Recent Advancement on Breast Cancer Detection and Treatment

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Declaration

It is hereby declared that

1. The thesis submitted is my/our original work while completing my degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

The study does not involve any kind of animal and human trail.

Abstract:

Breast cancer is the most common cancer in women compared to men. The genetic and epigenetic factors, food habit, lifestyle, age vulnerability, poor diagnosis system, and substandard treatment set-up are linked to the higher mortality rate of this specific cancer type. Many traditional detection processes are being used to treat this cancer which includes conventional detections are monitoring CTC in blood sample, PET/CT, MRI, PCR and treatments like chemotherapy, radiotherapy, and hormone therapy. Surprisingly it has been noticed that the risk of breast cancer mitigated manifold due to recent advancement in both prognosis and treatment aspects of the disease. The purpose of this review is to discuss the recent progress in breast cancer diagnosis as well as its treatment with a focus on the ongoing clinal trail and effective drug delivery methods that poses higher chance of overcoming and decreasing the mortality rate with fewer side effects.

Keywords: Breast cancer; conventional; detection; diagnosis; progress; treatment

Dedication

I dedicate this work to my beloved parents who believed in me.

Acknowledgment

First, I am grateful to almighty Allah for giving me all the opportunities, sound health, and dedication to complete my project work.

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List of Acronyms

CEA	Carcinogenic Antigen
CA	Cancer Antigen
EVs	Extracellular Vesicles
sEV	Small Extracellular Vesicles
HCC	Hepatocellular Carcinoma
H1 (hnRNPH1)	Heterogeneous Nuclear Ribonucleoprotein
GPC-3	Glypican 3
mRNAs	messenger Ribonucleic Acid
Pttg1	Pituitary Tumor Transforming Gene
NLGN3	Nuroligin3
GPC-1	Glypican-1
ILC	Infiltrating Lobular Carcinoma
DCIS	Ductal Carcinoma in Situ
IDC	Intraductal Ductal Carcinoma
BRCA	Breast Cancer Gene
ER	Estrogen Receptor
BMI	Body Mass Index
MCF-7	Mivchigan Cancer Foundation-7
p21Cip1	Cyclin Dependent Kinase Inhibitor 1
p27Kip1	Cyclin Dependent Kinase Inhibitor 1B
G2	Cell Gap 2
TNBC	Triple Negative Breast Cancer
HER2	Human Epidermal growth factor receptor 2

IGF-1	Insulin-like Growth Factor 1
AMP	Adenosine Monophosphate
AMPK	AMP-activated Protein kinase
mTOR	Mammalian Target of Rapamycin
EGCG	Epigallocatechin-3-galate
RA	Resveratrol
CTCs	Circulating Tumor Cells
EpCAM	Epithelial Cellular Adhesion Molecule
CKs	Cyclin-Dependent Protein
M0	No Distant Cancer Spread has been Found
M1	Distant Cancer Spread Found
PET	Positron Emission Tomography
CT	Computed Tomography
FDG	Fluorodeoxyglucose
CE-MM	Cholesterol Enriched Membrane Micro-domain
PGR	Progesterone Receptor
ESR1	Estrogen Receptor 1
ERBB2	Erythroblastic Oncogene B 2
GAPDH	Glycereldehyde-3-phosphate dehydrogenase
ddPCR	Droplet Digital PCR or Pathological Complete Response
ML	Machine Learning
CMF	Cyclophosphamide, Methotrexate, and Fluorouracil
IBC	Inflammatory Breast Cancer
Gy	One Gray, International System of Units of 100 rads equals to an absorbed dose of 1 joule

Wks	Weeks
MRgFUS	MR Guided Focused Ultrasound
ExAblate	Non-invasive System Focused Ultrasound
RF	Radiofrequency
NADH	Nicotinamide Adenine Dinucleotide
RFA	Radiofrequency Ablation
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
Cas	CRISPR Associated
GDF15	Growth Differentiation Factor 15
MTT	Mean Transit Time
MAPK/ERK	Mitogen-activated Protein Kinase/Extracellular Signal-Regulated Kinase
PI3K/AKT	Phosphoinositide 3 Kinase/Serine or Threonine Protein Kinase
TFs	Transcription Factors
ER	Estrogen receptor
T47D	Epithelial Cells Isolated from a Pleural Effusion
RCTs	Randomized Controlled Trials
AA	African American
EpCAM	Epithelial Cell adhesion Molecule
CAV1	Caveolin1
EPI	Electronic Portal Images
SMS-ss-EPI	Simultaneous multi-Slice Readout-Segmented Echo Planer Image
UDFS	Unsupervised Discriminative Feature Selection
CAD	Computer-aided Diagnosis
DL	Deep Learning

CT	Computed Tomography
BCS	Breast-conserving Surgery
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeat
ZFNs	Zinc Finger Nucleases
TALENS	Trans-activating CRISPR RNA (tracrRNA)
SLNs	Solid-lipid Nanoparticles
NLCs	Nanostructured Lipid Carriers
TNFR	Tumor Necrosis Factor Receptor
PARP	Poly (ADP-ribose) Polymerase
EGFR	Epidermal Growth Factor Receptor
VEGF	Vascular Endothelial Growth Factor
NRP-1	Neuropilin-1
CNMs	Carbon-based Nanomaterials
APC	Antigen Presenting Cell
HLA	Human Leukocyte Antigen class-II
TIL	Tumor-Infiltrating Lymphocyte
MBC	Metastatic Breast Cancer
LMICs	Low- and Middle-income Countries

Chapter 1: Introduction

1.1 An Overview on Breast Cancer

Cancer is the second most fetal disease which can develop from any organs or tissue in our body due to abnormal cells proliferation. Soon it turns into metastasis phase and causes the mortality of cancer. According to WHO, 2.3 million women were diagnosed with breast cancer worldwide in year 2020 and 1 in 8 death is occurred due to breast cancer. United States of America most common type of cancer in women is breast cancer which is the most significant death issue in females (Jain et al., 2022). It is also common in Bangladesh. According to Islam et al., 2016, in Bangladesh the rate of this cancer is 22.5 per 100000 mostly in 15-40 age of women. Breast cancers are usually cancers of the internal lining of the milk ducts or the lobules that provide those organs with milk. Of all cancer cases in women, breast cancer alone makes 10.4%. Moreover, it is the most recurring non-skin cancer and the fifth foremost reason for cancer-related mortality worldwide (Jain et al., 2022). In 2004, 519,000 people around the world died from breast cancer. It was 7% of all cancer deaths and almost 1% of all deaths in that year (Jain et al., 2022). Many people may think that only women get breast cancer. However, men tend to have breast cancer more than females. Cancer insights appear that in 2020, the common cancer diagnosed in women is breast cancer which it is the fifth driving cause of cancer deaths around the world (Vajhadin et al., 2020a). The DNA and RNA of cancer cells are different from the DNA and RNA of the cells of the organism from which they originated. So when it is already compromised, the immune system misses them very easily (Jain et al., 2022). Screening of most used clinical breast cancer traits like CEA, CA 125, and CA153 are downward in terms of diagnostic sensitivity and particularity (Kabel, 2017). Hence, the world needs new biomarkers to diagnose breast cancer more accurately. Cell-shed extracellular vehicles (EVs) of 30 150 nm in diameter are called sEVs (Yan et al., 2017). A few molecules they maintain from their initial cells include proteins, microRNAs, mRNAs, and DNAs. Tumor growth and metastasis can be monitored non-invasively using markers found in serum electrolytes (sEVs). Multiple studies report the existence of mRNA in various diseases carried by sEVs (Ha et al., 2017). There have been new diagnostic biomarkers identified which are Hepatocellular carcinoma (HCC) biomarkers such as serum sEVs heterogeneous nuclear ribonucleoprotein H1 (hnRNPH1) and GPC-3 mRNA. Pttg1 and NLGN3 mRNAs in EVs have also been taken as markers for glioma diagnoses. According to the analysis, serum-derived EVs

from pancreatic cancer patients retain increased Glypican-1 (GPC-1), a biomarker for early pancreatic cancer detection (Ha et al., 2017).

1.2 Different Types of Breast Cancer

1. *In-situ* cancer
2. *Invasive (infiltrating)* cancer

In-situ carcinoma can further be classified into ductal carcinoma in situ (DCIS) and lobular cancer in situ (LCIS)
DCIS has many types such as

- Solid DCIS
- Cribriform DCIS
- Papillary and micropapillary DCIS

The invasive tumor can be classified into infiltrating/ invasive lobular (ILC) or ductal (invasive ductal carcinoma (IDC). They are further subdivided into:

- Classic ILC
- Solid ILC
- Alveolar ILC
- Tubulolobular ILC (Nounou et al., 2015)

However, the name “breast cancer” means anomalous development and expansion of cells that originate in the breast tissue. Most of the breast's tissues are made of Glands and stromal tissues (Jain et al., 2022). Glands which produce milk (lobules) also the ducts (milk passages) that are accommodated in the glandular tissues. Fatty and fibrous connective tissues, specifically stromal tissues, are located in the breast. Lymphatic tissue, which is part of the immune system, removes cellular fluids and waste from the breast. In the breast, a few different tumors can form at different points. Most breast tumors are caused by benign (non-cancerous) changes (Jain et al., 2022). It is not uncommon for women with fibrocystic change (a noncancerous condition) to experience lumpiness, fibrosis (the formation of scar-like connective tissue), cysts, and tenderness or pain in their breasts. The cells that line the breast ducts are where most breast cancers begin (ductal cancers). While most cancers begin in the cells that line the lobules (called lobular cancers), a few starts elsewhere. Also, Cells do not spread outside of the ducts of the breast and into the surrounding fatty and connective tissues (Jain et al., 2022). Common form of non-invasive breast cancer is ductal carcinoma in situ (DCIS) (90 percent), lobular carcinoma *in situ* (LCIS) cases are less, which is thought to indicate an elevated risk of breast cancer (Jain et al., 2022). Cells that penetrate the duct and lobular walls of the breast and invade the surrounding fatty and connective tissues. Metastasis (the spread of cancer to other organs) does not have to occur before cancer is invasive. Breast cancer is a disease that strikes women all too frequently (Jain et al., 2022). Lobular neoplasia (LCIS) "In situ" cancer means cancer which is not spread beyond the original growth site. An

increase in the number of cells in the breast milk glands (lobules) is an indication of LCIS (Jain et al., 2022). The most common form of non-invasive breast cancer, DCIS, is restricted to the breast's ducts. Ductal comedocarcinoma is a typical cause of ductal carcinoma-related structure when cancer invades the lymph nodes (ILC). Invasive lobular carcinoma (ILC) is another name for this type of cancer. Despite its origins in the breast milk glands (lobules), ILC frequently spreads to other body parts (Hosseini et al., 2016). ILC causes an estimated ten to fifteen percent of all breast cancers. IDC, or invasive ductal carcinoma, is another term for infiltrating ductal carcinoma. Intraductal ductal carcinoma (IDC) is cancer that begins in the breast and spreads into other tissues, including those in other parts of the body. Approximately 80% of all breast cancer cases are diagnosed as IDC (Jain et al., 2022). Medullary carcinoma which is a type of invasive breast cancer where the tumor and surrounding healthy tissue are clearly separated. Only 5% of breast cancer cases are medullary carcinoma. Cancer of the mucous membranes, carcinoma, or colloid carcinoma, which is less commonly found breast cancer that develops when the mucus-producing cancer cells are proliferate (Jain et al., 2022). Compared to other types of cancer, the prognosis for women with mucinous carcinoma is better. Tubular carcinomas are invasive type of breast cancer which originates in the tubules of the breast (Jain et al., 2022).

1.3 Prevalence of Breast Cancer

Six years after being diagnosed with breast cancer, almost two-thirds of women experienced a rehabilitative side effect. From 12 months to six years, the percentage of women reporting three or more side effects decreased, while those reporting no side effects remained stable at around 40% (Schmitz et al., 2012). There was only one complication in which prevalence increased over time: weight gain (Schmitz et al., 2012). Patients who have BRCA1 or BRCA2 mutations have a greater probability of developing this disease. Databases and conferences like Medline and EMbase were explored from January 2012 to December 2017 (Armstrong et al., 2019). A total of 70 studies were selected from a total of 17,872 records. Among the 58 large studies, the majority of BRCA1/2 mutations may vary. Ranging is 1.8 percent in Spain in sporadic breast cancer to 36.9 percent in the United States in estrogen/progesterone receptor low+ breast cancer (Armstrong et al., 2019). Approximately 2.9 to 3.0 percent of women in two extensive types of research were found to have a germline BRCA (gBRCA) mutation regardless of their family history, ethnicity, sexual orientation, or age. From 9.3% (Australia) to 15.4% (USA), the prevalence of gBRCA mutations in the four large, unselected studies of triple-negative breast cancer ranged widely (United States) (Armstrong et al., 2019). Mutations gBRCA were

found in 5% of early breast cancer patients in a large, untargeted, HR positive/HER2-positive study (United States). In two extensive, untargeted metastatic breast cancer investigations, the most gBRCA mutations were 2.7 percent at France and 4.3 percent in United States, Germany (Armstrong et al., 2019). There were only a few studies of localized advanced breast cancer, and they were not conducted in a random sample. As we have very little knowledge about the prevalence of BRCA mutations in this matter, more large-scale studies examining the disease's BRCA mutation prevalence are urgently required (Armstrong et al., 2019).

1.4 Cell Proliferation, Invasion and Migration

At every stage of breast cancer development, epidemiological studies show that ovarian hormones play a role. Reduced risk is associated with a young age of menopause and low body mass index (BMI), whereas increased risk is associated with ovarian hypertrophy with estrogen replacement treatment in postmenopausal women (Wang et al., 2021). Depo-Provera and oral contraceptives do not lessen the danger. In combination of proto-oncogenes and growth factors, estrogens and progestogens appear to impact on the breast cell proliferation also the breast cancer etiology in a positive way. (Wang et al., 2021).

