

## Breast Cancer: An Overview

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### ABSTRACT

The knowledge of breast cancer development and progression has grown in recent years and relatively development of novel therapeutic strategies, but for cancer mortalities in women breast cancer stands at 2<sup>nd</sup> position as cause.

In U.S. Approximately 39970 women & 450 men in the U.S. will be diagnosed from the disease in 2011.<sup>[1]</sup> Breast cancer is a hormone dependent disease.<sup>[3]</sup> Breast cancer occurs when breast epithelial cells grows in abnormal way. HER2/neu, ER, PR, BRCA1, BRCA2 are the well known influencing factors responsible for breast cancer initiation. The major issues that limit the currently available breast cancer treatment are high cost, poor availability and resistance to chemotherapeutic agents. To overcome this problem researchers are working on several novel approaches i.e. “Novel drug targets & Novel target therapies” Since from past few years, mammogram is playing a huge role for decreasing incidence rate in developed countries. Breast cancer is adversely affecting the “quality of life” of patients and its impact has been increasing on the Social capital, population structure and economic growth. Need for novel anti breast cancer agent and novel early diagnosis technique is necessary to combat one of the most serious crises facing Human development.

**KEYWORDS:-** Breast cancer, HER2/neu, ER, PR, BRCA1, BRCA2, Novel drug targets, Novel target therapies, Quality of life assessment, Mammogram, metastasize, Biopsy, Gene- therapy.

### INTRODUCTION

Breast cancer is a heterogeneous disease & since past 2 decades it has been estimated that breast cancer is a common malignancy in women of world. The data suggests that higher numbers of incidences are estimated in developed countries such as U.K., U.S., and CANADA but nowadays developing counties also suffers with the high numbers of breast cancer incidences. But past few years the incidences of breast cancer is continuously fallen in developed countries such as U.S., U.K. because of recent advancement in treatment & diagnosis approaches.

“The cells of breast become abnormally multiply without any control or order to form a cancerous tumor that is called Breast cancer”. Breast cancer starts from epithelial cell linings of the ducts (that work as a carrier of milk to the nipple) that called Ductal type of cancer. Similarly the other forms of breast cancer that starts in glands (that produce milk) that is called lobular cancer or in other parts of the breast. In case of later stage of breast cancer the cancerous tumor moves to other tissue or distance parts of the body. If in case of breast cancer cells spreads (metastasize), cancerous cells most often appear in site of bones, liver, lungs, or brain. Tumors that starts at site and

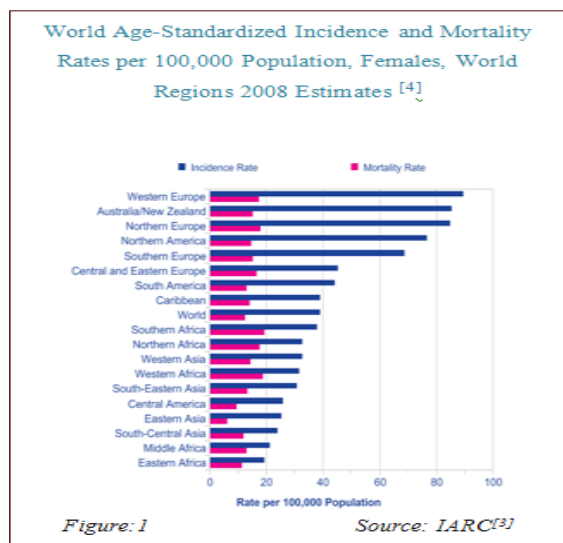
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then spread to other areas of the body are called metastasize cancer and this type of breast cancer is incurable.

