

Breast Cancer Factsheet

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Introduction

Breast cancer is the most commonly occurring female cancer in the world with an age-standardized incidence rate (ASR) of 39.0 per 100,000, which is more than double that of the second ranked cancer (cervical cancer ASR=15.2 per 100,000(1, 2)). Breast cancer accounts for 23% of all newly occurring cancers in women worldwide and represents 13.7% of all cancer deaths (1). It is the most frequent cancer in both developed and developing regions (estimated 690,000 new cases in each region) as well as the most frequent cause of cancer death in these regions (280,000 deaths in developing countries) of the world (1). Although incidence rates are higher in the West, the disability-adjusted life years (DALY's) show the highest burden for breast cancer in middle-income countries (3,144,000 vs. 1,856,000 in high-income and 1,626,000 in low-income countries), where there are increasing incidence rates and a higher proportion with late stage of disease at diagnosis (3). Male breast cancer is rare compared to female breast cancer, and has a different etiology and epidemiology (4); this fact sheet will focus on breast cancer in women.

Box 1. Statistics on breast cancer incidence and mortality in India and worldwide

Breast cancer incidence & mortality in India

- 22.9 age-standardized incident cases per 100,000 women (2008, (2))
- 11.1 age-standardized breast cancer deaths per 100,000 women (2008, (1))
- 90,659 deaths in India (2010, (5))
- Most common cancer for women in metropolitan cities (Delhi, Mumbai, Chennai, Kolkata, Bangalore) (2004, (5))

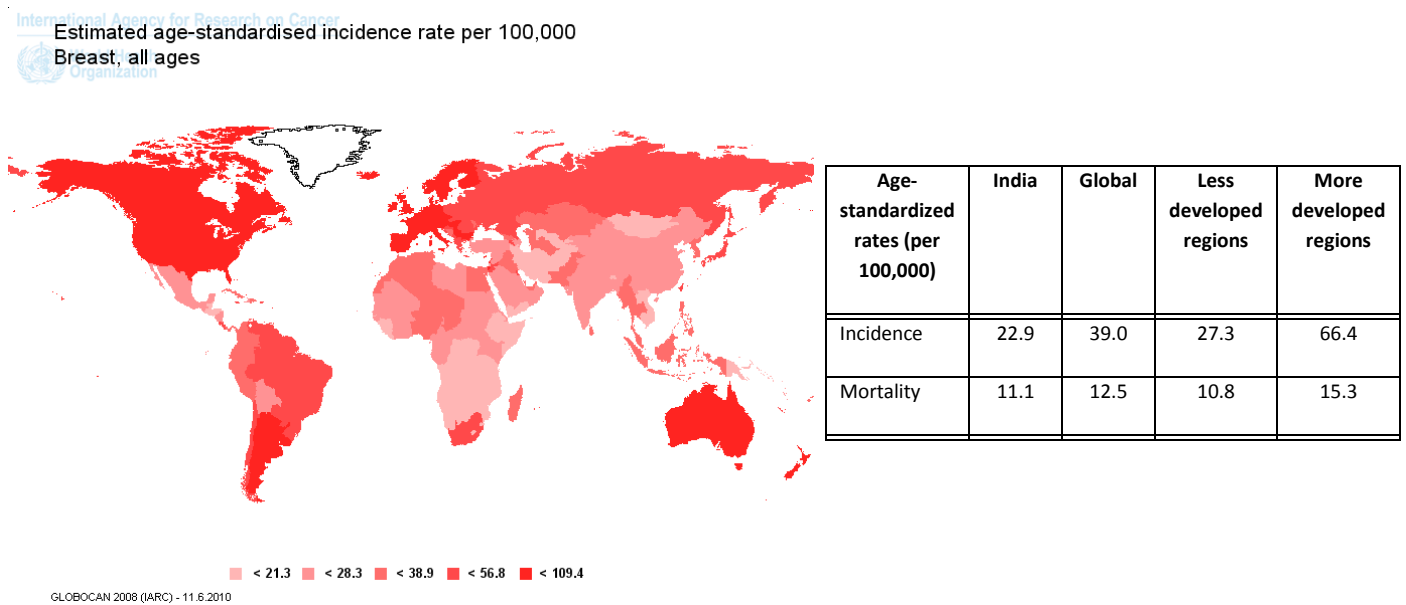
Breast cancer incidence & mortality worldwide

- 39.0 age-standardized incident cases per 100,000 women each year (2008, (1))
- 12.5 age-standardized breast cancer deaths per 100,000 women (2008, (1))
- 458,503 deaths (2008, (1))
- 6,629,000 DALY's (2004, (3))

Factsheet outline

- I. **Background** – morbidity and mortality rates, in India and globally
- II. **Definition of breast cancer** – definition and sub-types
- III. **Burden of breast cancer in India** – cancer registry-based incidence and mortality rates
- IV. **Epidemiology of breast cancer in India**
- V. **Risk factors**
- VI. **Breast cancer prevention, early detection and economics**
- VII. **Breast cancer staging, treatments and survival**
- VIII. **Breast cancer control**
- IX. **Gaps in breast cancer research practice in India**

Figure 1. *Age-standardised incidence rates of breast cancer around the world*



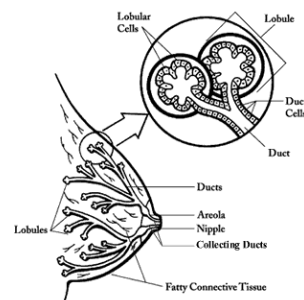
I. Background

In India, breast cancer is the second most common cancer (after cervical cancer) with an estimated 115,251 new diagnoses and the second most common cause of cancer-related deaths with 53,592 breast cancer deaths in 2008 (1). The age-standardised incidence rate for breast cancer in India is 22.9 per 100,000, one-third that of Western countries, and the mortality rates are disproportionately higher (6, 7). Like other cancers such as those of the lung, prostate and colon, the rates of breast cancer in persons of Indian origin living in Western countries are intermediate to their Western counterparts - who have much higher rates - and their Indian counterparts, who have much lower rates (8). Breast cancer accounts for 22.2% of all new cancer diagnoses and 17.2% of all cancer deaths among women in India. Breast cancer in urban areas of India is three times higher than in rural parts of the country.

