
CONSENSUS STATEMENTS

Overview of Breast Health Care Guidelines for Countries with Limited Resources

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■ **Abstract:** Among women around the globe, breast cancer is both the most common cancer and the leading cause of cancer-related death. Women in economically disadvantaged countries have a lower incidence of breast cancer, but poorer survival rates for the disease relative to women in affluent countries. Evidence suggests that breast cancer mortality can be reduced if resources are applied to the problem in a systematic way. The purpose of the Global Summit Consensus Conference was to begin a process to develop guidelines for improving breast health care in countries with limited resources—those with either low- or medium-level resources based on World Health Organization (WHO) criteria. Breast cancer experts and patient advocates representing 17 countries and 9 world regions participated in the conference. They reviewed the existing breast health guidelines, which generally assume unlimited resources. Individual panels then discussed and debated how limited resources can best be applied to improve three areas of breast health care—early detection, diagnosis, and treatment—and how to integrate these areas

in building a breast health care program. The panelists unanimously agreed on the guiding principle that all women have the right to access to health care. They also agreed that collecting data on breast cancer is imperative for deciding how best to apply resources and for measuring progress. The panelists acknowledged the considerable challenges in implementing breast health care programs when resources are limited, as well as the need to build a program that is specific to each country's unique situation. The panelists noted that the development of centralized, specialized cancer centers may be a cost-effective way to deliver breast cancer care to some women when it is not possible to deliver such care to women nationwide. In countries with limited resources, at least half of the women have advanced or metastatic breast cancer at the time of diagnosis. Because advanced breast cancer has the poorest survival rate and is the most resource intensive to treat, measures to reduce the stage at diagnosis are likely to have the greatest overall benefit in terms of both survival and costs. Women should have access to diagnosis and treatment if efforts are undertaken to improve early detection of breast cancer. The panels' findings outline specific steps for prioritizing the use of limited resources to decrease the impact of breast cancer around the globe. ■

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BACKGROUND

Progress in cancer care is made in a stepwise fashion. Scientific studies provide evidence of efficacy for differing approaches to early detection, diagnosis, and treatment. To realize the benefit of this evidence, incremental changes in cancer care need to be applied uniformly within a population. The critical purpose of cancer care guidelines in general, and breast cancer care guidelines in particular, is to provide a framework for standardizing care. Major efforts in the United States, Europe, and other parts of the globe have been made to write evidence-based cancer guidelines. Groups such as the National Comprehensive Cancer Network (NCCN) (1) have prioritized cancer care guideline development, focusing on breast cancer, where consistent strides in cancer treatment have been made.

The need for breast care guidelines is especially compelling in countries with limited resources, in which cancer mortality is high while access to cancer care is limited. Around the globe, breast cancer is the most common cancer among women. Internationally breast cancer is the leading cause of cancer-related deaths among women (2). More cases are diagnosed per capita in affluent populations, but more women with breast cancer die of their disease in economically disadvantaged countries (Fig. 1) (3).

Statistics from economically developed countries show that it is possible to favorably impact breast cancer mortality. In the United States, the rate of breast cancer mortality was essentially constant from the 1930s through the 1980s. Then in the early 1980s, widespread mammographic screening was initiated. At the same time,

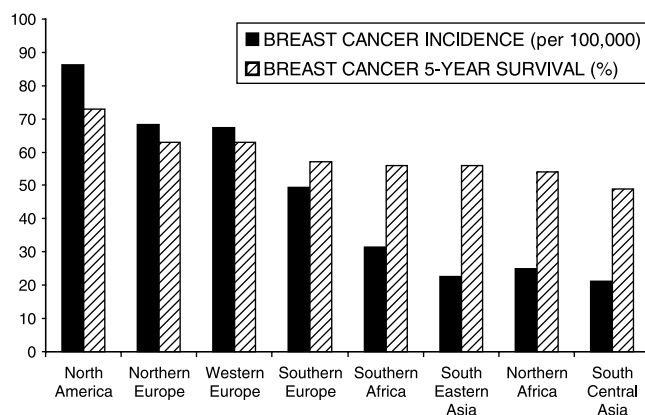


Figure 1. Breast cancer incidence and 5-year survival rate in different regions of the world. (Modified with permission from data of Greenlee et al. (3). Reprinted with permission from *Zentralblatt für Gynakologie*. 2002;124:1–3. Copyright 2002, J.A. Barth Verlag in Georg Thieme Verlag KG.)

prospective trials in the United States and Europe were showing improved breast cancer outcomes, especially with the use of systemic chemotherapy and hormonal therapy. It subsequently became clear that, for the first time, breast cancer mortality in the United States was decreasing by 1–2% per year beginning in the early 1990s (4). These findings are promising evidence that improvement in breast cancer survival is achievable when fully developed health care resources are applied to the task.

Existing guidelines indicate important directions for breast health care, but they do not show us where to start when resources are limited. Until now, breast health care guidelines have been written primarily by and for countries with high-level resources. Previously developed guidelines assume that resources are fully available and then define the evidence-based practices most likely to improve outcomes. The unfortunate but obvious limitation of such guidelines is that they do not apply to countries in which resources are constrained or unavailable, which collectively represent the majority of the world.

The World Health Organization (WHO) has initiated international cancer care efforts by creating guidelines for national cancer control programs (5). Within this context, WHO stratifies countries into those with low-, medium-, and high-level resources, defining three scenarios based on national economic status and health care organization (Appendix A) (5). A key next step is to define breast health care guidelines for countries with low- or medium-level resources, which for the purposes of this article we refer to collectively as “countries with limited resources.”

The purpose of the 2002 Global Summit Consensus Conference was to use the process defined by WHO to begin developing guidelines for achieving “priority actions” in breast cancer care (Appendix B) (5). Our monograph summarizes the findings and conclusions of three panels composed of internationally recognized experts in this field. Although this publication is the endpoint of the first Global Summit conference, it is a starting point for specific dialogue and scientific analysis as we move forward in reducing the tragic impact of breast cancer worldwide.

METHODS

The Conference

The Global Summit Consensus Conference, held in Seattle, Washington, on October 2–4, 2002, brought together breast cancer experts and patient advocates to develop consensus recommendations for the early detection, diagnosis, and treatment of breast cancer in countries

with limited resources. The participants, representing 17 countries and 9 world regions, followed the process charged by WHO to address breast cancer care in countries with low- or medium-level resources (5). Reviewing current evidence and existing breast care guidelines, panelists debated approaches for breast health care and specifically considered how this care may best be provided under the constraints of limited resources.

Each day of the conference was devoted to one of three topics: early detection (including screening), diagnosis, and treatment. During the morning sessions of each day, participants gave presentations on existing breast care guidelines, state-of-the-art breast cancer care, and the issues of providing breast health and breast cancer care to women in countries with limited resources. During the afternoon sessions, each Global Summit panel identified, discussed, and debated core issues for providing breast cancer detection, diagnosis, or treatment. Based on these discussions, the panel defined recommendations on the application of breast cancer care in countries with limited resources. Specifically each of the three panels was asked to address the question of where efforts can be applied in a country with limited resources to make the most significant advances. To document the major points covered during the discussion, each afternoon session was tape-recorded and transcribed and captured in notes by a medical writer. Both the transcripts and notes were made available to the panelists for the subsequent preparation of the consensus statements.

Parameters and Boundaries for Discussion

Focused choices were made to define and delineate the boundaries of each discussion. All three panels used the same definitions for countries with low-, medium-, and high-level resources as originally defined by WHO (Appendix A) (5). The Global Summit panelists did not attempt to re-create guidelines previously developed for countries with high-level resources. Instead, they reviewed and referenced those guidelines as starting points for developing the Global Summit recommendations, which only address care in countries with low- or medium-level resources. The NCCN guidelines for breast cancer screening, diagnosis, and treatment (1) were studied in detail, including the rules for consensus agreement. Common agreement was reached on certain parameters of discussion:

- The Global Summit Early Detection Panel acknowledged the controversial issues in mammographic screening, recognizing differences of opinion among the panelists about screening mammography in women

in their 40s and elected not to reiterate these issues. Instead, the panel focused on how to prioritize resource allocation in screening if a country determines that it should provide resources for screening.

- The Global Summit Treatment Panel focused on the treatment of women with localized invasive breast cancer. The panel elected to not make formal recommendations for the management of metastatic breast cancer.
- Formal economic analysis regarding the 2002 Global Summit recommendations was not performed. Instead, the panelists recommended that this type of analysis be considered for the next Global Summit in 2004, and that appropriate expertise be introduced to facilitate comparative economic study.
- In addition, it was decided that recommendations regarding breast cancer prevention would not be made during this 2002 session.

Monograph Preparation

The work product of the three Global Summit panels provides the substance of this monograph. Early detection, diagnosis, and treatment of breast cancer are rapidly evolving areas of medical care. Thus this document should be viewed as a work in progress and not as a template for indefinite application. We anticipate that the guidelines will be revised and refined in subsequent Global Summits.

The purpose of this overview is to describe the themes that were common to each of the three Global Summit panels and to give a brief synopsis of each panel's findings. The consensus statements from each panel, summarizing the three afternoon panel discussions, follow this overview. Selected individual position papers are provided after the consensus statements. These papers are summaries of the corresponding morning presentations. They provide specific data and discussion that were particularly useful for focusing the afternoon consensus discussions.

Scope and Duration of the Recommendations

The panelists at the Global Summit represented a broad spectrum of experts from countries with high-, medium-, and low-level resources. Panelists expressed diverse opinions based on evidence-based medicine, clinical experience, and differing practice environments. Thus the recommendations made by the panels represent a collective vision and interpretation of current data. There were topics on which panelists could not agree. In these cases, differing viewpoints are represented in the consensus statements as best as possible.

These consensus statements represent a work in progress—this monograph is a beginning rather than an

endpoint. The work published here will likely be revisited, revised, and refined in future iterations. We anticipate that the current recommendations will be scrutinized by future panels as new topics and other disciplines of expertise are brought to bear on breast health and breast cancer care in countries with limited resources. Although we do not think that the current version of the Global Summit guidelines will “expire” on some future date, we do expect that later iterations of the guidelines will clarify and may modify statements and positions represented here, based on new information and analyses.

CORE ISSUES IDENTIFIED DURING CONSENSUS DEBATES

Women’s Right to Access Health Care

A successful program for breast health care depends strongly on a woman’s ability to access health care. The panelists unanimously endorsed the core principle that all women have a right to access and receive health care equal to that of men. Population-based educational efforts are required to improve women’s awareness of the importance of breast health and to aid in their recognition of signs and symptoms that should prompt medical evaluation. Programs for providing care must be available, but are not in themselves sufficient. Support systems that allow access to the health care system should also be available. These support systems are likely to be especially important in countries with limited resources, where women play a crucial, ongoing role in the family unit and are often greatly concerned about the potential or actual financial and social consequences if they seek health care.

