

BREAST CANCER

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INTRODUCTION

The general aspects of cancer have been described in details in our first review article. It also includes the need for doing work in cancer which is a difficult area for in vivo testing. The article also speaks on two types of cancer [breast cancer in females & prostate cancer in males] which are prevalent globally & used in the drug development.

For every drug to be developed FDA scrutinizes very carefully the data before giving approval & marketing authorization.

We are very happy that we have written the article on breast cancer in the month of October 2012 which coincides with Breast Cancer Awareness Month, which is an annual campaign to increase awareness of the disease.

In this article we are presenting our work on breast cancer & evaluation parameters for new proposed breast anticancer drugs. The third part of the series to be published shall have prostate cancer.

Importance of Awareness¹

Breast cancer accounts for 19-34% of all cancer cases among women in India. In India the incidence/mortality ratio is 0.48 compared with 0.25 in North America. Late diagnosis is a major factor for this high mortality as most patients present in advanced stage of the disease. This is attributed to lack of awareness and non-existent breast cancer screening programs in rural resettlement colony in India. As breast cancer is a topic that is not freely discussed in India because of cultural taboo, there is an urgent need for information and education on awareness of breast cancer and its early detection measures.

Importance of Breast Cancer on basis of statistics

Based on National Cancer Institutes (NCI) SEER Cancer Statistics Review, It is estimated that 226,870 women will be diagnosed with and 39,510 women will die of cancer of the breast in 2012².

According to the National Alliance of Breast Cancer Organization, breast cancer is the

second most common form of cancer in women. It is a very important disease and needs continuous attention and dedication by the medical fraternity. It is a common myth that breast cancer occurs only in females; the fact is that even males can suffer from it, but the prevalence among males is quite low. The incidence ratio among male to female is approximately 1:100. Unfortunately no work is done for new anticancer drugs in drug development to the best of our knowledge. It was Dabur that came

out with Paclitaxel which is used as anticancer drug. Because of its lethality, breast cancer is the common field of research among science fanatics.

Breast cancers are potentially life-threatening malignancies that develop in one or both breasts. The structure of the female breast is important in understanding this cancer³ [see fig no. 1]

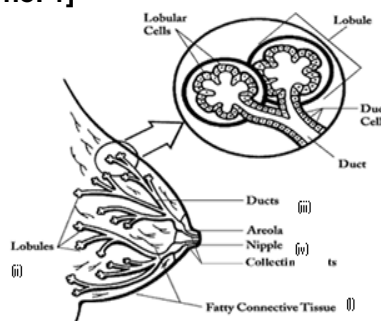


Fig. 1:

1. The interior of the female breast consists mostly of fatty and fibrous connective tissues.
2. It is divided into about 20 sections called lobes. Each lobe is further subdivided into a collection of lobules.
3. Structures that contain small milk-producing glands. These glands secrete milk into a complex system of tiny ducts.
4. The ducts carry the milk through the breast and converge in a collecting chamber located just below the nipple.

Breast cancer is either noninvasive (referred to as *in situ*, confined to the site of origin) or invasive (spreading).

Noninvasive Breast Cancer³

Noninvasive breast cancers include:

- Ductal carcinoma in situ (also called intraductal carcinoma or DCIS). DCIS consist of cancer cells in the lining of the duct. DCIS is a non-invasive, early cancer, but if left untreated, it may sometimes progress to an invasive, infiltrating ductal breast cancer.
- Lobular carcinoma in situ, or LCIS. Although it is technically not a cancer, lobular carcinoma in situ is a marker for an increased risk of invasive cancer the same or both breasts.

Invasive Breast Cancer³

Invasive cancer occurs when cancer cells spread beyond the *basement membrane*, which covers the underlying connective tissue in the breast. This tissue is rich in blood vessels and lymphatic channels that are capable of carrying cancer cells beyond the breast. Invasive breast cancers include the following:

- Invasive (also called infiltrating) ductal carcinoma. This is invasive breast cancer that penetrates the wall of a milk-passage duct. It comprises between 70 - 80% of all breast cancer cases.
- Invasive (also called infiltrating) lobular carcinoma. This invasive cancer has spread through the wall of a milk-producing lobule. It accounts for 10 - 15% of all breast cancers. It may sometimes appear in both breasts, sometimes in several separate locations.

Statistics of incidences⁴

[Based on age groups in Females]

From 2005-2009, the median age at diagnosis for cancer of the breast was 61 years of age. According to SEER incidence and mortality rate with respect to age is as follows-

Age group	% incidence and mortality
under age 20	0.0
between 20 and 34	1.8
between 35 and 44	9.9
between 45 and 54	22.5
between 55 and 64	24.8
65 and 74	20.2
between 75 and 84	15.1
85+ years of age	5.7

The age-adjusted incidence rate was 124.3 per 100,000 women per year. These rates are based on cases diagnosed in 2005-2009 from 18 SEER geographic areas.