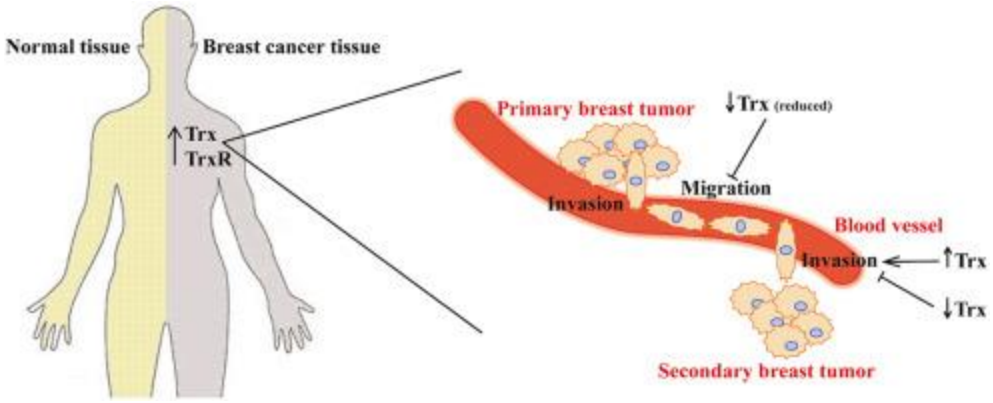

Figure 1: Cell Invasion and Migration in breast cancer (Bhatia et al., 2016)

Figure 1 shows the thioredoxin in invasion and migration of breast cancer, to improve breast cancer patient outcomes, targeting the Trx system with specific inhibitors such as auranofin or other specific inhibitors may result in decreased tumor invasion and migration (Bhatia et al., 2016). At the time of luteal phase, progesterone increases the number of terminal duct lobular unit cells in the uterus, while estrogen has been shown to increase interlobular ductal cell division. Terminal duct lobular unit cells are the primary source of most breast cancers (Wang et al., 2021). These cells grow to their full potential during pregnancy. The luteal phase is also a time of increased reproduction for them. On the other hand, exhibit a tremendous lot of diversity. A link between the rate of breast cell division and the level of blood hormones present

has not been investigated in any studies. Late luteal and early follicular stages are the peak of mitosis, which appear around three days before breast cell death. Breast cancer may be linked to the proliferation of breast stem cells, according to other studies. A reduction in mitotic activity indicates the activity of estrogen and progesterone receptors in breast cancers that are cured with endocrine therapy (Wang et al., 2021). All breast cancer cell line which are estrogen-dependent are also hormone-dependent breast cancers. By supplementing with progesterone, cell lines that are estrogen-dependent can be stopped from developing into endometrial cells. Researchers must do research to determine a biological explanation for the outcomes of numerous mammary cell proliferation experiments conducted in the context of breast cancer so that we have better comprehend findings of these investigations. Inherent in this relationship is the fact that estrogen, progestogens, breast cell multiplication, and the thread of breast cancer are all linked (Wang et al., 2021). Promoting effects of estrogens may be mediated by the estrogen receptor (ER) in breast cancer, according to research. Role of ER in breast cancer yet to be determined (Wang et al., 2021). As many of the breast tumors disclose both ER and ER, understanding the role of ER in breast cancer pathogenesis is critical. Adenovirus-induced expand in the expression of the ER in MCF-7 cells alters their phenotypes. MCF-7 cells that express only ER are more likely to develop tumors when exposed to estradiol. In contrast, when ER is introduced into MCF-7 cells, it inhibits cell expansion and stops tumor formation in a mouse xenograft model. This is accomplished by suppressing the transcription of the cyclin D1 and A genes, as well as increasing the appearance of p21Cip1, p27Kip1, and G2 cell cycle arrest, which is achieved by increasing the expression of p27Kip1 (Wang et al., 2021). Findings show that in MCF-7 cells, ER have opposing impacts on cell proliferation and tumor development (Wang et al., 2021). It is possible that estrogens that are ER-targeted can be useful in breast cancer chemoprevention because they do not have the breast cancer-promoting properties of estrogens in hormone replacement therapy. TNBC is a rare form of breast cancer that frequently spreads to the lungs and brain. It affects one in every 150 women diagnosed with the disease (Wang et al., 2021). Since they lack the ability to benefit from hormonal or HER2-targeted therapy, patients with TNBC have terrible outcomes. Recurrence and metastasis of TNBC4 are responsible for the death of 30–40% of TNBC patients, according to statistics (Wang et al., 2021). Radiation and chemotherapy remain the standard treatments for patients with TNBC to this day. TNBC progression and metastasis necessitates an urgent investigation into its underlying mechanisms so that provide new cure options for TNBC patients (Wang et al., 2021).

1.5 Risk Factors of Breast Cancer

Bioactive components included in meals can influence inflammatory processes. There are a variety of elements that might impact the outcome of a nutrition experiment, including dietary components, the right dietary pattern, the time of exposure, and other characteristics (chemical form, exposure length) which could have impact on the response to the nutrient (Martin & Weber, 2017.). Early menarche, nulliparity, and a later beginning of menopause are connected to an expanded risk of breast cancer (Martin & Weber, 2017.). Moderate activity and a longer breastfeeding time can both reduce ovulatory cycles, which may have the same protective effects as the shorter lactation duration (Martin & Weber, 2017.). Obesity has been related to an expanded risk of breast cancer in women. Women with postmenopausal estrogen comes mostly from estrone, which is synthesized in adipose tissue. As a result, people who takes estrogen are more prone to obesity (Martin & Weber, 2017.).

Table 1: Risk factors that are not dependent on lifestyle (Martin & Weber, 2017.)

Risk Factors	**Associated Risk**
Age	With increasing age, the risk of breast cancer increases.
Genetics	Inherited copy may increase the risk.
Ethnicity	White women carry BRCA more than other ethnic groups.
Dense Breast	The risk of cancer increases with dense breast tissue.
DCIS or LCIS	Chances of cancer increase in ductal carcinoma *in situ* or lobular carcinoma *in situ.*
Previous Cancer	History of cancer increases the risk.
Having a Child	Not having a child rises the risk of breast cancer.

Table 2: Risk factors associated with lifestyle (Martin & Weber, 2017.)

Risk Factor	**Associated Risk**
Overweight	Not maintaining normal BMI increases the risk of breast cancer.
Hormone Replacement Therapy	HRT increases the risk where combined HRT is the biggest risk factor.
Radiation Treatment	Use of radiation for treatment leads to cancer.

Contraceptive Pill	Taking pills increase the risk in late teens.
Alcohol and Smoking	10gm of alcohol per day may increase the risk by 7-10%.
Being Inactive	Less than 150 min of exercise in a week increase the risk.

Several non-hormonal risk factors for breast cancer have been connected to the disease, however estrogen exposure may be a contributing factor in some cases. For instance, hormone milieu alters the danger of being exposed with ionized radiation. In young ladies having mantle radiation for Hodgkin's lymphoma had a 75.3% risk risen of breast cancer when compared to age-matched control participants (Martin & Weber, 2017.). Victims of atomic bombings in Japan during World War II also had an extreme prevalence of breast cancer, which may be attributed to radiation exposure. Women who are exposed to radiation when they are still in their teens are more likely to get breast cancer (Martin & Weber, 2017.). Alcohol consumption may also be a nonhormonal risk factor. Several studies have found a co-relationship between the amount and duration of alcohol use and an elevated risk of breast cancer (Martin & Weber, 2017.). According to Nagata et al., Drinking alcohol has been shown to raise estradiol levels in the blood, raising the possibility that alcohol intake contributes to the initiation of breast cancer by exposing the body to more estrogen (Martin & Weber, 2017). Breast cancer has relationship with increased risk of certain dietary factors, according to research. Two of these risk variables such as high dietary fat intake and "well-done" flashy food consumption. The verification of these factors raising breast cancer risk is unclear due to study bias, inconsistent data, and challenges in obtaining newborn nutritional exposure histories (Martin & Weber, 2017.). Fat intake can raise estrogen levels in the blood, and well-done meat may include genotoxins. Breast cancer development may be influenced by factors other than hormones, such as frequent variant alleles of several genes. Breast cancer is likely caused by not only environmental but also genetic factors (Martin & Weber, 2017.).

1.6 Impacts of Diets

Excess weight and obesity have impact in USA and many more countries in the last two decades (Ross, 2010). As a result of this rise, conditions like hypertension, cardiovascular disease, type 2 diabetes and cancers likely to occur. Overweight is a complex disease affected by a wide range of genetic, environmental factors, not least of which are the foods we eat and the nutrients they contain. Breast, esophageal, pancreatic, colon/rectum, endometrial and kidney cancers are all at a higher risk is supported by epidemiological evidence (Ross, 2010).

Obesity's effect on cancer risk may vary depending on the type of cancer, and no specific biological mechanism is known for any of the cancers. Overweight and obesity have several metabolic consequences, including increased levels of IGF-1, insulin, adipokines, and pro-inflammatory cytokines (Ross, 2010). As a result of these metabolic changes, steroid hormone metabolism changes, resulting in a rise in estradiol as well as other hormones like as progesterone and cortisol. It has been found that AMPK, a crucial metabolic-sensory protein implicated in the prevention of metabolic diseases, is associated increasing risk of cancer. Many diseases, including cancer that can be prevented through the activation of AMPK by bioactive food components (Ross, 2010). When it comes to tea polyphenol (-) epigallocatechin-3-galate (EGCG) and resveratrol (RA), studies suggested that activation of AMPK is a mechanism for their anticancer properties (Ross, 2010). That's why research in the fields of nutrition and obesity is concentrating now on the impact of diet on signaling pathways that are dysregulated, as well as on innovative physical activity, behavioral and nutritional interventions. More needs to be understood about the role of food and dietary components in reduce (Ross, 2010). The connection between diet and cancer has improved in present years, but a lot more needs to be learned about diet and dietary components in cancer risk and prevention of cancer risk and promoting health (Ross, 2010). Cancer prevention biology has been aided by the results of clinical trials, epidemiological studies, preclinical models, and cell culture systems. More attention is needed to investigate emerging areas such as how diet and microbiome interact, and bioactive components included in meals have the ability to influence inflammatory processes (Ross, 2010). There are a variety of elements that might impact the outcome of a nutrition experiment, including dietary components, the right dietary pattern, the time of reveal with other characteristics that could alter the response to the nutrient, are still open questions. Isolated food components may not always have the same biological effects as the food as a whole because of interactions between the food's components (Ross, 2010).

1.7 Rationale of the Study

Breast cancer is a common disease nowadays, the conventional detection and treatment procedure have some complications which may increase the mortality rate and disease rate which need to be decreased in recent years:

- Despite chemotherapy, radiotherapy is used as treatment and PET, CT, MRI for detection in recent days, unfortunately, they are possessing series of complications like it affects pregnant women and diabetic patients because the radioactive material that is injected to the patient contains glucose.
- Advanced technology has no such complication which are more patient friendly.
- For example, oncoplastic treatment can help to uncover the correlation between risk of patient in case of surgery and treatment.
- Gene editing can play a vital role in both prognosis and treatment of breast cancer introducing CRISPR technology.
- How nanotechnology can help in breast cancer tumors.
- Electrochemical Cytosensors are helpful for detection at low cost and simplify the process.
- Imaging and microchip are helpful for heterogeneous cell separation.

For all these reasons this study is needed to discuss recent advancement of this sector.

1.8 Aim and Objectives of the Study

Aim:

Aim is to discuss the new breast cancer detection techniques and treatment options and their various aspects.

Objectives of the study:

- To provide information on the conventional detection and treatment methods for the breast cancer.
- To give an idea on the recent advancement on the breast cancer detection and treatment methods.
- To discuss how these advanced techniques can be used to diagnose the disease easily and improve the condition.
- To know the cost effective and easier technique to reduce the disease.

Chapter 2: Methodology

This review is accomplished based on the recent publications and research on PubMed, Google Scholar electronic database. More than 30 articles have been studied to complete this review paper. Compiling all the necessary recent investigations on Breast Cancer and various treatments used past years, this paper focuses mainly on recent detection and treatment of breast cancer. The following keywords were used to find the needed information: “Breast cancer” and “techniques” along with “recent,” “past,” “detection,” “treatment,” etc. Additionally, references from the articles found earlier were explored to specify potentially overlooked investigations to make this review more informative.

Chapter 3: Pathway and Other Related Factors

Pathophysiology of Breast cancer

Developing breast cancer due to the damage of DNA and exposure to estrogen may influence the genetic mutation. However, from time to time there might be BRCA1 and BRCA2 which are respectively inheritance of DNA defects or pro-cancerous genes (Simon et al, 2021). The family history of one patient that expand the development of breast cancer risk. The people whose parents or grandparents have ovarian cancer or breast cancer, they are more likely to affected with cancer. Cells that have aberrant DNA or developmental defects are attacked by the immune system in a healthy person. Those with breast cancer are unable to use this method, resulting in tumor development and spread (Simon et al, 2021).

3.1 Pathways

3.1.1 Estrogen Receptor (ER) Signaling Pathway

Breast cancer is intimately connected with the female hormone estrogen, which plays a role in its development and propagation. The nuclear estrogen receptor is responsible for the transcriptional maintenance for estrogen genes in the body (ER). The conformation of the estrogen receptor during ligand binding, its interactions with a large number of coregulators, and the presence of active elements in the promoter region of desired genes all influence the estrogenic effects on cells (Renoir et al., 2013). At the time of treating breast cancer, the estrogen receptor (ER) is a critical target to take into consideration. It is also believed that a range of polypeptide growth factors and their membrane receptors are related with the development and propagation of breast cancer (Cheskis et al., 2007). In addition to the several protein kinase pathways that promote cell survival and proliferation, these pathways also interact with the endoplasmic reticulum (ER) to increase the cell's ability to respond to stress. Activation of the extracellular receptor by growth factor cascade enzymes may result in the activation and amplification of signaling via the growth factor pathways by other enzymes in the system (Renoir et al., 2013). It is possible that ER activation that is not responsive to ligand would increase hormonal resistance situations. ER is not the only therapeutic option under consideration; researchers are also working on a novel strategy that will prevent the development of resistance to endocrine medication by targeting growth factor pathways (Osborne et al., 2001). A number of physiological and clinical settings in which ER-mediated signaling is crucial have been identified (Björnström & Sjöberg, 2005).

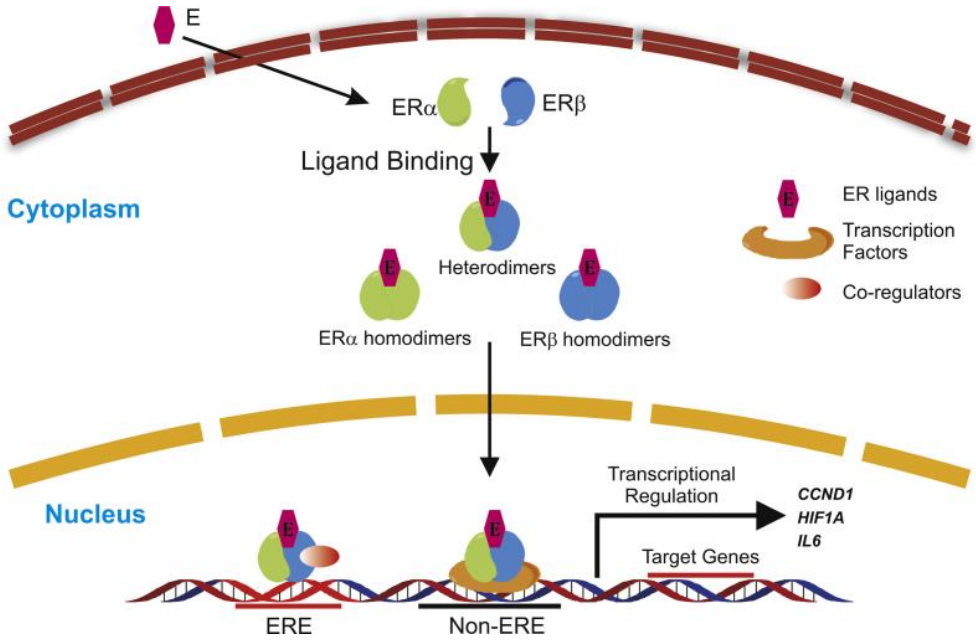

Figure 2: ER Signaling Pathway (Feng et al., 2018)

In this figure 2, high levels of estrogen receptor alpha (ERa) and a low amount of estrogen receptor beta (ERb) are seen in breast cancer cells (ERb). To regulate transcription, ligands need to bind with homo or heterodimers from nuclear hormone receptors. Target genes ERE regions are occupied by enzyme-regulated dimers, which binds to the ERE and recruit co-regulators in order to modulate transcription activity. Another method that ERs influence gene expression plays role as in the co-regulator of other transcription factors, which is another way that ERs influence gene expression has shown (Feng et al., 2018). These include It has been estimated that around 75% of breast cancers express the ERa hormone receptor, according to the International Agency for Research on Cancer. In breast cancer biology, the activation of the estrogen receptor (ERa) is tightly controlled and plays vital role in a variety of cross-talking processes (Cheskis et al., 2007). The interactivity of ERa with cyclin D1 which is of the most well-known routes for boosting the proliferation of breast cancer cells. Cyclin D1 is a critical initiator of CDKs 4 and 6 that aids in the coordination of the transition from the G1 to the S phase of the cell cycle in a large number of cancer cells (Zwijsen et al., 1997). It is most often used in diagnose breast cancer, and it is gaining more popularity over time (Liu et al., 2021). There is some overlap between the tissue expression patterns of ERb and Era (Bejnordi et al., 2017). The quantity of ERb in breast tissue decreases as cancer progresses, which explains why it is found in high concentrations in healthy breast tissue. Studies in vitro and in vivo confirmed its function for breast cancer suppressor in line with the pattern of expression seen in these studies (Bejnordi et al., 2017). The accumulating evidence that ERb is involved in the

formation of breast tumors suggests that it may be just as essential as ERa in the development of mammary cancers, if not more significant (Cheskis et al., 2007).

