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An overview on breast cancer

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Abstract
The aim of this study was to give a brief explanation about Breast Cancer, its causes, factors that cause breast cancer, diagnosis, treatment, etc. in India and in World. Also given a brief description of Cancer, and its types. Breast cancer is the most common female cancer in the world, Breast cancer incidence is rising all over the world, at different rates. Many clinical and genetic factors have been found to increase a woman's risk of developing the disease. Current strategies to decrease a woman's risk of developing breast cancer include primary prevention, such as avoiding tobacco, exogenous hormone use and excess exposure to ionizing radiation, maintaining a normal weight, exercise, breastfeeding, eating a healthy diet and minimizing alcohol intake. The objective of this study was too aware the women from various causes of breast cancer.

Keywords: Breast cancer, Gene Therapy, Breastfeeding, Diagnosis

Introduction
Breast cancer is the most common cancer overall among women in both developed and less developed regions of the world, representing 25% of new cancer cases among women, and the second cause of death in developed regions after lung cancer [1].
Breast cancer is cancer formed in the breast cells. Breast cancer is the most common malignancy in women, but it can occur less frequently in men. The incidence of breast cancer is increasing in the last decades of life. 75% occur in women over the age of 50, while 50% occur in women over the age of 65. The reason for breast cancer is unknown, but there is a risk factor for its occurrence. When it comes to malignancy in a particular case, breast cancer is known that there are certain risk groups of people who are at higher risk of this disease [2].
Two different genes responsible for breast cancer have therefore been identified. In women who carry one of these two types of genes, there is a high risk of developing cancer. But if these women develop cancer, the prognosis and the possibility of death are the same as in women who do not carry the gene. These genes that are responsible for the development of breast cancer are called BRCA or Breast cancer gene. It stands for Breast Cancer BRCA1 and BRCA2, two different genes that have been found to play a huge role in the development of breast cancer. These genes play an important role in preventing breast cancer. They help repair DNA changes that can lead to cancer and uncontrolled tumor growth. They are also known for suppressing tumors or tumor suppressors. In some people, these suppression genes do not work properly. If the BRCA gene is mutated, then the DNA repairing is no longer effective and also in helping prevent breast cancer. People with gene mutations are more likely to develop breast cancer at a younger age. The differences between the two genes are that, BRCA1 - creates a tumor that does not grow under the action of estrogen hormones, while BRCA2 - creates a tumor that needs estrogen hormones to grow.
In Figure 1, Breast anatomy: Each breast contains 15 to 20 lobes of glandular tissue, arranged like the petals of a daisy. The lobes are further divided into smaller lobules that produce milk for breast-feeding. Small tubes (ducts) conduct the milk to a reservoir that lies just beneath your nipple [3].

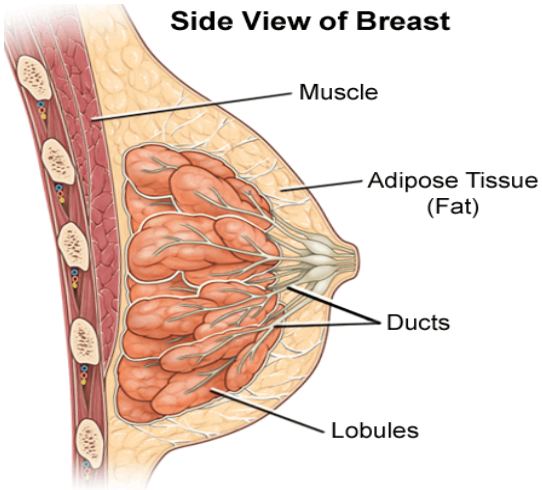

Fig 1: Breast Anatomy

Types of Breast Cancer
According to site
Non-Invasive
Breast Cancer cells that are confined to the ducts and do not invade surrounding fatty and connective tissues of the breast. Ductal carcinoma in situ (DCIS) is the most common form of non-invasive breast cancer (90%). Lobular carcinoma in situ (LCIS) is less common and considered a marker for increased breast cancer risk.

Invasive Breast
Cancer cells that break through the duct and lobular wall and invade the surrounding fatty and connective tissues of the breast. Cancer can be invasive without being metastatic (spreading) to the lymph nodes or other organs [4].