Risk Factors⁵

Age and gender

Risk of developing breast cancer increases with age. Most advanced breast cancer cases are found in women over age 50. Women are 100 times more likely to get breast cancer than men.

Family history of breast cancer

About 20 - 30% of women with breast cancer have a family history of the disease.

Genes

Some people have genes that make them more likely to develop breast cancer. The most common gene defects are found in the BRCA1 and BRCA2 genes. These genes normally produce proteins that protect one from cancer. If a parent passes a defective gene, then there is an increased risk for breast cancer. Women with one of these defects have up to an 80% chance of getting breast cancer sometime during their life.

Menstrual cycle

Statistically it has been reported that women who got their periods early (before age 12) or went through menopause late (after age 55) have an increased risk for breast cancer.

Alcohol use

Majority of Indian women are away from it but drinking more than 1 - 2 glasses of alcohol a day may increase risk for breast cancer which must be occurring in metropolitan cities.

Childbirth

Women who have never had children or who had them only after age 30 have an increased risk for breast cancer. Being pregnant more than once or becoming pregnant at an early age reduces your risk of breast cancer.

DES

Women who took diethylstilbestrol (DES) to prevent miscarriage may have an increased risk of breast cancer after age 40.

Hormone replacement therapy (HRT)

Risk for breast cancer increases if person have received hormone replacement therapy with estrogen for several years or more.

Obesity

Obesity has been linked to breast cancer, although this link is controversial. The theory is that obese women produce more estrogen, which can fuel the development of breast cancer.

Radiation

Radiation therapy as a child or young adult to treat cancer of the chest area, have a much higher risk for developing breast cancer.

Prognosis⁶

Advanced anti-cancer technology and effective combination therapy have together increased the lifetime of patients with breast cancer. However, even after treatment, possibility of breast cancer spreading to other parts of the body cannot be ruled out unless the later was identified and treated in the curable stage. Breast cancer may come back to haunt one's life even after complete removal of tumor from breast tissue and nearby lymph nodes. Thus in the nutshell, more advanced the breast cancer more are the chances of revisit.

Detection and Diagnosis⁷

Breast cancer is sometimes found after symptoms appear, but many women with early breast cancer have no symptoms. This is why getting the recommended screening tests before any symptoms develop is so important. The three major ways which are conventional methods to screen for breast cancer are self examination, clinical

examination, and mammography. Since none of the methods is 100% effective, it is suggested that all three be used regularly.

Given below is a list of tests used in breast cancer detection and diagnosis:

Detection

- Breast Exam
- Mammography
- Ultrasound
- Breast MRI

Diagnosis

- Fine Needle Aspiration
- Core Needle Biopsy
- Breast Tumor Pathology
- Sentinel Lymph Node Biopsy

One of the new breast cancer detection techniques being studied is:

Digital Tomosynthesis^{8a,b,c} [Advanced Technique]

Digital tomosynthesis is an imaging method in which multiple X-ray images are taken of a stationary, compressed, breast.

Signs and Symptoms⁵

Breast cancer does not show any signal in its initial stages and therefore regular check up of breasts is an essential step towards identification of breast cancer in its early curable stage.

	Symptoms
Women	<ul style="list-style-type: none"> • Breast lump or lump in the armpit that is hard, has uneven edges, and usually does not hurt • Change in the size, shape, or feel of the breast or nipple -- redness, dimpling, or puckering of breast tissues resembling the skin of an orange. • Fluid coming from the nipple -- may be bloody, clear to yellow, green, like pus.
Men	<ul style="list-style-type: none"> • breast lump • breast pain and tenderness
Advanced stage	<ul style="list-style-type: none"> • Bone pain • Breast pain or discomfort • Skin ulcers • Swelling of one arm (next to the breast with cancer) • Weight loss^[1] • Paget's disease- eczematoid skin changes such as redness, mild flaking of the nipple skin, burning, pain, itching and many more

If person shows any signs or symptoms stated earlier then that might mean breast cancer then breasts will be thoroughly examined & if physical exam suggest breast cancer might be

present, more tests will probably be done which include imaging tests, looking at samples of nipple discharge, or doing biopsies of suspicious areas.

Diagnostic mammograms

Mammography is a specific type of imaging that uses a low-dose x-ray system to examine breasts. While mammography is the best screening tool for breast cancer available today, it does not detect all breast cancers. Also, a small portion of mammograms indicate that a cancer could possibly be present when it is not (called a false-positive result). Mammograms are not perfect at finding breast cancer.

Magnetic resonance imaging (MRI) of the breast

MRI scans use radio waves and strong magnets instead of x-rays.

Breast ultrasound

Ultrasound, also known as sonography, uses sound waves to outline a part of the body.

Ductogram

This test, also called a galactogram. It helps to determine the cause of nipple discharge.

Computed Tomography (CT or CAT) Scan

A CT or CAT scan is a diagnostic imaging procedure that uses a combination of x-rays and computer technology to produce images.