3.1.2 Human Epidermal Growth Factor Receptor 2 (HER2) Pathway

They are referred to as human epidermal growth factor receptors (EGFRs) 1 through 4, and they are found in both normal tissues and many different types of cancer (Oda et al., 2005). Among the EGFRs is the HER2/NEU (also known as c-ERBB2), which is a member of the HER family of protein (Sergina & Moasser, 2007). In addition to an external domain and an intracellular domain, the receptor Tyrosine Kinase 2 (HER2) protein has two transmembrane sections (Arteaga & Engelman, 2014).

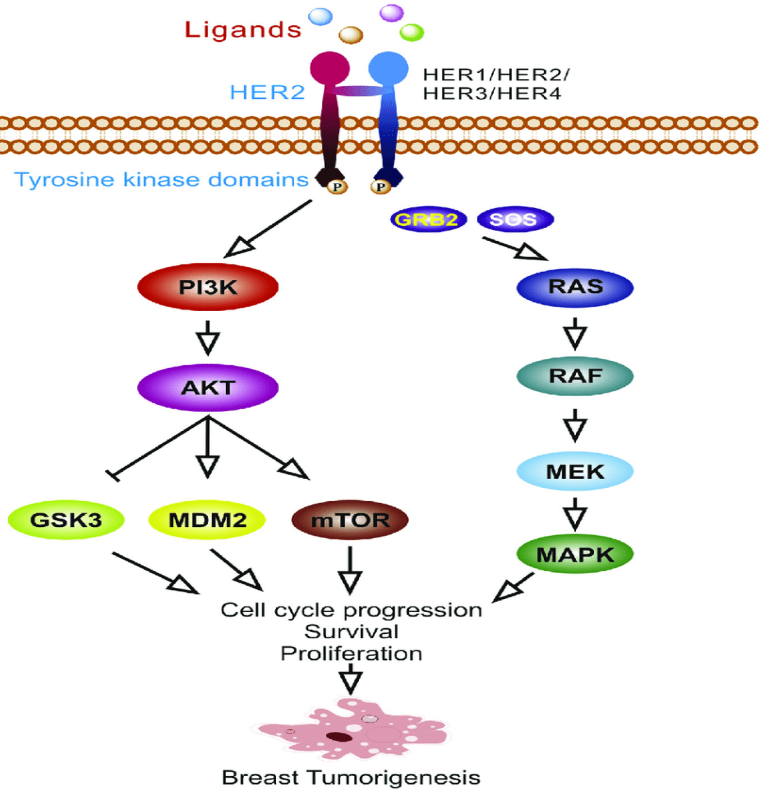

Figure 3: HER2 Signaling Pathway (Feng et al., 2018)

In figure 3 it shows, Cell membrane containing HER2 have receptor tyrosine kinases react with many ligands. Phosphorylation occurred due to downstream cancer signaling pathway like: P13k/AKT (Feng et al., 2018). Because HER2 is constitutively active, it prefers to form dimers with other molecules, which enables it to influence many cellular processes via a variety of different pathways (Garrett et al., 2003). Binding and dimerization of ligands to the intracellular domain of the HER2 protein operates a variety of downstream signaling pathways, also the mitogen-activated protein kinase which is MAPK, phosphatidylinositol 4,5-bisphosphate 3-kinase and tumorigenesis are related to this pathway (Burgess, 2009).

Overexpression of HER2 protein results HER2 signaling amplification which is the reason of cell growth of the tumor, proliferation also migration (Slamon et al., 1987). A targeted medicine is a medication that targets specific molecules in signaling pathways which are crucial to the genesis and development in cancer. Targeted medicines are the most effective therapy for cancer patients who have been accurately diagnosed (Arteaga & Engelman, 2014). It has been known for some time that the gene HER2 is associated with breast cancer, but novel mechanisms have just been uncovered to explain this association (Arteaga & Engelman, 2014) and (Slamon et al., 1987). MED1, a new intermediate factor, has recently been demonstrated to have a significant impact on HER2-driven tumorigenesis (Yang et al., 2018), though this interaction recognized for quite some time before to this. 116 Cancer stem cells (CSCs) and inflammation also been linked to the precancerous effect of the human epidermal growth factor receptor (HER2) in breast cancer (Liu et al., 2018). Breast cancer cells that express the human epidermal growth factor receptor 2 (HER2) are more likely to metastasize (Schwartz & Erban, 2017). The progesterone and progesterone-induced hormone paracrine signals, which promote the migration of primary tumor cells, may stimulate the activation of mammary stem cells. There have been reports of stem cell features associated with HER2-stimulated stem cells that are consistent with this hypothesized impact (Hosseini et al., 2016). The outcome is that HER2 testing is used in order to identify people who are a suitable candidate for expensive and potentially resistant cancer treatment options (Hosseini et al., 2016). In the quest for improved specificity, HER2 molecular analysis has emerged as a critical component of the diagnostic breast cancer patient (Yang et al., 2018).

3.1.3 The Phosphoinositide 3-Kinase (PI3K) Pathway

PI3K activity and the onset of cancer have been extensively studied. For example, a Hodgkin's lymphoma patient had a PI3K p85 subunit that was mutated (McCubrey et al., 2007). Cell line derived from lymphoma. The p110 of the PI3K a gene's component in humans, PI3KCA is frequently altered genes like some others, in the disease of cancer (McCubrey et al., 2007). In LNCaP human prostate carcinoma cells, the pathway PI3K most frequently activated by growth factors (McCubrey et al., 2007). Other studies have directly linked PI3K activity to a wide range of diseases. of human malignancies, such as breast cancer and lung cancer Melanomas (are among them). The fact that Akt (also known as protein S100A4) (McCubrey et al., 2007). In addition to its role in the malignant transformation of cells, PI3K downstream kinase PKB hormonal resistance can be induced. Akt activation has the potential to have an impact. expression and control of hormone responses receptors, which makes hormone ablation

ineffective treatments (McCubrey et al., 2007). Activated Akt has been found in more than half of the patients studied. detection of activated Akt in primary AML samples is A poor prognosis is associated with it. Also, the Akt a pathway has been found to regulate MRP-1 (multidrug resistance protein-1) and drug resistance in the body. AML These findings support the hypothesis (McCubrey et al., 2007). PI3K signaling has a significant impact on cancer development and progression. Resistance to drugs. Targeted inhibition of the central an excellent choice is apparent in the parts that make up this pathway in the improvement of new therapeutic strategies (McCubrey et al., 2007). Observations have shown both Raf/MEK/ERK also PI3K/Akt overexpression cancer pathways include a poorer prognosis in AML single pathway overexpression. It's possible that combining two or more inhibitors could have a positive effect on the disease. medical intervention in the fight against certain types of cancer (McCubrey et al., 2007).

3.1.4 Renin Angiotensin System (RAS) Signaling Pathway

Tyrosine kinase, also known as receptor RTK, facilitates communication between the cell and the external environment by phosphorylating receptor tyrosine kinase. The stimulation of cell proliferation, development, the foundation of cell survival and death, metabolism and cell motility, signaling molecules is facilitated by the Ras pathway (Moon, 2021). Hyperactivation of Ras signaling contributes significantly to breast cancer growth and progression, despite the rarity of Ras mutations in the disease (Moon, 2021). Oncogenic Ras is activated by GTPase activating proteins, growth factor receptor overexpression, and cytokine stimulation. One way to treat breast cancer effectively is to control oncogenic Ras (Moon, 2021). Oncologists have used the Ras signaling pathway and its mechanisms to find new ways to treat the disease. Posttranslational modifications of Ras, such as farnesyltransferase and geranylgeranyl transferase 1 that is essential in the treatment of breast cancer, as have a receptor called EGF receptor (EGFR) or anti-cancer therapies targeting receptor. EGF-mediated Ras, activation in progression of breast cancer has been revealed by the discovery of new Ras targets in breast cancer (Moon, 2021). Some of these alternative pathways for Ras signaling could lead to new treatment options for breast cancer. There have been important discoveries about the direct inhibition of Ras activity despite the difficulties in targeting the protein. Further research may shed light on the targeting Ras effects also protein and clinical significance of it (Moon, 2021).

3.2 Gene Mutation

3.2.1 Breast Cancer Gene 1/2 (BRCA1/2) Mutations in Breast Cancer

At Couch et al., 2014 point of view, a women having a breast cancer patient in her family history are two times more susceptible compared with a new patient. As a result, the names BRCA1 and BRCA2 are relevant in term of breast cancer research (Narod, 2010). Breast cancer is prevented by BRCA proteins, which repair DNA damage via a process known as homology-directed repair (HDR). This process is analogous to and cooperative with other tumor-suppressing strategies (Trainer et al., 2010). According to a research, this increase the possibility of breast cancer by a factor of five to six for women who had BRCA gene deletion types mutations and/or loss of BRCA gene function by a factor of five to six (Siegel et al., 2018). Despite the fact that some BRCA mutations may be handed down from mother to daughter, no difference has been shown in the frequency of breast cancer among BRCA mutation carriers with or without an close family history (Metcalfe et al., 2018). Recent study shows, women who have the BRCA gene mutation are at an elevated chance of developing breast cancer and other malignancies if they smoke cigarettes, they will assist in the identification of high-risk groups and the efficiency of preventative measures (Ko et al., 2018). ER and ERBB2 are not expressed in the tumors of patients with BRCA1 mutation-related breast cancer who do not express ER or ERBB2. However, basal epithelial markers are expressed in the tumors of these patients, which have already been shown to be related with ER/ERBB2-negative tumors in clinical research (Molyneux et al., 2010). It does not matter how many cells have the potential to change their phenotypic tumor phenotypes are not always reflected in the histology of the tumor (Molyneux et al., 2010).

3.2.2 Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA) Oncological Mutation in Breast Cancer

For transport of PI3K to the membrane, the growth factor-activated receptor tyrosine kinase, also known as the RAS protein, interacts with p85 either directly or via adaptor proteins (Mukohara, 2015). The activation of PI3K, as well as the translational stimulation of downstream AKT and mTOR, increases the anti-apoptotic and cell-cycle progression activities of the cell (Fruman & Rommel, 2014). Because of the activation of PI3K, it is possible to have increased growth, anti-apoptosis, cell-cycle progression, and translational activity (Engelman, 2009). For the most part, the PI3K/AKT/mTOR pathway is the most often initiated oncogenic pathway in breast cancer (Mukohara, 2015). The most prevalent mechanisms of PI3K increase are PIK3CA mutations and PTEN protein loss, both of which have been identified. Many

cancers, notably breast cancer, have been shown to have PIK3CA gene which starts amplifying even before PIK3CA mutations were discovered (P. Liu et al., 2009). It is more common for these mutations to be detected in luminal (HR-positive/HER2-negative) tumors, especially in tumors with less harmful characteristics (Mukohara, 2015). Research issued in the Journal of Clinical Oncology, one-third of breast cancer patients with ER-positive breast cancer and PIK3CA-mutant tumors acquired resistance to PI3K inhibitors, resulting in an exceedingly poor overall survival rate. Although there is some disagreement on though PIK3CA mutations are valuable predictive markers in the treatment of breast cancer patients, the issue is currently being debated (Mukohara, 2015).

3.3 Other Factors

3.3.1 Tumor Heterogeneity and Evolution of Breast Cancer

Intratumor heterogeneity, which is caused by the presence of multiple cellular populations within a single tumor, intratumor heterogeneity in breast tumors from different patients and intratumor heterogeneity in breast tumors from the same patient are two additional hallmarks of malignancy that have been identified (Ellsworth et al., 2017). Most significant obstacles to made of effective therapies and tailored medicine for breast cancer is intratumor heterogeneity (Marusyk et al., 2012). Using estrogen receptor expression to determine both hospital and therapeutic consequences of tumor heterogeneity for cellular phenotypes in breast cancer, which was first rigid tumors to be studied, the clinical and therapeutic consequences of tumor heterogeneity for cellular phenotypes were established (Beca & Polyak, 2016). The phenotypic plasticity and development of clonal stem cells of cancer, as well as EMT in cancers, are all thought to be responsible for the tumor's heterogeneity (Polyak, 2011).

3.3.2 Breast Cancer Metastasis

Cancer metastasis necessitates the control of a wide range of biological processes prior to the manifestation of overt sickness (Meacham & Morrison, 2013). Cancer spread is still a mystery; however, it is widely accepted that the metastatic cascade contains many pathways. Neoangiogenesis and tumor cell differentiation occur simultaneously. The initial tumor, its intravasation, survival, and spread which causes lymphatic and systemic vascular adhesion that targets, extravasation and subsequent development of metastatic tumors parenchymal foci and the final presentation of a disease a clinically apparent secondary area of metastasis (Chambers et al., 2002). Various kind of breast cancer that have migrated to other places of the body, making it tough to identify risk factors and create effective care (Vogelstein et al., 2013).

Emerging techniques that assess distributing tumor cells in patients with primary stage breast cancer metastases have showed good results in assuming and diagnosing the disease's primary phases (Riggi et al., 2018).