Stages of breast cancer [5].
The stages of breast cancer ranges from 0-4
- Stage 0
- Stage I
- Stage II
- Stage III
- Stage IV

Cancer stage is based on four characteristics
- The size of the cancer
- Whether the cancer is invasive or non-invasive
- Whether cancer is in the lymph nodes
- Whether cancer has spread to other parts of the body beyond the breast.

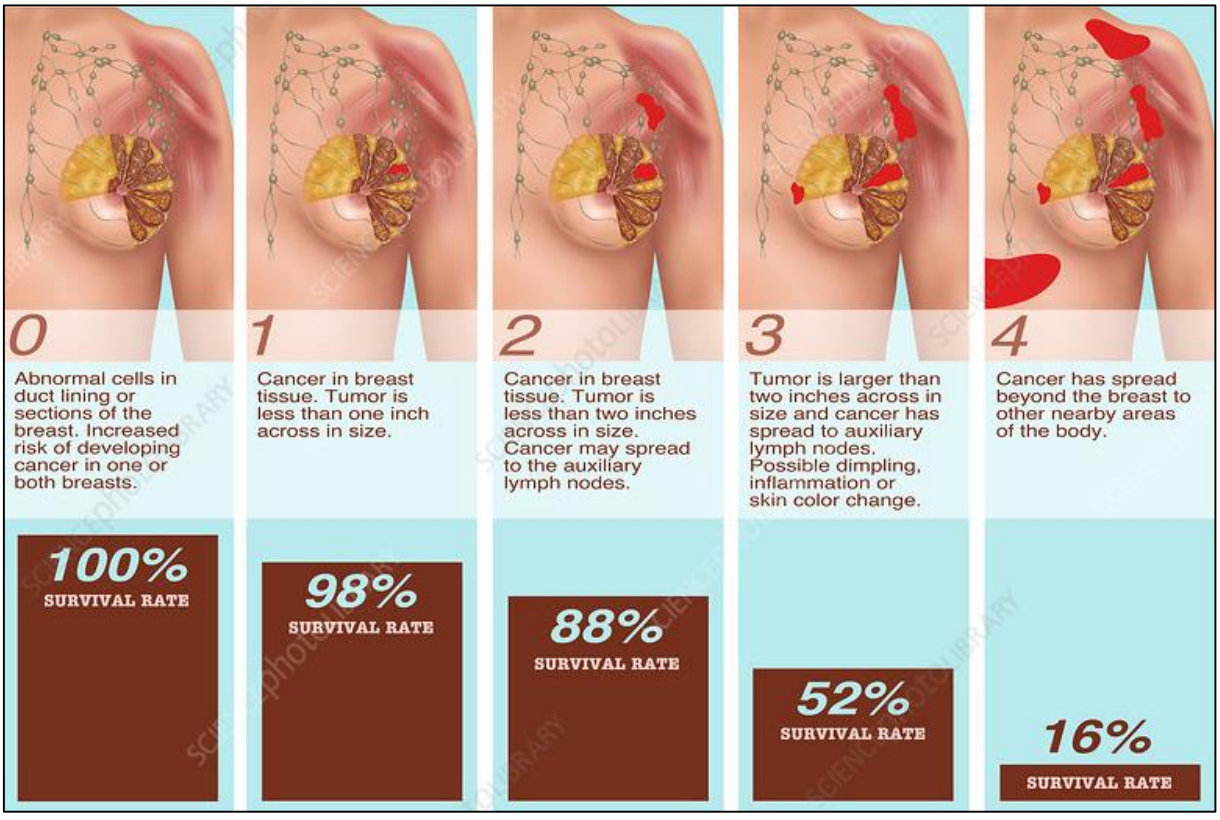

Fig 2: Stages of Breast cancer

Cancer may also describe as-
- Local
- Regional
- Distant

1. Stage 0
This breast cancer means that breast cancer cells have developed, but they cannot spread to any other surrounding tissues, or to the lymph nodes or other organs.

2. Stage I
The first stage of breast cancer means that tumor size is less than 2 cm. The I stage is divided into two Stage IA & Stage IB.