Guidelines and Standards of Care

There was strong consensus among panelists that the Global Summit guidelines for countries with limited resources should in no way be interpreted as giving permission, either explicitly or implicitly, for the provision of inadequate care to populations from regions where resources are scarce. We are not codifying substandard care, which could lead to inappropriate denial of good care for all. On the contrary, we fully endorse current guidelines developed for countries with high-level resources as providing excellent benchmarks for future development. The goal of the Global Summit guidelines is to help provide a logical pathway by which countries, health care systems, and institutions can sequentially work toward better care for their populations. We continue to seek better technology and approaches to health care in general

and breast care in particular, with the ultimate goal of cure for all patients, regardless of resources.

Barriers to Progress

The health care strategies that the panels propose are often complex and difficult to implement in countries with limited resources. In such countries, breast cancer may be overshadowed by more pressing public health problems such as malnutrition, epidemic infectious disease, and certain other cancers (such as cervical cancer). The many factors challenging formal public health programs in such countries may include political instability, cultural barriers, human rights issues, a high rate of population migration, and isolation of some segments of the population.

Breast cancer and its treatment impact the patient, the patient’s family, and society in many ways beyond the purely medical. Consequently breast health care programs must incorporate and respect the cultural and religious values and other social milieus of the patient. Specific barriers to health care vary from country to country and culture to culture. For example, Global Summit participants noted many different reasons why a woman in a limited-resource country may not seek out a health care provider when she finds a breast lump: she may not know that the lump may be cancer and a threat to her life; she may believe that the lump is cancer but thinks that cancer is incurable; she may not place a high value on her own life; she may not be able to distinguish the lump from other lumps she has experienced (e.g., lactation-related lumps); she may be reluctant to have her breasts examined for cultural reasons; she may not have access to care; or she may rely on self-medication.

Discussion of women’s health in general and breast health in particular may be taboo in some countries, and these social boundaries need to be considered and addressed. Unless women are provided with this critical health information, their situation is unlikely to change and breast cancer mortality rates may be higher than necessary. Thus a key question for health care ministries is how this information can be provided in ways that will be accepted by the community at large.

Common Requirements for the Development of Breast Health Care Programs

Education. Education of health care providers and the public about breast health and breast cancer detection, diagnosis, and treatment is central to the provision of high-quality breast cancer care. Education is particularly

critical to early detection, which in turn is central to appropriate resource use.

Data Collection. Collecting data is key to all aspects of breast health care. Data assist in assessing the effectiveness of breast cancer care and in identifying areas to which limited resources may be applied to optimize this care. Data collection is essential for showing that early detection efforts are having an impact, and ideally is accomplished in a stage-specific fashion. Many countries and regions currently have no processes in place for collecting the most basic of data (e.g., breast cancer incidence). A detailed cancer registry is a long-term goal, but simpler approaches may be more feasible while health care programs are becoming established. Cancer registries help determine how effective breast cancer care is in the region of the registry and strategies for resource allocation that are most likely to improve that care. Thus cancer registries are pivotal for the success of a breast cancer program.

It is difficult to determine the true incidence of breast cancer in many countries with limited resources. In some health care systems, a low reported cancer incidence might be an artifact of a low rate of detection and/or an inability of women to access the system. In other systems, internally driven factors may make collected data inaccurate. For example, some national health care systems may reward hospitals for having more favorable outcome statistics. This practice creates a disincentive for accurate reporting of advanced-stage disease. Ultimately each health care ministry must consider its own issues to achieve accurate data collection.

The consensus of all three panels was that proper data registries are a driving need in all countries to allow for monitoring of progress. However, panelists also acknowledged that each country must individually assess how to perform the data collection process.

Centralized Cancer Centers. Providing a basic structure for the proper diagnosis and treatment of cancer is critical for the success of a public health cancer program. One comprehensive strategy is to create government-oriented, cost-effective, centralized diagnostic and treatment centers—cancer centers—strategically located in certain geographic regions, where surgical procedures, basic radiotherapy equipment, and essential anticancer agents for the treatment of highly curable forms of cancer and agents for pain control are available (6). In most limited-resource settings, it is unrealistic to try to establish high-level care throughout a region. The cancer center approach ensures that at least a portion of the population can receive ade-

quate care, with the important goal that as more resources become available, additional centers can be established, creating an integrated health care network.

KEY FINDINGS

Importance of Early Detection

In contrast to most abundant-resource countries, where less than 10% of women with breast cancer present at late stages, clinical stage III is the stage at presentation in about 50% of women in countries in Africa, Asia, and Latin America. Data from academic institutions such as the Breast Unit at the University of Sao Paulo, Brazil, and the Institute of Neoplastic Diseases of Lima, Peru (7), and from various regions of India (8) clearly illustrate this phenomenon. However, the 5-year breast cancer survival rate on a stage-per-stage basis does not differ substantially for women in limited- and abundant-resource countries. For example, data obtained from a series of patients who attended the Breast Unit of the Hospital Erasto Gaertner in Curitiba, Brazil, show that the 5-year survival rate of that patient population was similar to what could be observed in community hospitals in most abundant-resource countries (7, 9). This highlights the critical importance of reducing the stage at diagnosis in the limited-resource setting and provides a strong rationale for promoting public education and awareness of the importance of early detection of this disease.

Late diagnosis of breast cancer significantly increases the probability that a woman has occult distant metastases. That in turn negatively impacts the effectiveness of treatment, making it less likely that treatment will reduce mortality.

Efforts toward the early detection of breast cancer should be focused on implementing cost-effective public health strategies to improve early detection in women with cancer that is producing symptoms and to promote large-scale mammographic screening in asymptomatic women with a predefined risk for developing the disease. The Early Detection Panel panel suggests implementing a screening program in a sequential fashion, when cancer diagnosis and treatment are already available, accessible, and affordable. Therefore, establishing screening programs is a lower priority than developing treatment programs in limited-resource countries. Once diagnosis and treatment are available, implementation of screening programs can begin.

Screening Mammography

The role of breast cancer screening in reducing breast cancer mortality has been a source of heated international

debate. Randomized trials in many parts of the world have suggested that screening mammography reduces breast cancer mortality. However, other trials have failed to show this benefit or have suggested that the benefit does not occur until women are older than 50 years of age. Most cancer specialty groups in the United States, such as the American Cancer Society (10), have concluded that mammographic screening saves lives and recommend that women in the United States have mammograms annually or every 1–2 years beginning at age 40 years.

Unfortunately widespread use of mammographic screening is not a realistic goal in most countries with limited resources, at least at the present time. Many do not have the equipment, trained personnel, or supplies to organize such programs. Where equipment is available, its quantity is often limited, such that it must be reserved primarily for breast cancer diagnosis rather than for screening. Therefore other measures for early detection, such as education and awareness, become the key tools in public health strategies.

Breast Self-Examination and Clinical Breast Examination

Breast self-examination (BSE) is also a topic of controversy. A recently reported randomized trial of programs teaching BSE in Shanghai, China (11), suggests that this practice, in the absence of mammographic screening, does not reduce breast cancer mortality. Future studies need to analyze whether other modalities that are less resource intensive than screening mammography can be used with reasonable anticipation of reducing the morbidity or mortality of breast cancer. Although formal efforts to teach BSE have not been found to reduce breast cancer mortality, clinicians have not discouraged women from performing BSE. It is still regarded as a core component of breast health awareness that contributes to early diagnosis. Women who choose to perform BSE should be aware that most lumps are not cancer and that they may be at increased risk for having negative biopsies. The panelists recommend that all women be familiar with their breasts and seek medical advice if they notice any changes.

Clinical breast examination (CBE) is another area of discussion and debate. CBE is central to breast health evaluation and is a primary method of diagnosis in countries with limited resources. The consensus of the panel is that CBE should be part of routine health examinations, whether it is used as a screening test in women who do not examine themselves, or as a diagnostic test for women who have breast lumps by BSE. This practice may serve to increase breast health awareness on the part of both the woman and the health care provider; it may encourage a

woman to see her provider more often; and it may help reduce the cancer stage at diagnosis. The value of these benefits is likely to be most striking in countries where women typically present with more advanced breast cancer. To this end, educating health care providers about the importance of CBE and training them in proper CBE technique is critical. Nevertheless, we lack data showing improved survival on the basis of screening programs that exclusively use CBE for screening. Studies in countries with limited resources in which patients commonly present with locally advanced disease could be very informative in this regard.

Breast Cancer Diagnosis

A “clinical diagnosis” refers to a diagnosis based on findings noted on a history, a CBE, or breast imaging studies (e.g., mammography and ultrasound). A “pathologic diagnosis” refers to a diagnosis resulting from microscopic examination of cells or tissues that allows a lesion to be properly categorized pathologically. A key issue in breast cancer diagnosis is that the diagnosis must be made with tissue sampling and cytopathologic analysis. This issue has implications for early detection and treatment. In some areas of the world, a breast cancer diagnosis is made by mastectomy. In the event that the woman actually has a benign condition that clinically mimics cancer, the mastectomy is unnecessary and may have devastating effects. Therefore tissue sampling before definitive treatment of breast cancer is critical.

Breast Cancer Treatment

Surgery has been the mainstay of breast cancer treatment since the late 19th century. Halsted’s classic report describing his results with radical mastectomy (12) heralded a new era in cancer treatment. This operation, which appears morbid and disfiguring by many modern standards, demonstrated that local control of malignant growth can be achieved through wide excision of both the tumor and the tumor-containing tissue bed. In 1948 Patey and Dyson (13) showed that removal of the pectoralis muscles during radical mastectomy does not impact long-term survival after the operation for the majority of women with breast cancer, thereby showing the safety of modified radical mastectomy.

Breast-conserving therapy with lumpectomy and breast radiation therapy represents an advance in cancer care, both for preserving the breast and for demonstrating a conceptual advance in understanding breast cancer biology. Halsted’s concept that breast cancer spreads in series from the breast to the lymph nodes and finally to distant metastatic beds

was displaced by the concept of Fisher et al. (14) that breast cancer exists and spreads as a systemic disease from inception. Two recent 20-year follow-up reports on randomized breast-conservation studies from the American National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial (comparing lumpectomy, lumpectomy with radiation, and mastectomy) (15) and the Milan study (comparing breast-conserving therapy and Halstedian radical mastectomy) (16) essentially end further debate, confirming the overall equivalence of breast-conserving therapy and mastectomy for treating breast cancer.

Today local-regional and systemic therapies are recognized to be separate but related issues. As such, surgery and systemic therapies are complementary rather than competitive. More extensive and morbid surgery cannot replace systemic therapy, which treats micrometastatic disease. Conversely, neither cytotoxic chemotherapy nor hormonal therapy appears able to replace proper breast-conserving therapy (excision of gross tumor with negative margins plus radiation of the remaining breast and, when appropriate, lymphatic beds) or mastectomy.

