

Challenges and opportunities in the design and implementation of breast cancer clinical trials in developing countries

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Breast cancer is an increasingly recognized public health concern in developing countries. The clinical spectrum is heterogeneous but largely characterized at presentation by a more advanced stage, the presence of various adverse factors and low rate of survival. The quantum of ongoing clinical trials in breast cancer is low and inadequate to address the needs of these populations. There are several design challenges in setting up breast cancer trials in the developing world, the most notable being the acquisition of informed consent, inducement and/or coercion of participants, adequacy of control arms in randomized trials, tropical infections and ethnic variations in drug metabolism. The main implementation challenges include scarcity of infrastructure and skilled human resources, variable delivery of standard breast cancer care, inadequate breast cancer pathology standards and deficient regulatory framework in many regions. There are several opportunities for conducting clinical trials that include a large number of less-heavily treated, advanced-stage patients and lower cost. There is a trend towards an increasing number of clinical trials in these regions that is likely to be sustained in the future.

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Recent reports have highlighted the increasing incidence of breast cancer in developing countries. These countries currently face the challenge of controlling a disease previously considered uncommon. Compounding this challenge is the paucity of data on incidence, risk factors, patterns of care and outcome of breast cancer from these regions. Nevertheless, the trends in incidence and mortality are convincing enough to warrant further concern and action. The emerging dimension in this story is the globalization of clinical cancer research, including breast cancer research, in the past decade, leading to a ‘booming’ clinical trial industry in some parts of the developing world [1]. The reasons behind this so-called ‘outsourcing’ are multifactorial and include reduced costs of research, availability of trained personnel and infrastructure and, perhaps most importantly, large treatment-naïve or less-heavily treated patient populations.

This review examines the challenges in the design and implementation of breast cancer clinical trials in developing countries and briefly mentions some of the opportunities for research in these regions.

Epidemiology & clinical spectrum of breast cancer in developing countries

Although the incidence of breast cancer varies widely throughout the world, the majority of developing countries have lower incidence compared with developed

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countries. The reported incidence of breast cancer in developed countries is 66.4 per 100,000, whereas it is only 27.3 per 100,000 in developing countries [2]. Despite the lower incidence, the total burden of breast cancer is almost equal in the developing and developed world, with an estimated 692,000 and 691,000 new cases annually, respectively [2]. The disparity between incidence and burden is attributable mainly to a large and rapidly growing population in developing countries. Breast cancer incidence in many countries such as China and India has shown an increasing trend in the past two decades. African countries also report a doubling in the last 10 years but this could be due to changes in disease tracking and reporting [3]. There are considerable variations in breast cancer incidence between developing countries [4]. For example, the age-standardized incidence rates (ASR) per 100,000 population are 18.8, 42.5, 80.8, 35.3 and 26.9 in Algeria (Setif), Egypt (Gharbiah), Brazil (Sao Paulo), China (Shanghai) and India (Mumbai), respectively [4]. These are much lower than the incidence in North America and Europe, where the ASR are generally in the range of 60–100 per 100,000. The increasing incidence of breast cancer has been particularly noted in the urban regions of developing countries; for example, data from the Mumbai Cancer Registry reveal an average annual percentage change in breast cancer incidence of +1.1% per year since 1975 [5]. The underlying reasons for this increase include changes in reproductive patterns and ‘westernization’ of lifestyles in urban areas, and is an area of active research by many epidemiological groups.

In contrast to incidence, the mortality due to breast cancer in developing countries shows a much lower differential with the developed world, being 10.8 versus 15.3 per 100,000 of the population, respectively, indicating a higher case:fatality ratio [2]. The most important contributing factors to this concerning statistic are advanced stage at presentation, deficiencies in healthcare delivery in developing countries and, to some extent, overdiagnosis due to widespread population screening in developed countries [6]. Data from several hospital-based Indian cancer registries show that the fraction of patients presenting with regional disease or distant metastasis is greater than that seen in the Surveillance, Epidemiology and End Results database in the USA [101–103]. Data from other developing countries confirm this observation [7,8]. There are wide variations within developing countries with respect to breast cancer healthcare delivery and the survival rates reflect this disparity [9]. For example, China, Singapore, South Korea and Turkey showed 5-year age-standardized relative survivals of

76–82% in breast cancer compared with 52% in India and 46% in Uganda [9].

