



SIRO Clinpharm



CONDUCTING
BREAST CANCER STUDIES
IN INDIA



Incidence and distribution of breast cancer in India

India is a country with wide ethnic, cultural, religious, economic diversities and variations in the health care infrastructure. The health care facility pattern is heterogeneous, with numerous regions where the benefits of breast cancer awareness, early diagnosis and multidisciplinary treatment programs have not yet reached¹.

Global breast cancer incidence increased from 641,000 (95% confidence intervals 610,000—750,000) cases in 1980 to 1,643,000 (1,421,000—1,782,000) cases in 2010, an annual rate of increase of 3.1%². For women aged 15—49 years, twice as many breast cancer cases were recorded in developing countries than in developed countries. This variation in incidence may be due to multiple factors, including geographic variation, racial/ethnic background, genetic variation, lifestyle, environmental factors, socioeconomic status, the presence of known risk factors, utilization of screening mammography, stage of disease at diagnosis and the availability of appropriate care³.

The health care burden related to breast cancer in India has been steadily mounting. Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India^{5, 6}. As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta and Trivandrum where it constitutes > 30% of all cancers in females⁸. In the rural areas, breast cancer is the second most common cancer in women after cervical cancer⁸. The age standardized incidence rates (AARs) range from 6.2 to 39.5 per 100,000 Indian women. The AARs vary from region, ethnicity, religion, with the highest incidence reported at 48.3 per 100,000 women in the Parsi community of Mumbai⁸.

Disease pattern and presentation of breast cancer in India differs from the West in the following ways:

1. While the majority of breast cancer patients in western countries are postmenopausal and in their 60s and 70s, the picture is quite different in India with pre-menopausal patients constituting about 50% of all patients².
2. The average age of breast cancer patients, at presentation, has been reported to be 50–53 years in various population-based studies conducted in different parts of the country⁷ while a significant proportion of Indian breast cancer patients are younger than 35 years of age.
3. Majority of patients present in Stage I: 1–8%; Stage II: 23–58%; Stage III: 29–52%; Stage IV: 6–24%⁽¹⁰⁾



Stage	Patients %			
	Mumbai	Trivandrum	Chennai	Lucknow
I	7.8	4.4	1	4
II	57.4	42.3	23	33
III	28.9	40.5	52	47
IV	5.9	12.8	24	9
Unstaged				7

4. Only about 5% of all patients managed had a family history of breast cancer.
5. Higher rates of breast cancer were observed amongst Christians and Parsis, than in Hindus and Muslims.^{11,12}
6. Pathology: Invasive ductal carcinoma not otherwise specified (IDC NOS) was found to be the most common type (88%) followed by infiltrating lobular carcinoma (3.7%), colloid carcinoma (1.1%), ductal carcinoma in situ (DCIS) (1.1%) and metaplastic types (0.9%).¹³
7. 70% patients were reported as having grade III disease.¹⁴
8. A high proportion of patients were reported to have a high S-phase fraction, aneuploidy and other poor prognostic features on histology.¹⁴
9. The average tumor size has been 5.4 cm¹. The presentation is similar in many other developing countries.¹⁵

The quality of breast cancer treatment is dictated by many factors besides a patient's own outlook and may include where the patient lives, access to a medical institution, how much can she afford to spend on her treatment, whom does she trust etc. Few patients are treated at well-equipped centers in a protocol-based manner, with compromised multimodality therapy, based on factors such as the economics, tolerance, nutritional deprivation etc.² In spite of having world class medical facilities and treatment options, patient access to these facilities remains a challenge. Furthermore, compliance with the treatment is hampered due to the social stigma associated with the disease.



The 5-year overall survival rate has been estimated to be 62%. The 5-year actuarial patient survival has been:

- 90% for stage I
- 78% for stage II
- 57% for stage III
- 22% for stage IV

Westernization of lifestyle has led to an increase in the incidence of breast cancer in India. Thus, the Indian breast cancer patients have higher loco-regional recurrences and poorer overall survival.

