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OPPORTUNITIES AND CHALLENGES ASSOCIATED WITH BREAST CANCER: AN OVERVIEW

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Abstract

Breast cancer is the most common type of malevolent tumour in females, constituting about 30% of all cancers in females worldwide. Incidence rate of disease has increased by 20% since 2008 globally. Moreover, the complexity of disease arises due its variable nature and several types. However, in the past few years, mortality rate of disease has been reduced significantly due to adoption of various treatments like surgery, radiation, chemotherapy etc, and emergence of breast cancer screening. At present, chemotherapy is the most efficient treatment for disease. However, their side effects cause a long term provocation on patient's health. Thus, there is a need to develop a new treatment strategy that can only target the malignant cells without causing any harm to the adjacent body cells. Nanomedicines are auspicious alternative for treatment of breast cancer. Nanomedicines refer to materials having biomedical applications and have size range below 100 nm. A variety of nanocarriers are available like polymeric nanoparticles, dendrimers, nanotubes, liposomes, etc. Some of the nanocarriers like liposomes (Doxil) and nanoparticles (Abraxane) have been used successfully for breast cancer treatment. These nanomedicines hold immense potential to refine treatment strategies against breast cancer. They can enhance the pharmacodynamics and pharmacokinetics profiles of conventional treatments and may optimize the efficacy of existing drugs. Site specific delivery of anticancer drugs using nanocarriers results in increased therapeutic efficiency of conventional drugs. Nanomedicines based approaches are used to understand the interaction of cancerous cells with their surrounding cells. This review provides insight knowledge about the pathophysiology, current risk factors, types of breast cancers, and targeted drug delivery for breast cancer using nanomedicines approach to conquer the limitations of conventional therapy.

Keywords: Breast cancer, pathophysiology, risk factors, types, markers, nanomedicines,

Introduction

Cancer is a group of diseases that makes changes in the body cells so that cells grow in an uncontrolled manner and spreading to various parts of body. Breast cancer is one of the most occurring malignance in women (Ando and Catalano, 2011). It is the first tumour found in females for which targeted therapies were developed. The most common cause of breast cancer is ageing of population in the industrialized world (Malhotra *et al.*, 2010). Mostly all types of cancer develop a lump in different parts of body known as tumour. Breast cancer originates either from the breast tissue containing glands for milk production known as lobules or in the ducts which connect lobules to nipples (Agarwal and Ramakant, 2008). It can be developed in men also but it is 100 times more common in women than men. It can occur in any cells of the mammary gland and it shows a wide range of morphological features, various immunohistochemical profiles and histopathological subtypes. It is a diverse group of diseases divided into three types: (a) Human epidermal growth factor receptor 2 positive (HER2+), (b) Triple negative breast cancer and (c) Estrogens positive / progesterone positive or both. Many of the agents that target estrogens and HER2 receptors are most affluent cancer therapeutics. It is one of the leading causes of death in women worldwide. Main cause of death in women in developing countries and second cause of death in women in developed countries (Mohamed *et al.*, 2013).

Current worldwide scenario of breast cancer

Every year breast carcinoma is being detected in 1.3 million females worldwide and 465,000 deaths were reported from the disease (Saranath and Khanna, 2014). In United Kingdom (UK) the risk of breast cancer in women has risen to 47,000 in the age group of 50-69 years. It is expected that in coming year's majority of new cases of breast cancer will be diagnosed globally (Bray *et al.*, 2004). Almost 100,000 new cases are estimated to be detected in India annually. According to ICMR data breast Carcinoma is among the commonest cancer in females of Delhi, Kolkata and Mumbai, and in the rural area it is the second most cancer in females after cervix cancer (Althuis *et al.*, 2005). According to American cancer society 2018, 266,120 new cases of invasive carcinoma will be detected in females and 63,960 cases of in situ carcinoma will be detected. Cases of breast cancer depending upon the age groups are represented below in **Table-**1 (Forbes, 1997).

Table 1 : Cases of breast cancer based on the age group.

Age group	Invasive carcinoma cases (%)	In situ carcinoma cases (%)
<40	3	4
40-49	20	15
50-59	28	23
60-69	28	27
70-79	16	19
>80	6	12

Pathophysiology of breast cancer

Women's breast is mainly composed of group of fat cells called adipose tissue. This tissue originates from collarbone and it moves down to underarm covering the middle of the ribcage (Kelsey *et al.*, 1993). A healthy women breast contains 12-20 different sections called lobes. Each lobe is composed of various smaller lobules (milk producing gland). Lobes and lobules are joined by milk ducts which help to carry the milk to the nipple. Inside adipose tissue is a network of ligaments, lymph nodes, lymph vessels and

fibrous connective tissue (Smith *et al.*, 2003). Lymph system is basically a network of lymph vessels and nodes moving throughout the body. Lymph system which is the part of immune system, distributes disease fighting cells and fluids to various parts of body similar to blood circulatory system (Archambeau *et al.*, 1995). Lymph nodes are bean shaped structures which act as filters by separating unhealthy cells from normal cells. Type of breast cancer is determined generally on the basis of growth of cancerous cell in different sites of the breast such as lobes, lobules or ducts. When cancer cells are present in lymph nodes, this type of cancer is invasive as from lymph nodes it will move to different parts of body through lymph vessels. When cancer is present in nearest lymph nodes then it helps the physician to identify how far the cancer has spread and nearby nodes are tested for the presence or absence of cancerous cells (Nelson *et al.*, 2013).