In a recently reported systematic analysis of breast cancer over a 30-year period, it was found that 23% of women with breast cancer were between 15 and 49 years of age in the developing countries, compared with 10% in the developed countries [10]. An analysis of breast cancer patients presenting to a large tertiary-care center in India in one calendar year revealed that 8.1% of breast cancer patients were younger than 35 years of age compared with 1.9% in the Surveillance, Epidemiology and End Results database [11]. The median age at diagnosis is between 45–50 years in most series of breast cancer patients in developing countries, which is approximately 10–15 years less than that seen in developed countries [12]. Although the age-specific incidence of breast cancer is low in young women in developing countries compared with their older counterparts [101,102], the younger age of patients at presentation is likely due to a higher proportion of young people in the population of developing countries (a base-heavy population pyramid). However, the contribution of other biological factors cannot be entirely ruled out. Whatever the reasons, the considerable proportion of young patients has social, economic, healthcare delivery and research implications in developing countries. The prognostic implications of younger age at diagnosis are controversial, with some studies suggesting an adverse impact [13], whereas population-based survival data do not support this assessment.

Breast cancer patients from developing countries also display a number of other adverse factors such as higher grade, lower levels of hormone receptor expression and the higher fraction of patients with triple-negative phenotype [11,14–17]. For example, in the above mentioned report, 77.9% of patients had grade III tumors, approximately 50% of patients had expression of estrogen and/or progesterone receptors in their tumors and approximately 30% had triple negative disease [11]. There are several implications for the design and conduct of clinical trials in developing countries as a direct consequence of this clinical spectrum.

Ongoing breast cancer research in developing countries

The number of industry-sponsored breast cancer clinical trials being conducted in developing countries has shown an increasing trend in recent years. Nevertheless, only a small fraction of breast cancer clinical trials are conducted in the developing world [18]. Data gathered from the Clinicaltrials.gov database reveal that of 3902 breast cancer

studies being conducted worldwide, only 64 (1.6%) are being conducted in India, 279 (7.2%) in China, Korea and Taiwan and 131 (3.4%) in the Middle East, in contrast to 2342 (60.0%) in the USA [104]. In the next 5 years, India is projected to conduct merely 5% of all global clinical trials. The situation is more imbalanced with respect to Phase I studies – data from the Clinicaltrials.gov database reveal 40 studies in China and India compared with 729 in the USA and Europe [105]. Thus, early drug development is virtually negligible in the developing world. The number of breast cancer publications from developing countries is similarly low. For example, a search of the PubMed database limited by clinical trials showed that there were 72 breast cancer publications from India, 195 from China and 3671 from the USA [106]. The small number of publications results in an inadequate baseline in pathology, patterns of care and outcomes in developing countries. This presents several design challenges in breast cancer trials, including difficulties in sample size calculation due to widely varying projections of outcome in the control arms. Studies utilizing comparisons with historical controls are also fraught with significant uncertainty. Thus there are several important barriers for sponsors, funding agencies and investigators to overcome before they can consider conducting breast cancer clinical trials in developing countries.

Challenges in the design of breast cancer clinical trials in developing countries

It is abundantly clear that the clinical spectrum, patterns of care and outcome of breast cancer is different in the developing world. Therefore, while designing breast cancer clinical trials, the ‘one-type-fits-all’ approach may not be prudent. The discussion in this section will highlight a few factors that argue for differential designing of breast cancer clinical trials in developing countries. They are discussed in order of perceived importance and some are applicable not only to breast cancer but also to other malignancies.

■ Informed consent

The informed consent documents of industry-sponsored multinational trials are detailed and accurate but often contextually inappropriate for developing countries. Translation into local languages often fails to adequately convey the essence of the study to ordinary subjects in these locations. Institutional review board oversight of the informed consenting process is also variable and often inadequate. An analysis of 300 informed consent documents submitted for ethical review at a large tertiary care center in India revealed excellent coverage of benefits, risks,

confidentiality and withdrawal of consent, but other aspects such as alternatives to trial participation and compensation for injury were inadequately covered [19]. Another survey of trial participants in a large tertiary care center in India revealed that an overwhelming number of subjects participated in clinical trials on the advice of a physician [GOGTAY N ET AL. PERS. COMM.]. This is a common theme observed in routine care and research settings in developing countries – healthcare decisions have less participation from patients compared with current developed-world norms. This probably reflects some of the cultural differences between these regions. The developed world’s emphasis on individual autonomy underlies the modern practice of informed consent in clinical trials, which is sometimes at variance with the paternalistic/beneficence model of physician–patient relationship that is still prevalent to varying extents in many developing countries. The patients’ ability to comprehend and assimilate complicated trial designs is also questionable.

