CHAPTER 1

INTRODUCTION

1.1. Cancer

The term cancer refers to a malignant neoplasm and arises from the transformation of a single normal cell. Cancer cells are structurally and biochemically different from normal cells. Development of cancer is a complex process; involving genetic changes, as well as the influence of other epigenetic factors (hormonal action, co-carcinogen and tumor promoter effects) that are not in themselves cancer producing, but increase chance of that the genetic mutations will result in cancer. These changes are result of point mutations, gene amplification or chromosomal translocation, often due to the action of certain viruses or carcinogens. The four important characteristics of cancer cells are uncontrolled proliferation, loss of differentiation and function, invasiveness and metastasis. The uncontrolled proliferation may cause changes in growth factors and/or receptors, intracellular signaling pathways; especially those controlling the cell cycle and apoptosis, telomerase expression and tumor related angiogenesis.1,2

1.2. Cancer Etiology

Cancer is a disease resulting when the controls that regulate normal cell growth break down. A normal cell turns into a cancer cell because of one or more mutations in genetic material, which can be acquired or inherited. The growth and development of normal cells are subject to a multitude of different types of control. Any initial events such as life style, environmental or occupational factors, some medical therapy (chemotherapy, radiotherapy, immunosuppressant therapy) and/or hereditary factors causes damage or mutation of genetic material and transform a normal cell to cancer cell.
A fully malignant cell appears to have lost most of the controls. However, this loss of control occurs, or the progression from a normal cell to a malignant cell is a multistep process, each step corresponding to the breakdown of a normal cellular control mechanism. The normal growth controls become ineffective because of mutations in the cellular genes coding for components of the regulatory mechanisms. Cancer can therefore be seen as resulting from the accumulation of a series of mutations in the malignant cell. Growth and proliferation of normal cells are influenced by proteins known as growth factors. When growth factors bind to receptors on the cell surface, there occurs a cascade of enzymes that stimulate cell signaling pathways and gene transcription proteins in the nucleus, which encode for proteins that regulates cell growth and proliferation. The coordination and integration of cellular signaling process is referred as signaling transduction. Proto-oncogenes are responsible for encoding several components of signal transduction pathways including growth factors, growth factor receptors, signaling enzymes and DNA transcription factors. Abnormal forms or excessive quantities of these stimulatory proteins disrupt normal cell growth signaling pathways, leading to excessive growth and proliferation and ultimately a malignant transformation. For example epidermal growth factor receptor (EGFR), trigger cell signaling pathways that influence cell growth, proliferation, survival, tissue invasion and metastasis. The family comprises of four related receptors. EGFR is over expressed in human tumors including cancer of lung, head and neck, bladder, ovary, breast, prostate, colon and glioblastoma. Amplification of HER2/neu gene or over expression of the protein is present in 10-34 % of invasive breast cancer and is associated with a more aggressive cancer growth pattern and poor clinical outcome.

Two important changes that can occur in the biology of cells that leads to cancer are activation of proto oncogenes to oncogenes and the inactivation of tumor suppressor genes. The proto-oncogenes are genes that normally control cell division, apoptosis and differentiation, which can be converted to oncogenes by
virus or carcinogen. Damage to cellular DNA can result in mutations leading to development of oncogenes and loss or inactivation of tumor suppressor genes. Tumor suppressor genes are normal genes that encode for proteins that suppress inappropriate cell division or growth. Mutation of these genes can inactivate these, eliminating the normal inhibition of cell division. Alterations of a 3rd class of genes, DNA repair genes, which encode for proteins that correct errors that may arise during DNA duplication are also implicated in cancer. Mutations in these genes further contribute to the accumulation of genetic changes that promote cancer progression. Additional genetic changes are required for tumor invasion of normal tissues and metastases.²

1.3. Breast Cancer

Breast cancer is a malignant (cancerous) growth that begins in the tissues of the breast. Most breast tumors are benign. Benign breast tumors are abnormal growths, but they do not metastasize and hence they are not life threatening. But some benign breast lumps can increase the risk of malignant change. Usually breast cancer either begins in the cells of the lobules, which are the milk-producing glands, or the ducts, the passages that drain milk from the lobules to the nipple. Less commonly, breast cancer can begin in the stromal tissues, which include the fatty and fibrous connective tissues of the breast. Over time, cancer cells can invade nearby healthy breast tissue and make their way into the underarm lymph nodes, small organs that filter out foreign substances in the body. Once cancer cells get into the lymph nodes, they have a pathway to invade other parts of the body. The lymph system is the major route through which breast cancer can spread. Lymph nodes consist of small, bean-shaped groups of immune cells (cells that fight infections) that are connected by lymphatic vessels. Lymphatic vessels are like small veins, except that they carry a clear fluid called lymph (instead of blood) away from the breast. Breast cancer cells can enter lymphatic vessels and begin to grow in lymph nodes. Most lymph vessels of the breast lead to lymph nodes under the arm. These are called axillary nodes. If breast cancer cells reach the underarm lymph nodes and keep
on growing, they cause the nodes to swell. The doctor needs to know whether cancer cells have spread to lymph nodes because if they have, there is a higher chance that the cells have entered into the bloodstream and metastasized to other parts in the body. The more lymph nodes that have cancer in them, the more likely the cancer will be found in other organs, too. This could affect the treatment plan. The anatomy of normal breast tissue is depicted in figure 1.1.

![Breast anatomy diagram](http://www.breastcancer.org/pictures/breast_anatomy/)

A- Duct, B – Lobules, C- Dilated section of duct to hold milk, D- Nipple, E-fat, F- Pectoralis major muscle, G- chest wall

### 1.3.1. Types of breast cancers

There are many types of breast cancer, but some of them are very rare. Rarely breast cancer can be a mix of different types or a mixture of invasive and in situ cancers.

**I. Ductal carcinoma in situ (DCIS):** This is the most common type of non-invasive breast cancer. DCIS means that the cancer is confined to the ducts. It has not spread through the walls of the ducts into the tissue of the breast and so cannot spread to lymph nodes or other organs. Nearly all women with cancer at this stage can be cured.
II. **Lobular carcinoma in situ (LCIS):** This begins in the milk-making glands (lobules) but does not go through the wall of the lobules and cannot spread to other parts of the body. It is not a true cancer or is pre-cancer, but having LCIS increases a woman's risk of getting cancer later. For this reason, it's important that women with LCIS make sure they have regular mammograms and follow-ups. Women with lobular carcinoma in situ (LCIS) have a 7 to 11 time’s greater risk of developing cancer in either breast.

III. **Invasive (or infiltrating) ductal carcinoma (IDC):** This is the most common type of breast cancer. It starts in a milk passage (a duct), breaks through the wall of the duct, and invades the tissue of the breast. From there it may be able to spread to other parts of the body. It accounts for about 8 out of 10 invasive breast cancers.

IV. **Invasive (infiltrating) lobular carcinoma (ILC):** This cancer starts in the milk glands (the lobules) and then spreads through the wall of the lobules. It can then spread to other parts of the body. About 1 in 10 invasive breast cancers are of this type.