Women often discover a breast lump incidentally. Family physicians are approached initially who refer the patient to General Surgeons or Gynecologists. If breast cancer is suspected, they are then referred to Medical Oncologists. Surgical oncologists only treat patients during surgical resection. Regular follow up is performed by both Medical and Surgical Oncologists.

Breast Cancer: Clinical Trials Scenario in India

India is often cited as the ideal destination for clinical trials. A Rabo bank report says that India has the largest pool of patients for many diseases, including cancer and diabetes.

Clinical cancer research has undergone progressive globalization over the past decade. In the year 2002, the percentage of submitted studies conducted exclusively in USA decreased from a high of 80% to a recent level of 24%⁹. Similarly, in June 2010, the ClinicalTrials.gov registry indicated that while the bulk of early stage (phase I and II) clinical trials are conducted in North America, over half of phase III and IV trials are being conducted in other parts of the world.



What has led to this dramatic shift in the location of clinical trials?

(1) DETECTION TECHNIQUES:

MAMMOGRAPHY:

Mammography facilities are present in most private hospitals and private diagnostic centers which are mainly located in the metropolitan centers. Not all Government and Municipal hospitals have mammography services and the imaging may be sub-optimal. Increasingly, mobile mammography vans are being made available in some cities.

PATHOLOGY:

Pre-operative diagnosis is based predominantly on clinical and incisional or excisional biopsy.

In a study from a major North Indian teaching hospital, almost 75% of the patients referred for management of operable early breast cancers (EBC) had had an incisional or excisional biopsy not intended for treatment of breast cancer.

Hereditary susceptibility to breast cancer has led to the identification of several susceptibility genes, including BRCA1, BRCA2, TP53, PTEN/MMAC1 genes. However, there is little data available on the expression of these genetic mutations in Indian patients with breast cancer.

Diagnosis is based on triple assessment which includes: clinical examination, radiological investigation (Mammogram, ultrasound, MRI) and pathological correlation. Needle Biopsy/FNAC is often performed for diagnosis. Hormone receptor status is determined by biopsy and the use of molecular assessment tools.

Molecular techniques like Immunoperoxidase are done for the detection of hormone receptors (estrogen and progesterone receptors) and for HER-2/c-erbB-2 (HER-2) receptors.

From published data, approximately 60 to 70% of Indian breast cancer patients are ER/PR positive, while approximately 10 to 15% are HER-2 positive. Approx. 15% are ER/PR and HER-2 positive. Very few patients (5%) test negative for all three receptor types.

Management Practices:

Typically, breast cancer management follows international guidelines. The National Comprehensive Cancer Network (NCCN) guidelines are widely followed in India for diagnosis and treatment of breast cancer. The use of biological agents is relatively limited.



Awareness and preventive measures in India:

A positive history of breast cancer in close blood relatives is associated with an elevated likelihood of a woman developing breast cancer. There is increasing awareness among Indians about breast cancer in recent times.

(2) Human resources and technical skills

India has an excellent higher education system, which produces a large number of graduates with advanced degrees in the basic sciences, medicine, laboratory technology and information technology. Many of them have been trained in the US and/or Europe and are exposed to ICH guidelines for GCP. India has a large English-speaking technical workforce comprising of 3–4 million scientists and about 500,000 doctors. The presence of highly qualified, English speaking health care and technical professionals supports the case for conducting clinical trials in India.

(3) Cost Efficiency

Typically, a 30–50% cost saving over a similar trial in the US or Europe is seen in India. Investigator and site fees are approximately one-half of those in the United States. Further, costs to the sponsor for providing trial-related medication, investigations, and hospitalization could be as low as 30% of those seen in America. Domestic travel costs for monitoring sites, support services (such as printing and translation) and local courier fees are also less expensive. A 2004 study by Rabo India Finance found that in India, phase I trials cost less than half of similar trials in the United States, while Phase II and III trials cost less than 60% of their American equivalents.²⁰ Since clinical research costs are primarily driven by labor, much of this cost difference is attributable to the lower salaries of physicians, nurses and study coordinators in developing countries.¹⁷

(4) Infrastructure

India's medical infrastructure facilities consist of almost 14,000 hospitals, 700,000 specialty hospital beds and 500,000 medical professionals. 17,000 medical students graduate every year from over 221 medical colleges.