■ Ethical challenges

There are several ethical challenges in the conduct of breast cancer trials in developing countries. One of the important ones is the provision of standard component of healthcare in a clinical trial, including the control treatment in randomized trials, free of cost to subjects. This is often necessary to ensure adequate accrual because many otherwise eligible subjects would not be able to participate for economic reasons. The very low penetrance of public and private health insurance in developing countries is one of the important reasons for patients’ inability to afford many standard treatments for breast cancer, such as taxanes, growth factors, trastuzumab and so on. This, however, raises concerns about inducement to participate in such ‘paid-for’ clinical trials. There could also be an element of coercion of potential trial subjects under such circumstances that has to be specially guarded against. The informed consent process has to be particularly strong in such situations to avoid potential exploitation of vulnerable subjects. A related ethical challenge is in ensuring adequate control and intervention arms in trials [20–23]. A recently presented randomized trial conducted exclusively in the Asian region compared paclitaxel plus placebo with paclitaxel plus lapatinib in patients with metastatic HER2-positive breast cancer as first-line treatment and proved a significantly superior outcome in the lapatinib arm [24]. The control arm of this trial would have been an unacceptable standard in most developed countries but was the locally practiced standard in this patient population. Another ethical concern is that of equitable access to medications

that have been proven efficacious in clinical trials in developing countries to women in the same regions [25]. This is particularly true of the highly expensive targeted therapies that, for economic reasons, are only accessible to a small fraction of the population in developing countries [11].

■ Subject eligibility

There are several challenges and barriers in ensuring fulfilment of eligibility criteria in breast cancer studies. The most important one in the context of breast cancer trials is the one that requires exposure to an expensive prior treatment as an inclusion criterion. For example, most trials in metastatic HER2-positive breast cancer would currently require receipt of standard HER2-targeted therapy earlier in the disease course, which may not be true of most subjects in developing countries. One strategy to circumvent this problem is to allow stratified inclusion (by prior therapy) in such clinical trials [26]. Nevertheless many breast cancer trials are probably not implemented in developing countries for this reason.

Another challenge is ensuring appropriate performance status (most often measured by the Eastern Cooperative Oncology Group or Karnofsky scales) and estimated life expectancy, especially in trials in metastatic disease. Patients with metastatic breast cancer in developing countries have higher disease burden and more multivisceral involvement that may lead to a poorer performance status. The prevalent protein and calorie undernutrition in developing countries may further impact on the performance status. In one large study from India, undernutrition was associated with poor performance status with an odds ratio of 17.78 [27]. One way to ensure adherence to performance status criteria in developing countries is to require explicit description of patient's general condition using standard questionnaires rather than broad determination of the performance status grades by the investigators.

■ Challenges due to ethnic variations

Several interethnic differences can impact the responsiveness of developing country patients to approved and investigational cancer drugs. These include environmental influences on drug metabolism (e.g., smoking, alcohol and herbal medicine use), variations in drug targets (e.g., the higher incidence of activating mutations of EGFR receptor in lung cancer patients from Asia) and genetic polymorphisms in drug related genes [28–30]. As an example of the latter, an Asian study revealed a variant of the enzyme CBR3 (11G>A) that was more common in Chinese compared with Caucasian patients (57 vs 36%)

and resulted in lower conversion of doxorubicin to doxorubicinol, greater hematological toxicity and higher response rate to single agent doxorubicin [31]. Undernourishment can also potentially affect drug disposition. As drug doses are usually derived from early-phase studies conducted in better nourished individuals in developed countries, there are lingering questions about the applicability to developing country populations [32]. Nutritional anemia, especially that due to iron deficiency, is also widespread among women in developing countries, with caveats similar to energy undernutrition.

■ Infections

Infections are more common and somewhat distinct in the developing world. There is a higher frequency of tropical infections, such as malaria and tuberculosis, in trial subjects. A recently reported Phase II trial of sorafenib in metastatic breast cancer was characterized by an unusually high incidence of tropical infections in patients enrolled from India [33]. The toxicity signals for new drugs could therefore be considerably impacted due to such unusual infections. Tropical infections should always be considered, while designing and interpreting trials that include patients from developing countries.