Risk Factors for Disease

Incidence of breast cancer depends upon various factors such as hormonal, hereditary and other lifestyle factors which play a major role in mutation of DNA. Normal cells get converted into cancerous cells due to mutation. Among all 60-70% of patient diagnosed with breast cancer have no relation with risk factors. Some of the risk factors for breast cancers are smoking, alcohol, dietary factors which are listed in **Figure-1** and are described in subsequent sections (Mansfield, 1993).

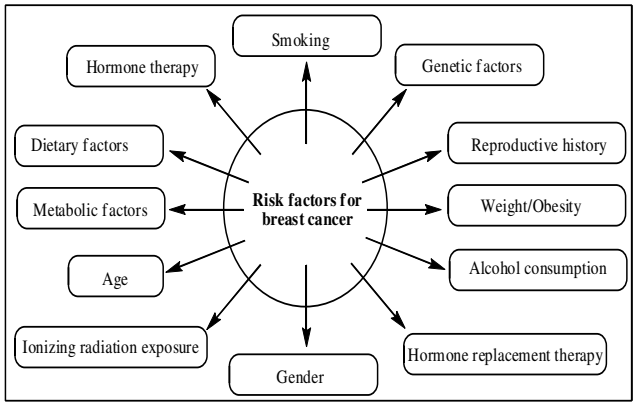

Fig. 1 : Different risk factors associated with breast cancer.

(i) Hormone therapy

Hormones such as estrogen and progesterone play a beneficial role in breast tumour formation. Patient having family history of breast cancer, it is not clear whether endogenous or exogenous factors act simultaneously with the genetic factor. Earlier, a study was conducted in which the hormonal levels throughout the menstrual cycle for 30 women's having risk of breast cancer and their result was compared with the control groups, so it was found that no possible difference was observed in plasma levels of prolactin, luteinizing hormone and follicle stimulating hormones at any stage of menstrual cycle (Pike *et al.*, 1983). Metabolites from urine of females were also analyzed and it was found that for women's having higher risk of breast cancer excreted less amount of estrone and estradiol as compared to control groups. From this study it can be concluded that breast cancer breast cancer risk is associated with abnormality in estrogens at a particular stage of ovulatory cycle.

(ii) Metabolic factors

Although there are many factors involved that may contribute to the risk of cancer development such as genetic, cultural or nonspecific. Previously, it has been hypothesized that both prevention and risk are basically due to difference in metabolic and secretary levels. Females having dry cerumen genotype have very less level of secretary activity in epithelial cells in breast duct as compared to women having wet cerumen genotype. Difference in metabolic and secretary levels may reduce the risk of cancer by providing protection to breast ducts of women having dry cerumen from environmental carcinogens (Pasanisi *et al.*, 2006).

(iii) Weight or obesity

Obese females may have increased chance of exposure of breast tissue with estrogens due to low production of 2-OH estrogen compounds resulting in hyperestrogenic state. Reabsorption of hormones is majorly affected by dietary fat. Excess fat and obesity are linked with low level of sex hormones binding globulin and as a result more amounts of sex hormones would be available for targeting breast tissue. High amount of fat in diet can also lead to excess production of prolactin and pituitary hormones (Bianchini *et al.*, 2002).

(iv) Dietary factors

Diet plays an important role in the incidence of breast cancer. According to National Academy of Sciences strong possible relation between dietary components and cancer is fat. High amount of fat intake and less carotene and fibre intake may leads to increased risk of breast cancer (Howe *et al.*, 1990).

(v) Hormone replacement therapy

Hormone replacement may increase the risk of breast cancer upto 69%. Undergoing hormone therapy for longer period of time did not result in increased risk of disease except in females who had previously undergone for hormone therapy, females with benign breast disease and women's who might have experienced menopause after the age of 43 (Beral, 2003).

(vi) Alcohol consumption and smoking

Many studies have indicated a strong relation between increased risk of breast cancer and alcohol consumption. Alcohol may alter or causes damage to DNA leading to cancer formation. Smoking may cause estrogens' metabolism and leading to increased hydroxylation of estradiol (O'Connell *et al.*, 1987).

(vii) Age

Age is one of the main risk factors for breast cancer and most of cases are diagnosed after age of 50. Hopper *et al.* reported 463 cases (>51%) out of total 896 cases of breast cancers between age 40-60 years (Hopper *et al.*, 2018). Similarly, study by Choi *et al.* showed highest numbers of newly diagnosed cases in the age between 40-50 years, however, the numbers of cases decreases at higher ages (Choi *et al.*, 2018). DNA-methylation is a feature of biological age in which pyrimidine ring of cytosine of CpG island becomes methylated by methyltransferase (Pouliot *et al.*, 2015; Jazwinski and Kim, 2019). DNA-methylation increases upto peak level (~80%) in the age 41-55 and has been identified as an important biomarker for breast cancer (Tsang *et al.*, 2016; Salta *et al.*, 2018).

(viii) Reproductive history

Various aspects of reproductive history such as parity, first birth age, menarche age, menopause etc. have been identified to affect breast cancer risk (Hanf and Hanf, 2014). The pregnancy decreases risk and menopause in older increases risk of ER+ breast cancer. The progesterone induces Th2 cytokines during pregnancy which involved in pro-tumorigenic responses. The menarche starts in response to elevated levels of circulating estrogens and menarche in early age increases risk of breast cancer. The fluctuation in estrogen and progesterone during menstrual cycle has profound effect on extracellular matrix, immune cells, and mammary epithelial cells (Anderson *et al.*, 2017). Study by Khalis *et al.* indicated that early menarche and nulliparity increase the risk of breast cancer, whereas an early age at first full-term pregnancy reduces the risk of breast cancer (Khalis *et al.*, 2018).