Many specialty oncology centers exist in the major cities which are well equipped with state-of-the-art facilities, including spiral CT scanner, gamma cameras, linear accelerator etc. Ethics Committees have been established in various hospitals to coordinate the ever increasing interest of international and domestic sponsors¹⁸.



CONDUCTING BREAST CANCER STUDIES IN INDIA

The data collected by population based cancer registries and hospital based cancer registries are limited. The registries at New Delhi, Mumbai, Chennai, Bangalore, Bhopal, and Barshi are in the network of Indian Council of Medical Research. Other organizations manage the registries at Ahmedabad, Aurangabad, Nagpur, Pune, Calcutta, and Karungapally (Fig 1).

Fig1. This map of India shows the locations of the cancer registries in India





(5) Health Services

Health services in India are delivered by both private and government institutions. The government institutions consist of 145 medical colleges which are recognized by the Indian Medical Council. Patients have access to free treatment in 104 government institutions across the country. Most of the cases at these hospitals are malignant in nature and are treated by the general surgeons.

Many of the semi-autonomous and autonomous government hospitals have modern infrastructure with highly experienced doctors and are thus able to provide patients with world class treatment at nominal cost. As a result, these hospitals attract large number of patients from across the country.

(6) High patient enrolment rate

India has a huge population base of more than 1 billion people, who are genetically, culturally and socio-economically diverse. It is this diversity which global biopharmaceutical companies wish to leverage to accelerate recruitment in their clinical trials. Patient recruitment and site data taken from the Clinical Trial Registry of India shows that in the years 2009-11, each site was able to recruit an average of 9.7 patients²².

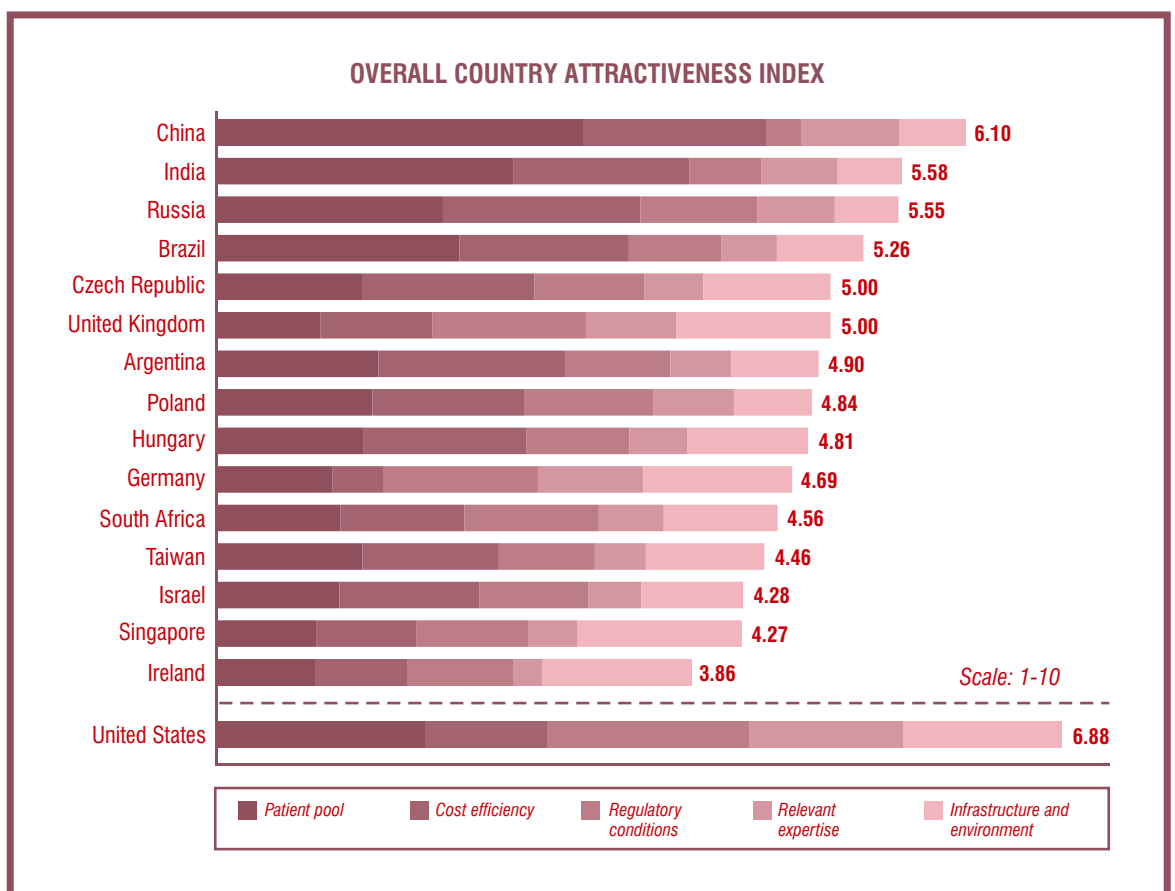
Currently, just over 1% of the population is covered by private insurance leading to out of pocket payments for medical care amounting to 98.4% of total health expenditures by uninsured households²³. Doctors are more open to enrolling their patients in clinical trials, as a means of enabling free access to costly chemotherapy medications and diagnostic tests.



