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Busting Breast Cancer Myths: A Deep Dive into Epidemiology, Risk Factors and Effective Management

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Abstract:- Breast cancer is marked by uncontrolled cell growth leading to invasive tumors in the breast ducts and lobules. Risk factors include modifiable elements like lifestyle choices and nonmodifiable factors such as age and genetic mutations. Global epidemiology sheds light on prevalence and contributing factors, crucial for prevention and management. Classification involves histopathological and molecular criteria, encompassing various subtypes. Diagnosis relies on imaging techniques like mammography and biopsies, with minimal radiation exposure. Treatment includes hormone treatment, targeted therapy, radiation, chemotherapy, surgery, and immunotherapy, with immune checkpoint inhibitors such as PD-1 and PDL-1 being used in particular. The intricate tumor microenvironment involves diverse cell types and factors like hypoxia and exosomes, presenting challenges and opportunities for therapeutic advancements in the breast cancer management.

Keywords:- *Breast Cancer; Biopsy; Chemotherapy; Tumor-Resistance; Microenvironment.*

I. INTRODUCTION

Uncontrolled cell proliferation in the breast tissue, originating from the lobules or breast duct linings, defines the characteristic nature of breast cancer [1]. The majority of instances of breast cancer present as invasive, and the disease progresses by causing malignant tumors to form when unchecked cells invade surrounding breast tissue from the breast ducts or lobules [2].

II. EPIDEMIOLOGY

A. Global Condition /Incidence/Causes

Breast cancer stands as the one of primary global public health concerns [3]. Investigating and identifying novel insights into the predisposition of breast cancer is pivotal for advancing efforts in both prevention and management, ultimately aimed at mitigating its impact on public health. This study aimed to analyze the global burden of disease, including incidence rates, mortality rates, and associated risk factors associated for breast cancer spanning from 1990 to 2019, with a future projection up to 2050, providing valuable insights to inform strategic initiatives for breast cancer management worldwide [4]. The study's findings reveal that regions characterized by low socio-demographic index (SDI) levels are anticipated to bear the greatest burden of breast cancer in the future. Additionally, in the year 2019, metabolic hazards emerged as the predominant global risk factor contributing to deaths associated with breast cancer [5]. Breast cancer, being an almost ubiquitous malignant tumor, has become a significant menace to global health, with the associated burden of disease, as measured by the global burden of disease (GBD), posing a substantial threat, particularly to women's health worldwide [6]. In 2020, breast cancer held the distinction of being the most prevalent malignant tumor globally, projecting an estimated 2.261 million new cases and 685,000 fatalities, highlighting its significant impact on a global scale [7].

B. Risk Factors

The risk factors for breast cancer were divided into two categories: modifiable and non-modifiable [8].

Table 1: Modifiable and Non-Modifiable Risk Factors for Breast Cancer

Non-Modifiable Factors	Modifiable Factors
Female Sexuality	Alcohol intake
Older age	Diethylstilbesterol
Ancestral History (breast or ovarian cancer)	Physical activity
Mutation in the Genetics	Excessive exposure to artificial light
Pregnancy and breastfeeding	Being Overweight and Obese
Race/Ethnicity	Hormonal replacement therapy
Menstrual period and menopause	Smoking Habit
Previous radiation Therapy	Insufficient vitamin
Non-cancerous breast disease	Supplementation
Weight of breast tissue	Processed food consumption
History of breast cancer	Exposure to chemical entities

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➢ *Non-Modifiable Factors*

- *Female Sexuality*

Because of the higher hormone stimulation associated with being a woman, this is the main risk factor for having a higher chance of developing breast cancer [9]. Women possess estrogen and progesterone hormones within their breast cells, and elevated levels of estrogen and androgen hormones are linked to a higher risk of breast cancer. The endogenous estrogen hormone plays a crucial role not only in breast cancer but also in the development of endometrial and ovarian cancers [10]. The significance of the endogenous estrogen hormone extends beyond female reproductive cancers, impacting male reproductive cancer, including male breast cancer. Heightened levels of this hormone, whether in postmenopausal or premenopausal women, contribute to an increased probability of developing breast cancer [11].

- *Older Age*

Age is the primary risk factor, as evidenced by research showing a strong correlation between those over 50 and the prevalence of breast cancer [12]. Examining the relationship between the distinct molecular subtypes of cancer and patient age highlights that aggressive subtypes, like triple-negative, are predominantly diagnosed within the 40-age group [13]. In younger women, breast cancer tends to present with larger sizes, advanced stages, positive lymph nodes, and is frequently associated with a more aggressive course [14].

- *Ancestral History*

Breast cancer in the family is most significant risk elements in various studies [14]. When two or more incidences of breast cancer are identified in people under 50 years of age, it is noteworthy to have a family history of the disease. Women who do not carry the BRCA mutation, despite this family history, can still develop breast cancer [15]. There's a higher risk for early-onset breast cancer, which is frequently linked to BRCA1 and BRCA2 gene mutations [16].

- *Mutation in the Genetics*

Gene mutations in the BRCA1 and BRCA2 genes caused breast cancer, which are inherited via the dominant autosomal pattern.

- *Pregnancy and Breast Feeding*

Women are much more likely to get breast cancer during their first pregnancy. The association between placental detachment during pregnancy and an increased risk contributes to the likelihood of developing enlarged breast cancer [28]. Preeclampsia contributes to breast cancer during pregnancy by raising levels of hCG, alpha-fetoprotein (AFP), IGF-1 binding protein, and insulin-like growth factor-1 (IGF-1). It also decreases estrogen and IGF-1 levels. Studies reveal a negative correlation between pregnancy-related nausea and vomiting and the prevalence of breast cancer [29].

- *Menstrual Period and Menopause*

The influence of ovarian hormones, beginning in puberty and persisting throughout the menstrual cycle, combined with factors such as the frequency of pregnancies and the onset of menopause, establishes a correlation between reproductive factors and breast cancer [30]. Around age 45 to 50 is when menopause usually starts. Studies on cases have indicated a relationship between the proportion of breast cancer and an older menopausal age [31].

- *Breast Tissue Density*

Breast weight is the ratio of glandular tissue and fibrous (fibroglandular tissue) in the breast relative to the adipose tissue [32]. A higher density of the breast in younger females is associated with a lower Body Mass Index (BMI), especially during pregnancy and breastfeeding periods [33]. An augmentation in breast tissue density is frequently linked with an increased susceptibility to breast cancer, and this connection is evident in both premenopausal and postmenopausal women [34].

➢ *Modifiable Factor*

- *Alcohol Consumption*

Drinking alcohol raises the possibility of getting malignant breast cancer [35]. Increased alcohol consumption induces elevated estrogen levels and disrupts hormonal balance in the female reproductive system. Drinking alcohol before becoming pregnant raises your chance of breast cancer. Excessive alcohol consumption further contributes to an elevated BMI, adding to the overall risk [36].

- *Being Overweight and Obese*

Numerous studies examine the connection between obesity and breast cancer [37]. The highest risk of developing estrogen receptor-positive breast cancer is seen in overweight postmenopausal women, according to a significant correlation. Postmenopausal women with obesity have higher cancer death rates and deteriorating cancer outcomes [38]. The increase in women's body fat the alteration of pro-carcinogenic hormone levels and the elevation of inflammatory levels [39].

- *Hormonal Replacement Therapy (HRT)*

Alternatively known as postmenopausal hormone therapy, this treatment involves the use of endocrine disruptors (HRT) and selective estrogen receptor modulators (SERMs) [40]. The researchers conducted a study, and the results indicated that among 1 million women using Hormone Replacement Therapy (HRT), there was an increase in the mortality rate and a heightened risk of developing breast cancer [41]. The results revealed that the risk was reduced when using the Estrogen-Progesterone or Estrogen-Dydrogesterone method [42]. This treatment is used in postmenopausal women who have the BRCA1 mutation, and crucially, it has no effect on chance of getting breast cancer or making it worse [43].

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III. DEATH TOLL

In 2003, more than 40,000 individuals succumbed to invasive breast cancer in the United States, with over 210,000 new cases documented. This marked a decline of approximately 2,000 annual deaths compared to the peak year of 1995. Over a million new instances of breast cancer are reported each year, making it the most frequent malignancy among women globally [44]. Over 80% of every 10,000 persons in Western countries will get breast cancer at some point in their lives. Notably, there is an increasing incidence rate in the developing world as well. Between 1975 and 1990, the most substantial increases (ranging from 1% to 5%) were observed in Asia [45]. Genetic inheritance, specifically family history involving BRCA1, BRCA2, or p53 germline mutations, is associated with the risk of breast cancer. Caribbean region experienced the highest increasing rate, rising from 16.52 to 26.36, while Western Europe saw a decreasing rate from 37.57 in 1990 to 36.00 in 2015. The American Cancer Society reports that breast cancer is the second most prevalent cause of cancer-related fatalities among women in the United States, projecting approximately 252,710 invasive and 63,410 non-invasive cases in 2017. The anticipated death toll due to breast cancer was approximately 40,610 in the same year [46]. Per the American Cancer Society's 2017 report, there was a decrease in the death rate for women over 50 in 2007 but no increase in the death rate for those under 50. 11,400 instances of breast cancer fatalities occurred in the UK in 2014; of those cases, 75 affected men and the remainder 11,300 affected women. Moreover, estimates suggest that the number of instances of breast cancer in the UK will rise by 2% between 2014 and 2035 [47].

Table 2: Mutation in the Genetic Factor Causes Breast Cancer and Associated Syndrome with Major Functions and Associated Breast Cancer Risk

Penetration	Gene	Chromosome Location	Associated Syndrome	Major Function	Breast Cancer Risk	Reference
High	BRCA1	17q21.31	Breast cancer, Ovarian Cancer, Pancreatic cancer, Fanconi anaemia	DNA repair cell cycle control	45-87%	[17]
	BRCA2	13qq13.1	Breast cancer, Ovarian cancer, Pancreatic cancer, Prostate cancer, Fanconi anaemia	DNA repair cell cycle	50-85%	[18]
	TP53	17p13.1	Bellary cancer, Melanoma, Breast cancer, Colorectal cancer, Hepatocellular carcinoma, Pancreatic cancer, Osteosarcoma, Adrenocortical carcinoma	DNA repair cell cycle control induction of apoptosis induction of senescence maintenance of cellular metabolism	20-40 %(even up to 85%)	[19]
	CDH1	16q22.1	Breast cancer , Ovarian cancer, Endometrial cancer, Gastric cancer, Prostate Cancer	Regulation of cellular adhesion control of the epithelial cells	63-83%	[20]
	PTEN	10q23.31	Breast cancer, Cowden syndrome, Prostate cancer, Autism syndrome, Lhermitte Duclos syndrome	Cell cycle control	50-85%	[21]
	STK11	19q13.3	Breast cancer, Peutz-Jeghers syndrome, Pancreatic cancer, Melanoma, Testicular tumor	Cell cycle control maintenance of energy homeostasis	32-54%	[22]
	ATM	11q22.3	Breast cancer, Lymphoma, T-cell Prolymphatic leukaemia, Ataxia-telangiectasia	DNA repair cell cycle	20-60%	[23]
	PALB2	16q12.2	Breast cancer,	DNA repair	33-58%	[24]

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			Pancreatic cancer, Fanconi anemia			
	BRIP1	17q23.2	Breast cancer, Fanconi anemia	Involvement in the BRCA1 activity	ND	[25]
	CHEK2	22q12.1	Breast cancer, Li-Fraumeni syndrome, Prostate cancer, Osteosarcoma	Cell cycle control	20-25%	[26]
	XRCC2	7q36.1	Fanconi anemia, Premature ovarian failure, Spermatogenic failure	DNA repair	ND	[27]

IV. CLASSIFICATION OF BREAST CANCER

Breast cancer is primarily categorized into two main classifications: histopathological breast cancer and molecular classification [48].