II. Definition of breast cancer

Breast cancer is a tumor that starts from cells of the breast tissue, either in cells that line the ducts that carry milk to the nipples (ductal cancer) and/or in cells that line the lobules, which are glands involved in milk production (lobular cancer, Figure 2). Breast tumors can be benign or malignant, the former are not life-threatening, can usually be removed, do not invade adjacent tissues or spread to other parts of the body and can include fibrocystic tissue, fibroadenomas and benign breast disease. Malignant breast tumors are cancerous and can invade surrounding tissues or metastasize to other parts of the body via the lymphatic system (lymphatic vessels and lymph nodes), such as the liver and bone. If cancer cells have spread to the surrounding lymph nodes, there is a much higher probability that the tumor has entered the bloodstream and metastasized to other parts of the body (4).

Figure 2. *Anatomy of a female breast*



American Cancer Society

The histological classification of breast cancer includes adenocarcinomas, cancers that originate in the glandular tissue, which include the ducts and lobules and sarcomas, cancers that originate in the connective tissue of muscle, fat or blood vessels (9). Carcinoma in situ (CIS) is an early stage form of cancer where the tumor is confined to the layer of the cells where the cancer began and it has not invaded deeper breast tissue or spread to other areas of the body (9). Breast cancer includes the following types of disease (4):

1. **Ductal carcinoma in situ (DCIS)** is the most common type of non-invasive cancer in women, where cancer cells have not spread beyond the duct walls into surrounding breast tissue. The prevalence of DCIS is strongly correlated with mammographic screening and in countries such as the US, can be as high as 18% of all newly diagnosed cancers (10) but in countries such as India, represents a very low proportion of total disease since most cases present in late stage (11).
2. **Invasive or infiltrating ductal carcinoma** originates in the breast duct, has broken through the wall of the duct into surrounding fatty tissue of the breast and is capable of metastasizing to other organs of the body through the lymphatic system and bloodstream. This represents about 80% of breast cancers. (9)
3. **Lobular carcinoma in situ (LCIS)** is not cancer but is sometimes classified as a non-invasive breast cancer and women who have this condition are more likely to develop invasive breast cancer in the future (9).
4. **Invasive or infiltrating lobular carcinoma** originates in the milk-producing glands or lobules of the breast and can spread to other parts of the body. This is less common and represents about 1 in 10 breast cancer diagnoses (10).
5. **Other (less common) types of breast cancer:** inflammatory breast cancer (1-3% of all breast cancers), triple negative breast cancers, mixed tumors, medullary carcinoma (3-5% of all breast cancers), metaplastic carcinoma, mucinous carcinoma, paget disease of the nipple, tubular carcinoma, papillary carcinoma, adenoid cystic carcinoma (adenocystic carcinoma), phyllodes tumor and angiosarcoma (9, 10).

Estrogen receptor (ER) and Progesterone receptor (PR) status

Confirmed carcinomas of the breast are subjected to a test to determine the estrogen receptor (ER) and progesterone receptor (PR) status. Breast cancers that contain estrogen receptors on the outside surface of their cells are ER-positive cancers while those with progesterone receptors are called PR-positive cancers. Women who are positive for either or both receptors generally have a better prognosis because they are more responsive to hormone therapy than without any of these receptors (9). In the U.S., 75% of all invasive cancers are either ER+ or PR+ (12). A recent study based on the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Cancer program found that ER+/PR+ status was lower in breast cancer patients who were Indian/Pakistani compared to Caucasian cases (69.4% vs. 78.2% (13)).

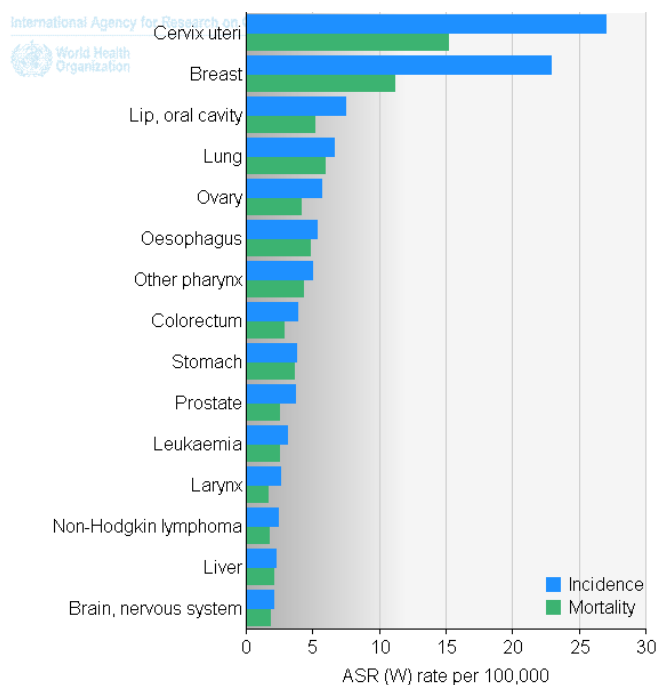
HER2/neu status

The HER2/neu gene codes for a growth-promoting protein and breast cancer cells that are HER2-positive tend to have too many copies of the gene and too much of the protein (9). As a result, these tumors tend to grow and metastasize more aggressively. Twenty to 25% of breast cancers diagnosed in the U.S. are HER2+ (10).