CONDUCTING BREAST CANCER STUDIES IN INDIA

Practical considerations for conduct of breast cancer clinical trials in India:

India's favorable demographics offer a vast opportunity for conducting oncology clinical trials. A recent report from the consulting firm AT Kearney¹⁸ has rated India as one of the most attractive destinations for conducting clinical trials. The report evaluated emerging destinations for clinical trials based on parameters like availability of patient pool, cost efficiency, regulatory environment, available expertise and infrastructure.¹⁸



Numerous publications and reports have spelled out the advantages of shifting clinical trials to emerging locations of Asia with the proverbial “pot of gold” being cost efficiency and faster time to market. However, the cultural diversity and varied regulatory structures of the Asian countries provide significant operational challenges to the uninitiated. Given below are some operational insights for succeeding in Asia.



Operational Feasibility Planning:

"People don't plan to fail; they fail to plan."

- John L. Beckley

Currently, activities related to clinical operations make up 50-60% of the clinical trial timeline¹⁹. Any delay in these timelines due to unforeseen circumstances can result in disastrous financial implications for the clinical development program. Such costly delays can be avoided by including feasibility studies in the clinical trial plan. Studies have shown that clinical trials in which prior feasibility has been conducted face fewer delays and reduced risk of patient enrollment²¹. A thorough evaluation of the scientific and operational 'do-ability' of the clinical study can go a long way in identifying potential impediments well in advance. Detailed study feasibility helps in assessing availability of an appropriate patient population and identification of possible regulatory challenges. Additionally, site feasibility helps in identification of suitable sites with necessary infrastructure, projection of an accurate recruitment rate and investigators with suitable clinical trial experience. Leveraging of data generated from clinical trials conducted in the past further helps in augmenting the clinical trial plan.