In countries with limited resources, implementation of the major advances of the 20th century may be hindered by a lack of health care resources. As a one-time intervention, surgery is available to women with breast cancer who can travel to hospitals and be admitted for care. Radiation therapy, on the other hand, is considerably less available, particularly when the therapy requires multiple sessions over time. Its cost is typically prohibitive for women without insurance, governmental subsidy, or private wealth. As a result, the application of breast-conserving therapy, although feasible, may not be practical. Similarly, systemic chemotherapy, when available, is very costly. Yet of the three categories of treatment, it is systemic therapy that provides the most significant mortality reducing benefit. Thus the separation widens between countries with limited resources and countries with abundant resources. Cancer detected by imaging, such as ductal carcinoma in situ, may be a disease of wealthy countries, whereas countries with limited resources find themselves faced primarily with locally advanced disease, for which treatment options are limited, costly, and less likely to save lives.

CONCLUSION

It is possible to help women with breast cancer in countries with limited resources. Focused attention on education among women and health care providers can lead to early breast cancer detection. Accurate diagnosis can help ensure that a woman receives appropriate treatment and that women

without cancer are not erroneously treated for the disease. Breast cancer treatment is more practical and less resource intensive when cancer is in an early stage at the time of diagnosis.

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Appendix A. World Health Organization Definitions of Low, Medium, and High Levels of Resources (5)

Low level of resources (scenario A)	This scenario refers to low income countries where resources for chronic disease are completely absent or very limited. Many such countries may have great political and social instability. A considerable proportion of the population is rural. Infant and adult mortality rates are high. Communicable diseases and malnutrition are a major cause of morbidity and mortality, especially for children. Life expectancy is relatively low. Cancer is not one of the main problems in general, but over 15 years of age it can be one of the leading causes of death. The majority of cancer patients are diagnosed in advanced stages.... Health care services are often delivered by informal means, and alternative medicine is a major component. Infrastructure and human resources for cancer prevention or control are nonexistent or very limited in quantity, quality and accessibility...."
Medium level of resources (scenario B)	"Countries in this scenario are often considered 'middle-income' countries. The majority of the population is urban and life expectancy is over 60 years. The country has been through the epidemiological transition, and cancer is usually one of the leading causes of disease and mortality. There is a high exposure to risk factors, especially tobacco, diet, infectious agents, and carcinogens in the workplace. Infrastructure and human resources for developing cancer prevention, early detection, diagnosis, treatment, and palliative care are available but with limitations in quantity, quality, and accessibility. Weaknesses can be identified in organization, priority setting, resource allocation, and information systems for adequate monitoring and evaluation. Primary prevention and early detection are usually neglected in favor of treatment-oriented approaches, without much concern regarding their cost-effectiveness...."
High level of resources (scenario C)	"This scenario is appropriate for industrialized countries with a relatively high level of resources for health care. In these countries life expectancy is over 70 years, and cancer is a major cause of death for both men and women. Many elements of a cancer control programme are in place, but they may not be well integrated into a comprehensive national system. Further, coverage of the population may be uneven, with particular groups such as those in rural areas, indigenous people and recent immigrants having difficulty accessing services. Reorganization of the system could bring benefits in terms of greater cost effectiveness and improved reach and acceptability of services."

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Appendix B. World Health Organization Priority Actions for National Cancer Control Programs, According to Level of Resources (5)

Component	All countries	Scenario A: low level of resources	Scenario B: medium level of resources	Scenario C: high level of resources
National cancer control program	<ul style="list-style-type: none"> • Develop a national cancer control program to ensure effective, efficient and equitable use of existing resources • Establish a core surveillance mechanism to monitor and evaluate outcomes as well as processes • Develop education and continuous training for health care workers 	<ul style="list-style-type: none"> • Consider the implementation of one or two key priorities in a demonstration area with a stepwise approach • Consider palliative care as an entry point to a more comprehensive approach • Use appropriate technologies that are effective and sustainable in this type of setting 	<ul style="list-style-type: none"> • When initiating or formulating a cancer control program, consider implementation of a comprehensive approach in a demonstration area using a stepwise methodology • Use appropriate technologies that are effective and sustainable in this type of setting 	<ul style="list-style-type: none"> • Full, nationwide implementation of evidence-based strategies guaranteeing effectiveness, efficiency, and accessibility • Implement a comprehensive surveillance system, tracking all program components and results • Provide support for less affluent countries
Early diagnosis	<ul style="list-style-type: none"> • Promote early diagnosis through awareness of early signs and symptoms of detectable and curable tumors that have high prevalence in the community, such as breast and cervical cancer • Ensure proper diagnostic and treatment services are available for the detected cases • Provide education and continuous training to target populations and health care providers 	<ul style="list-style-type: none"> • Use low-cost and cost-effective community approaches to promote, in a first phase, early diagnosis of one or two priority detectable tumors in a pilot area with relatively good access to diagnosis and treatment 	<ul style="list-style-type: none"> • Use low-cost and cost-effective community approaches to promote early diagnosis of all priority detectable tumors 	<ul style="list-style-type: none"> • Use comprehensive nationwide promotion strategies for early diagnosis of all highly prevalent detectable tumors

Appendix B. Continued

Component	All countries	Scenario A: low level of resources	Scenario B: medium level of resources	Scenario C: high level of resources
Screening	<ul style="list-style-type: none"> • Implement screening for cancers of the breast and cervix where incidence justifies such action and the necessary resources are available 	<ul style="list-style-type: none"> • If there is already infrastructure for cervical cytology screening, provide high coverage of effective and efficient cytology screening for women ages 35–40 years once in their lifetime or, if more resources are available, every 10 years for women ages 30–60 years 	<ul style="list-style-type: none"> • Provide national coverage cytology screening for cervical cancer at 5-year intervals to women ages 30–60 years 	<ul style="list-style-type: none"> • Effective and efficient national screening for cervical cancer (cytology) of women more than 30 years old and breast cancer screening (mammography) of women more than 50 years old
Curative therapy	<ul style="list-style-type: none"> • Ensure accessibility of effective diagnostic and treatment services • Promote national minimum essential standards for disease staging and treatment • Establish management guidelines for treatment services, essential drugs list, and continuous training • Avoid performing curative therapy when cancer is incurable and patients should be offered palliative care instead 	<ul style="list-style-type: none"> • Organize diagnosis and treatment services, giving priority to early detectable tumors 	<ul style="list-style-type: none"> • Organize diagnosis and treatment services, giving priority to early detectable tumors or to those with high potential of curability 	<ul style="list-style-type: none"> • Reinforce the network of comprehensive cancer treatment centers that are active for clinical training and research and give special support to the ones acting as national and international reference centers

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Early Detection of Breast Cancer in Countries with Limited Resources

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■ **Abstract:** Breast cancer is commonly diagnosed at late stages in countries with limited resources. 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. Early detection of breast cancer entails both early diagnosis in symptomatic women and screening in asymptomatic women. Key prerequisites for early detection are ensuring that women are supported in seeking care and that they have access to appropriate, affordable diagnostic tests and treatment. We therefore propose the following sequential action plan: 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. Public education and awareness can promote earlier diagnosis, and these goals can be achieved in simple and cost-effective ways, such as dissemination of messages through mass media. All women have the right to education about breast cancer, but it must be culturally appropriate and targeted and tailored to the specific population. When resources become available for screening, they should be invested in screening mammography, as it is the only modality that has

thus far been shown to reduce breast cancer mortality. Clinical breast examination (CBE) and breast self-examination (BSE) are important components of routine breast care in countries with access to mammography and are important for general breast health education in all countries. However, the evidence does not support the use of CBE and BSE as lifesaving screening methods at this time, recognizing that data from countries with very limited resource are lacking. When widespread screening is not possible, screening can begin in an institution, city, or region, or by targeting screening to women at highest risk. A pilot program can be an ideal way to define the best approach to screening. To succeed, early detection efforts must include the health care providers with whom women have contact; these providers may be physicians, nurses, midwives, traditional healers, or others. There are tremendous differences among and within countries, and a program to promote early detection must be tailored to each country's unique situation. ■

Key Words: awareness, breast self-examination (BSE), clinical breast examination (CBE), developing countries, diagnosis, early detection, education, mammography, screening

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A number of breast cancer screening guidelines have been developed for countries with a high level of resources. In this article we focus on the central aspects of breast cancer screening and early detection that could form the core of a breast cancer program in countries with limited resources.

METHODS

An international group of breast cancer experts and patient advocates met in Seattle, Washington, on October 3, 2002, to develop consensus recommendations for early detection of breast cancer (including screening) in countries with limited resources. The group, representing 17 countries and 9 world regions, followed a process initiated by the World Health Organization (WHO) to address cancer care in countries with low- or medium-level resources (1), specifically focusing on breast cancer.

In the morning, conference participants gave presentations on topics related to early detection of breast cancer and current approaches and barriers to early detection in countries with limited resources. In the afternoon the Early Detection Panel, a subgroup of conference participants, reviewed the current evidence and existing guidelines on breast cancer screening and early detection, debated approaches for achieving these goals under the constraints of significantly limited resources, and drafted preliminary recommendations. The final work product of this panel is the substance of this article. The methods are described fully in the overview (2).

FINDINGS AND RECOMMENDATIONS

Definitions and Terms

The Global Summit panels define countries with limited resources as those countries with low- or medium-level resources, as described by WHO (1). This consensus statement on early detection is intended to outline options for action plans in a country or region using existing health care resources, and define approaches that have the greatest likelihood of reducing breast cancer morbidity and mortality in those countries and regions. By necessity, the specific action plan will differ among and within countries.

The panel acknowledged a key distinction between “early detection” and “screening” (Fig. 1). We define early detection as the identification of breast cancer at a point in its natural history when it can be treated with techniques that have the least physical impact and the greatest chance of producing a cure. Early detection occurs through the careful response by clinicians to the concerns expressed by women in the course of routine care and/or at the time they present with a symptom. It may include programs by which breast cancer that is causing symptoms (e.g., a palpable breast mass) can potentially be diagnosed at an earlier stage.

