



Insights of Breast Cancer and Barriers to its Therapy

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ABSTRACT

Breast cancer is the most common cancer across the globe occurring commonly in women population, and it is one of the main causes of mortality in women. In 2018, 1,62,468 new cases and 87,090 death cases of breast cancer were registered in India. In these recent years, lots of studies were conducted in breast cancer related to treatment and management, but in spite of getting so much advancement in the treatment of breast cancer still, the mortality rate of women is increasing day by day. Numerous factors are acting as barriers or challenges in breast cancer preventive therapy. It includes lack of knowledge regarding the treatment of cancer and patient getting insecure about treatment, fear of having side effects, cost of treatment and the efficacy of the drugs being prescribed. The study intended to determine the perceived insights and barriers to treatment of breast cancer.

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1. Introduction

Cancer is a group of diseases identified by unmanageable growth and expansion of abnormal cells that cause life risk leading to death if not managed. The phenomenon of conversion of a normal cell to a tumor cell is called malignancy (Seyfried & Huysentruyt, 2013). Programmed cell death (APOPTOSIS) in healthy tissues is restored by defiant cell growth in cancer cells (Elmore, 2007). The most frequent cancers in the globe are lung cancer, skin cancer, colorectal cancer, bladder cancer, and breast cancer. Globally it is surveyed that, about 1 in 6 deaths is due to cancer (World Health Organization, 2018). In India, breast cancer is the leading cause of cancer-related mortality in women causing 13% death around the globe (World Health Organization, October 2010).

Breast cancer can be said as the malignant tumor (a tumor occupy other tissues and spread or metastasize into other parts of the body) that develops in the cells of the breast. It is the most common cancer form, which has high morbidity and mortality, and it is second to lung cancer. Despite the standard treatment, the significance of the disease increases year after year. It can occur in both male and female, but male breast cancer is rare (Palanisamy, 2017). Cancer of the breast is ranked number one in Indian women with a rate of 25.8 per 100,000 women and mortality rate of 12.7

per 100,000 women (Malvia, 2017). The Indian Medical Research Council estimated that India could record more than 17 fresh cancer instances and 8 lakh disease fatalities by 2020 (India today, May 2016). An article by Times of India mentioned that, according to statistics in 2017, in India, cancer has been reported at 0.7 million, representing females, after China and the US as the third largest instances of cancer. In India, breast cancer is the most known cancer in women, which reports 14% of all other cancers in women (Bray et al., 2014). In 2018, 1,62,468 new cases and 87,090 death cases of breast cancer were registered in India.

When cells in the breast start to increase uncontrollably, it causes breast cancer. Factors evolving breast cancer are early menarche, late menopause, genetic causes, family history, race, ethnicity, drinking alcohol, having dense breast tissue, overweight or obese. The hormones oestrogens and progesterone are of essential importance in the prognosis of this disease. Hormone balance disorder of the body is accountable for the progression of this disease. Nearly all breast cancer cells show the initial appearance of receptors for these hormones. In some cancer cells, Human Epidermal Growth Factor Receptor 2 (HER2) receptors are sometimes spotted. Hormone-targeted therapy results depend on the nature of these receptors. Some breast cancer cells fail to disclose any types of receptors interaction, which are termed as triple negative cancer.

The stage and prognosis of cancer cells can be identified by a staining process called immunohistochemistry and a scoring system called NPI is appointed for this process. The Nottingham prognostic index (NPI) is based on the factors like tumor size, lymph node stage, and tumor grade can spot the advancement and aggressiveness of cancer. This NPI system is built on the differentiation of cancer cells that is between Well-differentiated cancer cells (grows slowly) and poorly differentiated cancer cells (metastasize rapidly). The scoring system is like:

- 3–5 points: Grade I - Well differentiated
- 6–7 points: Grade II - Moderately differentiated
- 8–9 points: Grade III - Poorly differentiated (Adhikary, 2018)

Most breast cancers are diagnosed as small tumors within a range less than or equal to 2cm. It mostly gets diagnosed at early stages. It is evaluated that 5-10% of cancer is due to genetic defects that are inherited from family (Reeder & Vogel, 2008). 70,218 mortality cases of women who had breast cancer were reported in 2012 with the mortality rate of 12.7 per lac population, thus categorizing it as number one killer in women (Peng et al., 2009). One in seven women will be likely to develop breast cancer in the course of their lifetime. The prevalence of this disease in women older than 90 years of age is lesser [10]. Breast cancer is commonly identified by sure signs and symptoms or screening tests that are helpful in the diagnosis of the disease and its degree of spread [8].