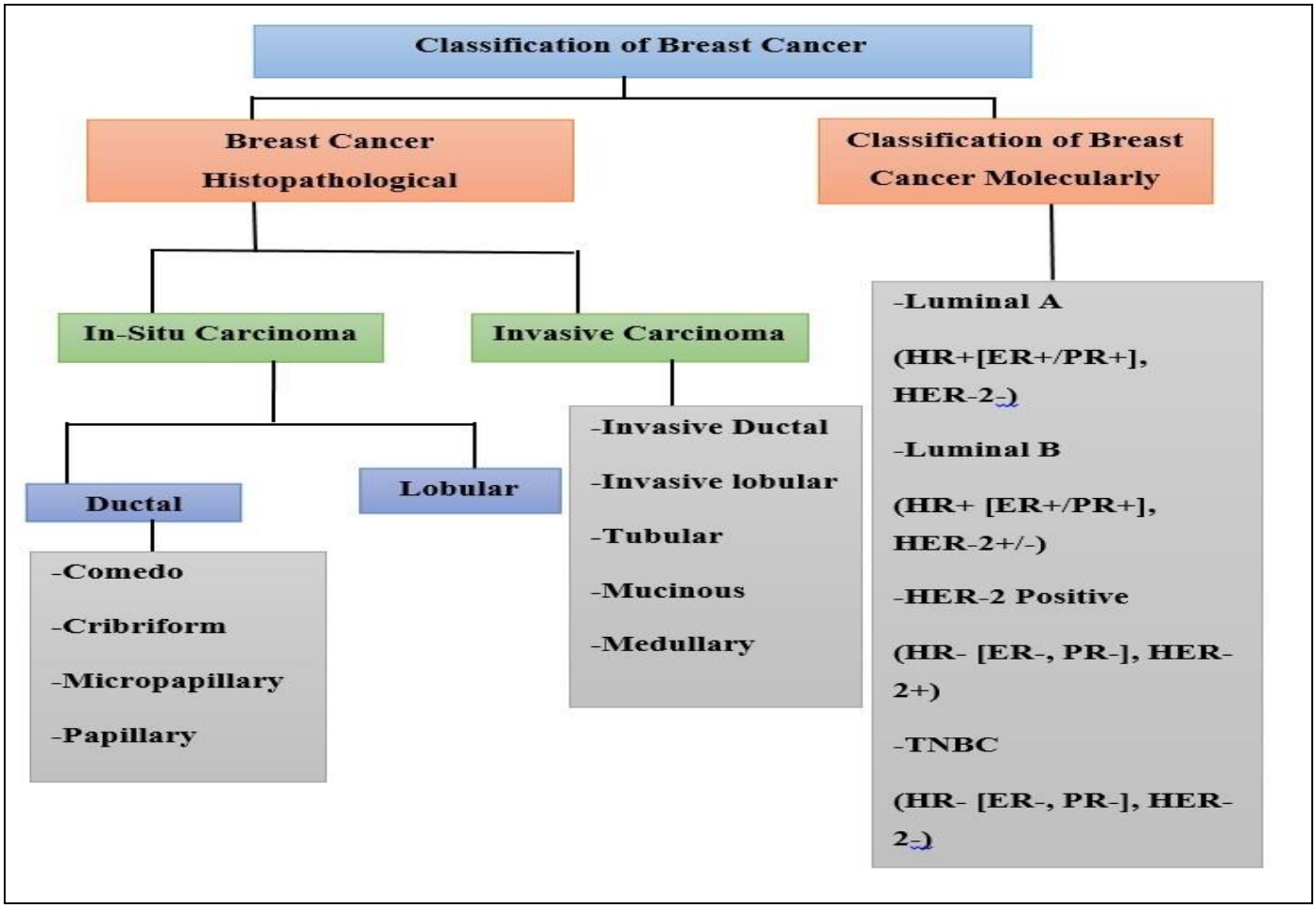

Fig. 1: Classification of Breast Cancer

A. *Breast Cancer Histopathology*

Histopathological categorization divides biopsy specimens into two categories based on their optical microscope characteristics: Both invasive and in-situ carcinomas [48].

➢ *In-Situ Carcinoma*

When discussing breast cancer, the term "In-situ" implies a collection of unchecked cells that are localized or "in its place," which is taken from the Latin term with the same meaning [49]. These unchecked cells multiply in their typical cellular surroundings. The subtype known as "in-situ carcinoma" includes both ductal carcinoma and lobular carcinoma in-situ [50].

- *Ductal Carcinoma in-Situ (DCIS)*

Ductal carcinoma in-situ, also known as intra-ductal carcinoma, is a precancerous or non-invasive form of breast cancer in which abnormal cells are forming inside the milk ducts. This phase signifies the onset of breast cancer, yet the

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cells stay restricted to the ducts, decreasing the likelihood of invasive breast cancer. Research reports indicate that 80-85% of cases fall into this category. Changes in breast size, shape, and palpable thickness beneath the arms are identifiable indicators. These features serve as a general classification system for ductal carcinoma in situ [51].

- *Comedo DICS*

Comedo carcinoma, alternatively known as comedonecrosis, represents a specific subtype in the classification of breast cancer [52]. Derived from Latin, "Comedo" translates to "eat up." The nuclear grade of ductal carcinoma in situ (DCIS) has been associated with the extracellular matrix glycoprotein tenascin. These variables are linked to comedocarcinoma, a condition in which abnormal cells proliferate in the breast [53]. Comedocarcinoma is categorized as an early-stage and aggressive intraductal carcinoma, specifically reflecting three stages of breast cancer. Mammography or biopsy techniques are usually used for diagnosis [54].

- *Cribriform DCIS*

Distinguished by its low-grade characteristics and gradual growth within the breast, this infrequent type of breast cancer frequently appears in the initial phases of breast cancer, particularly within ductal carcinoma in situ [55]. Presenting in a mixed form when occurring alongside other breast cancer types, this particular type is labeled as pure cribriform when not combined with other breast cancers. Symptoms may include small lumps or thickened areas in the breast, with ultrasound and mammogram examinations being common diagnostic methods. Surgical intervention is often the primary treatment for cribriform ductal carcinoma in situ (DCIS) [56].

- *Papillary DCIS (PDCIS)*

Papillary ductal carcinoma is a subtype of breast papillary carcinoma (PCB), often referred to as malignant papillary carcinoma. Bloody nipple discharge is not always related with male papillary ductal cancer in situ. Presence of comedonecrosis tissue characterizes this type. Strong indicators that differentiate it from other types include the presence of a fibrous capsule and the absence of peripherally situated myoepithelial cells, suggesting it as an encapsulated papillary carcinoma rather than papillary ductal carcinoma in situ [57].

- *Lobular Carcinoma in Situ*

Breast cancer that starts in the lobule that produces milk but stays contained there without spreading to nearby breast tissue is known as lobular carcinoma in situ [58]. Immunohistochemistry demonstrates positive results for E-cadherin, p120 catenin, Estrogen receptor (ER), and progesterone receptor (PR) in lobular carcinoma, with a negative result for human epidermal growth factor-2 (HER-2). The PCR test and microdissection methods are used to evaluate genetic alterations on chromosomes 16q, 17q, 17p, and 13q [59]. Breast needle core biopsy diagnosis of Lobular carcinoma in situ (LCIS) [60].

B. Invasive Carcinoma

When a breast cancer is invasive, it has spread from its original location in the milk-producing gland or duct to the surrounding breast tissue [61]. Through the lymphatic or circulatory systems, invasive breast cancer can travel from one area of the body to another. The two most prevalent forms of breast cancer that invade tissue are invasive ductal carcinoma and invasive lobular carcinoma. Tubular, medullary, mucinous, and infiltrating ductal carcinomas are among the less prevalent forms of invasive breast cancer [62].

➢ *Invasive Ductal Carcinoma*

Invasive ductal carcinoma, commonly known as infiltrating ductal carcinoma, stands as a prevalent subtype of invasive breast cancer, embodying the malignant nature of this form of breast cancer [63]. Originating from the lining of the milk duct or gland, invasive ductal carcinoma initiates its growth in the small tubes of the milk ducts, responsible for carrying milk from the breast lobules to the nipple. As the cancer progresses, it breaks through the duct walls, permeating the breast tissue and increasing its chance of metastasizing through the lymphatic and circulatory systems to other areas of the body. Diagnosis typically involves the use of mammograms and biopsy methods [64].

➢ *Invasive Lobular Carcinoma*

Originating from the milk glands' lobules, invasive lobular carcinoma is a common subtype of invasive breast cancer. Notably, it is considered a rare occurrence in male breast cancer cases [65]. Histologically, invasive lobular carcinoma can manifest in various types, including classical, mixed, solid, alveolar, tubulomolecular, and pleomorphic. Molecular characteristics of this subtype include decreased or absent E-cadherin expression, which is essential for preserving cell viability [66]. Invasive lobular carcinoma is associated with genomic mutations in genes such as FOXA1, RUNX1, and TBX3. Further modifications to the PI3K pathway within this subtype include mutations in PIK3CA, PTEN, and AKT1 [67].

➢ *Invasive Tubular Carcinoma*

Tubular invasive carcinoma is an unusual kind of invasive breast cancer [68]. Under the microscope, it appears tube-like in structure. Representing less than 2% of all cancers, this type is categorized as a low-grade carcinoma [69]. It is distinguished by its molecular lack of Human Epidermal Growth Factor Receptor 2 (HER2). Originating from the mammary duct, this type of carcinoma spreads by infiltrating the surrounding healthy tissue [70].

➢ *Invasive Mucinous Carcinoma*

Male breast cancer patients have also been shown to have a rare form of invasive breast cancer called mucinous invasive carcinoma. This particular carcinoma is considered a rare type, characterized by abnormal and uncontrolled cell growth associated with the production of mucin [71]. Originating from the epithelial cells that line the skin internally and produce mucin, mucinous invasive carcinoma is characterized by its low-grade nature and typically does not metastasize to other parts of the body [72]. Progesterone

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and estrogen receptors are usually positive in mucinous invasive carcinoma, although Human Epidermal Growth Factor Receptor-2 (HER-2) is usually negative [73].

➢ *Invasive Medullary Carcinoma*

One kind of invasive breast cancer that is uncommon is called medullary invasive carcinoma. Medullary characteristics are connected to the development of medullary carcinoma, which is frequently connected to a germline mutation in the BRCA1 gene [74]. The mushy, gray-tan surface of medullary cancer might have a nodule or lobule-like appearance. HER-2 and hormone receptors (ER and PR) are both negative in medullary carcinomas according to immunochemistry study [75]. EGFR, P-cadherin, p53, smooth muscle actin, keratins 5/6 and 1, and EGFR are among the genes expressed in medullary cancer. The presence of a mutated p53 gene significantly contributes to the distinctive characteristics and progression of medullary carcinoma [76].

V. MOLECULAR BREAST CANCER

Molecular breast cancer is characterized by the presence of hormone receptors, which can be identified through immunochemistry analysis based on the specific hormones. ER, PR, and HER, or the human epidermal growth factor receptor, are some examples of these receptors [77]. Within the categorization of molecular breast cancer, the receptors are divided into subtypes. Basal-like breast cancer, HER2 - positive breast cancer, and luminal breast cancer are further classifications for molecular breast cancer [78]. Using in situ hybridization (ISH) and immunohistochemistry (IHC), the luminal group is examined. This involves looking at the HER2 receptor as well as two hormone receptors: the progestogen and estrogen receptors. There are two subtypes of the luminal group: luminal-A and luminal-B [79].

A. Luminal-A

Luminal-A is the name of a molecular breast cancer subtype. It is characterized by features such as tubular carcinoma and low-grade histological characteristics, similar to those seen in classic invasive ductal carcinoma and invasive lobular carcinoma [79]. Genes associated to estrogen receptors and luminal epithelial cells are highly expressed in luminal-A subtypes. The results of an immunohistochemistry examination of luminal-A cancers show that they are negative for human epidermal growth factor-2 but positive for the estrogen and progesterone receptors. Furthermore, there is little Ki-67 protein expression in Luminal-A malignancies. Luminal-A is frequently linked to gene alterations related to PI3KCA, MAPK3K1, GATA3, and CCDN1 amplification [80].

B. Luminal-B

Breast cancer with a unique subtype known as Luminal-B can be further divided into two categories: HER-2 negative Luminal-B and HER-2 positive Luminal-B. In Luminal-B like HER2 negative cases, immunohistochemistry shows positivity for Estrogen receptor, negative or low expression of progesterone receptors, HER2 negativity, and high levels of Ki-67. Conversely, HER2-positive tumors that resemble Luminal-B also lack Ki-67, overexpress HER-2, lack progesterone receptor, and show positivity for the estrogen receptor. These subtypes are distinguished by decreased expression of genes linked to luminal epithelium and the ER, overexpression of HER-2-related genes, and increased expression of genes related to proliferation. In light microscopy, luminal-B tumors can resemble pleomorphic invasive lobular carcinoma, micropapillary carcinoma, or invasive ductal carcinoma. Transcription linked to Myc, transcription related to FOXM, transcription related to Rb, and transcription related to TP53 are all mutated in Luminal-B [80].

C. Her-2

Cells include a receptor tyrosine protein kinase called HER2, or ERBB2. The ERBB2 gene, or erythroblastic oncogene B, is found in the avian genome. Positioned on the long arm of the human chromosome, ERBB2 is a known proto-oncogene. Breast cancer is classified molecularly, with HER-2 being one subtype. This subtype is further divided into subgroups that are HER-2 positive and HER-2 negative. Hormone receptors, including the progesterone and estrogen receptors, are positive in HER2-positive individuals, supporting the HER2 positive status [81]. Negative status for progesterone and estrogen receptors along with HER2 positivity is the hallmark of HER2-negative (HER2-) breast cancer. The HER2-related gene expression in this subtype is strong, but the ER-related gene expression is low. The most common cancers linked to HER2-status are pleomorphic invasive lobular carcinoma and high-grade invasive ductal carcinoma. For estrogen and progesterone receptors, immunohistochemistry shows HER2 positive and negative. The amplification of HER2 and the activation of signaling pathways, including phospholipase Cγ, PKC, MAPK, PI3K/Akt and STAT, are the genetic mutations found in HER2-negative breast cancer [82].