By comparison, screening for a disease means using tests on individuals or populations without any signs or

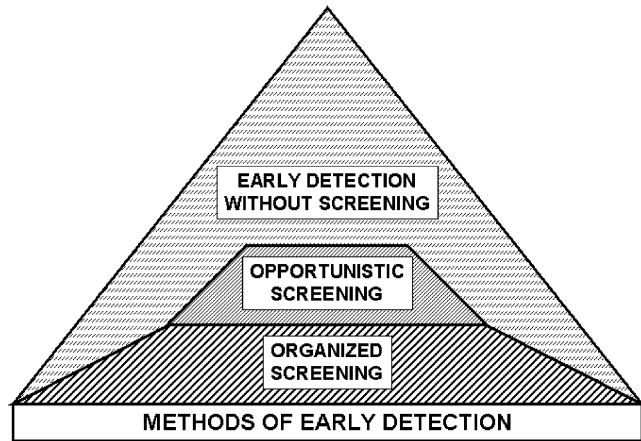


Figure 1. Early detection strategies with and without screening. Early detection without screening entails education of the population and health care providers to respond to the first signs or symptoms of breast cancer. By teaching women to see providers when they first note changes and by teaching providers to evaluate changes when they are first noted, cancers potentially can be diagnosed at earlier (although still clinically apparent) stages. Early detection programs that consist of education require the fewest resources, are an appropriate first step in countries with limited resources, and may have the greatest impact in countries where women commonly have advanced breast cancer at diagnosis. *Opportunistic screening*, when individual women obtain screening tests outside of a formal program, may facilitate early diagnosis of nonpalpable breast cancers, but only among those individual women who have resources to have these tests and the necessary follow-up diagnostic tests. *Organized screening* refers to the establishment of a formal screening program for a specific population by a facility, institution, regional government, or national health care ministry. It is the approach most likely to achieve early detection among a broad segment of the population, but it is also the most resource-intensive screening approach to early detection.

symptoms of the disease of interest in order to identify those who are more likely to have the condition. Screening is a public health strategy that involves administering these tests to a well, asymptomatic population. It is important to understand that with any screening test, those with a positive test result are not guaranteed to have the disease (i.e., the result may be false positive), and those with a negative test result are not guaranteed to avoid it (i.e., the result may be false negative). The purpose of screening is to define a subgroup that warrants further evaluation. Screening mammography is one tool for improving early detection; like all screening tests, it results in some false positives and some false negatives.

Because screening can take many forms, it is important to be clear about the forms under consideration. The panel reviewed screening evidence and balanced it against the availability of resources using the WHO framework (1). We distinguish between “opportunistic screening” and “organized screening” programs (Fig. 1):

- Opportunistic screening occurs when, outside of a formal screening program, a health care provider refers an individual who has no symptoms of breast cancer for a screening test, such as a mammogram. If the screening test shows an abnormality, then the woman and the provider take responsibility for coordinating and completing the diagnostic evaluation of that abnormality.
- Organized screening occurs as part of a program that coordinates outreach within a specific community (e.g., through mailed correspondence), encouraging women to obtain screening tests, such as mammograms, at set time intervals. The screening program must have the resources to perform screening tests and to complete diagnostic evaluations on those women who have abnormal results on their screening test.

Organized programs involve implementation of an explicit policy that specifies the screening method, the age groups that will be invited, and the screening interval, which may vary by age in the target population. These programs also typically involve a management team responsible for implementation, a health care team responsible, along with the individual, for decisions and care, a quality assurance structure, and a registry for identifying cancers that occur in the target population over time. There are many examples and variations on this basic theme of organized screening (3).

Appropriate Context for Breast Cancer Early Detection Programs

Ample evidence documents that diagnosis of breast cancer at an early stage is associated with improved breast cancer survival when proper treatment is available. Until we have a definitive cure for breast cancer, the best method to reduce breast cancer mortality is early detection combined with proper treatment. Programs for early detection of breast cancer have limited value if the existing health care services cannot provide proper breast cancer treatment. Breast cancer treatment must be available, promptly accessible, and affordable to those women in whom screening or other early detection strategies identify breast cancer if the initiative is to achieve the goal of reduced mortality. Thus if it does not already exist, an infrastructure whereby stage-appropriate treatment is provided should be developed before the early detection program is put in place. It may be necessary to concurrently build capacity in all areas—screening, early detection, diagnosis, and treatment. Because screening requires considerable resources, limited resources may be better invested in general early detection strategies, diagnosis,

and treatment, since they are prerequisites for screening, when resources ultimately permit.

A central tenet of the WHO guidelines for introducing cancer control programs is that when implementation of new health care programs requiring resources is being considered, competing health issues in the country or region must also be considered (1). Developing breast cancer programs might take resources away from other programs that would properly have priority in that country. For example, in some countries and regions, cervical cancer may be a more urgent problem among women than breast cancer.

In countries with limited resources, WHO recommends general measures for early detection of cancer (education about its early warning signs), but not necessarily screening for breast cancer (1). WHO specifies that starting screening for breast cancer should be based on cancer incidence and the availability of resources. In countries with the lowest level of resources, organized cancer treatment is typically unavailable. Such countries also have a very limited ability to perform breast imaging, so any available imaging equipment likely needs to be reserved for diagnostic purposes. Breast cancer screening would thus have a lower priority in this setting.

Considering this information, the Global Summit Early Detection Panel suggests the following sequential approach to build toward a breast cancer screening program: 1) promote the empowerment of women to obtain health care, 2) develop the infrastructure to diagnose and treat 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. These recommendations for early detection and screening are in line with WHO guidelines (1).

WHO does not advocate breast cancer screening in countries with low- or medium-level resources, based on the rationale that resources in such countries need to be reserved for cancer diagnosis and treatment, and possibly for screening for cervical cancer (1). By contrast the Global Summit Early Detection Panel suggests that screening can be implemented in countries with limited resources within centralized cancer facilities at which breast cancer treatment is available. Although such programs will not cover a country's entire population, they will provide care to a portion of the population that has access to the facility. This recommendation is based on the premise that institution-based screening could be a pilot program for more extensive programs covering larger populations, and ultimately the entire population, as resources become available.

A successful institution- and region-based screening program was developed in the Ukraine, described in an article by Zotov and Shyyan (4). In this pilot program, there was a dramatic downward shift in the stage of breast cancer at diagnosis within a short time after the introduction of screening mammography in the population studied. This experience indicates that screening is feasible and can be very effective in a limited-resource setting. Pilot programs provide an opportunity to gain early insight into what does and does not work. They can also lead to advocacy efforts to help garner resources and funding, as well as increase awareness of breast cancer. Pilot programs should ideally be set up so that they will be self-perpetuating (e.g., through building, enhancing, and redistributing resources within a country instead of reliance on finite outside resources).

Early Detection Programs Without Formal Screening

Breast cancer has the potential for devastating physical and psychological consequences, and early detection has many potential benefits. The goal of early detection is to diagnose breast cancer at a point in its progression when it can be treated with techniques that have the least physical impact and the greatest chance for curing the disease. In the absence of formal screening programs, early detection occurs in response to either a finding on clinical breast examination (CBE) or concerns expressed by a woman in the course of routine care and/or at the time she presents with a symptom.

Evidence. Randomized trial data and service screening data support the efficacy of breast cancer screening, and there is a consistent inverse association between tumor size at diagnosis and survival. Therefore a theoretical argument can be made that early detection of breast cancer, even when it is causing symptoms, provides some chance for a longer life. However, there have been no clinical trials specifically studying early detection in women with symptomatic breast cancer that prove this to be the case. Nevertheless, the totality of the evidence tells us that even among women with symptomatic breast cancer, the earlier treatment can be initiated, the better the circumstances for the woman and her family.

Recommendations. There was general consensus on the panel as to whether it should recommend promotion of general measures (education and awareness) for early detection of breast cancer in all countries. One could argue that even these measures should not be promoted in countries with low-level resources if diagnosis and treatment are not available. The panel considered this point

and noted that, if relative incidence and mortality rates of breast cancer support it, improving awareness of breast cancer through education may promote the development or redirection of resources to diagnosis and treatment, which is a necessary first step for any breast care program. Thus the panel supports the promotion of public education and awareness about breast cancer in most countries, regardless of their resource level, but recognizes that these efforts need to occur hand in hand with the establishment of diagnosis and treatment programs.

Potential Benefit. The degree of potential benefit from early detection programs without screening should increase with the degree to which women present with advanced disease. In other words, the benefit of such programs will be more obvious in countries where women commonly present with locally advanced or metastatic disease. Breast cancer is typically diagnosed at late stages in limited-resource settings. For example, at the Cancer Institute in Chennai, India, more than three-quarters of breast cancers are diagnosed at stage III or IV (Table 1) (5). Early detection strategies to shift the stage at presentation to predominantly stage I or II could significantly benefit women in these countries, whether or not such strategies included mammographic screening of asymptomatic women. In these settings, it is possible to promote early detection through education and awareness programs whereby women are encouraged to seek medical care when palpable breast masses are relatively small, rather than waiting until the masses are large (T3 lesions > 5 cm), ulcerating through the skin (T4 lesions), or associated with gross lymph node involvement (N2 lesions).

Furthermore, treatment of early stage breast cancer is typically simpler and more cost effective than treatment of advanced disease, as discussed in Carlson et al. (6). Therefore when health care resources are scarce, early detection positively impacts the delivery of breast cancer treatment, in that treatment in an earlier stage is likely to be less complex and more affordable.

Table 1. Stage of Breast Cancer at Diagnosis at the Cancer Institute in Chennai, India (3)

Stage	Distribution (%)
I	1
II	23
III	52 ^a
IV	24 ^a

^aCancer was locally advanced or metastatic at diagnosis in 76% of women.

Approaches to Education. Education and awareness alone may result in a favorable shift in the stage of breast cancer at presentation. Education can be achieved with very simple, cost-effective, pervasive, and popular means, such as radio and television advertisements and programs. The Global Summit panelists consider it axiomatic that education about breast cancer is a right of all women. To be responsible, that education needs to be culturally appropriate and targeted toward and tailored to the individual population so that it can have the greatest benefit. It is important to educate men as well as women, because men can facilitate early detection in their partners and help reduce barriers to care, because they may be able to impact health care resource allocation for breast cancer, and because men too can develop breast cancer. Specifically public education should stress 1) the signs and symptoms of breast cancer, 2) that breast cancer can kill, 3) that breast cancer can be effectively treated and need not kill, 4) that seeing a provider earlier for a breast problem is much better than seeing one later, 5) that the treatments for breast cancer are not formidable, 6) that most breast lumps are not cancer, and 7) and that breast cancer is diagnosed by biopsy rather than mastectomy.

In addition to educating the public, it is also important to educate health care providers, especially those with whom women are most likely to have contact. These providers may be physicians, nurses, midwives, traditional healers, or others. Evidence suggests, for example, that nurses can play a key role in breast health care programs in countries with limited resources (7). What these providers share in common across countries and regions is the trust that the public places in their advice. In many countries, health care providers do not routinely provide CBE. Therefore, in addition to general education about breast health, providers should be given instruction in CBE (discussed subsequently). This examination may detect breast cancer and may also increase the likelihood that women in these countries will have a conversation with their health care providers about fears or concerns that they have about their breasts. Lack of communication about the disease can be a major stumbling block in reducing its impact.

We can identify from existing examples those factors that are likely to make education and early detection programs succeed or fail. Programs that are forced on a population are more likely to fail, such as family planning efforts in India (8–10). In contrast, programs that use popular means of communication to get messages across, for example, the use of radio in India to convey messages about cervical and breast health, may be more likely to succeed. Clearly, to maximize the effectiveness of health

education strategies, decisions about these strategies must take into consideration the existing social context.

