal is to advance to the maximal level. Of note, a given level refers to the set of therapies at that level. Depending on each country's unique situation, this level can be applied to any health unit; therefore different levels may coexist within a country. For example, a country may have numerous community clinics that provide treatment at the basic level, a few hospitals that provide treatment at the limited level, and one national cancer center that provides treatment at the enhanced or maximal level. How these facilities are linked nationally (e.g., for referral) will be country specific.

In developing these guidelines, the panel first reviewed the evidence on the strengths and weaknesses of each cancer therapy, and devised checklists of the resources required to deliver that therapy safely and effectively. The resulting overviews of each therapy are presented in Tables 1–4. Next, for each of four disease stages—stage I,
stage II, LABC, and metastatic and recurrent breast cancer—the panel stratified therapies by level after extensive consideration and discussion of the previously described analytic endpoints. The resulting recommendations for resource allocation are presented in Tables 5–8.

For further discussion and comments on the integration of recommendations for treatment and the allocation of resources with the conclusions from other panels (Early Detection and Access to Care, Diagnosis and Pathology, and Health Care Systems and Public Policy) see the overview article (7). Selected areas are identified where disagreement exists among the panels regarding stratification levels for resources.

### Table 3. Therapy Overview: Adjuvant Endocrine Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Required resources</th>
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<tbody>
<tr>
<td>Adjuvant endocrine therapy</td>
<td>Adjuvant endocrine therapy in women with ER- or PR-positive or unknown breast cancer substantially reduces the risks of disease recurrence and death</td>
<td>Optimally requires availability of ER and PR determination Benefits are limited in low-risk breast cancer Compliance varies</td>
<td>Pathology&lt;sup&gt;a&lt;/sup&gt; Tumor steroid hormone receptor content Number of involved axillary lymph nodes Tumor size Tumor histologic grade Resources for management of toxicities Pharmacy/drug distribution</td>
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<tr>
<td>Specific adjuvant endocrine therapies</td>
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<td>Tamoxifen</td>
<td>Improves disease-free and overall survival in all age groups and nodal subsets and with or without chemotherapy in ER- or PR-positive or unknown disease Reduces the risk of second, contralateral breast cancers Appears to maintain bone mineral density in postmenopausal women Inexpensive Known long-term toxicity profile</td>
<td>Toxicity: Hot flashes Thromboembolic disease Endometrial carcinoma Cataracts</td>
<td>Same as for adjuvant endocrine therapy (see above); resources for management of toxicities should include gynecology</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>In postmenopausal women with hormone receptor-positive resected breast cancer: Anastrozole is superior to tamoxifen Anastrozole or exemestane sequentially with 2–3 years of tamoxifen is superior to tamoxifen alone Extended therapy with letrozole following 4.5–6 years of tamoxifen is superior to 5 years of tamoxifen alone There is no increase in thromboembolic events or endometrial cancer</td>
<td>Absolute difference between aromatase inhibitors and tamoxifen alone in terms of disease-free survival is small Impact on survival is uncertain Substantially higher cost of aromatase inhibitors compared with tamoxifen alone Toxicity: increased risk of bone fracture, arthralgias</td>
<td>Same as for adjuvant endocrine therapy (see above)</td>
</tr>
<tr>
<td>Ovarian ablation</td>
<td>Effective therapy in the treatment of breast cancer in premenopausal women with ER- or PR-positive or unknown breast cancer Equivalent to CMF chemotherapy Oophorectomy plus tamoxifen may be considered an appropriate adjuvant endocrine therapy Likely to be a cost-effective strategy compared with chemotherapy alone</td>
<td>Long-term adverse effects of estrogen deprivation in young women High cost if LH-RH agonist used</td>
<td>Core surgical resources&lt;sup&gt;b&lt;/sup&gt; Pathology: same as for adjuvant endocrine therapy (see above) Resources for management of toxicities</td>
</tr>
</tbody>
</table>

<sup>a</sup>See the accompanying Diagnosis and Pathology guideline in this supplement (9).
<sup>b</sup>The same as the core surgical resources for breast surgery (see Table 1). CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; ER, estrogen receptor; LH-RH, luteinizing hormone–releasing hormone; PR, progesterone receptor.

### CONCLUSION

The treatment of breast cancer requires an integrated, multidisciplinary approach using multiple resources in a focused, disease-oriented manner. Existing evidence-based guidelines outlining optimal approaches to the treatment of breast cancer have been defined and disseminated, but do consider the multiple deficits in infrastructure and the availability of therapies in limited-resource countries. Marked heterogeneity exists among countries and also between regions of the same country with regard to social, economic, and health system development. Therefore a uniform approach for all limited-resource
countries is neither practical nor realistic. We propose a stepwise, systematic approach for building national or regional breast health treatment systems by stratifying health care resources into four levels—basic, limited, enhanced, and maximal—based on the contribution of incremental resources in improving clinical outcomes.

The therapy overview checklist tables, by listing the required resources for each intervention, can help in the

Table 4. Therapy Overview: Adjuvant Cytotoxic Chemotherapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Required resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic chemotherapy</td>
<td>Established role in the treatment of women with invasive breast cancer Combination chemotherapy is superior to single-agent chemotherapy</td>
<td>Expensive Absolute benefits decrease with increasing age Requires a chemotherapy-experienced health care team</td>
<td>Laboratory facilities to monitor white blood cell, red blood cell, platelet counts, and chemistry Ability to monitor cardiac function Echocardiography Electrocardiography Pharmacy services to compound the drugs Antiemetics Infusion facilities to administer intravenous chemotherapy Medical services to monitor and manage the toxicities of treatment Microbiology and general laboratory facilities Transfusion services for red blood cells and platelets Growth factors Hydration facilities Broad-spectrum antibiotics Pulmonary and cardiac support systems</td>
</tr>
</tbody>
</table>

Specific cytotoxic chemotherapy regimens

<table>
<thead>
<tr>
<th>Classical (oral) CMF</th>
<th>Equivalent to regimens of anthracycline-based chemotherapy An effective and less expensive adjuvant chemotherapy regimen</th>
<th>Prolonged treatment Multiple infusions Variable patient compliance</th>
<th>Same as for cytotoxic chemotherapy (see above)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline-based chemotherapy (e.g., AC, EC, or FAC)</td>
<td>Superior overall to CMF chemotherapy in unselected patients Generally a short course of therapy</td>
<td>Cardiac toxicity Expensive</td>
<td>Same as for cytotoxic chemotherapy (see above)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Taxane chemotherapy sequential to anthracycline-based chemotherapy is superior to anthracycline-based chemotherapy alone</td>
<td>Expensive Additional toxicity when given after or with anthracycline-based chemotherapy Benefit in ER-positive disease is small</td>
<td>Same as for cytotoxic chemotherapy (see above)</td>
</tr>
</tbody>
</table>

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; ER, estrogen receptor; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide.

Table 5. Treatment and Allocation of Resources: Stage I Breast Cancer

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment (adjuvant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Basic</td>
<td>Modified radical mastectomy</td>
<td>Breast-conserving whole-breast irradiation as part of breast-conserving therapy Postmastectomy irradiation of the chest wall and regional nodes for high-risk cases</td>
</tr>
<tr>
<td>Limited</td>
<td>Breast-conserving therapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Enhanced</td>
<td>Sentinel node biopsy</td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Sentinel node biopsy</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Breast-conserving therapy requires mammography and reporting of margin status.

<sup>b</sup>Requires blood chemistry profile and complete blood count (CBC) testing.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; ER, estrogen receptor; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.
organization of breast cancer treatment units. The goal of this practical approach is to make rational use of existing resources and to ensure equity in access to treatment services.

