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Breast Cancer: Classification, Risk Factors, Current Diagnostic Procedures and Therapeutics

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The aetiology of breast cancer is complicated. In population health, breast cancer significantly impacts the most typical invasive malignancy and the second most typical death source for women. The most crucial point for the best prognosis is identifying early-stage cancer cells. The conventional diagnostics test for breast cancer includes a physical examination, biopsy (Fine-needle aspiration biopsy, core needle biopsy, Surgical biopsy) and several imaging techniques like mammography (digital mammography, computer-aided detection and breast tomosynthesis), MRI (Magnetic Resonance Imaging). Several drugs are approved by Food and Drug Administration for breast cancer, among them, some are approved to prevent breast cancer; some are used to treat breast cancer and some drugs are used in combination mode. Clinical investigation reports

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revealed that breast cancer mortality decreased in association with smaller breast volume and hence to meet the goal exercise is highly recommended. Similarly, dietary fat has been proposed as one of the etiologic factors of breast cancer. Obesity, overweight and reduced physical activity, causes breast cancer. At an early stage, cancer detection could increase breast cancer survival rates significantly in the long term. In the present review we have represented the breast cancer, its current statistics, molecular classification, different causes, disease prognosis, diagnostic strategies, and management in details in a lucid way.

Keywords: Breast cancer diagnosis; classification; imaging; risk factor; tumour morphology.

1. INTRODUCTION

1.1 Breast cancer

Breast cancer is remarkably ubiquitous cancer and the following most root of death due to cancer in female. The term "breast cancer" refers to a particular cancer prototype that arises from the tissue and typically lines the interior of ducts that supply the milk to the ducts [1] Fig. 1A.

Extensively breast cancer covers 10.4% of all types of cancer occurrences among female. This makes it the second most frequent type of non-skin cancer and the fifth most general cause of death [1]. In 2004 worldwide breast cancer cause death around 519,000. Usually, it is common in women than men, though due to delay in diagnosis, the outcome is more unsatisfactory [1]. Cancer cells are much more similar to cells of the organism, and their RNA and DNA are identical to the organism from which they have originated [2]. This is the leading cause of these cancer cells not detected by the immune system, significantly if the immune system is weakened. Cancer cells are constructed from normal cells due to RNA and DNA mutation or genetic modification and RNA modification [2]. These alterations or mutations can occur spontaneously ill Law of Thermodynamics- raise of entropy. These may be induced by some other influences such as electromagnetic radiation (Gamma-rays, X-rays, Ultraviolet-rays, microwaves etc.), nuclear radiation fungi and bacteria, viruses (due to irritation, tissue inflammation, chemicals in the air, heat, mechanical cell-level injury, food and water, free radicals, ageing and evolution of DNA and RNA. All of the previously mentioned causes and conditions can result in a mutation that may lead to Cancer [2].

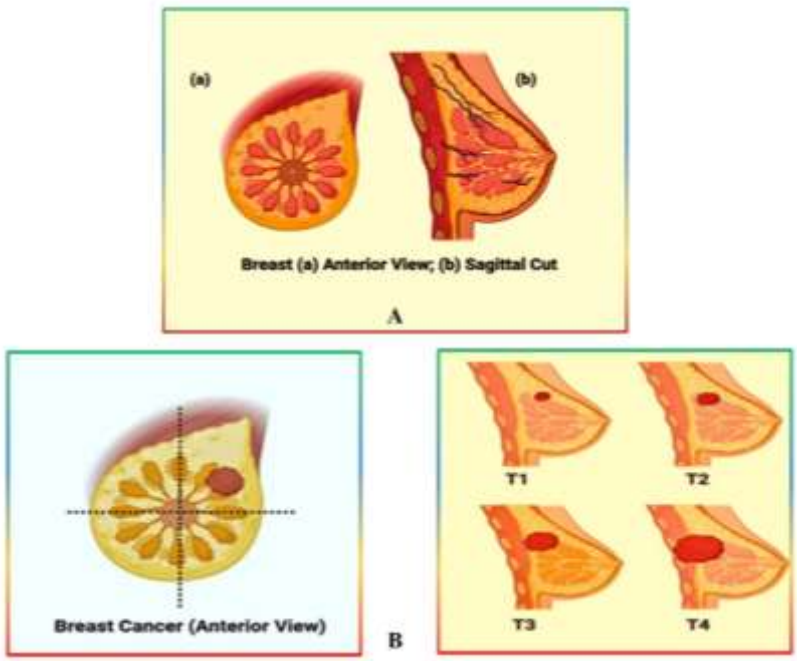

Fig. 1. [A] Anterior view and Sagittal cut of breast a. Anterior view and b; [B] Breast cancer anterior view

The best therapy method depends greatly on the type of breast cancer. Receptor-positive breast cancer fabricates 75% of all cases of cancer, making it the prevalent form. This form of cancer was found to respond to progesterone and estrogen-restricting and hormone-progression therapies [3]. It developed in response to these hormones. The other one is HER2-positive; it is characterized by cells that make a lot of the HER2/neu protein. It contains 20–30% of breast cancers that are receptor-positive [3] Read as HER2-negative HER2/neu-overproducing cancer [3] (Fig. 1B).

2. MOLECULAR CLASSIFICATION OF BREAST TUMORS (CANCEROUS)

In 2000, Dr Perou published an article on tumour stratification based on their molecular-genetic profile [4]. The profile counts the etiopathogenetic factors of tumors and their response to treatment. There are two types of epithelial cells: luminal and basal [4]. Apart from these well discriminate basal and luminal epithelial cells in glandular tissue, undifferentiated progenitor cells, and stem cells exist. Breast tumour classification is done after analyzing several genes regulating cell division and stromal and glandular breast cells' growth [4] (Fig. 2).