Positron Emission Tomography (PET)

Positron emission tomography (PET) is a type of nuclear medicine procedure that measures metabolic activity of the cells of body tissues.

Molecular Breast Imaging

The new technology, called Breast-Specific Gamma Imaging, also known as Molecular Breast Imaging, or BSGI/MBI, may be used with selected patients as a secondary procedure to mammography, ultrasound and MRI. Beaumont Hospital, Troy is the first hospital in Southeast Michigan to use this technique.

Biopsy

A breast biopsy is a procedure in which samples of breast tissue are removed with a special biopsy needle or during surgery to determine if cancer or other abnormal cells are present.

Nano-Magnets to Detect Breast Cancer

Researchers from the University of Houston have developed a better, cheaper hand held tool for locating sentinel lymph nodes in breast cancer patient.

somo-v ABUS device[New]⁹

The latest ultrasound screening device for Dense Breasts Approved by the US FDA on Sept. 18, 2012.

If breast cancer is diagnosed, more tests will be carried out to confirm if the cancer has spread. This is called staging, which decides future treatment. Breast cancer stages range from 0 to IV. The higher the staging number, the more advanced the cancer.

TRIPLE NEGATIVE BREAST CANCER¹⁰

Triple negative (TN) breast cancer is an aggressive subtype of breast cancer that accounts for 10-15% of breast cancer cases. The term "triple negative" describes tumors that do not produce significant amounts of any of the proteins listed above; TN tumors are ER minus (ER-), PR minus (PR-), and HER2 minus (HER2-). In the U.S. TN breast cancer occurs more often (>10%) in African American women than in non-African American women. The reasons for the differences in TN breast cancer occurrence in different populations is not yet clear but is an active area of research.

Cancer Staging¹¹

Staging is important for identifying appropriate treatment options for a particular cancer and individual.

TNM Staging

One common method of staging is the T/N/M system, which identifies three important characteristics

of cancer and assigns a level of severity to each of those characteristics to determine an overall degree of severity for the patient's cancer.

- The "T" component labels the size of the tumor and is accompanied by a number 1-4 that further identifies the size and local spread of the tumor. A higher number indicates either a larger tumor or one that has a greater effect on the surrounding tissues.
- The "N" component describes lymph node involvement and a number from 0-2 indicates the level of lymph node involvement, where a higher number indicates a more severe condition. A relatively small tumor that has spread to surrounding lymph nodes may be classified as a more severe N1 or N2 cancer despite its small size.
- The "M" component indicates if any distant metastases were identified with the cancer, M0 indicates that there are no distant metastases, and M1 indicates that there are distant

metastases associated with the cancer. Another letter that corresponds to the system or organ affected by the metastasis may also be paired with the M. This gives further information about the cancer's severity, since the site of metastasis may alter a patient's prognosis.

Each tumor is assigned a series of identifiers, which include a T, an N, and an M component. Together these labels give insight into the severity of the cancer. This set of values is then used to establish a simpler, overall stage for the cancer, which is then described as stage I, II, III, or IV. For example, a T1, N0, M0 tumor is most likely a stage I cancer. This simplified staging method can help physicians and patients make treatment decisions and also give an indication of the prognosis.

Centres for Detection & Diagnosis In INDIA

HealthCare Global Enterprises Ltd-----

Bangalore.

Kokilaben Dhirubhai Ambani Hospital & Medical Research-----**Mumbai.**

Oncopath Diagnostics-India's first virtual Cancer Pathology centre-----**Pune.**

Chennai Breast Centre is a one stop comprehensive centre-----**Chennai.**

Pathophysiology^{12a,b}

Role of Genetics

Normal cells have the ability of controlled division, they remain attached to a particular tissue after divisions, do not invade other tissues and undergo apoptosis when they are not needed. Cells are protected from apoptosis until they are needed by several proteins and pathways like PI3K/AKT pathway, RAS/MEK/ERK pathway. Normally a protein, PTEN turns off the PI3K/AKT pathway when the cell is not needed, hence apoptosis occurs. The PTEN coding gene when mutated fails to turn off the PI3K/AKT pathway and hence growth and division of breast cells goes on without any vigilance, leading to breast cancer. Mutations leading to breast cancer have been linked to estrogen exposure. Also, over-expression of leptin in breast adipose tissue leads to intensified cell proliferation and cancer. Genes like, p53, BRCA1 and BRCA2 are involved in DNA damage repair. Mutations in these genes lead to a handicapped DNA repairing system and so uncontrolled cell growth with damaged DNA copy.

As defined in our earlier article, cancer is abnormal growth of the normal cells. This also applies to breast cancer.

Breast Cancer Treatments^{13 a,b}

The treatment given for cancer is variable and dependent on a number of factors including the type, location and damage stage of disease and the health status of the patient. Most treatments are designed to either directly kill/remove the cancer cells or to lead to their eventual death by depriving them of signals needed for cell division. Other treatments work by stimulating the body's own defenses against the cancer cells.

Often the different types of treatment are used in combination, either simultaneously or sequentially.