V. **Inflammatory breast cancer (IBC):** This uncommon type of invasive breast cancer accounts for about 1 - 3% of all breast cancers. Instead of single lump or tumor, in IBC the skin of the breast will look red and feel warm. It also may make the skin thick and pitted something like an orange peel. The breast may get bigger, hard, tender, or itchy. In its early stages, IBC is often wrongly diagnosed as infection. Because there is no defined lump, it may not show up on a mammogram, which may delay diagnosis. It has a higher chance of spreading and a worse outlook than invasive ductal or lobular cancer.¹ ²

Because of the plausible association between early detection and improved outcome, it is the duty of every physician to distinguish breast abnormalities at the earliest possible stage and to initiate a definite diagnostic workup, during clinical examination. It is for this reason that all women should be trained in
breast self-examination (BSE), which may lead to early detection of breast cancer with reduced mortality.

1.4. Breast Cancer: An Epidemiological Overview

According to the World Health Organization’s World Cancer Report, the cancer burden is a major disease burden worldwide, but there are marked geographical variations in incidence overall and at specific sites. In terms of incidence, the most common cancers worldwide (excluding melanoma skin cancers) are lung (12.3% of all cancers), breast (10.4%) and colorectal (9.4%). Breast cancer is a serious public health problem all over the world and in many regions including Europe and Australia. The approximate estimation is that there are 13, 84,000 of new cases of breast cancer annually worldwide (Globocan report 2008). The number is high in the developed countries and lower in developing countries. However, the mortality rate is lesser in developed countries and higher in developing countries.

There is substantial variation in breast cancer rates among different countries, with high rates in North America and Western Europe, intermediate rates in South America and Eastern Europe and low rates in Asia. Internationally there is a decline in mortality rate in recent years, which may be attributed to early detection and improved treatment options available at present. However, breast cancer is the 2nd most common cancer in the world with 10.4% of the global cancer burden. There are large disparities in the global cancer burden. Global breast cancer incidence and mortality as depicted by the Globocan report in 2008 is given in table 1.1.
Table 1.1 Global Breast cancer incidence and mortality (IARC Globocan report 2008)\(^6\)

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Regions</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>World</td>
<td>13,84,000</td>
<td>4,58,000</td>
</tr>
<tr>
<td>2</td>
<td>More developed regions</td>
<td>6,92,000</td>
<td>1,89,000</td>
</tr>
<tr>
<td>3</td>
<td>Less developed regions</td>
<td>6,91,000</td>
<td>2,69,000</td>
</tr>
<tr>
<td>4</td>
<td>WHO Africa region</td>
<td>58,000</td>
<td>37,000</td>
</tr>
<tr>
<td>5</td>
<td>WHO East Mediterranean region</td>
<td>61,000</td>
<td>31,000</td>
</tr>
<tr>
<td>6</td>
<td>WHO Americas region</td>
<td>3,20,000</td>
<td>82,000</td>
</tr>
<tr>
<td>7</td>
<td>WHO Europe region</td>
<td>4,50,000</td>
<td>1,39,000</td>
</tr>
<tr>
<td>8</td>
<td>WHO South East Asia region</td>
<td>2,03,000</td>
<td>93,000</td>
</tr>
<tr>
<td>9</td>
<td>WHO Western Pacific region</td>
<td>2,79,000</td>
<td>73,000</td>
</tr>
<tr>
<td>10</td>
<td>WHO IARC membership (21 countries)</td>
<td>7,29,000</td>
<td>2,10,000</td>
</tr>
<tr>
<td>11</td>
<td>USA</td>
<td>1,82,000</td>
<td>40,000</td>
</tr>
<tr>
<td>12</td>
<td>China</td>
<td>1,68,000</td>
<td>44,000</td>
</tr>
<tr>
<td>13</td>
<td>India</td>
<td>1,15,000</td>
<td>53,000</td>
</tr>
<tr>
<td>14</td>
<td>European Union</td>
<td>3,32,000</td>
<td>85,000</td>
</tr>
</tbody>
</table>

1.5 Breast Cancer Indian Scenario

Breast cancer ranges from 19 to 45% of all cancers among Indian women in various geographical locations. According to the national and regional cancer registries, breast cancer is the most common cancer among women in Delhi, Mumbai, Kolkata, Ahmadabad and Thiruvananthapuram. In all other cancer registries it is listed as the 2\(^{nd}\) leading site of cancer. The age standardized incidence rates vary from 9 to 28.6/100000 women, the lowest being from the rural area based registry, Bharshi, of Maharashtra state. The number of breast cancer cases is rising rapidly in India. It is reported that one in 22 women in India are likely to get breast cancer during the life time. This number is definitely high among American women; one in 8 being the victim of this
The recent increased incidence of breast cancer among Indian women is thought to be due to the adoption of western lifestyle; i.e., late marriages and pregnancies, nursing fewer children and weaning earlier. All these causes altering hormone flows, putting them at high risk for breast cancer. Currently India reports roughly 1, 00,000 new cases every year. The overall rate is estimated as 80 new cases /1 lakh population, per year. By contrast this was 23.5 in 1990. The incidence varies between urban and rural Indian women.

According to the two year (1999-2000) consolidated report of the population based cancer registries, published by Indian Council of Medical Research (ICMR), the crude incidence of cancer among men per 1 lakh population was observed highest in Chennai (92.5), followed by Mumbai (68.9), Delhi (68.1), Bhopal (63.3), Bangalore (60.1), and Bharshi (38.8). Similarly, among females the highest crude rate per 1lakh population was observed in Chennai (103.0), followed by Mumbai (83.0), Delhi (81.6), Bangalore (77.5), Bhopal (62.8) and Bharshi (45.8). The leading sites of cancer for each gender based on proportion relative to all sites of cancer shows that breast cancer was at the highest position except in Bharshi and Bhopal, where cancer of cervix was at the highest rate. Table 1.2 depicts detailed picture of crude rate (CR) as well as age adjusted rates (AAR) of breast cancer during the years 1999-2000.

Table. 1.2. Breast cancer incidence as per population based registries in few Indian cities.
Over 50% of breast cancers in India are reported at stage III or IV, leading to poor survival rate and increased treatment costs. The over all survival rates of breast cancer patients in United States over last few decades has improved from 75% to 89% presently. The population based cancer reports and the individual center’s cancer statistics says, over all 5 year survival for Indian breast cancer patients is roughly less than 60%. This knowledge is an indication for us to take it as an urgent need to spread cancer awareness and create screening facilities available in the country at affordable cost for early detection and improved survival.\textsuperscript{6}

The chances of prolonged symptom free survival of women with breast cancer are related to early diagnosis and treatment. The rise in incidence of 0.5–2% per annum has been seen across all regions of India and in all age groups but more so in the younger age groups (< 45 years). In general, breast cancer has been reported to occur a decade earlier in Indian patients compared to their western counterparts.\textsuperscript{7} While the majority of breast cancer patients in western countries are postmenopausal and in their 60s and 70s, the picture is different in India with premenopausal patients constituting about 50% of all patients. More than 80% of Indian patients are younger than 60 years of age. The average age of patients in 6 hospital-based cancer registries ranged from 44.2 years in Dibrugarh, 46.8 years in Delhi, 47 years in Jaipur, to 49.6 years in Bangalore and Chennai. The average age of breast cancer patients has been reported to be 50–53 years in various population-based studies done in different parts of the country. A significant proportion of Indian breast cancer patients are younger than 35 years of age. This proportion varies between 11% (Tata Memorial Hospital Mumbai) to 26% (Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow).\textsuperscript{7}

1.6. Signs and Symptoms of Breast Cancer

Common symptoms found with breast cancer are masses, pain, erythema, nipple discharge, and enlarged lymph nodes. The most common complaint is a breast
mass. Masses that are smooth and rubbery are due to a fibro adenoma and occur in the 20s or 30s while cysts are commonly found in 30s and 40s. There are two types of breast pain, cyclic (related to a woman’s menstrual cycle) and non-cyclic (often experienced only in certain area of the breast) pain. This pain may sometimes be caused by injury or trauma to the breast such as after a breast biopsy. It is seen in both pre and post menopausal women and is most commonly seen in 40 to 50 years old women. These pains often subside after few years and are not usually associated with breast cancer, but the possibility still exists and hence should be discussed with a physician. Another symptom is erythema, an abnormal redness of the skin because of dilation of the superficial capillaries of the skin of breast which then leads to inflammation. The tumor or cyst may cause this hypersensitive inflammatory reaction, although it is not known for sure.