## INCIDENCES

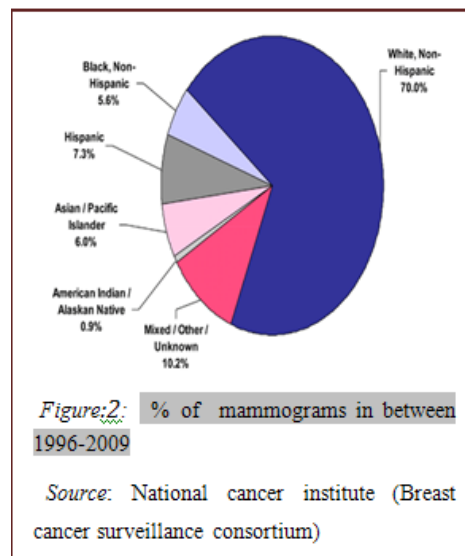
“Breast cancer is a hormone-dependent disease. The age during menarche, 1<sup>st</sup> pregnancy, & fulltime menopause is the major factor responsible for the incidence of breast cancer in women.” [2].

**BY AGE:** The breast cancer age standardized incidences of the world in 2008 (figure-1[3]) estimated by the ICD (International classification of disease) coding system set by the W.H.O. the data suggests that the incidences of breast cancer was high in Europe & U.S. countries than African & Asian countries. But from past few years the incidence rate are continuously coming down in developed countries [U.K. & U.S.]. It is estimated by American cancer society that the major factor behind reduced incidence rate is the regular mammograms.



## Mammograms impact on incidence

In developed countries routine mammogram is playing a key role for decreasing incidence rate. Figure:2 shows the data of women who taken mammogram in between 1975-2009.



## PATHOLOGY

Breast cancer initiation and development has different types of pathways that depends on the various factors or receptor those responsible for the breast cancer initiation and progression.

Mutation in epithelial cell, HER-2, ER, PR, BRCA1 and BRCA2 are the main target or receptor for development of the breast cancer.

## Pathology of hereditary breast cancer:

Various risk factors are responsible for breast cancer have been identified such as positive family history, early minarch, and a positive family history, late menopause, and nulliparity. The cause of breast cancer may include any one of this genetic, hormonal, lifestyle, dietary and environmental cause. A number of genes conferring high risk of breast cancer includes BRCA1 and BRCA2<sup>[4][5]</sup> P53 “Li-fraumeni syndrome”<sup>[6]</sup> & PTEN “Cowden syndrome”<sup>[7]</sup> have been identified where P53 and PTEN are associated with rare cancer syndrome. Almost it is clear that variants of many genes mediate the overall susceptibility of breast cancer. These genes are evidenced in literature such as RAD51, ATM, CHEK2, BRIP1, PALB2, and NBS1<sup>[8-</sup>

<sup>12]</sup>conferring small to moderate risk of breast cancer.

<b>Stage I</b>	Tumour up to 2cm No lymph nodes affected No evidence of spread beyond the breast
<b>Stage II</b>	Tumour between 2cm and 5cm and/or; Lymph nodes in armpit affected No evidence of spread beyond armpit
<b>Stage III</b>	Tumour more than 5cm Lymph nodes in armpit affected No evidence of spread beyond armpit
<b>Stage IV</b>	Tumour of any size Lymph nodes in armpit often affected Cancer has spread to other parts of the body

Source: [info.cancerresearchuk.org](http://info.cancerresearchuk.org)

It has been well known that BRCA1 and BRCA2 germ line mutation resulting in breast cancer differ in different cases and the difference lies in morphology, molecular, and immune phenotype vary in age matched sporadic & familial breast cancer in non BRCA1 or 2 patient cases.<sup>[13-16]</sup> BRCA1 and BRCA2 perform regulation of cell cycle, DNA repair, transcriptional regulation & chromatin remodeling, regulation of RAD51 activities and DNA recombination respectively.

BRCA1 and BRCA2 functions loss leads to following activities such as non-conservative/error prone, potentially mutagenic and ultimately result into genomic instability contributing to the cancer predisposition.<sup>[17]</sup>

### Clinical symptoms

The general symptoms of breast cancer at early stage such as...

- \* Presence of lump or swelling as a mass.
- \* Arm pit (lymph node) swelling.
- \* Bloody or clear discharge from nipple.
- \* Nipple pain and retracted inverted nipple.
- \* Unusual breast pain

Advanced stage of disease also some symptoms are mainly occurs such as...