Management of breast cancer depends upon various stages of cancer. There are a number of treatment regimens which got well known over the past decades are chemotherapy, radiotherapy and tele-therapy, surgery and hormonal therapy (Shalini et al., 2010) and the anticancer drugs like 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel/paclitaxel, carboplatin and antiestrogens (raloxifene or tamoxifen) used for the treatment of breast cancer (Karen et al., 2002). Tamoxifen is a specific modulator of the estrogen receptor being used since past three decades for the treatment of breast whereas selective estrogen receptor down regulators (SERDs) drugs like letrozole, anastrozole and exemestane are used to inhibit aromatase enzyme for producing estrogens for the treatment of breast cancer. The most frequently used therapy of breast cancer is the anthracyclines class of drugs, Epirubicin, and doxorubicin (Hum et al., 2016). The therapy has been modernized over the past decades, but still the mortality rate of patients is increasing day by day. Improper use of drugs can be hazardous to patients (Manichavasagam et al. 2017). In clinical practice, nonsensical prescriptions of drugs are common. The cost of the use of the nonsensical drug is enormous in the name of both inadequate stock and adverse clinical outcome of the

treatments which can have risks but no clinical benefits. Use of multiple drugs side by side, which is commonly known as polypharmacy has been seen linked with adverse drug reactions, medication errors, and drug-drug interaction. Treatment with more than three drugs usually gets cases of a drug interaction. Hence, this can be another problem for mortality (Sjoqvist & Birkettm, 2003).

Another problem, which can be considered as significant, is barriers between physicians and patients to the therapy - lack of confidence in physicians for identifying appropriate high-risk patients. There are specific tools which had never been used for identifying suitable candidates for preventive therapy (Pentareddy et al., 2015; Kanwal & Gupta 2012). Lack of knowledge, limited training in risk counseling, having worries about the medications side effects, lack of evidence, etc. are some barriers of the physicians. Fear of having side effects, high treatment cost, beliefs/concerns about the medications, confusion between chemotherapy and chemoprevention, having little or no knowledge about the disease are some barriers at the patient side. These factors lead to a higher mortality rate in patients with breast cancer (Park, 2015; Feuer et al., 1993). Therefore, this review aimed to determine the perceived insights and barriers to treatment of breast cancer.

2. Etiology of Breast Cancer

The possibilities of getting breast cancer can swiftly increase with age through premenopausal and steadily increase through post-menopausal in life (Franca et al., 2012). The probability of having a risk of breast cancer grows with age but are seen rare before the age of 20 years (McPherson et al., 2003). Having cancer in one breast can surely increase the probability of having cancer in another breast by four times whereas patients having a history of any ovarian, endometrial or colon cancer increase the possibility of 1–2 times for developing breast carcinoma (Kelsey & Bernstein, 1996). Having a benign tumor in the breasts can increase the likelihood of having breast cancer by becoming malignant (Jacobs et al., 1999). The causes of breast cancer are:

- Obese women after menopause can have a high risk of getting breast cancer as the fatty tissues increases producing a hormone (oestrogen/progesterone).
- Scarcity of exposure to the sun as well as having vitamin D deficiency is thought to be the primary cause of breast cancer (Alco et al., 2014).
- Women having a family history of breast cancer are 2-4 times more prone to getting breast cancer. Mother, daughter, and sister fall on first-degree family members

who can be considered holding the threat whereas in case of having aunt or grandmother who has a history of breast cancer fall under second-degree family members will also increase the possibility of getting breast cancer.

- Alcohol consumption also has a risk of getting breast cancer.
- Environmental factors can result in the development of breast cancer.
- Two genes, BRCA1 and BRCA2 increase the possibility of having Breast cancer. Among the joint investigation of 22 researchers, 11 accepted that at 70 yrs. of age carrying BRCA1 gene, the chance of getting breast cancer is 65% and those carrying BRCA2 gene have 45% possibility of getting breast cancer (Nkondjock & Ghadirian, 2004). 5-10% causing breast cancer can transfer from father or mother to the next generation in the family.

3. Associated Risks of Breast Cancer

Breast cancer, after affecting the breast, slowly grows to other areas of the body mostly affecting the lungs, liver, muscles, the bone, and lastly the brain. The associated risks of breast cancer are likely to be:

- Thickening of the breast tissue and itchy, dry and cracked skin around the breast.
- Improper treatment may lead to the malignant growth of lymph nodes that causes swelling in the arms.
- Malignant tumors can grow in lungs causing chronic cough and diseases like pneumonia or bronchitis. It can also cause difficulty in breathing and dyspnea.
- Spreading of cancer to the liver can cause severe swelling, edema, and jaundice and at very advanced stages can cause (if spread all over liver) liver cirrhosis leading to death.
- Later stages when it spreads to muscle and skeletal systems causing stiffness of joints, muscle pain and hence can cause risk of getting fractures, a problem in movement.
- At the last stage, it can spread to the brain affecting it, causing dementia, seizures, headache, difficulty in speaking, and even blindness.

Other effects to be likely can be loss of appetite, sudden weight loss, feeling extremely tired, and so on (Kristeen, 2018).

4. Clinical Presentation of Breast Cancer

Some of the symptoms of breast cancer are the development of:

- A new lump or mass,

- Alteration in breast shape or size and having pain about all of the time in breast or armpit,
- Rash on skin
- Rash on surrounding the nipple,

Other symptoms of breast cancer likely can involve:

- Swelling of the breast even if there is no sensation of a lump.
- Irritation in the skin (sometimes orange peel like).
- Pain in the breast or nipple.
- Reddening or inwards turning of the nipple.
- Scaling and thickening of breasts.
- Fluids are releasing other than breast milk from breasts.