2.1 Basal-Like Tumors

Basal-like tumors are from cells that resemble basal cells of the epithelial lining in ductal-lobular units (terminal portion) [5]. They exhibit negative expression for estrogen, progesterone and HER2 receptors and project positive expression for Cytokeratins5,6 during immunohistochemistry. They indicateed that tumors with worst progenesis [5].

2.2 Luminal Tumors

The cells are present with in the terminal ductal-lobular units, i.e., luminal epithelial cells are akin to the luminal tumors. They are segregated into two subgroups based on estrogen receptors' expression and are exemplify by their gene expression and protein expression with positive immunohistochemistry staining in contrast to special cytokeratins 8, 185. While the A subgroup has more substantial estrogen receptors, B subgroup has minor expression than A [5].

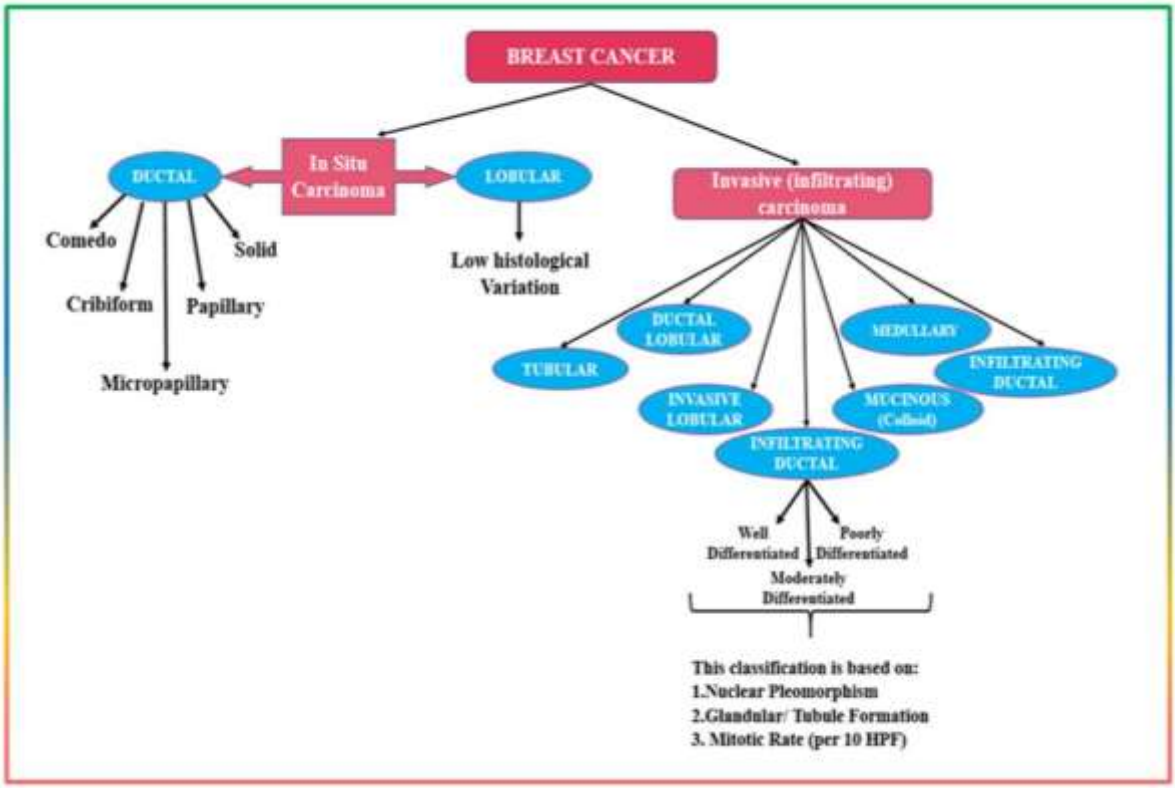

Fig. 2. Stages of tumor progression

Oestrogen receptor (ER) positive (HER-2 negative), 50-60% of all tumors illustrate germline mutation in BRCA2 [5].

2.3 Salient Features

- HER2-negative and ER-positive tumors are slow-growing and respond well to hormonal therapy.
- Further, they are sub-divided into low proliferation which is more common types and high proliferation which is fewer common types [6].
- The low proliferation generally upset older men and women and is normally observed on routine mammographic screening. In this group, histological types are Adequate or steadily differentiated lobular, tubular, or mucinous carcinomas [6].
- High proliferation groups can discriminate in lobular carcinomas and are mostly combined with BRCA mutations [5].

2.4 Estrogen Receptor Negative Tumors or Her2 Positive Tumors

HER2 tumors due to their rare molecular-genetic profile shape a diverse group of tumors [5]. They show positive staining for epithelial growth receptor 2 and negative staining for estrogen receptors [6]. They usually have a feeble prognosis in resemblance to luminal tumors. Among those 10-20% of tumors are HER2 positive tumors. It is relevant with amplification of HER2 gene on chromosome 17 [5]. (Fig. 3A)

2.5 Salient Features

- Young women who are TP53 mutation carriers are mainly affected by these types.
- Few of them may apocrine type [6].
- Less than ten years are the survival rate [6].
- ER-positive cancers react to 15% to chemotherapy. Triple positive tumors are the higher level of the tumour [5] (Fig. 3B).

2.6 Er-Negative or Her-2 Negative Tumors

2.6.1 Salient features

- Young women who are TP53 carriers get affected [6].
- Poor diagnosis; poorly differentiated though high grade and triple-negative tumors.
- Histological variations consist of adenoid cystic, metaplastic, medullary, and secretory [6].