- **Stage IA**

The tumor measures up to 2 cm and cancer have not spread outside the breast; no lymph nodes are involved.

- **Stage IB**

There is a tumor in the breast that is no larger than 2 cm, and there are small groups of cancer cells larger than 0.2 mm but not larger than 2 mm in the lymph nodes. On the 1st stage, the survival rate during 5 years is almost 100%.

3. Stage II

Stage II is divided into subcategories known as IIA and IIB**.**

- **Stages IIA**

It this tumor size is less than 2 cm.In this tumor spread to no more than 3 lymph nodes under the arm, forming metastases more than 2 mm in diameter.

- **Stages IIB**

The tumor is larger than 2 cm but not larger than 5 cm, small groups of breast cancer cells larger than 0.2 mm but not larger than 2 mm are found in the lymph nodes.

4. Stage III

Stage III is divided into subcategories known as IIIA, IIIB, and IIIC.

- **Stage IIIA**

Indicates that tumor is not more than 5 cm and has spread to not more than 9 lymph nodes in the axilla or formed metastases in the lymph nodes in the mammary gland, but not to internal organs.

- **Stage IIIB**

In this stage, the tumor starts growing in the chest and skin but did not form metastases in the internal organs**.**

- **Stages IIIC**

It describes invasive in which tumor start starts developing. In this cancer effect more than 10 axillary lymph nodes. The tumor may be any size and may have spread to the chest wall and the skin of the breast.

5. Stage IV

It is described as invasive breast cancer that has spread beyond the breast and nearby lymph nodes to other organs of the body, such as the lungs, distant lymph nodes, skin, bones, liver, or brain [6].