At many times, nipple discharges is associated with non-malignant changes and may often be caused by hormonal changes. Discharge is of concern when it is bloody, sticky and clear, brown or black, is spontaneous, or unilateral. About 90% of bloody discharges are due to papilloma (non-cancerous tumor that has a branch or stalk which reaches into the breast duct) or infection. There are chances for these to be malignant when occurring unilaterally, so further diagnostic testing should be performed. Enlarged lymph nodes are yet another symptom. This occurs due to the production of additional white blood cells which helps ward off infection and also due to metastasis of cancer cells. The only way to find out whether the cause of swelling is cancerous or not, is biopsy. However, some signs are more associated with being benign, such as, a node that is less than one centimeter in size, is soft, rubbery and tender.

1.7. Risk Factors for Developing Breast Cancer

a) Endogenous and exogenous hormone exposure

The most validated reason for breast cancer is estradiol exposure. In early menarche and late menopause, there is increased number of menstrual cycles
leading to extra estradiol production. For same reason, women whose cycles are shorter than 25 days; women who have used conventional animal estrogens or synthetic hormone for more than five years; and those women who used birth control before their first pregnancy, before 20, or for more than five years before 35, double/possibly triple the risk for breast cancer. The risk declines with increasing parity; with each birth reducing the risk by an average of 7% and 43% per year of breast feeding. This is mainly because of reduction in estradiol exposure. Both current and recent use of combined oral contraceptives moderately increase breast cancer risk compared with rare users. 

b) Anthropometric factors

Height, weight, body mass, measured as body mass index (BMI) and fat distribution have been reported as risks to breast cancer. There is a modest increase in risk with increased adult height (height reflects the number of ductal cells that develop in the breast, or that increased height reflects the action of growth hormone). Data from a pooled analysis show that, premenopausal women with a BMI < 21 kg/m², compared with women with BMI > 31 kg/m² had about 50% reduction in risk. Obesity is however associated with increased risk in post menopausal women also.

c) Age

Breast cancer is a disease associated with advancing age. In general the biology of the disease is influenced by age and the age itself is a prognostic factor of the disease. The most significant risk factor for cancer overall is age; women over the age of 50 have four times the incidence of breast cancer compared to women below 50. Two-thirds of all cases are in those over age 65. Cancer incidence increases as the third, fourth, or fifth power of age in different physiological sites. For the interval between birth and age 39, 1 in 72 men and 1 in 51 women will develop cancer; for the interval between ages 40 and 59, 1 in 12 men and 1 in 11 women will develop cancer; and for the interval between ages 60 and 79, 1 in 3 men and 1 in 5 women will develop cancer. But there are important age
related differences with respect to the frequency of different tumor subtypes with respect to hormone receptor status and pathological grade. In general younger patients show a higher frequency of estrogen receptor (ER) negative, high grade tumors, and there is a high frequency of ER positive and low grade tumors among older women.\textsuperscript{11-13}

d) Ionizing radiations

Radiation exposure is believed to increase breast cancer risk. The carcinogenic effect of ionizing radiation is heavily dependent on age at exposure, it is moderately high when occurs during childhood and after forty it imparts low or minimal risk.\textsuperscript{14}

e) Hereditary, dietary and life style factors

Women whose mothers had breast cancer are at twice the risk for developing this disease, and the younger the mother is at the time of diagnosis, the greater the risk. If a sister has breast cancer, the risk can increase even more. Diets high in fat are also linked to this illness; because more fat cells produce more estrogen, and promote early onset of menstrual cycle and longer exposure to hormones.\textsuperscript{12}

f) Lack of physical activity

Lack of regular, physical exercise can also be a risk factor, because exercise directly decreases estradiol absorption and improves immune response. Physical activity reduces endogenous estrogen and progesterone levels. Physical activity is found to have protective effect among women who are most active in occupational and/or recreational activities.\textsuperscript{15}

g) Alcohol consumption

Alcohol affects circulating ovarian hormone levels. Compared to nondrinkers, daily consumption of one to two drinks was associated with a 10% and 21%
respective increase in breast cancer risk. A woman consuming 2-5 alcoholic drinks daily had 41% increased risk compared to those who do no drink.\textsuperscript{16}

h) Stress

Decades of research have shown that stress contributes to the cause and complications of cancer, emotional and psychosocial stress contribute to the onset and progression of breast cancer and cancer mortality.\textsuperscript{17} The transcendental meditation technique reduces stress and improves emotional well-being and mental health in older breast cancer patients. In a two year randomized controlled study conducted by Nidich et al among 130 with breast cancer, 55 years and older, the women were randomly assigned to either the transcendental meditation technique or to a usual care control group. Patients were administered quality of life measures, including the Functional Assessment of Cancer Therapy-Breast (FACT-B), every six months for two years. The participants reported that their meditation practice was easy to do at home and had significant benefits in their overall quality of life.\textsuperscript{17}

1.8 Diagnosis of Breast Cancer

Early detection and diagnosis are keys to successful treatment of cancer. Breast self-examination (BSE), clinical breast examination by a care giver, and mammography has been advocated as useful screening tools. Only breast self-examination, screening mammography alone, and screening mammography with clinical examination have been evaluated in randomized controlled trials. Magnetic Resonance Imaging (MRI) is being assessed and may be more accurate than mammography. A substantial fraction of breast cancers are first detected by patients themselves by BSE leading to increased biopsies and systematic diagnosis, reducing breast cancer mortality. Genetic screening for BRCA1 and BRCA2 mutations and other markers of breast cancer risk has identified a group of women at high risk for breast cancer. Unfortunately, when to begin and the optimal frequency of screening have not been identified. Mammography is less sensitive at detecting breast cancers in women carrying BRCA mutations,
possibly because such cancers occur in younger women, in whom there will be denser breast tissues present. Dense breasts have less fatty tissue, than those which are not dense and cancer tumors are easier to see in a mammogram when they are surrounded by more fatty tissues. The histological diagnosis of a tumor is the most important determinant of how a malignancy will be treated. This is because a tumor’s histological classification influences its natural history, pattern of progression and responsiveness to treatment. A surgical biopsy or excision of the primary tumor, followed by a microscopic and a biochemical evaluation by a pathologist, can provide the most accurate histological diagnosis.\textsuperscript{3, 13}

\textbf{1.9 Staging of Breast Cancer}

Staging is the process that determines the extent of or spread of the disease. Staging and morphology of breast tumors has important implications for treatment and prognosis. Staging helps to determine the anatomic invasion of the disease. Staging of cancer is carried out, based on the size of the tumor, whether the cancer is invasive or not, involvement of lymph nodes, and whether the cancer has spread beyond the breast tissues. The ultimate aim of staging is to organize the different factors and classify the features of the cancer into categories, in order to explore the prognosis and treatment guidelines for healthcare professionals to facilitate harmonization of therapeutics in breast cancer treatment across the globe.