(ix) Genetic factors

Family history is the important genetic risk factor related to breast cancer and accounts for 5-10% of all case of breast cancer. The genetics of breast cancer susceptibility involved high-penetrance mutations in various genes such as *BRCA1*, *BRCA2*, *PTEN*, *p53*, *CDH1* and *STK11*. There are large numbers of moderate penetrance variants in the genes such as *ATM*, *CHK2*, *BRIP1*, *RAD51C*, *PMS2* and *PALB2* with predispose the disease (De Silva *et al.*, 2019). Very recently, Pan *et al.* reported a deleterious mutation in *FANCC* gene (a breast cancer suppressor) in a *BRCA1/2*-negative case (Pan *et al.*, 2019).

(x) Miscellaneous factors

There are some additional risk factors also which involved in breast cancer development and progression such as exercise, gender, stress or anxiety, exposure to ionizing radiation etc. These factors affect the circulating hormonal levels, breast immune system, DNA-repairing mechanism and apoptosis (Siewierska *et al.*, 2018; de Roon *et al.*, 2018; Kirsch-Volders *et al.*, 2010; Antonova, 2011; Kaur and Asea, 2012; Wang *et al.*, 2018).

Signs and symptoms

One of the most common symptoms of breast cancer is breast lump. Some non-lump symptoms such as itching, pain, swelling, rashes and burning are also seen (Koo *et al.*, 2017). The study of Dye *et al.* reported that breast lump is the first symptom encountered by patients (Dye *et al.*, 2012). Table-2 represents total number of patients having different symptoms whereas Figure-2 depicts different symptoms encountered by patients (Tasmuth *et al.*, 1995).

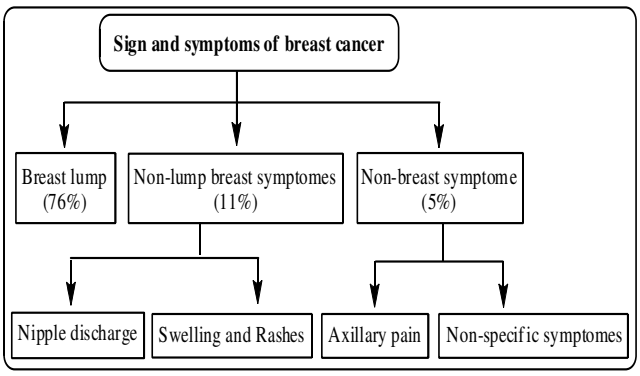

Fig. 2 : Signs and symptoms related to disease.

Table 2: Number of cases with different signs and symptoms.

Symptoms	No. of patient having these symptoms
Breast lump	82.6%
Itching	11.6%
Pain	1.4%

Types of breast cancer

Malignancies related to breast are adenocarcinomas, constituting 95% of breast cancers. Invasive carcinoma is further classified into ductal and lobular carcinoma depending upon the site from where tumour originates. Invasive ductal carcinoma accounts for 55% are the most common form of invasive carcinomas. Breast carcinoma is mainly divided into ductal carcinoma in situ (DCIS) and invasive ductal carcinoma. In situ carcinoma is a non-invasive form of cancer which remains confined to its place and does not spread to other body parts (Li *et al.*, 2005).

(i) Ductal carcinoma *in situ* (DCIS)

Ductal carcinoma involves Multiplication of epithelial cells limited to ducts and lobules and is characterized by formation of obligate, non-obligate and nuclear atypia. Myoepithelial cells present in the outer layer of ducts may get decreased in number. Movement of DCIS throughout the ducts and lobules is known as lobular cancerization. DCIS is known as the precursor lesion for development of invasive carcinomas. Morphological features and different grades of DCIS are being represented in **Table-3** (Makki, 2015).

Table 3: Morphological features and different grades of DCIS

Morphological types of DCIS	Grades of DCIS
Papillary	Low grade
Micro papillary	Intermediate grade
Solid	High grade
Comedo	High grade

(ii) Lobular carcinoma in situ (LCIS)

It is the multiplication of small intralobular uniform cells. From the follow up programme of womens with LCIS it was found that it constitutes a risk factor. In 70% of cases it is multicentric and bilateral in rest 30-40% of cases. Atypical changes are rarely observed, there are two main markers for distinguishing LCIS: high molecular weight and lack of E-cadherin and β-catenin. It develops in 25-30% of patient suffering with invasive carcinoma *in situ* (Weigelt *et al.*, 2010).

(iii) Invasive ductal carcinoma (IDC)

IDC is also known as infiltrating ductal carcinoma in which cancer cells have moved to other parts of breast tissues. Appearance is usually determined from the subtypes of IDC rather than the types or grade of DCIS. They are classified into many subtypes on the basis of location, amount, features and cell types. They have wide range of morphological variation and are defined as the group of tumors classified on the basis of cytoarchitectural features (Borst and Ingold, 1993).

(iv) Tubular carcinoma

It is a rare, well differentiated and distinct type of breast carcinoma with better prognosis. Tubular carcinoma is mostly found in elderly women and having very less lymph node metastasis. They are determined microscopically by the presence of oval, elongated tubules. When invasive lobular

and tubular carcinoma is differentiated to various body parts, it is known as tubulolobular carcinoma (Bloom *et al.*, 2004).