- **Surgery**

Often the first line of treatment for many solid tumors. In cases in which the cancer is detected at an early stage, surgery may be sufficient to cure the patient by removing all cancerous cells. Benign growths may also be removed by surgery.

- **Radiation**

May be used in conjunction with surgery and/or drug treatments. The goal of radiation is to kill the cancer cells directly by damaging them with high energy beams.

- **Chemotherapy** A term used for a wide array of drugs used to kill cancer cells. Chemotherapy drugs work by damaging the dividing cancer cells and preventing further reproduction.

- **Hormonal Treatments**

These drugs are designed to prevent cancer cell growth by preventing the cells from receiving signals necessary for their continued growth and division.

- **Targeted Therapy**

This class of drugs is relatively new in the treatment of cancer. They work by targeting specific proteins and processes that are limited primarily to cancer cells or that are much more prevalent in cancer cells.

- **Antibodies**

This treatment involves the use of antibodies to target cancer cells. While antibodies are naturally occurring proteins in our bodies, the antibodies used in the treatment of cancer have been manufactured for use as drugs. The antibodies may work by, either depriving the cancer cells of necessary signals or causing the direct death of the cells; because of their specificity, antibodies may be thought of as a type of specific inhibitor.

Biological Response Modifiers

These treatments involve the use of naturally occurring, normal proteins that stimulate the body's own defenses against cancer.

Vaccines

The purpose of cancer vaccines is to stimulate the body's defenses against cancer. Vaccines usually contain proteins found on or produced by cancer cells. By administering these proteins, the treatment aims to increase the response of the body against the cancer cells.

1. A vaccine known as L-BLP25 (Stimuvax), that targets cancer cells, given in combination with the standard hormonal therapy for breast cancer, significantly increases survival when tested in mice.[For more details see Futurity.org --vaccine]¹³
2. A breast cancer vaccine, AE37 already shown to elicit a powerful immune response in women with varying levels of HER2 expression has the ability to improve recurrence rates and is well tolerated in an adjuvant setting, according to new research from a clinical trial led by researchers at The University of Texas.[For more details refer site of MD Anderson Cancer Center]^{13d}

- **Complementary and Alternative Medicines[CAM]**^{13e}

These treatment methods are not practiced by conventional western medicine. They can include herbal, animal derived, and mind-body approaches to treating cancer. The scientific evidence about the efficacy of these treatments either refutes cancer fighting claims or is inconclusive at the present time.

The following five types of treatment are recognized by the National Center for Complementary and Alternative Medicine

- **Whole medical systems**

These include culturally based healing traditions such as traditional Chinese medicine (acupuncture) and Ayurveda (a therapy originating in India that uses herbs, massage, and yoga), as well as Western medical systems such as homeopathy and naturopathy.

- **Mind-body medicine**

These therapies involve the mind's capacity to influence the body's functions. They include prayer, hypnotherapy, meditation, imagery, visualization, music therapy, and art therapy.

- **Biologically based practices**

These include nutritional therapy, supplements, vitamins, and herbal medicine.

Manipulative and body-based practices Included here are massage therapy as well as chiropractic and osteopathic manipulation.

- **Energy medicine**

These therapies, which are based on the energy fields that surround and permeate the body, include reiki and qigong. [Qigong is a powerful system of healing and energy medicine from China].

Under CAM the development is more pronounced on Chinese system of medicine

The Food and Drug Administration (FDA) is responsible for approving drugs that can be used by oncologists to treat cancer and also evaluates drugs or other products that may be able to reduce the risk of cancer.

Research In Drug Discovery and Development¹⁴

Drug development for human cancer is a lengthy and costly business, and many potentially promising therapeutics never make it to the clinic - yet in breast cancer, the past 10 to 15 years have seen the introduction of several new anticancer agents (paclitaxel, docetaxel, capecitabine and vinorelbine), two new classes of endocrine therapies (the aromatase inhibitors letrozole, anastrozole and exemestane; and the pure oestrogen receptor (ER) antagonist fulvestrant), and most recently targeted biological therapies against the human epidermal growth factor receptor-2 (HER2),(trastuzumab, lapatinib) and vascular endothelial growth factor (bevacizumab). For each drug, the clinical development process has spanned a minimum of 10 to 15 years, culminating in large expensive pivotal registration trials, each costing millions of dollars in research and development expenditure.

While the incremental benefit provided by each new therapy in advanced breast cancer

may be relatively small, three of these therapies (taxanes, aromatase inhibitors, trastuzumab) have now been incorporated into adjuvant therapies in early breast cancer where they are likely to make a much greater impact on survival in this disease. While these are indeed notable success stories, the challenges now faced by the next generation

of molecularly targeted therapeutics are substantial.

Leading companies like Merck, Pfizer, Abbott Laboratories, Novartis, AstraZeneca, Eli Lilly, GlaxoSmithKline and many more are continuously engaged in drug discovery and many new molecules are undergoing clinical research.