The establishment of a “minimum standard of care” as a foundation on which to build an incremental model for improving breast cancer care is proposed. The incremental allocation of resources based on our recommendations leads to the development of a multidisciplinary breast cancer treatment system that gives priority to the most effective, resource-sensitive treatment interventions. This incremental approach facilitates the establishment of the best breast cancer treatment possible across the broad spectrum of health care resources available in diverse regions on a global scale. Thus health benefits for both women with breast cancer and society in general are optimized.

**PANELISTS**

Alexandru Eniu, MD (panel cochair), Cancer Institute I. Chiricuta, Cluj-Napoca, Romania; Robert W. Carlson, MD (panel cochair), Stanford University, Stanford, California; Zeba Aziz, MD, Allama Iqbal Medical College, Lahore, Pakistan; Rajendra A. Badwe, MD, MBBS, Tata Memorial Hospital, Parel, Mumbai, India; F. Nuran Senel Bese, MD, Tütüncü Mehmet Efendi Cad. Dr. Rifat Paşa Sok, Istanbul, Turkey; José Bines, MD, Instituto Nacional de Câncer, Rio de Janeiro, Brazil; Jamie G. de la Garza-Salazar, MD, Instituto Nacional de Cankerología,

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**Table 6. Treatment and Allocation of Resources: Stage II Breast Cancer**

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment (adjuvant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Basic</td>
<td>Modified radical mastectomy</td>
<td>—b</td>
</tr>
<tr>
<td>Limited</td>
<td>Breast-conserving therapyd</td>
<td>Breast-conserving whole-breast radiation as part of breast-conserv ing therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postmastectomy irradiation of the chest wall and regional nodes for high-risk cases</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Sentinel node biopsy</td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Reconstructive surgery</td>
<td></td>
</tr>
</tbody>
</table>

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

*b Requires blood chemistry profile and complete blood count (CBC) testing.

d Breast-conserving therapy requires mammography and reporting of margin status.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.

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**Table 7. Treatment and Allocation of Resources: Locally Advanced Breast Cancer**

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment (adjuvant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Basic</td>
<td>Modified radical mastectomy</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Postmastectomy irradiation of the chest wall and regional nodes</td>
<td></td>
</tr>
<tr>
<td>Enhanced</td>
<td>Breast-conserving therapyd</td>
<td>Breast-conserving whole-breast irradiation</td>
</tr>
<tr>
<td>Maximal</td>
<td>Reconstructive surgery</td>
<td></td>
</tr>
</tbody>
</table>

*a Requires blood chemistry profile and complete blood count (CBC) testing.

*b Breast-conserving therapy requires mammography and reporting of margin status.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.
Mexico; Gail Geller, ScD, Johns Hopkins University, Baltimore, Maryland; Gabriel N. Hortobágyi, MD, University of Texas MD Anderson Cancer Center, Houston, Texas; Julio Alberto Ibarra, Jr., MD, Orange Coast Memorial Medical Center, Fountain Valley, California; Raimund Jakesz, MD, Vienna Medical University, Vienna, Austria; Arun Kurkure, MD, Indian Cancer Society, Cooperage, Mumbai, India; Richard R. Love, MD, Ohio State University Comprehensive Cancer Center, Columbus, Ohio; Sherif Omar, MD, National Cancer Institute Cairo University, Cairo, Egypt; Tatiana Soldak, MD, CitiHope International and Belarusian Breast Cancer Screening and Early Diagnosis Project, Andes, New York; Bhadrasain Vikram, MD, International Atomic Energy Agency of the United Nations, Vienna, Austria; Cheng Har Yip, MD, University Malaya Medical Center, Kuala Lumpur, Malaysia.

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BREAST HEALTH GLOBAL INITIATIVE

Breast Cancer in Limited-Resource Countries: Health Care Systems and Public Policy

Benjamin O. Anderson, MD,*‡ Cheng-Har Yip, MD,† Scott D. Ramsey, MD, PhD,‡ Rafael Bengoa, MD,§ Susan Braun, MA,¶ Margaret Fitch, RN, PhD,§ Martijn Groot, MSc,† Helene Sancho-Garnier, MD,© and Vivien D. Tsu, PhD, MPH,¢ for the Global Summit Health Care Systems and Public Policy Panel

*University of Washington, Seattle, Washington; †University of Malaya Medical Center, Kuala Lumpur, Malaysia; ‡Fred Hutchinson Cancer Research Center, Seattle, Washington; §World Health Organization, Geneva, Switzerland; ¶Susan G. Komen Breast Cancer Foundation, Dallas, Texas; †Toronto Sunnybrook Regional Cancer Center, and Supportive Care, Cancer Care Ontario, Toronto, Canada; ‡Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands; ©International Union Against Cancer (UICC), Geneva, Switzerland, and Regional Cancer Center, Montpellier, France; and ′Program for Appropriate Technology in Health, Seattle, Washington

Abstract: As the largest cancer killer of women around the globe, breast cancer adversely impacts countries at all levels of economic development. Despite major advances in the early detection, diagnosis, and treatment of breast cancer, health care ministries face multilevel challenges to create and support health care programs that can improve breast cancer outcomes. In addition to the financial and organizational problems inherent in any health care system, breast health programs are hindered by a lack of recognition of cancer as a public health priority, trained health care personnel shortages and migration, public and health care provider educational deficits, and social barriers that impede patient entry into early detection and cancer treatment programs. No perfect health care system exists, even in the wealthiest countries. Based on inevitable economic and practical constraints, all health care systems are compelled to make trade-offs among four factors: access to care, scope of service, quality of care, and cost containment. Given these trade-offs, guidelines can define stratified approaches by which economically realistic incremental improvements can be sequentially implemented within the context of resource constraints to improve breast health care. Disease-specific “vertical” programs warrant “horizontal” integration with existing health care systems in limited-resource countries. The Breast Health Global Initiative (BHGI) Health Care Systems and Public Policy Panel defined a stratified framework outlining recommended breast health care interventions for each of four incremental levels of resources (basic, limited, enhanced, and maximal). Reallocation of existing resources and integration of a breast health care program with existing programs and infrastructure can potentially improve outcomes in a cost-sensitive manner. This adaptable framework can be used as a tool by policymakers for program planning and research design to make best use of available resources to improve breast health care in a given limited-resource setting.

Key Words: breast cancer, cancer control, delivery of health care, evidence-based guidelines, health care rationing, health care reform, health planning, health policy, limited-resource countries, resource allocation

In high-resource countries with well-established health care systems, substantial improvements in reducing breast cancer mortality have been made in recent decades (1,2). Compared with low- and medium-level resource countries whose health care systems typically lack core infrastructure elements (3), countries with well-funded health care systems have higher rates of breast cancer incidence, but also have better overall rates of breast cancer survival (4). Early breast cancer detection and comprehensive cancer treatment appear to play synergistic roles in creating improved outcomes in these countries (5). In contrast, breast cancer case fatality rates are highest in economically disadvantaged countries, where survival is worsened due to the advanced stage of disease at initial presentation combined with inadequate resources to provide standard cancer therapy (6,7). Even in the best of circumstances, it is difficult and costly to treat women with late-stage breast cancer, which is more likely to have a poor outcome regardless of the extent of therapy.