III. Burden of breast cancer in India

Although breast cancer is the second most common cancer in all Indian women (Figure 3), recent data from the Atlas of Cancer in India project – a study to assess nationwide patterns of cancer incidence across urban and rural parts of the country (<https://canceratlasindia.org>) - suggest that breast cancer is the most common cancer in metropolitan cities (Figure 4) and is predicted to be the most common type of cancer in the coming decade (5). Data from the Atlas project suggest that certain districts display even higher rates (eg, Chandigarh 39.5 per 100,000, North Goa 36.8 per 100,000) than those reported by the population-based registry in New Delhi (28.9 per 100,000). In the metropolitan cities, breast cancer is the leading cancer diagnosis in women, with rates nearly twice as common as cervical cancer. In Bangalore, Chennai, Delhi, Mumbai and Kolkata, the age-adjusted incidence rates are 30.9, 33.0, 31.4, 29.3 and 20.6 per 100,000 (14). Breast cancer is also the leading cancer in cities such as Bhopal and the Kamrup Urban district and (24.6 and 17.5 per 100,000) while the rates are much lower in rural areas such as the non-urban Ahmedabad district and Barshi (9.2 and 9.4 per 100,000). The rates in Northeastern states are generally lower and often intermediate to the urban and rural regions (Imphal West District, Mizoram and Sikkim have breast cancer age-standardised rates of 14.6, 14.1 and 6.8 per 100,000(14). Mortality data on breast cancer is inconsistent and inadequate and there are no good nationwide data to provide reliable estimates (11). A recent report by the Indian Council of Medical Research predict the number of breast cancer cases in India to rise to 106,124 in 2015 and to 123,634 in 2020 (5).

Figure 3 . Age-standardised incidence and mortality rates of most common cancers in India, 2008.

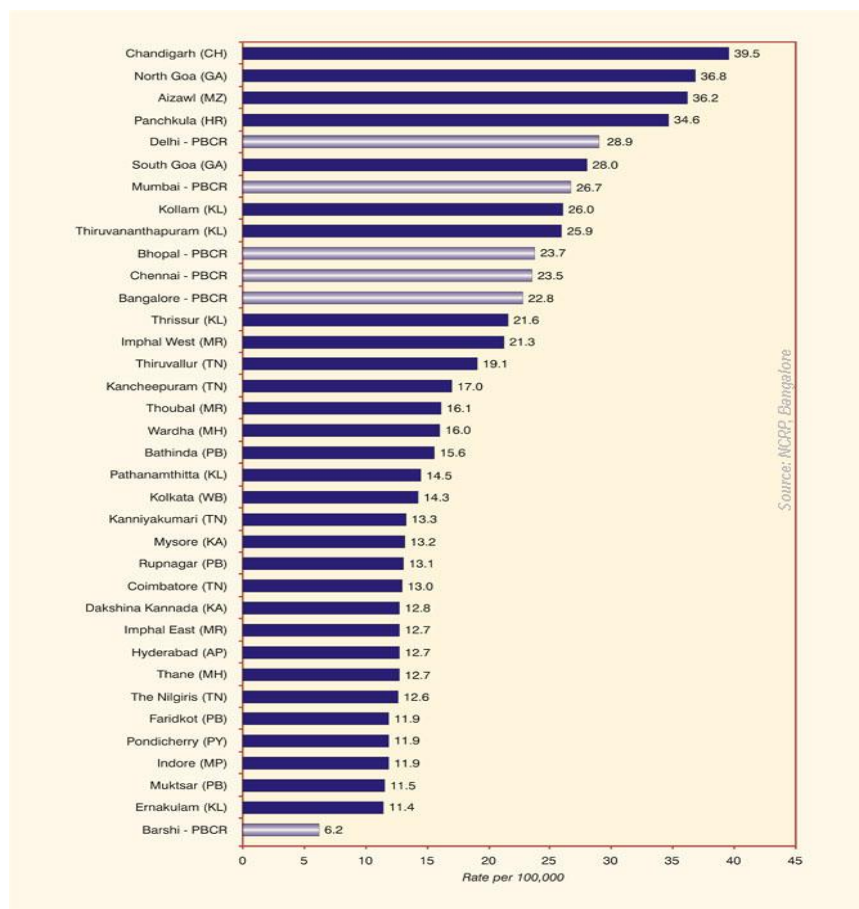


GLOBOCAN 2008 (IARC) – 11.6.2010

IV. Epidemiology of breast cancer in India

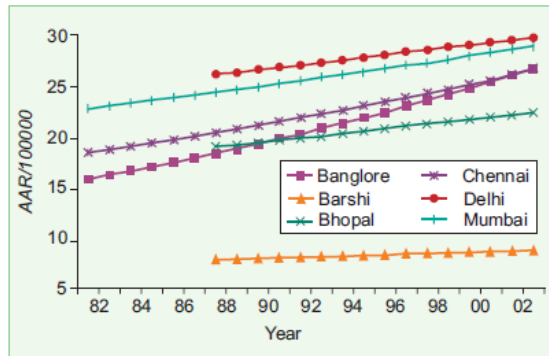
Age incidence rates in India suggest that the disease peaks at a younger age (eg, 40-50 years) than in Western countries (1) and as a result, the majority of new diagnoses occur in pre-menopausal women. Studies have shown a rising trend with steadily increasing rates since the mid-1980's (14-18) with the largest increases observed in Mumbai (Figure 5). According to National Cancer Registry Programme projections, the number of breast cancer deaths in India will climb to 106,124 in 2015 and to 123,634 in 2020 (5). The majority of new cases are advanced stage -locally advanced or higher stage- at the time of diagnosis (19, 20). The increasing burden of disease may be associated with lifestyle factors such as later age at marriage, age at first birth, reduced breastfeeding and westernization of diet and physical activity patterns (11, 21). Breast cancer rates tend to be higher in women of higher education and in specific communities that have adopted a more westernized lifestyle, such as the Christians and the Parsis, and is lowest in the Muslim communities (22). Differences in the prevalence of transforming growth factor beta signaling pathway associated gene polymorphisms (TGFB1 & TGFB1) may also be linked to the lower rates observed in certain sub-populations such as those from western India compared to the Parsis (23).