The most popular system of staging is the American Joint Committee on Cancer (AJCC) TNM system. In TNM staging the cancer is described by the size of tumor (T), lymph node involvement (N) and whether cancer has metastasized (M) or not. Once the pathologist knows the T, N, and M characteristics, they are combined in a process called stage grouping, and an overall stage is assigned.\textsuperscript{1-2, 18,19} Table 1.3 depicts TNM staging comprising of stages 0-IV and their substages. The grade of tumor indicates the aggressiveness and is based on the degree of differentiation of cells.

Table 1.3. Salient features of different stages of breast cancer
<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Non-invasive breast cancers, e.g. Ductal carcinoma in situ (DCIS) and Lobular carcinoma in situ (LCIS).</td>
</tr>
<tr>
<td>Stage I</td>
<td>Invasive breast cancer (cancer cells are breaking through to or invading neighboring normal tissue). The tumor may measure up to 2 cm and no lymph nodes are involved.</td>
</tr>
<tr>
<td>Stage II A</td>
<td>Cancer cells are found in the axillary lymph nodes or the tumor measures 2 cm or less and have spread to the axillary lymph nodes, or the tumor is larger than 2 cm but not larger than 5 cm and has not spread to the axillary lymph nodes.</td>
</tr>
<tr>
<td>Stage II B</td>
<td>The tumor is larger than 2 cm and not larger than 5 cm and has spread to the axillary lymph nodes, or the tumor is larger than 5 cm but has not spread to the axillary lymph nodes.</td>
</tr>
<tr>
<td>Stage III A</td>
<td>Invasive breast cancer where no tumor is found in the breast, cancer is found in axillary lymph nodes that are clumped together or sticking to other structures, or cancer have spread to lymph nodes near the breastbone, or the tumor is 5 cm or less and has spread to axillary lymph nodes that are clumped together or sticking to other structures.</td>
</tr>
<tr>
<td>Stage III B</td>
<td>Invasive breast cancer in which the tumor may be any size and has spread to the chest wall and/or skin of the breast and may have spread to axillary lymph nodes that are clumped together or sticking to other structures or cancer may have spread to lymph nodes near the breastbone.</td>
</tr>
<tr>
<td>Stage III C</td>
<td>Invasive breast cancer, there may be no sign of cancer in the breast or, if there is a tumor, may be of any size and may have spread to the chest wall and/or the skin of the breast, and the cancer has spread to lymph nodes above or below the collarbone, and the cancer may have spread to axillary lymph nodes.</td>
</tr>
<tr>
<td>Stage IV/ Metastatic</td>
<td>Describes invasive breast cancer in which, the cancer has spread to other organs of the body such as lungs, liver, bone, or brain. This means that the breast cancer has spread beyond the breast and nearby lymph nodes and/or to other organs.</td>
</tr>
</tbody>
</table>

The stages of cancer may also be classified as early stage, and advanced stage breast cancer. Although these terms are not medically precise (they may be used differently by different doctors). The general idea of how they apply to the official staging system is given below.
Early stage: Stage 0, Stage I, Stage II, Some stage III

Later or advanced stage: Other stage III, Stage IV

Table 1.4. TNM staging and corresponding stage groupings typically used by physicians

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Stage grouping</th>
<th>TNM classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1 N0 M0</td>
<td>T1 = T ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>II A</td>
<td>T0 N1 M0</td>
<td>T2 = T &gt; 2 cm but not &gt; 5 cm</td>
</tr>
<tr>
<td></td>
<td>T1 N1 M0</td>
<td>T3 = T &gt; 5 cm, M0 = No distant metastasis</td>
</tr>
<tr>
<td></td>
<td>T2 N0 M0</td>
<td></td>
</tr>
<tr>
<td>II B</td>
<td>T2 N1 M0</td>
<td>N1 = metastasis to movable ipsilateral axillary lymph node</td>
</tr>
<tr>
<td></td>
<td>T3 N0 M0</td>
<td>T &gt; 5 cm, no lymph node metastasis</td>
</tr>
<tr>
<td>III A</td>
<td>T0 N2 M0</td>
<td>N2 = metastasis to ipsilateral axillary L.N., fixed to one another or other structure</td>
</tr>
<tr>
<td></td>
<td>T1 N2 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 N2 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 N1/N2 M0</td>
<td></td>
</tr>
<tr>
<td>III B</td>
<td>T4 N0/N1/N2 M0</td>
<td>T4 = T of any size with direct extension to chest wall or skin</td>
</tr>
<tr>
<td>III C</td>
<td>Any T /N3 M0</td>
<td>N3 = metastasis to ipsilateral internal mammary lymph node</td>
</tr>
<tr>
<td>IV</td>
<td>Any T any N M1</td>
<td>Distant metastasis, including ipsilateral supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

1.10 Clinical Management of Breast Cancer

A critical component of clinical cancer management is assessing the response to therapeutics. The follow up should include physical examination (all sites of the disease are physically measured and recorded in a flow chart by date) and assessing the therapeutic response (usually requires periodic repeated imaging tests that were abnormal at the time of staging). If imaging tests results does not show any abnormality, then repeat biopsy of previously involved tissue is
performed in order to document complete response by pathologic criteria. A complete response is defined as disappearance of all evidence of disease, and a partial response as 50% reduction in the sum of the products of the perpendicular diameters of all measureable lesions. Progressive disease is defined as the appearance of any new lesion or an increase of 25% in the sum of the products of the perpendicular diameters of all measurable lesions. Tumor shrinkage or growth that does not meet any of these criteria is considered stable disease. Some sites of involvement (e.g., bone) or patterns of involvement (e.g., diffuse pulmonary infiltrates) are difficult to quantify.³

1.10.1. Surgery

Surgery is usually the first line of treatment for breast cancer, which depends on many factors as follows. The doctor will suggest the type of surgery that’s most appropriate for the patient based on the stage of cancer, and what is acceptable in terms of patient compliance. The options available are lumpectomy, also known as breast-conserving surgery, (removal of only the tumor and a small amount of surrounding tissue), modified radical mastectomy (MRM) (the tumor and a small amount of the breast tissue around it as well as lining of chest muscles below the tumor and some of the lymph nodes under the arm are removed). Mastectomy is the removal of all of the breast tissue. Lymph node removal or axillary lymph node dissection may also be performed during lumpectomy and mastectomy if the biopsy shows any evidence of breast cancer being spread outside the milk duct, lobule or breast tissue.³²⁰

1.10.2 External beam radiotherapy

External beam radiotherapy, is the local treatment by directing rays of ionizing radiations towards the tumor from a distance, has become the integral part of treatment of breast cancer. The aim is to target cancer cells as possible, causing minimal damage to other normal tissue in the vicinity. The ionizing radiations employed in radiotherapy, has the ability to penetrate the tissues of the body and also to destroy cells within the tissue. The four types of radiations usually
employed in radiotherapy are Alpha, Beta, or Gamma rays from radioactive isotopes and X-ray produced from electricity. These have different strengths and absorption depths. The aim of radiation therapy is to damage selectively the genetic structure of cancer cells, the DNA present in nucleus. Unfortunately these radiations also damage the healthy tissues as well. Mostly, rapidly dividing cells (bone marrow, skin, hair follicles, and gastrointestinal epithelium) are highly radiosensitive and respond to radiations showing, early acute reactions. Fortunately these cells are able to replace themselves quickly due to high mitotic rate, immediate rearrangement of healthy cells appear and replace the damaged tissue. The important morbidities due to radiotherapy are skin reactions, hair loss, nausea and vomiting, bone marrow depression, nutritional requirements and bowel disturbances. Radiotherapy may be employed as curative or for palliation as in the case of bone metastasis.  