Health care ministries from countries with limited resources face organizational, financial, and cultural
barriers that hinder their ability to create and support breast health care programs. Breast care guidelines from economically privileged regions have limited applicability in limited-resource settings, highlighting a need for modified guidelines that take into account the ubiquitous deficits in infrastructure and resources, substantial implementation costs, and competing health care demands. In October 2002, the Global Summit Consensus Conference was held in Seattle, Washington, to develop recommendations for breast health care in countries with limited resources. Panel member statements noted that within any given health care system, early detection, diagnosis, and treatment are inextricably linked issues (8). Early detection of breast cancer is not helpful if cancer treatment is unavailable. Cancer treatment of curable disease cannot and should not be initiated until a definitive pathologic diagnosis is made (9). Treatment is more expensive and less successful when disease is more advanced at the time of diagnosis (10). Thus systemwide deficits can make breast cancer seem difficult or impossible to treat, despite the proven successes in developed countries with standard therapy protocols combining surgery, radiation therapy, and systemic therapy to reduce cancer recurrence rates by more than half (11).

Early breast cancer detection is a core area of focus, because early cancers have a better prognosis with treatments that are more affordable and less resource intensive to provide. At the 2002 Global Summit, a sequential action plan was proposed, linking early detection to improved outcome: 1) promote the empowerment of women to obtain health care, 2) develop infrastructure for the diagnosis and treatment of breast cancer, 3) begin early detection efforts through breast cancer education and awareness, and 4) when resources permit, expand early detection efforts to include mammographic screening (12). Although this protocol is appealingly logical, its application hinges on the organizational capacity, resource allocation, and institutional “buy-in” of the health care system in which it is applied. For this reason, it was determined that during the second round of guideline development held in 2005, a specific focus on health care systems was needed to better characterize those obstacles so that pathways to improvement can be devised. This report summarizes the work of the Health Care Systems and Public Policy Panel.

**METHODS**

An international group of breast cancer experts and advocates met at a summit in Bethesda, Maryland, January 12–15, 2005, to formulate consensus recommendations for health care systems and public policy as they apply to breast care in countries with limited resources. In the morning, summit participants gave presentations on related topics and current systems and policies, as well as barriers in parts of the world where resources are markedly constrained. In the afternoon, the Health Care Systems and Public Policy Panel, a subgroup of conference participants, reviewed the current evidence, debated systems and policy strategies under the constraints of limited resources, and drafted preliminary recommendations. The panel, representing nine countries with resource levels spanning the spectrum, followed a process similar to that followed in the first Breast Health Global Initiative (BHGI) summit (8), based on methods initiated by the World Health Organization (WHO) (3) to address cancer care in countries with limited resources (i.e., those with low- or medium-level resources).

One of the panel’s aims was to make specific recommendations about resource stratification for health care systems and public policy. The stratification scheme specifies four levels: basic, limited, enhanced, and maximal. These levels refer to the services and facilities to be used in a health unit (e.g., a community, a city, or a region) and not necessarily to a country overall; the different levels were conceptualized as coexisting within a country.

The methods used are described in greater detail in the accompanying overview (13). The final work product of the Health Care Systems and Public Policy Panel is the substance of this report.

**FINDINGS**

**Challenges to Cancer Care**

Countries with limited resources face numerous challenges in designing and implementing programs to improve cancer care. Although financial constraints are one obvious barrier to improving breast cancer outcomes, health care ministries face a variety of other barriers, including a lack of scientific and epidemiologic information to guide resource planning, a shortage of trained professionals to provide necessary clinical care, competing health care crises, political insecurity, wars, or combinations thereof that divert attention from long-term health care issues, and social and cultural factors that obstruct the timely and effective delivery of care (3). In particular, efforts aimed at early cancer detection are impeded by public misconceptions about breast cancer that make women reluctant or unwilling to seek care when they notice early symptoms (14).
Organizational Obstacles to Health Care Delivery  

Health care systems in countries with limited resources are generally overburdened, inadequately funded, and structurally challenged to meet their intended goals. Although 75% of the world’s population lives in low- and middle-income countries, only 6% of the gross national expenditure is spent on health care in such countries (15). Resource-constrained countries suffer from a lack of trained medical personnel, inadequate facilities, insufficient funding for equipment and supplies, and inequity of access to care between rural and urban populations (16,17).

Typically health care allocations are driven by crisis management rather than long- or even midrange strategic planning. Inefficient health care management and disorganized governmental structures contribute to the financial burdens faced in health care (18). In addition, the apportionment of resources is often based on bureaucratic procedures or political goals rather than on coherent public health policy (19). Systematic disorganization in the public health care system makes it difficult or impossible for women to receive appropriate care in a timely fashion, and major components of health care infrastructure and resources necessary to implement improved breast cancer care are often lacking (20). These multiple barriers combine synergistically to prevent effective cancer diagnosis and treatment in general and in breast cancer care specifically.

Lack of Recognition of Cancer as a Major Public Health Issue  

Cancer is often not a stated priority for health care expenditures in countries with limited resources. Because infectious diseases typically dominate the health care agendas of such countries, cancer control efforts generally fall behind other priorities of the national health authorities. Although the majority of cancers are curable if detected and treated in the early stages, about 80% of all patients with cancer in the developing world have advanced-stage disease at initial presentation (16).

Limited-resource countries typically lack population-based data on cancer incidence and mortality, aggravating the degree to which cancer is underappreciated as a significant health care challenge (21). Health care ministries have limited evidence-based guidance on how cancer in their countries can best be addressed. Findings from studies performed in populations from wealthy countries may not have much relevance or applicability in limited-resource settings because of differences in social and cultural factors, lifestyles, and available technology (22), among other factors.

Although cancer may have a low priority on the formal health care agenda, resources are inevitably spent on cancer when patients require care for advanced-stage disease. Such unplanned use of resources may not only be associated with poorer outcomes, but may also be more costly than planned, systematic use (23). As infectious diseases become better controlled and the population ages in low-resource countries, cancer becomes an increasing public health problem (2,24). Because cancer is an inevitable social and health care burden, and because its incidence is increasing, the World Health Organization (WHO) recently passed an important and sweeping cancer prevention and control resolution that creates a mandate for member countries and the WHO director-general to address cancer care, including prevention, early detection, diagnosis, treatment, and palliation of symptoms of cancer, around the globe (25). This call for countries to address cancer control is a novel opportunity for ministers to act to address cancer in general, and breast cancer specifically, as a core national health care issue.

Health Care Personnel Shortages  

Recruitment, training, and retention of health care professionals constitute a very difficult problem in limited-resource countries. Physicians, nurses, and allied health care personnel are few in number and often are most lacking in regions of greatest health care need (26). Funds are insufficient to fully equip hospitals and provide competitive salaries for appropriately trained health personnel. Limited-resource countries are often unable to provide their professionals with an opportunity for career development and adequate remuneration. They lack the infrastructure required for professionals to carry out their work, leading to frustration and disenchantment with the system. Collectively these factors make it difficult to attract new professionals and to retain those who have already been trained.

While manpower shortages span all disciplines in medicine, they are particularly well exemplified in international nursing. WHO reported that in 2004, the nurse:population ratio ranged across countries from fewer than 10 nurses per 100,000 population (Uganda, Liberia) to more than 1000 nurses per 100,000 population (Norway, Finland), a variation of more than 200-fold (27). The average nurse:population ratio in Europe, the region with the highest ratio, is 10 times that of the regions with the lowest ratios—Africa and Southeast Asia—and the nurse:population ratio in North America is 10 times that in South America. Similarly the average nurse:population ratio in high-income countries is almost eight times that of low-income countries (26). The chasm in health care staffing between the “haves” and “have-nots” is vast.
Loss of Health Care Professionals by Migration  
In addition to inherent manpower shortages, there is the problem of health care professionals migrating from rural to urban areas, transitioning from public to private health sectors, and immigrating from poorer to richer countries (28). The loss of trained health care professionals to other countries is often called a “brain drain,” as professionals are actively pulled away by wealthy countries offering better opportunities. This loss can also be termed “brain flight,” in that professionals are sometimes fleeing from a system that cannot offer them a viable career commensurate with their training and potential for professional growth. Thus both low- and high-resource countries play a role in this migration phenomenon (29).

