In contrast to western high-income nations, the incidence and mortality from breast cancer are increasing in most low and middle-income countries worldwide. Current approaches to breast cancer control developed for populations of high-income societies should not be directly transferred without evaluation. A relevant research agenda includes population differences in tumor biology and metabolism of systemic therapies, cultural and psychosocial issues, and operations in healthcare systems. Highest priority should be given to assessments of clinical downstaging and basic systemic treatment effectiveness in low and middle-income populations. Partnerships of existing organizations in high-income nations with those in low and middle-income countries are currently the most feasible sources of research support.

KEYWORDS: breast cancer, research, global, international, developing countries, low and middle income countries, LMC, cost efficacy, technology transfer.

The way you frame a problem dictates how you approach it.

Jonathan Mann

Beginning more than decade ago, mortality rates from breast cancer leveled off and began to decline in some western high-income countries. In contrast, data describing low and middle-income countries (LMCs), although less conclusive, indicated increases in both incidence and mortality. A review of available information strongly suggests a crucial role for research in applying the experience and knowledge of high-income societies to the challenges of women and breast cancer throughout the world. This article provides the background critical to development of a research agenda that can support effective and cost-effective allocation of resources to breast cancer globally, as well as the mechanisms through which this agenda may be accomplished.

Global Breast Cancer: The Problem and Its Context

Projecting to 2010, the annual global burden of new breast cancer cases will be 1.5 million, and an ever-increasing majority will be from LMCs. Half will be Asian, poor and premenopausal. Incidence rates vary 5-fold or more, from 115 per 100,000 in North American communities to approximately 20 per 100,000 in India, Korea, Thailand, and Vietnam. Earlier age at first full-term pregnancy, greater...
parity, and calorie-limited diets, each associated with lower incidence rates, are believed to be responsible for some or more of these rate differences; thus, as economic development decreases poverty and changes reproductive and dietary habits, significant increases in currently low rates are expected in many countries with large populations.\textsuperscript{4,8,9} Mortality data are much less certain, but these suggest much higher incidence and mortality ratios in LMCs.\textsuperscript{4} Absent efforts to initiate, improve, and sustain cancer registration programs and better cause-specific mortality data, benchmarks against which to measure breast cancer interventions will not be available in the foreseeable future for many countries.

In western countries, there is a predominance of postmenopausal cases, whereas in LMCs, the case burden is generally overwhelmingly premenopausal.\textsuperscript{4,5} This reflects not only the younger age skew of populations in LMCs relative to western nations but also differences in age-related incidence rates. In western countries, incidence increases with age throughout life, whereas many LMCs experience a leveling or possibly a slight drop in rates after menopause.\textsuperscript{6}

Successfully addressing healthcare problems associated predominantly with women requires a consideration of “structural violence” as defined by Paul Farmer: the diffuse and indirect oppressive societal forces whose routine application limits individual choices in the extreme. Poverty, political, and religious terrorism, market colonialism, and race and class discrimination all have sex dimensions.\textsuperscript{10} The expense, technological sophistication, and medical specialization required for optimal breast cancer management also brings these forces into play. Poverty is an obvious example, but one whose impact is seemingly less appreciated by privileged observers. Consider a single example from a study currently conducted by the author in Bangladesh, where multiple focus groups revealed that afflicted women were aware that their breast masses were serious, and they were afraid of the consequences of not seeking treatment. They had to choose day in and day out, however, between using their families’ limited financial resources to pay for a bus trip and other costs attendant to getting help and the higher priorities of purchasing food and school supplies for their children. Recent survey data indicate stunted growth in 43% of Bangladeshi children.\textsuperscript{11}

**Global Biological, Clinical, Cultural, and Health System Issues**

There is limited evidence suggesting major differences in breast cancers associated with ethnic, and presumably genetic, populations. The clinical phenotype of inflammatory breast cancer, with its associated poor prognosis, appears to occur more frequently in North African (Maghreb) populations.\textsuperscript{12} One study suggests a greater frequency of hormone receptor-negative genotype breast cancers in Africans, which would parallel the greater frequency similarly suggested in African Americans.\textsuperscript{13,14} South Asian physicians have suggested, based on limited data, that tumors in their patients are infrequently hormone receptor-positive.\textsuperscript{15} Although recent data have found evidence for population differences that could be associated with variance in the rate percentage of hormone-positive tumors, studies using careful tissue management procedures found no significant differences in the hormone-receptor status of tumors in populations of Filipinos, Vietnamese, Taiwanese, Indian, and Bangladeshi relative to western women.\textsuperscript{14,16,17}