(v) Mucinous carcinoma

It is a rare subtype of breast carcinoma linked with better prognosis, it usually occurs in elderly patients and women with postmenopausal symptoms. Other words that are used to describe these tumors include mucous, colloid and mucoid carcinoma. These tumors consist of clusters of epithelial cells having mild nuclear atypia. Cluster of cells are expressed as solid and acinar forms (Memis *et al.*, 2000). **Figure-3** represents classification of disease based on site of tumour formation (Malhotra *et al.*, 2010).

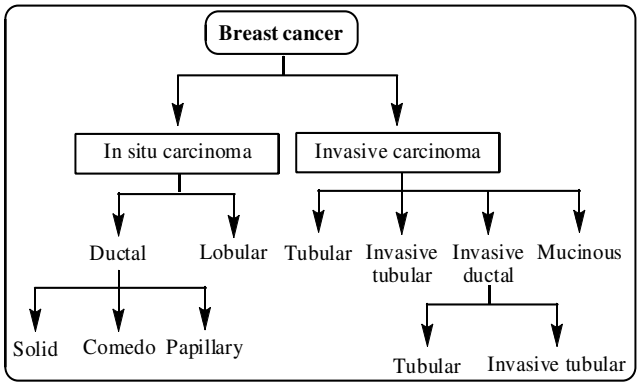

Fig. 3 : Classification of breast cancer based on the site of tumour formation.

Role of *BRCA1*and *BRCA2* genes in breast cancer

The two most common genes present in autosomal dominant in high penetrance form are BRCA1 and BRCA2. Both the genes produce tumour suppressor gene protein (TSGs) which involved in the protection against development of the disease. BRCA1 is located on chromosome 17 and any mutation in this gene causes increased risk of breast cancer. BRCA2 gene is usually located on chromosome 13 and known as acrocentric chromosomes present in men (Mehrgou and Akouchekian, 2016). Mutation in both the genes leads to hereditary breast cancer which accounts for 5-10% of cancer cases. Mutation in functional BRCA1 or BRCA2 in women increases risk of developing breast cancer up to an 80-85% (Goodwin *et al.*, 2012; http://www.cancer.ca).

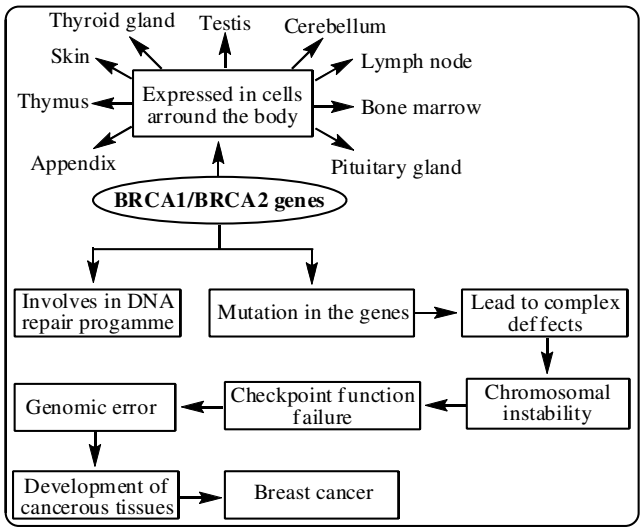

Fig. 4 : Mechanism of BRCA1/2 genes in breast cancer development.

Thus, one of the major progresses in cancer field was identification and role of BRCA1 and BRCA2 genes in human. They are involved in pathway for repairing DNA damage like transcription, regulation and recognition. Exact mechanism of BRCA1/2 mutation leading to breast cancer is still unknown. These genes are present throughout the body; they also interact with different proteins present in biological process. BRCA1/2 mutation is known as germline mutation which is passed to next generation. BRCA1 is involved in different phases of cell cycle and regulates different events whereas; BRCA2 gene is involved in controlling DNA damage. Figure-4 represents mechanism of cancer development by BRCA1/2 genes (Cavanagh and Rogers, 2015).

Markers for breast cancer

Molecular markers are used to detect the disease at early stage and are also used to determine the treatment required. Figure-5 represents different types of markers for breast cancer (Donepudi *et al.*, 2014).

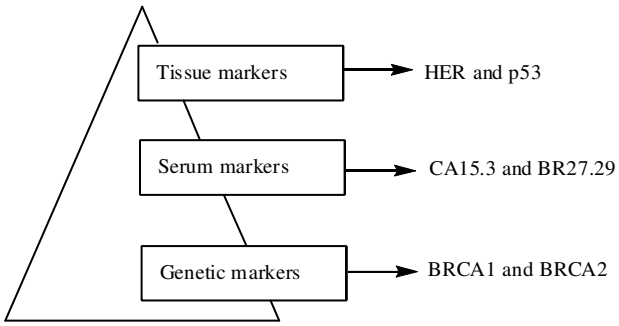

Fig. 5 : Different markers for breast cancer.