D. Breast Cancer with Triple Negativity

Triple-negative breast cancer (TNBC), which is distinguished by its heterogeneity, is often confused with basal-like breast cancer. It is devoid of the HER-2, progesterone, and estrogen receptors. This subtype's HER2 overexpression is caused by gene amplification. Genes linked to proliferation and basal epithelium are highly expressed in TNBC, but HER2 and ER-related genes are less expressed. Adenoid cystic carcinoma, medullary carcinoma, metaplastic carcinoma, and high-grade invasive ductal carcinoma are the malignancies linked to TNBC. TNBC frequently has a prominent mutation in the BRCA1 gene. The subtypes of TNBC that are further classified include mesenchymal, basal-like immune-suppressed, basal-like immune-activated, and luminal androgen receptor. The TNBC-related signaling pathways include the Hedgehog signaling pathway, Wnt/β-Catenin pathway, Poly (ADP-Ribose) Polymerase (PARP) inhibitors, Rapalogs, EGFR, TGF-β signaling pathways, and CSPG4 protein signaling pathways [83].

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VI. BREAST CANCER DIAGNOSIS

A. Mammography or Mammogram

A low-dose x-ray device is used in mammography, a specialist medical imaging exam, to view the inside of the breasts [84]. Mammography exams, or mammograms as they are more often called, are used to identify and diagnose breast disorders in women. This x-ray examination is instrumental in aiding doctors in the diagnosis and treatment of various medical conditions [85]. X-rays, utilizing small doses of ionizing radiation, are crucial for producing images inside the body and represent one of the oldest medical tests for imaging [86].

B. Mammograms Digitally

Full-field digital mammography (FFDM), another name for digital mammography, is a type of mammography in which electronics are used in place of x-ray film to create pictures of the breast [87].

C. Computer-Aided Detection (CAD)

Systems that analyze digital pictures in digital mammography look for anomalous regions of bulk, calcification, or density that might be signs of cancer [88]. The Computer-Aided Detection (CAD) technology highlights certain areas on the pictures, alerting the radiologist to carefully examine them [89].

D. Breast Tomosynthesis

Computerized tomography (CT) imaging is a technique that is also used in breast tomosynthesis, also known as digital breast tomosynthesis and three-dimensional mammography. In this method, 3-D breast imaging is achieved by reconstructing the breast in three dimensions using a sequence of thin "slices" or images [90]. Even while the radiation dosage in certain breast tomosynthesis systems is somewhat greater than in a typical mammogram, it is still below the permitted limits for mammogram radiation set by the FDA. Furthermore, several techniques use doses that are quite similar to those used in conventional mammography [91].

E. Exposure to Low Doses of X-Ray Radiation Causing Breast Cancer

According to the available experimental data [55–57], the dose-response curve shows an upward concave pattern at relatively low doses below 50–100 mGy, which is partially explained by "nontargeted effects." As a result, BEIR-7 included a dosage and dose-rate effectiveness factor, or DDREF, which has to be used with reduced risk estimations. Although BEIR-7 indicates a 95% credible interval between 1 and 3, De Gelder et al. used a DDREF of 1.5 to assess the risk of breast cancer related with screening mammography. Using the population's baseline incidence of breast cancer as a reference, the study calculated risk and looked into the relative incidence of radiation-inhibited breast cancer. Screening, diagnosis, and detection of breast cancer are mostly accomplished by mammography, which uses low-energy x-rays (usually around 30 kVp). The primary objective of mammography programs is to identify small (<1 cm) masses and micro calcifications, typically recognizing characteristics linked to breast cancer. Mammographic screening is predominantly employed for asymptomatic women in the 40-45-year-old age group at 2-year intervals, initiating the first screening at age 40. Women with normal screening mammograms proceed to the subsequent round of screening. Successful mammographic screening contributes to the earlier detection of cancer at an average earlier stage, resulting in reduced mortality rates [92].

F. Ultrasound

In order to treat women, non-invasive ultrasound imaging is a safe and painless medical procedure. These tests use sonography to produce images, providing a sound-based representation of the human body's interior [93]. In ultrasound, a small probe, referred to as a transducer, is used along with gel applied to the skin's surface. This transducer is a crucial component of the ultrasound device, containing crystals responsible for generating and receiving sonic pulses. The transducer functions as a device that transforms energy, sending high-frequency sound waves into the body through the gel and from the probe [94]. Sound waves are captured by the probe as they go up and down or bounce back, and a picture is subsequently produced by a computer. Unlike procedures using radiation or x-rays, ultrasound exams capture real-time images that vividly depict the structure and movement of internal breast organs [95].

G. Magnetic Resonance Imaging (MRI)

The non-invasive medical technique known as MRI uses radiation frequency pulses, a strong magnetic field, and a computer to produce precise images of the body's internal organs. Unlike some imaging techniques, MRI does not use radiation (x-rays) [96]. Medical professionals utilize detailed Magnetic Resonance Imaging (MRI) pictures to study the body and detect diseases. Radio waves, a strong magnetic field, and computer technology are used in magnetic resonance imaging (MRI) to provide exact images of the structures inside the breast in connection to breast cancer. It serves as a valuable additional tool for breast screening, often used alongside mammography or ultrasound. Breast MRI is particularly effective in further assessing abnormalities detected during mammograms, screening high-risk individuals, and evaluating the extent of the disease post-diagnosis. Additionally, it proves instrumental in determining the integrity of silicone breast implants without exposing individuals to ionizing radiation [97].

VII. BREAST BIOPSY

An essential part of treating breast cancer is a breast biopsy, which entails taking a sample of breast tissue for diagnostic purposes. The extracted tissue is sent to a specialized laboratory, where pathologists, experts in the analysis of blood and body tissues, examine the samples. The pathologist then conducts a thorough examination of the tissue or blood samples to provide a diagnosis. Breast biopsies are typically recommended for areas in the breast that exhibit concerning features, such as painless lumps that are hard, irregularly shaped, and different from the surrounding breast tissue. Additionally, changes in the skin

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covering the mass, including thickening, redness, or an orange hue, may indicate the presence of breast cancer [98].

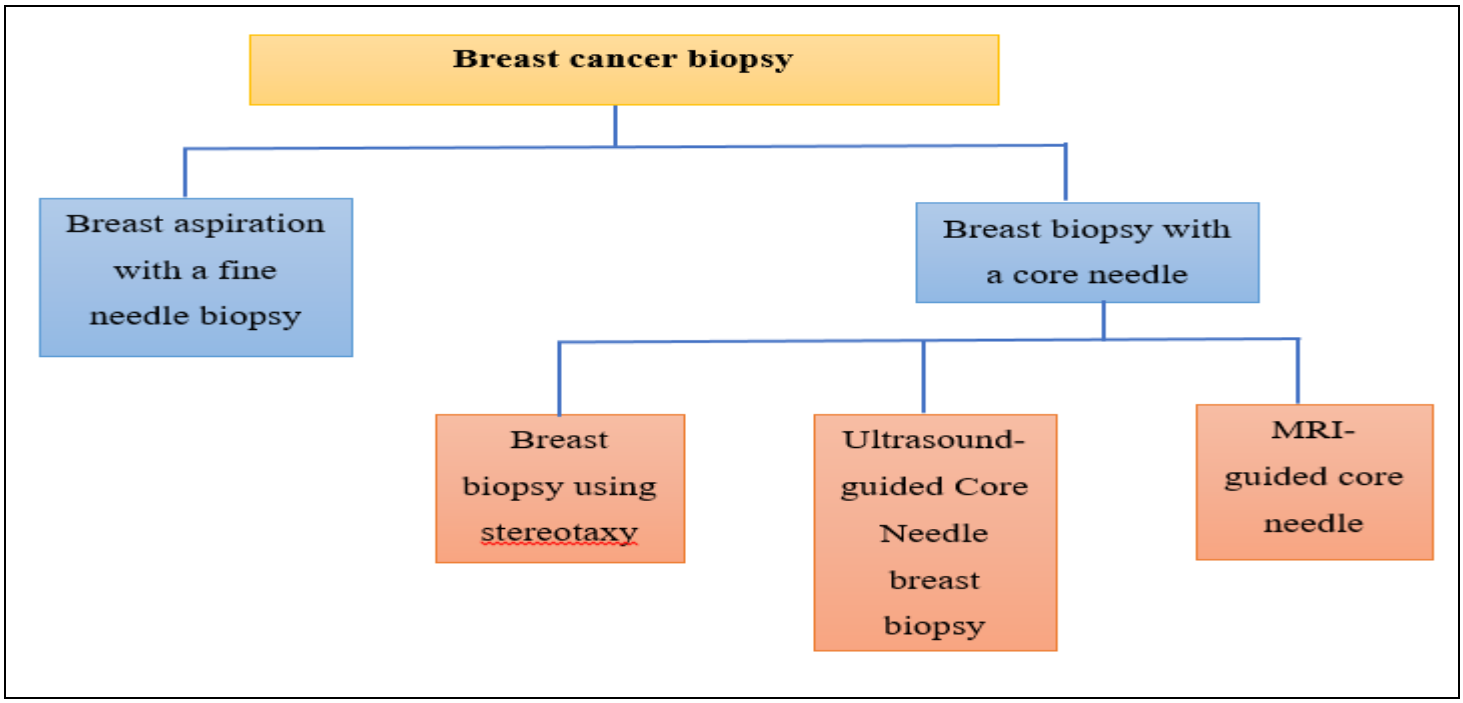

Fig 2: Treatment Based Breast Cancer Biopsy Classification

A. Biopsy with Fine Needle Aspiration

The simple process known as fine needle aspiration (FNA) involves passing a small needle through the skin in order to remove tissue or fluid from a solid mass or cyst. This technique can sample cysts, despite the fact that they are frequently tiny and somewhat unpleasant. Following collection, the tissue sample is submitted to a pathology facility for thorough examination [99]. Thin needle goal biopsies are commonly employed when suspicious masses, such as breast masses or enlarged lymph nodes detected through imaging tests like x-rays, ultrasound, or mammography. This procedure is relatively non-invasive, less painful, and quicker compared to other tissue sampling methods, including surgical biopsy. Additionally, thin needle goal is a faster technique for cyst aspiration [100].

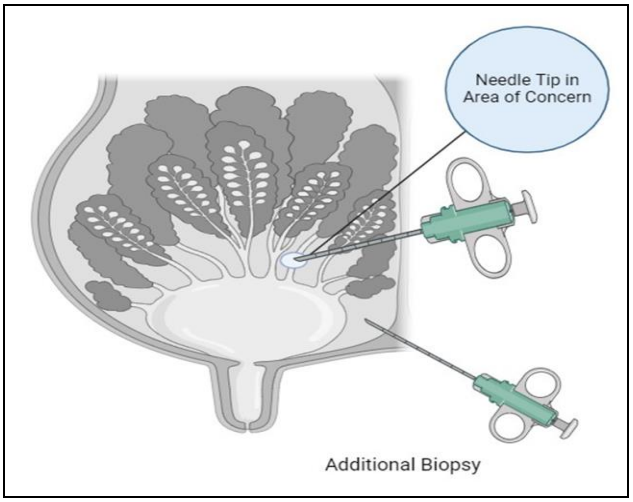

Fig. 3: Biopsy with Fine Needle Aspiration

➢ *Conducting a Biopsy using Fine Needle Aspiration (FNA)*

The thin needle goal biopsy serves as a simple and rapid method for diagnosing breast cancer. During this treatment, samples of fluid or cells from benign (noncancerous) breast cysts—fluid-filled sacs inside the breast—will be obtained. Whether the lump is palpable or not, a fine needle is used to perform the biopsy without the need for local anesthesia, making it a painless test. Palpable breast lumps can cause anxiety, and diagnostic mammography is recommended for women over 30 years old in such cases. In order to properly place the mass for the needle, the surgeon cleans the skin at the point of entrance and feels and studies the mass. Imaging methods like ultrasound or x-rays could be required for accurate localization if the lump cannot be felt. A computer is used to determine exact coordinates and two mammograms taken at various angles in stereotactic mammography. Using the ultrasound monitor as a guide, the surgeon cuts the target with the needle [101]. Imaging methods could be required if the mass is not palpable in order to identify it exactly. This method is made easier by stereotactic mammography, which uses two mammograms taken at various angles and a computer to determine exact coordinates. The surgeon directs the needle to the appropriate location while keeping an eye on the ultrasound screen. A blood test feels like what happens when a needle is inserted. By creating a vacuum/negative pressure and then retracting the needle, the sample is collected. This process may require several needle insertions in order to produce a suitable sample. After the procedure, a small bandage is applied, and normal activities can be resumed. While there are no associated risks, some discomfort or bruising at the needle insertion site may occur. It's important to contact your doctor promptly if you

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experience persistent bleeding, swelling, fever, or pain not alleviated by paracetamol. Avoid taking aspirin for discomfort, as it may exacerbate bruising [102].

B. Breast Core Needle Biopsies

During a core needle biopsy, a physician extracts breast tissue fragments from a suspicious region observed on imaging tests or during an examination using a hollow cylinder needle. Breast tissue is extracted into the needle more easily during a vacuum-assisted core biopsy by using a suction device. To precisely target an irregular location, a doctor may employ a spring-loaded instrument that rapidly inserts and withdraws the needle from tissue in contact with the tumor. However, imaging tests are often used to guide the needle accurately into the desired location. Stereotactic biopsies, ultrasound, and MRI are examples of imaging tests employed, including breast tomosynthesis or mammography [103], [104].