Breast cancer typically is diagnosed by medical imaging, screening tests like mammograms, breast ultrasound, breast MRI scans and is naturally confirmed by doing a biopsy and other techniques that can help in detecting breast cancer in its early stages (Kanwal & Gupta 2012). It's better to get to know about the symptoms of breast cancer as well as detecting breast cancer as early as possible, can help it for getting better treatment.

5. Pathophysiology

The breast is a complex tubulo-alveolar organ secured within an asymmetrical connective tissue (Stingl et al., 2005). Starting from pregnancy to dementia period; the breast comes across chains of conversion. The atypical breast comprises of a stratified epithelium cell which contains two different cells that are myoepithelial and epithelial and are surrounded by a basement membrane and fastened within a pattern of blood vessels, stromal and lymphatic cells (Stingl et al., 2006). The cause of the cellular diversion in breast disorders depends on the prime development process of the breast. This diversion can be caused due to neoplastic alteration in myoepithelial or epithelial cells or from stem cell that can have the potential to evolve into myoepithelial or epithelial cells (Gusterson et al., 1982). As stated by the oncology of breast cancer, it is said that the neoplastic cells are different than the healthy cells present in the body.

The healthy cells present in our body have restricted growth or procedure to maintain the organization and activity of tissues whereas cancerous cells without any help of external spur do have a lengthy and chronic extension (Evan & Vousden, 2001). There are a lot of causes that can raise the malignant tumors to evolve into breast cancer. All the factors are demonstrated below through a flowchart. Two pathways, The Ras/Raf/Mitogen-activated protein kinase (MEK)/ extracellular-signal-regulated kinase (ERK) pathway and phosphoinositide 3-kinase/ Protein Kinase B (P13K/AKT) pathway protect healthy cells from cell suicide, but during mutation (transformation), these cells are not able

to commit suicide when not required and therefore develops into cancer (Cavaliere et al., 2006). This also happens when there is an excess articulation of leptinin breast adipose tissue, causing the growth of cancer cells (Jarde et al., 2011). Enzyme telomerase rejects the chromosomal shortening allowing replication of cells (Hanahan & Weinberg, 2000). From angiogenesis, tumor cells get nutrition and oxygen (Jain, 2005).

Cancer cells have to interrupt their boundaries and can enter into the blood lymphatic tissues or other tissues of the body to construct secondary tumour (Fig.1.) (Gupta & Massagué, 2006).

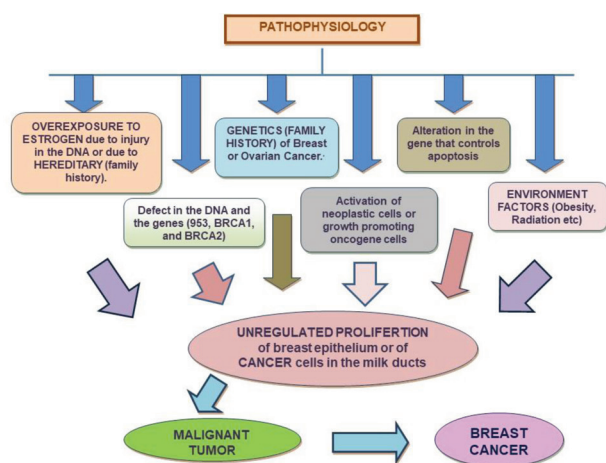


Figure 1: Pathophysiology of Breast Cancer

6. Stages of Breast Cancer

There are several stages of breast cancer, which depends upon the type and size of the tumor as well as depends upon the area invaded by the tissue cells in the breast (Heim et al., 1997).

There are five stages of breast cancer:

Stage 0: This stage is known as non-invasive stage of the tumor. It contains both cancerous and non-cancerous tumor cells that develop at any part of the breast, but there is no confirmation of the tumor spreading to surrounding tissues or that area. Ductal cell carcinoma in situ (DCIS) is an example of stage 0 breast cancer (Bednarek et al., 1997).

Stage I: This stage is also known as Invasive Breast Carcinoma. There are two categories of this stage- 1A and 1B. At 1A stage, the tumor size can be up to 2cm, and no lymph nodes are involved here. At 1B stage, tumor size larger than 0.2 mm and lymph nodes are involved (Segal et al., 2001).

Stage II: There are two categories of this stage- 2A and 2B. In 2A, tumor size varies between 2cm to 5cm and is detected naturally in axillary lymph nodes or sentinel lymph nodes

but not detected in breasts. In 2B, tumor size can be more than 5cm but are not detected in the axillary lymph nodes (Moran et al., 2014).