2.6.2 Histological classification of breast tumors

It is segregated into two groups; non-invasive and invasive [7].

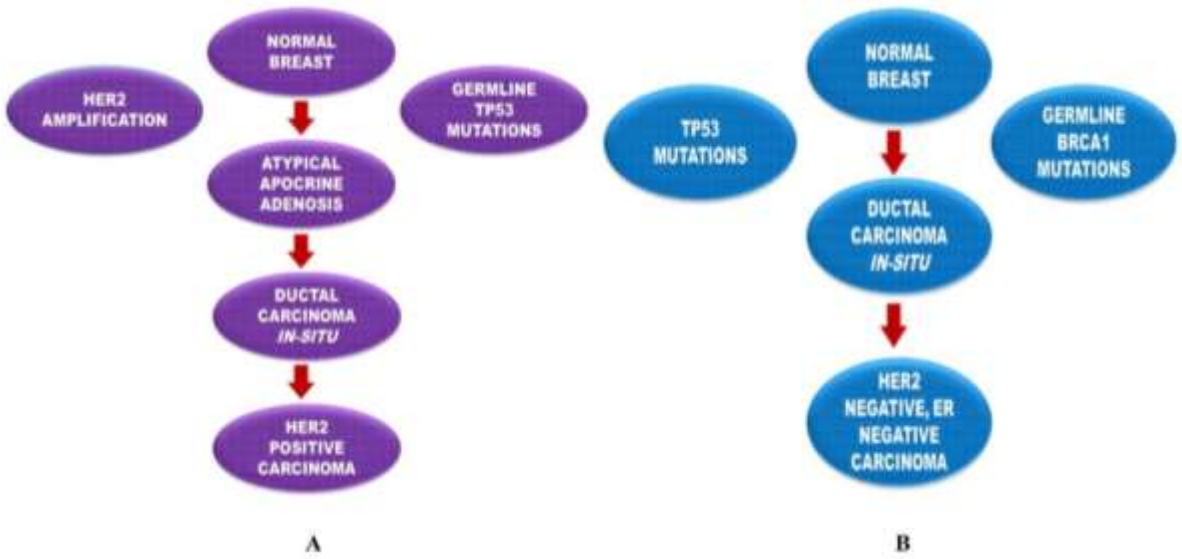

Fig. 3. [A] HER2 Positive carcinoma developmental pathway; [B] HER2 negative and ER-negative carcinoma developmental pathway

2.6.3 Invasive

Invasive breast tumors invaded the specific basement membrane and mainly are lesions. These are:

- Inflammatory carcinoma
- Tubular carcinoma
- Metaplastic carcinoma
- Medullary carcinoma
- Mucinous carcinoma
- Invasive lobular carcinoma

2.6.4 Non-invasive

lesions restrained to lobules and ducts and have not to go through the limiting basement membrane [7].

- Lobular carcinoma
- Ductal carcinoma

2.6.5 Classification (TNM) of breast carcinoma

Union for International Cancer Control rules is executed using the TNM classification concerning nodal status (N), Primary tumour size (T), and the absence/ presence of distant metastases (M) (staging) [8].

For each disease, there are two different TNM classifications:

1. Clinical /cTNM based on imaging and clinical examination.
2. Pathological (pTNM) and it is based upon postoperative histological examination. (Table 1).

2.7 Risk Factors for Carcinoma Breast

2.7.1 Age

It is unusual before 25 years, but exceptional in familial cases. At the age of 70-80 years, it has the highest peak but after that declines in incidence occur. At the age of less than 11 years, menarche increases risk by 20% compared to menarche at age greater than 14 years [9].

2.7.2 Geography

It is seen from a survey study that there is an appreciable variation in the volume of breast tissue (bra cup size) of women according to birth country. Women born in Asia and Africa have smaller breast size than women born in the USA. In developed countries, six times higher incidence, but the incidence is rising in developing countries [9].

2.7.3 Genetic Factors

- Mutations in familial ovarian and Cancer (BRCA2), familial breast and ovarian cancer (BRCA1), culpable for 1% of all breast cancer (CHEK2), p53, i.e., Li-Fraumeni syndrome [10].
- Family pedigree of breast cancer – it affects first-degree relatives who do not transfer a settled breast cancer gene mutation [9].
- Over interpretation of HER2/ proto-oncogene.
- Amplification of MYC and RAS genes [9].

2.7.4 Breastfeeding

It is observed that longer the span of breastfeeding, breast carcinoma is less [9].

2.7.5 Hormonal influence

Excess level of estrogens (nulliparity, long period of reproductive life, increasing age, first child at a late age and exogenous estrogens) [9].

2.7.6 Environmental factors

Radiation exposure, alcohol intake, phytoestrogens, tobacco, the light at night, metals such as arsenic, beryllium, cadmium, chromium, nickel etc., Endocrine disrupting chemicals (bisphenol A, Paraben, Phthalates, polybrominated diphenyl ethers, Perfluoroalkyl substances) and organochlorine pesticides (which has estrogen-like effects) [1].

2.7.7 Proliferative carcinoma of the contralateral breast or endometrium

Proliferative carcinoma of the contralateral breast or endometrium have several similar dangerous factors [1].

2.7.8 Breast density

High breast thickness on mammography has a 4-5 times greater risk of ER-positive and ER-Negative cancers [1].

2.7.9 Obesity

Women with obesity and less than 40 years have an ovulatory cycles and lower progesterone levels reduce the risk of carcinoma breast. At the same time, postmenopausal obesity raises the risk associated with estrogen synthesis in fat depots [11]. Obesity is measured by BMI or body mass index. This is known to be linked to an earlier age at menarche, an increased chance of postmenopausal breast cancer, and a decreased likelihood of premenopausal breast cancer. BMI may be more crucial, but it may not be the exact measure of body fatness [11].

