BREAST HEALTH GLOBAL INITIATIVE

Breast Cancer in Limited-Resource Countries: Early Detection and Access to Care

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

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

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

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

The growing burden of breast cancer in low-resource countries demands adaptive strategies that can improve on the too common pattern of disease presentation at a stage when prognosis is very poor. Although it is commonly argued that interventions focused on adult chronic

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

METHODS

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

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

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

FINDINGS AND RECOMMENDATIONS

The Importance of Early Diagnosis

The following discussion is framed by the consensus that there is solid evidence supporting the value of diagnosing breast cancer at an early stage (5,6,8–12). Individual randomized controlled trials (RCTs) (13,14)

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

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

and meta-analyses (15,16) have demonstrated the advantage of an invitation to screening, and detailed analysis of tumor characteristics and long-term survival have demonstrated the prognostic advantage of incrementally smaller tumors at the time of diagnosis (6). Although the technology of mammography offers the unique advantage of detecting occult breast cancer, the data on tumor size and survival also indicate there is an advantage to detecting palpable tumors at the earliest opportunity (14,17,18). The reduction in mortality in the RCTs of mammographic screening was predicted by reductions in the rates of lymph node-positive disease, and the magnitude of the reduction in the rate of advanced disease is a good surrogate of the eventual mortality reduction (16) (Table 2).

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

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

	Relative risk	
RCT	Mortality (95% CI)	Node-positive breast cancer
HIP	0.78 (0.61–1.00)	0.85
Malmo	0.78 (0.65–0.95)	0.81[a]
Two-County	0.68 (0.59–0.80)	0.73
Edinburgh	0.78 (0.62–0.97)	0.80
Stockholm	0.90 (0.63–1.28)	NK
NBSS-1	0.97 (0.74–1.27)	1.40
NBSS-2	1.02 (0.78–1.33)	1.17
Gothenburg	0.79 (0.58–1.08)	0.80
Overall	**0.80 (0.73–0.86)**	—

CI, confidence interval; HIP, Health Insurance Plan; NBSS-1, Canadian National Breast Screening Study-I; NBSS-2, Canadian National Breast Screening Study-II; NK, not known; RCT, randomized controlled trial.
[a]For the Malmo trial, we used stage II or worse because data for nodal status are not available.

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

Breast Awareness

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

goal of detecting a greater proportion of breast cancers when they are asymptomatic, but also downsizing symptomatic breast cancers as well.

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

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

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

Clinical Breast Examination

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

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

Recently Pisani et al. (35) published the first results of an ambitious RCT in the Philippines designed to evaluate the efficacy of annual CBE performed by trained nurses and midwives. The target population was women 35–64 years of age residing in 12 municipalities in Manila ($n \approx 340{,}000$), and the units of randomization were 202 health centers in the municipalities. The first round of screening took place in 1996–1997, and of 151,168 women offered CBE, 92% agreed to participate in the study. However, the study was closed after the first round

because of the unwillingness of the majority of women who screened positive to participate in follow-up examinations. Among 3479 women with positive findings on screening, only 1220 (35%) completed a diagnostic follow-up examination. Forty-two percent of women actively refused any further investigation, including a home visit, and 23% were not traceable. Although follow-up was very poor, the results of this study are not entirely dissuasive of the potential to screen with CBE. Test sensitivity for annual examination was 53.2%, and for biennial examination was 39.8%. Further, the investigators documented an improvement in stage at diagnosis in examined women. Pisani et al. (35) concluded that the aborted study offered some valuable lessons for introducing CBE screening, including having realistic expectations about the necessity of ongoing training and monitoring of examiners, and for newly trained personnel to acquire greater levels of experience. No less important is identifying and overcoming culturally related health beliefs that could be a major barrier to the success of a screening program.

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

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

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

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

Formal BSE

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

in node-positive disease and an 11% reduction in stage T2 or worse disease in the group offered BSE training. This suggests that in the future, if follow-up was continued, a reduction in mortality of similar size would be evident.