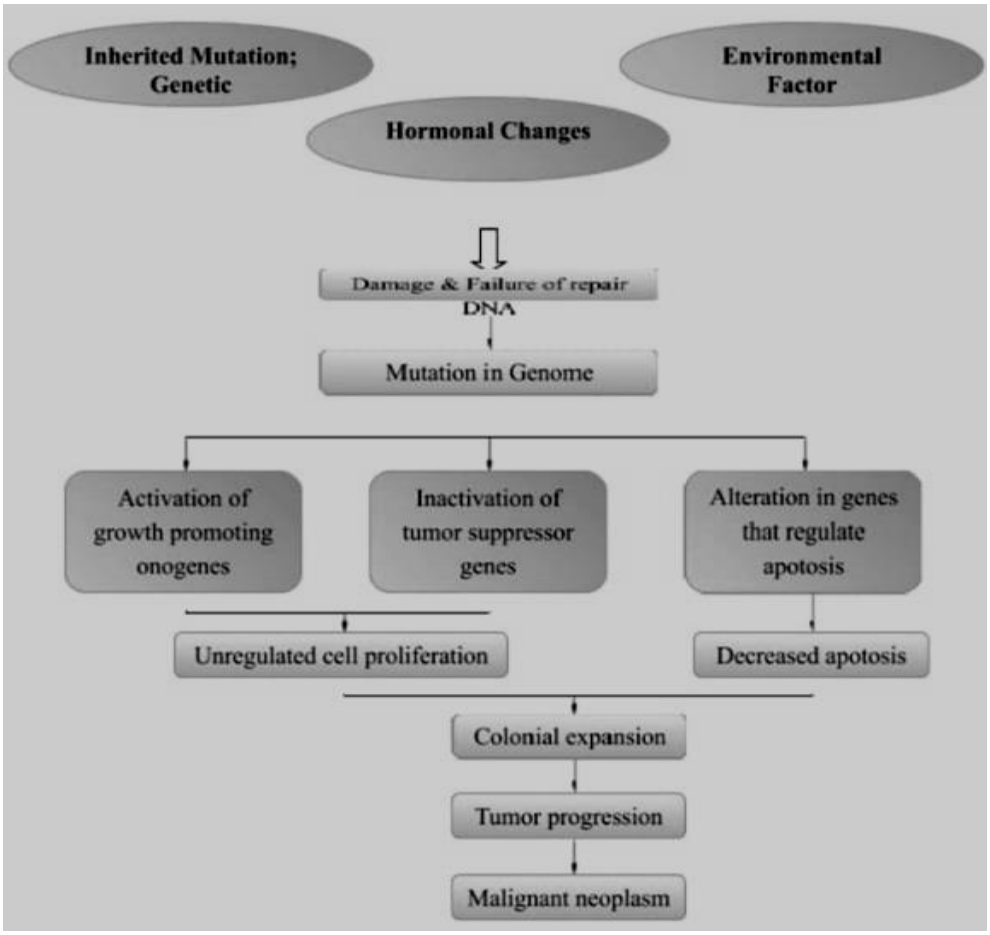

Fig 3: Pathology Pathway for breast cancer

Symptoms of breast cancer

The first sign of breast cancer is a new lump or mass in the breast that you can feel, the lumpm is painless, hard, and has uneven edges is more likely to be cancer. But sometimes cancers can be tender, soft, and rounded. So, as soon as any unusual changes are seen the person should go to the physician[7]. They are some of the main symptoms that may be seen during breast cancer are.

- Swelling of all or part of the breast.
- Skin irritation or dimpling.
- Breast pain.
- Nipple pain or the nipple turning inward.
- Redness, thickening of the nipple or breast skin.
- A nipple discharge other than breast milk.
- A lump in the underarm area.

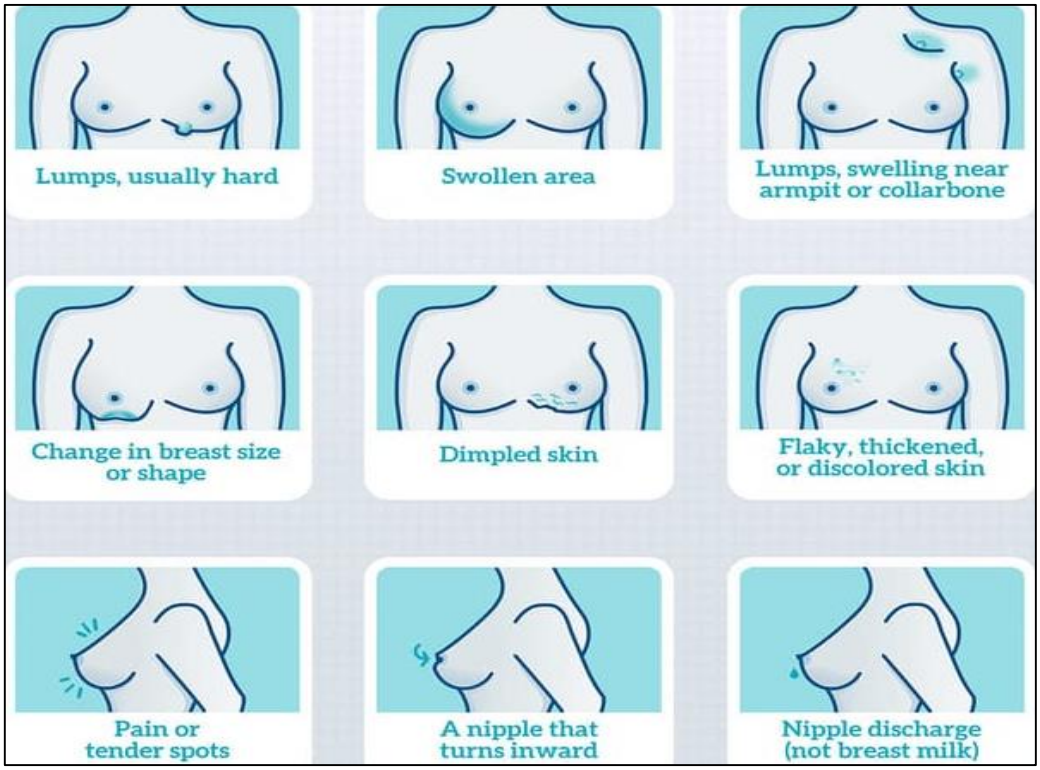

Fig 4: Symptoms of Breast cancer [8]

Causes of breast cancer

Environmental factors

Slightly more control women reported one or more environmental factors as risks for breast cancer. However specific chemicals were rarely identified by participants, who generally referred to broad factors such as 'pollutants', 'toxins' or 'additives' in describing environmental risks. A number of chemicals found in the environment, such as benzene (found in vehicle exhausts), are known carcinogens although with no definite connection to breast cancer. Some pesticides have been shown to mimic the effects of oestrogen and it is plausible that they could increase breast cancer risk, although the current epidemiological evidence is weak [9].