Stage III: There are three categories of this stage- 3A, 3B, and 3C. In 3A, tumors can invade up to 4-9 axillaries or sentinel lymph nodes but not detected in the breast. In stage 3B, it is known as inflammatory breast cancer as it causes red, warm and swollen skin of the breast and the tumors can be any size causing swelling or ulcers on the skin of the breast and can invade up to 9 axillaries or sentinel lymph nodes. In Stage 3C, tumor invasion can be up to 10 or more axillaries lymph nodes and also lymph nodes above or below the clavicle (Jacquillat et al., 1990).

Stage IV: This is the last stage and the advanced and metastatic stage of cancer. In this, the tumour spreads to other areas of the body like lungs, liver or brain, etc. (Neuman et al., 2010).

7. Types of Breast Cancer

Breast cancer is divided into six different classes. They are classified as follows:

Non-Invasive Breast Cancer: This type of cancer does not expand far from the place where it is situated in the lobules or ducts (West et al., 2017). Ductal carcinoma in situ is an example of non-invasive breast cancer. Development of atypical cells inside the milk ducts can lead to the formation of Ductal Carcinoma, but does not expand to the presence of tissue or external areas as it is “in-situ” meaning “in place” but can develop into invasive breast cancer if not treated (Posner & Wolmark, 1992). Under this class, it is divided into two types:

- *Lobular-Carcinoma In-Situ:* They are also known as non-invasive breast cancer that grows in the breast lobules (Inoue et al., 2017) that do not grow outside the breast lobules (Clauser et al., 2016).
- *Ductal Carcinoma In-Situ:* It is a common type of non-invasive breast cancer which grows in the breast duct (milk ducts). Ductal comedocarcinoma is an example of this type of cancer (Nakhlis & Morrow, 2003).

Invasive Breast Cancer: Another name of invasive breast cancer is metastatic breast cancer (Stevanovic et al., 2006). When cells grow in the lobules or milk ducts and break into the breast tissue, it occurs into invasive breast cancer (Harris et al., 2016). These cells can proceed from breasts to different areas of the body between the immune system and systemic circulation (Ziperstein et al., 2016). This type of cancer mostly occurs in the female population, and they can spread to other parts of the body, even if when the tumor is small in size (Prabhakaran et al., 2017). These cells can expand to the brain, lungs, liver,

and bones, causing cancer (Page et al., 2017). Invasive breast cancer is divided into five types:

- *Infiltrating Lobular Carcinoma*: This type of cancer develops from the lobules of the breast then gets spread to other parts of the body (Arpino et al., 2004).
- *Infiltrating Ductal Carcinoma*: This type of invasive breast cancer develops from the milk ducts of the breast and spreads to duct wall by saturating the fatty tissues of the breast and spreading to other areas of the body (Somari et al., 2003).
- *Medullary Carcinoma*: it's a type of invasive breast cancer that forms a wall between healthy tissue and medullary tissue hence separating each other (Mateo et al., 2017).
- *Mucinous Carcinoma*: Also known as colloid carcinoma and it's very uncommon and is produced by the cancer cells that form mucus (Anuradha & Lakshmi, 2017).
- *Tubular Carcinoma*: They are a specific type of invasive breast cancer, and generally, females having tubular carcinoma have better hopes than females having another kind of invasive breast cancer (Priya & Prasaad, 2017).

Inflammatory Breast Cancer: It is a type of breast cancer that is very abnormal and rapidly arising. Here the cancer cells obstruct the lymph vessels and channels of the breast skin leading to swelling of breasts with prominent hollow ridges (Joglekar-Javadekar, 2017). Treatments like radiation therapy, surgery, chemotherapy, and imaging are done through proper observation. Early reporting can help in the use of adjuvant chemotherapy or loco-regional treatment like surgery or radiation can cause fast improvement in the disease (Cariati et al., 2005).

Paget's disease: It's atypical breast cancer that causes change to the nipple of the breast that can comprise of red rashes (itchy) on the nipple, bleeding or fluid discharge from the nipple, a lump in breasts, conversion in nipple shape, etc. (Errichetti et al., 2017). It affects only one breast most of the time and is both common in men and women. A punch biopsy is used to diagnose Paget's disease (Merrill et al., 2017).

Phyllodes Tumor: It is a rare kind of breast cancer that grows in the connective of the breast, which can be benign or malignant and can be removed by surgery (Sera et al., 2017). At least ten females die each year in the USA due to this type of cancer (Nozad et al., 2017).

Triple-Negative Breast Cancer: This is a devastating heterogeneous disorder that mostly seen in premenopausal females. Triple negative breast cancer caused due to deficiency of three receptors, which are progesterone receptor, human epidermal growth factor II, and estrogen receptor (Liedtke et al., 2008).

8. General Treatment and Management of Breast Cancer

Breast cancer is commonly treated with the combination of surgery, radiation therapy, chemotherapy, hormonal therapy and targeted therapy, which is done for reducing the size of the tumor and spread of the tumor (National Cancer Institute, 2012). People at an advanced stage of breast cancer are given palliative care. Pain and symptomatic treatment are an essential part of this care. The survival rate of cancer depends upon the type of cancer and stage of cancer (Murthy et al., 2011). Chemotherapy is a vital treatment part of the management of cancer. Chemotherapy alone or in combination with radiotherapy or surgery has given effective and curative results (Longo, 2012). These treatments are highly complex and are associated with a lot of adverse effects. In a breast cancer study, the incidence of adverse drug reactions (ADRs) in patients undergoing chemotherapy was seen at 39.1% (Chopra et al., 2016).