Chapter 4: Conventional Detection and Treatment of Breast Cancer

4.1 Conventional Detection Techniques

4.1.1 Monitoring Circulating Tumor Cell (CTC) in the Blood Sample

The term "circulating tumor cells" (CTCs) refers to cancer cells that are circulating in the bloodstream and have spread from the initial or metastatic site of a solid tumor, either spontaneously or because of surgical intervention. Metastatic lymph nodes and CTCs have been shown to be related in studies and to help determine the various cancer prognosis (Yanwu et al., 2017). Tumor embolisms are formed when tumor cells different from tumor tissue and mixed into the bloodstream, where they move, attach, and aggregate to produce tumor embolisms. The process is the most common form of breast cancer distant metastasis, and it has a significant impact on patient survival and prognosis (Yanwu et al., 2017). The identification of migrating tumor cells in the peripheral circulation of breast cancer patients is critical in the diagnosis, prognosis evaluation, treatment regimen selection, and prediction of metastasis and occurrence of the disease. The expression of HER-2 (human epidermal growth factor receptor 2), ER (estrogen receptor), and PR (progesterone receptor) in triple-negative breast cancer is all negative (TNBC). About 10% to 17% of all breast cancers are classified as TNBC, which is identified by a high malignant degree, easy recurrence, and distant metastasis (Yanwu et al., 2017). TNBC patients' outcomes were examined, which aimed in the determination value and role of preoperative and postoperative CTC monitoring. detection of CTC Cell Search detected a CTC in peripheral blood (Yanwu et al., 2017). It was determined that CTCs were counted as units in 7.5 ml of peripheral blood and that the CTC-positive detection rate was calculated for each unit in light of the fact that the surgical resections had been completed and the endpoints of progression-free survival and overall survival had been set, Results of CTC baseline and postoperative CTC levels were compared for a period ranging from 3.2 to 37.6 months (Yanwu et al., 2017). Predictive survival (PS) is described from surgical therapy time to diagnosis of recurrence of cancer for the first time or to the end of follow-up, while overall survival (OS) is defined from surgical treatment to death. The advancement of CTC detection technology is important to the widespread use of these agents in clinical settings. Assays for CTCs have been performed on a variety of different platforms (Yan et al., 2017). Any technology that is intended for clinical use must first show its validity in terms of both analytic and clinical terms60. CellSearch® is the only system used to patients

having metastatic breast should be monitored using technology that has been authorized by the FDA so far (Yan et al., 2017). As the only semi-automatic system, CellSearch® has made a significant contribution to the development of standards for the enumeration of CTCs. Because of the loss of EpCAM expression in CTCs during the EMT process, its enrichment/capture technology relies on EpCAM, which has a low sensitivity and efficiency (Yan et al., 2017). There are a few other CTC detection methods in meta-analysis, including RT-PCR that uses mRNA expression of epithelial markers like EpCAM or CKs to determine the status of CTCs in some studies (Yan et al., 2017). The median agreement between academic readers and VC for the CTC definition (no CTC vs. CTC) was 92 percent (range 69 to 97 percent) with a median of 0.83. (Range: 0.37 to 0.93). The definition of CTC was widely agreed upon by readers. In M0 the patients who have low CTC counts, there was a lower level of agreement (Yan et al., 2017). Before this indicator could be used clinically, it would require a standard or uniform protocol for CTC measurement. The current study had a number of flaws. Because most studies in this meta-analysis used patients receiving a single therapy without a negative control, this meta-analysis had some limitations. The complexity of patient characteristics and therapeutic details such as frequency, treatment, dose. Led to significant sample heterogeneity in some studies (Yan et al., 2017).

4.1.2 Positron Emission Tomography/Computed Tomography (PET/CT)

Patients with unclear or limited-use conventional imaging results, positron emission tomography (PET) and PET/CT may be employed to offer additional information. While FDG PET is not recently utilized in hospital practice to identify or evaluate axillary lymph nodes which is the aspects of ongoing research (Waks & Winer, 2019). Bone scintigraphy or diagnostic CT should not be substituted for FDG PET as an adjunct to conventional staging procedures. When conventional imaging results are inconclusive, PET/CT has already demonstrated effective way in breast cancer regimentation, response evaluation, and problem resolution. In these instances, FDG PET typically shows difficult-to-treat local or distant illness (Waks & Winer, 2019). Patients with advanced metastatic cancer, PET has shown unique capacity to assess the effect of chemotherapy. For near to 44% of patients with doubted to be the further occurrence, Eubank et al found that FDG PET changes treatment options, revealing a more widespread disease than CT and avoiding local surgical procedures for patients with metastatic cancer (Waks & Winer, 2019). The combination of FDG PET/CT and integrated PET/CT provides for much accurate further staging of breast cancer but PET alone, and this information is likely to be therapeutically useful in this situation. FDG PET and FDG PET/CT

can help asymptomatic cured breast cancer patients with growing tumor markers without no clinical symptoms (Waks & Winer, 2019). Compared to traditional imaging, FDG PET accurately diagnoses metastatic illness. When used to diagnose recurrent tumors in patients with elevated tumor marker levels, FDG PET/CT was 90% accurate and changed hospital settlement for 51% of patients. FDG PET/CT is more sensitive, specific, accurate, and predictive than CT alone (Waks & Winer, 2019). For staging recurrent or metastatic breast cancer, FDG PET and PET/CT is most useful. Currently, these are the only clinical uses of FDG PET/CT in breast cancer for which Medicare and Medicaid are routinely reimbursed (Waks & Winer, 2019). New evidence advised that FDG PET/CT can be useful in the assessment of local nodal spread in LABC also advanced axillary disease. Now only FDG also fluoride PET are utilized clinically. Studies in the future may use tracers over FDG, such as 18F fluorestradiol by which image estrogen receptor can be expressed, to better view tumor biology (Waks & Winer, 2019).

4.1.3 Magnetic Resonance Imaging (MRI)

Breast cancer detection in the clinic typically begins with mammography or ultrasound. Researchers claim that imaging with magnetic resonance spectroscopy (MRI) reveals additional details about the body (Aristokli et al., 2022b). In terms of allover sensitivity and specificity, MRI had 94.6 percent (range 85.7 percent–100 percent) and 74.2 percent (range 25 percent –100 percent), respectively, while mammography had 85.5 percent (range 62.9 percent–98.8 percent) (Aristokli et al., 2022b). An ultrasound's overall sensitivity and specificity were found to be 67.2 and 76.8 per cent, respectively (ranging from 26.9 per cent to 87.5 per cent) (Aristokli et al., 2022b). MRI (CE-MRI) also showed a 90.5 percent (range 80.9 percent –100 percent) and 52.6 percent (range 15% –76.1 percent) overall sensitivity and specificity for CE-MM, while CE-MRI showed a 91.5 percent (range 81.9 percent –93.8 percent) and a 64.7 percent (range 43.7 percent –85.7 percent) allover sensitivity with specificity for CE-MRI. MRI has the highest sensitivity, regardless of breast type, density, or history, while mammography has the lowest sensitivity (Aristokli et al., 2022b). The correlation of US and MRI or MM and MRI or MRI + MM + US increases sensitivity even more. Based solely on breast density, US was found to be the most accurate method for determining the tumor's size, type and history (Aristokli et al., 2022b). It is critical to identify the best method for breast cancer screening, which will improve cancer management. When compared to using modalities alone, combining techniques improves diagnostic ability. Using

CE-MM in dense breast tissue when MRI is contraindicated is a viable option, as it is with high sensitivity that is in the type of detecting the breast cancer (Aristokli et al., 2022b).

4.1.4 Polymerase Chain Reaction-Quantitative (PCR)

As the main cause of cancer in women worldwide, breast cancer is a major health concern. Prognosis depends heavily on exact timely treatment. Breast cancer screening can be done using clinical diagnostic methods, but an accurate diagnosis of the disease remains a critical need (Aristokli et al., 2022b). The detection of four sEV-derived mRNAs which are PGR, ESR1, ERBB2 and GAPDH, by four tiny extracellular vesicles (sEVs) using 4-plex digital PCR is described here. (Aristokli et al., 2022b). Including and except the ML models, researchers compared the diagnostic results. Results show that ML-assisted analysis can improve breast cancer diagnosis even with a single marker, and that combination of biomarkers including a suitable ML diagnostic model can also improve diagnostic performance (Aristokli et al., 2022b). Breast cancer diagnosis can be significantly improved using multiple gene expression profiles (sEV-derived mRNA) and ML, which gives excellent combination of markers (Aristokli et al., 2022b). It is possible to measure four sEVs mRNAs simultaneously and compare their relative expression levels using the multiplex ddPCR. Breast cancer diagnostic models were constructed using data from four-plex ddPCR in different groups A combination of sEV-derived mRNA analysis and machine learning (ML) has never been used before for breast cancer detection according to (Aristokli et al., 2022b). ML model requires the development of a 4-plex ddPCR assay. Optimizing probe concentrations and annealing temperatures improves droplet cluster dispersion, which is required for multiplex detection (Aristokli et al., 2022b). The ddPCR assay has a high sensitivity for multiple target detection when performed under optimal reaction conditions. Furthermore, detection limits of PGR, ESR1, and ERBB2 mRNAs are 27; 20, and 5, respectively, per reaction for the three mRNAs under consideration. As demonstrated by the findings of this experiment, the 4-plex ddPCR provides good levels of stability in terms of LOQ and CV when it comes to GAPDH gene quantification (Aristokli et al., 2022b). In order to properly interpret experimental data, proper SEVs sample preparation is essential because of the high soluble protein and lipoprotein concentrations in plasma, and because of the little amount of SEVs present and the low yield of RNA extraction. Ultracentrifugation is demonstrated that the most successful approach for isolating EVs from plasma when compared to the other six regularly used methods of EV separation (Ming et al., 2020) and (Tian et al., 2020). Ultracentrifugation is capable of extracting high purity sEVs, as evidenced by the characterization of sEVs performed in

accordance with the MISEV criteria. The efficiency with which sEVs RNA can be extracted continues to be a problem (Ming et al., 2020). The simultaneous three unique detection sEV-derived mRNAs helps the separation of healthy, benign, and non-cancerous groups is impossible to achieve without the assistance of ML. Multimodality detection, on the other hand, has been shown to improve the diagnostic efficiency of distinguishing breast cancer patients from healthy people, but the improvement of the diagnostic efficiency of separating breast cancer patients from benign also non-cancer groups significantly has not been shown (Ming et al., 2020). The need for a diagnostic model based on ML to improve breast cancer detection is therefore even greater. sEV nucleic acid biomarkers can be detected and quantified using this strategy's by which specific RNA sequences can be flexible (Aristokli et al., 2022b). Immuno-ddPCR for single sEV protein profiling can be enhanced by integrating this multiplex digital quantification technology with other technologies. There is also the computer model known as machine learning (ML) that can be used to learn from a wide variety of data sets. As a result, the method will pave the way for better cancer diagnosis in the future (Aristokli et al., 2022b).

4.2 Treatment Options

4.2.1 Chemotherapy

Recent advances in the use of cytotoxic chemotherapy both with the patient with advanced and early-stage breast cancer have been made possible by many landmark studies that is demonstrable survival improvements for novel medicines in the previous decade (Hassan et al., 2010). Despite these advances, it is impossible to acknowledge the best possible way of action for a given patient based solely on a literature review or a decision-making algorithm (Hassan et al., 2010). Understanding the molecular biology of breast cancer provides new avenues for developing new treatments. Patients with breast cancer could benefit from personalized treatments that consider their specific molecular characteristics (Hassan et al., 2010). Adjuvant chemotherapy will be spared for a group of patients whose health is improved by better use of a panel of biomarkers (Hassan et al., 2010). This will allow to develop more personalized treatments. It will be simpler to devise novel treatment regimens for people who are not being benefited from previous therapies if we have a better grasp of tumor biology (Hassan et al., 2010). As a result of the introduction of new and revolutionary medications that have been demonstrated to be beneficial in clinical trials, as well as advances in tumor biology, the outlook for breast cancer patients has improved significantly, both in the adjuvant and metastatic settings (Hassan et al., 2010). Patients who have low risk of further occurrence for

those adjuvant systemic therapies like endocrine therapy, anti-HER2 therapy, and chemotherapy, are effective in reducing the risk of distant and local further occurrence (Bonadonna & Valagussa, 2010). The extensive use of adjuvant systemic cure breast cancer has resulted in a reduction in the death rate for the disease (Bonadonna & Valagussa, 2010). Adjuvant cytotoxic chemotherapy regimens have changed over time, from single alkylating drugs to polychemotherapy regimens integrating anthracyclines and taxanes, among other agents. There have been considerable developments in adjuvant systemic therapy in general, and adjuvant chemotherapy, throughout the last several decades (Bonadonna & Valagussa, 2010). Despite the fact that predictive variables (hormone receptor expression and HER2 overexpression) have been widely used to guide endocrine therapy and anti-HER2 therapy, predicting the effectiveness of chemotherapy has shown to be more difficult to predict (Bonadonna & Valagussa, 2010). Multiparameter gene expression tests are currently being utilized in randomized trials to better correctly select patients those are prone to be benefited from adjuvant chemotherapy, allowing for more precise patient selection. When CMF was administered in full or near-full doses (85% or more of the planned dose), it was found to be effective (Bonadonna & Valagussa, 2010). Only 77% of patients who received 12 cycles of CMF at this dose level as adjuvant therapy survived five years without relapse, compared to 45% of those who received only radical mastectomy. The 5-year survival rate without relapses was 48%, while the 5-year survival rate with relapses was 67% in the subgroup that received less than 65% of the planned dose (Bonadonna & Valagussa, 2010). Compared to a control group, these results are strikingly similar. Axillary lymph node involvement, but not menopausal status, influenced the five-year results for each dose level. The clinical benefit of combination chemotherapy requires the administration of the full dose, according to findings (Bonadonna & Valagussa, 2010). Surgery, radiation, and hormone therapy is now routinely used in conjunction with neoadjuvant chemotherapy and taxanes to help patients having IBC have already gone through a mastectomy (Sinclair & Swain, 2010). It has been shown that obtaining a pathologic fully reacts to neoadjuvant chemotherapy has prognostic significance in patients with locally advanced breast cancer and IBC (Sinclair & Swain, 2010). Despite encouraging results, high-dose chemotherapy is still an experimental treatment that must be thoroughly studied in the future (Sinclair & Swain, 2010). In IBC, the angiogenesis promoter vascular endothelial growth factor (VEGF) is abundantly expressed, making angiogenesis pathway a promising therapeutic target. To develop more targeted therapies to enhance patient outcomes in this aggressive type of breast cancer, researchers must first get a deeper knowledge of the complicated biology of IBC (Sinclair & Swain, 2010).