The outward migration of nurses severely affects some low-resource countries (30). Nursing recruits who cross national borders are often relatively young, well skilled, and expensive to train. Factors pulling nurses to destination countries include better pay, career, and educational opportunities. Factors pushing nurses to leave source countries include low pay, poor career prospects, and in some countries, political instability and violence. Inadequate collection of workforce data makes it difficult to quantify nurse migration to other countries in comparison to unemployment or underemployment of nurses within a country (29).

The practice of active recruitment of health care workers by countries with higher levels of resources has generated controversy in recent years because of its potential to exacerbate migration out of some limited-resource countries (31). In the case of nursing, a driving force for increased international recruitment has been the nursing shortages in developed countries. Shared language, common educational curriculum, and postcolonial ties between countries tend to be the factors determining which low-resource countries are being targeted as sources of nurses (26,29).

Social and Cultural Barriers to Cancer Care  
A variety of noneconomic barriers impede the early detection and effective management of cancer in limited-resource settings. These include a host of cultural and ethnic beliefs and taboos, which can vary between different countries, religions, and cultures (32). Failure to recognize these internal obstacles can doom the success of any cancer care program, even when adequate resources are provided (14). If patients lack trust in their health care system, believe that cancer cannot be cured, or face discrimination or loss within their community by virtue of having a cancer diagnosis, they will predictably fail to use cancer services, no matter how accessible and affordable they may be. Patients will commonly turn to alternative health care strategies and traditional healers, believing them to have equal or superior ability to address difficult health problems (33). It should be noted that these issues are not limited to low-resource countries. For example, in developed countries, minority ethnic, inner-city women are significantly less likely to participate in free screening mammography programs than are women from the suburbs (34).

A recently reported trial in the Philippines studying the value of clinical breast examination (CBE) for early breast cancer detection illustrates the critical nature of social obstacles to early detection of cancer (35). The Philippines CBE trial was prematurely closed because a full 65% of the trial participants, while willing to undergo initial CBE in the absence of logistical and financial barriers, and despite coming from a relatively educated population, refused to undergo necessary follow-up diagnostic studies to determine if their palpable lumps represented cancer. The authors pointed out that women attend breast cancer screening in anticipation of having a negative finding (36) and that screening is not a stressful procedure for those with negative mammography (37), but receipt of an abnormal result is associated with considerable psychiatric morbidity (38), potentially leading to a low level of compliance with follow-up. Unfortunately the trial was not designed to determine as a primary end point which reasons led patients to avoid subsequent diagnostic studies after a positive CBE. The authors concluded that culturally related health beliefs can constitute a major obstacle to early diagnosis, and that awareness and access need to be addressed first, both in terms of designing studies and in terms of implementing new programs related to cancer detection, diagnosis, and treatment.

A tragic consequence of advanced-stage cancer presentation is that treatment fails to cure the disease in the great majority of cases, thereby propagating common social myths such as the belief that cancer is invariably fatal, regardless of its extent at diagnosis or treatment (32). If women commonly avoid seeking care until their disease is undeniably extensive, they create a self-fulfilling prophecy by virtue of the fact that the disease is truly incurable at that point (39). Moreover, advanced breast cancer requires more aggressive treatment, including mastectomy, cytotoxic chemotherapy, and radiation therapy, further adding to the fears and barriers that keep women from seeking care. In the worst-case scenario, the public comes to believe that the treatment, rather than the cancer, causes death. These beliefs, which are difficult to shake once established in the social network, can undermine if not shut down any efforts toward early detection programs. Because the social stigmata of cancer can be so powerful, they must
be fully understood before any improved strategy is implemented within a limited-resource country (14).

Resource Allocation in Cancer Program Development

Trade-Offs in Health Care System Organization There is no perfect health care system because a system must strike a compromise in meeting the many diverse health needs of the population it serves. Specifically, a health care system must achieve a balance among four primary health care system trade-offs (40–43): equity in access, scope of services, quality of care, and cost containment (Fig. 1). Inevitably, certain of these needs will be better met than others. Given the diversity of health care systems worldwide and the fact that there is no perfect system, it is inappropriate to rank different health care systems in a single-variable, linear fashion. However, systems can be ranked in terms of multiple care-related metrics, such as equity of access and quality of life, a practice that can be useful because it provides benchmarks for improvement (44,45).

Setting priorities for health care in general, and breast cancer care specifically, is particularly difficult in limited-resource environments in light of the many aforementioned issues. By creating evidence-based guidelines that stratify health care interventions into specific levels and through programmatic proposals based on cost-neutral implementation strategies (discussed in a later section), health care ministries can be offered realistic options for planning the delivery of breast health services within their public health system.

Approaches to Implementing Disease-Specific Programs There are two general approaches for implementing new disease-specific programs, such as a program to address breast cancer: the vertical approach, whereby the program runs parallel to, but is separate from other disease-based programs, and the horizontal approach, whereby the new program is integrated with the existing system and programs (46). The vertical approach can be beneficial in that specialized care can be implemented because of the disease-specific focus, but it can also be problematic when different diseases end up competing for the same resources. In a purely vertical approach, addressing one disease may compromise the ability to address others when resources are scarce. In contrast, by integrating a new program within a common coordinated structure using existing resources and infrastructure, the horizontal approach allows resource utilization to be optimized at the same time that comprehensive health care needs are met (47). For example, many countries already have infrastructure in place for other services, such as community nurses who visit villages to provide maternal and child care, and a breast health care program may be able to piggyback on this infrastructure (Fig. 2). The combination of the delivery of one intervention with existing successful delivery mechanisms is receiving heightened attention in the international health policy community, although some suggest combined delivery approaches could have a detrimental effect on equity of care unless health care coverage is nearly universal (46).

Macropolicy versus Micropolicy National health care planning directly affects health care delivery at a local level. For example, national health care financing strategies can positively or negatively affect access to health services or health outcomes in communities in limited-resource countries (48). In resource-poor settings, illness imposes high and regressive cost burdens on patients and their families (49). The limited evidence available suggests that, in general, user fees deter health care system use. Conditional cash payments for patient compliance may improve the use of needed interventions, but can create perverse incentives (48). Universal health care provides optimal patient access in that all persons have access to the system. The idea that universal health care is necessarily more costly is not substantiated by experiences in the United Kingdom and Canada (50). However, cost containment in these systems may come in exchange for a limited scope of services provided, slow response to and integration of new technology and pharmaceutical agents, or such prolonged wait times for service that health outcomes are negatively affected (51,52). In some circumstances, certain high-risk populations, such as the poor, may need to be targeted for specific health programs in lieu of a “total population” approach in order to circumvent the otherwise inequitable distribution of health care resources in favor of the economically advantaged (53). Any intervention strategy designed to improve outcome for a given disease must be considered within the context of the health care system in
which it is being applied to ensure that the strategy is in alignment with financial support and incentives (48).