Site Selection:

Selection of an adequate number of suitable sites is imperative for the timely completion of patient recruitment. The main attributes for site selection are:

- Qualification of investigators
- Experience in conducting clinical trials in breast cancer
- Availability of adequate support staff
- Adequate pool of patients
- Availability of necessary infrastructure for IP storage & handling
- Capabilities for EDC/RDC
- Availability of suitable diagnostic and therapeutic equipment
- Advantageous geographic location with good connectivity
- Past experience of regulatory inspections



India has several large public hospitals providing world-class oncology care at affordable costs. These hospitals are primarily located in the metro cities and certain Tier-I cities attract large number of patients from all across the country, thereby providing a ready patient population. Strong ethics committees coupled with investigators with relevant clinical trial experience make these sites ideal for conducting breast cancer clinical trials. Furthermore, these sites follow well established GCP guidelines and have robust internal SOPs for conducting clinical trials. In addition to these “model sites” which are present in the metros, there are several other small to medium sites located in Tier-I cities which can be tapped for conducting breast cancer trials.

Patient Recruitment:

It is important to note that having a large pool of patient population does not necessarily translate into fast patient recruitment, without a thorough understanding of the patient recruitment process. Development of a robust patient recruitment plan can go a long way in not only expediting the recruitment process, but may also help in increasing the number of patients per site and identifying potential barriers to recruitment, ahead of time. This can potentially reduce the number of sites required, thereby producing significant cost savings. The following points need to be taken under consideration while designing a patient recruitment plan:

- Lack of awareness about the clinical trial process amongst doctors
- Negative perceptions about clinical research amongst patients
- Presence of a strong doctor-patient relationship
- Multiple languages
- Cultural sensitivities

Statistics show that more than half of all protocols require one or more amendments with Phase II and III protocols having 2.7 and 3.5 amendments respectively²¹. One of the top reasons cited was the difficulty in recruiting patients. Clearly defining target patients, site characteristics, recruitment goals and budgets during the protocol design stage contributes to the development of an effective patient recruitment plan.



Over the past few years, various clinical trials have been conducted in India in breast cancer. Majority of the trials have been conducted in Tyrosine-specific protein kinases receptor inhibitors.

Some of the drugs are as follows:

- Sorafenib, Bevacizumab - Angiogenesis inhibitors
- Lapatinib, Trastuzumab, Neratinib - HER-2 receptor inhibitors
- Afatinib - Epidermal growth factor receptor (EGFR) inhibitor
- Endoxifen - Anti-estrogen
- Non pegylated Doxorubicin (NPLD)
- Certain vaccines such as Stimuvax

Some of these drugs such as Trastuzumab (Roche), Lapatinib (GSK), generic Sorafenib and Bevacizumab are available in India for treatment of breast cancer and other oncology indications.

Conclusion:

Over the past decade India has become an attractive destination for conducting breast cancer clinical trials with its large patient population, experienced investigators and suitably equipped sites. However, there are several challenges for sponsors who are thinking about conducting trials in India for the first time. In such a scenario, partnering with a clinical research organization with an established regional presence and an in-depth understanding of the ground realities of the region would lead to a mitigation of the risks of conducting breast cancer clinical trials in India.



REFERENCES:

- 1) Breast Cancer Care in India: The Current Scenario and the Challenges for the Future. Gaurav Agarwal, Pooja Ramakant Breast Care (Basel) 2008; 3(1): 21–27.
- 2) Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis Mohammad H Forouzanfar MD, Kyle J Foreman MPH, Allyne M Delossantos BS, Prof Rafael Lozano MD, Prof Alan D Lopez PhD, Prof, Dr Christopher J L Murray MD, Mohsen Naghavi MD The Lancet - 15 September 2011.
- 3) The global breast cancer burden: variations in epidemiology and survival. Hortobagyi GN, de la Garza Salazar J, Pritchard K, Amadori D, Haidinger R, Hudis CA, Khaled H, Liu MC, Martin M, Namer M, O'Shaughnessy JA, Shen ZZ, Albain KS; ABREAST Investigators. Clin Breast Cancer. 2005 Dec;6(5):391-401.
- 4) Agarwal G, Pradeep PV, Aggarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. World J Surg. 2007; 31:1031–40.
- 5) Nandakumar A, Anantha N, Venugopal TC, Sankaranarayanan R, Thimmasetty K, Dhar M. Survival in breast cancer: a population-based study in Bangalore, India. Int J Cancer. 1995;60:593–6.[PubMed]
- 6) National Cancer Registry Programme Consolidated report of the population based cancer registries 1990–1996. New Delhi: Indian Council of Medical Research; 2001.
- 7) Sledge GW. Cancer research in the developing world. 41st Annual Meeting of ASCO 2005. Educational book, pp. 698–671
- 8) National Cancer Registry Program Consolidated report of the population based cancer registries 1990–1996. New Delhi: Indian Council of Medical Research; 2001
- 9) Paymaster TC, Gangadharan P. Cancer in Parsi community of Bombay. Int J Cancer.1970;5: 426–31.
- 10) Nair MK, Sankaranarayanan R, Nair KS, Amma NS, Varghese C, Padmakumari G, Cherian T. Overall survival from breast cancer in Kerala, India, in relation to menstrual, reproductive, and clinical factors. Cancer. 1993;71:1791–6.
- 11) Saxena S, Rekhi B, Bansal A, Bagga A, Chintamani, Murthy NS. Clinico-morphological patterns of breast cancer including family history in a New Delhi hospital, India – a cross-sectional study. World J Surg Oncol. 2005;3:67



- 12) Dinshaw KA, Budrukkar AN, Chinoy RF, Sarin R, Badwe R, Hawaldar R, Shrivastava SK. Profile of prognostic factors in 1022 Indian women with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys.* 2005;63:1132–41
- 13) Is Breast Cancer the Same Disease in Asian and Western Countries? Stanley P. L. Leong, Zhen-Zhou Shen, Tse-Jia Liu, Gaurav Agarwal, Tomoo Tajima, Nam-Sun Paik, Kerstin Sandelin, Anna Derossis, Hiram Cody, William D. Foulkes *World J Surg.* 2010 October; 34(10): 2308–2324.
- 14) Desai SB, Moonim MT, Gill AK, Punia RS, Naresh KN, Chinoy RF. Hormone receptor status of breast cancer in India: a study of 798 tumors. *Breast.* 2000;9:267–7
- 15) Navani S, Bhaduri AS. High incidence of oestrogen receptor negative progesterone receptor positive phenotype in Indian breast cancer: fact or fiction? *Indian J Pathol Microbiol.* 2005;48:199–201
- 16) Mittra I. Breast screening: the case for physical examination without mammography. *Lancet.* 1994; 343:342–4.
- 17) Making the most of existing health workers. In: *Working together for health: the World Health Report 2006.* Geneva: World Health Organization, 2006: 66 - 95. (Accessed January 30, 2009, at <http://www.who.int/whr/2006/chapter4/en/index.html>.)
- 18) Bailey W, Cruickshank C, Sharma N. Make your move: taking clinical trials to the best location. AT Kearney
- 19) Parexel R&D Statistical SourceBook 2006/07
- 20) Clinical Trial Recruitment Best Practices and Performance Benchmarks: The Wise Investments Survey. Veritas Medicine. April 2006
- 21) “Most Protocols Require Multiple Amendments”, Tufts Center For Drug Development, September 2011.
- 22) Clinical Trial Registry of India. www.ctri.in
- 23) PwC Healthcare in India – Emerging market report 2007



About the Authors:



Ajit Nair, PhD

President - Global Operations

Ajit Nair is the President of SIRO Clinpharm's Global Operations. He provides leadership, vision and direction to the growth of SIRO's global operations and is focused on creating an efficient and responsive organization to service the growing client pool at SIRO. He looks at strategic issues concerning integration across various operational geographies and global delivery models.



Rajendra Talele

Senior Vice President – Clinical Operations Asia & Europe

Mr. Talele is responsible for overseeing the execution and operational excellence of Clinical Research, including Clinical Project Management, Clinical Monitoring and Clinical Documentation departments. He has over 16 years of experience working with the Pharmaceutical industry and Clinical Research Organizations based out of India.