Figure 4. District-wise comparisons of age-adjusted breast cancer incidence rates (per 100,000) under the National Cancer Registry Programme, ICMR, supported by WHO



Recent evidence (13, 24) suggests that breast cancer in Indian and Caucasian women may differ given the younger age at diagnosis, higher proportion of high-grade (45.7% for grades III & IV vs. 38.7%) and hormone receptor-negative tumors (30.6% ER-/PR- vs. 21.8%), higher incidence of inflammatory cancer (1.4% vs. 0.8%) and larger proportion with early-onset disease (<40 years, 16.2% <40 yrs vs. 6.23%).

Figure 5. Trends in age-adjusted breast cancer incidence rates (per 100,000) for six population-based cancer registries in India under the National Cancer Registry Programme (NCRP), ICMR (1982-2005 (5).



V. Risk factors for breast cancer

The most important modifiable and non-modifiable risk factors are listed in Table 1 with a brief description of characteristics that may be unique in South Asian populations.

Non-modifiable risk factors:

- 1) **Age.** Older age increases the risk of breast cancer and most women are over the age of 60 when they are diagnosed although there is evidence that Indian women are more likely to develop breast cancer at earlier ages than their Western counterparts (13) and that breast cancer peaks from ages 45-50 years in India (3). Recent data comparing Indians and Caucasians in the US show that 29.9% of Indians/Pakistanis living in the US had pre-menopausal breast cancer compared to 18.9% of Caucasians (13).
- 2) **Height.** Adult height is positively associated with the risk of developing breast cancer (25); a pooled analysis yielded a relative risk = 1.02 (0.96, 1.10) for each 5 cm increase in height for pre-menopausal cancer and RR=1.07 (1.03, 1.12) for post-menopausal cancer (26). For other childhood growth patterns, including age at maximal height and growth velocity, the associations are less consistent because the biological pathways are more complex (27).
- 3) **Personal history of benign breast or other breast disease.** A history of atypical hyperplasia, lobular carcinoma in situ or ductal carcinoma in situ (as determined by a breast biopsy) increases the risk of developing invasive breast cancer. This is usually measured by history of a biopsy, which have ranged from a 10% to more than 3-fold increase depending on the study (see Table 1 below):

Table 1. Range of risk estimates associated with history of biopsies for benign breast disease

Study	Relative risk estimates # of biopsies (< 50 yrs)	Relative risk estimates # of biopsies (≥ 50 yrs)	Reference
BCDDP – Breast Cancer Detection Demonstration Project (28)	RR=1.70 (1 biopsy) RR=2.88 (2 biopsies)	RR=1.27 (1 biopsy) RR=1.62 (2 biopsies)	Gail MH, Brinton LA, Byar DP, et al. <i>JNCI</i> 1989.
CASH - Cancer and Steroid Hormone(29)	RR=1.97 (1 biopsy) RR=3.89 (2 biopsies)	RR=1.77 (1 biopsy) RR=3.13 (2 biopsies)	Wingo PA, Ory HW, Layde PM, et al. <i>AJE</i> 1988.
NHS – Nurse’s Health Study (30)	RR=1.67 (1 biopsy)	RR=1.72 (1 biopsy)	Spiegelman D, Colditz GA, Hunter D, et al. <i>JNCI</i> 1994.
BCPT – Breast Cancer Prevention Trial (31)	RR=1.11 (1 biopsy) RR=1.23 (2 biopsies)	RR=1.34 (1 biopsy) RR=1.80 (2 biopsies)	Fisher B, Costantino JP, Wickerham DL, et al. <i>JNCI</i> 1998.

- 4) **Family history.** A family history of breast cancer in the mother, father, sister or daughter increases the risk of breast cancer and the risk is even stronger if the family member was diagnosed before the age of 50 years old and/or with pre-menopausal breast cancer (18). Specifically, if a woman has a first-degree relative >50 years diagnosed with post-menopausal breast cancer, her risk increases by 80% (32) whereas a first-degree relative with pre-menopausal breast cancer increases a woman’s risk by 330% (32). The risks increase for a higher number of first- and second-degree relatives diagnosed with breast cancer (33). A history of ovarian cancer in other relatives (in the mother’s or father’s families) also increases the risk of breast cancer (33).
- 5) **BRCA1/BRCA2.** Having mutations in BRCA1, a gene on chromosome 17 that controls cell growth or BRCA2, a gene on chromosome 13 that suppresses cell growth, are associated with a 40-80% increased risk of breast cancer (32). Mutations in these genes are also associated with increased risks of ovarian, prostate and other types of cancer as well.
- 6) **Menstrual history: ages at menarche and menopause.** Women who have an early age at menarche (<12 years) have a 30% increased risk of breast cancer while those who have a late age at menopause (>60 years) will have a 20-50% increased risk of disease (32).
- 7) **Breast density on mammogram.** Women with higher breast density have a higher risk of being diagnosed with breast cancer (OR=5.23, 95% CI: 1.70, 16.13 (34)).
- 8) **Medical history of Hodgkin’s lymphoma.** Women diagnosed with Hodgkin’s lymphoma who received a chest irradiation dose ≥40 Gray between 25-55 years, have a 29% increased risk of developing breast cancer (35).