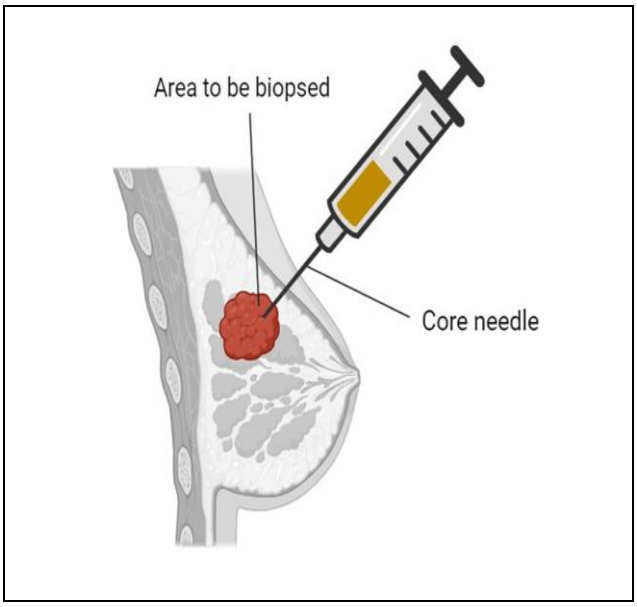

Fig. 4: Core Needle Biopsy

Utilizing imaging tests including MRIs, ultrasounds, and mammograms, core needle biopsies are performed as an outpatient treatment. In the initial step, a thin needle administers numbing medicine, followed by the core needle biopsy, where local anesthesia is applied to the biopsy site. Simultaneously, a tiny incision, approximately ¼ inch, is made. In order to take a sample of the breast tissue, a biopsy needle is placed into this incision. Proper location is ensured by applying pressure, and imaging tests, along with microscopic tissue markers, known as clips, are utilized and positioned at the biopsy site [105].

➢ *Breast Biopsy Types using Core Needle*

- *Breast Biopsy using Stereotaxy*

Tomosynthesis-guided breast biopsy, or stereotactic biopsy, uses mammography images from several angles to pinpoint the biopsy site. When deciding where to inject the needle in the abnormal area, the physician uses a computer program that analyzes breast x-rays. Often, this kind of biopsy is used to look at suspicious microcalcifications, tiny tumors, or other aberrant spots that would be difficult to see on an ultrasound [105]. Before taking a picture, the breast is carefully positioned and squeezed inside the mammography device to make sure the issue region is visible. Local anesthetic, or numbing medicine, is used after the breast has been cleaned. Following the biopsy instrument's insertion into the breast, further images are acquired to verify the instrument's correct placement for sample collection. A number of biopsy samples are then gathered. After the tool is removed, the breast is marked with a biopsy clip. To ensure the marker is properly positioned, a second mammography is performed [106].

- *Core Needle Biopsy Guided by Ultrasound*

Before the biopsy of a specific area, a breast ultrasound is conducted to visualize the region. After the ultrasound, the skin is cleansed, and local anesthetic (numbing medication) is injected [107]. The needle is guided to the appropriate location using ultrasound, and there may be a sensation of pressure as it is inserted. Usually, a biopsy marker, or clip, is positioned at the biopsy site, and many biopsy samples are gathered. To confirm the correct placement of the clip, a mammogram is often performed after the biopsy [108].

- *Core Needle Biopsy with Ultrasound Guidance*

Breast MRI is utilized to locate the area of concern and perform a biopsy. After positioning the device correctly to collect samples, an MRI is conducted to confirm its placement. Following the collection of many biopsy samples, the device is taken out of the breast and a clip (also known as a biopsy marker) is used to mark biopsy site. After the biopsy, a mammography is usually done to make sure the clip is positioned appropriately [109].

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VIII. TREATMENT

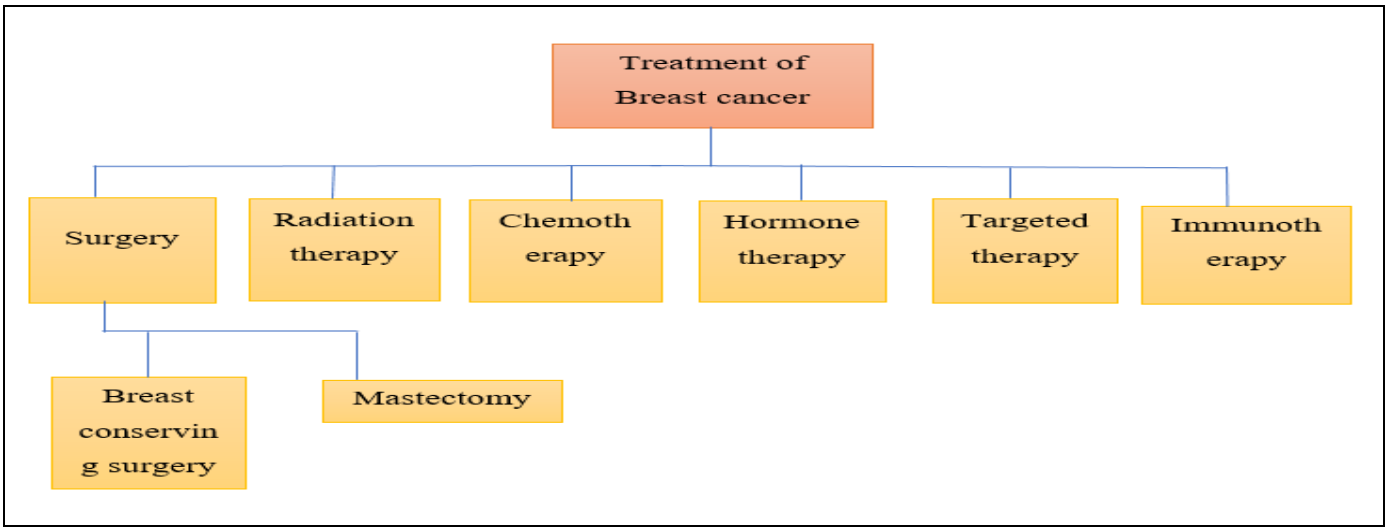

Fig. 5: Treatment of Breast Cancer

A. *Surgery*

Surgery is a crucial component of breast cancer treatment for nearly all women, with various types of procedures, including mastectomy and breast-conserving surgery, being performed based on individual circumstances to effectively eliminate cancer [110].

➢ *Reconstructive Surgery of the Breast*

Breast-conserving surgery, also known as segmental mastectomy, quadrantectomy, lumpectomy, or partial mastectomy, is a surgical procedure designed to excise the malignancy, wherein only the breast tissue surrounding the malignant area is removed. The extent of breast tissue removal is determined by factors such as the location and size of the tumor [111].

➢ *Mastectomy*

Mastectomy is a comprehensive treatment approach involving the removal of the entire breast, encompassing all breast tissue and potentially adjacent tissues. When a patient has cancer in both breasts, a double mastectomy—which involves removing both breasts—may be necessary [112].

B. *Radiation Therapy*

Radiation therapy is a treatment for breast cancer that employs high-energy X-rays or protons to kill rapidly proliferating cells. High-energy particles are used in this painless and undetectable technology to kill cancer cells more efficiently than healthy ones. Breast cancer can be treated with radiation therapy from the outside or within [112].

- External Radiation- radiation therapy for breast cancer involves using equipment that delivers radiation to the breast from outside the body, a widely employed approach in cancer treatment.
- Internal Radiation- also known as brachytherapy, this radiation therapy involves the brief insertion of radioactive devices by a doctor directly into the cancerous region of the breast. This short-term radiation treatment effectively reduces the risk and is applied across various stages of the disease, with the duration of treatment varying accordingly.

C. *Chemotherapy*

Chemotherapy plays a crucial role as a secondary treatment for breast cancer, employing anticancer drugs to target and treat breast cancer tumors. The three types of breast cancer chemotherapy include neoadjuvant chemotherapy, adjuvant therapy, and palliative chemotherapy [113].

➢ *Adjuvant Therapy*

Chemotherapy is used during breast cancer surgery to lessen the possibility of the cancer cells' microscopic metastasis—the process by which they spread to other regions of the body. Adjuvant therapy is intended to eradicate any residual malignant cells; imaging tests are used to identify breast cancer and direct the adjuvant therapy regimen [114].

➢ *Neoadjuvant Chemotherapy*

Neoadjuvant chemotherapy, sometimes called preoperative chemotherapy, is given prior to surgery in order to reduce the size of breast cancerous tumors. This is particularly useful in situations when the cancer has progressed to lymph nodes or includes big tumors [115]. Chemotherapy medications used as adjuvants or neoadjuvants include anthracyclines (doxorubicin, Adriamycin, and Epirubicin), taxanes (paclitaxel, Taxol, and docetaxel, Taxotere), capecitabine (Xeloda), cyclophosphamide, Cytoxan, and carboplatin (Paraplatin). These medications are injected into veins for administration. Chemotherapy side effects include hair loss, altered nails, mouth sores, exhaustion, diarrhea, and heightened infection susceptibility [116].

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D. Targeted-Therapy

Targeted medication therapy focuses on drugs that directly target proteins or receptors on breast cancer cells. These drugs work to destroy cancer cells, and an example of targeted therapy is the use of monoclonal antibodies. Trastuzumab, epratuzumab (Perjeta), and margetuximab (margenza) are examples of targeted drugs commonly used in breast cancer treatment [117]

- Trastuzumab (Herceptin) - One effective therapy for breast cancer, regardless of stage, is trastuzumab. It can be administered as a standalone treatment, especially after chemotherapy, and is frequently used in combination with chemotherapy. Whether given as an adjuvant (after surgery) or neoadjuvant (before surgery) therapy, this medication is typically prescribed for six months to a year to treat early breast cancer. As long as the medication is still effective, advanced breast cancer treatment usually consists of continuing visits. The drug is administered intravenously (IV). A variant of trastuzumab, known as trastuzumab and hyaluronidase injection (Herceptin Hylecta), is delivered subcutaneously (under the skin) over a short period [118].
- Pertuzumab (Perjeta) - Intravenous (IV) administration of this HER2 monoclonal antibody in conjunction with trastuzumab and chemotherapy is a viable treatment option for early-stage or metastatic breast cancer. This can be done either before to or following surgery [119].
- Margetuximab (margenza) - When combined with chemotherapy, this HER2-targeting monoclonal antibody can be used to treat advanced breast cancer; it is usually used after at least two previous HER2 inhibitors. Administration is done intravenously (IV) [120].

E. Immunotherapy-

Immunotherapy targets certain proteins involved in the immune response, therefore maximizing the immune system's capacity to recognize and eradicate cancer cells [121].

➢ *Immune Checkpoint Immunotherapy Inhibitors*

An essential part of the body, the immune system guards against infections and helps the body stay healthy. The proteins known as "checkpoints," which activate immune cells, are involved in controlling immune responses. These checkpoints provide breast cancer cells with an opportunity to elude immune system responses. Certain checkpoint protein-targeting medications aid in reestablishing the immune system's ability to combat breast cancer cells [122].

➢ *PD-1 Inhibitors*

(Pembrolizumab for breast cancer)- PD-1, a protein on immune system T cells that commonly stops them from attacking healthy body cells, is the target of pembrolizumab (Keytruda). These medications improve the immune system's capacity to combat breast cancer cells by blocking PD-1, which lowers the growth of tumors. Triple-negative breast cancer is treated with it in addition to chemotherapy [122].

➢ *Hormone Therapy*

Hormones are physical, chemical messengers that have different effects on different parts of the body's cells and tissues. In premenopausal women, the ovaries produce estrogen and progesterone, while other tissues, such as skin and fat, contribute to the hormone levels in both premenopausal and postmenopausal individuals. In both pregnancy and the menstrual cycle, progesterone is essential. Because they are controlled by these hormones, estrogen and progesterone play a major role in breast cancers, sometimes referred to as hormone-sensitive or hormone-dependent breast cancers. Hormones that bind to proteins called estrogen receptors (ERs) and progesterone receptors (PRs), which are present in hormone-sensitive breast cancer cells, activate the proteins. Certain genes are expressed differently by the active receptors, which encourages cell division. Breast cancers without ERs are called ER-negative, while those without PR are called HR-negative. Hormonal therapy, also known as hormonal therapy, is used as a treatment approach [123].

Menopausal hormone therapy (MHT), which is used to treat menopausal symptoms, should not be confused with endocrine therapy, commonly referred to as hormone treatment. Hormone therapy for breast cancer involves a combination of estrogen and progesterone, which is distinct from MHT. Since the ovaries are a premenopausal woman's main source of estrogen, this medication is used to limit ovarian function. Ovarian ablation, the process of either inhibiting or removing ovarian function, is one way to lower the levels of estrogen in these individuals. Surgical ovarian ablation include either radiation treatment, which is usually irreversible, or oophorectomy, which is the removal of the ovaries. Luteinizing hormone-releasing hormone (LHRH) agonists, another name for gonadotropin-releasing hormone (GnRH) agonists, are drugs that momentarily reduce ovarian activity. Through GnRH mimicking, these medications disrupt the signals that cause the ovaries to release estrogen [124]. LH and LHRH, the hormone that releases luteinizing hormone, control the generation of progesterone and estrogen in premenopausal women. In reaction to the hypothalamus' production of LHRH, the pituitary gland produces both follicle-stimulating hormone (FSH) and lethal hormone (H). LH and FSH stimulate the ovaries to create progesterone and estrogen, which have an effect on the endometrium (the uterine lining). During the menstrual cycle, the brain and pituitary are influenced by the peak levels of estrogen and progesterone, which inhibits the synthesis of LHRH, LH, and FSH [125].