4.2.2 Radiotherapy

Breast conserving therapy may not necessitate postoperative radiotherapy that covers the entire breast. For many women, post-operative radiotherapy deters them from pursuing a breast-conserving procedure and instead opts for mastectomy because of the time and resources required (Vaidya et al., 2004). Many of these disadvantages could be alleviated whether radiation may be given immediately after surgery. However, local recurrence in the breast is when the breast-conserving surgery is found to most frequently occur right in front of the primary tumor, although most of mastectomy samples have tiny cancers scattered throughout the breast, only the tumor itself may require radiotherapy (Vaidya et al., 2004). In order to complete the whole local treatment in one session, clinical experts have deployed new technologies to deliver radiation to the most at-risk areas (Vaidya et al., 2004). The premise is based on the rationale and various delivery ways of intraoperative radiotherapy. The time, money, and breasts could all be saved if current randomized trials support this method (Vaidya et al., 2004). As adjuvant lymph node irradiation following radical surgery, as irradiation treating chest wall recurrence, and as palliative therapy for breast cancer metastases in bones, lungs, brain, it has been proven to be effective (Krug et al., 2017). However, breast irradiation as a conservative treatment has received attention. To reduce the risk of recurrence after surgery, radiotherapy is used in breast conservative treatment. Irradiation techniques, effects and side effects, the risk of radiation-induced cancer, and the indications for this treatment (Krug et al., 2017). This is a treatment that has been tried and tested in Japan. In terms of local control and survival, both breast conservation treatment and a modified mastectomy were found to be equally effective. Radiotherapy can treat recurrent or advanced breast cancer and alleviate symptoms in many cases. 192-Ir brachytherapy with a high dose rate showed excellent local control of tumors that were previously untreatable with external radiation (Krug et al., 2017). Hyperthermia and radiotherapy are also effective in treating superficial tumors (tumors with a depth of less than 3 cm). Radiation therapy has shown complete remission for years in patients with lung and brain metastases (Krug et al., 2017). Patients with bone and brain metastases receive 30 Gy/2 wks of radiotherapy to relieve symptoms. The high success rate of radiotherapy in relieving symptoms should be communicated to oncologists. There has been a drastically betterment in the prognosis of women with breast cancer since the advent of multimodal treatment options (Krug et al., 2017). In a vast range of hospital situations, from DCIS to advanced breast cancer, radiotherapy is an essential element of multimodal treatment concepts that are used to both cure and alleviate symptoms (Krug et al., 2017).

4.2.3 Non-Surgical Ablation

Non-surgical ablation methods include MRgFUS (MR guided Focused Ultrasound). In a previous clinical trial comparing MRgFUS to local treatment, it found to be effective (Furusawa et al., 2007). MRFUS was utilized to treat 21 new invasive and benign ductal carcinoma patients. A core-needle biopsy was used to diagnose. Patients were all treated with Signa Excite 1.5T MRI and ExAblate 2000 version 2.6/4.1 FUS (Furusawa et al., 2007). Not all 21 MRgFUS patients were irradiated. Metastases of Lymph node examined by dissection or sentinel lymph node biopsy. Re-MRgFUS was utilized to treat recurrences or aberrant areas of residual malignancy after surgery. All 21 patients were female. The average age is 54. (Range: 34-72) (Furusawa et al., 2007). The tumor has a diameter of 15 mm on average (range: 5-50). As for the number of treatments, single treatment was received by 17 patients and four patients received a double treatment. The average amount of time spent observing is 14 months (range: 3-26) (Furusawa et al., 2007). A single case of pure mucinous carcinoma recurrence was observed. For the remaining 20 cases, MRI revealed no signs of recurrence. In two cases, skin burns were discovered. The tumor had left a dimple in the patient's skin. MRgFUS is better tool for control the breast cancer locally, but the patient for whom it is indicated must be carefully selected. Additionally, patients who were treated solely with MRgFUS must be monitored for long time (Furusawa et al., 2007). Breast cancer treatment is evolving from surgical excision to ablative local control to meet patient desire for less intrusive techniques (Noguchi et al., 2006). Under general anesthesia, RF ablation was tested on patients with invasive or non-invasive breast cancer. There was no doubt in any patient's mind that he or she had a localized lesion before RF ablation (Noguchi et al., 2006). The patient had the choice of a total mastectomy with sentinel lymph node biopsy or axillary lymph node dissection. The histology of tumor that had been surgically excised was investigated using H&E and NADH staining. RF ablation-related complications were avoided in ten of the patients (Noguchi et al., 2006). Tumors ranged in size from 0.5 to 2.0 centimeters on average. On histological examination of the removed tissue, which was stained with H&E, researchers discovered a range of tumor cell changes, from coagulation necrosis to the appearance of normal tumor cells. That was without staining of tumor cells which are viable in the RF-ablated area by NADH-diaphorase, which was found in all patients (Noguchi et al., 2006). When treating localized cases of invasive or noninvasive breast cancer, RF ablation appears to hold promise as a minimally invasive ablation technique. In the meantime, more research is needed before RF ablation used to cure patients with small breast cancers (Noguchi et al., 2006). An MRI scan was done before and after the ablation. Pathologists analyzed the extracted specimens using

haematoxylin-eosin and nicotinamide adenine dinucleotide diaphorase staining (Ohtani et al., 2011). One RFA treatment killed all tumor cells in 40 patients. The overall ablation success rate was 87.8% (36/41). The only treatment-based complication was a superficial burn in one case. In 25/26 (96.2%) of the cases, the tumor was no longer enhanced on MRI after RFA (Ohtani et al., 2011). In one case, an MRI showed a possible presence of residual cancer, which was confirmed pathologically. MRI could be a useful tool for assessing therapeutic efficacy. RFA may be an alternate therapeutic chance for people with early-stage breast cancer who do not choose to undergo breast-conserving surgery. Diagnostic and therapeutic advances in the early detection and treatment of breast cancer have made significant strides in the recent decade (Ohtani et al., 2011). Currently, less intrusive ways of breast cancer therapy are being used more often in the United States. Several major randomized studies show no difference in survival between BCS and mastectomy for women with primary breast cancer. For clinically node-negative breast cancer, sentinel lymph node biopsy replaced with axillary lymph node dissection, allowing for better staging and less morbidity (Ohtani et al., 2011). There is a push to replace minimally invasive substantial advances in breast cancer treatment, surgery is no longer required to remove the main tumor. The main tumor can be removed by cryosurgery, laser ablation, thermoablation, or high-intensity focused ultrasound, although radiofrequency ablation (RFA) seen to be the most challenging. Cosmetically acceptable breast preservation is a primary goal of breast-conserving treatment (Ohtani et al., 2011). Tumor treatment without resection has a lot of appeal due to the fact that the amount of tissue removed has an effect on the cosmetic results. This is attributable to advances in detection modalities like as magnetic resonance imaging (MRI) and the widespread use of screening mammography (Ohtani et al., 2011). For primary breast cancer, however, RFA is not yet widely accepted as a treatment option due not having evidence supporting its routine use as a standard therapy, particularly in terms of achieving complete tumor cell death throughout the ablated area. RFA may use as a local treatment option for early breast cancer (Ohtani et al., 2011). If RFA was performed immediately or 1–2 months after RFA, breast-conserving surgery (Bp 1.5 cm), performed under general anesthesia or local anesthesia, was performed. There were 7 of the 41 patients who underwent surgery immediately following RFA under general anesthesia (Ohtani et al., 2011). Local anesthesia and sedation were used in the remaining 32 patients to perform RFA after which the remaining breast-conserving surgery was performed 1–2 months after RFA. All but one patient underwent a single RFA treatment. The only treatment-related complication was a superficial burn above the ablated area in one patient (Ohtani et al., 2011).

Chapter 5: Recent Advancements in Breast Cancer Detection

5.1 Gene Editing Technologies in Breast Cancer Detection

The deadly nature of cancer claims the lives of an estimated 8.5 million people every year, according to research (Hazafa et al., 2020). CRISPR-regulated protein-9 (Cas9), a strong element in the therapy of cancer cells, RNA-domain containing endonuclease-based genome engineering has recently been proved to be highly precise, accurate, not time consuming, and cost-effective with little off-target effects (Hazafa et al., 2020). CRISPR/Cas9, a novel genome-editing method, has showed promise in reducing tumor target genes and identifying new ones in solid tumors. Inhibitors and chemotherapies drug resistance genes were identified as targets of CRISPR/Cas9 in our study of tumor cell development in the breast, lung, liver, colorectal, and prostate. Current issues and roadblocks were examined, as well as recommendations for the future for a clearer picture (Hazafa et al., 2020). Due of tumor heterogeneity, researchers have had difficulty finding effective therapies for breast cancer. Despite their efficacy in breast cancer research, 2D cell culture techniques cannot represent the body's heterogeneity (Ebrahimi et al., 2022). 3D cultivation of tumor cells and breast cancer organoids has facilitated the development of novel medications and biomarkers in breast cancer research (Ebrahimi et al., 2022). The CRISPR/Cas9 method has also enabled more extensive research of tumor behavior in physiologically relevant models (Ebrahimi et al., 2022). Several human malignancies, including ovarian, prostate, and breast, have been shown to express growth differentiation factor 15 (GDF15), a TGF-family member (Li et al., 2018). Nonetheless, GDF15's significance in cervical cancer is unknown. GDF15 expression was detected in normal cervix and cervical cancer lesions using antibody-based immunohistochemistry. Formation of tumor assays, growth curves, and flow cytometry used to investigate GDF15 expression in cervical cancer cells (Li et al., 2018). In these tests, the cell cycle, MAPK/ERK signaling, and PI3K/AKT signaling were studied. If C-myc had a specific binding site on the GDF15 promoter, an immunoprecipitation assay was conducted. GDF15 and ErbB2 were found to be linked by means of inhibitor treatment and immunoprecipitation assays. During cervical carcinogenesis, GDF15 expression increased over time (Li et al., 2018). When cervical cancer cells were cured with exogenous rhGDF15 or when gene editing technology was used, the proliferation of the cancer cells increased both in vitro and in vivo also transition from G0/G1 to S phase of the cell cycle was dramatically accelerated (Li et al., 2018). Expression of CyclinD1 and CyclinE1 was elevated in GDF15-overexpressing and GDF15-treated cervical cancer cells, although the expression of p21 was reduced in both conditions. C-myc played a role in the positive response

of GDF15/C-myc/GDF15 through attaching to the E-box motifs in the promoter of GDF15, which resulted in the formation of a loop with positive feedback (Li et al., 2018). GDF15 and ErbB2 were shown to form a protein complex in cervical cancer cells. In conjunction with ErbB2, GDF15 increase the development of cervical cancer cells by upregulating CyclinD1 as well as CyclinE1 while reducing p21 with the PI3K/AKT as well as MAPK/ERK signaling pathways according to (Li et al., 2018). An unstable genomic event called chromothripsis can lead to the development of cancerous chromosomal aberrations. DNA stitching can result in extensive translocations and copy-number changes when transcription factors (TFs) frequently interact with their targets over long distances (Lin et al., 2020). Chromothripsis initiation has been studied, but few studies have examined how transcription factors (TFs) plays role in this process for tumor propagation. Whole genome sequencing data from the Cancer Genome Atlas (TCGA) cohort of breast cancers was used to investigate chromosomal rearrangements across and within individual chromosomes (Lin et al., 2020). The binding sites for estrogen receptor (ER) in the MCF-7, T47D, and MDA-MB-134 breast cancer cell lines were identified with univariate K-means clustering. By employing nanopore sequencing technology, it was possible to confirm the high frequency of rearrangements discovered within ATC loci on 17q23 also an ER hub on 20q13 (Lin et al., 2020). Breast cancer cell lines along with patient-derived circulates breast tumor cells were used to investigate the effects in pharmacological inhibition with a potentially druggable target gene on the 17q23 chromosome (Lin et al., 2020). Inter- and intra-chromosomal rearrangements of these areas appears faster in ER-positive cancers also in ER-negative tumors. Sites for ER-binding proteins can be found on these five 17q regions, as well as on other chromosomes, were frequently found to be in or near the regions where rearrangements occurred. Consistent upregulation in 96 chromothriptic loci in advanced luminal tumors was linked to this chromothriptic event (Lin et al., 2020). An ER hub on 20q13 coordinately regulates a subset of these 17q23 loci through long-range chromosome interactions, according to genome-editing analysis. Phenothiazine antipsychotics can target Tousled alike Kinase 2 (TLK2), a locus plays a role in damage of DNA checkpoint control (PTZs). Antiproliferative effects of PTZs were more prominent in TLK2-positive cells than in TLK2-negative cells (Lin et al., 2020).

5.2 Screening Mammography

Specific mortality can be reduced by detecting breast cancers while they are still treatable through screening. In the United States, mammography, digital breast tomosynthesis, ultrasound, and magnetic resonance imaging (MRI) are all used for breast cancer screening

(Fiorica, 2016). The recent screening guidelines in the United States were developed by five major medical organizations (Fiorica, 2016). Breast cancer screening in women remains a contentious issue due to a lack of consensus in those guidelines. The Breast Imaging Reporting along with Data System lexicon, which corresponds to show hospital management for mammography screening, the data allows the clinician to tailor breast cancer screening to each individual patient (Fiorica, 2016). Detection of breast cancer in its earliest stages is made possible by routine mammography screening, but TNBC detecting is hard and has a less survival rate than non-TNBC when found in its earliest stages (Bayard et al., 2021). A 40 percent having higher breast cancer mortality rate is attributed to the fact that TNBC is as common in African American (AA) women as in White American (WA) (Bayard et al., 2021). To address breast cancer disparities, screening mammograms should be studied. Results for TNBC patients who received treatment at two metropolitan cancer centers in the northeast and Midwest from 1998 to 2018 were analyzed (Bayard et al., 2021). 756 cases of TNBC, 301 of which (39.8%) were detected on mammograms. TNBC was detected in 46 percent of the 189 AA patients and 38 percent of the 460 WA patients ($p = 0.16$). Screen-detected disease was detected in only 25.3% of the 257 TNBC cases under the age of 50, compared to 47.3% of the 499 TNBC cases over the age of 50. More than 73% of screen-detected tumors were T1 lesions, compared to 32% of those that were not (Bayard et al., 2021). Those with screen-detected TNBC were prone to be node-negative (51,9% vs. 40,4%; p 0.0001) than those without it. A statistical significant difference in 5-year allover survival between screen-detected TNBC and nonscreen-detected TNBC (p 0.0001) (Bayard et al., 2021). Patients with a history of alcoholism were found to be the most affected. For patients in both cities, screening-related survival rates were nearly identical. Screening mammograms can reduce breast cancer disparities in African American women by detecting TNBC at an early stage (Bayard et al., 2021).