Modifiable risk factors:

- 9) **Age at first child.** Women who have never had children or those who are more than 30 years at the time of their first child's birth are twice as likely to develop breast cancer than women who had their first child before the age of 20 years (32). Moreover, women who have five or more children have half the risk of breast cancer as women who have never had a child (18). These associations are more consistently observed for hormone receptor-positive breast cancer.
- 10) **Hormone replacement therapy.** Women who have taken menopausal hormone therapy (estrogen + progestin for at least 5 years) have a 20% greater risk of developing breast cancer (32).
- 11) **Breastfeeding.** Women who do not breastfeed or breastfeed for shorter durations are at a higher risk of developing breast cancer. Specifically, a 4.3% reduction in risk has been observed for each additional year of breastfeeding (36).

VI. Breast cancer prevention and early detection

The risk of breast cancer may be lowered to the extent that one can make lifestyle changes consistent with modifiable risk factors (see previous section on "Risk factors for breast cancer") and may be modified by menopausal and/or hormone replacement therapy status (37). In addition, healthy lifestyle choices such as limiting alcohol intake (2+ drinks versus none associated with a 20% increase (32)) maintaining a healthy body weight (80th vs. 20th percentile, RR=1.2-1.9 (32)), high dietary soy intake (20-25% for highest intake (38)) and engaging in regular physical activity (20-80% risk reduction with for leisure time physical activity in post-menopausal women) may help lower one's risk (18). Dietary factors related to red meat, carbohydrate intake, fruits and vegetables, caffeine, micronutrients such as carotenoids, and dietary fat have been investigated with no clear associations (33). There is some evidence to suggest that environmental factors with estrogenic properties (eg, pesticides) may play a role in the etiology of this disease, however there is no consistent epidemiological evidence or long-term data in humans to support this.

The best way to protect one's self is through early detection. Breast cancer screening includes three methods of early detection: 1) breast self-exams (monthly) starting in the 20's; 2) clinical breast exams (every 3 years) starting in the 20's; and 3) mammographic screening (annually) starting at the age of 40 years (9):

- 1) A **clinical breast exam** (CBE) is performed by the clinician or other health professional and involves a systematic examination of the breast skin and tissue. The health professional is looking for signs and symptoms or if any changes occur, including development of a lump or swelling, skin irritation or dimpling, nipple pain or retraction (turning inward), redness or scaliness of the nipple or breast skin, or a discharge other than breast milk. In countries where mammography is widely practiced, the CBE does not provide additional efficacy in mortality reduction and in resource-poor countries.
- 2) A **breast self-exam** (BSE) is performed by the woman herself and involves a similar examination as the CBE of the breast skin and tissue based on palpations by her hands. The woman is examining the look and

feel of her breasts as well as any signs, symptoms or changes to the breasts. While the BSE is recommended so that women understand their breasts for detecting any suspicious changes over time, the epidemiological evidence does not support BSE as an effective screening tool for reducing breast cancer mortality (39, 40).

- 3) A **mammogram** is an x-ray of the breast that uses very low levels of radiation (0.1-0.2 rads per picture). The images capture calcifications (benign) and masses, which include benign cysts that are fluid-filled, benign solid tumors and cancer. To confirm that an abnormal mass is cancer, a biopsy is undertaken and may be a fine-needle biopsy, core biopsy or surgical biopsy (56). An approximate 12-15% reduction in breast cancer mortality is associated with mammography screening for women aged 40-69 years (40).

Breast cancer screening in India

In 1984, the government of India established the National Cancer Control Programme (NCCP) with the following four goals:

1. Primary prevention of tobacco-related cancers;
2. Early detection of easily accessible sites;
3. Augmentation of treatment facilities; and
4. Establishment of equitable, pain control and palliative care network throughout the country (26).

Twenty one regional cancer centres were established under this program, which are more treatment-oriented with a focus on improvements in radiation oncology (26). The centres are not oriented towards prevention and early detection and they provide only opportunistic screening (41). There is no organized, systematic (or government-funded) population-based screening program for breast cancer in India (24, 42).

Evidence from developed countries shows that mammography reduces breast cancer mortality in women aged 50-69 years (43), which has led to population-based screening programs for older women in developed regions of the world such as Europe, North America, Australia and Japan (44). In India, breast cancer incidence peaks before the age of 50 years, and a recent review of the evidence (45) in younger women (aged 39-49 years) based on 8 trials conducted between 2001-2008, suggests that mammographic screening is also beneficial in this younger age group. The authors reported that screening mammograms were associated with a 15% reduction in breast cancer mortality (95% CI: 0.75, 0.96 (45)). The results are similar for women aged 50-59 years (0.86, 95% CI: 0.75, 0.99)(45), but less than women aged 60-69 years (0.68, 95% CI: 0.54, 0.87) (46). The authors also noted that false-positive rates and additional imaging work-up were drawbacks to mammographic screening in this age group. The review did not show an overall mortality reduction for breast self-exams or clinical breast exams, but in developing countries such as India, the lower incidence rates, limited access to health care, fewer treatment facilities, and advanced-stage distribution of disease may yield different optimal screening strategies, such as the CBE. Three randomized trials have been launched to evaluate CBE as the primary screening measure - in one, it failed due to poor community acceptance (Philippines), and in the other two (Egypt, India), the trials are still ongoing (40).

In 1998, a cluster-randomized controlled trial was initiated by Tata Memorial Hospital in women aged 35-64 years living in Mumbai slums to test the screening efficacy and cost-effectiveness of health education and two screening tools, including the CBE for breast cancer (42). Preliminary results suggest that CBE increases the rate of early stage disease with 18.8 per 100,000 in the intervention group compared to 8.1 per 100,000 in the control group, and slightly reduces the rate of advanced breast cancer with 19.6 per 1,000 in the intervention group compared to 21.7 per 100,000 in the control group (42), however the completion of all four rounds of screening and 8-year follow-up will not yield results until after 2013. In the meantime, other studies such as those based on simulation models suggest that the CBE may be an effective screening tool in Indian women. In one such study (47), the cost-effectiveness of different screening tools was compared for the Indian context and the authors found that an annual clinical breast exam (CBE) yielded a similar mortality reduction as biennial mammography (23.3% vs. 25.8%) at only half the costs (47).