Tools for Breast Cancer Screening

When looking for breast cancer in countries or regions with high-level resources, there are three commonly discussed techniques: mammography, CBE, and breast self-examination (BSE). Recently there has been much controversy over the effectiveness of screening mammography in reducing mortality from breast cancer. Scientific and professional organizations and expert panels currently offer a variety of recommendations and guidelines for mammography as a public health practice. Although the evidence for screening mammography's effectiveness is imperfect, all organizations agree that it is currently the best approach available for the early detection of breast cancer when adequate resources make its appropriate use possible. Based on reviews by the International Agency for Research on Cancer (IARC) (11) and the U.S. Preventive Services Task Force (USPSTF) (12), this panel concurs that efficacious screening has been shown only with mammography.

Although mammography is the screening procedure of choice for identifying breast cancer in asymptomatic women, it is complicated to use screening mammography in one step (13). Formal breast cancer screening typically includes multiple steps: the identification and referral of appropriate women to screening facilities, the evaluation of those with abnormal results on screening tests, and finally the treatment of those with cancer. Successful screening requires high-quality screening tests, facilitation of the transition between steps in the screening process, and continual reevaluation of the process (13).

Two limitations of mammographic screening are its cost and technical complexity. As a result, mammographic screening is generally not applicable to countries with limited resources. Many countries do not have the equipment, trained personnel, or supplies to organize a national or even a regional mammography screening program. Thus an important question for the future is whether screening programs using other modalities such as CBE and/or BSE have value. For example, a recent randomized trial evaluated the efficacy of using BSE for breast cancer screening in Shanghai, China (14). Data from the trial suggest that BSE, in the absence of mammographic screening, does not reduce breast cancer mortality. Future studies need to analyze whether other modalities less complex than screening mammography can be used with reasonable anticipation of reducing the morbidity and mortality of breast cancer.

Breast ultrasound is a singularly important tool in breast cancer diagnosis. It is valuable in evaluating localized lesions in the breast and in guiding needles for tissue sampling. Ultrasound complements mammography, particularly in determining the nature of small lesions in the breast. However, most panelists felt that the current evidence does not support breast ultrasound as a stand-alone modality for breast cancer screening.

Screening Mammography. The Global Summit Early Detection Panel reached a consensus that when a country has sufficient resources to start breast cancer screening, it should use mammography to screen. Mammography is the only screening modality that has evidence from randomized trials showing a reduced mortality in women who were offered screening. CBE and BSE play important, unique, and supplemental roles in overall breast health care and early cancer detection (discussed subsequently and in the articles by Weiss (15) and Albert and Schulz (16)). However, we lack evidence showing that these modalities, when used alone, reduce breast cancer mortality.

The primary criticism of screening mammography is the fact that a subset of women will have false-positive results, which can have a range of adverse consequences among women without breast cancer. We will not reiterate this debate here, as it has been covered extensively by others (17). However, the panel agrees that health care providers should educate women about screening, including giving them information about the potential benefits and limitations of screening tests. For example, women should be told that mammography will not detect all breast cancers and that some women with positive findings on their mammograms will undergo a biopsy that will ultimately show that they have a benign condition.

The strongest evidence supporting the efficacy of screening mammography is for women 50–74 years of age, although the degree of confidence is due more to the degree to which the trials' designs directly and indirectly were more relevant to this age group than to women younger than 50 years. Evidence also supports the value of mammography for women 40–49 years of age, and although mammography is less cost effective in this age group, the potential for mortality reduction is similar to that observed in older women (17). Inasmuch as the incidence of breast cancer increases with increasing age, and because the efficiency of breast cancer screening improves as measured by sensitivity, specificity, and positive predictive value, the likelihood of negative outcomes from mammographic screening decreases as age increases. In the United States, the USPSTF (12) has concluded that in

randomized controlled trials, mammography reduced breast cancer mortality rates among women 40–74 years of age. Based on this, Tommy Thompson, Secretary of the U.S. Department of Health and Human Services, issued a statement formally recommending that all women in the United States 40 years of age and older undergo screening mammography at 1- to 2-year intervals (18).

Ultimately a country using screening mammography should consider making resource-dependent decisions about the age at which screening should begin, after carefully reviewing existing data. Of importance is that the age distribution of breast cancer may differ by geographic region. For example, although the age-adjusted incidence of breast cancer is considerably lower in Singapore than in the United States, 47% of breast cancers in Singapore are diagnosed in women younger than age 50 years (19). Other countries may have older median ages of diagnosis and/or may elect to start screening mammography at age 50 years or some age beyond that, when the absolute risk reduction of breast cancer mortality is the greatest.

Clinical Breast Examination. CBE is a standardized procedure whereby a health care provider examines a woman's breasts, chest wall, and axillae. A woman removes her clothes from the waist up for this examination. The examination typically consists of 1) visual inspection of the breasts while the woman is in the upright position with her arms relaxed and then raised above her head, 2) palpation of the axillae and supraclavicular fossae while the woman is in the upright position, and 3) palpation of the breasts while the woman is in both the upright and supine positions. The provider examines the breasts visually for symmetry and inspects the skin of the breast, areola, and nipple for edema, erythema, puckering, dimpling, or ulceration, all of which can be evidence of underlying masses. The provider palpates the regional axillary nodes to assess symmetry and nodularity. Normal axillary nodes can be palpable, especially in thin women. Enlarged, hard, matted, or fixed nodes can indicate cancer. The provider palpates the breasts for asymmetric masses, thickenings, or densities. A detailed CBE can take several minutes to complete (20).

Like mammography, CBE can be either a screening test or a diagnostic test, depending on the clinical setting in which it is applied. If a woman is not aware of any abnormalities in her breast and her health care provider finds a cancer using CBE, then CBE is a "screening test." In that scenario, the cancer would not have been detected had the CBE not been performed. On the other hand, as women's self-awareness

increases through breast health education and as women proactively see providers for self-detected breast changes, the role of CBE shifts. If a woman notices a change in her breasts or finds a change when she examines herself, and the health care provider then identifies that change as a possible cancer using CBE, then CBE is a “diagnostic test.”

Available data regarding the influence of CBE on breast cancer mortality are summarized in an article by Weiss (15). In another article, Albert and Schulz (16) summarize the clinical uses of CBE. We will not repeat these data and analyses here.

The panel is of the consensus that CBE should be part of routine health examinations, whether it is used as a screening test in women who do not examine themselves, or as a diagnostic test in women who have found a change themselves. This practice should increase breast health awareness on the part of both the woman and the health care provider, it may encourage a woman to see her provider more often, and it could reduce the cancer stage at diagnosis. The value of these benefits would be most striking in countries where women typically present with locally advanced breast cancer. To this end, educating health care providers about the importance of CBE and in proper CBE technique is critical.

The panel was unable to come to a consensus about whether screening CBE should be recommended in women already receiving mammographic screening. The available data suggest that CBE does not add much benefit in women who are already being screened by mammography, that CBE requires resources, and that CBE may meet with cultural barriers in some areas of the globe. However, CBE has general qualities that suggest benefit through its routine use. CBE detects some cancers that do not show up on mammograms; it might be useful while a country is getting a mammography screening program up and running; it might be useful in women at higher risk; and it might have the benefit of reassuring women, which is a significant quality of life issue. In the United States, CBE is considered standard care for routine health care, and to that end it is difficult to separate out its use within a mammographic screening program.

The panel agrees that CBE alone is not recommended for screening as a substitute for mammography. If a country is ready to screen but in only a limited capacity, it can target mammography to specific high-risk women (e.g., based on risk factors or high incidence in certain regions) and continue general early detection measures in other women. For countries that do not have resources for mammography, the use of CBE alone for screening was proposed as a possible research topic.

Breast Self-Examination. BSE is a formalized practice that a woman is taught for examining her own breasts. BSE is done in an attempt to find breast cancers earlier than they would ordinarily be detected in the absence of any screening practice. During BSE, a woman systematically palpates each breast using her contralateral hand, with her ipsilateral arm raised above her head. She performs the examination in both lying and standing or sitting positions. In the past women were taught to squeeze the nipple to identify bleeding or discharge, but this aspect of BSE is no longer emphasized because most nipple discharges are physiologic and do not require diagnostic evaluation. If possible, the woman should also inspect her breasts in a mirror for evidence of asymmetry or dimpling. A complete BSE can take up to 15 minutes to perform in a thorough fashion.

Screening by BSE is an attempt to teach asymptomatic women proper BSE procedures and to encourage them to practice BSE regularly (usually monthly). A program of BSE screening generally includes one or more instruction sessions, either with individual women or groups of women, taught by a trained instructor, use of printed educational material, and a system to encourage and remind women to practice BSE regularly. A formal BSE screening program is therefore not a trivial activity, but an effort that requires the use of public health resources and facilities.

BSE screening should be distinguished from breast health awareness. Health education activities could promote breast health awareness by urging women to become familiar with the feel and appearance of their breasts, and to seek medical evaluation if they notice changes in their breasts such as the development of a lump or nipple discharge (see “Approaches to Education”). This type of health education is usually limited to the use of printed materials and mass media and requires fewer resources than formal BSE instruction.

Evidence for the efficacy of teaching BSE to reduce mortality from breast cancer has recently been reviewed (11,15). Two randomized trials of BSE have been conducted in St. Petersburg, Russia (21), and in Shanghai, China (14). Neither showed a reduction in the risk of dying from breast cancer in women who were taught BSE. In addition, in both trials, women in the instruction groups had more benign breast biopsies than women in the control groups. Based on these results, plus the results of multiple observational studies, a working group of the IARC (11) concluded that there is inadequate evidence that BSE can reduce mortality from breast cancer.

In the study in Shanghai (14), most of the breast cancers that developed in women in both the instruction and control

groups were detected when fairly small and not widely disseminated. These women all had ready access to medical care. BSE instruction thus conferred no additional benefit in women with a generally high level of breast health awareness and access to medical care. In a subsequently published analysis of these data, Smith et al. (17) pointed out that there was a relatively high rate of self-detection of localized breast cancer in the control group, suggesting that a significant proportion of the women in the Shanghai study were highly responsive to new breast symptoms without formal instruction in BSE. Therefore, in a highly aware population, there may be a limit to the potential of BSE to measurably improve on what is achieved through incidental self-detection.

Because the use of BSE as a screening tool has not been shown to reduce mortality in two randomized controlled trials, BSE cannot be recommended as a substitute for mammography in breast cancer screening. However, we do not have evidence about the impact of BSE in countries in which the population has more limited breast cancer awareness and in which women typically present with late-stage breast cancer. BSE may have a general benefit in terms of awareness and motivating women to see a health care provider if they find a lump, and earlier response to symptoms may help reduce the cancer stage at diagnosis. In addition, BSE may be an effective primary tool in breast health education and may increase general awareness when initiating a new program for early breast cancer detection. The panel recognizes that promoting BSE might challenge cultural norms. In some parts of the world, women do not touch their breasts, and thus it may take time to transition from breast health education to the acceptance of BSE in these cultures.

The panel concludes that programs to teach women BSE are not likely to reduce mortality from breast cancer. Therefore, in the absence of other screening or early detection programs, creating a large infrastructure that provides only formal BSE instruction may not be the best investment of limited resources. Such resources may be better directed toward breast health education, treatment, and if feasible, mammographic screening.