■ Other design issues

Another concern is potential contamination of the control arm due to over the counter availability of the experimental intervention, especially drugs that have long been in use for other indications. A currently proposed multinational collaborative project on the utility of aspirin as an adjuvant treatment in breast cancer is grappling with this concern. Multiple biopsy biomarker studies using fresh, frozen tissue are often built into breast cancer trials today and pose a challenge with regards to storage of the frozen tissue and maintenance of a cold chain. Transnational transfer of biological specimens requires special regulatory permissions, which differ from country to country and can be particularly challenging in some locations [107].

Challenges in the implementation of breast cancer clinical trials in developing countries

Health is a low priority in developing countries and this is even more the case with noncommunicable diseases. The national expenditures on health in developing countries, as a fraction of their gross domestic product, are much lower than many developed countries [107]. Therefore, fewer resources are available for clinical and translational research. The lack of funding mechanisms for investigator

initiated clinical trials in these countries makes it extremely difficult for both individual investigators and collaborative groups to mount credible and relevant clinical trials.

There are several logistical concerns in trial implementation in these regions. Although industry-sponsored clinical trials usually have adequate provisions for monitoring drug storage, drug accountability and patient compliance using standardized logs, the same may not be true of all investigator-initiated studies in developing countries. This could potentially impact both the efficacy and toxicity outcomes in patients recruited in these regions. Developing countries are also deficient in infrastructure and human resources. For example, in many parts of the developing world, one radiation center serves a population of 1–4.9 million people, which is much higher than the average in developed countries [2]. In many parts of Africa radiation centers are nonexistent. The number of practicing oncologists is lower – per capita and in absolute numbers – in developing countries. Therefore, oncologists who can act as investigators are relatively small in number and those available are often overworked. Data show that India and other developing countries have fewer qualified oncologists per million of the population compared with many developed countries [108]. Other components of the clinical research infrastructure, such as research assistants, pharmacists, nurses, pharmacies, office space, hospital beds and so forth, are also often deficient in many centers in developing countries.

Inadequate pathological evaluation of breast tumors has been a continuing reality in most developing countries. There exists a lack of standardization in preanalytical variables, including tissue handling and preservation, analytical variables, reporting and monitoring/quality control [34]. While a detailed discussion of the deficiencies in breast pathology in developing countries is beyond the scope of this review, a few salient points merit brief mention. Preanalytical variables are the most susceptible to lack of standardization [35]. Breast lumps are often excised by general surgeons in nonspecialist, noninstitutional settings that are often physically remote from the testing laboratory. There is often disregard for, or lack of knowledge of, cold-ischemia time and the duration and adequacy of fixation for antigen processing. The fixative used is often different (e.g., formal saline) from the recommended neutral buffered formalin. The number of sections obtained from the tumor tissue is often inadequate. There are several analytical variables that are also prone to nonstandardized performance in developing

countries. The most important ones include lack of inclusion of, or comparison with, appropriate internal and external controls. Postanalytically there is a lack of standardization in interpretation and reporting of results. For example, currently in developed countries the fraction of cells and intensity of staining for ER and PR expression need to be reported, which is often not the case in pathology reports from developing countries. Similarly there is nonstandardized interpretation and reporting of other tumor- and lymph node-related variables such as margins, grade and so forth. There are additional impediments in HER-2 testing such as use of nonstandardized antibodies and lack of fluorescent *in situ* hybridization testing for equivocal expression. Moreover, internal and external quality assurance programs are often inadequate. The experience at a large tertiary care center in India, where ER expression increased with conscious attention to preanalytical variables, is instructive [36]. These considerations affect vital aspects of any clinical trial, such as inclusion and analysis based on grade, receptor status and so on. Moreover, central pathology review prior to study inclusion is difficult in many developing countries because of the wide geographic spread and resulting long turnaround times.

The routine management of breast cancer, including surgery, radiation and systemic therapy, needs further refinement and improvement [8]. This is demonstrated by the higher case:fatality ratio in developing countries [37]. There is perhaps less appreciation of the need to deliver evidence-based breast cancer care in a multidisciplinary setting [38]. Most clinical guidelines for breast cancer have been formulated in developed countries and their applicability to the developing world context is sometimes questionable. Compliance to these guidelines is often neither monitored nor reported. The variability in routine care of breast cancer patients makes it particularly challenging to interpret the results of clinical trials conducted in therapeutically disparate settings. While stratification by enrolling center is one strategy to mitigate this challenge, it is not a perfect solution.

A particular challenge in the implementation of breast cancer trials in many developing countries is the singular lack of cooperative research group culture [39]. This creates difficulties for investigators in formulating patient registries and collaborative therapeutic trials and makes accrual in studies slower than usual. These challenges are particularly germane to investigator studies since industry-sponsored trials are able to overcome some of these hurdles by hiring the services of CROs.