The odd relationship between obesity in pre- and postmenopausal women may result from the two age groups' varying prevalence's of progestin receptor positive (ER+/PR+) / oestrogen receptor-positive tumors [9].

Table 1. TNM classification

T	It is the elementary tumour
TX	Reckoning the main tumour is impossible
T0	There is no indication of the original tumour.
Tis	Carcinoma in situ: intralobular or intraductal carcinoma
T1	Tumors are mainly less than 2cm in the finest extent.
T1mic	0.1 cm of micro-invasion or fewer
T1a	Less than 0.5 cm but in excess of 0.1 centimetre
T1b	Less than 1 centimetre but >= 0.5 centimetre in
T1c	>= 2 centimetre but < = 1 centimetre
T2	Less than 5 centimetres, but at their largest, tumors are more than 2 cm.
T3	The largest extent of tumors is greater than 5 centimetres.
T4	Tumors can be of any size and only extend directly through the epidermis or chest wall.
T4a	Expansion to the chest wall
T4b	Breast swelling
T4c	Both the 4a and the 4b
T4d	This includes provocative carcinoma.
N	Regional Lymph nodes
NX	There is no way to determine regional lymph nodes.
N1	In motile ipsilateral lymph nodes, metastasis occurs.
N2	Without clinically obvious axillary lymph node cancer
N2a	Metastasis is fixed in axillary lymph nodes to other structures or with one another.
N2b	Metastasis can occur only in clinically visible internal mammary lymph nodes.
N3	The unilateral infraclavicular lymph node developing metastases
N3a	A lymp node in the infraclavicular
N3b	Internal mammary duct metastases.
N3c	Lastly, metastasis in the lymph node above the clavicle.
M	Distant Metastasis
MX	Distant metastasis cannot be determined.
M0	There are no lone metastases.
MO (i+)	Absence of any symptoms or clinical indications of metastases in addition to the presence of tumour cells that can be seen under a microscope or by a molecular test in the blood, non-regional lymph nodes > 2mm. No, radiological or clinical confirmation of metastases.
M1	Distant metastasis histologically verifies or clinically evident via classical or imaging examination methods, greater than 0.2 mm.
Postoperative TNM classification	
pT	primary tumour
pN	regional lymph nodes

2.7.10 Medicine used for breast cancer treatment

For the therapy of breast cancer, there are numerous medications on the market. Medicines that have been endorsed here by FDA. (Figs. 4, 5)

2.7.11 Dietary natural products

The primary bioactive ingredients in dietary raw product perform a decisive part in the treatment and prevention of breast cancer (Table 2).

Table 2. Natural foods and their primary anti-breast cancer potent ingredients

Cereals				
Natural Product	**Constituents**	**Study Type**	**Main Effect and Possible Mechanism**	**Ref.**
Sorghum	Extracts	in vivo	promoting cell cycle arrest, suppressing tumour growth and metastasis	[12]
	3-deoxyanthocyanin	in vitro	promoting apoptosis by downregulating the Bcl-2 gene and up regulating the p53 gene	[13]
Barley	Extracts	in vivo and in vitro	exerting pro-apoptotic activities and anti-proliferative	[14]
Wheat	germinated wheat flour	in vitro	promoting growth and induce apoptosis	[15]
Fruits				
Natural Product	**Constituents**	**Study Type**	**Main Effect and Possible Mechanism**	**Ref.**
Pomegranate	luteolin, punicic acid, ellagic acid	in vitro	increases adhesion and decreases migration of breast cancer cells and inhibits growth	[16]
Mangosteen	α-mangostin	in vitro	Prohibits apoptosis and lower the expression of pS2 and ER alpha	[17]
Mangosteen	α-mangostin	in vitro	induces apoptosis via modulating MAPK	[18]
			and HER2/PI3K/Akt signalling pathways	[19]
Citrus fruit	Hesperidin	in vitro	anti-proliferative effect is seen	
Citrus fruit	Naringin	in vitro	suppress growth potential by heading β-catenin pathway	[19]
		in vivo	prohibiting cell proliferation and promoting G1 cycle arrest and cell apoptosis through inflect β-catenin pathway	[19]
Apple	pectic acid	in vitro	induces apoptosis and suppress cell growth	[20]
		in vivo	hinders tumor metastasis in mice through over-expression of P53	[20]
Grape	Anthocyanin	in vitro	Through inhibiting the expression of Snail it decreases invasion, migration and bone turnover and phosphorylated STAT3	[21]
Jujube	triterpenic acids	in vitro	Prohibits apoptotic cell death	[22]
Grape	amurensin G		Suppresses VEGF production	[23]
Mango	pyrogallol	In vitro	Suppressing proliferation through arbitrating the AKT/mTOR signaling pathway	[24]
Cranberry	NA	In vitro	Inducing apoptosis & G1 phase arrest	[9]