➢ *Restricting the Production of Estrogen*

Aromatase inhibitors function by preventing enzymes—specifically, aromatase—from acting. Aromatase is responsible for producing estrogen in the ovaries and other tissues. Since premenopausal women tend to overproduce aromatase in the ovaries, aromatase inhibitors are primarily prescribed for postmenopausal women. When used alongside medications that suppress

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ovarian activity, these inhibitors can also be employed by premenopausal women [125].

➢ *Three Primary Methods for Breast Cancer Treatment*

- *Adjuvant Treatment for Breast Cancer in its Early Stages*

The FDA has approved adjuvant hormone therapy for both men and women with ER-positive breast cancer in the premenopausal and postmenopausal phases. Menopausal women may be administered aromatase inhibitors such as anastrozole, letrozole, and exemestane, although premenopausal women are encouraged to utilize tamoxifen. Combining ovarian suppression with an aromatase inhibitor, as opposed to tamoxifen alone, resulted in improved odds of recurrence-free survival in premenopausal women with early-stage ER-positive breast cancer [126].

- *Treatment of the Metastatic Breast Cancer*

The initial treatment for hormone-sensitive breast cancer in postmenopausal women with local progression or metastasis involves the approved use of two aromatase inhibitors, anastrozole and letrozole. Additionally, postmenopausal women with advanced breast cancer whose health has gotten worse after receiving tamoxifen therapy may be given both of these drugs in addition to the aromatase inhibitor exemestane. It is recommended that men undergoing aromatase inhibitor treatment for advanced breast cancer convert to GnRH agonists [127].

- *Neoadjuvant Breast Cancer Treatment*

In an effort to shrink the tumor before surgery, hormone therapy, also referred to as neoadjuvant therapy, has been studied in clinical trials for breast cancer (24). These trials have demonstrated the effectiveness of neoadjuvant hormone treatment, particularly with aromatase inhibitors, in shrinking breast cancer in postmenopausal individuals. However, the extent of its efficacy in women who have not yet reached menopause remains uncertain.

IX. TUMOR RESISTANCE AND MICROENVIRONMENT

The ability to support angiogenesis, invasion, and metastasis, as well as genetic instability and mutations that permit unchecked growth, medication resistance, evasion of cell death, elevated inflammation, and metabolism, are among the characteristics of cancer. When an anti-tumorigenic situation finally gives way to a pro-tumorigenic one, the tumor microenvironment (TME), which is primarily responsible for carcinogenesis, is made up of stromal cells and extracellular matrix (ECM). Biomolecular substances such as growth factors, cytokines, enzymes, and chemokines are how cells in the stromal environment—fibroblasts, endothelial cells, mesenchymal stem cells (MSCs), cancer-associated macrophages (CAMs), and cancer-associated fibroblasts (CAFs)—interact with the extracellular matrix (ECM). Cancer development and treatment resistance have been linked to exosomes and apoptotic bodies. This comprehensive understanding includes the pivotal role of the hypoxic TME in both carcinogenesis and resistance [128].

A. The Tumor Microenvironment's Stromal and Immune Cells' Biological Roles

➢ *Associated with Cancer: Fibroblasts*

Fibroblasts are important because they contribute to medication resistance and carcinogenesis in the tumor microenvironment. They first show signs of being anti-tumorigenic and play a role in forming the extracellular matrix (ECM) that separates tumor cells from healthy tissue in the early phases of tumor growth [128]. A myofibroblast phenotype, which is marked by enhanced extracellular matrix formation and the release of pro-tumorigenic proteins, is acquired by cancer-associated fibroblasts (CAFs) as they develop. Similar to myofibroblasts, CAFs are permanently engaged and actively promote cancer by angiogenesis, microRNA, cytokines, releasing factors, and activating tumor-promoting signaling pathways. Growing factors, cytokines, and extracellular matrix (ECM) are only a few of the elements of the tumor microenvironment that CAFs continue to produce and interact with throughout carcinogenesis [129].

➢ *Cancer Associated-Endothelial Cells*

The deepest layer of blood arteries is produced by newly created endothelial cells during the early stages of carcinogenesis. This thin vascular endothelium not only separates blood from tissues but also facilitates the delivery of essential ions and water, along with transporting all detrimental metabolic waste products. Furthermore, the bloodstream serves as a conduit for immune cells to reach tumors. Although the spreading of blood vessels is crucial for providing oxygen and removing carbon dioxide during the early stages of carcinogenesis, the continued growth of tumors necessitates an increased supply of oxygen and efficient disposal of metabolic waste [130]. The activation of hypoxia-induced transcription factors triggers the formation of vascular networks. By acting on endothelial cells, these substances promote the synthesis of growth factors like PDGF and epidermal growth factor (EGF), which aid in the formation of new blood vessels. Cancer-associated endothelial cells play a crucial role in promoting carcinogenesis through activities like immunosuppression, growth factor secretion, and facilitation of tumor cell migratory behavior. Additionally, these endothelial cells contribute to the infiltration of immunosuppressive myeloid cells into tumors. According to studies, endothelial cells linked with cancer may influence anti-tumor immunity by obstructing the infiltration of cytotoxic T cells and promoting the migration of immune-suppressive cells into the tumor. Furthermore, compared to normal endothelial cells, cancer-associated endothelial cells have a larger angiogenic potential, which increases drug resistance [131].

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➢ *Cancer Associated-Macrophages*

Macrophages function as the body's clean-up crew, typically circulating in the blood as monocytes. In response to infections or injuries, monocytes transform into macrophages, aiding in the removal of pathogens and contributing to tissue healing and repair. Similar to janitors maintaining a building, macrophages play a crucial role in keeping the body in good condition. Macrophages in the innate immune system present antigens and carry out phagocytosis in response to the presence of pathogens [132]. M1 macrophages are involved in antigen presentation and pathogen phagocytosis, and they are predominant during the early phases of carcinogenesis. M2 macrophages proliferate in the tumor microenvironment and actively contribute to immune suppression and wound repair since tumors are frequently compared to non-healing wounds. Factors such as oxygen deprivation and various cytokines contribute to the increased presence of M2 macrophages deep within the tumor. Throughout the process of carcinogenesis, macrophages infiltrate tumors, sometimes constituting up to a third of the tumor mass at certain stages [133]. High tumor macrophage counts are associated with poor survival rates in several types of cancer. This relationship results from the release of several cytokines by macrophages, which promote angiogenesis and aid in the development of new blood vessels. Furthermore, according to recent research, cancer-associated macrophages (CAMs) are important mediators of chemotherapy drug resistance, including paclitaxel and 5-fluorouracil. CAMs have also been shown to increase cancer stem cells' (CSCs) capacity to proliferate tumors and to increase treatment resistance [134].

➢ *Cancer Associated-Neutrophils*

In the initial stages of carcinogenesis, tumor microenvironment neutrophils exhibit dual characteristics, possessing both favorable and non-tumorigenic qualities. Numerous cytokines, including IL-6, are released by neutrophils, which encourage inflammation. They also generate matrix metalloproteases (MMPs), which break down components of the extracellular matrix (ECM) to help in modifying the matrix and encourage tumor cell invasion and metastasis [135]. It has been demonstrated that neutrophils and cancer are related, and that they contribute to the development of acquired resistance to cancer therapy through immune system suppression, angiogenesis promotion, and increased tumor cell multiplication. The efficacy of cancer drugs, such as immune checkpoint inhibitors and traditional cytotoxic treatments, is hampered by signaling cascades that are started by cancer-associated neutrophils. Incorporating drugs designed to target cancer-associated neutrophils alongside standard therapy has the potential to sensitize tumor cells to medications, mitigating drug resistance and preventing relapse [136].

➢ *T-Cells*

T-cells are present in the tumor microenvironment throughout different stages of tumor development, equipped with receptors designed to identify specific antigens. For instance, T-cells with specialized receptors can recognize unusual antigens present in cancerous cells. Furthermore, cytotoxic T-cells contribute to the suppression of the formation of new blood vessels by the production of the pleiotropic cytokine interferon-gamma [137]. Thus, in the tumor microenvironment, cytotoxic T lymphocytes have anti-tumorigenic action. Another type of T cell found in this environment is CD4+ T cells, which primarily contribute to the immunological response and can differentiate into various cell types over time. For instance, CD4+ T cells may transform into T-helper 1 cells, known for inducing inflammation and correlating with improved patient well-being in specific tumors. Regulatory T cells represent another T cell subtype observed in tumors [138].

➢ *B-Cells*

B-cells play a crucial role in antibody production within the human body and release various cytokines. Although B cells are mostly located in the lymph nodes and on the outskirts of tumors, they are not as common inside the tumors themselves. Throughout the carcinogenesis process, the primary function of B cells is to communicate with T cells, facilitating the targeting of tumor cells by T cells [139], [140]. T lymphocytes receive antigens from B cells, playing a vital role in the production of anti-tumor cytokines such as interferon (IFN). While B cells generally contribute to anti-tumor responses, studies reveal that in certain tumors, B lymphocytes can exhibit pro-tumorigenic characteristics. By producing cytokines including transforming growth factor (TGF) and interleukin-10 (IL-10), a specific group of immune cells known as regulatory B cells complicates their role in the tumor microenvironment [140].

➢ *Natural-Killer Cells*

Innate killer cells play a crucial role in eliminating virus-infected blood cells and can be categorized into two functional subtypes: those that directly kill tumor cells and those that release inflammatory cytokines, fostering immune cell engagement in tumor cell destruction through inflammation. Because natural killer cells recognize and destroy circulating tumor cells, they play a crucial role in stopping metastasis after tumor development. Utilizing adhesion and cytokine receptors, both natural killer cells and innate killer cells selectively target cellular entities, sparing normal healthy cells. Despite their effectiveness in eradicating tumor cells in circulation, natural killer cells are less potent within the tumor microenvironment [141].

➢ *Dendritic Cells*

Antigens are presented to T cells by dendritic cells, which are mostly in charge of identifying and seizing antigens. Typically located in lymph nodes, dendritic cells aid T cells in responding to pathogen infections. Depending on the surrounding milieu, dendritic cells within tumors may have either pro- or anti-tumorigenic characteristics. Tolerance of tumor cells by dendritic cells can be brought about by an overabundance of cytokines, with pro- or anti-tumorigenic substances, hence impeding an efficient immune response. Studies have shown that tumors may take advantage of dendritic cells, and there is evidence that treatment resistance may result from local dendritic cells training tumor cells to produce T lymphocytes that inhibit the tumor [142].

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➢ *Hypoxia within the TME*

Insufficient oxygen supply, a consequence of the slow development of new blood vessels (angiogenesis), is a defining characteristic of uncontrolled tumor cell proliferation in some sections of a growing solid tumor. This leads to low oxygen levels, with certain tumors having less than 2% oxygen, resulting in hypoxia [143]. Crucially, unregulated vasculature due to angiogenesis within a growing tumor results in uneven oxygen distribution, leading to hypoxia in certain regions. Tumor cells in these hypoxic areas exhibit a distinct phenotype, becoming more aggressive and resistant to standard treatments. Oxygen gradients are a common feature in solid tumors, and as the tumor expands, de novo angiogenesis creates leaky blood vessels, raising interstitial fluid pressure. The presence of leaky blood vessels aids tumor cell metastasis, allowing easy exit of tumor cells with discontinuous endothelium. Hypoxic environments contribute to immunosuppression, with cancer-associated M2 macrophages found in these conditions. TME hypoxia serves as an independent prognostic factor in cancer, predicting unfavorable outcomes. Innovative approaches targeting both tumor hypoxia and specific TME components are essential [144].

➢ *Exosomes and Exosome miRNAs in Tumour Microenvironment*

Releasing continually into the extracellular space, exosomes, which range in size from 30 to 200 nm, are essential for promoting cell-to-cell contact between stromal cells and tumor cells [145]. Exosomes come in a variety of contents that vary according to where they come from. The behavior of tumor cells and intercellular communication can be influenced by several growth factors, cytokines, and signaling molecules found in exosomes derived from precursor cells. Typically, the contents of exosomes support carcinogenesis by influencing processes like angiogenesis, migration, and metastasis. It has been noted that under low oxygen and nutrition environments, tumor cells release more exosomes, which causes stromal cells to become pro-tumorigenic cells like CAFs and CAMs [146].

➢ *Advanced in Therapeutic Targeting of TME*

Recent years have witnessed notable advancements in cancer treatment, driven by combinations of medications and immunotherapy. As a primary approach in cancer treatment, chemotherapy focuses on swiftly dividing melanoma cells and boasts a broad application [147]. Cancer, stemming from genetic mutations, undergoes progression marked by significant biochemical and metabolic alterations that adversely affect physiological processes over time. Advances in cancer treatment have been achieved by precisely targeting specific subsets of cancer cells within the tumor microenvironment (TME), including cancer stem cells (CSCs). Immunotherapy, notably through immune checkpoint blockade like PD1, has shown remarkable efficacy in treating cancer by targeting various immune cells within the TME [148]. Immune checkpoint inhibitors, either antibodies or medications, act by blocking checkpoint proteins in immune system cells like T cells and certain cancer cells. The interaction between programmed death ligand 1 (PDL-1) on cancer cells and programmed death 1 (PD-1) on normal healthy cells plays a crucial role in maintaining immune responses. In this interaction, when cancer cell PDL-1 binds with PD-1 on normal cells, it suppresses the immune response of normal cells to the presence of the tumor. By inhibiting the interaction between PDL-1 and PD-1, checkpoint inhibitors enable normal cells to mount an immune response in the presence of malignancy [149].