Current treatment strategy for breast cancer

Conventional therapies are restricted to surgery, chemotherapy and radiation which have many limitations like pain, trauma, and damage of non-cancerous cells/tissues. Many conventional chemotherapeutics such as gemcitabine, doxorubicin, pemetrexed, vinorelbine, nab-paclitaxel, platinum salts, irinotecan, etoposide etc. have been developed to treat metastatic breast cancer. The development of drug-resistance, lack of selectivity, poor response rates are major limitations of conventional chemotherapeutics. So targeted therapies are being developed with improved site selectivity, specificity and improved potency etc. Tamoxifen is the first selective therapy for breast cancer; it was tested initially with the aim to use it as an oral contraceptive. However, it does not control pregnancy in females and later tamoxifen was used to prevent hormonal positive breast cancer due to its property to inhibit breast cancer cell division. Trastuzumab (herceptin) is being used for the treatment of HER2 positive breast cancer. All the treatment approaches are based on inhibition of biomolecules involving in pathology of breast cancer. Earlier, Lu *et al.* have been reported peptide SP90-conjugated liposomal doxorubicin that improves the therapeutic index of the drug by its increasing selective accumulation in tumors (Lu *et al.*, 2013). The lipid-based nanocarriers for doxorubicin, daunorubicin and paclitaxel are being used clinically in cancer therapy (Lu *et al.*, 2013). Similarly, targeted therapies for PARP1 inhibitors are also being used and thus nanomedicine formulations play a vital

role in the site targeted delivery of drugs (Imyanitov and Hanson, 2004).

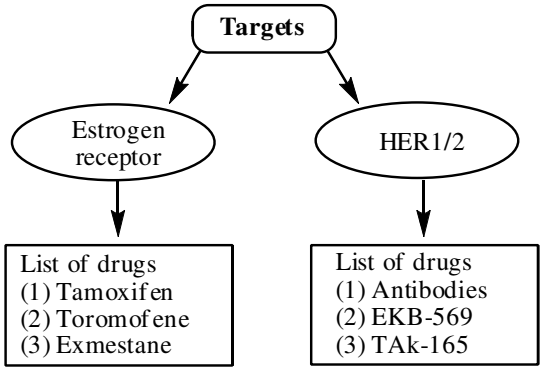

Fig. 6: Drugs acting on different targets for the treatment of breast cancer.

Triple negative cancer

Triple negative breast cancer is an aggressive form of breast cancer recognised by increased risk of recurrence and minimal survival in comparison with hormone receptor positive types. Two recent strategies used for treating triple negative breast cancer involves: targeting of DNA repair defect pathway and targeting of Poly (ADP-ribose) polymerase (PARP1) enzymes (Dent *et al.*, 2007).

(i) Targeting DNA defects

DNA damage pathway and DNA repair response are important for maintaining genomic stability and avoiding malignant transformation. Body cells are exposed to variety of exogenous and endogenous molecules. Two main pathways such as non-homologous and homologous recombination are used for repairing. BRAC1 and BRAC2 play an important role in homologous recombination (Farmer *et al.*, 2005).

(ii) Targeting PARP1 enzyme

PARP1enzymes are being used for base excision repair. This enzyme is activated with regard to DNA damage and imitates the generation of ADP- ribose polymerase at DNA damage site, which make chromatin structure relaxed and involves transfer of repairing protein to DNA break site.

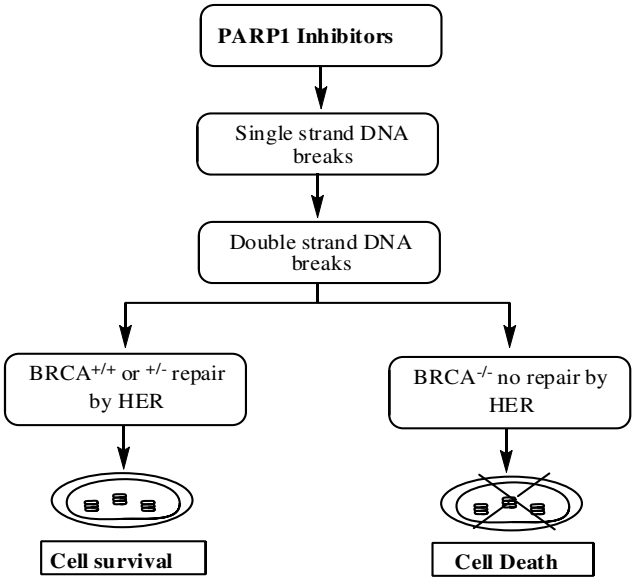

Fig. 7 : Mechanism of PARP inhibitors for inhibiting cancer.

BRAC1/2 genes are sensitive to inhibition of PARP enzymes. Mechanism of PARP inhibitors for inhibiting cancer formation is described in Figure-7 (Telli and Ford, 2010).

Table 4 : List of FDA approved PARP inhibitors used for treatment of cancer.

Drug Name	Manufacturer	Route of Administration	Phases of clinical trials
Veliparib (ABT-888)	Abbott Laboratories	Oral	I, II
PF-01367338	Pfizer Inc.	Intravenous	II
Olaparib (AZD-2281)	AstraZeneca	Oral	I, II
Iniparib	AstraZeneca	Intravenous	I, II, III
CEP-8963	Bipar Sciences Inc./ Sanofi-aventis	Oral	I
MK4827	Cephalon Inc.	Oral	I

Conventional modalities for treatment of breast cancer

Surgery is the most common approach in the treatment of breast cancer. Surgery is followed by neoadjuvant therapy to diminish tumour bulk. Usually surgery is being preceded by adjuvant therapy to minimize the chance of metastases. Malignant cells that may not be visible during surgery can be destroyed by radiation to minimize the chance of recurrence. In radiation therapy (RT) cancer cells are exposed to radiation directly. But there are some side effects of RT like peeling, itching and redness (Sharma *et al.*, 2013). **Figure-8** represents chemotherapeutics used for treating breast cancer depending upon the targets (Mieog *et al.*, 2007).