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

Mammography

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

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

Social and Cultural Considerations

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

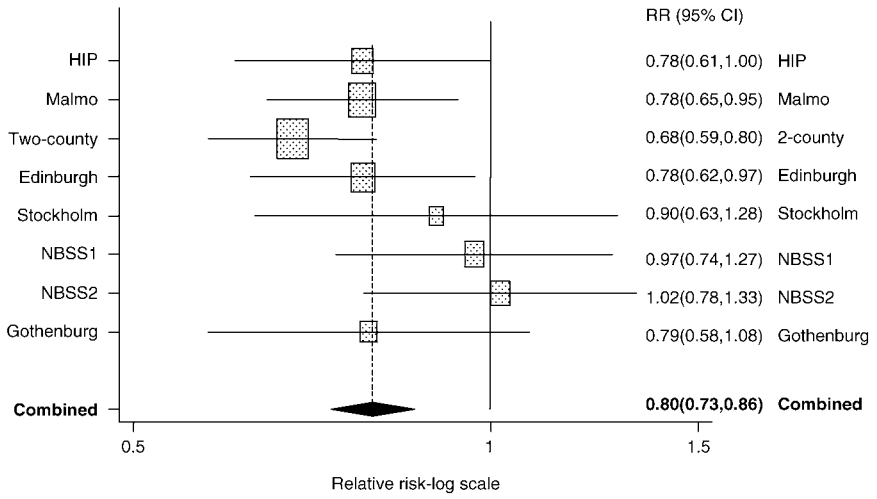

Figure 1. Relative risk of mortality associated with an invitation to screening in the randomized trials of breast cancer screening, all ages (16).

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

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

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

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

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

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

Implementing Evaluation Programs

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

The effectiveness of a program is a function of the quality of the individual components. The success of the program is judged not only by its impact on breast cancer

morbidity and mortality, but also by the organization, implementation, execution, and acceptability of the program; for example, a program with a low acceptability in the population will never reach its objectives. There are several handbooks on the evaluation and monitoring of health interventions (47), and in particular, screening programs (48). Planning for the evaluation and monitoring of an intervention should take place at the same time as planning the intervention.

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

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

CONCLUSION

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

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

Although there is a rich body of literature related to breast cancer interventions in higher-resource countries, in particular the United States and Europe, the published literature related to interventions focused on early detection in lower-incidence/low-resource areas is quite limited. However, the goal of earlier breast cancer detection and prompt, appropriate therapy is clear enough, and there is little need to entirely reinvent the wheel. Over the past several decades there has been an accumulation of both cross-cultural and locally specific experience in low-resource countries, both among health workers and as documented in the published literature, in programs focused on family planning (53), oral rehydration therapy (54), breast-feeding (55), cervical cancer (56,57), oral cancer (58), infectious disease (59,60), HIV and AIDS (61), and others. Many of these programs are ongoing and may be appropriate vehicles for introducing breast health awareness. Further, many of the behavioral interventions

focused on disparate targets have been built on a set of common denominators that have meaning to the target population and have also benefited from prior experience within and across populations. Here, in many respects, well-documented failures may be as informative as successes. Although not addressed in detail here, the implementation of more complex, higher-resource interventions can initially be risk based, with higher-risk women identified through questionnaires or interviews during opportunistic encounters for health care. This strategy also requires careful evaluation, because risk-based strategies in the West have not successfully identified a significant proportion of incident breast cancer cases through careful targeting of women with known risk factors (62).

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

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Acknowledgments

Financial support for this work is described elsewhere in this supplement (7,63). The Early Detection and Access to Care Panel wishes to acknowledge the participation of the following individuals in the discussions leading to the generation of these guidelines: Benjamin O. Anderson, MD, University of Washington, Seattle, Washington; Justus P. Apffelstaedt, MD, MBA, University of Stellenbosch, Tygerberg, South Africa; Zeba Aziz, MD, Allama Iqbal Medical College, Lahore, Pakistan; Rajendra A. Badwe, MD, MBBS, Tata Memorial Hospital, Parel, Mumbai, India; Nuran Senel Bese, MD, Tütüncü Mehmet Efendi Cad. Dr. Rıfat Paşa Sok, Istanbul, Turkey; Susan Braun, MA, Susan G. Komen Breast Cancer Foundation, Dallas, Texas; Oladapo Babatunde Campbell, MD, University College Hospital, Ibadan, Nigeria; Emmanuel Amurawaiye, MD, Lakeridge Health Corporation, Oshawa, Ontario, Canada; Kathleen M. Errico, PhD, ARNP, University of Washington Breast Health Center and Seattle University, Seattle, Washington; Margaret, Fitch, RN, PhD, International Society for Nurses in Cancer Care,

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