PANELISTS

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Diagnosis of Breast Cancer in Countries with Limited Resources

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■ **Abstract:** Accurate diagnosis is a necessary step in the management of breast cancer. In women with breast cancer, diagnosis can confirm the presence of the disease, reduce treatment delays, and clarify the predictive and prognostic features of the cancer, which help in planning treatment and counseling women. In women with benign breast conditions, accurate diagnosis avoids erroneous treatment for breast cancer, which can have devastating consequences for the woman and unnecessarily consumes resources. The panel distinguishes between a “clinical diagnosis” of breast cancer (one based on signs and symptoms and imaging findings) and a “pathologic diagnosis” of breast cancer (one based on microscopic examination of cellular or tissue samples). The panel agrees that all women should have a pathologic diagnosis of breast cancer before they are given definitive treatment for the disease, no matter how strongly their clinical findings suggest cancer. The tools for clinical diagnosis include history, clinical breast examination, ultrasound, and diagnostic mammography; these tools provide valuable information and play important supplemental roles in ascertaining the presence of breast cancer. Mammography and ultrasound also help determine the extent of disease within the breast, which is essential when breast-conserving therapy can be offered to women. The tools for pathologic diagnosis include fine-needle aspiration biopsy,

core needle biopsy, and standard surgical biopsy. The panel noted that each of these tools has potential benefits and limitations in the limited-resource setting, and concluded that the choice among them must be based on the available tools and expertise. The triple test—checking for correlation of pathology findings, imaging findings, and clinical findings—was identified as a critical practice in diagnosing breast cancer. Panelists uniformly agreed that mastectomy should not be used to diagnose breast cancer, noting that accurate diagnosis can be made by less invasive means. Expertise in pathology was identified as a key requirement for ensuring reliable diagnostic findings. Several approaches were proposed for improving breast pathology, including training pathologists, establishing pathology services in centralized facilities, and organizing international pathology services. ■

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

Cancer diagnosis is the basis of cancer treatment. Therefore approaches for diagnosing breast abnormalities are fundamental to breast health care and breast cancer treatment. In this article we focus on the central aspects of breast cancer diagnosis that should form the core of a breast cancer program in countries with limited resources. We define countries with limited resources collectively as those with low- or medium-level resources according to World Health Organization (WHO) criteria (1).

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METHODS

An international group of breast cancer experts and patient advocates met in Seattle, Washington, on October 4, 2002, to develop consensus recommendations for the diagnosis of breast cancer in countries with limited resources. The group, representing 17 countries and 9 world regions, followed a process initiated by the WHO to address cancer care in countries with low- or medium-level resources (1), specifically focusing on breast cancer.

In the morning, conference participants gave presentations on topics related to the diagnosis of breast cancer, and current approaches and barriers to diagnosis in countries with limited resources. In the afternoon the Diagnosis Panel, a subgroup of conference participants, reviewed the current evidence and existing guidelines on breast cancer diagnosis, debated approaches to diagnosis under the constraints of significantly limited resources, and drafted preliminary recommendations. The final work product of this panel is the substance of this article. The methods are described fully in the overview (2).

FINDINGS AND RECOMMENDATIONS

Definitions

A diagnosis characterizes a disease process into specific categories that reflect the disease's natural history and biology. In addition, diagnosis provides prognostic and predictive information that is useful in appropriate management and in designing treatment plans. Thus the importance of accurate diagnosis cannot be overemphasized.

The panel distinguishes between "clinical diagnosis" and "pathologic diagnosis." Clinical diagnosis refers to a diagnosis based on history, a clinical breast examination (CBE), and breast imaging studies (e.g., mammography and ultrasound). These findings may suggest a benign or malignant diagnosis. Pathologic 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 "final word" on a given diagnosis.

Health care providers may strongly suspect breast cancer in women who have certain signs or symptoms or certain findings on imaging tests. In countries with limited resources, at least half of the women with breast cancer have signs or symptoms at the time of diagnosis. Although the clinical diagnosis may strongly suggest the presence of breast cancer, it may nonetheless be incorrect. Only tissue

sampling for a pathologic diagnosis can confirm the presence or absence of breast cancer.

Goal of Diagnosis

The Global Summit Diagnosis Panel finds that 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 noninvasive breast lesions, thereby leading to timely and appropriate care. The panel discussed four specific areas in which improvements can help achieve this primary goal: public education about the signs and symptoms of breast cancer, performance of clinical breast examination (CBE) by health care providers, use of diagnostic breast imaging, and obtaining a pathology diagnosis before treatment.

Public Education

All Global Summit panels identified public education about breast health and breast cancer to be a core requirement for improving breast care in countries with limited resources (2). Education about the warning signs of breast cancer may promote earlier diagnosis of breast cancer (3).

Public education can prompt women to seek medical care at an earlier point in the clinical course of the disease. Lack of education about breast cancer is often one of the barriers preventing women from seeking care when they notice a breast change. Providing the public with information about the importance of cancer diagnosis and treatment can increase the likelihood that they will see a provider in a timely manner. Similarly it may also increase the likelihood that they will agree to the necessary diagnostic tests and treatments that can improve their prognosis and save lives.

Clinical Breast Examination

Clinical breast examination (CBE) is a standardized procedure whereby a health care provider examines a woman's breasts, chest wall, and axillae, and it can be used as either a screening test or a diagnostic test (3–5). When used as a diagnostic test, CBE plays a fundamental role in providing information about breast changes that may signal the presence of cancer. A breast mass, nipple discharge, or changes in the skin and/or nipple are frequent initial symptoms of breast cancer which require prompt attention (6).

CBE is an integral component of the triple-test diagnosis of breast masses (7,8). The triple test entails the correlation of clinical, pathologic, and imaging findings (9). In combination with the appropriate use of fine-needle aspiration biopsy (FNAB) or core needle biopsy (CNB), CBE may help to better manage breast cancer.

Breast Imaging

Diagnostic Mammography. Diagnostic mammography is complementary to physical examination in evaluating women with signs and symptoms of breast cancer, and it provides a more accurate assessment of the extent of disease in women known to have cancer (10). Diagnostic mammography also provides additional information about the contralateral breast, since a small but significant percentage (3–5%) of women with breast cancer will have synchronous or metachronous cancer in the other breast (11).

However, the panel did not achieve a consensus on the relative need for diagnostic mammography in countries with limited resources. Establishing and maintaining a high-quality diagnostic mammography program is relatively costly (12), and diagnostic mammography cannot replace the need for a pathologic diagnosis in women with signs or symptoms of breast cancer. In addition, in countries with limited resources, few women are able to undergo breast-conserving therapy since this therapy is also resource intensive (13). Thus 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 did agree that at some point in the development of a breast care program, the introduction of diagnostic mammography is a necessary step. The decision as to when this step should be taken must be made by each country individually, based on available resources and other factors.

The panel recognized that approaches to treating breast cancer hinge on the stage at the time of diagnosis, since treatment for locally advanced cancer is different from that for early stage breast cancer (13). Mammography can help distinguish early stage from late-stage cancer, although this benefit varies depending on the patient and the cancer.

Ultrasound. 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. Ultrasound has three important contributions in this group of women. It can be used to distinguish simple cysts from solid masses (14), it can provide the health care provider with an estimation of the likelihood of malignancy in a solid mass (15), and it can be used to guide tissue sampling for a pathology diagnosis (16,17).

The panel did not fully agree about the relative roles of breast ultrasound and mammography in the diagnosis of a breast finding. In countries with high-level resources, mammography is a basic standard of imaging and is

supplemented by ultrasound. However, in some areas of the world ultrasound is being evaluated as a primary imaging tool rather than as a secondary imaging tool. Therefore this was identified as a possible topic for discussion in future global summits.

Pathology Diagnosis Before Breast Cancer Treatment

The diagnosis of breast cancer carries prognostic and therapeutic implications that are life changing for a woman. The Global Summit Diagnosis Panel strongly and uniformly recommends that all women suspected of having breast cancer have an accurate pathologic diagnosis that confirms the presence of the disease before they are given definitive treatment. This includes women who have clinical findings strongly suggestive of cancer. A pathologic 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. Whether the pathologic diagnosis is obtained by FNAB, CNB, or surgical biopsy, this sampling allows the health care provider to diagnose the woman and to discuss treatment options with her before definitive surgery.

It may be necessary to educate health care providers about the safety of FNAB and CNB. In the past, some investigators expressed concerns that needle sampling might promote metastasis of the cancer. However, extensive experience with these methods has shown this not to be the case.

The panel uniformly agrees that mastectomy should not be used as a method for diagnosing breast cancer. If a woman undergoes a mastectomy and is later found not to have breast cancer, the psychosocial consequences are devastating. Mastectomy constitutes a modality of treatment, not diagnosis. Therefore, even if the clinical impression is strongly suggestive of cancer, some type of tissue sampling must be performed before mastectomy. Several less invasive methods of tissue sampling are available and beneficial (18,19).

Methods of Tissue Sampling to Distinguish Benign from Malignant Lesions

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. When selecting among these methods, the panel recommends that countries consider several factors, including the clinical findings, the available expertise required for each method, and the available resources. Two groups of methods are reliable for obtaining a pathologic diagnosis: surgical biopsy

(incisional or excisional biopsy) and minimally invasive (percutaneous) biopsy (FNAB and CNB).

Surgical Biopsy. Surgical biopsy is the traditional method of obtaining a pathologic diagnosis of breast lesions, and it is considered the gold standard. Surgical biopsy provides tissue for histologic diagnosis, and it takes advantage of techniques and pathology training currently available in most countries. The disadvantages of surgical biopsy include its invasive nature and its substantial costs when the procedure is performed in an operating room. However, costs are reduced if it is performed in an outpatient setting (20).

In countries with limited resources, a majority of women with breast cancer have large primary tumors at the time when they seek medical care (15). Sampling tumors with minimally invasive procedures such as FNAB or CNB is the most cost-effective approach if these procedures are properly performed (21–23).

Minimally Invasive Biopsy. The Global Summit Diagnosis Panel agrees that FNAB can play an important role in the diagnosis of breast cancer in countries with limited resources, and introduction of this procedure therefore deserves consideration. If FNAB is used as a diagnostic test, the accuracy of interpretation must approach that of diagnosis by frozen sections. Although such accuracy has been achieved and reported in a few studies, the reported overall diagnostic accuracy of breast FNAB varies considerably (range 50–95%) among different institutions (24–26).

Accurate interpretation of breast FNAB requires clear guidelines for specimen acquisition, staining, and preparation. It is also essential to adhere to well-established cytomorphic criteria for an accurate interpretation. The terminology used for reporting FNAB results should approximate that of surgical biopsy and should incorporate pertinent diagnostic and prognostic information. Institutional and operator experience (27), differences in technique (28), adequacy of sample quality (29), and follow-up procedures (30) account for most of the reported differences in accuracy. Panelists noted that it is important to understand that breast FNAB is quite different from exfoliative cytology. Guidelines have been formulated to suggest educational requirements for pathologists who are interested in performing and interpreting breast FNAB (31).