- \* Bone painfulness (metastases in bone)
- \* Loss of appetite (Metastases in liver)
- \* weight loss (Metastases in liver)

### CURRENT TREATMENT APPROACHES & THEIR IMPACT

**Cancer treatment can be local /systemic therapy:**

\* Local therapy: It includes Surgery and Radiation therapy:

The process in which involves x-rays or other types of high energy radiations either for killing cancerous cells or to inhibit their growth.

The two types of radiation therapy are used in treatment of breast cancer.

1) External radiation therapy: - The process in which a machine that present from outside the body uses for sending radiation toward the cancerous cells and destroyed them.

2) Internal radiation therapy: - In this process involves the use of radioactive substance by wire, seeds, needle, (sealed) catheters for delivery it into or near by the cancerous cells/tumors.

The area of skin treated by radiation therapy may show some **side effects** after **radiation therapy** such as itchy, tenderness, redness, dry and breast may feel tight and heavy.

**Surgery:** Remove the cancer from the breast.

\* **Breast-conserving surgery:** The removal of the cancer cells from breast but not the breast with the help of an operational procedure.

\* **Lumpectomy:** A minor surgery for removal of the lump i.e. tumor as well as normal surrounding tissues.

\* **Partial mastectomy:** It is a surgery process for the removal of cancerous breast part including surrounding normal tissue and suspected or

required chest muscles epithelial lining under cancerous breast part may get removed.

\* **Total mastectomy:** As the name suggest that in this process whole breast has removed that called total mastectomy and for biopsy of the under arm lymph node at the time of breast surgery that may be removed.

**Side effects with surgery** i.e. pain, bleeding, swelling, and infection are possibilities seen after the surgery process

### Biopsy of Sentinel lymph node

The removal of sentinel lymph node in between surgery for the purpose of Sentinel lymph node biopsy.

In this method a specific radioactive substance is use to inject near the tumor and radioactive substance flows through the ducts of lymph to the lymph node than removed 1<sup>st</sup> lymph node who received the substance and examine either lymph node has cancerous cells or not.

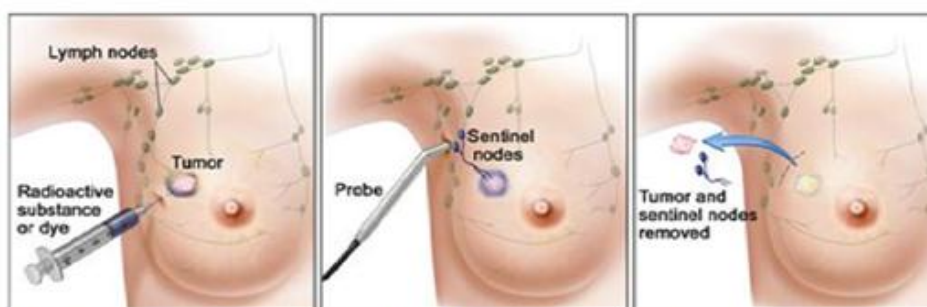


Figure3: "process of sentinel lymph node biopsy" Source: Breastcancer.org

### Systemic therapy

#### Chemotherapy:

The main approach of chemotherapy in cancer treatment is to stopping cancer cells to divide or killing them by the use of drugs. Two types of chemo therapy methods are mostly used

systemic chemotherapy and regional chemotherapy.

Adjuvant therapy are given after the completion of surgery process to reduce the chance of recurrence of breast cancer and neoadjuvant therapy are given before the surgery process to reduce or shrink the tumor size, surgery related decisions are made after neoadjuvant therapy.



Figure: 4 improvement in chemotherapy approach

Source: American cancer society

Side effects with chemotherapy i.e. diarrhea, fatigue, fertility issues, memory loss,

menopause and menopausal symptoms, mouth and throat sores, vaginal dryness.

**Targeted therapy:** Targeted therapies are one of the important options to treat breast cancer with the help of drugs. The mechanism of targeted therapy is to identify the cancerous cells or tumors and directly attack on cancerous cells or tumors without causing any kind of harm to normal cells of the breast.

Nowadays tyrosine kinase inhibitors & monoclonal antibodies are mainly used as a targeted therapy for breast cancer.

A monoclonal antibody, Trastuzumab (Herceptin) is useful in treatment of HER-2 patient and trastuzumab blocks the effects of the HER2 protein. Tyrosine kinase inhibitors inhibit the tumors growth by blocking the signals that are needed for growth of tumors.