5.3 Electrochemical Cytosensors

Cancer patients' venous blood can be tested for the presence of circulating tumor cells (CTCs) originating from primary tumor (Vajhadin et al., 2020b). With the rapid growth of CTC monitoring in blood samples, it has significant potential for the detection also cure of metastatic breast cancer. For sensitive detection enumeration, electrochemical cytosensors are electrochemical biosensors of specific cells utilizing least invasive approaches (Vajhadin et al., 2020b). With a focus on electrochemical cytosensors in recent advances in the detection of CTC from breast cancer. Using these cytosensors, these platforms can identify breast cancer

cells. Also discussed are ways to boost signals and create re-usable cytosensors that are electrochemical in nature (Vajhadin et al., 2020b). Accurate diagnosis is critical to determining of the disease's stage and designing an appropriate treatment plan include electrochemical immunoassay for the identification of breast cancer cells that concurrently assesses two co-expressed tumor markers, human mucin-1 and carcinoembryonic antigen, on the surface of cancer cells (Li et al., 2010). According to the results of the experiments, an electrochemical reaction can only be noticed when both tumor markers are present on the surface of the tumor cells. It is possible to quickly identify between cells like acute leukemia cells CCRF-CEM along with normal islet beta cells and the breast cancer cell MCF-7 using this technology (Li et al., 2010). It shows that the created cytosensor may be utilized to selectively monitor MCF-7 breast cancer cell line with good repeatability and a low detection limit, so increasing its therapeutic potential even more (Li et al., 2010). It estimate breast cancer is the second most fatal malignancy in women, and that its metastasis is the leading cause of cancer-related sickness and death (Vajhadin et al., 2020a). Patients with cancer who have venous blood drawn can be examined for the presence of circulating tumor cells (CTCs), which are those cells that have spread from their main tumor. The monitoring of CTCs in blood samples has expanded tremendously in recent decades, and it has enormous potential in use of detection and treatment in metastatic breast cancer, particularly in the elderly (Vajhadin et al., 2020b). When it comes to electrochemical cytosensors, which are electrochemical biosensors used in sensitive detection along with enumeration of targeted cells using less invasive methods, advantages of electrochemical biosensors are like simplicity, low cost, and a low limit of detection can be found in electrochemical biosensors (Vajhadin et al., 2020b). Developments in detection of the CTC from breast cancer, along with particular emphasis upon electrochemical cytosensors, these platforms are capable of identifying breast cancer cells thanks to the use of these cytosensors. Also available are techniques for boosting signal strength as well as the development of re-usable cytosensors that are electrochemical in nature. Biomarkers for the identification of breast cancer cells, as well as biorecognition components, are being investigated (Vajhadin et al., 2020b). CTCs may be identified using an ultra-sensitive electrochemical detection approach that use lessen graphene oxide/gold nanoparticle like a support material and CuO nanozyme as a catalyst to identify the presence of the cancer cells. It was discovered that when the MUC-1 protein was overexpressed on the membranes of MCF-7 cells and an aptamer for MUC-1 was utilized, an electrochemical cytosensor could be used to detect the presence of tumor cells (Tian et al., 2018). Using an ultrasensitive electrochemical cytosensor that combines a CuO nanozyme nanoprobe, the researchers were able to identify

CTCs for the first time. Under optimal experimental settings, the proposed cytosensor demonstrated excellent performance against MCF-7 circulating tumor cells (Tian et al., 2018). A huge detection range of 50 to 7 103 cells mL 1 was achieved with good selectivity and reproducibility, while detection limit to 27 cells mL 1 was reached with acceptable selectivity and reproducibility. It is simple for cytosensors to distinguish CTCs from genuine blood samples when MUC-1 and MUC-1 aptamer are used together (Tian et al., 2018).

5.4 Imaging and Microchip Devices

Circulating tumor cells (CTCs) incredibly rare also in presence of them it can indicate a poor prognosis with high risk of metastasis. Due to several technical difficulties, CTCs have not been thoroughly studied despite their promising clinical applications (Kim et al., 2014). Because of the epithelial-to-mesenchymal transition, recent CTC detection ways use the epithelial marker EpCAM, but increasing prove suggests that CTCs indicate heterogeneous EpCAM expression as a result of this transition (EMT) (Kim et al., 2014). Microchip filters with 3-dimensional flow which can be separated heterogeneous populations of cells with markers for CTCs are described in this study. Mammosphere-cultured breast cancer cells were used to select a target because of their EMT-inducing properties (Kim et al., 2014). Caveolin1 (CAV1) expression is increased in these cells, but EpCAM expression is decreased. Increased throughput of several orders of magnitude is possible with the new device, which utilizes a CAV1-EpCAM conjugated bead (Kim et al., 2014). Even more importantly, the increasing capture yield from metastatic breast cancer patients also cells gained using numerous EMT markers is enabled by this platform. Understanding these EMT regulated phenotypes may lead to boost detection methods and the development of effective cure and prevention strategies for cancer metastasis (Kim et al., 2014). Microchip arrayed nanostructured FPI microchips were used to detect a cancer biomarker without the need for a label. The receptor was a mouse anti-human PSA monoclonal antibody (mAb) (f-PSA) (Muluneh & Issadore, 2014). The top detection range of current nanostructured FPI microchips may be altered dynamically by adjusting the quantity of PSA mAb bound on the sensor surface in that test. The control studies show that our immunoassay procedure can identify the cancer biomarkers trace levels in complicated biofluids (Muluneh & Issadore, 2014). The arrayed nanostructured FPI microchip dependent platform may be an attractive technological instrument for point-of-care diagnostics as well as anticancer medication screening and development (Muluneh & Issadore, 2014). Micro-magnetic sensors and actuators have emerged as extremely effective instruments in the detection and monitoring of cancer. The miniaturization and integration of these technologies

into microfluidic systems makes it possible to perform molecular diagnostics in clinical settings more readily (Muluneh & Issadore, 2014). Magnetic nanoparticles, which take advantage of biological material's naturally low magnetic susceptibility, may be used to identify molecular targets in unprocessed clinical samples (such as blood or sputum) with great sensitivity, a technique known as magnetic resonance imaging (MRI) (Muluneh & Issadore, 2014). The use of magnetic microchip-based diagnostics has made it feasible to isolate and detect uncommon cells, as well as to quantify sparse soluble proteins, which were previously impossible. Magnetically labeled biomarkers and their clinical applications may be detected using microchips, and these techniques are also applicable in clinical settings (Muluneh & Issadore, 2014).

5.5 Diffusion-Weighted Imaging (DWI)

According to Kishimoto et al., 2020, 94 individuals also surgically proven malignant breast lesions with undergone HR-DWI and high-resolution CE-MRI. Radiologists blinded with the final diagnosis recognized, characterized, and assessed the lesions using HR-DWI and BI-RADS descriptors. After that, the HR CE-MRI was assessed (Kishimoto et al., 2020). The morphological approaches were compared using Kappa statistics. Readings by Reader B revealed 81 mass lesions also 33 non-mass lesions (Kishimoto et al., 2020). Divergent viewpoints dominated the rim enhancement assessment. Enhancement/signals were moderate to good (kappa = 0.34–0.49). Variable agreement in heterogeneous, clumped, and condensed-ring patterns Size assessment correlated strongly with mass and non-mass lesions (Kishimoto et al., 2020). In a breast diffusion-weighted imaging experiment, prototype simultaneous multi-slice single shot EPI is compared to an existing readout segmented echo planar imaging (ESI) procedure. Between September 2017 and December 2018 and 26 women with breast cancer were scanned with rs-EPI and SMS-ss-EPI at 3 T (Sanderink et al., 2021). Diffusion-weighted imaging can help diagnose breast cancer and assess treatment effects (DWI). The b-value map uses thresholder DWI images to obtain crisp pictures of prostate lesions by changing the window width and center (Zhao et al., 2019). A study comprised 25 patients with invasive ductal breast cancer who completed preoperative MRI exams, which included DWI at 3T, before undergoing surgery (Zhao et al., 2019). The prevalence of breast cancer in women has climbed considerably in recent years, particularly among young women. For radiologists who work with DCE-MRI pictures, segmenting DCE-MRI images for accurate diagnosis and detection of breast cancer is therefore a critical task to perform (Khaled et al., 2022). Thresholding is a simple approach for picture segmentation that anybody may utilize. When it

comes to breast DCE-MRI analysis for lesion identification and segmentation, radiologists all accept that optimizing using a multi-level thresholding approach is critical in distinguishing breast lesions from dynamic DCE-MRI (Khaled et al., 2022). Following the use of the anisotropic diffusion filter to denoise MR images, preprocessing is performed in order to adjust for Intensity Inhomogeneities (IIHs). Segmenting the preprocessed MR images is accomplished using the SPBO algorithm. After that, all lesions are removed from the segmented pictures and plotted on the original magnetic resonance images as a result of the procedure (Khaled et al., 2022). The suggested technique was used to evaluate sagittal T2-weighted DCE-MRI slices from 50 individuals who had had a T2-weighted DCE-MRI scan. The accuracy of 99.44 percent, the sensitivity of 96.84 percent, and the Dice Similarity Coefficient (DSC) of 93.414 percent are all achieved by the suggested automatic segmentation technique. Breast DCE-MRI segmentation is employed for lesion detection, and multi-level thresholding with student psychologically based optimization is applied for lesion detection (Khaled et al., 2022). Using Dynamic Contrast Enhanced Magnetic Resonance Imaging, breast cancer (BC) diagnosis can be made more accurate, according to the Journal of Biomedical Signal Processing and Control (DCE-MRI). Because DCE-automatic MRI depends on characteristics retrieved from lesions, precisely segmenting lesions is required (Khaled et al., 2022). Automating 4D DCE-MRI lesion segmentation is predicted to minimize effort, observer variability, and increase diagnostic accuracy. Despite the dataset's complexity, their suggested ensemble technique beats previous methods, with a mean Dice Similarity Coefficient (DSC) (Khaled et al., 2022). 107 radiomic characteristics were extracted from 111 patients carefully annotated and separated into discovery and test sets (Militello et al., 2021). A feature calibration also pre-processing stage chose features with high reliability and no redundancy. To build a prediction model, a Support Vector Machine (SVM) was trained using multiple unsupervised feature selection approaches and then studied (Militello et al., 2021). AUROC was used to assess the prediction model's accuracy. The test used withheld data. The strongest enhancement phase SVMs and SVM-based models performed best on the blinded test set, yielding encouraging results when assessing whether a breast lesion was malignant or not (Militello et al., 2021). To accurately segment the breast and tumor using DCE MRI is crucial in the diagnosis of breast illness. They demonstrate an attention-guided joint-phase-learning network that can autonomously segregate the breast and malignancies (Qiao et al., 2021). Instead of the conventional multichannel inputs, a novel network with five distinct streams was designed. In order to depict breast tumor dynamics, a novel time-signal intensity map was created using DCE-MRI pixel values (Qiao et al., 2021). The fusion of the streams allowed for

the incorporation of all tumor data. Weighted loss was used to segment breast tumors. With a global feature vector, a self-attention module is employed to enhance breast areas and suppress non-breast tissue characteristics in the net's self-awareness algorithm (Qiao et al., 2021). Also, breast and tumor segmentation performed better than previous multi-channel networks by 0.92 and 0.86 Dice coefficients. The model was expanded to 59 examples from two distinct MRI machines and attained a Dice coefficient of 0.83, demonstrating its resilience. Using autonomously created masks may improve in accuracy and speed of breast tumor diagnosis (Qiao et al., 2021).

5.6 Computer-Aided Diagnosis (CAD)

It has been found that CAD-assisted reading increases sensitivity but decreases specificity. Also, the patients with CAD have a lower recall rate. There were 986 recalls and 49 cancers among 12,860 mammograms (Dromain et al., 2013). There was a 19.5 percent increase in the number of cancers detected by CAD alone. Birdwell et al. looked at 8682 patients in the future. Recalling 10% of the patients yielded 8 percent of findings and 7 percent of the cancers that were uncovered where 2 of the 29 cancers found. In a working clinical environment, Ko et al. translate 5016 mammograms without and with CAD. With the use of CAD, the recall rate went from 12 percent to 14 percent. There were six percent of the 107 biopsy patients who had CAD (Dromain et al., 2013). 48 CAD and CAD-free cancers found, the radiologist found 43 and 45, respectively. The radiologist found 8 cancers that CAD missed (Dromain et al., 2013). Gur et al observed no difference in cancer diagnosis between radiologists using CAD also who did not. As recently as 2007, another study by Fenton et al. found that the use of computed tomography (CAD) in screening mammogram interpretation was linked to lower accuracy, a higher rate for biopsies, and was not clearly linked to a higher detection rate for invasive breast cancer (Dromain et al., 2013). Based on a review of 222.135 women's screen-film mammograms, CAD raised sensitivity from 80.4 to 84.6 percent, lowered specificity from 90.2 to 87.26 percent, and increased the number of biopsies while lowering the likelihood of invasive cancer diagnosis by 12 percent (Dromain et al., 2013). *In situ* ductal carcinoma detection rates rose 34%. Because of these differences in detection rates, it has been suggested that the setting, volume of cases, many of radiologists dedicated to interpreting mammograms, and radiologists' experience with CAD are all factors that contribute to these discrepancies (Dromain et al., 2013). Small discoveries, radiologist attention, or intricate architectural design might induce false negative mammography. As an additional reviewer for screening mammograms, the radiologist benefits from using a computer-aided design (CAD) system

(Dromain et al., 2013). But computer-aided design must not disregard the radiologist's full mammography examination (CAD). Radiologists, not computer-aided design systems, should be the final arbiters of any image (Dromain et al., 2013). No studies showed an increase in sensitivity also cancer detection rate (CDR) when CAD was added but no significant differences were found in CDR and sensitivities between groups in this study (Henriksen et al., 2019). Only one study found a decrease in specificity when CAD was added to SR. The RR was observed to be different between the two groups in only one investigation. Except in two cases, CAD enhanced RR, sensitivity, and CDR (Henriksen et al., 2019). Sensitivity and CDR did not differ from DR. Studies with extended follow-up durations, high-volume readers along with digital mammography need to assess CAD's effectiveness (Henriksen et al., 2019). The CAD's sensitivity is determined by the results of a mammogram. According to three studies, CAD had a sensitivity rate > 90% for detecting malignant microcalcifications, whereas other findings had a sensitivity rate below 90% (Henriksen et al., 2019). Studies show, Microcalcifications were discovered by CAD in 90 percent to 100 percent of cases, whereas only 66 percent to 67 percent of masses were detected. In cases when carcinomas *in situ* are more easily detected than invasive tumors, CAD is the preferred method (Henriksen et al., 2019).

5.7 Deep Learning (DL)

On chest CT, malignant breast tumors frequently have an irregular form and no defined boundary. 85.7 percent of the 1249 preoperative chest CTs we evaluated were done following a breast cancer diagnosis. Internal test set, deep learning system recognized 96.5 percent of breast tumors with 13.5 FP/case and 96.1 percent with 15.6 FP/case, that was the first time that deep learning was used to detect breast cancer on the chest (Koh et al., 2022). Deep learning does not have any established metrics. It is tough to explain the sensitivity or FP rate for breast cancer detection on chest CT. The threshold candidate probability of 0.3 was applied for both of the internal along with external test sets. Internal and external test sets had sensitivities of 88.5 and 90.7 percent, respectively, when candidate probabilities of 0.4 were utilized as cutoff values (Koh et al., 2022). Greater the sensitivity, the more likely it is that FP cases will occur. As a result, it's critical to pick a cutoff value that strikes a balance between sensitivity and frame rate. A radiologist may miss small and subtle breast lesions during a screening because they are difficult to detect (Koh et al., 2022). For larger lesions, the deep learning algorithm performed better when we evaluated its performance based on lesion size. Algorithms were more sensitive to breast lesions in external sets than in internal sets because of greater breast

lesion mean size (Koh et al., 2022). Overall sensitivity for lesions smaller than 2 cm reached more than 90%, which is more than enough to detect small breast cancers. Deep learning can identify and classify objects using convolutional neural networks14 or single-phase detection methods (Koh et al., 2022). Chest and abdominal CT scans with two-phase detectors were employed in various studies to identify lung nodules and vertebral fractures. 20 Medical imaging does not frequently use RetinaNet for detection tasks. Research shown that RetinaNet outperformed the two-stage object detector in detecting mammography masses (Koh et al., 2022). Breast cancer diagnosis on chest CT using RetinaNet was evaluated. CT scans of the chest can identify inadvertent breast cancer. Deep learning may increase sensitivity of incidental breast cancer detection on chest CT (Koh et al., 2022). This work used a deep learning system to determine breast tumors on chest CT and confirmed the results in internal and external datasets. This study collected 1170 preoperative chest CT images for algorithm development (n = 1070), 100 internal tests and 100 exterior tests after a breast cancer diagnosis. Breast cancer detection using chest CT was developed and tested using RetinaNet. Averaging 13.5 false positives per case, the program accurately recognized 96.5 percent of the internal test cases. The exterior test set needed 116 FPs to detect 96.1 percent of the malignancies (Koh et al., 2022). The threshold candidate probability of 0.3 was applied for both internal and external sets of tests. According to the internal test set, 88.5 percent of cases were sensitive, whereas 90.7 percent of cases were sensitive with 5.24 FPs/case (Koh et al., 2022). The deep learning system correctly identified breast cancer on chest CT in both internal and exterior tests (Koh et al., 2022). Using deep learning algorithms to detect metastases, hematoxylin and eosin-stained tissue slices of lymph nodes from breast cancer patients might increase diagnostic accuracy and efficiency (Bejnordi et al., 2017). Participants, setting, and design. Deep learning algorithms for pathologist interpretation or challenge competition. Deep learning methods ROC analysis is used to detect whether a slide or picture has lymph node metastases (Bejnordi et al., 2017). Pathologists in the simulation exercise assessed the diagnostic as either certainly normal, possibly normal, or doubtful (Bejnordi et al., 2017). In a challenge competition, certain deep learning systems surpassed an experienced pathologist analyzing whole-slide photos without time limits. A clinical evaluation will be required to evaluate the method's clinical utility (Bejnordi et al., 2017).