Of more critical clinical relevance are emerging data that suggest there may be major differences in genetically determined host metabolic pathways for systemic treatment agents among genetically dissimilar populations. As a result, it is possible that drugs like tamoxifen, the alkylating agents and the taxanes, could have different efficacy and toxicity profiles when used in the treatment of patients from racially distinct groups.\textsuperscript{18-21} Tamoxifen, the most widely used systemic therapy for breast cancer, is a pro-drug that needs to be metabolized to a more active form, endoxifen, for greatest therapeutic effect.\textsuperscript{18,19} Emerging data indicate that there are major differences among populations in metabolic functioning due to polymorphic forms of critical genes that govern metabolizing enzymes. When certain polymorphic forms of the genes are present, tamoxifen therapy appears ineffective, and it has been suggested that these polymorphic gene forms occur in as much as 40% of some populations.\textsuperscript{18,19} A widely used and recommended chemotherapeutic agent, doxorubicin, is associated with greater likelihood of life-threatening neutropenia and cardiac toxicity in Chinese compared with Caucasian populations.\textsuperscript{20,21} These observations, combined with the “threshold effect” for some chemotherapy regimens,\textsuperscript{22} strongly suggest the need for rigorous investigation and evaluation of treatments used among various genetic groups, as these treatments were developed in exclusively higher income, northern European populations. Evidence for such differences makes a strong case against assuming that current systemic therapy programs should be directly transferred to LMCs without investigation.

The mediating effects of psychosocial and cultural variables on the impact of breast cancer inter-
Interventions in LMC populations are understudied. Personal representations of illness that guide health behavior vary across cultures. These representations underlie and influence women’s response to prevention and screening campaigns, as well as the likelihood of initiating and complying with treatment and follow-up. A cultural variable of immediate impact is the restriction on public travel for women in many societies, limiting their access to diagnostic and treatment facilities.

Health systems are notably complex, and strategies that are effective and efficient in high-income countries may be inappropriate for countries with lower breast cancer incidence, fewer resources, and competing demands from high-incidence health problems such as communicable diseases. Only recently have there been models to address the “affordability gap” in pharmaceuticals for LMCs. Cause-specific mortality data against which to measure breast cancer interventions will also not be available in the foreseeable future in many countries for lack of a registry infrastructure. Population-level mortality data on breast cancer provide an essential yardstick for evaluating the success of an intervention.

Application of Available Current Breast Cancer Control Strategies in LMCs

In high-income countries, a combination of screening or case finding and disease management based on clinical trial data has contributed to recent decreases in breast cancer mortality. Even if assumed safe and effective, current recommended systemic treatment strategies are, for the most part, not cost effective in LMCs. When the World Health Organization (WHO) commission standard is used for calculations, the incremental cost to save a year of life should be less than the annual per capita income of a country. In operable breast cancer, primary surgery plus either adjuvant hormonal therapy with surgical oophorectomy and/or tamoxifen is cost effective in LMCs.

LMC policy makers often focus more on cost effectiveness of health interventions than USA analysts do. However, in the absence of relevant data on efficacy and toxicity, practicing physicians who diagnose and manage breast cancer in LMC countries use strategies that were developed for high-income nations. As an IARC publication has noted, there is enormous pressure to use expensive patented drugs.

There are few well-developed national or international clinical trials involving LMCs that address the shortfall in efficacy and toxicity data referred to earlier. The most important and best established international cancer efforts (The Framework Convention on Tobacco and Health and the Global Alliance for Vaccines and Immunization [GAVI]) do not target breast cancer risk factors. In low-incidence countries, there have generally been few public health efforts in education, screening, and palliative care. Available randomized clinical trial data from 3 LMCs do not support the (often implied) assumption that educational and systematic “downstaging” efforts would contribute to decreased mortality from breast cancer in developing countries. Nearly two-thirds of screen-positive women in a Philippine trial were reluctant to seek a biopsy, attributed by the authors to a belief that effective treatment did not exist, or it was unavailable. This observation and these data mean only that there is absence of proof for the benefit of downstaging efforts in LMCs and not that there is proof for the absence of benefit.

A Global Research Agenda for Breast Cancer

In summary, the burden of breast cancer cases is increasingly shifting to low-incidence LMCs. When the WHO commission’s standard is applied, most currently applied strategies in high-income countries are not cost effective in LMCs. The foregoing discussions have emphasized that there are only limited data, biological, clinical, cultural, or health system, that evaluate any interventions in LMCs. The less-than-optimal history of general economic development efforts in the last 50 years strongly suggests that any proposed intervention be the subject of rigorous research and formative evaluations.

Any effort should take into account a local country’s healthcare and other priorities and seek sustainable goals, investigating public health approaches that are potentially cost effective and culturally relevant. Horizontal integration with existing healthcare systems is necessary to avoid enhancing breast cancer treatment resources at the expense of other disease-specific initiatives. Such efforts will require not only the development of better data to guide policy but also the establishment of an equitable framework for collaboration with the local organizations that implement these approaches. These efforts must be executed on the basis of agreement on core values and mutual trust.

Expanding the heterogeneity of interests and expertise represented at the table for such research is critical. Social science acumen applied to knowledge of the local culture and its institutions is needed to effectively implement studies. Leveraging existing social structures is not only efficient, but it also facilitates a sustainable research program by integrating public health initiatives into ongoing local development. As an example, a clinical trial in Bangladesh,
which is being conducted by the author and will be evaluated in trials randomized by village, is partnering with a social-development performance-art organization to create a culturally appropriate presentation on serious breast problems and their successful management.