Chemoprevention

Several randomized controlled trials have evaluated the chemopreventive effects of tamoxifen in reducing the incidence of breast cancer in healthy and high-risk women (31, 48-52). The results are mixed - a few trials showing a reduction in ER-positive breast cancer associated with tamoxifen (31, 53) while others showed no statistically significant differences for reducing the risk of invasive breast cancer (50, 51). Some studies have shown that women on tamoxifen have higher rates of endometrial cancer and pulmonary emboli and a meta-analysis of vascular and neoplastic events (54) showed that while tamoxifen is associated with significantly increased risks of endometrial cancer (RR=2.7, 95% CI: 1.94, 3.75), gastric cancer (RR=1.31, 95% CI: 1.01, 1.69), strokes (RR=1.49, 95% CI: 1.16, 1.90) and pulmonary emboli (RR=1.88, 95% CI: 1.77, 3.01), it's associated with significantly reduced risks of myocardial infarction deaths (RR=0.62, 95% CI: 0.41, 0.93). Initially approved by the U.S. Food and Drug Administration (FDA) as a drug for the prevention and treatment of osteoporosis in post-menopausal women, raloxifene has been found in recent trials to lower invasive breast cancer risk to the same extent as tamoxifen. As a result of additional trials investigating raloxifene for chemoprevention, the FDA has now approved raloxifene for women with osteoporosis or those at high risk of breast cancer (33).

Economics of breast cancer in India

The WHO *Global Burden of Disease* showed that the number of disability-adjusted life years attributable to breast cancer was 6,629,000 worldwide and 1,222,000 in South East Asia (3). Although there are no available data estimating the cost of the breast cancer burden in India, the DALY's would be comparatively high considering the earlier age and later stage at diagnosis for Indian women compared to those in the West. Studies have evaluated the most cost-effective screening strategies for India, and in one such study in the *Journal of National Cancer Institute*, the authors compared the clinical breast exam to mammography in terms of its cost-effectiveness using micro-simulation models and reported that a single CBE at age 50 had a cost-effectiveness ratio of Int.\$793 per life saved with a 2% reduction in breast cancer mortality(47). The cost-effectiveness increased to Int.\$1341 per life gained for every 2 years a CBE was conducted, and Int.\$1135 per life gained for every 5 years a CBE was conducted, for women aged 40-60 years (47). The WHO Commission on Macroeconomics and Health suggests

that a cost-effectiveness ratio that is less than the per capita GDP is “very cost effective”, and in this analysis it was estimated at 50% of India’s GDP (47).

VII. Breast cancer staging, treatments and survival

Breast cancer staging

A staging system is used to classify the extent of disease based on the tumor size (≤ 2 , 2-5, >5 cm), location (eg, ducts, lobules), involvement of lymph nodes and whether or not tumor has spread to surrounding tissue (eg, chest wall, skin of breast) or distant organs (eg, lungs, liver, brain, bone). Breast tumors can spread via the tissue (invasion of surrounding tissue), the blood or the lymph system and are categorized as Stage 0, I, IIA, IIB, IIIA, IIIB, IIIC or IV(9).

Breast cancer treatment

There are several treatment options for women diagnosed with breast cancer that include surgery, chemotherapy, radiation therapy, hormonal therapy and targeted therapies. The most appropriate treatment depends on the woman’s risk profile and stage of disease, which can range from I-IV and is based on the tumor size, location, involvement of lymph nodes and whether or not tumor has spread to surrounding tissue or distant organs. Treatment options include (9, 55):

1. **Surgery** includes lumpectomy (removal of a lump and the surrounding tissue), which is also called breast-conserving surgery, mastectomy (removal of all the breast tissue although muscles underneath breast are no longer removed), lymph node removal (or axillary lymph node dissection) which takes place during time of lumpectomy or mastectomy if biopsy shows that breast cancer has spread. Other options include preventive surgeries such as prophylactic mastectomy for women at high-risk and prophylactic ovary removal to lower estrogen production in the body.

Emerging evidence from trials suggest that the removal of axillary lymph nodes is *not* a determinant of breast cancer recurrence and survival in early-stage patients, which is contrary to prevailing practices (56-58). In one trial of 856 early-stage patients, dissection of lymph nodes with evidence of spread did not influence breast cancer 5-year recurrence or mortality rates (57). In another trial (the National Surgical Adjuvant Breast and Bowel Project B-32 study) of 3,986 node-negative patients, women were randomized to axillary lymph node dissection or no further surgery; the investigators found that the intervention was not associated with disease control or survival but was associated with significantly greater morbidity, including shoulder abduction deficit, arm volume, arm numbness and tingling (58). In another study of 5,539 women undergoing breast-conserving surgery, immune system assays which are more sensitive in detecting micro-metastases in node-negative women, were not associated with improved survival (56).