Alcohol use

Drinking alcohol is a one of the most important factor to cause breast cancer [10]. Alcohol consumption is increasing in many countries and is an important cause of cancer worldwide. Most people know that heavy drinking can cause health problems. But many people might not know that drinking alcohol also can raise their risk of getting cancer. Use of alcoholic drinks associates with the risk of cancers of mouth, throat, pharynx, voice box, larynx, esophagus, liver, colon, rectum, pancreases, stomach and breast etc. Alcoholic beverages such as beer, wine, and liquor have a potential vector for increasing risk of women's health by misbalance of hormones and receptor which lead to breast cancer. Alcohol promotes the level of estrogen and other hormones associated with hormones, receptors which are responsible to cause breast cancer [10].

Tobacco use

Smoking increases the risk of many types of cancer (including cancers of the lung, kidney and pancreas). Although findings on a possible link to breast cancer remain mixed, there's growing evidence smoking may slightly increase the risk of breast cancer. More research is needed before solid conclusions can be made about a potential link between smoking and breast cancer. Some studies have shown smoking before a first childbirth may increase the risk of breast cancer. Others have found no link between the two [11]. Tobacco smoking may be one of the few modifiable risk factors for breast cancer. The following is a summary of information from epidemiological studies on smoking and breast cancer [12].

Genetic risk factors

The attribution of breast cancer development to inherited or genetic factors was the most commonly identified cause among control women, a finding previously re-ported by others [13]. About 5% to 10% of breast cancer cases are thought to be hereditary, caused by gene changes (mutations) inherited from a parent. Inherited mutations in BRCA1 or BRCA2 are the most common cause of hereditary breast cancer. Women with BRCA mutations have a high risk of developing breast cancer during their lifetime. When they do develop it, they are often younger than other women with breast cancer who are not born with one of these gene mutations. Mutations in other genes are less common causes of inherited breast cancer [14].

DES exposure

DES exposure slightly increases risk of breast cancer. Diethylstilbestrol (DES), also known formerly as stilboestrol, is a synthetic nonsteroidal estrogen of the stilbestrol group which was first synthesized in 1938. It is also classified as an endocrine disruptor [15]. Human exposure to DES occurred through diverse sources, such as dietary ingestion from supplemented cattle feed and medical treatment for certain conditions, including breast and prostate cancers. From about 1940 to 1971, DES was given to pregnant women in the mistaken belief it woul ld reduce the risk of pregnancy complications and losses [16].

Overweight
Obesity is the most common disease. It raises the risk of having breast cancer, especially for women after menopause. Obesity is a complex, multifaceted condition and that active avoidance of excessive weight for height, irrespective of menopausal status, has a direct and consistent bearing on the number of women who die from this disease. Thus, it is critical to fully investigate how obesity impacts the carcinogenic process in the breast [17].

DNA changes
Most likely cause to changes in the genetic material (DNA) in our cells. DNA changes are often related to our lifestyle, but some can be due to age and other factors. Cancer is intimately related to the accumulation of DNA damage, and repair failures (including mutation prone repair and hyperactive repair systems) [18].

Previous chest radiation
Women who had radiation to the chest for another cancer as a child or young adult are at a much higher risk than those who did not [19].

Post-menopausal hormone therapy (PHT)
Increased risk in women who use or recently used combined PHT for many years.

Recent use of hormonal contraceptives
Slightly higher risk than in women who never used them, but this goes down after use stops.

Dense breast tissue
Women with denser breast tissue (as seen on a mammogram) have a higher risk of breast cancer.

More menstrual cycles
Slightly higher risk if a woman started menstruation early or went through menopause late.

Not breast feeding
Some studies suggest that breastfeeding may slightly lower breast cancer risk [20].