Brunk opines that adjuvant radiation therapy after lumpectomy reduces the risk of recurrent breast cancer within 10 years by nearly 15% and reduces the overall chance of dying from the disease within 15 years by nearly 4%, results from a large long-term analysis demonstrated. Clinical studies indicate that breast cancer patients treated with breast conserving surgery (BCS) without radiotherapy are at greater risk of recurrence and mortality compared to those receiving BCS plus radiotherapy.  

1.10.3 Adjuvant chemotherapy  

Chemotherapy is used as systemic therapy either in neoadjuvant (before surgery) or adjuvant (after surgery) setting and affecting the whole body. Neoadjuvant chemotherapy may be used to reduce the size of the tumor and to destroy cancer cells where ever they are located. Adjuvant chemotherapy works throughout the system to kill cancer cells that may have spread through out the body. The drugs used in chemotherapy works best on rapidly dividing cells, thus makes chemotherapy particularly effective against cancer. When used right after surgery chemotherapy has additional advantage, being optimized for time and
sequence. After surgery the cancer cells have broken away from the primary tumor and these relatively young and small clusters are located somewhere in the body. These single cell or clusters have plenty of oxygen and nutrients, and they are dividing quite rapidly. This is perfect time for chemotherapy as these drug work best on rapidly dividing cells. In the past, most commonly used regimens for the treatment of breast cancer in early and advanced stage were; 1) cyclophosphamide, methotraxate and 5 fluorouracil (CMF) 2) 5 Fluorouracil, adriamycin and cyclophosphamide (FAC) 3) adriamycin and cyclophosphamide (AC). Comparative trials in both metastatic and adjuvant settings have shown that the anthracycline containing regimens are more effective, achieving consistently higher response rates, longer time to progression and improved survival rates. Later anthracycline and taxane containing regimens have proven to be more effective than AC or FAC regimens. Addition of taxane to anthracycline containing regimen is considered standard care in lymph node positive breast cancer. Dose dense therapy, the repeated administration of drugs within shorter duration in adjuvant setting has resulted in statistically significant improvement in disease free and overall survival.\(^2, 3\)

1.10.3.1 Chemotherapeutic agents in Breast cancer \(^1, 21-24\)

a) Anthracyclines

Anthracyclines are cytotoxic antibiotics widely used group of drugs in cancer chemotherapy. The main anticancer anthracycline is doxorubicin. Daunorubicin, idarubicin, epirubicin and mitoxantrone are other related compounds. They are prodrugs, which are converted to active metabolites and form a complex with DNA and topoisomerase II. After binding with DNA, anthracyclines cause breakage of DNA strand at 3' phosphate back bone, allowing uncoiling of super coiled DNA. Alternately, these generate semiquinones intermediates that can react with oxygen to produce superoxide anion radicals, which in turn oxidize DNA the bases. The recommended dose is 60-75 mg/m\(^2\) as intravenous (I.V.) infusion over a period of 10-15 minutes at 3 weeks intervals. The drug is metabolized by the liver and cleared by biliary excretion. The plasma level of
doxorubicin and daunorubicin are multiphasic, with a terminal half life of 30 hours. Specific adverse drug reactions (ADRs) include cardio toxicity; with hypotension, tachycardia, arrhythmias, and cardiomyopathy. Congestive cardiac failure is unique to daunorubicin and doxorubicin. Nausea, vomiting, stomatitis, alopecia, and bone marrow depression are other side effects.

b) Cyclophosphamide

Cyclophosphamide is nitrogen mustard, alkylating agent, probably the most commonly used alkylating agent in cancer chemotherapy. It is a pro drug and in the liver it is converted to the active metabolite aldophosphamide, which is then converted to phosphoramidemustard and acrolein. Phosphoramidem is thought to be responsible for cytotoxic activity and acrolein causes side effects. Cyclophosphamide forms reactive carbonium ions and transfer the alkyl groups and binds with covalent bonds to various cell organelles. Thus the cell organelles are not available for normal metabolic reactions. Alkylation of DNA strand, results in its breakage or miscoding, abnormal base pairing and/or cross linking. It is also an immunosuppressant and has radiomimetic activity. Usual recommended dose is 600 mg/m² intravenous bolus every 3 weeks intervals, in combination with other drugs. The drug is well absorbed orally and half life is 7 hours. Specific ADRs includes haemorrhagic cystitis due to acrolein. Other toxic effects include nausea and vomiting, bone marrow depression. Cyclophosphamide myelosuppression affects particularly the lymphocytes.

c) 5 Fluorouracil

Fluorouracil is a pyrimidine analogue and interferes with 2’ deoxythymidilate by thymidilate synthetase. Thymidine and cytosine are two pyrimidines present in the DNA. They compete with natural nucleotides, and are incorporated in to DNA in place of natural nucleotides and inhibit DNA synthesis. 5 Fluorouracil get activated into a nucleotide metabolite and inhibits the enzyme thymidilate synthetase. This in turn blocks the synthesis of thymine and DNA synthesis. Also the active metabolite may get incorporated into DNA/RNA leading to inhibition of their synthesis. Administered as intravenous infusion, 5
fluorouracil has a short half life of 10-20 minutes. Major part of the drug is metabolized by an enzyme dehydropyrimidine dehydrogenase. Metabolic degradation occurs in many tissues, particularly in liver. Intravenous administration produces peak plasma level and plasma clearance is rapid. Five to ten percent of the I.V. dose is excreted intact in urine. It enters cerebrospinal fluid in minimal amount. ADRs include Nausea, mucositis, diarrhea, bone marrow depression, and neurotoxicity.

d) Methotrexate
Methotrexate is an antimetabolite (4 amino substituted folic acid analogue) and widely used folate antagonist in cancer chemotherapy. Methotrexate acts by competitively binding irreversibly, with folate reductase and blocking the conversion of dihydrofolic acid to tetrahydrofolic acid. Tetrahydrofolic acid is an essential co enzyme required for the conversion of folate to tetra hydro folic acid. Thus DNA synthesis is inhibited. This will prevent replication of cells. It is absorbed through intestine and excreted through urine. The recommended dose is 2.5 mg-10 mg daily. The unwanted effects include depression of bone marrow and damage to the epithelium of gastrointestinal tract and pneumonitis.