Chapter 6: Current Advancements in Breast Cancer Treatment

6.1 Oncoplastic Treatment

Studies have shown that adjuvant treatment should be started immediately after initial treatment, according to current findings. Surgery for breast preservation is becoming more common, as is oncoplastic surgery (Dogan et al., 2013). In order to determine if these applications delay adjuvant treatment, further research is needed. A study included 288 breast cancer patients with surgery and who received adjuvant treatment at clinic (Dogan et al., 2013). Medical records were obtained that included information according to patient's age and BMI as well as any co-existing conditions, such as smoking and menopausal status. The number of chemotherapy cycles also the time between surgery and the conclusion of chemotherapy and radiotherapy all calculated (Dogan et al., 2013). Radiotherapy took an average of 3.9 months (SD) and chemotherapy took an average of 19.5 days (range, 13-41 days) (Dogan et al., 2013). Only an early wound problem after breast surgery delayed adjuvant chemotherapy. The interval between surgery and adjuvant therapy influences breast cancer survival. Adjuvant treatments can be started immediately following breast and axillary surgery, according to research (Dogan et al., 2013). Adjuvant treatments were not delayed in oncoplastic or breast conserving surgery patients. The initiation of adjuvant treatments necessitates cross-disciplinary cooperation (Dogan et al., 2013). Oncoplastic, BCS or breast conserving surgery is not proven to be beneficial in rigorous studies, despite widespread use of oncoplastic techniques around the world. However, consensus recommendations for clinical practice are needed to clarify the function of oncoplastic BCS in early breast cancer therapy (Rocco et al., 2021). Following a literature review, oncoplastic conserving surgery of breast should be preferred rather than normal breast conserving surgery due to the treatment of operable breast cancer in mature women who are eligible for breast conserving surgery (Rocco et al., 2021). With no randomized data and no standard instruments for measuring clinical results or patient values, oncoplastic surgery outcomes have little proof. Oncoplastic BCS received strong support from a third of the panel, despite some areas of disagreement. It's safe to assume that this reflects a consensus on the relative difficulty of these techniques, as well as the complications they entail, as well as their effect on patient well-being and financial resources (Rocco et al., 2021). Breast cancer patients have benefited greatly from oncoplastic surgery. Breast conservation surgery can be performed with the help of plastic surgery techniques in cases unfavorable tumor site or big tumor-breast imbalance (Almeida et al., 2021). Two, three, and four, oncoplastic breast conserving surgery reduces the need for re-excision, which can also improve one's self-esteem

and sexuality as well as their overall quality of life. Also some studies have found that oncoplastic breast conservation surgery which associated with a higher rate of postoperative complications and patients in most of these studies had a wide range of oncoplastic surgery types, as well as a wide range of postoperative complications that weren't standardized (Almeida et al., 2021). Non-conservative tumors may be candidates for oncoplastic surgery. Despite being utilized to treat bigger and more numerous tumors, surgery re-excisions were less common also were unrelated with greater rates of mastectomy conversion or local recurrence. Even though the oncoplastic group had more overall complications, both groups had a similar incidence of major complications. If it is used properly, breast conservation surgery can be a viable option for many women (Almeida et al., 2021).

6.2 Gene Editing

Core-shell nanoparticles have a remarkable gene transfection efficiency. The delivery of a pHR-pCas9 system allows for precise editing of the CTCF gene insert. Metastatic breast cancer can be treated with pHR-pCas9-carrying core-shell nanoparticles (Duan et al., 2022). When it comes to refractory cancer, such as metastatic breast cancer, clustered regularly interspaced short palindromic repeat or CRISPR, technology holds huge promise. CRISPR system delivery via non-viral carriers is still a major problem to be solved (Duan et al., 2022). Precision CTCF gene inserting by core-shell at nanoparticles (NPs) with dual plasmids (pHR-pCas9) are described to avoid metastatic breast cancer. This is the first time such NPs have been reported (Duan et al., 2022). The pHR-pCas9-carrying core-shell NPs may increase cell viability and receptor - mediated endocytosis release, allow the exact implantation and rigid transcription with CTCF gene, and which limit the migration, metastasis, colonization of the cell in metastatic breast cancer, according to findings of the current study (Duan et al., 2022). Furthermore, the finding of the pHR-pCas9-carrying core-shell demonstrates that the new mechanism of metastasis might related with the core-shell with the upregulation of CTCF protein and the subsequent downregulation of STOM protein. To treat severe illness, researchers have developed a universal nano strategy that can deliver gene-editing systems in a non-viral manner (Duan et al., 2022). Genome editing engineering technology for the treatment of cancer has advanced significantly in recent years, and it is now capable of making changes to any gene inside an afflicted region by adding or eliminating mutations (Hazafa et al., 2020). The employment of DNA domain binding traditional approaches such as transcriptional activator-like effector nucleases (TALENS) also zinc finger nucleases (ZFNs) to develop animal and cellular cancer models and perform therapeutic research has

tremendously benefitted the field of molecular biology (Hazafa et al., 2020). However, due to intricacy and more time needed tactics, their use has been restricted. Although the use of RNA interference (RNAi) in cancer therapy research is regarded a fantastic foundation for gene expression because of its short-lived knockdown effects, it must be delivered on a continual basis in order to attain the acceptable degree of knockdown (Hazafa et al., 2020). Because of the simplicity along with less time-consuming related abilities and the high accuracy, efficiency, CRISPR-associated protein-9 (Cas9), a new RNA domain-containing endonuclease related genome engineering tool, has created for the treatment of cancer. It achieved a tremendous amendment in the expression of gene also gene therapy in the present day because of the simplicity along with less time-consuming capacity with high accuracy and efficiency (Hazafa et al., 2020). It is superior to other technique of genome editing like TALENs and ZFNs because of minimal less targeting effects and less time-consuming target ability of CRISPR/Cas9 compared to other genome editing approaches. While older approaches (such as those using TALENs, ZFNs, and RNAi) for editing particular sections of DNA are available, the CRISPR-Cas9 system requires just a short complementary sequence (also known as sg-RNA), which may be used to target specific areas of DNA. Based on available evidence, the prokaryotic adaptive immune system (Escherichia coli) was the first to find CRISPR/Cas9, which is believed to be a good anti-phages and antiviral system by the scientific community (Hazafa et al., 2020). CRISPR/Cas9 is comprised of three basic components: the CRISPR RNA, the trans-activating CRISPR RNA (tracrRNA), and the endonuclease Cas-9. The CRISPR RNA is the fundamental component of the system. In the CRISPR/Cas9 system, there are numerous unique variations that may each shows a different role in certain situations (Hazafa et al., 2020). Another study discovered that the gene editing tool CRISPR-I drastically reduced the expression of endogenous genes in HeLa cells, including CXCR-4 and CD-71. According to the scientific literature, when comparing CRISPR/Cas9 to ZFNs and TALENs, more than 79 percent of the genomes in human pluripotent stem cells are modified. When compared to RNAi, CRISPR/Cas9 has effect as genome editing technology in an effective way, with less off-target effects. Luminal (ER-positive) subtypes of breast cancer account for around 70% of all cases, with 30% of these individuals developing resistance to endocrine treatments (Hazafa et al., 2020). Breast cancer incidence and recurrence rates must be reduced, however, if the disease is to be eliminated completely. The CRISPR/Cas9 technology currently used to find novel also revolutionary treatment targets for breast cancer. Both 2D and 3D tumor-chip models were utilized to investigate the effectiveness of several chemotherapies in conjunction with CRISPR/Cas9 in cure of breast cancer in laboratory (BRCA1m and PARP1m). For both

BRCA1m and PARP1m, three different Journal shows chemotherapeutic drugs, including doxorubicin, gemcitabine, and docetaxel were more effective when used in a tumor-culture model 2D rather than a tumor chip model of 3D (Hazafa et al., 2020). CRISPR-associated sgRNA which is a component of the CRISPR genome editing system that has been shown to effectively knockout both alleles of the APOBEC3G gene in breast cancer cure by inhibiting the transition of cell cycle from G1 to S phase also inhibiting cell proliferation. This is accomplished as block the cell cycle transition in G1 to S phase and inhibits cell proliferation. In a recent study, CRISPR/Cas9 deleted with success, the individual along with co-knockout CXCR7, CXCR4 genes both in the TNBC cell line (MDA-MB-231) in the time of cure breast cancer (Hazafa et al., 2020). In case of the suppressing tumor cell proliferation, tumor growth, also invasion, conquering of MASTL may come an excellent option in terms of cure breast cancer. As a result, many new proteins and genes have been discovered breast cancer using CRISPR/Cas9 by preclinical studies which is a significant path of cure in breast tumors (Hazafa et al., 2020).

6.3 Nanotechnology for Breast Cancer

TNBC is recognized to display the most aggressive phenotype and acquire resistance to chemotherapy because of the three primary receptors which are estrogen receptor (ER), progesterone receptor (PR) along with the human epidermal growth factor receptor 2 (HER2), are lacking (Jain et al., 2020). Patients suffering from breast cancer also thoracic cancer can profit from its considerable therapeutic benefits. The benefits of nanotechnology include its small size (nanometric), active and passive targeting capacity to connect various targeting moieties, controlled release, and site-targeting, to name a few (Jain et al., 2020). An in-depth look at current treatment options for BC/TNBC is presented that breast cancer stem cells have a vital role in recurrence. There have been numerous studies on chemotherapeutic agents delivered via nanocarriers, including polymeric metallic/inorganic nanoparticles, and lipid-based nanoparticles which are liposome, solid-lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), all of which have shown promising outcomes when used in the cure of BC and TNBC, as well as breast cancer stem cells (Jain et al., 2020). Additionally, nanomedicine has been brought up regarding breast cancer and tumor necrosis factor receptor (TNFR) as well as other molecular which targets poly (ADP-ribose) polymerase (PARP), epidermal growth factor receptor (EGFR), and Vascular endothelial growth factor (VEGF) (VEGF) (Jain et al., 2020). There are nano-formulations like micelles and fullerenes that can penetrate the leaky capillarieLiposomal and nanoemulsion formulations can also penetrate the

leaky capillaries. In case of hormone negative breast cancers, the tumor heterogeneity in endothelial cells, the thick collagen-rich tumor, the extra-tumor matrix also the intra-tumor pressure in the complex tumor microenvironment all work against passive diffusion of nanocarriers (Jain et al., 2020). On the other hand, have been able to successfully deliver drugs via passive targeting, utilizing the EPR effect. However, Paclitaxel coupled along with modified polyethylene glycol (PEG) micelles that employed in the treatment of individuals with TNBC. The linker 4-nitrophenyl chloroformate was used to conjugate PEG with PTX, resulting in a PEG with eight hydroxyl groups (Jain et al., 2020). Targeting the neuropilin-1 (NRP-1) receptor with iNGR-conjugated micelles in TNBC has been shown to be efficacious. In comparison to Taxol® and non-targeted micelles which shown a greater path in TNBCIn a separate research investigation, PTX-bound albumin liposomes were shown to effective nano-carrier for delivery of drug in TNBC and were proven to be an efficient nano-carrier for drug administration in TNBC (Jain et al., 2020). The tumor location revealed significant accumulation of a lipid-based nanocarrier with a particle size of 400 nm, which was shown to be efficacious. There have been numerous studies on the EPR effect since its discovery in the 1980s, including commercial products like Doxil® and Caelyx® (Jain et al., 2020). Tumor specificity is provided by the EPR mechanism, resulting in a 20-30% increase in tumor accumulation over normal tissue. However, the EPR effect has some drawbacks that must be taken into consideration. Tumor microenvironment, tumor pressure, surrounding tissue biology, and new tumor leakiness all play a role in the EPR effect (Jain et al., 2020).

6.4 Stem Cell Therapy

Differentiation the ability to self-renew, as well as the ability to maintain homeostasis, are three of the most important qualities of stem cells, which are required for the normal functioning of the body, particularly important during embryonic development (Palomeras et al., 2018). Nevertheless, oncologists face enormous difficulties and dangers because of the same characteristics in tumor development were the first to discover BCSCs in 2003 (Palomeras et al., 2018). It was developed that when CD44 and epithelial surface antigen (ESA), and CD24 (a P-selectin ligand) were injected to the mammary fat pads of NOD/SCID mice, they were able to sustain development (Palomeras et al., 2018). Breast cancer cells that were 100 times more abundant in CD44/CD24+ were unable to generate malignancies when implanted into NOD/SCID mice. Cells with a CD44+/CD24+/ESA+ phenotype that is more commonly related with basal than luminal breast cancer cell lines, were extracted from established breast cancer cell lines and were shown to be capable of re-creating the original cell line in culture (Palomeras

et al., 2018). Cell lines that have already been created can be used to study BCSC features, which could be a cost-effective model for drug development. It has been discovered that ALDH+ cells can originate tumors, but that they only slightly overlap with the CD44+/CD24 population, indicating that the phenotypically segregated cells do not represent the entire population of BCSCs (Palomeras et al., 2018). According to recent research, BCSCs may be a component of two interconvertible dynamic mesenchymal-epithelial transition (MET)-EMT states that give rise to more proliferative epithelial-like BCSCs (ALDH+), which are found quite regionally within cancer, and much more quiescent mesenchymal-like BCSCs (CD44+/CD24+), which are found more peripherally within cancer (Palomeras et al., 2018). For mismatch between stem cell characteristics and phenotypically distinct populations of cells, this is an obvious solution. Stem cells of cancer and tumor initiating cells may have a role in treatment resistance, according to some research and treatment failure and recurrence, according to increasing evidence (Palomeras et al., 2018). The discovery, isolation, and characterization of BCSCs, as well as the creation of new drugs that target this subpopulation, have all seen significant progress in recent years. As a result of the emergence of BCSC resistant clones in the absence of a combination, the pharmacological targets provided here are promising for the creation of a BCSC-directed treatment. BCSCs have the capability of switching in stem-like also non-stem states, therefore a combination therapy that also targets highly separated progenitors with the bulk tumor population is important when treating cancer stem cells (Palomeras et al., 2018). When more and more women are diagnosed with breast cancer, a new problem arises. These patients were able to beat their cancer because of early detection and treatment advances, but these therapies frequently have negative cardiovascular side effects, which might result in aberrant heart function (Sharp & George, 2014). Cardiotoxicity has been linked to both chemotherapeutic also with the radiation therapy, these may cause loss in cardiac muscle and vascular structure deterioration, which may gradually proceed to heart failure (HF) (Sharp & George, 2014). Breast cancer survivors may be diagnosed with dilated or restrictive cardiomyopathy as a result of this cardiomyocyte toxicity (DCM or RCM). Except for heart transplantation, there is presently no medication available that can replace the cardiac myocytes that are destroyed during cancer treatment (Sharp & George, 2014). A new generation of cancer medicines must be created in order to avoid or reverse the heart damage induced by cancer treatments. Myocardium that has been lost or is deteriorating should be regenerated with the help of these new therapeutics (Sharp & George, 2014). For individuals with heart failure, cell-based treatment has been investigated for the last

several decades for its therapeutic potential. Survivors from cancer with cardiomyopathy may benefit from stem cell therapy, according to the findings (Sharp & George, 2014).