Effective program implementation also requires that national and international health care policymakers recognize the roles of both macropolicy and micropolicy in health care administration. The health care delivery strategy can affect quality, coverage, cost, sustainability, and equity (46). If well designed and implemented, changes in national-level policy can facilitate improvements at the regional or local level. For example, a health care ministry could define educational programs that allow midwives or nurses in the rural areas, as part of their job, to conduct CBE and teach women breast health awareness. For this reason, senior health care administrators must have a detailed understanding of disease management to understand the broader implications of their policy decisions, or at least need to be well advised as to evidence-based approaches for improved outcome in targeted diseases (54). Health care policymakers need to work closely with informed health care experts to design successful health care strategies, especially in areas of preventive care (55). As such, tailored disease-specific guidelines become a core resource for effective health care policymaking.

Economic Modeling in Breast Cancer Care

Financial Impact of Breast Cancer Care In addition to its human burden in terms of morbidity and mortality, cancer poses a fiscal burden on a nation’s health care budget. To use values from a developed country as an example, the U.S. National Institutes of Health estimated the overall costs for cancer to be US$189.8 billion in 2004 in the United States, with breast cancer accounting for 15–20% of all cancer costs (56,57). The economic burden of breast cancer in low-resource countries is largely unknown.

Because health care budgets are always pressured by needs that exceed available resources, interventions designed to improve breast cancer care and outcomes must be not only clinically effective, but also cost effective, to be included in formal clinical practice guidelines. Cost-effectiveness analyses can provide useful information for planning and developing breast cancer control policy. For example, they can be used to inform budget development, to justify the allocation of scarce resources to national breast cancer control programs, and to identify the most efficient ways of delivering screening, diagnostic, and treatment services.
**Cost-Effectiveness Analysis in Breast Cancer** Many cost and cost-effectiveness analyses have been performed for breast cancer in recent years. A MEDLINE search using the Medical subheading terms “breast neoplasms” and “costs and cost analysis” with a further restriction of “cost” as a title word identified 317 citations. Most of these studies included some sort of simulation modeling approach in which information from different sources is combined to create a simplified version of reality.

Nearly all cost-effectiveness studies have been performed using treatment algorithms and clinical and economic data from developed countries (57). Most of these studies evaluate early diagnosis by screening or evaluate treatment options for specific stages of disease (58). Unfortunately, findings of cost-effectiveness studies for developed countries cannot be directly translated to allocate resources or make policy decisions in countries with limited resources. The differences in health care systems, epidemiology of disease, availability of trained personnel and equipment, resource costs, and cultural factors are too great to permit such extrapolation. Furthermore, in many cases the interventions described in these models require a level of breast cancer care that is not available in a limited-resource country. Finally, severe resource constraints in such countries force much more restrictive policies toward the use of new technologies. In these settings, new technologies will not be adopted unless much higher thresholds of economic value are achieved.

Although the circumstances across countries differ greatly, simulation modeling can assist in determining how clinically effective therapies can be applied in cost-effective ways to improve outcomes in limited-resource countries. Recognizing the value of economic modeling, WHO has created a methodology called generalized cost-effectiveness analysis (GCEA) that uses a standardized framework and modeling software (59). This approach differs from the traditional cost-effectiveness analysis, as GCEA requires the analyst to consider what would happen, starting from today, if all resources in the health sector could be reallocated. This situation is called the “counterfactual” against which all interventions should be evaluated. The cost-effectiveness of all possible interventions for a specific disease, individually and in combination, is assessed in relation to this counterfactual (59).

These simulation modeling analyses are designed to provide a broad assessment of the cost-effectiveness of a wide range of interventions. The methodology is standardized and thus allows comparisons to be made with recent cost-effectiveness analyses for other health care interventions that follow the same analytic approach (60–63). In terms of breast cancer, a statistical model evaluating the outcomes and costs of different interventions at different stages of disease would be very informative. It would be rational to hypothesize that breast cancer treatment is more cost effective when used to treat early stage rather than late-stage disease, because treatment for the former is simpler and less expensive, and has a better outcome (23). Such a mathematical model could assist health care leaders in identifying cost-effective strategies to reduce breast cancer-related fatality rates given their country’s specific characteristics and health budget constraints. This information can be used in government discussions about health care reform and budget allocation.

**RECOMMENDATIONS**

The 2005 Global Summit panels developed a stratification scheme that maps out a sequential, systematic approach to building capacity for breast health care in the limited-resource setting. This stratification scheme defines an approach for top-down policy reform, according to which services and facilities are assigned to four resource levels:

- **Basic**—Applies to facilities, services, or activities that are absolutely required to have a breast cancer program (i.e., without these, a health unit is not ready to have a program).
- **Limited**—Applies to facilities, services, or activities that provide a large improvement in outcome relative to the basic level, particularly as related to cancer survival.
- **Enhanced**—Applies to facilities, services, or activities that provide a small improvement in outcome relative to the limited level, but may improve important options for patients undergoing cancer diagnosis or treatment.
- **Maximal**—Applies to facilities, services, and activities that may be used in some high-resource countries and may be recommended by guidelines that assume the availability of unlimited resources, but that should be considered a lower priority than those resources in the basic, limited, or enhanced levels.

These levels refer to the interventions (e.g., pathology services, imaging or treatment facilities, cancer registry) applied in a given health unit (an institution, city, region, or country), and not necessarily to a country overall; different levels can and likely will coexist within the same country. In addition, these levels are incremental; for example, the limited level assumes that a health unit has all the interventions needed for the basic level and now has resources to add more. In this way, the scheme provides
a logical, systematic framework for building capacity. The short-term goal is for a health unit to advance to the next level once it has all of the interventions of a given level (i.e., to raise the bar).

The Health Care Systems and Public Policy stratification scheme (Table 1) is based on the recommendations of the other three Global Summit consensus panels (64–66). These stratified guidelines are intended to be used as a flexible framework that can be adapted to individual settings to improve breast health care.

Although a health care ministry may consider their long-term goal to be reaching the maximal level of health care resources, it is critical to recognize that some of the resources at this level are extremely costly and demanding of infrastructure for ongoing support. Maximal-level resources should not be given a higher priority than basic-, limited-, or enhanced-level resources. It is a mistake to purchase expensive tools for purposes of prestige, for example, investing in positron emission tomography (PET) imaging when other fundamental tools are unavailable. The more fundamental resources are needed to make the more expensive tools useful; when obtained out of sequence, the maximal-level resources typically end up being underused or unused.

### Table 1. Resource Allocation for Health Care Systems and Public Policy

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Services</th>
<th>Facilities</th>
<th>Record keeping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>Primary care services</td>
<td>Health facility</td>
<td>Individual medical records and service-based patient registration</td>
</tr>
<tr>
<td></td>
<td>Surgical services</td>
<td>Operating facility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pathology services</td>
<td>Pathology laboratory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oncology services</td>
<td>Pharmacy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nursing services</td>
<td>Outpatient care facility</td>
<td></td>
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<tr>
<td></td>
<td>Palliative services</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Imaging services</td>
<td>Imaging facility</td>
<td>Facility-based medical records and centralized patient registration</td>
</tr>
<tr>
<td></td>
<td>Radiation oncology services</td>
<td>Radiation therapy</td>
<td>Local cancer registry</td>
</tr>
<tr>
<td></td>
<td>Peer support services</td>
<td>Clinical information systems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early detection programs</td>
<td>Health system network</td>
<td></td>
</tr>
<tr>
<td>Enhanced</td>
<td>Opportunistic screening programs</td>
<td>Centralized referral cancer center(s)</td>
<td>Facility-based follow-up systems</td>
</tr>
<tr>
<td></td>
<td>Cancer follow-up</td>
<td>Population-based cancer registry</td>
<td>Regional cancer registry</td>
</tr>
<tr>
<td></td>
<td>Rehabilitation services</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Population-based screening program</td>
<td>Satellite (noncentralized or regional cancer centers)</td>
<td>National cancer registry</td>
</tr>
<tr>
<td></td>
<td>Individual psychosocial care</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Roles of Various Sectors in Improving a Health Care System

Improving a health care system so that it can deliver better breast health care can best be accomplished if multiple sectors act in collaboration (67); that is, improvements are most likely to be achieved when health care ministries and governmental agencies, nongovernmental organizations (NGOs), and public and patient groups work together (24,68,69). The relative contribution of each sector will depend on the country’s governmental structure, the extent of focus on health care and breast cancer, available resources, the strength of the NGO sector, and the ability of patients, survivors, and advocates to “raise their voices.” Women’s health advocacy and consumerism have had a direct impact on oncology care in the United States, having the greatest effect when the activities of advocates and health care professionals are coordinated and aligned to guide policymakers toward effective and desirable change (68).