The details are given in Table no.1

PHARMACEUTICAL COMPANY	NEW MOLECULES	USE
MERCK	18F-FLUOROTHYIMIDINE	DIAGNOSIS OF BREAST CANCER
ENDOCEUTICS	ACOLBIFENE	PREVENTION OF BREAST CANCER
ASCEND THERAPEUTICS	AFIMOXIFENE	PREVENTION OF BREAST CANCER
BIPAR SCIENCES	INIPARIB	METASTATIC TRIPLE NEGATIVE
ELI LILLY	RAMUCIRUMAB	FOR RECURRENT, REFRACTORY METASTATIC, TUMOR-TARGETED GENE THERAPY
GENTA	TESETAXEL	ADVANCED BREAST CANCER
JOHNSON & JOHNSON	TRABECTEDIN	METASTATIC BREAST CANCER
ROCHE	TRASTUZUMAB-DM1	ADVANCED METASTATIC
GLAXOSMITHKLINE	PAZOPANIB AND LAPATINIB	INFLAMMATORY BREAST CANCER.

Medication¹⁵

Medicines are used to treat breast cancer and also to help relieve side effects of treatment.

Chemotherapy

Chemotherapy often uses several medicines together. Some of the most commonly used medicines are:

- Carboplatin.
- Cyclophosphamide.
- Docetaxel.
- Doxorubicin.
- Fluorouracil.
- Paclitaxel.

Hormone therapy

Tamoxifen or an aromatase inhibitor is recommended for estrogen receptor-positive (ER+) breast cancer. These medicines stop estrogen from fueling ER+ breast cancer.

- Tamoxifen is a medicine that blocks the effect of estrogen on breast cancer cells and normal breast cells.
- Aromatase inhibitors, such as letrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin), are medicines that stop estrogen production in postmenopausal women. Aromatase inhibitors are used to treat early estrogen receptor-positive (ER+) breast cancer. They are also used to treat metastatic or recurrent ER+ breast cancer. An aromatase inhibitor can be used alone or after tamoxifen treatment.

Targeted therapies

- Targeted therapies use medicines or substances that go directly to the cancer cells and don't harm normal cells. They include monoclonal antibodies and tyrosine kinase inhibitors.
- Trastuzumab (Herceptin) is recommended after surgery and chemotherapy for HER-2/neu breast cancer. This medicine is a monoclonal antibody that targets the HER-2 protein. It helps chemotherapy work better.
- Lapatinib, a tyrosine kinase inhibitor, may be used to treat women who have HER-2+ cancer that has progressed even after they have taken trastuzumab.
- PARP inhibitor therapy is another kind of targeted therapy for triple-negative breast cancer (cancer cells that do not have estrogen or progesterone receptors or large amounts of HER2/neu).
- Clinical trial such as investigating hereditary breast cancer was launched in May 2006 in UK. This trial is a phase II trial comparing the platinum-based chemotherapy drug, carboplatin, to the current recommended treatment, docetaxel. The study aims to determine whether carboplatin is a safe and potentially more effective treatment than

docetaxel for breast cancers caused by the inheritance of faulty BRCA genes. Women in the study all have BRCA-associated breast cancer that has spread to other parts of the body.

Stem cells in Breast cancer^{16a,b}

Though the earlier detection and better treatments are bringing hope to people with both early and advanced disease, the survival rate for those with advanced, metastatic breast cancer has not changed significantly for decades. The conventional therapies for advanced breast cancer are limited because they target the wrong cells. These therapies were designed to shrink cancers by killing all the cells in a tumor. Therapies could be more effective, and cause fewer side effects, if they were aimed specifically at a small group of cells within the tumor called cancer stem cells. Breast cancer stem cells - the first to be identified in a solid tumor - were discovered in 2003 by scientists at the U-M Comprehensive Cancer Center in the U.S.A. U-M scientists discovered that just a few cancer stem cells are responsible for the growth and spread of breast cancer. So knowing the percentage of stem cells in a breast tumor could help determine which patients need more aggressive treatment.

Unless the cancer stem cells are destroyed, the tumor is likely to come back and spread malignant cells to other parts of the body, a process called metastasis.

All cells have a unique pattern of proteins, like a fingerprint, on their surface membranes. All breast cancer stem cells have a surface protein marker called CD44, along with very low levels or no levels of markers called CD8, CD4, CD24 and lin. Using specialized equipment and techniques, scientists can separate cells with this combination of protein markers from millions of other cells in a tumor sample.

Chemotherapy and radiation will kill most malignant cells and shrink the tumor, but the cancer often comes back, because these therapies don't kill the stem cells. To cure metastatic breast cancer, treatment must eliminate the cancer stem cells and chemotherapy and radiation alone cannot do that.