Spices				
Natural Product	**Constituents**	**Study Type**	**Main Effect and Possible Mechanism**	REF
Ginger	10-gingerol	in vitro	suppresses metastasis and proliferation, inducing cell cycle arrest	[25]
Ginger	6-gingerol	in vitro	Prevents metastasis by prohibiting MMP-2 and -9.	[26]
Ginger	6-shogaol	in vitro	Preventing invasion by lowering MMP-9 expression through blockade of NF- κB activation	[27]
			prohibiting invasion by suppressing invadopodium formation	[28], [29]
Ginger	6-dehydrogingerdione	in vitro	Inducing cell cycle arrest and apoptosis in G2/M phase	[30]
Garlic	allicin	in vitro	Inhibiting metastasis and invasion	[31]
Garlic	S-allylmercaptocysteine	in vitro	Inducing cell cycle arrest and mitochondrial apoptosis	[32]
Garlic	diallyl trisulfide	in vitro	Inducing apoptosis via:- subsequent	[33, [34]
			activation of AP-1 and JNK and over production of ROS	[35]
		in vitro and in vivo	- upregulating Bax ,FAS and p5 & down-regulating Bcl-2 and Akt	
Red chili pepper	capsaicin	in vitro and in vivo	-promoting apoptosis - preventing growth and migration	[36]
Black cumin	thymoquinone	in vitro and in vivo	promoting apoptosis through:	[37]
		in vitro	- suppressing Akt phosphorylation	[38]
		in vitro	- causing p38 phosphorylation via ROS generation Promoting proliferation by the process of the PPAR activation pathwayregulating E2 and COX-2	
Black cumin	extracts	in vitro	inducing apoptosis and inhibiting metastasis	[39]
Saffron	crocetin	in vitro	inhibiting metastasis, proliferation and invasion through lowering MMP expression	[40]
Black pepper	piperine	in vitro in vivo	- prohibiting growth, metastasis and motility,promoting apoptosis,	[41],
			suppressing the lung metastasis	[42], [43]
Rosemary	extracts	in vitro	exerting antitumor activity via mediation of HER2 and ER-α signalings	[44]
Clove	eugenol	in vitro and in vivo	Preventing proliferation and growth, promoting apoptosis via targeting the E2F1/surviving pathway	[45]

2.7.12 Physical examination

Breast self-examination, or consistent examining, is still believed an essential way towards early detection of breast cancer early, which leads to successful treatment. Breast self-cross-examination is a pragmatic screening tool,

correctly when used in consolidation with legitimate check-ups: mammography, and ultrasound or MRI in some cases [46]. It recommends that all women routinely perform breast self-exams as part of their general breast cancer screening strategy [46]

2.7.13 Imaging techniques

The use of imaging methods like mammography and MRI, frequently in conjunction with manual breast examinations, aids in the interpretation of breast cancer [47]. However, the only method to be certain is to collect some tissue from the questionable area and perform further testing look at it with a lens [47].

2.8 Mammography

Mammography is renowned for its expertise in capturing replica of the breast's interior. A small-dose X-Ray is used. A mammogram is a specific examination that primarily discovery and scrutiny of diseases in females [47]. A segment of the body exposed to a tiny quantity of radiation during an X-Ray procedure produces images of the interior of the body [47].

2.9 Full-Field Digital Mammography (FFDM)

are used to spawn mammographic images of the breast [48].

2.10 The Computer-Aided Detection (CAD)

The Computer-Aided Detection (CAD) system is an instrument for finding cancer signs by scanning mammographic images for regions with abnormalities in density, mass, or calcification. These areas on the pictures are highlighted by the system, which informs the radiologists to closely examine these regions [49].

The imaging method known as Magnetic Resonance Imaging uses radio waves to construct precise pictures of inner body [50]. Radiation is not necessary for MRI because it does not use X-rays. Breast MRI is used for breast cancer in a variety of ways, including:

- screening high-risk females (due to a gene anomaly or a background of the family)
- helps to collect thorough information about a suspicious region discovered on a mammogram or ultrasound.
- monitor the recurrence after treatment[50].

2.11 Ultrasound of Breast

Sound waves are used in ultrasound portray of the organ to design images of the intramural breast tissues. It is intact, non-invasive and has no purpose of radiation. It is used to help diagnose breast lumps or other abnormalities, that doctor may have found during a physical exam, mammogram or breast MRI [51].

2.12 Biopsy

A small sample of breast tissue is abolished during a biopsy process to be tested in the lab. To examine a suspicious area in your breast and decide whether it is breast cancer, you can have a breast biopsy. Breast biopsy procedures come in a variety of varieties [52].

Breast biopsies aid medical professionals in recognizing and diagnosing anomalies in the cells that make up breast lumps, other unusual breast changes, and suspicious or alarming discoveries on mammograms or ultrasounds. The breast biopsy's lab results help determine whether a patient requires additional surgery or other medical care [52].

3. OTHER ASPECTS OF BREAST CANCER DIAGNOSIS

In the last few years, CAD practice have been enlightened. A diagnosis made by a radiologist using the results of computerized analysis of medical images is known as CAD [53]. When identifying lesions and making diagnostic choices, pictures can serve as a "second opinion." Based on mammography technologies, there are two kinds of CAD systems: one is predicated on the traditional scenario [56].

This instrument seems to be a useful diagnostic tool where breast cancer is suspected, since the technique can easily be applied to the skin over the tumor, or the ipsilateral areola, in the case of a deep-seated neoplasm [46]. Computer-aided detection or analysis (CAD) system employs laptop technology to detect anomalies in mammograms, such as masses, calcifications, and architectural distortions; radiologists then use the results to make diagnoses [54], can play a key role within the early detection of carcinoma and assist to minimize the death charge among ladies with breast most cancers.