In a study in Taiwan on breast cancer patients, the traditional way of treatment was done. Here, Chinese herbal products containing dang-qui was prescribed to breast cancer patients. Dang-qui (*Angelica sinensis radix*) has a long history of its use in traditional Chinese pharmacopeia since 1590 AD by Shi-Zhen Li written in classical Chinese text named Ben Cao Gang Mu, Compendium of Materia Medica. Many women with breast cancer use alternative medicine, which includes herbs, vitamins, homeopathy, and Chinese herbal products (CHPs) to reduce symptoms of breast cancer. In Japan, South Korea, China, and Taiwan have a history of use of traditional Chinese medicine (TCM) by medicine practitioners (Lai, 2012).

In the modern treatment of breast cancer, treatment depends upon stages of breast cancer. In early breast cancer, Local, regional therapy is done where surgery is done to cure breast cancer by removing the tumor. Lumpectomy and radiation therapy are also done in most breast cancer patients. Radiation therapy is used for the treatment of bone metastasis. Some require post-mastectomy radiation therapy, but naturally, they are used in locally advanced breast cancer. Simple or total mastectomy is the removal of the entire breast without cutting up underlying muscle or axillary nodes. A new procedure has been seen introduced in many centers in the United States, which involves lymphatic mapping and sentinel lymph node biopsy. Systemic adjuvant therapy consists of systemic therapy followed by local treatment (surgery or radiation) when it is not in the metastatic stage.

Preoperative systemic therapy, also known as neoadjuvant therapy, is gaining popularity nowadays for both treatments of an early and advanced stage of breast cancer. It decreases the size of the tumor without the need for surgery. Common adjuvant chemotherapy combination regimens for

breast cancer used are AC (doxorubicin+cyclophosphamide) followed by paclitaxel, FAC (fluorouracil+doxorubicin+cyclophosphamide), CAF (cyclophosphamide+doxorubicin+fluorouracil), TAC (docetaxel+doxorubicin+cyclophosphamide), FEC (fluorouracil+epirubicin+cyclophosphamide), CMF (cyclophosphamide+methotrexate+fluorouracil), CEF (cyclophosphamide+epirubicin+fluorouracil). *Metastatic* single agent chemotherapy drugs are paclitaxel, docetaxel, capecitabine, gemcitabine, vinorelbine, and doxorubicin. Metastatic combination regimes are docetaxel+capecitabine, doxorubicin+docetaxel, epirubicin+docetaxel. Anthracyclines (doxorubicin and epirubicin) are referred

to as the most active class of chemotherapy regimen in the treatment of metastatic breast cancer. Tamoxifen is used in hormonal therapy for the treatment of breast cancer. Aromatase inhibitors (anastrozole, letrozole), antiestrogens (tamoxifen), Selective Estrogen Receptor Degraders (fulvestrant), progestins, androgens, estrogens are some endocrine therapies used for the treatment of metastatic breast cancer. Cytotoxic therapy and Biologic therapy are other therapies for the treatment of breast cancer. Trastuzumab is a drug used in biologic therapy of breast cancer.

Recent Studies in Advancement and Current Clinical Approaches For The Treatment of Breast Cancer

TITLE	SUMMARY
Drug prescription pattern of breast cancer patients in a tertiary care hospital in West Bengal: Cross-Sectional and questionnaire-Based Study	Here 28 Female patients diagnosed with breast carcinoma of different types and grades, with an average age of 51yrs (± 10.5) ranging from 28 to 73 years with an average weight of 55.3 kg (± 8.68) ranging from 40 to 78 kg, and average body surface area (BSA) of 1.47m ² attending the Surgical OPD and Department of Radiology, were included in the study. In the study, the menopausal status of the patients was identified, and the drugs prescribed to the patients were evaluated. The study revealed 7(25%) patients were premenopausal, and 21(75%) patients were post-menopausal. The most common drugs used in the study were Cyclophosphamide(20%), followed by docetaxel(13%), doxorubicin(12%), 5-fluorouracil(12%), paclitaxel(9%), epirubicin(9%), tamoxifen(8%), letrozole(7%), trastuzumab(6%), and carboplatin(4%). Hence, the study tried to evaluate the epidemiological profile of the disease, the risk factors associated with them, and the treatment provided to these cancer patients (Adhikary et al., 2018).
Breast Cancer and Non-steroidal Anti-Inflammatory Drugs: Prospective Results from the Women's Health Initiative	This study analyzed data from the prospective cohort Women's Health Initiative (WHI) Observational Study to observe the effects of aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs) on regular use on breast cancer risk and was outlined to label some vital causes of morbidity and mortality socially and geographically. 1392 cases of breast cancer were taken for the study. Women with a history of cancer were included, whereas women having no medical update or data were excluded. 80,741 women were analyzed, among which only 1392 identified breast cancer were examined. It was seen that about 21% of women taking NSAIDs twice a week for 5yrs brought a decrease in risk of breast cancer, whereas women with the use of 10yrs brought a 28% decrease in breast cancer. Ibuprofen, if used for the long term can bring a reduction in the risk of having breast cancer by 49% were the same in the case of aspirin, only 21%. It was seen that regular use of medication like Aspirin or other NSAIDs is good against breast cancer (Harris et al., 2003).
Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population-based cohort study	The study was conducted to distinguish whether some selective serotonin reuptake inhibitor (SSRI) antidepressants can reduce the effect of tamoxifen by preventing its bio-activation by cytochrome P450 2D6 (CYP2D6). When tamoxifen is needed to be given with an antidepressant, then preference needs to be given to antidepressants that present little or no inhibition of CYP2D6. Out of 24430 patients going through tamoxifen treatment for 13 years, 7489 patients were given at least one antidepressant. Paroxetine was the most commonly given SSRI including next sertraline then citalopram, venlafaxine, fluoxetine and lastly fluvoxamine. 1074 women died during the treatment, among which 374 cause of death was due to breast cancer (Kelly et al., 2010).