e) Taxanes (Paclitaxel and Docetaxel)
Taxanes are mitotic spindle poisons, derived from a naturally occurring compound found in the bark of the Yew tree. The drug binds to the beta tubulin of microtubules and asserts mitosis. Cell killing is dependent on both drug concentration and duration of cell exposure. The drug induces polymerization of microtubules, stabilizing the microtubules to make them nonfunctional. Paclitaxel is given by intravenous infusion and docetaxel is given orally. Paclitaxel, at dose of 175 mg/m² by intravenous infusion over a 3hours in 3 weeks interval or 80-100 mg/m² over 1 hour every week is employed in breast cancer treatment. The drug is metabolized in liver by microsomal enzymes and excreted through gut. Drugs that induce or inhibit microsomal enzymes may alter plasma levels of paclitaxel. Dose may be reduced in liver dysfunction. The vehicle used to administer paclitaxel can cause allergic reactions. Pretreatment with dexamethasone, diaphenhydramine and H2 blockers is used to prevent
allergic reactions. Albumin bound Paclitaxel is free from allergy and less neurotoxic. Specific side effects include mylosuppression, myalgia, allergic reactions, mucocytosis, hypotension, arrhythmias, and peripheral neuropathy. Neutropenia occurs after 8-11 days after a dose and reverses rapidly by 15-21 days. Administered along with filgrastim (granulocyte colony stimulating factor) 250 mg/m² over 24 hours is well tolerated. The drug undergoes extensive metabolism by hepatic cytochrome CYP2C8. Less than 10% of the dose is excreted in urine intact. Paclitaxel clearance is nonlinear and decreases with increasing dose. The half life is 10-14 hours.³

In an interactive survey conducted among Indian oncologists with respect to perceptions and choices in systemic management of triple negative breast cancer, upfront chemotherapy with anthracyclines and taxanes were emphasized. However, docetaxel was preferred over paclitaxel, because of concern about sequence dependent synergistic cardiac toxicity between anthracycline and paclitaxel.²⁴

f) Trastuzumab

Cancer cells express several antigens which may be targeted by monoclonal antibody. Recombinant technology has led to the creation of humanized antibodies that overcome the immunological problems. Trastuzumab is a recombinant humanized monoclonal antibody used in targeted therapy, in over expression of transmembrane Human Epidermal growth factor-Receptor protein 2 (HER2) in breast tumor. The drug binds to HER2 sites in breast cancer tissue and inhibits the proliferation of cells that over express the HER2 proteins and thus decrease the number of cells in the S phase. The usual recommended dose is 4 mg/kg intravenously as loading dose, then 2 mg/kg as maintenance dose. In patients with metastatic breast cancer, over expression of transmembrane HER2 is seen in 15-30% of patients. Trastuzumab specifically targets the extra cellular domain of HER2 growth receptor that has intrinsic tyrosine kinases activity. Trastuzumab binds to HER2 sites in breast cancer tissue and inhibit the proliferation of cells and thus decrease the number of cells in the S phase.²⁴
g) Capecitabine

Capecitabine is a pyrimidine analogue and is indicated for locally advanced breast cancer. It is also prescribed in combination with docetaxel after failure of cytotoxic chemotherapy in metastatic breast cancer. Capecitabine is a prodrug that is enzymatically converted to 5 fluorouracil in the tumor, where it inhibits DNA synthesis and slows growth of tumor tissue. The recommended dose of XELODA is 1250 mg/m² orally within 30 minutes after a meal. Capecitabine is administered in a 21 day cycle consisting of 14 days of therapy followed by a 7 day rest period.²⁵

1.10.3.2. Adjuvant hormone therapy in breast cancer

Malignant tumors which are originated in response to endogenous hormones (e.g., uterus, breast and prostate) may be treated by endocrine therapy, provided, the tumors express hormone receptors on the cell membrane. Principle of endocrine therapy is based on inhibition of tumor growth by blocking the receptors or by eliminating the endogenous hormone stimulation. Adjuvant hormone therapy is an integral part in hormone therapy of estrogen receptor positive breast cancer. Antiestrogen (tamoxifen) and aromatase inhibitors (letrozole /anastrozole) are two classes of drugs commonly employed for endocrine therapy in breast cancer treatment.²⁶,²⁷

Tamoxifen is a selective estrogen receptor modulator anti-estrogen and found to be extremely useful in both early stage and metastatic breast cancer. It is also approved as a chemo preventive agent in women with high risk for breast cancer. Tamoxifen act as competitive partial agonist inhibitor of estradiol, binding to the estrogen receptors in estrogen receptor positive (ER+ve) tumors. It is readily absorbed following oral administration, with peak concentrations measurable after 3 to 7 hours. Tamoxifen chemoprophylaxis reduces breast cancer risk and improves life expectancy and does so in a cost-effective manner in postmenopausal women of age younger than 55yrs. In a meta-analysis, tamoxifen saved 29 quality-adjusted life years (QALYs) at a cost of $11,530 per QALY per 1,000 women treated.²⁷ However, tamoxifen increases the risk for
developing uterine carcinoma, weight gain, mood swings, hot flushes, blood clots and cataracts. Due to these adverse effects, it is important to critically evaluate risk/benefit while choosing the options and regular monitoring is required.

The enzyme aromatase is expressed in liver, adipose tissues, muscles, skin and breasts including breast malignancies. Aromatase reaction is responsible for the extra gonadal synthesis of estrogen from androstenedione. Peripheral aromatization is an important source of estrogen in post menopausal women. Aromatase inhibitors prevent the synthesis of estrogen and bring down estrogen level in these women. Anastrozole and letrozole (1mg and 2.5mg oral) are two non steroidal aromatase inhibitors used in treatment of early stage and advanced breast cancer. These reduce peripheral and local aromatization within the tumor in estrogen receptor positive breast cancer. Gnant et al have reported the long-term clinical efficacy including disease-free survival and disease outcomes assessed in patients receiving anastrozole or tamoxifen with or without zoledronic acid. Analysis of the Austrian breast and colorectal cancer study Group trial-12 at 48 month’s follow-up showed that addition of zoledronic acid to adjuvant endocrine therapy significantly improved disease-free survival. 28

1.10.3.3. Management of Chemotherapy Induced Nausea and Vomiting.

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of in pharmacological management of cancer. With the correct use of antiemetic, CINV can be prevented in almost 70% to up to 80% of patients. The goal of each antiemetic therapy is to abolish nausea and vomiting. The development of the 5-HT3-receptor antagonists (5-HT3RAs) in the early 1990s were one of the most significant advances in the chemotherapy of cancer. The novel antiemetic, the neurokinin1-receptor antagonists (NK-1RA), has recently been developed, for e.g., aprepitant. The emetogenic potential of the chemotherapeutic agents used is the main risk factor for the degree of severity of CINV. In regard to their emetogenic potential, the chemotherapeutic agents are classified into four emetic risk groups; high risk (90), moderate (30 to 90), low (10 to 30), and
minimal (< 10), as suggested by standard guidelines. Hence, antiemetic prophylaxis is directed toward the emetogenic potential of the chemotherapeutic agents. Patient-related risk factors, including age, gender, a history of low alcohol intake, episodes of emesis during pregnancy, impaired quality of life, and previous exposure with chemotherapy are known to increase the risk for CINV. Table 1.5 gives the list of commonly used drugs as antiemetic in cancer chemotherapy.