In 2006, Cancer Center investigators began the world's first clinical trial of a treatment targeted at breast cancer stem cells. The study was designed to test the safety and tolerability of a new drug in 35 women with advanced, metastatic breast cancer that did not respond to traditional therapy. The experimental drug called MK-0752 blocks a

signaling pathway involved in stem cell growth and development. Patients received the experimental drug in combination with chemotherapy. Researchers believe using a two-drug combination - one to kill cancer stem cells and one to kill the other cells in the tumor - will prove to be the best strategy.

An examination of biopsies showed that the number of cancer stem cells in the tumor decreased after treatment. The pharmaceutical company that owns the experimental drug is determining whether to proceed with additional clinical trials. Cancer stem cells have recently been isolated from several different solid tumors. In breast cancer, the CD44⁺CD24^{-/low} population is considered to comprise stem-like cells. The identification of cancer stem cells has provided new targets for the development of therapeutics.

Breast Cancer & Pregnancy¹⁷

Breast cancer is the most common malignancy occurring during pregnancy. Because more women delay childbearing, the diagnosis of cancer during pregnancy will likely increase. The hormonal changes in the body during pregnancy can accelerate its growth. The disease can be devastating to both the mother and child, so it is essential that pregnant women and their health care providers continue to perform routine breast exams throughout pregnancy.

Patent and Market Size of Breast Cancer Drugs¹⁸

The market for breast cancer drugs represents an area of potential opportunity in both developed and developing countries. Due to effectiveness and advancement in technology, a large number of companies are focusing to develop innovative breast cancer drugs. Further, the companies are forming alliances and agreements to develop effective treatment methods for breast cancer. The details of the companies developing such drugs are mentioned in Table no.1 of the article.

By 2017, Espicom forecasts a modest increase in the number of players in the market-place compared to 2010, with Roche, and GlaxoSmithKline to a lesser extent, triumphing with targeted therapies directed against the specific subset of breast cancer patients with HER2-positive disease.

Inventions for a World free from Breast Cancer have improved from 63% in the early 1960s to 90% in recent years. This reference estimates that sales of leading brands achieved sales of US\$12.7 billion in 2010, with growth due to expanding sales for a number of existing

treatments rather than the launch of new products. Sales were split between chemotherapies, hormonal therapies and novel molecular targeted therapies, with the majority of these agents used in combination. By 2017, Espicom estimates that a total of ten products will command a 77% market share, with the current therapies, Roche's Herceptin and Avastin, along with GSK's Tykerb/Tyverb, accounting for over 80% of these sales and Herceptin is expected to continue as the clear market leader.

By 2019, combined sales of emerging therapies will account for more than one-quarter of the overall market for breast cancer drug treatments, according to the study, which looks at the market over the next decade in the US, France, Germany, Italy, Spain, the UK and Japan.

By 2017, most chemotherapeutic drugs will be available as generics. In addition to anticipated expiry of patent for Sanofi's, Taxotere (docetaxel) and Eli Lilly's, Gemzar (gemcitabine) in 2009-2010, and the US patent on Roche's, Xeloda (capecitabine) in 2013, which results in decrease sales by almost 40% from over US\$2.4 billion in 2010 to around US\$1.5 billion in 2017. This general trend is mitigated somewhat by the newer chemotherapeutic drugs, which are demonstrating sales growth and carving out market share due to their improved safety and efficacy compared to older more established agents.

By 2017, Hormonal therapies (the aromatase inhibitors) will suffer from patent expires in all major markets by 2012, and the report expects significant generic competition and sales for this group to decline by over 92% from US\$3.4 billion in 2010, to just US\$259 million in 2017. With widespread generic versions of the leading selective oestrogen receptor modulator, tamoxifen, the overall market share of branded hormonal therapies will decline as sales fall from US\$4 billion to US\$1.4 billion, a drop of 65%. These declines will be tempered by the relative success of AstraZeneca's Faslodex.

Research in India ¹⁹

Extensive research work on breast cancer detection, treatment including at genetic level has been carried out and ongoing in India. Some of the Institutes are; Department of Surgical Oncology, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, [New Delhi], Cancer Foundation of India, [Kolkata], Regional Cancer Centre, [Trivandrum] and the Kerala State Health Services, ACTREC & ICMR.

The Advanced Centre for Treatment, Research and Education in Cancer (ACTREC) is the new research center of the Tata Memorial Centre and hospital (TMC and TMH). ACTREC plays major role in drug development and emerging therapies, use of cell lines for treatment and prevention of cancer in India. Role of cell lines in the in vitro evaluation has already been described in our first article. As a part of basic research experiments have been initiated to evaluate the role of human sodium iodide symporter (hNIS) as a biomarker for breast cancer diagnosis and treatment using imaging techniques at ACTREC. It also involved in vivo studies on small animal models.

Indian council of medical research (ICMR) is one of the biggest entities contributing the advanced research in India. Highlights of breast cancer research at ICMR:

- Elucidated role of candidate genes mainly BRCA1, BRCA2 and CYP17 in breast cancer susceptibility in Indian women
- Established mutation database for BRCA genes in Indian breast cancer patients, potential founder mutation in Indian patients, high frequency of mutations in early onset group.
- Elucidated the role of detoxifying enzyme genes such as GST in breast cancer in high-incidence regions.