Use of liposomal doxorubicin for adjuvant chemotherapy of breast cancer in clinical practice	This study speaks about the clinical application of liposomal doxorubicin in adjuvant chemotherapy of breast cancer and clarifies the therapeutic effects, side effects of PEGylated liposomal doxorubicin (PLD) and non-PLD (NPLD) in clinical research. It was seen at the end of the study that combined PLD regime have shown more significant therapeutic effect in the treatment of HER-2positive and negative breast cancer. Combination with doxorubicin was seen asvital treatment therapy among the anthracyclines even they are essential for the treatment of breast cancer. PLD and NPLD both have been seen working effectively in the treatment of most of the stages of breast cancer (Zhao et al., 2017).
Melatonin, a Full-Service Anti-Cancer Agent: Inhibition of Initiation, Progression, and Metastasis	This study said about the use of melatonin therapy with other traditional or usual cancer treatment therapies, which by exploratory results encouraged using melatonin by its advantages, which can improve the health of the patients. It was seen that melatonin reduced the amount of acute typical cell damage and also melatonin protects the heart from any damage due to chemotherapy. It was stated that melatonin is a non-toxic endogenously molecule that can be used for the benefit of chemotherapy treatments (Reiter et al., 2017).
Treatment Modification in Young Breast Cancer Patients	It is on the treatment modification in young breast cancer patients. This study deals with the need for particular contemplation in young women like new treatment modification in endocrine therapy and ovarian suppression, fertility protection, and family planning, and genetic counselling. Detecting breast cancer less than 36yrs of age will require genetic counselling and testing, even if there is no family history of breast or ovarian cancer. Amenorrhoea and elevated gonadotropins such as follicular stimulating hormone (FSH) are irresponsible markers of infertility in women who have taken chemotherapy (Scharl et al., 2016).
Palbociclib: A new hope in the treatment of breast cancer	In this study article, a new drug called Palbociclib was tested. It is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor, which is a new drug, currently has the approval for the treatment of ER+ and HER2- breast cancer in Feb 2015. 10 out of 37 patients were having a good result after giving four cycles of the drug at phase I. It was noted that 6 out of 37 have triple negative breast cancer, 2 out of 37 having HER2+ and 29 out of 37 having ER+/HER- breast cancer. Hence, a starting dose of palbociclib was given 125 mg per day for 21 days daily then after a leave of 7days the dose will be reduced to 100 mg per day followed by at end dose it will be 75 mg per day. Grape juice was seen having food interaction of palbociclib (Palanisamy, 2017).
Neoadjuvant treatment of breast cancer- Clinical and research Perspective	This study reveals about the new advancements made in neoadjuvant therapy where Two groups are mainly concentrated for neoadjuvant therapy, which includes, HER2 and triple negative breast cancer. Neoadjuvant therapy is used for reducing the size of a tumor to avoid mastectomy and the axilla to avoid axillary clearance so that it can be used to conduct sentinel node biopsy. The study was to improve the long term treatment outcome and to decrease the mortality rate. Anthracycline and taxane therapies are the conventional treatment regimen nowadays, and therefore, the primary aim of this study was to increase complete pathological response to improve the survival rates of breast cancer (Loibl et al., 2015).
nab-Paclitaxel dose and schedule in breast cancer	In this study, we get to know about the dose of nab-paclitaxel, which is accepted for breast cancer treatment. Even if combined therapy has been seen ascompetent, still single nab-paclitaxel treatment is better in an unselected patient population. There are always trials going on the combination therapy for knowing whether the patient with a more aggressive disease should be treated or not. There were a total of five trials of nab-paclitaxelin Metastatic Breast Cancer with 15 patient population. Dose for nab-paclitaxel was recommended 260 mg/m2. A patient going on treatment with nab-paclitaxel experienced less toxicity then patient going on the treatment of the same regimen but with the metastatic setting. Nab-paclitaxel combined with bevacizumab also seen effective in the treatment of metastatic breast cancer, and the treatment cost was seen feasible for patients (Martín, 2015).