Recent approaches in management of breast cancer
Gene Therapy
It is generally accepted that cancer arises because of an accumulation of multiple molecular genetic defects that culminate in a cellular phenotype characterized by unregulated growth. Based on the knowledge, a variety of gene therapy strategies have been developed as potential new therapies for cancer [21]. Current knowledge of proto-oncogene and tumor suppresser genes in the genesis of malignancy has stimulated the development of gene therapy tactics directed at ablating or restoring such genes, respectively. In other strategies, cancer cells are endowed with the ability to convert a systemically delivered prodrug to a toxic metabolite, or a target for destruction by replicating viral vectors conversely transfer of drug resistance genes into normal cells may provide chemoprotection during high dose antineoplastic treatment. Finally, immune system modulation can activate anticancer drug defense mechanisms [22].

Oncogenes Inactivation
Several oncogenic proteins have been identified and associated with various malignancies. The most commonly applied approach in clinical trials to date has been use of antisense strategies. Transcription of oncogenes also can be inhibited by using adenoviral gene E1A, which interfere with the transcription of erbB-2, a strategy useful in treating cancer that over express this oncogenic protein, such as breast and ovarian cancer [23].

Augmentation of Tumor Suppresser Genes
More than 24 tumor suppresser genes have been identified, and mutations in these genes have been associated with a variety of neoplastic conditions. Several clinical trials are under way to deliver p53 using adenoviral vectors to a variety of cancers. Similarly, viral vectors have been utilized to introduce a retinoblastoma gene and breast cancer gene BRCA1 into bladder and ovarian cancer, respectively [24]. In some situations, this approach will fail, because the mutant gene exhibits dominant negative effects on the normal gene. To circumvent this problem for p53 gene therapy, a genetic repair strategy rather than a gene augmentation approach could be more effective [25].

Cell-Target Suicide
A conversion of a pro drug to a toxic metabolite by genetically engineering tumor cells is an attractive way to create an artificial difference between normal and neoplastic tissue. This can be achieved by the expression of a gene that confers a dominant, negatively selectable phenotype to the cancer cells, such as cell death imparted by expression of a prodrug-metabolism enzyme. Greater selectively in killing malignant cells will be obtained by transferring a gene that is not normally found inhuman beings (e.g. HSV-thymidine kinase), rather than by overexpression an endogenous gene [26]. The prototype for this approach utilizes the HSV-1 Thymidine kinase gene given to combination with produg ganciclovir in a manner distant from mammalian thymidine kinase. Phosphorylated ganciclovir is ultimately incorporated into DNA and inhibits DNA synthesis and transcription. The efficacy and safety on this approach is being tested in several clinical trials involving multiple malignancies [27].

Chemo protection Approach
The MDR-1 gene encoding the multidrug therapy transporter protein (also known as P- glycoprotein) has received much attention in this regard. This transmembrane protein transports a wide variety of chemotherapeutic agents (e.g. doxorubicin, vinaca alkaloids, epipodophyllotoxins and paclitaxel) and other drugs out of cells, thus protecting them from the agents' toxic effects [28].

Virus-mediated oncolysis
Certain viruses, including adenovirus, and HSV-1 can infect the lyse tumor cells. The use of oncolytic virus in combination with other gene based antineoplastic strategies has emerged as a promising addition to the multidimensional treatment cancers. Selective replication of virus in tumor cells leads to the cell lysis and to local dissemination of infective viral progeny to neighboring cancers cells. Most investigational uses of this strategy have utilized replication-competent adenovirus and HSV-1 [29].

Immunomodulation
Various cytokines can enhance immunity against cancer cells, and this observation has stimulated the development of

gene- based approaches to modulate the immune reaction in malignancy [30].

Ectopic Cytokine Expression

A variety of cytokine have been shown to decrease tumor growth when ectopically expressed in tumor cells or in there microenvironment. Some immunostimulatory agents do not alter the growth rate of the tumor initially, but lead to immunity against tumor growth if the animal is later challenged with wild type tumor cells [31].