**Health Care Ministries and Governmental Agencies** In developed countries, government is often an initiator in health care system improvement, both through health ministries and through budget allocations. Mediating reform through government channels is essential because no other organization has the purview to address the often sweeping changes that are needed (24). Typically governmental roles include:

- Enacting legislation for cancer research and control programs.
- Establishing budgetary priorities.
- Training and compensating research and health care personnel.
- Providing and paying for research, health care delivery, equipment, and supplies.
- Constructing and managing oversight programs, and enabling evaluation of programs and outcomes.
• Ensuring the longevity of the initiatives that are implemented.

However, in countries with limited resources, the government may be less likely to initiate system improvements because, at least in part, of the realities of financial constraints, lack of attention to specific populations that do not have political clout, or both. Women may be denied access to services because of a lack of resources and limited mobility (70). Champions for improvement or reform are instead likely to emerge from NGOs, cancer associations within the country, international organizations, or some combination of these (71).

The process of increasing governmental support for health care issues is stepwise. Achieving political commitment from the government requires that it have a rationale for devoting resources to health care and system improvements based on health care data and motivated by public will. Catalysts for cancer control from the nonprofit sector, the public, or patients can provide the necessary attention and impetus for political action by reporting on inequities within a health care system (72). Through such political action, ministries can be authorized to collect data, establish programs, expend funds, oversee activities, train professionals, and evaluate services and outcomes.

Improving capacity has become central to strategies used to develop health systems in low-income countries. Experience suggests that achieving better health outcomes requires both increased investment (i.e., financial resources) and adequate local capacity to use resources effectively. International donors and NGOs, as well as ministries of health, are therefore increasingly relying on capacity building to enhance overall performance in the health sector. A conceptual framework for mapping capacity and measuring the effects of capacity-building interventions can be useful to planners in the design of such interventions and provides a framework for monitoring and evaluating their effectiveness (73).

Some groups advocate for privatization of care as a method for improving health care delivery (74). It is often argued that the private sector is more efficient than the public sector in the production of health services and that government reliance on private provision would help improve the efficiency and equity of public spending in health. A review of the literature, however, shows little evidence to support these statements (75). Privatization will be unlikely to improve the equity of access because, by definition, this care is market driven. Furthermore, privatization of health care is typically directed at treatment rather than prevention. Because the financial incentives that drive treatment interventions are typically absent in preventive care programs, such programs need strong government involvement to be successfully implemented (76).

Medical facilities in low-resource countries are frequently established and funded by charitable organizations, often with excellent organizations and efficiency. In Senegal, Catholic health posts were shown to be significantly more efficient than public and other private facilities in the provision of curative and preventive ambulatory services at high levels of output (75). As resources become available, health ministries may increasingly provide key planning and funds for building, staffing, and maintaining cancer care institutions. Such institutions, with the support of NGOs, and eventually the government, can provide training for health care professionals. Governmental involvement and support of research, another important facet of health care improvement (discussed subsequently), should also increase as resources become available for this activity.

**Nongovernmental Organizations** NGOs can play a key role in initiating and supporting improvements in health care (71). Such organizations can create programs that provide the best available evidence to inform the public, can keep cancer control on the public agenda, and can pressure governments and decision makers on issues related to cancer control, either directly or indirectly, such as via the media. NGOs may serve as a catalyst for dialogue and collective action within national and local cancer organizations, both governmental and nongovernmental. Ultimately, well-coordinated public-private partnerships can greatly enhance national health care for specific diseases (77). In some limited-resource countries in eastern Europe, NGOs are beginning to be formed to advocate for increased resources and services for core areas such as reproductive health (78). Services for family planning, abortion, infertility, cervical and breast cancer, and violence against women are underdeveloped in these countries and represent areas of common interest for NGOs advocating for women’s health.

Because NGOs can drive policy by providing independent funding, consideration must be given to issues affecting an NGO’s motivations to ensure good alignment with the interests of the health care system overall (79,80). Case examples have been provided in which NGO participation was less helpful than anticipated. According to one study in Mozambique, a deluge of NGOs and their expatriate workers contributed to local health system fragmentation, undermined local control of health programs, and contributed to growing social inequality. Because national
health system salaries plummeted over the same period as a result of structural adjustment, health workers became vulnerable to financial favors offered by NGOs seeking to promote their projects in turf struggles with other agencies (81). Thus collaboration between NGOs and governmental health agencies needs to be an interactive “two-way street” where common goals are identified and coordinated.

There are several core activities within the NGO pur-view for cancer control. The first is creating information resources based on the scientific evidence base and developing support for information storage, access, and dissemination to both professional and lay audiences (79). A second core activity is advocacy to influence public policy (82). A third area of focus is lobbying for the education and training of professionals in all fields of cancer control and through direct support with fellowship grants, support of conferences and workshops, and provision of materials that can be adapted to be locally relevant. With all of these activities, emphasis is placed on collaboration between organizations, agencies, and groups working in similar areas to leverage resources.

Rapidly improving breast cancer care in countries that have limited resources or lack comprehensive cancer control programs, or both, may be accomplished by focusing on three areas that NGOs can partly address: early detection, adequacy and quality of treatment, and supportive care. Rates of early detection can be improved with a pair of strategies: screening (performing systematic examination by professionals of all individuals in a healthy targeted population) and early diagnosis (increasing the awareness of women and health professionals about early symptoms to facilitate rapid diagnosis). NGOs can actively address these strategies in four ways:

- Lobbying governments for optimal high-quality goods and services; to advocate for rational and strategic decision making based on needs and resources assessment; to implement or improve organized, proven, population-based intervention (either screening or early diagnosis); and to ask for quality assurance and equity.
- Raising public awareness about initial symptoms, the availability of care, and the potential for cure if the disease is detected early and treated appropriately through public policy advocacy; by creating and conducting public information campaigns; and by ensuring widespread distribution of carefully designed communication materials.
- Training professionals in the proper conduct of CBE, mammography, cytology, biopsy, treatment, and supportive care to implement only evidence-based interventions, and to accept quality control and evaluation processes.
- Supporting research and the adaptation of proven protocols for the level of resources available, to design more efficient strategies adapted to economic level and health systems.

Nongovernmental organizations can also promote caring for the practical and emotional needs of patients by creating structures such as welcome centers in hospitals, patient committees, support groups, phone services, or “hope lodges,” where patients may find an alternative to hospitalization. Cancer patients in many countries are often faced with formidable practical hurdles, such as the distance to treatment centers and the prohibitive costs of hospital stays and palliative care. In addition, patients and their families frequently experience a chronic lack of moral and psychological support. Hope lodges, which already exist in some countries, help resolve practical problems by allowing patients to undergo therapy at little or no cost for room and board, and by offering the benefits of shared experiences with fellow patients, and in some cases, professional psychological support. Although not unique in serving this role, NGOs can be primary drivers in supporting patients with cancer and their families by decreasing financial constraints that limit cancer care in many countries and by encouraging the adaptation of cancer control strategies in the face of these constraints.