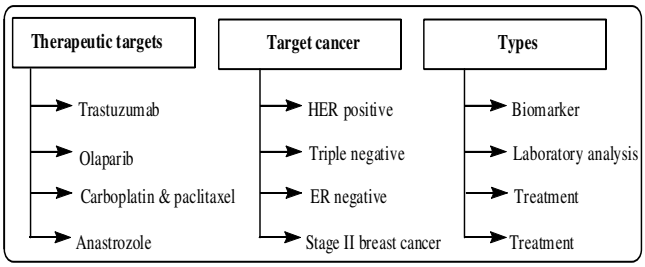

Fig. 8 : Various chemotherapeutics with their targets and types used for breast cancer treatments.

Adjuvant therapy

Adjuvant therapy depends upon two main factors: a) Patient risk of relapse, b) sensitivity to specific method. Final decision should be based upon patient health, age and co-morbidities. As per St. Gallen guidelines, decision should be based on intrinsic phenotype evaluated by ER/PR and HER2 assessment. In 2013, St. Gallen suggested that endocrine therapy is required for endocrine responsive histology and chemotherapy (CT) is required for non-responsive endocrine. Figure-9 represents different adjuvant therapy used for the treatment of breast cancer (Kaklamani and Gradishar, 2005).

Endocrine therapy (ET): This therapy is required either for blocking or balancing hormones. Choice of therapy also depends on patient's menopausal status. In premenopausal patients use of tamoxifen 20 mg/day for 5 years is standard. However, use of tamoxifen is linked with increased chances of thromboembolic complications. CT can be used as an

alternative. In postmenopausal patients, tamoxifen as well as anastrozole can be used in combinations (Gnant *et al.*, 2009).

Chemotherapy (CT): is being suggested in majority of triple negative breast cancer and HER2 positive cases. Four rotation of doxorubicin, cyclophosphamide (AC) is found equal to six cycles of cyclophosphamide, methotrexate and flurouracil (CMF) (Slamon *et al.*, 2001).

HER2 directed therapy: Trastuzumab in combination with AC and CMF minimize the chance of recurrence in patients with HER2. Due to its adverse effects Trastuzumab should not be administered routinely. It can also be given in combination with ET and RT which is found to be safe (Arnaout *et al.*, 2018).

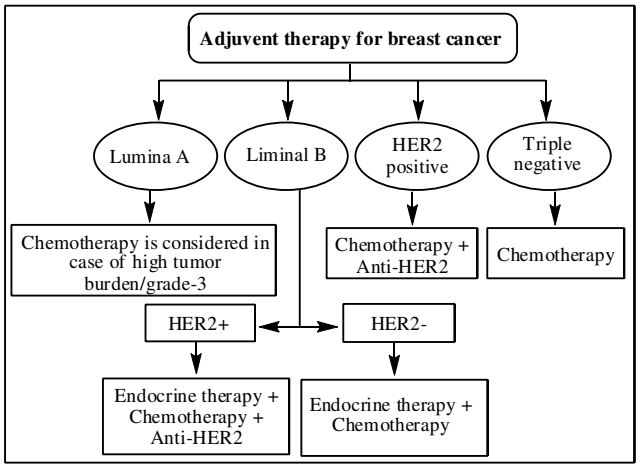

Fig. 9: different adjuvant therapy used for the treatment of breast cancer.

Neo-adjuvant therapy

This therapy is required in localized or advanced cancers, where mastectomy may be required due to cancer size; neo-adjuvant is mostly required for minimizing the extent of surgery. Treatment strategy employed in adjuvant therapy like CT, ET and targeted therapy can also be used preoperatively. In HER2 positive breast cancer; trastuzumab should be given in combination with taxane part of CT regimen, thus increasing chances of achieving complete response. Just like adjuvant therapy neo-adjuvant also minimizes the chance of tumour recurrence (Mauri *et al.*, 2005).

Possible side effects of chemotherapeutics

Depending upon medication and dose various side effects are being observed in breast cancer patients undergoing chemotherapeutics such as hair loss, fatigue, menstrual changes, nerve damage etc (Hassett *et al.*, 2006).

Nanomedicines for breast cancer treatment

Nanotechnology plays a crucial role for delivering chemotherapeutics to specific site in a targeted manner, thereby minimizing specific toxicity of conventional drugs and decreasing health related quality of life. Nanomedicines is define as the interaction of components (molecular and cellular); arrangement of atoms and molecules into smaller particles having size range between 1-100 nm (Saadeh *et al.*, 2014).

Over past few years, major development in nanomedicines and novel drug carriers has found safe and effective treatment strategies for breast cancer. To add on, advancement in molecular biology provides insight knowledge of breast cancer**.** As compared to conventional anti-cancer drugs, nanosized drug carriers have ability to conquer the limitations of chemotherapeutics by enhancing treatment efficacy while decreasing toxicity in normal body cells. Due to their characteristic feature such as high selective penetration in tumours, through enhanced permeability and retention effect (EPR). These nanomedicines hold immense potential to refine treatment strategies against breast cancer. The most common approach for delivery of drugs to targeted site using nanocarriers depends upon inorganic and organic particles. Different organic particles employed for delivery applications are dendrimers, liposomes, nanogels, micelles etc. They have flexible building blocks used for endocytosis and drug loading (Hare *et al.*, 2017). They also have multifunctional surface property that helps to carry cell to tumour vasculature. Figure-10 represents drug delivery approaches using nanocarriers for treatment of breast cancer. The approach of encapsulating anticancer drugs using nanocarriers is a better approach with respect to reduced side effects and better bioavailability of conventional drug (Parhi *et al.*, 2012).