As has been increasingly recognized in high-income countries, social science contributions to the design of biological and clinical studies will also be necessary. Psychosocial insight should inform the process of clinical research in areas such as the identification of educational messages, compliance instructions, and evaluation efforts that reach women and alter their behavior.23 An agenda for clinical and biological studies should address the following priorities.

- Downstaging by clinical breast examination
- Performing pharmacogenomic studies of systemic adjuvant therapy to establish and increase efficacy and safety of "standard" hormonal therapies in different populations.
- Performing pharmacogenomic studies to establish and increase efficacy of generic drug-systemic therapy approaches in hormone receptor-negative breast cancer
- Developing a model for closing the affordability gap for new systemic targeted therapies

With respect to the parameters to be investigated in downstaging trials, as noted earlier, an IARC working group has concluded that there is inadequate evidence that breast self-examination or clinical screening examinations reduce breast cancer mortality.34 Responding to the working group's recommendation, a randomized trial of clinical breast examination combined with breast self-examination, conducted in circumstances with few or no resources for mammographic screening, has been proposed.39 For an early indicator of downsizing benefits, cumulative incidence of stage III and stage IV diseases should be evaluated.

The most prevalent practical problem in managing breast cancer in LMCs is poor or no ability to measure tumor hormone-receptor status. Increasingly, it is being recognized that hormone receptor-positive cancer is a chronic disease, the optimal control of which depends upon use of specific hormonal therapy strategies.39 In these circumstances, in which the large majority of women in LMCs affected by breast cancer are premenopausal, surgical oophrectomy is a remarkably effective and cost-effective intervention.17,39 Optimal ways of using this therapy, however, remain to be defined. For all women with hormone receptor-positive breast cancer, as noted earlier, defining appropriate use of tamoxifen requires pharmacogenomic studies.19 In patients with hormone receptor-negative tumors, the previously mentioned issues of therapeutic thresholds and pharmacogenomic differences must be investigated if effective therapies are to be established for specific populations.

The universally high cost of cancer drugs prevents treatment of large portions of all populations. The development of alternative business models to bring the price of such drugs within reach of LMCs, such as those used with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) treatments,27 should be pursued. However, these efforts should be directed to treatment protocols validated in rigorous studies demonstrating efficacy and providing toxicity data specific to different LMC populations.

Inadequate and dysfunctional health systems present another research concern. Treatment and screening cannot be rigorously evaluated when health facilities and providers are lacking or limited. This is perhaps 1 lesson from the Filipino breast cancer downstaging study.33 One strategy is to piggyback ad hoc health system activities onto established development activities. Again, in Bangladesh, the author has created walk-in breast-problem clinics in rural computer schools as a way of reaching “captured” women, some of whom can then be treated in the ongoing clinical research effort. This model of pairing markedly different developmental activities has been successfully adopted in other settings.41 Information technologies (IT), using computers and/or cell phones, also hold significant potential to compensate for inadequate infrastructure. Last, regional registries may provide adequate sampling in the absence of resources for national systems.24

The long view provides a compelling case for international epidemiologic causation research with its potential for discovering "natural" public health prevention strategies, given the wide disease incidence range seen among countries.7,41 Here, again, the emphasis must be on thorough evaluation in the context of the target population. For example, prolonged lactation appears associated with reduced risk of premenopausal breast cancer, but one may question the appropriateness of encouraging this practice as a public health intervention in a population where the majority of women are malnourished or undernourished, such as in Bangladesh.

Finally, the evaluation of public health initiatives is an ongoing process. The implementation of any first-generation study reveals issues that can be addressed in further efforts. Epidemiological and
clinical advances, as well as changes in the socioeconomic context of care, will also alter goals and priorities as they redefine best-practice and cost-efficacy analyses.37

Organizational and Structural Support for Global Breast Cancer Research

The constituencies interested in global public health issues have been fleeting (as with communicable disease crises like severe acute respiratory syndrome [SARS]) or diffuse and limited (as with breast cancer). For example, the Global Forum for Health Research has focused very little on malignancies. The low incidence of breast cancer in LMCs, not irrationally, condemns this disease to less attention. Current circumstances do not support a sustainable international public health umbrella organization for breast cancer. In its absence, the interests and efforts of developed nations to drive such an agenda are critical. Partnerships with existing research, interest, and investigator groups in LMC countries offer the best opportunities for studies likely to benefit women in all countries.35,42,43 We must build from the strengths of USA and international clinical oncology cooperative groups, and organizations like the International Atomic Energy Agency and its Programme of Action for Cancer Therapy (PACT), as well as the International Cancer Treatment and Research (INCTR) group. Specific startup funds set aside by the private sector to initiate locally appropriate planning activities in LMCs are critical to this effort. However, this must not be a top-down process. Successful collaborations will be based on mutual benefit, shared decisions, and local ownership and management of programs.37 Such equitable research partnerships hold promise for creating the informational groundwork for more successful and sustainable breast cancer treatment worldwide.

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