Eribulin in advanced breast cancer: safety, efficacy and new perspectives	In this study, it is talked about the use of eribulin drug molecule in the treatment of advanced stage breast cancer. This study was done for comparing the clinical trial results with life and was concluded that it got satisfactory results in TNBC and also can be given with a lot of combined drugs without any toxicity. It is also seen to be helpful in the treatment of elderly patients. It is a synthetic compound derived from halichondrin B, which is a natural product formed from a marine sponge named Halichondria Okadai. Total of 1095 patient's data was investigated. Eribulin showed greater efficacy and potency when given with other anticancer drugs like paclitaxel. When eribulin treated in MBC patients, it showed reoxygenation by increasing the tumor oxygen saturation (SO ₂) and suppressing the TGF-β1, which can cause an antiangiogenetic effect (Garrone et al., 2017).
Pertuzumab and breast cancer: another piece in the anti-HER2 puzzle	The combination of pertuzumab with trastuzumab and docetaxel was approved by the FDA as first-line treatment for HER2-positive metastatic breast cancer, and also it is the first drug to be used in the neoadjuvant therapy by using a full pathological response as an endpoint in the Cleopatra trial. A dose of 420 mg iv for three weeks was considered. This combination of pertuzumab to trastuzumab enhanced neoadjuvant as well as metastatic treatment in HER2 positive breast cancer patients. New pertuzumab therapies or regimens are investigated for improving the toxic effects and efficacy of treatments in the future future (Gerratana et al., 2017).
Ribociclib for the treatment of advanced hormone receptor-positive, HER2- negative breast cancer	Ribociclib is a selective oral inhibitor of CDK4/6 which was known as LEE011 that was approved by the US FDA for first-line treatment of hormone-receptor-positive/HER 2-negative metastatic breast cancer after palbociclib. Neutropenia was the adverse effect seen. Hence, CDK4/6 inhibitors are undergrowth and have been found to have a significant action regarding the chronification of metastatic HR+/HER2- breast cancer. CDK4/6 inhibitors prevent the hyper-phosphorylation of pRB and stop the progression of the cancer cell cycle. A dose of 600 mg/day based on administrating three weeks on and then 7days off. Ribociclib, in combination with letrozole, was given in phase-I trails. Toxicities seen were neutropenia, nausea, vomiting, diarrhoea, and fatigue (López-Tarruella et al., 2017).
Docetaxel and cyclophosphamide as neoadjuvant chemotherapy in HER2-negative primary breast cancer	This prospective study evaluates the efficacy of TC NAC in the treatment of HER2- primary breast cancer. Docetaxel was combined with cyclophosphamide Neoadjuvant chemotherapy, and hence, the results stated that TC NAC had exhibited little effective in breast cancer except for the triple-negative type. Patient of 20-70 yrs. of age having stage I,II, or III were taken for this study. Patients diagnosed with HER2-, N0-N1, invasive breast cancer were considered for this study. A dose of 75 mg/m ² docetaxel and 600 mg/m ² Cyclophosphamide for four cycles every three weeks were given to the patients with HER2- Breast cancer for investigating The efficacy and safety as well as tolerability of NAC combined with cyclophosphamide and Docetaxel which was the primary objective of this study. The study design used here was prospective, open-label, and nonrandomized, which took place in seven institutions. 4+9 out of 52 patient completed The treatment, which got to be 94.2 %. Then, it was discontinued in three patients due to it caused adverse reactions like grade 3 skin eruption, skin pain, grade 4 leukopenia, and neutropenia. The mean dose intensity for docetaxel and cyclophosphamide were 24.3 and 192.3 mg/m ² per week, whereas the relative dose intensity of the same drugs were 97.1 and 96.2%. Combined therapy was seen effective the single drugs but still not every patient need them. This combined therapy was perceived as effective in the treatment of triple negative breast cancer (Nakatsukasa et al., 2016).

9. Physicians and Patient Barriers

In spite of having a vast number of breast cancer therapy for woman, there is a crucial barrier in it, and that is the lack of

having confidence in recognizing worthy risk patients. Most of the time physicians have not used the gail model or risk assessment model (Corbelli et al., 2014), which is nowadays

the best tool available for spotting appropriate candidates or patients for preventative therapy. Among a survey of 300 participants, only 33% of physicians using the gail model whereas, in the case of gynaecologists, it was 60%.

Not having good knowledge and inadequate training in risk assessment is the other factors of physicians that prevent them from using these tools. Different factors included are: the fear of having side effects, beliefs and knowledge regarding preventive therapy, uncertain between chemotherapy and chemoprevention, cost of treatment, and drug efficacy. Many women don't take treatment or medicines thinking them as "unnatural" or necessarily not needed and reject taking them unless are told that it is essential for treatment and there are some people who are afraid of taking treatment (Holmberg et al., 2015). There are other factors also like age, income or employment status, no insurance, etc. that leads to not seeking treatment. Women having low income fear to take treatment due to the high cost. Barriers between patients and doctors are like the language barrier, decision making, and cultural differences.