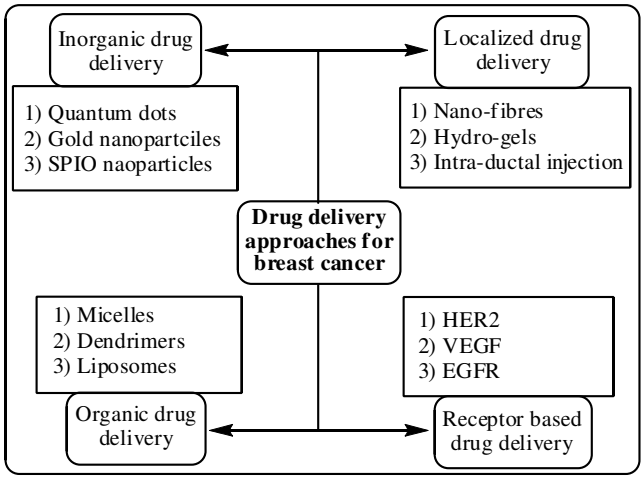

Fig. 10: Various drug delivery approaches using nanocarriers for treatment of breast cancer.

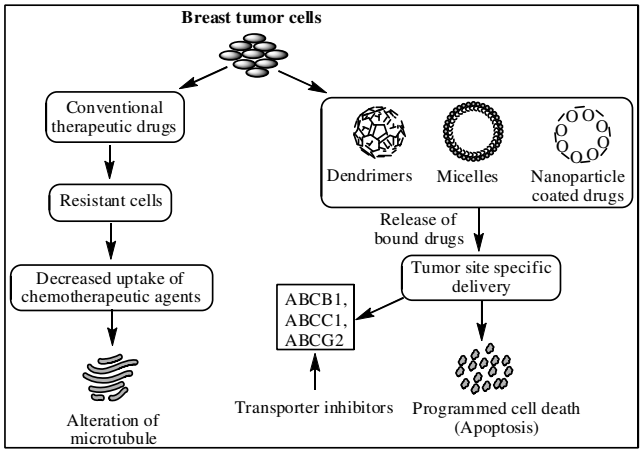

Fig. 11: Treatment strategy for nanocarriers in drug-resistant cancer cells.

Surface of nanoparticles can be modified easily, which allows nanocarriers to target specific cells, resulting in active targeting of particles. Molecules like peptides, antibodies are widely used to carry nanoparticles to specific site. Use of nanocarriers for delivery of drugs offers various advantages

related to free administration of drugs like; a) protecting drugs from degradation and b) better absorption inside body. Some nanocarrier have been approved by US Food and Drug administration (FDA) for treating breast cancer like Doxil® which is a first liposomal nanocarriers approved by FDA. Another is Abraxane® a chemotherapeutic drug paclitaxel in combination with albumin is being used for targeting breast cancer which was approved by FDA in 2005 (Vieira and Gamarra, 2016). Based on nanomedicine approach most relatable strategy for site specific targeting in drug resistant cancer cells is being shown in Figure-11 (Szakacs *et al.*, 2006). The natural chemosensitizers, when administered in combination, have also been shown to increase effectiveness of chemotherapy by inhibiting ABCB1, ABCC1 and ABCG2 transporters (Hamed *et al.*, 2019).

Delivery of chemortherapeutics to specific site is being achieved through two main process; passive and active targeting. Figure-12 represents targeting of nanocarriers to tumour site by active and passive targeting (Torchilin, 2010).

(i) Passive targeting

Targeted delivery for anticancer drugs has potential to minimize cytotoxicity and for better therapeutic effects. Cell targeting can be active or passive. Passive targeting relies on taking advantage of physicochemical properties of cancer cells. Tumour tissue contain large fenestrations in tumour vasculature followed from imbalanced angiogenesis, which allows nanoparticles to get accumulate in tumour tissue. Large fenestrations guide to improved passive targeting and drug retention to tumour site. Vascular permeability is also known as EPR effect. Nevertheless, EPR effect is the main phenomenon required for passive targeting for site specific delivery of drugs. EPR effect is inhomogeneous and its diversity may reduce delivery of drugs to specific site. Nanomedicines focus to improve the circulation time of conjugated drugs. Nanocarriers that only respond to malignant cells and deliver drugs at cancer site are part of passive targeting (Bazak, 2014).

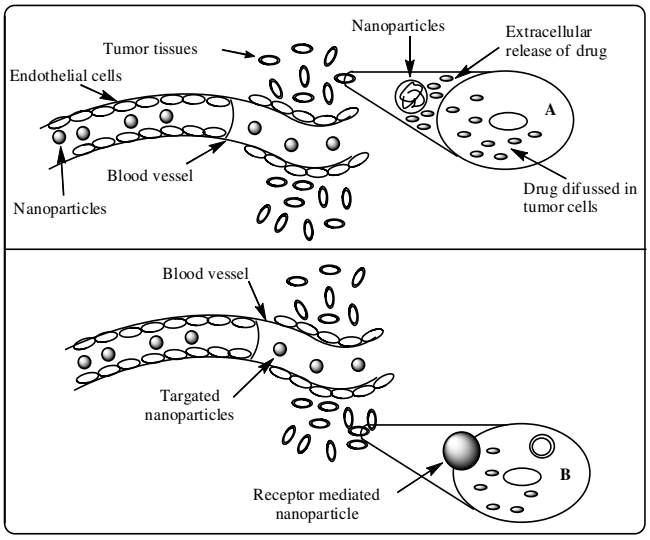

Fig. 12: Targeting mechanism of nanocarriers- (A) Passive targeting (B) Active targeting.