There are significant constraints in establishing long-term follow-up of patients in clinical trials in developing countries. The huge geographic spread in some of these countries, absence of national registration processes with unique citizen identification and the lack of linked death registries contribute to the difficulty of following up patients. Thus, early-stage breast cancer trials – for example those testing adjuvant therapies that require many years of follow-up – are particularly challenging to implement. Another important challenge in trial implementation is the regulatory process in developing countries, which is sometimes laborious, lengthy and inefficient. Moreover, there is often a lack of expertise in conducting exhaustive scientific and ethical reviews of complicated clinical trials. The quality of institutional review boards and ethics committees is variable. This can sometimes lead to protracted and tangential reviews with the important issues being obscured [40,41]. There is a recent trend towards self-assessment and accreditation by the review boards, which is likely to lead to improvement in the quality of their output [42]. There is also considerable variability in the guidelines and rules regarding compensation for trial-related injury. A recent draft from India that is under active consideration of the apex research regulator, has created considerable controversy by making suggestions such as compensation for any injury in a clinical trial, regardless of relatedness to the research intervention and including injuries caused by the standard of care component of the trial [109].

Opportunities for clinical research in breast cancer in the developing world

Alongside the challenges are several unique opportunities for breast cancer clinical trials in developing countries. There are large numbers of breast cancer patients, the tumors are almost entirely clinically apparent ones in contrast to a considerable fraction of screen-detected cancers in developed countries [43] and there is a higher proportion of young patients with large tumors exhibiting triple-negative phenotypes. Patients with metastatic disease are less-heavily treated than in the developed world. The preceding pattern is ideally suited to the conduct of rapidly accruing neoadjuvant ‘proof-of-concept’ and ‘window-of-opportunity’ breast cancer trials using innovative drugs and strategies. There is also considerable scope for conducting trials of drugs that have long been in usage for nonmalignant conditions but whose anticancer properties have recently gained prominence. Aspirin, metformin and propranolol are the most prominent examples of the latter strategy, which is likely to be feasible and lead to

cost-effective improvements in breast cancer outcomes. The recently reported preoperative progesterone trial [44] and the ongoing cluster-randomized screening by clinical breast examination [45], are examples of innovative and locally relevant strategies for breast cancer research in developing countries.

The proliferation of industry-sponsored trials in many developing countries has helped create a pool of researchers and other staff who are well versed in the modern philosophy of clinical research, including ethical implications. Thus these locations are likely to afford considerable benefits in terms of reduction in the cost of clinical research, while maintaining high quality of output. However, there is a lack of basic and translational research capacity in many centers in these locations, which needs rectification.

Prioritization & requirements for conducting breast cancer clinical trials in developing countries

It is evident from the preceding discussion that there is considerable heterogeneity between and within developing countries with respect to the incidence and survival of breast cancer and the available infrastructure and expertise for carrying out clinical trials. From an overall perspective, it would be useful to consider a framework for prioritization of breast cancer clinical trials in developing countries.

■ Research question

It is of paramount importance that the research question(s) are relevant to the local context when a clinical trial is planned in a developing country institution. The most relevant themes include cost-effective treatments for locally advanced or large operable breast cancer, feasible modifications in surgical and radiation techniques that may result in superior or equivalent outcomes (e.g., hypofractionated schedules of radiation), optimization of available imaging and diagnostic resources, establishment of tumor registries as part of clinical trials with documentation of long-term outcome and studies aimed at improvement of healthcare delivery to a larger fraction of patients. As a corollary, there are other themes that would be less relevant to many developing country institutions. These, for example, would include studies in screen-detected small tumors and those involving resource-intensive inputs, such as radiotracer-guided sentinel lymph node mapping, accelerated partial breast irradiation using sophisticated equipment and so forth.

■ Regulatory & ethical oversight

It would be critical to ensure adequate regulatory mechanisms for evaluation of trial protocols from the local perspective before implementation in developing

countries. The importance of ensuring credible informed consent has been emphasized above.

■ Adequacy of infrastructure & logistics

Before initiation of clinical trials, institutions and centers in developing countries need to be evaluated for adequacy of trained research staff who are versed in the principles of GCP, storage of trial medications, maintenance of trial records and source documents, delivery of a reasonable level of standard breast cancer care to non-trial patients, safety reporting standards and so on. Many of these functions are undertaken by CRO in industry-sponsored trials. However, investigator and collaborative institutional trials need to pay particular attention to these aspects. As detailed above, a vital aspect of modern clinical trials in breast cancer is the accuracy and detail in pathology

reporting. Multicenter or multinational breast cancer trials should try to ensure centralized pathology assessment of all tumor samples or at least a quality check of a subset.