6.5 Radionuclide Therapy

The effectiveness of cancer diagnosis and treatment is improved by nanotechnology. Cancer nanotechnology could benefit from carbon-based nanomaterials. Various radiolabeled carbon-based nanomaterials are available (Jaymand et al., 2021). Carbon-based nanomaterials that have been radiolabeled are effective cancer treatment tools. Conventional cancer treatment modalities could benefit from nanomaterials, which are highly complex multifunctional structures (Jaymand et al., 2021). Nanomaterials and nuclear medicine isotopes can be combined to create radiopharmaceuticals that are more precise and effective. Due to their remarkable physical and chemical properties, carbon-based nanomaterials (CNMs) have received unprecedented attention (Jaymand et al., 2021). Molecular recognition ligands can be attached to CNMs, allowing them to serve as carriers for large doses of radionuclides. Radionuclides can be delivered more effectively using a variety of carbon quantum dots, fullerenes, carbon nanotubes, graphene, nanodiamonds. CNMs have been shown in studies to be effective as theragnostic systems as well as radiopharmaceutical nanocarriers (Jaymand et al., 2021). Breast cancer deaths are primarily due to a lack of early detection of the disease, which leads to tumor spread in later stages (Ahmadpour & Hosseinimehr, 2019). There is an urgent need for a SPECT/PET-based early-stage breast cancer diagnostic tool with high sensitivity that can be developed quickly (Ahmadpour & Hosseinimehr, 2019). Breast cancer tumor initiation and progression may be aided by receptor overexpression, as evidenced by numerous studies (Ahmadpour & Hosseinimehr, 2019). The use of radiolabeled biomolecules to target a specific receptor is appropriate in the early detection of breast cancer. Recent years peptide-based radiopharmaceuticals have gained attention because favorable pharmacokinetics, which can be used for breast cancer imaging (Ahmadpour & Hosseinimehr, 2019). These peptides can be prepared using various characterizing techniques that allow for efficient for clinical use of SPECT radionuclides. SPECT radiopharmaceuticals based on peptides for breast cancer imaging and targeting is also including in this sector (Ahmadpour & Hosseinimehr, 2019).

6.6 Radiopharmaceutical

The relationship following the cancer immunoediting paradigm, communication in tumor cells also their immune system is a continuous process, with three main phases, were elimination (García-Aranda & Redondo, 2019). In that phase the cancer cells are recognizing and destroys

cancer cells successfully. A substance's propensity to induce an immunological response also known as immunogenicity, is critical to the immune system's ability to eradicate tumor cells (García-Aranda & Redondo, 2019). Tissue tumor cells produce new antigens, which are digested and delivered on the cell surface as antigen-derived peptides in conjunction with the HLA class I antigen receptor, (HLA-I). APCs identify, process, and present antigen-derived peptide on the surface of the tumor microenvironment, which may be identified with the helper T cell receptors which helps to the activation along with maturation of B-cells and cytotoxic T cells via Human Leukocyte Antigen class-II receptors (HLA-II) (García-Aranda & Redondo, 2019). For example, in response to the activation of T cells with co-stimulatory signals from APCs, T cells recognize, and attack tumor cells based on neoantigen presentation by HLA-I and the activation of FAS and caspases (García-Aranda & Redondo, 2019). There are some tumors that can grow while they are under control during this phase by the immune system. This phase is called Equilibrium. Treatments for cancer or immune surveillance may result in uncontrolled proliferated cells, resistant or non-immunogenic phenotype, which can lead to tumor development also metastasis, among other consequences (García-Aranda & Redondo, 2019). For patients having breast cancer, Cell immunotherapies like Chimeric Antigen Receptor T cell therapy and Tumor-Infiltrating Lymphocyte (TIL) therapy, that are related to the isolation of antitumor T cells from primary tumors, further ex vivo expansion, activation, and reinfusion of such cells into the patient, are also proving to be effective both preclinical, clinical trials (García-Aranda & Redondo, 2019). Technologies such as next-generation sequencing and bioinformatics are being developed, in a similar vein, are now essential tools for identifying and improving personalized translational immunotherapy studies based on neoantigens, as well as for the development of neoantigen vaccines that will trigger T-cell responses specific to neoantigens via the activation of antigen-presenting cells (García-Aranda & Redondo, 2019). Nanoparticle findings are no less significant, as they have been recommended as the most asset in overcoming the limits of current immunotherapy, as they have the potential to boost overall anticancer immune responses while causing the least amount of systemic adverse effects (García-Aranda & Redondo, 2019). Some breast cancer nanoparticles, such as complexes of titanium dioxide, silica, and gold are used which can cause micrometer-sized gauze to form in the tumor microenvironment and drug resistance. Despite this, some breast cancer nanoparticles have previously been shown that they are effective in combating the immune-suppressive impact of the tumor microenvironment and treatment resistance, in delivering antigens and adjuvant to tumor cells, and in decreasing the negative effects of anticancer medications (García-Aranda & Redondo, 2019). Use of

radiopharmaceuticals in cancer treatment and diagnosis is critical. To deliver drugs in specific locations nanocarriers can be used. Nanoparticle radiolabeling provides a novel platform for both diagnosis and treatment (Shende & Gandhi, 2021). Nanoparticles that have been radiolabeled can be used to detect tumor cells precisely and to treat them with the least amount of side effects possible. Loss of appetite, hair loss, diarrhea, anemia and edema have all been reported as side effects of chemotherapy for cancer patients in the past (Shende & Gandhi, 2021). Due to their ability to emit radiation and aid in the accurate visualization of infected cells in the human body that cause low harm, radiopharmaceuticals have emerged the previous two decades have seen significant advancements in management and cure of cancer. Radionuclide's malignancies of the lung, brain, and breast are among those that have shown biological activity, are currently being identified or developed (Shende & Gandhi, 2021). Tissue cancer cells can be targeted using radiopharmaceuticals in combination with chemotherapy drugs, antibodies, or peptides. For managing cancer at preclinical and clinical stages nanotechnology-based radiolabeled theragnostic systems such as PET, single photon emission CT, computerized tomography, molecular magnetic resonance imaging (MRI) along with fluorescence imaging are all approaches that may be used to image metallic polymeric silica liposomes and dendrimers labeled with nanoparticles can be included. Which strongly support the idea that nuclear medicine and nanomedicine are useful to diagnose and treat cancer patients who have fewer side effects (Shende & Gandhi, 2021).

6.7 Targeted Therapy

When it comes to MBC or metastatic breast cancer, targeted therapies have made tremendous progress. TNBC treatment should be guided by the principles of personalized therapy (Gu et al., 2016). Clinical trial design can be improved by the patient selection be optimized, and predictive biomarkers be developed. MBC treatment should be guided by plasma DNA monitoring over time. Breast cancer treatment has recently seen promising advances thanks to Clinical trials which are being used to assess new medications and therapy combinations (Gu et al., 2016). At the moment, the diagnosis and treating hormone receptor (HR) and epidermal growth factor receptor (HER2) positive breast cancer in distinct ways from treating triple negative breast cancer is a possibility (TNBC) (Gu et al., 2016). To combat resistance in the clinic, some preclinical studies have shown several targetable pathways with the HER2, endocrine targeted therapies (Gu et al., 2016). Because of improved disease-free survival, Everolimus, a mTOR inhibitor, and palbociclib, a CDK4/6 inhibitor licensed in the cure of HR-positive metastatic breast cancer (MBC) (DFS). DFS in pertuzumab and trastuzumab, taxanes

are added, HER2-positive breast cancer can be improved (Gu et al., 2016). Chemotherapy must be used in conjunction with targeted therapy to diverse subset of TNBC. Nevertheless, the selection of patients and the development of predictive biomarkers for TNBC targeted therapy development remain major challenges (Gu et al., 2016). The aggressiveness of triple-negative breast cancer (TNBC) is as it is a breast cancer subtype (Lyons, 2019). A subtype of breast cancer characterized by its molecular markers and clinical response to targeted treatment is known as triple-negative breast cancer, or TNBC (Lyons, 2019). Cytotoxic chemotherapy has been the mainstay of treatment for TNBC until recently. Molecularly targeted approaches to TNBC, however, are now showing promising clinical activity (Lyons, 2019). Obaparib and talazoparib have been approved for the cure of germline BRCA mutation-associated breast cancer (gBRCAm-BC), while atezolizumab in conjunction with nab-paclitaxel has been approved most recently due to PD-L1+ advanced TNBC have all been recently approved targeted therapies for TNBC (Lyons, 2019). In order to improve patient selection for checkpoint inhibition, new biomarkers are needed. Cancer patients who receive first-line treatment with chemo and checkpoint inhibitors are more likely to respond than those who receive chemotherapy alone (Lyons, 2019). Conjugates of antibodies and drugs are a hot topic because they have the potential to re-examine previously developed cytotoxic that failed in development due to toxicities (Lyons, 2019). As a result of recent advances in tumor sequencing, new small-molecule drugs, such as AKT inhibition, are now being tested in clinical trials. Because of increasingly difficult to treat TNBC using a "one size fits all" approach based on molecular subtyping, its molecular traits, as well as its clinical response to a focused therapy strategy and the term "TNBC" may become obsolete soon (Lyons, 2019).

Chapter 7: Future Directions and Challenges

7.1 Early Diagnosis and Public Facilities for Treatment

Early diagnosis of women is most important part of breast cancer detection and treatment. As most of the patients cannot be aware of whether they are going through this disease or not it possibility the risk of having breast cancer and not treating on time (Rivera-Franco & Leon-Rodriguez, 2018). Awareness should be increased by self-monitoring and consulting a doctor should be encouraged. This is how early diagnosis can help in decreasing the mortality rate and starting the treatment earlier. Breast cancer effects not only developing country but also developed countries as well (Rivera-Franco & Leon-Rodriguez, 2018). Delaying first childbirth, decreasing the number of children a woman has, as well as reducing the time she breastfeeds increase the risk in developing countries (Rivera-Franco & Leon-Rodriguez, 2018). According to Rivera-Franco & Leon-Rodriguez, 2018, 40-60% mortality rate is seen among the people of underdeveloped countries. In addition, there is a lack of survival data in developing countries. Breast cancer survival rates in LMICs countries like Brazil, India, Bangladesh, and Algeria are lower than in the US or Sweden. Early detection programs are sorely lacking, which leads to high proportions of women who have the disease in later stages and insufficient diagnostic and treatment facilities, which accounts for the low survival rates (Rivera-Franco & Leon-Rodriguez, 2018). In order to improve care in developing countries, it is critical to emphasize health education and emphasize on more public facilities which can provide treatment (Rivera-Franco & Leon-Rodriguez, 2018).

7.2 Vaccine (NeuVax)

A highly expressed immunogenic peptide from the HER2 protein, Nelipepimut-S which known as E75, are identified in breast cancer (Schneble et al., 2014). The active ingredient is Neopimut-S in combination with granulocyte-macrophage colony-stimulating factor which is in the NeuVaxTM (Galena, OR) vaccine for high-risk, disease-free patients with breast cancer (Schneble et al., 2014). There are many question about the mechanisms of action of NeuVax and other cancer vaccines, particularly given the lack of correlation between immunologic data and clinical outcomes in multiple cancer vaccine trials (Schneble et al., 2014). To better understand how this peptide vaccine may impact the immune system. Studies showed that certain immunologic assays may be able to predict clinical benefit (Schneble et al., 2014). Immune homeostasis and cellular specialization are orchestrated by complex molecular mechanisms (Benedetti et al., 2017). Ongoing treatments in the fight against breast cancer

along with surgical removal of the tumors as well as radiation and chemotherapy, all of which are related to side effects and even the potential for recurrence (Benedetti et al., 2017). The development of these vaccines is under investigation by a number of laboratories in an effort to have a long-lasting response with the least side effects, anti-breast cancer vaccine can activate the body's defenses. These vaccines have not yet been approved to use in clinical trials (Behravan et al., 2019). Some preventive and therapeutic breast cancer vaccines are in various stages of development, with one (NeuVax) having completed clinical trial phase III. It can be said believe that a breast cancer vaccine is within reach, given the recent advances in immunotherapy (Behravan et al., 2019).

7.3 Three-Dimensional Biochemical Modeling

In vitro 3D breast tumor models play a vital role in the study of breast cancer today, providing valuable information about the disease. Ambiguous host environment of an in vivo model, these models not only help us better understand homeostasis, cellular differentiation, and tissue organization, but they also include an environment for cancer research (Aristokli et al., 2022a). The models must also be improved so that they can be used regularly and so that they can better shows the complexity in tumor microenvironment and thus help advance our understanding of cancer biology. It will take cross-disciplinary research to find a solution to these issues. Developing more effective therapeutic strategies will undoubtedly benefit from these enhancements (Huerta-Reyes & Aguilar-Rojas, 2021).

7.4 Challenges

Sometimes there are false negative and false positive results that may be altered. There are also some challenges like the new technologies to detect cancer showed time-consuming, in treatment targeting the specific cells are also challenging.

Chapter 8: Conclusion

To conclude the new novel approaches to diagnosis and treatment of breast cancer are improving which can be a benchmark towards decreasing mortality rate and specify the cancer cell. Variations in survival rates are expected to improve in the future. Breast cancer has seen a tremendous shift in screening methods, early diagnosis, and treatment breakthroughs because of these changes, there has been an increase in survival. Breast cancer staging and classification methods have undergone numerous changes by the time. The ability to do molecular subtyping is essential for conducting clinical research also for a thorough understanding of the illness. Technology to detect distant metastases, recurrence, and response to breast cancer treatment is constantly evolving. New breast cancer therapies are being researched to bring them into clinical use. Most of the new pharmacological agents that specifically target breast tumor cells have been described in research publications and patents in recent years. Conjugation of therapeutic drug particle with targeted moiety, diagnostic drug particle, or drug carrier in order to create a new carrier system that can perform various duties and functions, such as functioning as an effective drug delivery vehicle and a diagnostic instrument.

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