Novel Drug Delivery Systems (NDDS) for Breast Cancer²⁰

Novel drug delivery systems (NDDS) have many benefits, which include improved therapy by increasing the efficacy and duration of drug activity, increased patient compliance through decreased dosing frequency and convenient routes of administration and improved targeting for a specific site to reduce un-wanted side effects.

Thermally Targeted Delivery of a c-Myc Inhibitory Peptide in Vivo Using Elastin-like Polypeptide^{20a}

Researchers at the University of Mississippi Medical Center developed a polypeptide (CPP-ELP-H1) that is responsive to heat and inhibits breast cancer cell growth by blocking the activity of c-Myc, an oncogenic protein.

Liposome-based drug delivery in breast cancer treatment^{20b}

Long circulating macromolecular carriers such as liposomes can exploit the 'enhanced permeability and retention' effect for preferential extravasations from tumour vessels.

“Firing missiles” a missile launching system^{20c}

It can accurately fire at “the target” (cancer cells) they aim for, and the “missile” includes a targeting agent and the bomb (BikDD) - wrapped in fatty balls called liposomes, delivered through intravenous injections that triggers cell suicide — directly to the breast cancer cell or other targeted cancer cells, to eliminate the cancer cells without harming healthy cells.

Recommended Nutraceuticals Supplements for Breast Cancer Patients²¹

The recognized association between nutrition and cancer has been acknowledged by the American Cancer Society and the National Cancer Institute. Depending upon the chemotherapy regimen certain important protective botanical factors may be helpful as supplements. It include Vitamins C and E (alpha and gamma-pherols) and the antioxidant bioflavonoids (colored botanical factors) such as beta carotene, xanthophylls and ellagic acid which can be consumed by selecting at least ten servings of fruits and vegetables each day. Coenzyme Q10 [CoQ10] can be beneficial to breast cancer patients undergoing treatment as it is an important part of the release of energy within each cell. Selenium is a trace element that is important in the regulation of detoxification enzyme activity in the liver and other cells of the body. Soy protein may be beneficial to breast cancer patient. Sulfur amino acids are important in the detoxification process necessary for the liver to remove any chemotherapy agents. Vitamin D3 provides a protective role in breast cancer . Flaxseed Found to Reduce Breast Cancer. Onions significantly reduces the risk of breast cancer. This was also confirmed in the European Journal of Epidemiology of December, 1998, which showed that the greater the consumption of both raw onions

and garlic, the lower the risk of developing breast cancer.

CONCLUSION

In the past, breast cancer was one of the most dreaded forms of cancer due to its fatality rate and because complete recovery often required breast removal. Now, however, treatment options have been expanded and there is a higher probability of full recovery than ever before. It is recommended that every woman should do monthly self-examination and go for mammograms every one to three years to prevent occurrence of breast cancer. Drug developers are focusing on new targets to increase efficacy, reduce toxicity, and avoid strong competition. There are a number of innovative early stage approaches targeting the key signaling pathways in cancer cells. These include PI3K inhibitors, IGFR inhibitors, and CDK inhibitors. Future breast cancer treatment will rely on new combination regimens, identification of new molecular targets, and increased use of biomarkers. The oncology market is undoubtedly moving towards personalized therapy and the breast cancer market is no exception. The outcome of treatment of breast cancer is gradually improving.

It is recommended that women of every family should consult the oncologist from time to time. The women's from rural areas should brought to Metropolitan cities for check-up.

Methods for the early detection of cancer are of utmost importance and are an active area of current research.

The State government particularly in rural India should establish cancer centers and bring in cancer awareness amongst the people of the state. Failing State government, the Central government, Health organizations and NGO's should take over and do the activity.

Glossary

SEER	A premier source for cancer statistics in the US
BRCA1	BReast CAncer gene one & its function is to repair cell damage and keep breast cells growing normally.
BRCA2	BReast CAncer gene two & its function is to repair cell damage and keep breast cells growing normally.
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human Epidermal Growth Factor Receptor 2 & is oncogene.
PI3K/AKT pathway	Is an intracellular signaling pathway important in apoptosis and hence in cancer.
RAS/MEK/ERK pathway	Play key roles in the transmission of proliferative signals from membrane bound receptors.
PTEN	Phosphatase and tensin homolog is a protein, encoded by PTEN gene & mutations of this gene are a step in the development of many cancers.
CD44	Is a cell-surface glycoprotein involved in cell-cell interactions, cell adhesion and migration.