(ii) Active targeting

For enhancing targeting efficiency of nanocarriers active targeting was introduced. Targeting molecules like protein or antibodies is being attached to nanocarrier or direct targeting of particular receptors by these drugs. This mechanism is based upon ligand-receptor interactions. Overexpression of antigens in tumour is a potential target to attain drug uptake by endocytosis. In few cases, ligand like folic acid is being attached to nanocarriers which are also essential for tumour growth (Ozturk-Atar *et al.*, 2018). There are several approaches has been developed for site specific delivery of anticancer chemotherapeutic agents in the form of nanocarriers (**Figure-13**) (Iturrioz-Rodriguez *et al.*, 2019; Nam, 2019; Fortuni *et al.*, 2019; Niu *et al.*, 2018).

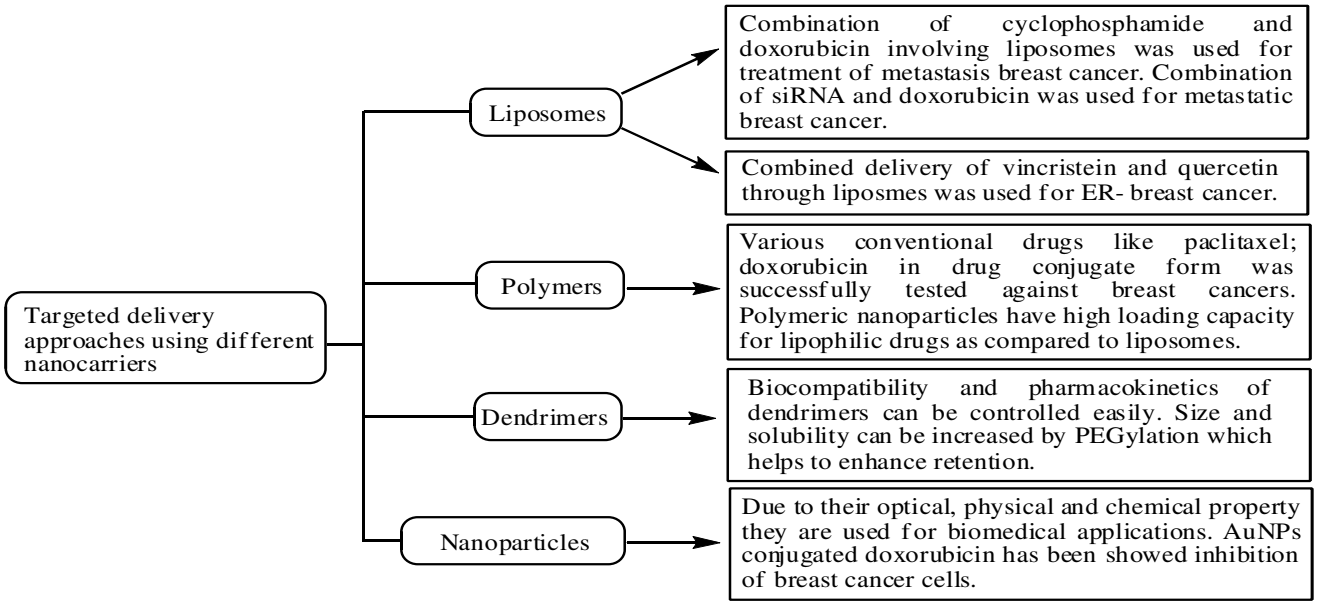

Fig. 13: Overview of different nanocarriers used for delivery of drugs to specific site.

Conclusion

From this study it is concluded that breast cancer is globally leading cause of mortality among all cancers in women of all age groups. However, age group of 40-60 is most susceptible to development of breast cancer. There is involvement of several risk factors in the progress of disease such as genetic, hormonal therapy, dietary factors, obesity, stress, reproductive history etc. The breast lump is a most

common symptom of disease along with itching, pain, swelling, rashes and burning. Breast adenocarcinomas is dominant form of disease, however, on the basis of morphological features and grades cases are divided into various types with makes more complex disorder. Mutations in *BRCA1* and *BRCA2* genes are profound genetic events in development disease. Complexity of disease is the main limiting factor for early detection and diagnosis of breast cancer. Although, continuous efforts identified some important markers in routine use for disease such as *BRCA1/2*, *CA15.3*, *BR27.29*, *HER*, and *p53*. The conventional treatment for breast cancer involves various limitations and can cause life threatening adverse effects. Hence, to conquer these problems targeted therapies as nanocarriers are being evaluated which efficiently deliver chemotherapeutics to specific site without causing toxicity to other cells. Ongoing efforts by researcher and scientist in nanomedicines will consistently develop new platform for nanocarriers. In upcoming years nanomedicine will showcase their potential not only in oncology but in various other fields also.

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Conflict of interest:

Authors have no conflict of interest for this study.

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