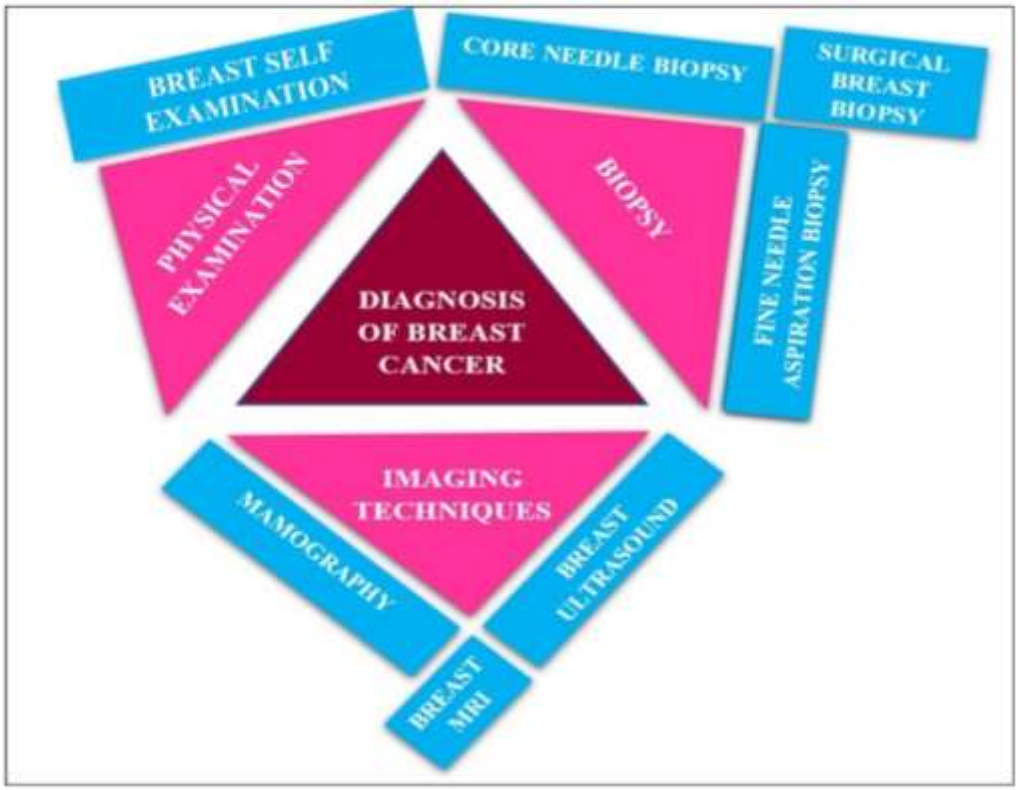

Fig. 4. Diagnostics for breast cancer

Fig. 5. Drugs approved by FDA against breast cancer

Additionally, it aims to promote research on the identification and diagnosis of cancer and related methods, as well as picture processing, computer technology, and radiological imaging, and to bring additional research scientists to the field of CAD for carcinoma [55].

Therefore, a study was conducted to correlate the survival of antagonist patients chosen from International Breast Cancer Study Troop trial participants with that of women who turn pregnant following medication for early-stage breast cancer CAD [53]. According to the research, subsequent pregnancies do not negatively impact the prognosis of early-stage breast cancer. The higher survival observed in this may merely reflect a healthy patient selection bias, but is also consistent with an antitumor effect of the pregnancy [57]. Utilizing diffuse reflectance spectroscopy and natural fluorescence spectroscopy, a calculation has been built up which enables effective grouping of typical breast tissue, fibrocystic change, fibro-adenoma, and invading ductal carcinoma as far as genuinely significant boundaries [53].

The combined yields of diffuse reflectance spectroscopy and intrinsic fluorescence spectroscopy reflects promising results for differentiating of breast cancer from benign breast lesions and permits a prospective clinical study [53] (Fig. 6).

3.1 Genetic Testing

Apart from various types of testing for diagnosis of breast cancer genetic testing has grown attention over the years. The important role of genetic testing is in hereditary risk assessment in breast cancer[58]. Due to the improvement in sequencing techniques and modification in gene patent laws genetic testing has increased a lot over the years. To understand genetic testing in proper manner one must understand the difference between the genetic testing, germline, and somatic testing. Genetic test deals with specific genes. It identifies the heritable mutation in a specific gene, whereas genomic test deals with group of genes. It interprets the expression/ sequence of a group of genes or entire genome. Germline mutation present from the time of fertilization and passes in all the cells of whole body over generations. BRCA1 or BRCA2 gene mutation is an ideal example for germline mutation [58]. The types of tests involve a sample of person's saliva or tissue, blood sample etc. Until, by the traditional Sanger sequencing methods each gene was tested and sequenced separately. It seems that this technique is cost effective and then comes the next-generation sequencing technique, where multiple-gene are sequenced and it seems more fruitful. Some of the genetic test and company for breast cancer:

1. Myriad Genetics company test myRisk of multiple genes (25 genes, including BRCA1, BRCA2, and PALB2) by blood DNA sequencing and the target population is high risk individuals [58].
2. Gene Dx (BRCA1 and BRCA2 Sequencing) company test BRCA1& BRCA2 genes through Blood or oral rinse and through Next-generation sequencing. The target population is high risk individuals [58].
3. Myriad Genetics (PANEXIA) test BRCA2 and PALB2 genes through blood and DNA sequencing process and target population is same individuals at risk for hereditary breast and pancreatic cancer.
4. Myriad Genetics test Single Site BRAC Analysis and Quest Diagnostics test BRCAvantage™, Single Site of BRCA1 or BRCA2A (single mutation previously identified in another family member) by Blood or oral rinse and DNA sequencing. The targeted population is individuals with family members with an identified mutation in BRCA1 or BRCA2[58].