REFERENCES

- Somdatta P, Baridalyne N. Awareness of breast cancer in women of an Urban Resettlement Colony. *Indian J Cancer* 2008;45:149-53
- November 2011 SEER data submission, posted to the SEER web site, 2012. seer.cancer.gov
- Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez M, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA*. 2008 May 14;299(18):2151-63.
- The changing global patterns of female breast cancer incidence and mortality Freddie Bray, Peter McCarron, and D Maxwell Parkin Author information Copyright an License information *Breast Cancer Res*. 2004; 6(6): 229–239. Published online 2004 August 26. doi: 10.1186/bcr932
- Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB, et al. Breast cancer. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2009 Feb;7(2): 122-92. [PubMed Health]
- Warner E. Clinical practice. Breast-cancer screening. *N Engl J Med*. 2011 Sep 15;365 (11):1025-32. [PubMed Health]
- "Mammography and Other Breast Imaging Procedures." American Cancer Society (6- 19-2002). <http://www.cancer.org/Healthy/FindCancerEarly/ExamandTestDescriptions/MammogramsandOtherBreastImagingProcedures/mammograms-and-other-breast-imaging-procedures>.
- A) Niklasan LT, Christian BT, Niklason LE, Kopans DB, Castleberry DE, Opsahl-Ong BH, Landberg CE, Slanetz PJ, Giardino AA, Moore R, Albagli D, DeJule MC, Fitzgerald PF, Fobare DF, Giambattista BW, Kwasnick RF, Liu J, Lubowski SJ, Possin GE, Richotte JF, Wei C-Y, Wirth RF. 1997. *Radiology* 205(2);399-406 [PUBMED] . 8B) Smith AP, Hall PA, Marcello DM. Emerging technologies in breast cancer detection. 2004. *Radiologic Management* 26(4):16-24 [PUBMED]. (8C) Lewin JM, D'Orsi CJ, Hendrick PE. 2004. *Radiologic clinics of North America* 42(5) 871- 874 [PUBMED]
- <http://www.u.systems.com>.
- Demicheli R, Retsky MW, Hrushesky WJ, Baum M, Gukas ID, Jatoi I. Racial disparities in breast cancer outcome: insights into host-tumor interactions. *Cancer*. 2007; 110(9): 1880-1888. [PUBMED]
- American Joint Committee on Cancer. *AJCC Cancer Staging Manual*, 5th ed. Philadelphia: Lippincott-Raven, 1997.
- Roles of the Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR pathways in controlling growth and sensitivity to therapy-implications for cancer and aging, Linda S. Steelman, et al. *AGING*, March 2011, volume.3.No.3 (12B) allagainstcancer.blogspot.com/2012/10/pathophysiology.html
- Abeloff, Martin D. *Abeloff's Clinical Oncology*. 4th ed. Philadelphia: Churchill Livingstone, 2008. (13B) Edmund H. Duthie Jr., Paul R. Katz, Michael L. Malone. *Practice of Geriatrics*. 4th ed. Philadelphia: Saunders, 2007. (13C) Drug-vaccine combo better for breast cancer, Health & Medicine - Posted by Dorsey Griffith-UC Davis on Wednesday, May 23, 2012. (13D) Novel adjuvant therapy shows promise for women with a history of breast cancer in Phase II clinical trial MD Anderson News Release 05/16/2012 Elizabeth Mittendorf, M.D., assistant professor in the Department of Surgical Oncology at MD Anderson (13E) Alternative Breast Cancer Treatments, by Sara Calabro Medically reviewed by Pat F. Bass III, MD, MPH [<http://www.everydayhealth.com/breast-cancer/treating/complementary-and-alternative-therapy>]
- Are current drug development programmes realising the full potential of new agents? The scenario, Stephen RD Johnston, *Breast Cancer Research* 2009, 11 (Suppl 3): S21 doi:10.1186/bcr2440
- National Cancer Institute (2011). Male Breast Cancer Treatment PDQ-Patient Version. Available online: <http://nci.nih.gov/cancertopics/pdq/treatment/malebreast/Patient>.
- Cancer Gene Therapy (2012) 19, 707–714; doi:10.1038/cgt.2012.49; published online 17 August 2012, J Li et al.

- (16B)www.cancer.med.umich.edu/research/stemcells.shtml
17. Cancer J. 2010 Jan-Feb; 16(1):76-82. Breast cancer during pregnancy: maternal and fetal outcomes. Cardonick E, Dougherty R, Grana G, Gilmandyar D, Ghaffar S, Usmani A.
 18. Inventions for a World free from Breast Cancer, Dr. Shoaab Abdul Rahman Lund, 10 January 2012, www.herbacin.info
 19. www.icmr.nic.in and www.actrec.gov.in
 20. Novel Drug Delivery System for Anticancer Drug: A Review, Swatantra K.S. Kushwaha*1, et al, India, International Journal of PharmTech Research, CODEN (USA): IJPRIF ISSN : 0974-4304 Vol.4, No.2, pp 542-553, April-June 2012. (20A)
- Principal Investigator: Gene Leflore Bidwell, III, PhD, University of Mississippi Medical Center, ScienceDaily (Aug. 3, 2011).*
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21. The Cancer Nutrition Center Handbook, An essential guide for cancer patients & their Families, by Carolyn Katzin, MSPH, CNS