Language barrier:- Difficulty in speaking the same language and understanding the same language is a significant barrier between patients and doctors. The solution for this can be any interpreters like neighbours their relatives, etc., but oncologist may not be satisfied that the information or explanation provided by him/her understandable by the patient or not. Even worse happens if there are no interpreters. Medical terminology is also a barrier even for those who understand physician's language very well.

Cultural differences:- Cultural differences are there like physical activity and diet. Some patients may think that diet follow up is very general, and physical activity is too tough.

Treatment decision making:- Decision making depends on the patient or patient relatives. But, its physician responsibility to guide patients regarding therapy. There is a barrier of understanding for a patient that what physician is trying to say, this remains a question that is it beneficial to take the therapy or not.

In most cases, the patient of breast cancer is from developing countries in the most advanced stage of breast cancer. Barriers to use health care system is low maintained infrastructure, lack of information or missed information, economics, lack of resources. These are some points which delay the initial diagnosis process. Delay in diagnosis and treatment is related to various other barriers like age, education, place of living, low finance, no health insurance, work conditions and ethnic. In developing countries, because of fewer resources and low maintained infrastructure patient is not diagnosed early. Because of the lack of these services, detection of breast cancer in the early stages and treatment of breast becomes more expensive and more difficult.

Sociocultural barriers are also there like women don't have enough or no knowledge about the disease.

Women having less knowledge, they cannot detect early symptoms of breast cancer. Lack of information regarding the disease delays health care. Early signs and symptoms are not recognized by the patient like nodules, oedema, and erythema, sometimes friends and family give a different meaning to these signs and symptoms and patient don't take these symptoms seriously. Both less information or knowledge and socioeconomic myth lead to delay in the early diagnosis. First of all, there is a need to guide and educate women regarding breast cancer signs and symptom. Social myths are difficult to remove if once they are established, and these myths delay the early detection of disease, myths like cancer are deadly. Studies report show that fear of disease and lack of knowledge is a socioeconomic barrier. There are organizational barriers, no primary health care organization, and no organization regarding educating the females. The organizational barrier also creates a delay in detecting early symptoms in breast cancer - lack of patient counselling and lack of examinations with health care system or services.

In developing countries or developed countries, there are a lot of people who are suffering from breast cancer, a long line of patients means a long time for waiting; this is also a barrier to assess health care to breast cancer. Ineffective management of the health care system, unorganized infrastructure, less investment in policies of attention because of these points, women are not getting timely treatment. Most of the women lived far from cancer hospital, so patient counselling, transportation cost, and examinations become a barrier in providing good health care to a breast cancer patient. The long waiting list can lead to gap between the end of chemotherapy and breast surgery and this gap can cause progression of the disease

Patients don't stick to prescribed medications. A lot of patients fail to fulfill the initial prescription and fail to administer the drug regularly and cannot continue therapy on a long term basis. Discontinuation at a suboptimal therapeutic level can lead to treatment failure. Oncology has made a lot of efforts in developing effective treatments for increasing survival of cancer patients. Surprisingly adherence to prescription is a significant problem for medications such as chemotherapy and other life-saving drugs. Mostly used necessary treatment for breast cancer is hormonal therapy (adjuvant) for hormonal sensitive breast cancers, these oral agents are like tamoxifen and aromatase inhibitors, and these are prescribed for five years or longer. Nonetheless, surprisingly, breast cancer patients discontinue this therapy approximately seven to ten percent per year (hormonal therapy) (Hershman et al., 2010).

Conclusion

For any cancer to be diagnosed and treated successfully, proper plan is required to control it. The main target of the plan is to cure cancer patients or prolong their life, ensuring a better quality of life. For the effective diagnosis and treatment program, it must be linked to an early detection program, so that the patients can be treated at an early stage when there are higher chances of curing the disease. It also needs to be integrated with a palliative care program, so that patients with advanced cancers, who can no longer benefit from treatment, will get adequate relief from their physical, psychosocial and spiritual suffering. Moreover, awareness programs should be conducted to avoid various types of barriers such as patients related by educating the patients, family, and community members about the cancer risk factors and the preventive measures to prevent cancer. Though there are limited resources, diagnosis and treatment services should initially target all patients presenting with curable cancers that can be detected early.

Now a days, women are facing geographical, organizational and health service barriers added by social, cultural and economic ones, affecting the search for health care after diagnosing the signs and symptoms of gross changes in the breast morphology and access to consultation with specialists, examinations for diagnosis and treatment. The fact noted made it need of hour to analyse the outcomes so as to overcome the obstacles and its consequences relating to health care in the breast cancer so that the most effective treatment can be provided to the patient. It is also useful for health managers and professionals, due to their involvement in attention to breast cancer since the early detection until the high complexity treatment.

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