X. CONCLUSION

In summary, breast cancer is a multifaceted and diverse illness shaped by both adjustable and unalterable elements. Worldwide epidemiology offers essential perspectives for preventing and addressing the condition. Precise diagnosis through advanced imaging methods and limited radiation exposure is crucial. Various treatment approaches, such as hormone therapy, targeted therapy, radiation, chemotherapy, surgery, and immunotherapy, highlight the dynamic nature of breast cancer management. The intricate tumor microenvironment presents both challenges and possibilities for advancing therapies, underscoring the continuous requirement for research and innovation in this domain.

➢ *Declaration of Competing Interests*

The authors have no conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1]. K. Polyak, “Review series introduction Heterogeneity in breast cancer,” J.Clin.Invest., vol. 121, no. 10, 2011.

[2]. F. B. A. Makdissi, S. S. Santos, A. Bitencourt, and F. A. B. Campos, “An introduction to male breast cancer for urologists: epidemiology, diagnosis, principles of treatment, and special situations,” International Braz J Urol, vol. 48, no. 5, 2022, doi: 10.1590/S1677-5538.IBJU.2021.0828.

[3]. T. Tse et al., “Neoadjuvant chemotherapy in breast cancer: Review of the evidence and conditions that facilitated its use during the global pandemic,” Current Oncology, vol. 28, no. 2. 2021. doi: 10.3390/curroncol28020127.

[4]. M. Ghoncheh, Z. Pournamdar, and H. Salehiniya, “Incidence and mortality and epidemiology of breast cancer in the world,” Asian Pacific Journal of Cancer Prevention, vol. 17, 2016, doi: 10.7314/APJCP.2016.17.S3.43.

[5]. D. Clement, E. Agu, J. Obayemi, S. Adeshina, and W. Soboyejo, “Breast Cancer Tumor Classification Using a Bag of Deep Multi-Resolution Convolutional Features,” Informatics, vol. 9, no. 4, 2022, doi: 10.3390/informatics9040091.

[6]. S. Lei et al., “Global patterns of breast cancer incidence and mortality: A population-based cancer registry data analysis from 2000 to 2020,” Cancer Commun, vol. 41, no. 11, 2021, doi: 10.1002/cac2.12207.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24MAR416

[7]. T. Acheampong, R. D. Kehm, M. B. Terry, E. L. Argov, and P. Tehranifar, "Incidence Trends of Breast Cancer Molecular Subtypes by Age and Race/Ethnicity in the US From 2010 to 2016," JAMA Netw Open, vol. 3, no. 8, 2020, doi: 10.1001/jamanetworkopen.2020.13226.

[8]. N. O. Bazar, C. B. Hernández, and L. V. Bazar, "Risk factors associated with breast cancer," Revista Cubana de Medicina General Integral, vol. 36, no. 2, 2020, doi: 10.52916/otr204002.

[9]. Y. S. Sun et al., "Risk factors and preventions of breast cancer," International Journal of Biological Sciences, vol. 13, no. 11. 2017. doi: 10.7150/ijbs.21635.

[10]. H. Liu, S. Shi, J. Gao, J. Guo, M. Li, and L. Wang, "Analysis of risk factors associated with breast cancer in women: a systematic review and meta-analysis," Translational Cancer Research, vol. 11, no. 5. 2022. doi: 10.21037/tcr-22-193.

[11]. L. Tolessa, E. G. Sendo, N. G. Dinegde, and A. Desalew, "Risk factors associated with breast cancer among women in addis ababa, ethiopia: Unmatched case–control study," Int J Womens Health, vol. 13, 2021, doi: 10.2147/IJWH.S292588.

[12]. N. Fakhri et al., "Risk factors for breast cancer in women: an update review," Medical Oncology, vol. 39, no. 12. 2022. doi: 10.1007/s12032-022-01804-x.

[13]. V. Shetty, R. Kundapur, S. Chandramohan, S. Baisil, and D. Saxena, "Dietary risk with other risk factors of breast cancer," Indian Journal of Community Medicine, vol. 46, no. 3, 2021, doi: 10.4103/ijcm.IJCM_227_20.

[14]. X. Zeng et al., "Cardiovascular risk factors and breast cancer incidence in a large middle-aged cohort study," BMC Cancer, vol. 22, no. 1, 2022, doi: 10.1186/s12885-022-09604-2.

[15]. R. Krishnan, P. S. Patel, and R. Hakem, "Brca1 and metastasis: Outcome of defective dna repair," Cancers, vol. 14, no. 1. 2022. doi: 10.3390/cancers14010108.

[16]. Y. Song, W. T. Barry, D. S. Seah, N. M. Tung, J. E. Garber, and N. U. Lin, "Patterns of recurrence and metastasis in BRCA1/BRCA2-associated breast cancers," Cancer, vol. 126, no. 2, 2020, doi: 10.1002/cncr.32540.

[17]. A. Daniele et al., "Can harmful lifestyle, obesity and weight changes increase the risk of breast cancer in BRCA 1 and BRCA 2 mutation carriers? A Mini review," Hereditary Cancer in Clinical Practice, vol. 19, no. 1. 2021. doi: 10.1186/s13053-021-00199-6.

[18]. D. H. Choi, M. H. Lee, and B. G. Haffty, "Double heterozygotes for non-Caucasian families with mutations in BRCA-1 and BRCA-2 genes," Breast Journal, vol. 12, no. 3, 2006, doi: 10.1111/j.1075-122X.2006.00245.x.

[19]. A. N. Zghair, R. Sharma, M. Alfaham, and A. K. Sharma, "Upregulation of BRCA1, ERBB2 and TP53 marker genes expression in breast cancer patients," International Journal of Pharmaceutical Research, vol. 10, no. 2, 2018.

[20]. A. Rahim et al., "Association of ATM, CDH1 and TP53 genes polymorphisms with familial breast cancer in patients of Khyber Pakhtunkhwa, Pakistan," Afr Health Sci, vol. 22, 2022, doi: 10.4314/ahs.v22i3.17.

[21]. D. J. Turnham, N. Bullock, M. S. Dass, J. N. Staffurth, and H. B. Pearson, "The PTEN Conundrum: How to Target PTEN-Deficient Prostate Cancer," Cells, vol. 9, no. 11. 2020. doi: 10.3390/cells9112342.

[22]. S. J. Chung et al., "ADIPOQ/adiponectin induces cytotoxic autophagy in breast cancer cells through STK11/LKB1-mediated activation of the AMPK-ULK1 axis," Autophagy, vol. 13, no. 8, 2017, doi: 10.1080/15548627.2017.1332565.

[23]. M. Ahmed and N. Rahman, "ATM and breast cancer susceptibility," Oncogene, vol. 25, no. 43. 2006. doi: 10.1038/sj.onc.1209873.

[24]. S. Casadei et al., "Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer," Cancer Res, vol. 71, no. 6, 2011, doi: 10.1158/0008-5472.CAN-10-3958.

[25]. S. Seal et al., "Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles," Nat Genet, vol. 38, no. 11, 2006, doi: 10.1038/ng1902.

[26]. P. Apostolou and I. Papasotiriou, "Current perspectives on CHEK2 mutations in breast cancer," Breast Cancer: Targets and Therapy, vol. 9, 2017, doi: 10.2147/BCTT.S111394.

[27]. D. J. Park et al., "Rare mutations in XRCC2 increase the risk of breast cancer," Am J Hum Genet, vol. 90, no. 4, 2012, doi: 10.1016/j.ajhg.2012.02.027.

[28]. م. خمرنيا, ز. مرتضوي, م. عودي, م. دهمرده, ع. كسانى, and م. پيوند, "كودكان بدنى توده نمايه و مادر شير با تغذيه رابطه بررسى," زاهدان شهر در ي مورد مطالعه :دبستانى ساله 6-12 Razi Journal of Medical Sciences, vol. 27, no. 4, 2020.

[29]. Y. Y. Lei, S. Bai, Q. Q. Chen, X. J. Luo, and D. M. Li, "Clinical and pathological features and risk factors for primary breast cancer patients," World J Clin Cases, vol. 9, no. 19, 2021, doi: 10.12998/wjcc.v9.i19.5046.

[30]. P. Anagnostis, I. Lambrinoudaki, J. C. Stevenson, and D. G. Goulis, "Menopause-associated risk of cardiovascular disease," Endocrine Connections, vol. 11, no. 4. 2022. doi: 10.1530/EC-21-0537.

[31]. P. Anagnostis, S. A. Paschou, N. Katsiki, D. Krikidis, I. Lambrinoudaki, and D. G. Goulis, "Menopausal Hormone Therapy and Cardiovascular Risk: Where are we Now?," Curr Vasc Pharmacol, vol. 17, no. 6, 2018, doi: 10.2174/1570161116666180709095348.

[32]. S. S. Nazari and P. Mukherjee, "An overview of mammographic density and its association with breast cancer," Breast Cancer, vol. 25, no. 3. 2018. doi: 10.1007/s12282-018-0857-5.

[33]. T. Li et al., "The association of measured breast tissue characteristics with mammographic density

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24MAR416

and other risk factors for breast cancer," Cancer Epidemiology Biomarkers and Prevention, vol. 14, no. 2, 2005, doi: 10.1158/1055-9965.EPI-04-0490.

[34]. N. F. Boyd, L. J. Martin, M. Bronskill, M. J. Yaffe, N. Duric, and S. Minkin, "Breast tissue composition and susceptibility to breast cancer," Journal of the National Cancer Institute, vol. 102, no. 16. 2010. doi: 10.1093/jnci/djq239.

[35]. L. C. Thygesen, L. S. Mørch, N. Keiding, C. Johansen, and M. Grønbæk, "Use of baseline and updated information on alcohol intake on risk for breast cancer: Importance of latency," Int J Epidemiol, vol. 37, no. 3, 2008, doi: 10.1093/ije/dyn060.

[36]. I. Romieu et al., "Fiber intake modulates the association of alcohol intake with breast cancer," Int J Cancer, vol. 140, no. 2, 2017, doi: 10.1002/ijc.30415.

[37]. V. Vuong, V. Rao, and C. Ee, "Mindfulness-based Interventions and Yoga for Managing Obesity/Overweight After Breast Cancer: A Scoping Review," Integrative Cancer Therapies, vol. 21. 2022. doi: 10.1177/15347354221137321.

[38]. J. Mejia-Montilla, N. Reyna-Villasmil, and E. Reyna-Villasmil, "Overweight, obesity and breast cancer," Revista de Obstetricia y Ginecologia de Venezuela, vol. 82, no. 4. 2022. doi: 10.51288/00820414.

[39]. R. Nindrea, T. Aryandono, L. Lazuardi, and I. Dwiprahasto, "Association of overweight and obesity with breast cancer during premenopausal period in Asia: A meta-analysis," Int J Prev Med, vol. 10, no. 1, 2019, doi: 10.4103/ijpvm.ijpvm_372_18.

[40]. L. Holmberg and H. Anderson, "HABITS (hormonal replacement therapy after breast cancer - Is it safe?), a randomised comparison: Trial stopped," Lancet, vol. 363, no. 9407, 2004, doi: 10.1016/S0140-6736(04)15493-7.

[41]. K. I. Pritchard, "Hormonal replacement therapy in breast cancer," Annals of Oncology, vol. 13, no. SUPPL. 4, 2002, doi: 10.1093/annonc/mdf642.

[42]. R. Lea et al., "Use of Hormonal Replacement Therapy After Treatment of Breast Cancer," Journal of Obstetrics and Gynaecology Canada, vol. 26, no. 1, 2004, doi: 10.1016/S1701-2163(16)30696-X.

[43]. C. Duffau, A. Weyl, A. Gosset, F. Tremollières, C. Vaysse, and F. Dalenc, "Women with a very high risk of breast cancer: Contraceptives, hormonal replacement therapy use and personalized screening," Gynecologie Obstetrique Fertilite et Senologie, vol. 51, no. 5, 2023, doi: 10.1016/j.gofs.2023.03.001.

[44]. D. R. Youlden, S. M. Cramb, C. H. Yip, and P. D. Baade, "Incidence and mortality of female breast cancer in the Asia-Pacific region," Cancer Biol Med, vol. 11, no. 2, 2014, doi: 10.7497/j.issn.2095-3941.2014.02.005.

[45]. N. Azamjah, Y. Soltan-Zadeh, and F. Zayeri, "Global trend of breast cancer mortality rate: A 25-year study," Asian Pacific Journal of Cancer Prevention, vol. 20, no. 7, 2019, doi: 10.31557/APJCP.2019.20.7.2015.

[46]. G. Carioli, M. Malvezzi, T. Rodriguez, P. Bertuccio, E. Negri, and C. La Vecchia, "Trends and predictions to 2020 in breast cancer mortality in Europe," Breast, vol. 36, 2017, doi: 10.1016/j.breast.2017.06.003.