**Hormone therapy:** Hormones are one of the known causes of breast cancer. Hormone therapies are used against Estrogen<sup>+ve</sup> patient's treatment. Tamoxifen is well established drug for treatment of Estrogen<sup>+ve</sup> since past two decade. Tamoxifen is the 1<sup>st</sup> discovered target therapy drug in the history of any cancer target therapy. But side effects such as hot flashes, discharge from vagina etc. limits the tamoxifen.

#### Limitation of currently available treatment approaches

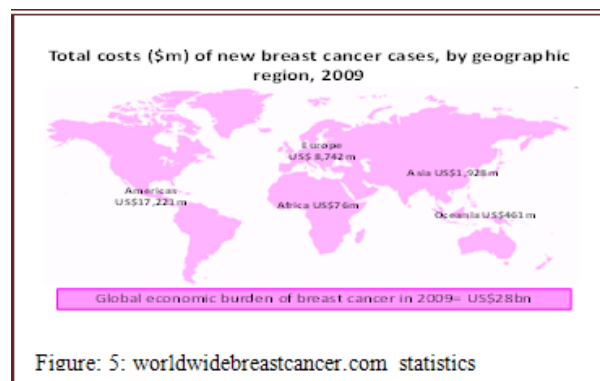
Hormone therapy, Targeted therapy, surgery and radiation therapy are the currently available treatment approaches for breast cancer. Chemotherapeutic agents (trastuzumab, tamoxifen, bevasuzumab, lapatinib etc.) are plays a major role such as in hormone therapy, before or after surgery process, targeted therapy but side effects with chemotherapy, high cost of trastuzumab, bevasuzumab etc. limits the currently available treatment. High cost also limits the availabilities of these drugs.

The majority of patients who survive with metastatic breast cancer they initially respond to trastuzumab but after one year of treatment they shown resistance to trastuzumab.

Chemotherapy, radiation therapy, and surgery are causes some side effects that limit this approaches.

#### Cost and Availability: -

Breast cancer treatment high cost is mainly due to expensiveness of chemotherapeutic drugs and drugs that are used in target therapy such as trastuzumab, tamoxifen, bevasuzumab etc. The figure: 5 show that the whole world suffers with breast cancer high cost. Breast cancer treatment is expensive so it is not widely available so majority of patients do not have proper access to treatment approach which limits the therapy & promotes breast cancer burden globally.



#### Treatment-refractory patient:

Treatment refractory patients are also one of the major issues for current treatment approach that limits the effective therapy and chemotherapeutic agents those used in breast cancer treatment. Research had shown that currently most of patients are unresponsive to chemotherapy treatment.

Various types of mechanisms are known in that Cancer cells become resistant to chemotherapy.

Here is one example for TRP. Expression of ABC transporters, including MDR1, leads to resistance through the active efflux of drugs, and each type of transporter is able to carry several different types of drugs, particularly anthracyclines and taxanes.<sup>[19]</sup>

### Initiative treatment approaches

#### Novel drug targets:

Breast cancer called a heterogeneous disease and the early stage diagnosis of breast cancer is still a major problem associated with early stage cure or treatment.

Nowadays, the researchers are mainly focused on novel drug targets approach for directly attack on the breast cancer specific target and terminate their action. Several of targets are found and currently in evaluation.

**Table: 1: - Novel drug targets in clinical trial**

Agents	Application	Clinical Phase of development	Targets	Ref.
Lapatinib and capecitabine versus capecitabine	Advanced breast cancer	iii	EGFR, HER+	20,21
Lapatinib and paclitaxel	Inflammanatory, neoadjuvent	ii	EGFR,HER+	22
Ad5CMV-p53 and docetuxel/doxorubicin	Primary BC, neoadjuvent	ii	p53	23
Tipifarnib and gemcitabine	Metastatic BC	ii	Ras, Farnesyl transferase	24
Tipifarnib and letrozole	Advanced BC	ii	Ras, Farnesyl transferase	25
Lanafarnib and anastrozole	Metastatic BC	ii	Ras, Farnesyl transferase	24
Bortezomib	Metastatic BC	ii	26S Proteasome	26
Bortezomib	Metastatic BC	i	26S Proteasome	28
Bevacizumab	Metastatic BC	i/ii	VEGF	29
Bevacizumab	Metastatic BC	ii	VEGF	30