The panel noted that it is critically important to recognize the inherent limitations of FNAB, such as sampling error and difficult interpretation in a small, but significant number of cases with certain lesions. These lesions include

atypical hyperplasia, low-grade carcinoma, papillary lesions, and fibroepithelial tumors (32). In addition, FNAB cannot reliably distinguish between invasive and noninvasive breast cancer (33).

CNB is also commonly used to obtain tissue samples from breast lesions, particularly nonpalpable and image-detected abnormalities (34). However, like FNAB, the success of this procedure depends on the selection of patients, the availability of experienced pathologists, and the appropriate correlation of the pathology findings with the clinical and imaging information. CNB has the same limitations as FNAB with respect to small sample size and difficulty in interpreting atypical and indeterminate lesions (35).

Vacuum-Assisted Biopsy. Vacuum-assisted breast biopsy has proven advantageous only in diagnosing lesions detected by mammography (calcifications) (36). It has no demonstrated benefit for diagnosing palpable lesions when compared with less costly and less invasive CNB programs. Because of both the expense and the lack of data supporting a benefit in improved diagnosis in palpable lesions, the panel does not recommend vacuum-assisted breast biopsy in countries without sufficient resources to maintain effective screening mammography programs.

Quality Assurance and Standardization of Pathology Procedures

Because treatment decisions and estimations of prognosis will be based on the results of 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 that consideration be given to 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. The panel recognizes the importance of standardizing pathology procedures and reports in order to better characterize a tumor and improve communication among health care providers. The panel also notes the importance of providing both diagnostic and prognostic information, including the status of hormone receptor expression.

Staging

A thorough clinical evaluation after the diagnosis of breast cancer can help determine the stage of the disease (37,38), which is important for estimating the prognosis and making choices between curative and palliative therapy. The panel recommends that health care providers perform a complete physical examination in women in

whom breast cancer has been diagnosed to check for clinically obvious indications of metastases to the lymph nodes and other areas. In addition, the panel notes that tests to assess the presence of metastases to the lungs, liver, and bone provide valuable information, if available resources permit such testing.

Expertise in Pathology

The panel noted that 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). Approaches for fostering a program in breast pathology are discussed by Masood (39).

Panelists acknowledge the differences in the availability of pathologists interested in breast pathology across the globe. Several approaches were proposed for improving breast pathology, including 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.

Communicating a Diagnosis of Breast Cancer

The panelists support the right of women to be told truthfully about a diagnosis of breast cancer. Specifically the panel views truth-telling as a part of education and notes that greater awareness of this disease can favorably impact breast cancer care. At the same time, panelists acknowledge and respect cultural differences in telling women of this diagnosis.

The panel emphasized the importance of telling women of a breast cancer diagnosis in a sensitive and appropriate way. Panelists noted that the diagnosis of breast cancer typically causes tremendous fear and anxiety for in women, particularly between the time of diagnosis and the time at which discussions about treatment begin. They therefore recommend that health care providers stay in contact with women after the diagnosis, and note that women should receive family and psychosocial support whenever possible.

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Treatment of Breast Cancer in Countries with Limited Resources

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■ **Abstract:** Early and accurate diagnosis of breast cancer is important for optimizing treatment. Local treatment of early stage breast cancer involves either mastectomy or breast-conserving surgery followed by whole-breast irradiation. The pathologic and biologic properties of a woman's breast cancer may be used to estimate her probability for recurrence of and death from breast cancer, as well as the magnitude of benefit she is likely to receive from adjuvant endocrine therapy or cytotoxic chemotherapy. Ovarian ablation or suppression with or without tamoxifen is an effective endocrine therapy in the adjuvant treatment of breast cancer in premenopausal women with estrogen receptor (ER)-positive or ER-unknown breast cancer. In postmenopausal women with ER- and/or progesterone receptor (PR)-positive or PR-unknown breast cancer, the use of tamoxifen or anastrozole is effective adjuvant endocrine therapy. The benefit of tamoxifen is additive to that of chemotherapy. Cytotoxic chemotherapy also improves recurrence rates and survival, with the magnitude of benefit decreasing with increasing age. Substantial support systems are required to optimally and safely use breast-conserving approaches to local therapy or cytotoxic chemotherapy as systemic therapy.

Locally advanced breast cancer (LABC) accounts for at least half of all breast cancers in countries with limited resources and has a poor prognosis. Initial treatment of LABC with anthracycline-based chemotherapy is standard and effective. Addition of a sequential, neoadjuvant taxane thereafter increases the rate of pathologic complete responses. Neoadjuvant endocrine therapy may benefit postmenopausal women with hormone receptor-positive LABC. After an initial response to neoadjuvant chemotherapy, the use of local-regional surgery is appropriate. Most women will require a radical or modified radical mastectomy. In those women in whom mastectomy is not possible after neoadjuvant chemotherapy, the use of whole-breast and regional lymph node irradiation alone is appropriate. In those women who cannot receive neoadjuvant chemotherapy because of resource constraints, mastectomy with node dissection, when feasible, may still be considered in an attempt to achieve local-regional control. After local-regional therapy, most women should receive additional systemic chemotherapy. Women with LABC that has a positive or unknown hormone receptor status benefit from endocrine therapy with tamoxifen. The treatment of LABC requires multiple disciplines and is resource intensive. Efforts to reduce the number of breast cancers diagnosed at an advanced stage thus have the potential to improve rates of survival while decreasing the use of limited resources. ■

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Key Words: breast-conserving therapy, chemotherapy, developing countries, endocrine therapy, hormonal therapy, mastectomy, radiation therapy, surgery

Breast cancer treatment guidelines have been developed for countries with a high level of resources (1–4). In this article we focus on the central aspects of treatment that should form the core of a treatment program for localized, invasive breast cancer in countries with limited resources. We define countries with limited resources collectively as those with low- or medium-level resources according to the criteria of the World Health Organization (WHO) (5).

METHODS

An international group of breast cancer experts and patient advocates met in Seattle, Washington, on October 2, 2002, to develop consensus recommendations for the treatment of breast cancer in countries with limited resources. The group, representing 17 countries and 9 world regions, followed a process initiated by the WHO to address cancer care in countries with low- or medium-level resources (5), specifically focusing on breast cancer.

In the morning, conference participants gave presentations on topics related to the treatment of breast cancer, and current approaches and barriers to treatment in countries with limited resources. In the afternoon the Treatment Panel, a subgroup of conference participants, reviewed the current evidence and existing guidelines on breast cancer treatment, debated treatment approaches under the constraints of significantly limited resources, and drafted preliminary recommendations. The final work product of this panel is the substance of this article. The methods are described fully in the overview (6).

FINDINGS AND RECOMMENDATIONS

Health Care Resources

Principles of Treatment. The treatment of invasive, local-regional breast cancer involves an assessment of the clinical and pathologic features of the breast cancer and of the health status of the woman, the application of therapy aimed at eradicating local disease in the breast and regional lymph nodes, the potential application of systemic therapy aimed at eradicating subclinical, micrometastatic disease, and follow-up after treatment for evidence of recurrent disease.

Analytic Endpoints. 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 panel's recommendations are made considering all of these endpoints and outcomes.

Staging Systems. The use of consistent, reproducible criteria for the staging of breast cancer allows for the comparison of various treatments, the selection of appropriate treatments, and estimation of the 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 (7,8). In this article we use the clinical staging system for breast cancer developed by the AJCC (7).

Early and Accurate Diagnosis Facilitates Treatment of Breast Cancer. Timely and accurate diagnosis of breast cancer is important to optimizing treatment. The treatment of early stage breast cancer is less resource intensive than that of advanced-stage breast cancer, and the outcomes are generally superior. Accurate histologic diagnosis of breast cancer is necessary to ensure that women with breast cancer are given optimal treatment and that healthy women are not erroneously given treatment for breast cancer. The availability of accurate tests for the presence or absence of estrogen (ERs) and progesterone receptors (PRs) in breast cancers is crucial for making decisions about systemic therapy. Accompanying consensus statements offer approaches for the early detection of breast cancer (9) and the diagnosis of breast cancer (10) when resources are limited.

Research. Although progress has been made in managing breast cancer, optimal treatments require further research. In countries with limited resources, large numbers of women with breast cancer are treated each year. Whenever possible, women should be encouraged to participate in simple and practical, well-designed clinical trials, as this benefits society and may benefit the woman.

STAGE I AND II DISEASE

Local Treatment

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, or a combination of both. Modified radical mastectomy is an effective local treatment for breast cancer using surgical techniques that are widely available (11). Modified radical mastectomy 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 time (12). Reconstruction of the breast provides many women with an enhanced body image and self-esteem, and better psychosocial adjustment, but it does not impact on the probability of disease recurrence or survival. Unfortunately the cost of breast reconstruction can be prohibitive in countries with limited resources, depending in part on whether that reconstruction is performed using implants, myocutaneous flap reconstruction, or a combination of the two.

Breast-Conserving Therapy. An alternative treatment to mastectomy is the use of breast-conserving surgery and radiation therapy (11,13,14). 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 is preservation of body image for the woman, which greatly improves her quality of life.

Breast-conserving therapy requires the following resources:

- High-quality breast imaging (mammography and ultrasound) to ensure that complete excision of the tumor is possible and is achieved.
- Surgical pathology services to ensure tumor-free margins of excision.
- Surgical services experienced in achieving a good cosmetic result while achieving a high frequency of negative pathologic margins of excision.
- Access to safe and effective radiation therapy.

Safe and effective radiation therapy, in turn, requires the following resources:

- Experienced radiation therapists.
- High-quality radiation sources.
- Radiation physics planning and high-quality treatment planning.
- Access to the therapy without long delay.
- Geographic accessibility.
- Support systems that allow a woman to receive the therapy over a period of weeks.

In special situations, wide excision of the tumor alone without radiation therapy may be considered. Studies evaluating the use of wide excision alone have found higher rates of recurrence in the local-regional area, but major differences in survival have not been observed (13,15).

However, the consensus of the Treatment Panel is that women who can undergo breast preservation without radiation therapy are at best a highly selected subgroup, comprising the exception rather than the rule. Thus, although selected women may be able to forego radiation therapy with an acceptable outcome, a health care system must be able to provide radiation therapy in order to offer surgery less than modified radical mastectomy for invasive cancer.

In addition to radiation therapy, adequate breast imaging (mammography and ultrasound) is critical for assessing the extent of disease, and adequate pathology resources for evaluating surgical margins are a core resource. If it is not feasible to perform detailed margin assessment because pathology resources are unavailable, it may still be reasonable to provide local control with surgery and radiation, if it is possible to create wide (>1.0 cm) margins, after the “quadrantectomy” skin-resecting approach advocated by Italian breast surgeons such as Umberto Veronesi in the 1980s.