[47]. M. Ghoncheh, Z. Pournamdar, and H. Salehiniya, "Incidence and mortality and epidemiology of breast cancer in the world," Asian Pacific Journal of Cancer Prevention, vol. 17, 2016, doi: 10.7314/APJCP.2016.17.S3.43.

[48]. Z. Hameed, S. Zahia, B. Garcia-Zapirain, J. J. Aguirre, and A. M. Vanegas, "Breast cancer histopathology image classification using an ensemble of deep learning models," Sensors (Switzerland), vol. 20, no. 16, 2020, doi: 10.3390/s20164373.

[49]. W. J. Gradishar et al., "Breast Cancer, Version 3.2022," JNCCN Journal of the National Comprehensive Cancer Network, vol. 20, no. 6, 2022, doi: 10.6004/jnccn.2022.0030.

[50]. C. F. Cowell et al., "Progression from ductal carcinoma in situ to invasive breast cancer: Revisited," Molecular Oncology, vol. 7, no. 5. 2013. doi: 10.1016/j.molonc.2013.07.005.

[51]. A. K. Casasent et al., "Multiclonal Invasion in Breast Tumors Identified by Topographic Single Cell Sequencing," Cell, vol. 172, no. 1–2, 2018, doi: 10.1016/j.cell.2017.12.007.

[52]. C. I. Li, D. J. Uribe, and J. R. Daling, "Clinical characteristics of different histologic types of breast cancer," Br J Cancer, vol. 93, no. 9, 2005, doi: 10.1038/sj.bjc.6602787.

[53]. L. F. Brown et al., "Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in breast cancer," Hum Pathol, vol. 26, no. 1, 1995, doi: 10.1016/0046-8177(95)90119-1.

[54]. K. Kerlikowske, "Epidemiology of ductal carcinoma in situ," J Natl Cancer Inst Monogr, no. 41, 2010, doi: 10.1093/jncimonographs/lgq027.

[55]. M. W. J. Louwman et al., "Uncommon breast tumors in perspective: Incidence, treatment and survival in the Netherlands," Int J Cancer, vol. 121, no. 1, 2007, doi: 10.1002/ijc.22625.

[56]. H. J. Burstein, "Systemic Therapy for Estrogen Receptor–Positive, HER2-Negative Breast Cancer," New England Journal of Medicine, vol. 383, no. 26, 2020, doi: 10.1056/nejmra1307118.

[57]. I. V. Gruber et al., "Measurement of tumour size with mammography, sonography and magnetic resonance imaging as compared to histological tumour size in primary breast cancer," BMC Cancer, vol. 13, 2013, doi: 10.1186/1471-2407-13-328.

[58]. C. Zarwan et al., "Longitudinal study of breast cancer risk markers," Breast Journal, vol. 27, no. 1, 2021, doi: 10.1111/tbj.14097.

[59]. J. M. Stalls et al., "Improving well-being for individuals with persistent pain after surgery for breast cancer, lobular carcinoma in situ, or ductal

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24MAR416

carcinoma in situ: A randomized clinical trial," Contemp Clin Trials, vol. 122, 2022, doi: 10.1016/j.cct.2022.106934.

[60]. G. Pravettoni, W. R. Yoder, S. Riva, K. Mazzocco, P. Arnaboldi, and V. Galimberti, "Eliminating 'ductal carcinoma in situ' and 'lobular carcinoma in situ' (DCIS and LCIS) terminology in clinical breast practice: The cognitive psychology point of view," Breast, vol. 25, 2016, doi: 10.1016/j.breast.2015.10.011.

[61]. J. Abadie et al., "Canine invasive mammary carcinomas as models of human breast cancer. Part 2: immunophenotypes and prognostic significance," Breast Cancer Res Treat, vol. 167, no. 2, 2018, doi: 10.1007/s10549-017-4542-8.

[62]. F. Nguyen et al., "Canine invasive mammary carcinomas as models of human breast cancer. Part 1: Natural history and prognostic factors," Breast Cancer Res Treat, vol. 167, no. 3, 2018, doi: 10.1007/s10549-017-4548-2.

[63]. N. A. Barsha, A. Rahman, and M. R. C. Mahdy, "Automated detection and grading of Invasive Ductal Carcinoma breast cancer using ensemble of deep learning models," Comput Biol Med, vol. 139, 2021, doi: 10.1016/j.compbiomed.2021.104931.

[64]. C. B. Chen, Y. Wang, X. Fu, and H. Yang, "Recurrence Network Analysis of Histopathological Images for the Detection of Invasive Ductal Carcinoma in Breast Cancer," IEEE/ACM Trans Comput Biol Bioinform, 2023, doi: 10.1109/TCBB.2023.3282798.

[65]. L. Dossus and P. R. Benusiglio, "Lobular breast cancer: Incidence and genetic and non-genetic risk factors," Breast Cancer Research, vol. 17, no. 1, 2015, doi: 10.1186/s13058-015-0546-7.

[66]. G. Arpino, V. J. Bardou, G. M. Clark, and R. M. Elledge, "Infiltrating lobular carcinoma of the breast: Tumor characteristics and clinical outcome," Breast Cancer Research, vol. 6, no. 3, 2004, doi: 10.1186/bcr767.

[67]. N. Wilson, A. Ironside, A. Diana, and O. Oikonomidou, "Lobular Breast Cancer: A Review," Frontiers in Oncology, vol. 10. 2021. doi: 10.3389/fonc.2020.591399.

[68]. B. Weigelt et al., "Refinement of breast cancer classification by molecular characterization of histological special types," Journal of Pathology, vol. 216, no. 2, 2008, doi: 10.1002/path.2407.

[69]. M. Colleoni et al., "Outcome of special types of luminal breast cancer," Annals of Oncology, vol. 23, no. 6, 2012, doi: 10.1093/annonc/mdr461.

[70]. M. V. Dieci, E. Orvieto, M. Dominici, P. Conte, and V. Guarneri, "Rare Breast Cancer Subtypes: Histological, Molecular, and Clinical Peculiarities," Oncologist, vol. 19, no. 8, 2014, doi: 10.1634/theoncologist.2014-0108.

[71]. B. Weigelt, F. C. Geyer, H. M. Horlings, B. Kreike, H. Halfwerk, and J. S. Reis-Filho, "Mucinous and neuroendocrine breast carcinomas are transcriptionally distinct from invasive ductal carcinomas of no special type," Modern Pathology, vol. 22, no. 11, 2009, doi: 10.1038/modpathol.2009.112.

[72]. T. Nagao, T. Kinoshita, T. Hojo, H. Tsuda, K. Tamura, and Y. Fujiwara, "The differences in the histological types of breast cancer and the response to neoadjuvant chemotherapy: The relationship between the outcome and the clinicopathological characteristics," Breast, vol. 21, no. 3, 2012, doi: 10.1016/j.breast.2011.12.011.

[73]. N. Wentzensen et al., "Ovarian cancer risk factors by histologic subtype: An analysis from the Ovarian Cancer Cohort Consortium," Journal of Clinical Oncology, vol. 34, no. 24, 2016, doi: 10.1200/JCO.2016.66.8178.

[74]. M. N. Mills et al., "Histologic heterogeneity of triple negative breast cancer: A National Cancer Centre Database analysis," Eur J Cancer, vol. 98, 2018, doi: 10.1016/j.ejca.2018.04.011.

[75]. F. Sanges et al., "Histologic subtyping affecting outcome of triple negative breast cancer: A large Sardinian population-based analysis," BMC Cancer, vol. 20, no. 1, 2020, doi: 10.1186/s12885-020-06998-9.

[76]. S. DUTTA, S. BANERJEE, A. BERA, S. MANDAL, and C. BANERJEE, "MEDULLARY CARCINOMA OF THE BREAST-EPIDEMIOLOGY, THE PATTERN OF CARE, AND TREATMENT OUTCOME: EXPERIENCE FROM THE TERTIARY CANCER CARE CENTER," Asian Journal of Pharmaceutical and Clinical Research, 2022, doi: 10.22159/ajpcr.2022.v15i9.45262.

[77]. Y. Liang, H. Zhang, X. Song, and Q. Yang, "Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets," Seminars in Cancer Biology, vol. 60. 2020. doi: 10.1016/j.semcancer.2019.08.012.

[78]. D. Kashyap et al., "Global Increase in Breast Cancer Incidence: Risk Factors and Preventive Measures," Biomed Res Int, vol. 2022, 2022, doi: 10.1155/2022/9605439.

[79]. J. J. Gao and S. M. Swain, "Luminal A Breast Cancer and Molecular Assays: A Review," Oncologist, vol. 23, no. 5, 2018, doi: 10.1634/theoncologist.2017-0535.

[80]. M. V. Dieci et al., "Neoadjuvant Chemotherapy and Immunotherapy in Luminal B-like Breast Cancer: Results of the Phase II GIADA Trial," Clinical Cancer Research, vol. 28, no. 2, 2022, doi: 10.1158/1078-0432.CCR-21-2260.

[81]. A. Chan, "Neratinib in HER-2-positive breast cancer: Results to date and clinical usefulness," Therapeutic Advances in Medical Oncology, vol. 8, no. 5. 2016. doi: 10.1177/1758834016656494.

[82]. A. Saleem et al., "Lapatinib access into normal brain and brain metastases in patients with Her-2 overexpressing breast cancer," EJNMMI Res, vol. 5, no. 1, 2015, doi: 10.1186/s13550-015-0103-5.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24MAR416

[83]. M. A. Medina et al., "Triple-negative breast cancer: A review of conventional and advanced therapeutic strategies," International Journal of Environmental Research and Public Health, vol. 17, no. 6. 2020. doi: 10.3390/ijerph17062078.
[84]. R. Hodgson et al., "Systematic review of 3D mammography for breast cancer screening," Breast, vol. 27. 2016. doi: 10.1016/j.breast.2016.01.002.
[85]. M. Kalager, M. Zelen, F. Langmark, and H.-O. Adami, "Effect of Screening Mammography on Breast-Cancer Mortality in Norway," New England Journal of Medicine, vol. 363, no. 13, 2010, doi: 10.1056/nejmoa1000727.
[86]. A. Bleyer and H. G. Welch, "Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence," New England Journal of Medicine, vol. 367, no. 21, 2012, doi: 10.1056/nejmoa1206809.
[87]. H. Li, K. R. Mendel, L. Lan, D. Sheth, and M. L. Giger, "Digital mammography in breast cancer: Additive value of radiomics of breast parenchyma," Radiology, vol. 291, no. 1, 2019, doi: 10.1148/radiol.2019181113.
[88]. J. Dheeba, N. Albert Singh, and S. Tamil Selvi, "Computer-aided detection of breast cancer on mammograms: A swarm intelligence optimized wavelet neural network approach," J Biomed Inform, vol. 49, 2014, doi: 10.1016/j.jbi.2014.01.010.
[89]. A. Jalalian, S. B. T. Mashohor, H. R. Mahmud, M. I. B. Saripan, A. R. B. Ramli, and B. Karasfi, "Computer-aided detection/diagnosis of breast cancer in mammography and ultrasound: A review," Clinical Imaging, vol. 37, no. 3. 2013. doi: 10.1016/j.clinimag.2012.09.024.
[90]. C. E. Comstock et al., "Comparison of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Breast Cancer Detection among Women with Dense Breasts Undergoing Screening," JAMA - Journal of the American Medical Association, vol. 323, no. 8, 2020, doi: 10.1001/jama.2020.0572.
[91]. N. Houssami and P. Skaane, "Overview of the evidence on digital breast tomosynthesis in breast cancer detection," Breast, vol. 22, no. 2. 2013. doi: 10.1016/j.breast.2013.01.017.
[92]. D. J. Brenner, "Does fractionation decrease the risk of breast cancer induced by low- LET radiation?," Radiation Research, vol. 151, no. 2. 1999. doi: 10.2307/3579774.
[93]. R. Guo, G. Lu, B. Qin, and B. Fei, "Ultrasound Imaging Technologies for Breast Cancer Detection and Management: A Review," Ultrasound in Medicine and Biology, vol. 44, no. 1. 2018. doi: 10.1016/j.ultrasmedbio.2017.09.012.
[94]. W. Teh and A. R. M. Wilson, "The role of ultrasound in breast cancer screening. A consensus statement by the European Group for Breast Cancer Screening," Eur J Cancer, vol. 34, no. 4, 1998, doi: 10.1016/S0959-8049(97)10066-1.
[95]. L. Guan and G. Xu, "Damage effect of high-intensity focused ultrasound on breast cancer tissues and their vascularities," World J Surg Oncol, vol. 14, no. 1, 2016, doi: 10.1186/s12957-016-0908-3.
[96]. G. L. G. Menezes, F. M. Knuttel, B. L. Stehouwer, R. M. Pijnappel, and M. A. A. J. Van Den Bosch, "Magnetic resonance imaging in breast cancer: A literature review and future perspectives," World Journal of Clinical Oncology, vol. 5, no. 2. 2014. doi: 10.5306/wjco.v5.i2.61.
[97]. N. Houssami et al., "An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence," Journal of Clinical Oncology, vol. 32, no. 5, 2014, doi: 10.1200/JCO.2013.52.7515.
[98]. M. Tellez-Gabriel, E. Knutsen, and M. Perander, "Current status of circulating tumor cells, circulating tumor DNA, and exosomes in breast cancer liquid biopsies," International Journal of Molecular Sciences, vol. 21, no. 24. 2020. doi: 10.3390/ijms21249457.
[99]. G. Goel et al., "Role of Axillary Ultrasound, Fine Needle Aspiration Cytology and Sentinel Lymph Node Biopsy in clinically N0 Breast Cancer," Indian J Surg Oncol, vol. 7, no. 4, 2016, doi: 10.1007/s13193-016-0520-6.
[100]. G. Dennison, R. Anand, S. H. Makar, and J. A. Pain, "A Prospective Study of the Use of Fine-Needle Aspiration Cytology and Core Biopsy in the Diagnosis of Breast Cancer," Breast Journal, vol. 9, no. 6, 2003, doi: 10.1046/j.1524-4741.2003.09611.x.
[101]. T. Kurita et al., "Roles of fine-needle aspiration and core needle biopsy in the diagnosis of breast cancer," Breast Cancer, vol. 19, no. 1, 2012, doi: 10.1007/s12282-010-0251-4.
[102]. A. M. Sadi et al., "Clinical relevance of DNA microarray analyses using archival formalin-fixed paraffin-embedded breast cancer specimens," BMC Cancer, vol. 11, 2011, doi: 10.1186/1471-2407-11-253.
[103]. E. A. Rakha and I. O. Ellis, "An overview of assessment of prognostic and predictive factors in breast cancer needle core biopsy specimens," Journal of Clinical Pathology, vol. 60, no. 12. 2007. doi: 10.1136/jcp.2006.045377.
[104]. H. Abe, R. A. Schmidt, C. A. Sennett, A. Shimauchi, and G. M. Newstead, "US-guided core needle biopsy of axillary lymph nodes in patients with breast cancer: Why and how to do it," Radiographics, vol. 27, no. SPEC. ISS. 2007. doi: 10.1148/rg.27si075502.
[105]. J. V. Horvat, D. M. Keating, H. Rodrigues-Duarte, E. A. Morris, and V. L. Mango, "Calcifications at digital breast tomosynthesis: Imaging features and biopsy techniques," Radiographics, vol. 39, no. 2, 2019, doi: 10.1148/rg.2019180124.
[106]. I. Barman et al., "Application of raman spectroscopy to identify microcalcifications and underlying breast lesions at Stereotactic core needle biopsy," Cancer Res, vol. 73, no. 11, 2013, doi: 10.1158/0008-5472.CAN-12-2313.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24MAR416