2. **Radiation therapy** includes external beam and internal (implantation of radioactive seeds) radiation, and is usually given after surgery to destroy any remaining cancerous cells left behind. While the former is a well-tested, long-standing treatment option, the latter has recently being developed and is still being studied for its efficacy and adverse effect profile, although evidence from at least 4 trials demonstrate a consistent lower recurrence rate when radiation therapy supplements surgery ((59-62). The advantages of internal radiation include a much shorter treatment interval, a localized and focused approach of radiation to the affected area (and hence lower dose exposure) rather than the whole breast and therefore fewer adverse effects related to radiation. Disadvantages are that benefits and side effects of this newer technology are not well-understood and that it requires extra training/expertise to be correctly carried out. Two European trials have shown that 10-16 Gy boosts can reduce recurrence by 4.6% to 3.6% at 3 years ($p=0.044$) (63) and from 7.3% to 4.3% at 5 years ($p<.001$) (64). A randomized clinical trial is underway (National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/RTOG 0413) to compare the effects of internal (partial breast) and external (whole-breast) irradiation in women with Stage 0, I and II breast cancer (65).
3. **Chemotherapy** is a systemic therapy that can be administered either before surgery (to shrink the tumor) or afterwards (to reduce the risk of recurrence). For early-stage disease, it is usually administered to help remove cancer cells from the body and to reduce the risk of recurrence. For advanced-stage disease, it is given to destroy as many cancer cells as possible. A meta-analysis of 60 trials and 28,764 women of combination chemotherapy versus no chemotherapy showed a 37% reduction in relapse and 30% reduction in death for women under the age of 50 years, and a 19% reduction in relapse and 12% reduction in death for women aged 50-69 years; the benefit on recurrence was present in all age groups and in the presence and absence of tamoxifen (66).
4. **Hormonal therapy** is a treatment option for hormone receptor-positive cancers. It can be given for early-stage disease to either reduce the amount of estrogen or block its action to reduce the risk of recurrence. It can also be given for advanced-stage or metastatic disease to shrink or slow the growth of existing tumors. Hormone therapy includes aromatase inhibitors, selective estrogen receptor modulators and estrogen receptor downregulators as well as surgical treatments such as removal of ovaries and fallopian tubes. Tamoxifen use of at least 5 years is associated with a 12% reduction in recurrence and a 9% reduction in mortality over a 15-year follow-up period, in ER-positive and ER-unknown breast tumors (66). The benefits of tamoxifen appear to be optimized at 5 years (66-69), with current recommendations to discontinue adjuvant tamoxifen after 5 years. Recent trials (Arimidex-Nolvadex study in postmenopausal women (ARNO-95) and the Intergroup Exemestane Study (IES)) have shown benefits of aromatase inhibitors over tamoxifen for disease-free survival and complications (70-72).
5. **Targeted therapies** target cancer cell properties specifically as opposed to chemotherapy which also destroys normal, healthy cells and includes treatments such as herceptin and tykerb, which both block cancer cell growth in HER2-positive breast cancers, and avastin, which blocks growth of new blood vessels depending for cancer cell growth (9, 55). Table 2 shows the results of 5 trials that have released data on the effects of adjuvant trastuzumab, an anti-HER2/neu antibody (73-77):

Table 2. Randomized controlled trials evaluating trastuzumab used as an adjuvant therapy

Trial	Sample size	Follow-up period	Outcomes & Results
BIG-01-01 (73)	5,090 patients	2 years	46% lower risk of first event (95% CI: 0.43-0.67), disease-free survival (DFS) of 8.4% at 2 years (95% CI: 2.1-14.8)
NSABP-B-31 & NCCTG-N9831 (74, 75)	3,676 patients	4 years	DFS difference of 11.8% at 3 years and 18% at 4 years; and 53% lower risk of distant recurrence (95% CI: 0.37-0.61) of trastuzumab treated patients vs. no trastuzumab
AVENTIS-TAX-GMA-302 (77)		3 years	HR=0.61 (95% CI: 0.48-0.76) DFS for anthracycline arms vs. HR=0.67 (95% CI: 0.54-0.83) for non-anthracycline arm.
FINHER (76)	232	3 years	HR=0.41 (95% CI: 0.21-0.83) with DFS of 89% vs. 78% assessing short course of trastuzumab

Breast cancer treatment in India

There is wide variation in the availability of facilities for breast cancer treatment in India, which ranges from poorly funded, under-resourced and under-staffed government hospitals with no mammography machines, to medical facilities at par with international standards for medical personnel, diagnostic and imaging services and the full array of surgical, radiation and medical treatment options, such as the TATA Memorial Centre, which is a national comprehensive cancer centre (7). The majority of women in India receive inadequate and inappropriate treatment due to poor infrastructure, limited financial resources and a social stigma surrounding the disease (7, 78).

Due to the late stage at presentation, radical mastectomy is the most common procedure used for breast cancer patients in India (79). Breast-conserving surgery and sentinel lymph node biopsy are rare due to poorly equipped centers and the often late stage at diagnosis (7). For chemotherapy, low-cost options are more often used (eg, cytoxan, methotrexate, and 5-FU (CMF) combination) than regimens which are found to be more effective (eg, anthracycline-based combinations) and radiation is expensive and not widely available (7, 79). For management of metastatic and triple negative breast cancer, a recent survey of 152 practicing nationwide oncologists revealed preferences for use of platinum agents and the use of oral agents (eg, capecitabine), despite the lack of evidence from large randomized trials that these should be the standard of care in such settings (80). These underlie the importance of implementing standardized, evidence-based guidelines in Indian settings.