4. EMERGING THERAPEUTICS FOR BREAST CANCER

4.1 RNA-Based Therapeutics

In the past few decades, paradigm-shifting research, particularly that involving non-coding RNAs (ncRNAs), has profoundly altered scientific views on the complexity of cellular signaling pathways [2]. There are numerous after effects akin with the use of many chemotherapeutic drugs in the medication of breast cancer. An appealing answer to these issues might be the practice of non-coding RNAs in breast cancer [2]. Studies have shown that specific miRNAs and lncRNAs urge the hormone, chemo-, and radio-subtlety of cancer cells, and it appears that there may be some chance for management of cancer patients who exhibit therapy resistance has improved. Thus, the future of ncRNAs being established as potential therapeutics seems very promising in the field of cancers including breast cancers [59]. The miRNA-based therapeutic strategies can open a path for combined

therapies- such as chemotherapy, endocrine therapy, or targeted therapy, combined with miRNA based therapeutic, with the intention of improving or combining anti-cancer benefits with decreased toxicity and raising the proportion of breast cancer patients who survive overall [60]. Different strategies have been undertaken to extend the fate of siRNA systemically and deliver siRNA to the sites of action [61]. MicroRNAs are involved with in many ways, hence it can be capitalized for designing therapeutics Since they can influence the cell response by simultaneously controlling multiple pathways whose prolixity is the foundation of the refusal to chemotherapeutics, miRNAs are potentially effective targets in this approach [62]. Considering that among the potential strategies herein discussed are challenges in targeting miRNAs, particularly in vivo, the use of PNA provides a workable technique to be tried shortly [62].

4.2 Nanotechnology Based Therapeutics

Zinc oxide nanoparticles (ZnONPs) has been widely used as an efficient drug delivery system in many biomedical applications. By using Rheum rhaponticum Waste (RRW) as a new bio platform, ZnONPs were created, and their anticancer effects on MCF7 cells were correlate to those of normal HFF cells [63]. Commensurate to the research, ZnONPs may one day be used to treat breast cancer as an effective biocompatible medication. The findings showed that the novel ZnONPs made from Rheum rhaponticum waste had a specific anticancer activity [63]. Nevertheless, there are many challenges which needed to be explained for applying them as an efficient cancer therapy strategy- including the need to find more details on their special molecular mechanism and also evaluating their impacts on different cells and tissues [63].

In order to improve a variety of factors, including time of blood circulation, biodistribution, and tumor cell-specific uptake, a therapeutic nanodrug formulation approach has been developed that readjust cell surface receptor-specific tying association and also maintains the essential synergy with blood and tumor tissue (called "DART" nanoparticles) [64]. The results support the continuing growth of the DART platform for both primary and metastatic tumors and provide novel perspectives on strategies for the efficient production of therapeutic nanoparticles [64]. The following factors should be taken into account by the researchers while using organic NPs for TPDT of breast cancer: (1) Engineering biocompatible and biodegradable organic nanoparticles for use with blood cells and blood coagulation is extremely important. (2) Organic nanoparticles' long-term and dose-dependent toxicity should be evaluated in clinical studies; (3) Organic nanoparticle absorption, biodistribution, and excretion should also be taken into account through rigorous clinical testing [65].