Nongovernmental organization interventions may require adaptation by the public in order to be successful. In 1997, a consortium of NGOs in Bangladesh began to implement health sector reform measures intended to expand access to and improve the quality of family planning and other basic health services (83). The new service delivery model entailed higher costs for clients and required that they take greater initiative than in prior programs. Clients had to travel farther to get certain services and pay more for these services than they did under the previous door-to-door family planning model. Beyond the need for establishing an appropriate pricing structure for these services, barriers to access, such as social concepts about gender, class, entitlement, the role of government, and obligations among people to participate in their own care require consideration and adaptation. Change was necessary for attitudes related to charging and paying for services, along with the institutional policies and practices that support them (83).
charity money, and establishing a research strategy. Because research is generally given a low priority in limited-resource countries, a significant part of a research unit’s budget is derived from charity grants. Accordingly, such organizations may have a strong influence on the orientation of cancer research. NGOs can be full-time partners in cancer control and consequently they must apply the same scientific rules and evidence-based strategies used by other partners involved in cancer control efforts. Data suggest that stakeholders have different agendas, and that donors predominate in determining the research portfolio. High-level consensus building at the national and international levels is necessary to ensure that the diverse agendas play a complementary role in support of health system objectives (84). Because of their direct impact on the population, such organizations can play a major role in convincing governments to create relevant cancer services and strategies, they can implement their own demonstration projects, and they can give important economic support to translational research. As such, the NGO becomes a link between public health care research and health care policy reform.

The Public, Patients, and Advocates The public, patients, and advocates also play both central and supportive roles in improving a health system so that it can deliver better health care. Community participation in health offers various advantages in health care and development, among which are helping communities to develop problem-solving skills, encouraging them to take responsibility for their health and welfare, ensuring that the needs and problems of the community are adequately addressed, ensuring that the strategies and methods used are culturally and socially appropriate or acceptable, and enhancing the sustainability of successful programs (85). Once organized, public health care advocacy groups can catalyze internal political action and system reform. However, it should also be recognized that these groups, which are common in individualistic societies with developed health care systems such as the United States, may find more obstacles to change in the hierarchical societies with unmet demand for regulated health care commonly found in low- and medium-level resource countries (86).

Health Care System Reform

Undeniably, moving a limited-resource health care system toward the goal of improved breast health care is a difficult endeavor requiring not only the initial commitment to change, but also ongoing effort toward that goal. Most often, system improvement is gradual and incremental rather than rapid and radical. Efforts are most likely to succeed when they are tied to specific goals (3). Of note, successful reform has implications beyond improved breast cancer outcomes; that is, it can serve as a model for better management of other diseases that also require multidisciplinary care.

Approaches to Reform To improve a health care system, efforts and resources can be applied with a top-down approach (i.e., starting at the minister or policymaker level) or with a bottom-up approach (i.e., starting at the grassroots/community level). Participatory models of care, in which the public is empowered through collective action, can be successful in motivating health care reform (82). Both approaches can be used at the same time to synergistically improve breast cancer outcomes.

There are two important components in any national initiative to improve health care: a policy component and an implementation component. The former entails setting government policy on the issue, while the latter addresses how that policy will be put into action. The policy component is typically addressed with policymakers, such as health ministers. They must be convinced that there is a need for a health care program based on data on the incidence and mortality of breast cancer, and that what is proposed is attainable and implementation is feasible within the budget constraints of their country. Policymakers obtain information on issues from multiple sources, therefore they may best be able to discern the need to consider a health care program if they are presented with a simple business case packaging the clinical, epidemiologic, and economic picture into a coherent plan to improve outcome. This case should tie economic terms to endpoints. For example, if reducing case fatality rates is the endpoint, models suggest that the down-staging of breast cancer at presentation (in the context of at least basic treatment) is the most cost-effective way of achieving the goal (23).

The implementation component may be addressed with policymakers, government agencies, NGOs, or other groups, and can be outlined in guidelines. Specifically, guidelines should delineate options for health care reform and propose ways of addressing the various constraints (manpower, education, equipment) to such reform in the limited-resource setting. However, guidelines can only generally address implementation because each country must tailor its own approach based on its unique circumstances. Of note, in some limited-resource countries, implementation may fail due to inefficient health management and corruption. External donors, on the basis of previous experiences, may prefer to start projects or programs with
an NGO; however, this approach may lead to verticality, with resultant discontinuation of the program if the NGO does not continue its funding or if a political regime change occurs (84). Continuity is an important consideration in any health policy change.

Working with Changing Leadership A major obstacle to health care reform for countries with all levels of resources is the short-term political obstacle of changing leadership. Because health care ministers commonly change more often than do political parties and leadership in power, health care ministers may be reluctant to undertake a long-term effort that could not be realistically achieved in a single term in office. They may be more amenable to undertaking a multistep plan of small interventions, so that visible progress can be made even in the short term.

Integrating a Breast Health Program into the Existing Health Care System To be effective and to ensure continuity and viability, a breast health care program should be integrated into the existing health care system whenever possible. Most limited-resource countries, especially middle-level ones, already have at least minimal health care infrastructure in place, and a breast health program should be integrated into that infrastructure. For example, nurses or midwives providing maternal and child health care in rural areas can also be trained to educate women on breast health and to carry out breast examinations. Unfortunately some health care systems are dysfunctional and unresponsive to the urgent needs of their populations. In such cases, it may not be possible to work within the system; that is, the system may need fundamental changes to be able to deal with breast cancer and other diseases.

National Cancer Centers as a Hub for Cancer Care Centralized centers of excellence serve as a core resource for a health care network, both for providing tertiary care of complex referred patients and for supporting the development of satellite cancer centers that can deliver care to peripheral regions of the country. Every country should strive to establish at least one center of excellence (i.e., a national cancer center). Such centers have the necessary expertise, facilities, and equipment to train health care professionals and to help coordinate and implement a cancer control program. When deciding where to locate such a center, as well as the smaller, linked health units (e.g., hospitals and clinics), consideration should be given to ensuring that they are readily accessible to the public.

Although establishing cancer centers and linked health units is an important step, it must be acknowledged that this approach will not solve problems for many women living in rural areas who cannot travel far to receive care. In limited-resource countries, referral from primary care to secondary- or tertiary-level facilities can be a relatively rare event (87). To meet the needs of such women, a program must also consider outreach approaches such as using visiting nurses and other physician extenders.

Breast health care requires multidisciplinary care including surgery, radiation therapy, medical oncology, pathology, and radiology. The breast unit concept, an approach to organizing multidisciplinary care, is a cost-effective way of managing breast cancer (88). As such, this concept may be a viable strategy in certain limited-resource settings. However, staffing breast units may be a major hurdle, and referring women to such units may be impractical because of factors such as transportation barriers.

Some limited-resource countries already have fairly well-established health care systems, but the public is reluctant to use them, in part because of system-related barriers such as long wait times, insensitivity of staff, or lack of female medical professionals. However, public use of such systems would likely increase if those barriers were reduced or removed. Therefore health care leaders should work to identify and dismantle barriers that deter the public from using existing facilities.