Table 1.5. List of common drugs used in CINV

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Drugs</th>
<th>Recommended Dose and route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-HT3RA Granisetron</td>
<td>2 mg oral, 1 mg/0.01 mg/kg intravenous</td>
</tr>
<tr>
<td>2</td>
<td>5-HT3RA Ondensetron</td>
<td>24 mg oral(high), 16 mg oral (moderate) and 8mg i.v.</td>
</tr>
<tr>
<td>3</td>
<td>5-HT3RA Palanosetron</td>
<td>0.25 mg intravenous.</td>
</tr>
<tr>
<td>4</td>
<td>Steroids -dexamethasone</td>
<td>Oral/i.v. 12 mg (highly emetogenic, with aprepitant), 20 mg without aprepitant; 8 mg (moderately emetogenic); 8 mg (high/moderate) days 2 and 3</td>
</tr>
<tr>
<td>5</td>
<td>NK1-RA Aprepitant</td>
<td>Oral 125 mg on day 1, 80 mg on days 2 and 3</td>
</tr>
</tbody>
</table>

1.10.3.4. Bisphosphonate in breast cancer

Bone is the most common site of metastasis associated with breast cancer affecting more than half of women during the course of their disease. Bone metastases are a significant cause of morbidity and mortality. The contributing factors of morbidity and mortality are pain, fractures, hypocalcaemia and spinal cord compression. Bisphosphonates by inhibiting osteoclast-mediated bone desorption, form the basis for standard care for tumor-associated hypocalcaemia. Bisphosphonates have been shown to reduce bone pain and improve quality of life. In a meta analysis evaluating skeletal events in women with metastatic breast cancer and early breast cancer comparing, treatment with bisphosphonate have ensured superior to control group. Overall, intravenous bisphosphonates reduce the risk of developing a skeletal event by 17 % (95% C
compared with oral bisphosphonates, which reduce the risk of developing a skeletal event by 16 % (95% CI 0.76-0.93). 

1.10.3.5. Complementary Alternative Medicines (CAM)

CAM is usually adopted by the patient themselves or by the advice of the friends and relatives. In a study conducted by Greenlee et al, they found that most (96.5%) women reported a history of using at least one form of CAM and 57.3% reported ever using four or more of the general CAM modalities. Each of the five general CAM modalities (botanicals, other natural products, special diets, mind-body healing, and body/energy/other treatments) was used by 63-75% of patients at least once in their lives. In the five years before diagnosis, CAM therapies used at least weekly by > 20% of women; included green tea, glucosamine, omega-3 fatty acids, prayer and rituals. CAM use was high (86.1% of participants) in the period immediately following diagnosis. Forty seven point five percentages used botanical supplements, 47.2% used other natural products, 28.8% used special diets, 64.2% used mind-body healing, and 26.5% used body/energy/other treatments. In multivariable analysis, frequent use of each CAM modality before and after diagnosis was associated with use of other CAM modalities and other health behaviors (i.e., high fruit/vegetable intake, lower BMI). 

Lue et al conducted a study among the Taiwanese women the authors reported that some participants used the power of religion to assist themselves in overcoming the discomfort during treatment, such as praying for health, safety, or dying without pain. The power of religious beliefs not only eased patient’s pain but also increased their confidence in facing the necessary treatment.

1.11. Outcomes Research

Outcomes research is the study of health care interventions, care delivery processes, and health care quality that are evaluated to measure the extent to which optimal and desirable outcomes can be achieved. It describes the final
outcomes of health events that occur as a result of a disease or its treatment. It is a concept focused on patient’s benefits in terms of disease free and overall survival rate, cost of treatment, quality of life, symptom control, and functional status. Outcomes research is the scientific discipline that evaluates the effect of health care interventions on patient related, clinical and humanistic and economic outcomes. Outcomes research methodologies include retrospective chart review, prospective clinical trials, observational studies and computer modeling studies. Examples of outcomes measures are the Economic, Clinical and Humanistic Outcomes (ECHO model). ECHO model provides a theoretical framework used in characterizing the types of pharmacoeconomic outcomes. In this model economic outcomes are described as the acquisition cost associated with care, labor cost associated with care, costs to treat ADRs, cost of treatment failure, cost of hospital readmission, costs of emergency visits and such other costs. Clinical outcomes include events after treatment, e.g., length of hospital stay, ADRs, hospital readmissions, cure, disability, death and such other events. Humanistic outcomes include patient satisfaction, functional status as measured by a validated instrument and quality of life assessment during or after treatment. Outcomes research may include perspectives of patients, hospitals, insurance companies etc. In essence clinical outcome represents the concept of physiologic health status and humanistic outcomes address the concept of psychosocial status. Outcomes can be terminal or intermediate when health events are described.32,33

Pharmacoconomics is a division of health economics and its primary goal is to identify measure and compare the costs and consequences of alternative pharmaceutical interventions. The objective of such an effort is to develop a rationale in allocating health care resources, assuring that each patient receives the most suitable treatment. Pharmacoconomics is a scientific discipline that assesses the overall value of health care products, services and programs as it provides information critical to the optimal allocation of health care resources. This concept aims at improving the efficiency of health care which means that
every resource that is used in health care (inputs), generate the greatest possible benefit (outputs). It has been defined as the description and analysis of costs of the drug therapy to health care systems and society. Pharmaco economics overlaps health care economics and pharmacy related clinical or humanistic outcome research.

Presently breast cancer is a serious problem faced by Indian women. The literature review revealed no studies taken up in the areas of economic, clinical and humanistic outcome analysis in the treatment of breast cancer. The studies related to cost and their effects can provide novel information for assessing the clinical practice. The evaluation of survival pattern and the adherence to treatment as well as the related predictors will be a source of reference for the practicing clinicians. The quality of life (QOL) assessment can help the health care professionals and clinicians in taking decisions for improving the QOL life of breast cancer patients. A good number of patients are being treated for breast cancer of various stages in Kasturba Medical College Hospital, Manipal. An outcome evaluation will be beneficial for the patients as well as the decision makers. In this context the relevance and need for carrying out such work is highly, timely and urgent.

1.12. Statement of the problem

What are the outcomes of pharmacological management of women with breast cancer in Shirdi Sai Baba Cancer Hospital and Research Center, Manipal?

1.13. Objectives

1.13.1. General Objective

To explore the outcome of Pharmacological management in women with breast cancer in a tertiary care Hospital in Udupi district, Manipal, Karnataka, India.576104.
1.13.2. Specific Objectives of the Study

i. To identify and describe the pattern of pharmacological management of women with breast cancer.

ii. To estimate the treatment associated economic outcome of pharmacological management among women with breast cancer.

iii. To identify clinical outcomes of pharmacological management among women with breast cancer by examining important predictors of survival.

iv. To measure the pattern of medication adherence in women with breast cancer and examine predictors of adherence to chemotherapy.

v. To compare the treatment related humanistic outcomes in women with breast cancer amongst different chemotherapy regimens.

1.14. Null Hypotheses

H\(_0\)_1: There will be no significant differences in the economic outcome when different pharmacological treatment regimens are adopted for treating women with breast cancer.

H\(_0\)_2: There will be no significant differences in the survival pattern among women with breast cancer when different pharmacological treatments are adopted at different stages of breast cancer.