[107]. A. Damera et al., "Diagnosis of axillary nodal metastases by ultrasound-guided core biopsy in primary operable breast cancer," Br J Cancer, vol. 89, no. 7, 2003, doi: 10.1038/sj.bjc.6601290.
[108]. L. Liberman, "Percutaneous image-guided core breast biopsy," Radiologic Clinics of North America, vol. 40, no. 3. 2002. doi: 10.1016/S0033-8389(01)00011-2.
[109]. I. Grady, T. Vasquez, S. Tawfik, and S. Grady, "Ultrasound-Guided Core-Needle Versus Vacuum-Assisted Breast Biopsy: A Cost Analysis Based on the American Society of Breast Surgeons' Mastery of Breast Surgery Registry," Ann Surg Oncol, vol. 24, no. 3, 2017, doi: 10.1245/s10434-016-5607-3.
[110]. S. Marla and S. Stallard, "Systematic review of day surgery for breast cancer," International Journal of Surgery, vol. 7, no. 4. 2009. doi: 10.1016/j.ijsu.2009.04.015.
[111]. R. Jeevan et al., "Reoperation rates after breast conserving surgery for breast cancer among women in England: Retrospective study of hospital episode statistics," BMJ (Online), vol. 345, no. 7869, 2012, doi: 10.1136/bmj.e4505.
[112]. O. Abe et al., "Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials," The Lancet, vol. 366, no. 9503, 2005, doi: 10.1016/S0140-6736(05)67887-7.
[113]. M. S. U. Hassan, J. Ansari, D. Spooner, and S. A. Hussain, "Chemotherapy for breast cancer (review)," Oncology Reports, vol. 24, no. 5. 2010. doi: 10.3892/or_00000963.
[114]. J. A. Azim, E. de Azambuja, M. Colozza, J. Bines, and M. J. Piccart, "Long-term toxic effects of adjuvant chemotherapy in breast cancer," Annals of Oncology, vol. 22, no. 9. 2011. doi: 10.1093/annonc/mdq683.
[115]. P. S. Bernard et al., "Supervised risk predictor of breast cancer based on intrinsic subtypes," Journal of Clinical Oncology, vol. 27, no. 8, 2009, doi: 10.1200/JCO.2008.18.1370.
[116]. S. Wei et al., "Metabolomics approach for predicting response to neoadjuvant chemotherapy for breast cancer," Mol Oncol, vol. 7, no. 3, 2013, doi: 10.1016/j.molonc.2012.10.003.
[117]. P. den Hollander, M. I. Savage, and P. H. Brown, "Targeted therapy for breast cancer prevention," Front Oncol, vol. 3 SEP, 2013, doi: 10.3389/fonc.2013.00250.
[118]. D. Y. Oh and Y. J. Bang, "HER2-targeted therapies — a role beyond breast cancer," Nature Reviews Clinical Oncology, vol. 17, no. 1. 2020. doi: 10.1038/s41571-019-0268-3.
[119]. B. Nami, H. Maadi, and Z. Wang, "Mechanisms underlying the action and synergism of trastuzumab and pertuzumab in targeting HER2-positive breast cancer," Cancers, vol. 10, no. 10. 2018. doi: 10.3390/cancers10100342.
[120]. H. S. Rugo et al., "Efficacy of Margetuximab vs Trastuzumab in Patients with Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial," JAMA Oncol, vol. 7, no. 4, 2021, doi: 10.1001/jamaoncol.2020.7932.
[121]. S. Adams et al., "Current Landscape of Immunotherapy in Breast Cancer: A Review," JAMA Oncology, vol. 5, no. 8. 2019. doi: 10.1001/jamaoncol.2018.7147.
[122]. P. I. Gonzalez-Ericsson et al., "The path to a better biomarker: application of a risk management framework for the implementation of PD-L1 and TILs as immuno-oncology biomarkers in breast cancer clinical trials and daily practice," Journal of Pathology, vol. 250, no. 5. 2020. doi: 10.1002/path.5406.
[123]. I. Caffa et al., "Fasting-mimicking diet and hormone therapy induce breast cancer regression," Nature, vol. 583, no. 7817, 2020, doi: 10.1038/s41586-020-2502-7.
[124]. R. T. Chlebowski and G. L. Anderson, "Changing concepts: Menopausal hormone therapy and breast cancer," Journal of the National Cancer Institute, vol. 104, no. 7. 2012. doi: 10.1093/jnci/djs014.
[125]. I. J. De Vries-van Leeuwen et al., "Interaction of 14-3-3 proteins with the Estrogen Receptor Alpha F domain provides a drug target interface," Proc Natl Acad Sci U S A, vol. 110, no. 22, 2013, doi: 10.1073/pnas.1220809110.
[126]. F. Andre et al., "Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update," Journal of Clinical Oncology, vol. 34, 2022, doi: 10.1200/JCO.22.00069.
[127]. A. Gennari et al., "ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer ☆," Annals of Oncology, vol. 32, no. 12, 2021, doi: 10.1016/j.annonc.2021.09.019.
[128]. S. Pavlides et al., "The reverse Warburg effect: Aerobic glycolysis in cancer associated fibroblasts and the tumor stroma," Cell Cycle, vol. 8, no. 23, 2009, doi: 10.4161/cc.8.23.10238.
[129]. A. Aboussekhra, "Role of cancer-associated fibroblasts in breast cancer development and prognosis," International Journal of Developmental Biology, vol. 55, no. 7–9. 2011. doi: 10.1387/ijdb.113362aa.
[130]. L. E. L. Terceiro et al., "The breast tumor microenvironment: A key player in metastatic spread," Cancers (Basel), vol. 13, no. 19, 2021, doi: 10.3390/cancers13194798.
[131]. J. Plava, M. Cihova, M. Burikova, M. Matuskova, L. Kucerova, and S. Miklikova, "Recent advances in understanding tumor stroma-mediated chemoresistance in breast cancer," Molecular Cancer, vol. 18, no. 1. 2019. doi: 10.1186/s12943-019-0960-z.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24MAR416

[132]. M. Tariq, J. Zhang, G. Liang, L. Ding, Q. He, and B. Yang, "Macrophage Polarization: Anti-Cancer Strategies to Target Tumor-Associated Macrophage in Breast Cancer," J Cell Biochem, vol. 118, no. 9, 2017, doi: 10.1002/jcb.25895.

[133]. X. Zhao et al., "Prognostic significance of tumor-associated macrophages in breast cancer: A meta-analysis of the literature," Oncotarget, vol. 8, no. 18. 2017. doi: 10.18632/oncotarget.15736.

[134]. C. B. Williams, E. S. Yeh, and A. C. Soloff, "Tumor-associated macrophages: Unwitting accomplices in breast cancer malignancy," npj Breast Cancer, vol. 2, no. 1. 2016. doi: 10.1038/npjbcancer.2015.25.

[135]. Y. Xiao et al., "Cathepsin C promotes breast cancer lung metastasis by modulating neutrophil infiltration and neutrophil extracellular trap formation," Cancer Cell, vol. 39, no. 3, 2021, doi: 10.1016/j.ccell.2020.12.012.

[136]. H. T. Snoderly, B. A. Boone, and M. F. Bennewitz, "Neutrophil extracellular traps in breast cancer and beyond: Current perspectives on NET stimuli, thrombosis and metastasis, and clinical utility for diagnosis and treatment," Breast Cancer Research, vol. 21, no. 1. 2019. doi: 10.1186/s13058-019-1237-6.

[137]. H. R. Ali et al., "Association between CD8+ T-cell infiltration and breast cancer survival in 12 439 patients," Annals of Oncology, vol. 25, no. 8, 2014, doi: 10.1093/annonc/mdu191.

[138]. S. Su et al., "Blocking the recruitment of naive CD4+ T cells reverses immunosuppression in breast cancer," Cell Res, vol. 27, no. 4, 2017, doi: 10.1038/cr.2017.34.

[139]. S. Garaud et al., "Tumor-infiltrating B cells signal functional humoral immune responses in breast cancer," JCI Insight, vol. 4, no. 18, 2019, doi: 10.1172/jci.insight.129641.

[140]. P. B. Olkhanud et al., "Tumor-evoked regulatory B cells promote breast cancer metastasis by converting resting CD4+ T cells to T-regulatory cells," Cancer Res, vol. 71, no. 10, 2011, doi: 10.1158/0008-5472.CAN-10-4316.

[141]. D. C. Nieman et al., "Moderate exercise training and natural killer cell cytotoxic activity in breast cancer patients," Int J Sports Med, vol. 16, no. 5, 1995, doi: 10.1055/s-2007-973015.

[142]. P. Michea et al., "Adjustment of dendritic cells to the breast-cancer microenvironment is subset specific," Nat Immunol, vol. 19, no. 8, 2018, doi: 10.1038/s41590-018-0145-8.

[143]. P. Prasad et al., "Multifunctional albumin-MnO2 nanoparticles modulate solid tumor microenvironment by attenuating hypoxia, acidosis, vascular endothelial growth factor and enhance radiation response," ACS Nano, vol. 8, no. 4, 2014, doi: 10.1021/nn405773r.

[144]. L. G. Coffman et al., "Ovarian Carcinoma-Associated Mesenchymal Stem Cells Arise from Tissue-Specific Normal Stroma," Stem Cells, vol. 37, no. 2, 2019, doi: 10.1002/stem.2932.

[145]. X. Yuan et al., "Breast cancer exosomes contribute to pre-metastatic niche formation and promote bone metastasis of tumor cells," Theranostics, vol. 11, no. 3, 2021, doi: 10.7150/thno.45351.

[146]. K. Hashimoto et al., "Cancer-secreted hsa-miR-940 induces an osteoblastic phenotype in the bone metastatic microenvironment via targeting ARHGAP1 and FAM134A," Proc Natl Acad Sci U S A, vol. 115, no. 9, 2018, doi: 10.1073/pnas.1717363115.

[147]. S. C. Chafe et al., "Targeting hypoxia-induced carbonic anhydrase IX enhances immune-checkpoint blockade locally and systemically," Cancer Immunol Res, vol. 7, no. 7, 2019, d oi: 10.1158/2326-6066.CIR-18-0657.

[148]. T. Xu, S. Yu, J. Zhang, and S. Wu, "Dysregulated tumor-associated macrophages in carcinogenesis, progression and targeted therapy of gynecological and breast cancers," Journal of Hematology and Oncology, vol. 14, no. 1. 2021. doi: 10.1186/s13045-021-01198-9.

[149]. X. Gu et al., "Nano-delivery systems focused on tumor microenvironment regulation and biomimetic strategies for treatment of breast cancer metastasis," Journal of Controlled Release, vol. 333. 2021. doi: 10.1016/j.jconrel.2021.03.039.