Overcoming Societal Barriers to Improving Breast Cancer Care In developing a health care system to address breast cancer, it may not be enough to simply establish a system and expect the public to use it. It may also be necessary to provide the public with the rationale for why they would want to use the system, especially in societies where there are substantial barriers to seeking care for cancer, such as a lack of awareness, fatalism, stigma, and fear. Societal barriers can be overcome by educating the public and including a message of empowerment for women to take charge of their own health.

Several parties can help overcome social barriers to breast health care. A potentially very effective way of promoting public participation is by involving the public itself or trusted community leaders to give the public a sense of ownership (53). In many communities in the developing world, the decision for intervention for women’s health rests with men (14). For this reason, men may need to be involved in interventions such as efforts to promote early detection.

A third influential group is breast cancer survivors. Survivors play a key role by showing, through their very
existence, that breast cancer is not invariably fatal, which is a critical step in convincing women to seek care. Moreover, these survivors can act as advocates in raising their voices to policymakers. Survivors also provide insight into obstacles related to a cancer diagnosis and reasons why women may feel disenfranchised from health care (89,90).

Research as a Tool to Improve Health Care Outcomes
In the limited-resource setting, the potential for establishing a regional or national research program grows over time and with economic development. Basic research laboratories are established, whether newly created or as an expansion of activities in existing institutions. Clinical research provides for protocol-driven care in which intervention suitable to the population and resource level can be tested and adopted.

Overcoming health care constraints and obstacles in the limited-resource setting requires novel thinking and creative approaches. When new ideas are developed, they must be implemented in ways that allow researchers to determine if the approach improves outcomes. For example, in countries where limited availability of pathology prevents prompt cancer diagnosis, one solution in remote areas may be cytopathology services using commonly available communication technologies to transmit images to centralized facilities. This intervention—cytologic diagnosis using telemedicine—and similar ones need to be studied in appropriately selected limited-resource countries, preferably with intervention and control arms.

Situational Analysis and Needs Assessment Different countries will require different solutions for the same health care problem, depending on their resources, their populations, the prevalence of disease, and other factors. Thus performing a situational analysis in a country is necessary before introducing any new intervention. Situational analyses may allow researchers and health care ministries to identify ways in which an existing system can be used to implement solutions for which the system was not originally designed.

A related form of research, needs assessment, should be considered in multiple areas. The availability of data to inform cancer control efforts should be assessed. Data registries, whether they are as broad as regional and national cancer registries or as limited as study-specific registries, are required to measure outcomes and the impact of interventions. Further needs assessment includes determination of the availability of manpower, training, and core equipment; the distribution and support of facilities; and the availability of funding for consumable supplies.

It is also relevant to perform needs assessments in the general community and in the medical community, including asking the public and health care professionals, respectively, what their needs are and what problems they face. This type of research is efficient and allows the tailoring of programs to a specific health care setting, but it can become expensive when it requires the hiring of skilled research professionals.

Economic Analyses New interventions designed to improve breast health outcomes must be both economically feasible and cost effective compared with alternative uses of limited funds. As previously noted, few if any cost-effectiveness studies related to breast cancer care have been conducted from the perspective of countries with limited resources. It is less expensive to treat early breast cancer than to treat locally advanced or metastatic breast cancer, yet the costs of identifying cancers at earlier stages must be weighed against the savings afforded through early detection (23).

Demonstration and Pilot Projects Demonstration projects (which show how an intervention can be applied on a small scale) and pilot projects (which test a research hypothesis on a small scale) can be vehicles for health care reform. For example, these projects might be used to evaluate the effectiveness of various approaches for the down-staging of disease at presentation. Screening by mammography was introduced in a pilot project in one territory of the Ukraine, a country in which about 30% of breast cancers were of stage III or IV at diagnosis at that time (20). The project found that 9% of cancers detected by mammography were in situ, while most were T1b (20%), T1c (48%), or T2 (22%), which represented a marked improvement in comparison with historical controls.

Outcomes Analyses It is important to monitor the efficiency and effectiveness of a breast care program. Although a policy may be present, implementation may not have been carried out, and even if the policy was implemented, for various reasons, it may be having no impact on outcome. Outcomes analysis can therefore be helpful in modifying policy and implementation. In countries with limited resources, two possible outcomes of interest are a decrease in the stage of the disease at presentation and a reduction in mortality from breast cancer. Of course, monitoring outcomes also requires resources, and these costs must be factored into the cost of the program.

Establishing data collection, including a cancer registry and a health information system, is key for outcomes analysis and will usually reside in the hands of governments,
although NGOs may also provide guidance and support (21). Unfortunately, in most limited-resource countries, there are few accurate data on the incidence and mortality of breast cancer. Regional and national cancer registries are nonexistent, very rudimentary, or are only hospital based.

Improving outcomes through guidelines hinges on guideline interventions being well implemented. To this end, countries must establish a structure and program for implementation, identify provider targets for the program (e.g., nurse practitioners), identify individuals who can assist in implementation (e.g., key opinion leaders), and develop measures of evaluation, quality control, and feedback to those who are to follow the guidelines. In this sense, implementing guidelines in limited-resource countries is very similar to doing so in wealthy countries. Nevertheless, resource limitations will force decision makers in countries with limited resources to be creative in following the steps of guideline implementation.

Research into best practices for guideline development and implementation in countries with limited resources is still in its infancy. Whenever possible, those developing and implementing guidelines should document their processes as well as their methods for implementing and monitoring outcomes. Ideally these documents should be published in peer-reviewed literature, but the Web also allows posting of documents on sites devoted to this cause. NGOs or groups such as WHO may consider hosting Web sites on which guideline developers and implementers from limited-resource countries can share their methods and experiences.

**CONCLUSION**

Health care systems provide the framework for improving outcomes for women with breast cancer in limited-resource countries. The barriers to reform are numerous and sometimes difficult to clearly identify; nonetheless, a firm understanding of the obstacles within these systems is a necessary initial step. Women themselves are stakeholders in the outcome and as such are an invaluable resource. Through education and organization, they can help facilitate needed change and save lives. Stratified breast health guidelines become the road map for addressing and curtailing the devastating morbidity and mortality of breast cancer.

**PANELISTS**

Benjamin O. Anderson, MD (panel cochair), University of Washington, Seattle, Washington; Cheng-Har Yip, MD (panel cochair), University of Malaya Medical Center, Kuala Lumpur, Malaysia; Scott Ramsey, MD, PhD (panel cochair), Fred Hutchinson Cancer Research Center, Seattle, Washington; Rob Baltussen, PhD, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands; Raphael Bengoa, MD, World Health Organization, Geneva, Switzerland; Susan Braun, MA, Susan G. Komen Breast Cancer Foundation, Dallas, Texas; Maira Caleffi, MD, Breast Center at Hospital Moinhos de Vento em Porto Alegre, and Breast Institute of Rio Grande do Sul, Porto Alegre, RS, Brazil; Leticia Fernandez, MD, National Institute of Oncology, Havana, Cuba; Margaret Fitch, RN, PhD, Toronto Sunnybrook Regional Cancer Center, and Supportive Care, Cancer Care Ontario, Toronto, Ontario, Canada; Joe Harford, PhD, National Cancer Institute, Bethesda, Maryland; D. Maxwell Parkin, PhD, University of Oxford, Oxford, England; Larissa Remennick, PhD, Bar-Ilan University, Ramat Gan, Israel; Sylvia Robles, MD, MSc, Pan American Health Organization, Washington, DC; Helene Sancho-Garnier, MD, UICC International Organization, Epidaure, CRLC Vald’Aurelle, France; Vivien D. Tsu, PhD, Program for Appropriate Technology in Health, Seattle, Washington; Hernan Vargas, MD, Harbor-UCLA Medical Center, Torrance, California.

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