H\(_0\)_3: There will be no significant differences in humanistic outcomes when different pharmacological treatment regimens are adopted.

All the hypotheses will be tested at 0.05 level of significance.

1.15. Assumptions

There are differences in the economic and clinical outcomes & in the QOL of patients when treated with alternative treatment modalities.

Alternative treatments are adopted at different stages of breast cancer.
The response to the treatment is dependent on age, stage of disease and treatment modalities.

1.16. **Variables**

Pharmaceutical practice and policy research, invariably involves investigation of relationships between variables. A variable is a concept (parameter) that can take on different values. Concepts, which are qualitative to estimate becomes variables in research investigations. As concepts are non observables (immeasurable) it becomes essential to convert these in to parameters (measurable) once they are operationally defined. Variables are classified as dependent, independent and extraneous. In any research the investigator is interested in studying the cause of some phenomenon and the independent variable is the presumed cause, where the dependent variable is the presumed effect. Same way in non experimental research, the independent variable logically has some effect on the dependent variable. In other words, independent variables are manipulated while dependent variables are measured and collected as data. Or the independent variable does the influencing and the dependent variable is being influenced. For example the cost of treatment is a dependent variable and other factors which influence the cost of treatment is independent variable. Extraneous variables are intervening variables, which may modify the dependent variables.\(^{34}\)

1.16.1. **Independent variables**

The independent variables are different pharmacological treatment regimen prescribed for breast cancer patients, stage of cancer at diagnosis, distant and nodal metastasis at the time of diagnosis, disease grade, hormone responsiveness and duration of illness.

1.16.2. **Dependent variables**

The dependent variables considered are pharmacological treatment related economic outcome, clinical outcome, humanistic outcomes and adherence to treatment.
1.16.3. Extraneous variables
For the present study age, family income, education, employment and marital status are considered relevant.

1.17. Operational Definitions

1.17.1. Economical outcome
Economic outcome is the impact of cost by the disease and treatment, and it includes the direct and indirect costs incurred due to the disease or treatment. In this study economic outcome refers to the amount of money in Indian rupees a breast cancer patient spends in connection with the diagnosis and treatment breast cancer and is described as direct costs including consultation cost, drugs cost, investigation cost, surgery related cost, radiotherapy cost and professional and service charges for the preliminary management of disease. Expenses at each subsequent visit after the preliminary course of treatment for follow ups are not included.

1.17.2 Clinical outcome
Clinical outcome represents the concept of physiologic health status and include the medical events that occur as a result of disease or treatment (e.g. number of recurrences, disabilities due to sickness, hospitalizations, number of disease free patients, metastases, death etc.).

1.17.3. Humanistic outcome
Humanistic outcome addresses the concept of psychosocial status. It reflects the patients’ self-assessment of the impact of disease or treatment on their lives and well being. Examples are general health, physical functioning, satisfaction, QOL etc. Humanistic outcome in this study refers to the global health, physical, emotional, cognitive and social functioning and different symptoms and side effects experienced by the patient during and/or after pharmacological treatment.

1.17.4. Adherence
Adherence to treatment refers to the extent to which a person’s behavior following a prescribed medication regimen corresponds to the advice from
health care professionals. Various factors including patient’s age, spousal/family support, socioeconomic factors, disease severity, co-morbidities, and cost of medications may affect medication use behavior. Patient’s follow up visits and the comments inscribed in the case sheet by the attending physician is considered as a means to measure of adherence to treatment.

1.18. Conceptual Framework

Theoretical basis for this outcome study is developed based on two conceptual frameworks, the modified ECHO planning model for pharmacoeconomic outcome research and Aday-Anderson model for determinants of health care utilization behavior.33-36

1.18.1. Modified ECHO Model

Modified ECHO model for this outcome study is based on the fact that evaluation of treatment alternatives is involved in the assessment of outcomes that are disease related. Breast cancer disease is evaluated for 3 important outcomes; economic, clinical and humanistic (quality of life). Clinical and humanistic outcomes are interrelated and each has intermediaries. A clinical intermediary refers to measurements of a patient’s physical or biomedical status used as surrogate for or to infer the degree of disease. Staging of breast cancer is an important clinical intermediary in this study. Clinical outcomes are the medical events that occur as a result of disease or treatment. Humanistic outcomes are the patient’s self assessment of the impact of disease or treatment on their lives or well being. Humanistic outcome has intermediary - patient’s perceptions (poor prognosis, cure and/or survival after treatment). The cost of treatment varies with different modalities of treatment adopted. The external controls are age of the patient, family income, educational status, marital status and disease stage and these will have an impact on the treatment choices adopted and thereby an expected change in the outcomes.
Humanistic Intermediaries
- Patient's perceptions on prognosis, cure, survival

Clinical Intermediary
- Staging of breast cancer.

Clinical Outcomes
- Poor prognosis
- Disease free survival

External Controls
- Age, education
- Family Income
- Marital status
- Stage of disease

Humanistic Outcome
- Functional score, symptom scores,
  - global health
  - side effects

Cost
- Cost of treatments

Figure 1.2. Modified Economic Clinical Humanistic Outcome planning model
1.18.2. Aday –Anderson model for determinants of health care utilization

Health care service utilization can be explained using the Aday-Andersen model. This model demonstrates health care-seeking behavior by classifying determinants of health care utilization into predisposing, enabling, and need-related factors. Predisposing factors refers to those which describe propensity of an individual or a group to use health care services. Examples are patient’s gender, age, and family history of breast cancer. Enabling factors are those that influence patients' ability to obtain access to health care services including income, accessibility to the health center, family support and insurance. Need characteristics can be defined as an individual's health status as perceived by the individual and/or as evaluated by the health care provider. It may be measured by examining the level of illness or presence of co morbidities. The present study assumes that each of these variables are independently associated with the use of medications, breast cancer recurrence, and associated healthcare service utilization and costs.\textsuperscript{37,38}

<table>
<thead>
<tr>
<th>Predisposing factors</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, family history, body mass index, place of residence, history of other cancers,</td>
<td>• Health care utilization visits, admissions,</td>
</tr>
<tr>
<td>physical activity, diet habits, exposure to radiations, age at menarche and menopause</td>
<td>different treatments</td>
</tr>
<tr>
<td>, hormone replacement therapy</td>
<td>• Health care cost</td>
</tr>
<tr>
<td></td>
<td>(Cost of treatments)</td>
</tr>
<tr>
<td></td>
<td>• Quality of life, systemic therapy side effects</td>
</tr>
<tr>
<td></td>
<td>• Disease free survival, Recurrence, Complications, Metastasis, Death</td>
</tr>
<tr>
<td>Enabling factors</td>
<td></td>
</tr>
<tr>
<td>Access to services, family income, insurance status, accessibility to the health</td>
<td></td>
</tr>
<tr>
<td>center, family support</td>
<td></td>
</tr>
<tr>
<td>Need related factors</td>
<td></td>
</tr>
<tr>
<td>Disease stage, severity of symptoms, duration of illness</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1.3. Aday-Anderson model for behavior of health care utilization.
Summary

This chapter has dealt with the background of the study, study rationale, statement of the problem, study objectives, null hypotheses of study, assumptions, operational definitions, conceptual frameworks and variables. The following chapters deal with review of literature, methodology, data presentation, discussions and summary.