Cetuximab and paclitaxel	Advanced BC	iii	EGFR	31
Erlotinib	Primary BC, Neoadjuvent	i	EGFR	32
Evorolimus(RAD-001)	Primory BC, Neoadjuvent	iii	mTORi	38
Evorolimus(RAD-001)	Metastatic BC, Bone metastatic	ii	mTORi	38
Pertuzumab		i	mAb, HER2	33
E1A		i	Transcriptional inhibitor	33
AutoVac <sup>®</sup>		ii	DNA Vaccine	33

#### **Novel target therapies: -**

Selection of agents, timing of initiation and discontinuation, and incorporation of novel therapies remain both a science and an art. For many patients, sequential use of different therapies can translate into years of prolonged survival with preserved quality of life. Several novel targets are currently in clinical trial.

**Table2:- Drug therapy** <sup>[34]</sup>

Drug therapy	Drug	In development	Cancer type
Polymeric-Nanoparticles (50–200)	Doxorubicin, Paclitaxel platinum based drugs, Docetaxel	Several products are in clinical trials (Phases I–IV) and in vivo	metastatic breast cancer

**Nanotechnology:** Clinical trial investigating efficacy of target based drug delivery system using nano-carriers approach leading to anti-tumor activity.

**Gene therapy:** recent vast knowledge of tumor suppressors genes and proto-onco genes in genesis of malignancy leads to development of various gene therapy tactics. Some are based on ablation or restoration of such vitally involved genes and some are based on immune system modulation which can activate the mechanism of anticancer drug defense targeting at drug resistance genes to combat drug resistance. <sup>[35]</sup>

**Oncogenes Inactivation:** - Antisense strategies to oncogenic proteins is widely undergoing via clinical trials. An approach is to inhibit the transcription of oncogene by E1A (adenoviral gene) that too hinders the transcription of erbB2 is useful in over expressing oncogenic protein cancer. <sup>[35]</sup>

**Augmentation of tumor suppressor genes: -** Over several number of tumors suppressor gene mutation associated with variety of neoplasia have been identified, and the strategies is to use the vector such as

adenoviral vector for delivery p53 and genetic repair strategy is another effective approach.<sup>[36]</sup>

**Cell- target suicide:** - An approach of creating an artificial difference between neoplastic & normal tissue via prodrug conversion into toxic metabolite by genetically engineering tumor cells.<sup>[37]</sup>

Chemo protection, ectopic cytokine expression, virus mediated oncolysis immune enhancement, immune modulation are some of the other important ongoing approaches to combat the burden of breast cancer.<sup>[36]</sup>, anti HER-2 target therapy.

## DISCUSSION

### Critical assessment on novel target therapy

Over expressions of HER-2 /neu protein have been evidenced in 20-30% of metastatic breast cancer and numerous numbers of patients are affected with HER-2 over expression.

HER-2(neu) is a potential novel target for treatment of metastatic breast cancer. Till now metastatic breast cancer is a incurable disease so a reliable & therapeutically effective drug (single/with combination) or novel target is

required for treatment or improvement in “disease free survival” of the patient but the major issue associated with anti HER-2 target therapy is most reliable or efficient ASSAY is not available for detection of HER-2 status (prognosis/response).

Some of the pre-clinical studies data suggests that some molecular targeted agents have given low response whenever they evaluate in clinical trial.<sup>[38]</sup>

Various challenging issues associated with Novel HER-2 target therapy such as side effects, high cost and resistance to chemotherapeutical agents, “incurability of metastatic breast cancer”.

## CONCLUSION

To successfully overcome with breast cancer, various novel target therapies & new diagnosis approaches are currently in clinical evaluation. Mammography plays a major role in reduction of incidences. Metastatic breast cancer still incurable but HER-2 is a potential novel target & will be useful for improve “quality of life” & survival of patients

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