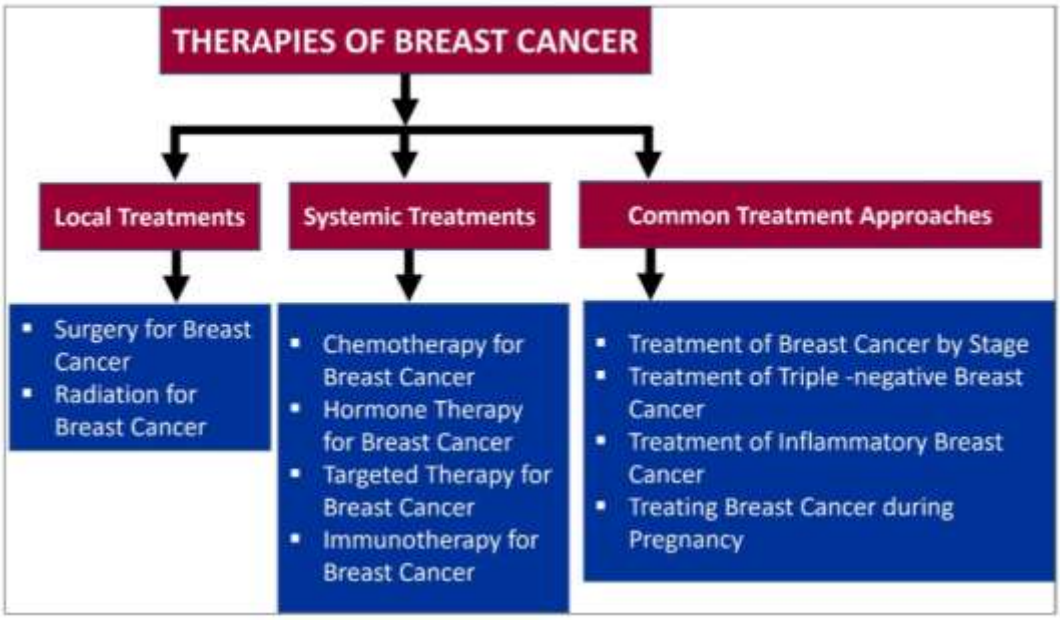

Fig. 6. Therapeutics for breast cancer

4.3 Combined Therapeutics

One of the biggest barriers in treating Cancer with chemotherapeutic drugs is the acquisition of drug resistance [66]. P-glycoprotein (Pgp) is a major mediator of the multidrug resistance to many lipophilic natural substances, including taxanes, doxorubicin, and vinblastine [66]. The substantial endeavor that has been made thus distant to combat this and other drug resistances have not been genuinely effective. reported that various orthotopic human breast cancer xenografts selected for high levels of Pgp and multidrug resistance responded well and in a durable manner to different continuous low-dosage chemotherapeutics, when used in amalgamation with an anti-vascular endothelial cell growth factor (anti-VEGF) receptor-2 (flk-1)-neutralising antibody (DC101) [67]. Taxol, adriamycin, and vinblastine were all found to be efficient when used in combination therapy, but chemotherapy protocols as monotherapies had little to no impact. Similar outcomes were attained when cisplatinum, a non-Pgp substrate drug, was applied to tumors that were immune to it. Ultimately, it was found that, when combined with another antiangiogenic medication—in this case, anti-VEGFR-2 restricting antibodies—vascular-targeting protocols, which frequently administer extremely low doses of specific chemotherapeutic drugs, can offer a stable and secure means of avoiding resistance to multiple drugs in established orthotopically developing tumors [66].

These results SU11248 treatment combined with docetaxel study revealed that SU11248 is quite effective in preclinical breast cancer models and also suggest that it can be useful in the clinical treatment of breast cancer [67].

According to research, in addition to preventing relapse, the combination of BI-2536 with doxorubicin and cyclophosphamide chemotherapeutic medicines produced a more comprehensive and rapid response, which is regarded as the most serious side effect the main danger posed by TNBC [68]. The observations, altogether suggested that in association with conventional chemotherapy, PLK1 inhibition is an attractive therapeutic approach, for the treatment of patients with TNBC [68]. This approach potentially reduces drug resistance, while simultaneously providing therapeutic anti-cancer benefits, such as reducing tumor growth and metastatic potential, arresting mitotically active cells, reducing cancer stem cell populations, and inducing apoptosis [69].

Immune checkpoint inhibitors are becoming highly popular and successful for the therapy of cancer, but they have not yet drawn much interest in the treatment of breast cancer [70]. On treatment of BRCA1-mutant breast cancers with cisplatin to increase their mutational load and then drugs in combination were targeted to two different immune checkpoint inhibitors, which gave promising results and suggested that a similar approach can work for patients [70].

Contrarily, a consolidation of curative drugs or the inclusion of chemotherapy to salutary compounds has shown a significant increase in outcomes and been demonstrated to be a successful approach for the treatment of TNBC [70]. This study clarifies the current clinical investigation status of numerous combinatorial medications for the treatment of TNBC as well as effective combinational pharmacological tactics [71].

Recent attempts to characterize TNBCs at the molecular level have identified a number of novel therapeutic targets, including immune checkpoints, androgen receptor, receptor and non-receptor tyrosine kinases, PARP1, and epigenetic proteins [72]. Key findings include that of the PARP inhibitor, olaparib, which extended progression-free survival in a trial of BRCA-mutated breast cancer and for which clinical approval (in this setting) appears forthcoming [72].

Another, findings suggest to conclude that SHP2 establishes a shared signaling node allowing MBC cells to engage a diversity of growth and survival pathways at the same time, including those derived from the ECM [73]. The triple combination of trastuzumab, tucatinib and capecitabine lowered the risk of disease progression or death by 52% in patients with HER2-positive BCB [74].

On the basis of altered apoptosis mechanisms, combined chemo-magnetic field-photothermal treatment applying Lf-Doxo-PMNSs demonstrated the apical anticancer action [74]. Therefore, depending on the observations, these can be used as a promising therapeutic platform with potential targeted drug delivery and high loading Furthermore, combining tranilast with Doxil nanomedicine, significantly improved immunostimulatory M1 macrophage content in

the tumorigenic tissue and improved the efficacy of the immune checkpoint blocking antibodies anti-PD-1/anti- CTLA-4 [74]. Capacity features as well as reducing cancer drug resistance [75]. On applying contact-free, thermography-controlled water-filtered infrared-A superficial hyperthermia, immediately followed by hypo-fractionated reirradiation, consisting of 4 Gy once per week up to a total dose of 20 Gy, resulted in very high overall response rates even in large-sized tumors [76].

It concentrated on improving combinations of chemotherapy, immunotherapy, gene therapy, and radiotherapy with other traditional therapeutic modalities, and prospective directions are also discussed [78]. This review aimed to highlight the importance of light in cancer therapy and further discussed the combinatorial strategies that promised to address the challenges of phototherapy [78].

5. CONCLUSION

There are several types of Cancer, and one of them is breast cancer and already discussed its aetiology is complicated. Extensively breast cancer covers 10.4% of all types of cancer occurrences among female. This makes it the second most frequent type of non-skin cancer and the fifth most general cause of death. As breast cancer significantly impacts the most typical invasive malignancy and the second most typical death source for women, several drugs are approved by FDA. Some are approved to prevent breast cancer; some are used to treat breast cancer and some drug combinations used in breast cancer. Discussing on the factors responsible for breast cancer, obesity is one of the principal causes of occurring breast cancer. Others are genetic factors, hormonal, environmental, breast feeding etc. To reduce obesity and simultaneously breast cancer most physical activities should be carried out. In the long term of survival early detection of cancer can be significant in case of survival. The most crucial point for the best prognosis is identifying early-stage cancer cells. There are several conventional diagnostics tests for breast cancer such as a physical examination, biopsy (Fine-needle aspiration biopsy, core needle biopsy, Surgical biopsy) and several imaging techniques like mammography (digital mammography, computer-aided detection, and breast tomosynthesis), MRI (Magnetic Resonance Imaging). The primary bioactive ingredients in dietary raw product perform a decisive part in the treatment and prevention of breast cancer such as naringin, ellagic acid, pectic acid and many more showed a great effect against breast cancer invitro and in-vivo.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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