■ Capacity building

It is important for institutions and groups in developed countries to engage with their counterparts in developing countries with the aim of helping the latter to create research capacity. In this context, translational studies involving imaging, pathology, gene-expression profiling, sequencing, bioinformatics, circulating tumor cells and so on, are likely to be useful for at least a few centers in the developing world. An obvious corollary is that developing countries should not be viewed only as recruiting centers for multinational trials in breast

Executive summary

Epidemiology & clinical spectrum of breast cancer in developing countries

- The incidence of breast cancer is low in developing countries, but the case:fatality ratio is higher and relative 5-year survival is lower compared with developed countries.
- The proportion of younger age patients is higher in developing countries, reflecting their population structures.
- Breast cancer cases in developing countries present with more advanced stage disease with more adverse features such as high-grade and hormone receptor-negative phenotype.

Ongoing breast cancer research in developing countries

- The number and proportion of worldwide breast cancer clinical trials ongoing in developing countries is low.
- The number of breast cancer publications from developing countries is low.
- There is an increasing trend in the number of ongoing pharmaceutical industry-sponsored breast cancer trials in developing countries.

Challenges in the design of breast cancer clinical trials in developing countries

- Informed consent is one of the most important challenges.
- Significant ethical concerns include inducement and/or coercion, adequacy of control arms of randomized trials and equitable postmarketing access of developing country populations to new drugs.
- Subject eligibility criteria, interethnic pharmacogenomic and environmental variations, tropical infections and control-arm contamination are other important concerns.

Challenges in the implementation of breast cancer clinical trials in developing countries

- Logistical challenges include drug transportation and storage, maintenance of cold chains and drug accountability.
- Adequately skilled and trained human resources for clinical research are scarce.
- Pathology standards for breast cancer are not standardized and are therefore widely variable.
- Delivery of routine breast cancer care is variable in quality and compliance to standard guidelines is varied.
- There are difficulties in establishing long-term follow-up of patients.
- The available regulatory framework for clinical research on human subjects is variable.

Opportunities for clinical research in breast cancer in developing countries

- The large numbers of breast cancer patients with less-heavily treated disease is an opportunity.
- Trials using the neoadjuvant approach are particularly applicable to these regions.
- The cost of conducting clinical trials is lower.

Prioritization & requirements for conducting breast cancer clinical trials in developing countries

- Trials with locally relevant themes such as cost-effective and feasible treatment strategies should be research priorities.
- Ensuring minimum standards in several domains in the participating institutions is important before embarking on clinical trials.
- Clinical and translational research collaboration between centers in developed and developing countries is important for building capacity.

Future perspective

- An increasing number of breast cancer trials are likely to be conducted in developing countries in the near future.
- Breast cancer research is likely to be an important priority in these regions.

cancer.

Conclusion

Breast cancer in developing countries has a number of epidemiological and clinical differences from that seen in developed countries. The patients are younger with tumors of a more advanced stage at presentation and may have a more aggressive phenotype. There are several challenges in the design and implementation of breast cancer clinical trials in developing countries that include (but are not limited to) informed consenting and other ethical issues, subject eligibility, pharmacoethnic issues, infections, establishment of biorepositories, inadequate infrastructure and human resources,

variable quality of pathology reporting, uneven adherence to standard management guidelines, difficulty in establishing long-term follow-up of patients, lack of organized research groups and a variety of regulatory issues. Despite the challenges, there are unique opportunities for therapeutic research in these countries, primarily in patients with locally advanced and metastatic diseases. Improvement in breast cancer care in these countries requires the conduct of reliable and reproducible clinical trials because the results of trials conducted in developed countries may not always be directly applicable.

Future perspective

The next few years are likely to witness an increase in breast cancer clinical trials in developing countries as a result of international collaborations. The near-term incentives for this trend are likely to be rapid accrual and reduction in research costs. However, an increasing number of centers in these regions will acquire capacity for high-quality, locally relevant research, resulting in their incremental influence in setting the research agenda. The increasing incidence and burden of breast cancer in urban areas of developing countries will result in this being one of the important research priorities. Considerable heterogeneity and inequity in breast cancer care and research, both within and between developing countries, is likely to persist for some time to come.

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