Breast cancer survival in India

Nearly all breast cancer cases are clinically detected in India (24), with the majority presenting with locally advanced disease (20). Nearly one-third of breast cancer patients have skin/chest wall involvement at the time of diagnosis and the stage at diagnosis is often worse in younger patients (81). A later stage at diagnosis and lower

survival have been linked to poor access to health care facilities and lower awareness, especially in the urban poor and rural populations as well as demographic factors such as lower education and literacy (82, 83). Even in states with higher literacy and awareness levels such as Kerala, only 15% of cancer patients seek medical assistance in a localized stage of disease (84). Data on cancer survival is limited in India due to scarce resources and incomplete follow-up of cancer registry cases although a few cancer registries meet the minimum criteria acceptable for the Cancer Incidence in Five Continents (CI5) series (85). A recent study based on these cancer registries (Bhopal, Mumbai, Barshi, Chennai and Karunagapally) found that the 5-year age standardized survival for breast cancer in India was 52% (minimum, 31% and maximum, 54%) (86). Lower survival was observed in rural (eg, Barshi) versus urban centers (eg, Chennai), which the authors attributed to the development of cancer health services. This was confirmed by the finding that differences in survival were larger when comparing rural (Barshi), semi-urban (Karunagapally) and small urban (Bhopal) registries than in comparing two different metropolitan cities (Mumbai and Chennai (86)). There are multiple factors that delay diagnosis in Indian women, ranging from limited availability and access to cancer health services, lower health literacy and a social stigma attached to breast cancer (24). One study in Eastern India showed that the majority of patients appear at a hospital at least several months after the onset of symptoms for multiple cancers, including the breast (87) and a systematic review confirmed that delays in diagnosis as short as 3-6 months are linked to poorer survival from breast cancer (88).

VIII. Breast cancer control

In high-resource settings, there are evidence-based guidelines for the early detection, diagnosis and treatment of breast cancer (36, 89-91). In low- and medium-resource settings, the Breast Health Global Initiative (BHGI) has suggested different guidelines for breast cancer early detection, diagnosis and control based on available resources – basic, limited, enhanced and maximal (92). For example, a health care system with basic resources should offer breast self-exams and clinical breast exams (CBE) as part of early detection, a diagnostic work-up that includes physical exam, CBE, surgical and fine-needle aspiration biopsies, modified radical mastectomy as a surgical option and ovarian ablation or tamoxifen for adjuvant/systemic therapy. Higher requirements would be suggested for detection, diagnosis and treatment for higher resource settings - limited, enhanced and maximal resource settings, progressively (60). Table 3 compares the suggested treatments for various stages of breast cancer in settings with basic versus maximal level of resources (92). In India, resources of the health care system vary widely within the country (11), the states and even the cities, and there are no national ICMR guidelines; instead, treatment allocation has to be considered and implemented according to the resources available for a particular patient and in a specific health care setting. In low- and middle-income countries where there is no good health infrastructure for a long-term programme of mammography, the World Health Organization supports early detection through clinical breast exam and patient signs and symptoms.

Table 3. Recommended guidelines on treatment from the BHGI according to available resources in each setting (92).

Stage of breast cancer	Recommended treatment according to Level of Resources	
	Basic	Maximal
Stage I	Modified radical mastectomy; ovarian ablation, tamoxifen	Sentinel node biopsy, reconstructive surgery; growth factors, dose-dense chemotherapy
Stage II	Modified radical mastectomy; ovarian ablation, tamoxifen; classical CMF, AC, EC or FAC	Sentinel node biopsy, reconstructive surgery; growth factors, dose-dense chemotherapy
Locally advanced	Modified radical mastectomy; neoadjuvant AC, FAC or classical CMF; ovarian ablation, tamoxifen	Reconstructive surgery; growth factors, dose-dense chemotherapy,
Metastatic (stage IV) and recurrent breast cancer	Total mastectomy; ovarian ablation, tamoxifen	Growth factors, Vinorelbine, Gemcitabine, Carboplatin, Fulvestrant

In July 2010, the Government of India announced that it would implement the National Programme for Prevention and Control of Cancer, Diabetes, Cardio-vascular Diseases and Stroke in 15 states/union territories, 100 districts, 700 community health centres and 20,000 sub-centres over a 5-year period. Of the proposed Rs. 1230.90 crore, Rs. 731.52 crore will be allotted for the National Cancer Control Programme (NCCP) on an 80:20 sharing basis between the Government of India and state governments, respectively. The NCCP, which was established in 1984, will use these funds to achieve their objectives towards improved methods of prevention, early detection and treatment (see *Breast cancer screening in India*, data not yet available).

IX. Gaps in breast cancer research practice in India: etiology, prevention and treatment

Surveillance: The increasing burden of breast cancer in Indian women warrants rigorous epidemiological investigations of trends observed in different rural, semi-urban and urban populations.

Risk factors: While the increasing rates can be partially attributed to changing family planning practices (age at first child and breastfeeding) and an increasingly westernized lifestyle (lower physical activity, higher fat diets, higher body mass index), specific causal factors in Indian women need to be identified and verified. Some reports suggest a more aggressive case profile at diagnosis in women of South Asian descent (13, 24), underlying the need for epidemiological investigations of the independent and interacting genetic and environmental determinants of breast cancer in multiple sub-populations.

Screening: There is a need for the evaluation of screening efficacy in Indian settings for determining the best screening strategy in different Indian sub-populations. One large-scale RCT on breast cancer (and cervical cancer) screening won't yield results until 2013 (42) (in the meantime, screening efficacy can also be evaluated using the case-control design). The efficacy of mammographic screening, clinical breast and self-breast exams have been thoroughly reviewed in Western countries, where the non-screened/usual care groups have high access to health facilities for diagnostic mammograms, to physicians for clinical breast exams and to various sources of information for conducting breast-self exams. These screening strategies need to be systematically assessed in the Indian context, where usual care for most women in India is defined by a lower level of resources for diagnostics and screening, of access and of health awareness. Observational studies should be evaluated in India to determine its own optimal cost-effective strategy.

Treatment: The best course of treatment in Indian women may differ if genetic studies reveal that certain treatments are more effective in certain sub-groups (eg, tamoxifen is more optimal in women with an active CYP2D6 pathway (93)). Overall, although the epidemiology of breast cancer etiology, prevention and treatment are well-characterized in Western populations, further evaluations of the genetic and environmental determinants, of the optimal screening strategy and best cost-effective course of treatments in Indian women are required in the future.

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