Immune enhancement

One such approach is to express on the surface of cancer cells highly immunogenic molecule, such as allotype MHC antigens. It has been long known those additional "costimulatory" pathways distinct from the T-cell are needed to achieve T cell activation. The molecules B7-1 (CD 80) and B7-2 (CD 86) stimulate one such pathway. The B7s, whose expression normally is limited to antigen presenting cells and other specialized immune effector cells, engage specific receptors on the T cells surface in concert with antigen binding to the T-cell receptor [32, 33].

Table 1: Summary of research needs in breast cancer identified by the panel and suggested actions [34]

1. De-escalate breast cancer therapies in early breast cancer without sacrificing outcomes	▪ De-escalation of chemotherapy, anti-HER2 therapy and radiotherapy ▪ Identification of prognostic and predictive biomarkers with the aim of delivering optimal treatments with minimal side effects ▪ Development of new study designs and level of evidence scales for de-escalation purposes
2. Explore optimal adjuvant treatment durations	▪ Study design integrating the possibility to investigate different durations of treatment from the start ▪ Patient selection for shorter treatments based on pathological complete response to neoadjuvant therapy or other surrogates such as biomarkers (e.g. tumor-infiltrating lymphocytes)
3. Develop better tools to identify patients with genetic predisposition	▪ Identification of new breast cancer susceptibility genes ▪ Development and use of new genetic tools including numerous susceptibility genes for screening ▪ Investigation of optimal surveillance and prevention strategies for high-risk patients ▪ Development of novel agents for hereditary breast cancer
4. Improve care in young patients with breast cancer	▪ Elucidation of the molecular characteristics of breast cancer in young women ▪ Investigation of the possible de-escalation of treatments (intensity and duration) ▪ Analysis of different aspects on the safety of fertility preservation methods and pregnancy after treatment
5. Develop tools to speed up drug development in biomarker-defined populations	▪ Well-designed clinical trials for effective drug development and approval based on a small, but correctly defined, group of patients ▪ Investigation of earlier endpoints ▪ Validation of biomarkers of response, concomitant with drug development
6. Identify and validate targets that mediate resistance to chemotherapy, endocrine therapy or anti-HER2 therapies	▪ Elucidation of mechanisms of resistance ▪ Identification of new targets to overcome resistance through combined therapies ▪ Identification of biomarkers of response and resistance
7. Evaluate the efficacy of local-regional treatments for metastatic disease	▪ Prospective trials to identify optimal local-regional treatment in terms of survival benefits ▪ Development and use of new techniques for unresectable metastases ▪ Evaluation of optimal management of distant metastases: brain, bone, liver and lung ▪ Combination of improved systemic therapies and local therapy techniques
8. Better define the optimal sequence of treatments in the metastatic setting	▪ Well-designed clinical trials to define the optimal sequence or combination of therapies, addressing the different possible lines of treatments previously received and different resistant profiles of metastatic breast cancer patients, with the possibility of re biopsies or liquid biopsies ▪ Development of novel agents as single agents, in sequence, or in combination with existent therapies
9. Evaluate the clinical impact of intra-patient heterogeneity (intra-tumor, intertumor and inter-lesion heterogeneity)	▪ Development of non-invasive techniques to capture the patient's tumor biology and dynamics ▪ Elucidation of the relationship between tumor heterogeneity, poor prognosis and resistance to therapy ▪ Analysis of tumor heterogeneity results to guide treatment decisions
10. Better understand the biology and identify new targets in triple-negative breast cancer	▪ Molecular profiling to better characterize triple-negative breast cancer ▪ Identification of new cancer pathways and new potential targets, along with the development of companion biomarkers ▪ Development of antibody-drug conjugates with identification of triple-negative breast cancer-specific markers

Conclusion

Finally concluded that Breast cancer is the most common malignant disease in women in world and it is second among cancer deaths in women. We are already aware of important risk factors that lead to cancer (smoking, obesity, lack of exercise, high alcohol intake) which are being addressed, with some success. Today there are so many approaches, which can be made for the treatment of the cancer of breast such as surgery, radiation therapy chemotherapy, hormonal therapy and recently nanotechnology and gene therapy. With advances in screening, diagnosis, and treatment, the death rate for breast cancer has declined. In fact, about 90% of women newly diagnosed with breast cancer will survive for at least five years. Research is ongoing to develop even more

effective screening and treatment programs.

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