Postmastectomy Radiation of the Chest Wall and Regional Lymph Nodes. The chest wall and regional lymph nodes are common sites of recurrent disease after modified radical mastectomy. Risk factors for local-regional recurrences have been identified and include large tumor size, positive margins of the resection, involvement of the skin or chest wall, and a large number of involved axillary lymph nodes. In North American breast cancer treatment guidelines, postmastectomy radiation 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 (1,16).

The use of postmastectomy prophylactic chest wall radiation therapy reduces the relative risk of local-regional recurrences in all groups of women, with the largest absolute risk reduction occurring in those with the highest risk for recurrent chest wall disease. Recent studies have demonstrated that radiation therapy of the chest wall and regional lymph nodes after mastectomy may also improve overall survival in women with axillary lymph node-positive breast cancer (1,16). This remains an area of substantial controversy and uncertainty (1,16). The resources needed for safe and effective postmastectomy radiation therapy are similar to those needed for breast-conserving radiation therapy (described previously).

Systemic Treatment

A substantial proportion of women with initial stage I or II breast cancer will ultimately experience relapse

of their breast cancer and death from breast cancer. A number of factors are independently prognostic for recurrence of disease, including the number of involved axillary lymph nodes, tumor size, tumor histologic grade, and tumor steroid hormone receptor content (17). These factors may be used to estimate a woman's individual risk for recurrence of disease and of death from disease when treated by local therapies 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 and/or endocrine therapy (18–20). The decision-making process regarding the use of systemic therapy is thus strongly influenced by the pathologic characteristics of the tumor, especially tumor size, number of involved axillary lymph nodes, and tumor steroid hormone receptor content.

Computer-based models for estimating the risks of breast cancer relapse and death and the benefits from adjuvant therapy in North American populations of women have been developed (21,22). The applicability of these models to non-North American populations has not been assessed.

The availability of careful pathologic assessment, including the determination of tumor ER and/or PR protein content, is central to making decisions about systemic adjuvant therapy (23,24). It is difficult to achieve accurate and reproducible results from tests for hormone receptor proteins. Fixing tumors with formalin can destroy hormone receptor proteins, particularly ER proteins. The best current technology for assessing hormone receptor proteins is immunohistochemical staining of sections of fixed and paraffin-embedded breast tumor tissues. Across different populations, approximately 55% of breast tumors will stain positive for both ER and PR proteins, 8% will stain positive for ER protein only, and 8% will stain positive for PR protein only; 29–39% of tumors will not stain positive for either receptor protein (24).

Endocrine Therapy. Many breast cancers respond to a wide variety of endocrine therapies. Benefit from these therapies may be predicted by the presence of ER and/or PR protein in the breast cancer. High-level evidence suggests that the use of adjuvant endocrine therapy in women with ER and/or PR-positive breast cancer substantially reduces the risks of disease recurrence and death (19). The benefit from endocrine therapy is substantial enough that if tests for hormone receptor proteins are not available, 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 seems to be similarly efficacious (25). Evidence suggests that 5 years of tamoxifen therapy is superior to shorter durations of therapy (19). Ten years of tamoxifen therapy provided no advantage over 5 years of therapy in two studies in women with lymph node-negative breast cancer (26,27). Ongoing studies are assessing the potential value of more than 5 years of treatment with tamoxifen.

The benefit of tamoxifen is additive to that of chemotherapy (19). Therefore the combination of tamoxifen and cytotoxic chemotherapy provides benefits greater than the benefits 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 reduces the risk of second, contralateral breast cancers.

Recent evidence from a trial with relatively short follow-up suggests that the selective aromatase inhibitor anastrozole is superior to tamoxifen for achieving disease-free survival in the adjuvant treatment of receptor-positive invasive breast cancer in postmenopausal women (28). The absolute difference between anastrozole and tamoxifen in terms of disease-free survival is small and must be balanced with the substantially higher cost of selective aromatase inhibitors. This trial and the results of other trials of selective aromatase inhibitors should provide more information to better assess the impact of these agents in this setting. At present, tamoxifen or anastrozole is appropriately used as adjuvant endocrine therapy in postmenopausal women. The aromatase inhibitors should *not* be used in the treatment of invasive breast cancer in premenopausal women.

Ovarian ablation (e.g., surgical oophorectomy or radiation ablation) or suppression (e.g., use of the gonadotropin-releasing hormone or luteinizing hormone-releasing hormone analogues) with or without tamoxifen is an effective therapy in the treatment of breast cancer in premenopausal women (20,29,30). Early studies of ovarian ablation or suppression in premenopausal women unselected for the hormone receptor status of their breast cancer found disease-free and overall survival equivalent to that of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) chemotherapy (20,31). Recent studies demonstrate that ovarian ablation plus tamoxifen may be superior to CMF chemotherapy in premenopausal women with hormone receptor-positive breast cancer (30). Indirect evidence also suggests that the addition of tamoxifen to ovarian ablation may provide additional

benefit. In premenopausal women with hormone receptor-positive breast cancer, oophorectomy plus tamoxifen may be considered an appropriate adjuvant endocrine therapy and is likely to be a cost-effective strategy compared with chemotherapy alone.

Cytotoxic Chemotherapy. Cytotoxic chemotherapy has an established role in the treatment of women with invasive breast cancer (18). In general, combination chemotherapy is superior to single-agent chemotherapy. In addition, the magnitude of risk reduction for recurrence or death achieved with combination chemotherapy decreases with increasing age. The efficacy of cytotoxic chemotherapy in women older than 70 years remains uncertain. The benefits achieved with cytotoxic chemotherapy are additive to those achieved with tamoxifen (19).

A number of effective cytotoxic chemotherapy regimens exist and the antitumor efficacies of these regimens are similar. In unselected women, anthracycline-containing chemotherapy appears to be superior overall to CMF chemotherapy (18). The addition of sequential taxane chemotherapy to anthracycline-based chemotherapy may be superior to anthracycline-based chemotherapy alone (32). Classical (oral) CMF proved to be equivalent to anthracycline-based chemotherapy in several clinical trials and represents an effective and less expensive adjuvant chemotherapy regimen (33).

Cytotoxic chemotherapy often requires intravenous administration and may be associated with serious and sometimes life-threatening complications. The use of cytotoxic chemotherapy thus requires the following resources:

- 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.
- 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, and pulmonary and cardiac support systems).

Surveillance After Treatment. After the treatment of breast cancer, women are at risk for the development of recurrent disease. Follow-up of women for recurrence of breast cancer after treatment includes history and physical examinations at increasing time intervals in conjunction with yearly

mammograms, and in women taking tamoxifen, pelvic examination. The use of surveillance chest radiographs, echocardiograms, computed tomography, and blood chemistries has not been found to substantially aid the diagnosis of recurrent disease or to enhance overall survival (34–36).

Stage III and Localized Stage IV Disease

Locally advanced breast cancer (LABC) encompasses breast cancer with a wide range of biologic behaviors. It includes large breast cancers (T3 tumors, those larger than 5 cm in diameter), those with advanced involvement of regional lymph nodes (N2, ipsilateral axillary lymph nodes fixed to surrounding structures or to each other; N3, ipsilateral internal mammary lymph node involvement), T4 tumors (chest wall involvement, edema, or ulceration of the skin; presence of satellite nodules; inflammatory carcinoma), and those with ipsilateral supraclavicular lymph node involvement as the only evidence of distant metastasis.

LABC represents 50–80% of all breast cancer cases in countries with limited resources (37,38). Approximately half of the women die of their disease within 5 years of diagnosis. The treatment of LABC is multidisciplinary, requires extensive staging, and normally requires the use of chemotherapy, surgery, and radiation therapy. LABC is thus an important health problem that consumes substantial resources in these countries. Such resources could be used more effectively if these cancers were detected at an earlier stage.

Compared with the treatment of LABC, the treatment of early stage breast cancer expands the available treatment options, improves overall disease outcome, and uses fewer resources. Thus efforts to diagnosis breast cancer earlier have both medical and fiscal advantages.

Neoadjuvant Chemotherapy

Initial treatment of LABC with anthracycline-based chemotherapy for four to six cycles is a standard and effective treatment (39). The addition of a sequential, neoadjuvant taxane after anthracycline-based neoadjuvant chemotherapy has been demonstrated to increase the rate of pathologic complete responses compared with anthracycline-based chemotherapy alone (40). Recent evidence suggests that neoadjuvant endocrine therapy may be beneficial in postmenopausal women with hormone receptor-positive disease (41).

Local-Regional Control for LABC

After an initial response to neoadjuvant chemotherapy, the use of local-regional surgery is appropriate. Most

women will require a radical or modified radical mastectomy. Selected women may be treated with wide local excision and whole-breast and regional lymph node irradiation. In those women in whom mastectomy is not possible after neoadjuvant chemotherapy, the use of whole-breast and regional lymph node irradiation alone is appropriate. In those women with LABC who do not have access to neoadjuvant chemotherapy because of economic constraints, mastectomy with node dissection, when feasible, may still be considered in an attempt to achieve local-regional control.

The principles for safe and effective radiation therapy are the same as those for stage I and II breast cancer (described previously). Resource constraints are at least as limiting as those for early stage disease. Because radiation therapy protocols are typically more complex and technically demanding for LABC than those for early stage disease, proper treatment of LABC with radiation therapy is typically even more difficult under conditions of limited health care resources.

Chemotherapy After Local-Regional Therapy for LABC

After local-regional therapy, most women should be treated with additional systemic chemotherapy. A number of chemotherapy regimens may be considered in this situation; generally, a chemotherapy regimen not used for neoadjuvant chemotherapy is preferred.

The principles for safe and effective systemic chemotherapy are the same as those for stage I and II breast cancer (described previously). Resource constraints are at least as limiting as those for early stage disease. Because chemotherapy protocols for LABC are typically more complex and toxic than those for early stage disease, proper treatment of LABC with systemic therapy is typically even more difficult under conditions of limited health care resources.

Endocrine Therapy for LABC

Women with LABC that is positive for ERs and/or PRs or that has an unknown receptor status benefit from “adjuvant” (or maintenance) endocrine therapy with tamoxifen.

CONCLUSION

The optimal treatment of breast cancer requires the ability to diagnose the disease early and accurately. Local treatment of early stage breast cancer involves either breast-conserving surgery followed by whole-breast irradiation. The pathologic and biologic properties of a

woman’s breast cancer may be used to estimate the probability for recurrence of and death from breast cancer, and to estimate the relative and absolute magnitude of benefit the woman is likely to receive from adjuvant endocrine therapy or cytotoxic chemotherapy. Substantial support systems are required to optimally and safely use breast-conserving approaches or cytotoxic chemotherapy as systemic therapy.

LABC is a common form of breast cancer in countries with limited resources and is associated with a poor prognosis. The treatment of LABC requires the availability of multiple disciplines and is relatively resource intensive. Efforts to reduce the number of breast cancers diagnosed at an advanced stage thus have the potential to improve rates of survival while decreasing the use of limited resources.

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